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Relation between Cognitive Function and Mortality in Middle-aged Adults

The Atherosclerosis Risk in Communities Study

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An independent, inverse association between cognitive function and all-cause mortality has been reported in elderly cohorts. The purpose of this study was to determine whether the same association exists in middle-aged persons. The Atherosclerosis Risk in Communities Study is a cohort study initiated in 1987 to investigate the development of atherosclerosis in middle-aged persons. Three cognitive function measures were included in the second cohort examination conducted from 1990 to 1992 when the participants were aged 48–67 years: the Delayed Word Recall Test (DWRT), the Digit Symbol Substitution Test (DSST) (a subtest from the Wechsler Adult Intelligence Scale-Revised), and the Word Fluency Test from the Multilingual Aphasia Examination. Cox proportional hazards modeling was used to determine whether all-cause mortality ascertained through 1997 was associated with each measure after adjustment for sociodemographic, biologic, psychologic, and behavioral risk factors. Without adjustment, there was a significantly lower mortality hazard associated with higher scores on all three measures. After covariate adjustment, the hazard ratios for the DWRT and the DSST remained significant (hazard ratio$_{\text{1-point DWRT score increment}}$ = 0.90, 95% confidence interval: 0.84, 0.97; hazard ratio$_{\text{7-point DSST score increment}}$ = 0.86, 95% confidence interval: 0.80, 0.93). Cognitive function measured in middle age appears to have prognostic importance for life expectancy similar to that reported in elderly adults.

cognition; cohort studies; mortality; risk factors

Abbreviations: ARIC, Atherosclerosis Risk in Communities; DSST, Digit Symbol Substitution Test; DWRT, Delayed Word Recall Test; WFT, Word Fluency Test.

There is a growing literature demonstrating that cognitive function measured in the elderly is a strong, independent predictor of subsequent mortality (1–5). The relation between cognitive function and mortality is observed using a variety of measures, including the Mini-Mental State Examination, selected subscales of the Wechsler Adult Intelligence Scale-Revised, and various other tests of verbal and nonverbal abilities.

Although a portion of the relation between cognitive function and mortality may be explained by the presence of chronic diseases that affect cognitive function (6, 7), the fact that cognitive function measures remain significant, independent predictors of mortality after accounting for a wide range of health, functional status, and behavioral measures suggests that the inverse relation between cognitive function and mortality in elderly persons is not entirely explained by organic disease. Furthermore, performance on cognitive function measures in epidemiologic studies is known to be associated with such socioeconomic status variables as race, education, and income (8–11). In reports that include both unadjusted and adjusted relative risks, the relation between education and mortality does not remain significant when

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cognitive function measures are included in the prediction equation (2–4, 12). Thus, the possibility that at least part of the observed association between socioeconomic status and mortality can be explained by confounding with cognitive function must be considered. A clearer understanding of the relation between cognitive function and mortality at different points in the life span could advance our understanding of the biologic and environmental determinants of life expectancy in human populations.

Because studies to date have reported on cognitive function measured in cohorts whose members were predominantly aged 65 or more years at inception, it has been difficult to establish whether the increased mortality risk associated with lower cognitive function reflects existing pathologic processes that have already led to cognitive decline, a lower lifetime level of cognitive functioning, or an interaction between these two conditions. To clearly elucidate the role of cognitive function as an independent predictor of morbidity and mortality outcomes in the population, one must measure it at a time when performance is less likely to be confounded by coexisting disease.

The Atherosclerosis Risk in Communities (ARIC) Study is a cohort study initiated in 1987 to investigate the development of atherosclerosis in a representative sample of persons 45–64 years of age at baseline. Three measures of cognitive function were included in the second cohort examination (visit 2) conducted from 1990 to 1992 when the participants were 48–67 years of age. Morbidity and mortality outcomes have been documented annually since that time. The purpose of the present study was to assess whether the cognitive function measures obtained at the visit 2 examination in this middle-aged population cohort were independently associated with all-cause mortality after adjustment for multiple known biologic and behavioral risk factors.

MATERIALS AND METHODS

The ARIC Study was undertaken as a prospective investigation of atherosclerosis in four communities in the United States beginning in 1987 (13). The four communities were Jackson, Mississippi; Forsyth County, North Carolina; Washington County, Maryland; and selected suburbs of Minneapolis, Minnesota. Probability sampling was used to select subjects for participation. By design, only African Americans were sampled in Jackson, Mississippi. The Forsyth County sample was approximately 14 percent African American, and participants in the remaining two communities were predominantly White. The original study protocol called for enrollment of 16,000 persons 45–64 years of age to participate in an in-home interview followed by clinical examinations every 3 years and annual telephone follow-up. Deaths in the cohort were ascertained through the annual cohort follow-up process, as well as by monitoring of local obituaries and hospital discharge summaries and by searching the National Death Index. The date and cause of death were verified by death certificate review. Complete data on the vital status of cohort members through 1997 were available for the present analysis. Details of the study methods have been published previously (13).

Study population

The study exclusion criteria were designed to eliminate from the analytic cohort persons who might have cognitive impairment due to known vascular disease (e.g., history of recent myocardial infarction or stroke) or a condition affecting the central nervous system. Because the relation between other health conditions and cognitive function is not clearly established, we attempted to adjust statistically for other significant health conditions that had the potential of influencing cognitive function at the time of the visit 2 examination.

Of the 15,792 individuals free of documented cardiovascular disease at the baseline examination, the following were excluded from the present analysis: 1) those with a history of stroke, transient ischemic attack, or myocardial infarction between the visit 1 and visit 2 examinations (n = 784); 2) those taking medications with known central nervous system effects, such as antidepressants and antipsychotics, at visit 2 (n = 2,024); 3) those who did not participate in the visit 2 examination (n = 1,357); 4) those who belonged to racial/ethnic groups other than White or African American (n = 41) and those who did not complete all three of the cognitive function measures at the visit 2 examination (n = 142). Thus, the final analytic sample consisted of 11,444 individuals.

Cognitive function measures

The second clinical examination of the ARIC Study cohort in 1990–1992 included three neuropsychologic tests to assess cognitive function: the Delayed Word Recall Test (DWRT) (14), the Digit Symbol Substitution Test (DSST) (a subtest of the Wechsler Adult Intelligence Scale-Revised) (15), and the Controlled Oral Word Association Test (Word Fluency Test (WFT)) of the Multilingual Aphasia Examination (16, 17). The DWRT is a 10-item memory test designed to screen for dementia. In the validation study of the DWRT, the optimal cutoff score for distinguishing between demented and nondemented subjects was <3 words recalled. Test-retest reliability over a 6-month period was reported to be 0.75 (14). The DSST is a timed test that involves the pairing of numbers with corresponding symbols according to a code that is visible to the participant. This test is widely used in neuropsychologic and epidemiologic contexts to assess sustained attention and psychomotor speed, and it has a test-retest reliability of 0.82 in middle-aged individuals (15). The WFT requires the examinee to generate as many words as possible that begin with three different letters of the alphabet. The test is useful for detecting frontal lobe damage and early mental decline in older persons (18); a test-retest reliability of 0.88 in older adults over a 19- to 42-day period has been reported (19). Cross-sectional associations among the three cognitive function measures and other health-related variables at the ARIC Study visit 2 examination have been published (20).

Covariates

Each clinical examination included a medical history interview and physical examination, anthropometric

measurements, and collection of blood samples for biochemical determination of cardiovascular risk factors, including plasma lipids, coagulation proteins, insulin, and glucose. Clinical and subclinical atherosclerotic diseases were documented by means of electrocardiogram, β-mode ultrasound measurement of carotid wall thickness (21), annual participant follow-up telephone interviews, and surveillance of community hospital admissions and deaths. Information on socioeconomic level, physical activity, and subjective perceptions of disease was also collected.

Variables included in the present analysis were chosen because of their potential to confound the association between cognitive function and mortality. They can be classified into three broad groups: 1) *sociodemographic factors*: age, race, educational attainment, occupation, and ARIC Study field center (the latter variable represents a combination of geographic and environmental factors that contribute to variation in mortality); 2) *biologic and psychologic markers of disease risk*: diagnosis of hypertension (measured systolic blood pressure of ≥140 mmHg or measured diastolic pressure of ≥90 mmHg or currently taking antihypertensive medication), diagnosed diabetes (fasting blood glucose of >126 mg/dl or currently taking antidiabetic medications), history of physician-diagnosed cancer reported at the visit 2 examination, history of coronary artery bypass surgery at the visit 2 examination, carotid wall thickness (mean of intimal-medial thickness measurements of the far wall for 1-cm lengths of the carotid bifurcation and of the right and left internal and common carotid arteries), plasma fibrinogen, body mass index, waist/hip ratio, total cholesterol, self-rated health (reported as excellent, good, fair, or poor), and "vital exhaustion" (a paper-and-pencil test that assesses perceived fatigue and depressed mood (22)); and 3) *health-related behaviors known to be associated with mortality*: smoking status (coded as current, former, or never), ethanol intake (coded as a dichotomous variable representing intake above and below 130 g per week, which was the 90th percentile in this population), and a measure of leisure time physical activity (assessed using a modified version of the Baecke et al. questionnaire (23) and summarized as an index ranging from 1 to 5 based on frequency, type, and intensity of activity, with lower scores representing less activity).

With the exception of educational attainment, plasma fibrinogen, and the leisure time sports participation index, which were measured at the ARIC Study baseline visit (1987–1989), all variables included in the analysis were measured at the visit 2 examination.

Statistical analysis

The distribution of each study variable in persons who were alive at the end of the follow-up period was compared with those in persons who had died. The statistical significance of differences between the two groups was calculated using analysis of variance or the chi-square test.

The three cognitive function measures had approximately normal distributions and were treated as continuous variables in the analysis. Because of the wide range of scores on the DSST and the WFT (0–93 and 0–99, respectively), the scores were divided into increments that corresponded to approximately one-half standard deviation. This permits interpretation of the hazard ratios as the change in hazard for a one-half standard deviation change in the covariate. Categorical variables, including education, ARIC Study center, smoking status, and drinking status, were coded as indicator variables in the survival models.

Cox proportional hazards survival analysis (24) was used to estimate the hazard ratios associated with increasing levels of performance on each of the three cognitive function measures. The first step in the analysis was to test the assumption of proportionality of the hazard ratios in unadjusted models and models containing different sets of covariates, using the methods of Grambsch and Therneau (25). This approach tests the null hypothesis of zero slope in a linear regression model of scaled Schoenfield residuals on time to failure. If the null hypothesis is not rejected, the hazard ratios associated with the set of covariates in the model can be assumed to be constant over the follow-up period. The proportionality assumption was not violated in any of the models considered. In addition, Martingale residuals were calculated for adjusted and unadjusted models and plotted against each cognitive function measure to assess the adequacy of the functional form of the cognitive function variables. Martingale residuals can be interpreted as the change over time in the difference between the observed number of failures and the number predicted by the model. If Martingale residuals plotted against an individual covariate produce an approximately linear curve roughly equal to zero at all points of the covariate, it can be assumed that the functional form of the covariate is adequate (25, 26). None of the smoothed residual curves deviated more than minimally from zero for any of the three measures, and we concluded that it was appropriate to treat each cognitive function measure as continuous in the survival models.

Because the cognitive test battery applied in the ARIC Study cohort was not developed as a comprehensive neuropsychologic assessment battery designed to yield a summary score, the association of each cognitive function measure with mortality was modeled separately. Modeling was carried out in a manner designed to estimate the effects of cognitive function on survival, taking into consideration the different groups of potential confounders. First, hazard ratios were calculated without adjustment for, then with adjustment for, each group of predictor variables (i.e., sociodemographic variables, biologic and psychologic predictors of mortality, and health-related behaviors) and finally with all of the candidate covariates. A final model was constructed that adjusted the hazard ratios associated with each cognitive function measure for all covariates that met the statistical significance criterion of $p < 0.05$. Before the final adjusted hazard ratios associated with cognitive function scores were calculated, we verified that their magnitude was not altered by the exclusion of any of the covariates that had nonsignificant p values. All statistical analyses were carried out using the Stata software package (27).

After we calculated the final models containing each cognitive function measure adjusted for significant covariates, we carried out two additional exploratory analyses. Because of the possibility of residual confounding of lower

TABLE 1. Causes of death in cohort members included in the analysis, Atherosclerosis Risk in Communities Study cohort, 1990–1997

Cause of death (ICD-9* codes)	All deaths		Mean time from visit 2 until death (years)
	No.	%	
Infectious diseases, including pneumonia (codes 1.0–139.9, 480.0–487.9)	6	1.25	4.17
Malignant neoplasms (codes 140.0–239.9)	231	48.23	3.63
Cardiovascular and cerebrovascular diseases (codes 401.0–404.0, 410.0–414.0, 430.0–438.0), distributed as follows	105	21.92	
Hypertensive heart disease ($n = 13$)			3.64
Ischemic heart disease ($n = 76$)			3.10
Cerebrovascular disease ($n = 16$)			3.98
Diabetes (codes 250.0–250.9)	14	2.92	3.80
Cirrhosis of liver (codes 571.0–571.9)	7	1.46	4.27
Accidents and injuries (codes 800.0 and above)	15	3.13	3.64
Other causes not classified above	101	21.09	4.02
Total	479	100.0	3.66

* ICD-9, *International Classification of Diseases*, Ninth Revision.

cognitive function scores with preexisting illness at the visit 2 examination, we ran the survival models after excluding deaths that occurred during the first year of follow-up ($n = 36$). In addition, to examine whether any observed associations between cognitive function measures and mortality were consistent across different causes of death, we repeated the survival modeling for deaths grouped into three categories: 1) deaths attributed to malignant neoplasms, 2) deaths attributed to cardiovascular disease, cerebrovascular disease, or diabetes, and 3) all noncardiovascular and noncancer deaths.

RESULTS

Of the 11,444 individuals included in the analytic sample, 482 died over an average follow-up time of 6.3 years. The causes of death, as ascertained by death certificate review for all but three of the participants who died, are listed in table 1.

The means or proportions of all study variables by cohort survival status as of December 1997 are reported in table 2. Survivors were more likely to be younger, female, White, more educated, and working in managerial or technical positions. Unadjusted mean scores on all three cognitive function measures were higher in survivors. Of the biologic and psychologic variables considered, only plasma total cholesterol and body mass index did not show statistically significant associations with survival status. Survivors were more likely to report a higher leisure time sports index score, current drinking, and never having smoked.

Because of the complex occupational coding used in the ARIC Study, we evaluated all models with occupational codes both included and excluded. Exclusion of the variable did not alter any of the associations between other covariates and mortality, so we omitted occupational codes from our models. We also substituted the number of pack-years smoked (collected at the visit 1 examination) for the categorical smoking variable in the survival models to ensure that residual confounding was minimized. The hazard ratios associated with cognitive function were not altered when smoking was expressed in terms of pack-years, and our results reflect models containing the categorical variable. Similarly, results were unaltered if the ethanol intake cutpoint was moved to the 99th percentile or 418 g per week. Finally, eliminating deaths that occurred during the first follow-up year did not alter the results in any way, and our findings reflect the inclusion of all deaths.

As shown in table 3, before adjustment for other covariates, there was a significantly decreased mortality hazard associated with increasing scores on each cognitive function measure. Adjustment for age and other sociodemographic variables reduced the magnitude of the inverse association somewhat. The hazard ratios for the DWRT and the DSST remained statistically significant, but the WFT score was no longer significantly associated with all-cause mortality after adjustment for age, sex, race, and education.

Adding the remaining biologic and lifestyle variables resulted in little additional attenuation of the hazard ratios associated with each measure. In the final models containing all covariates significantly associated with mortality, there was a 10 percent reduction in the mortality hazard associated with each 1-point increment on the DWRT, and there was a 14 percent reduction in the mortality hazard associated with each 7-point increment on the DSST. The hazard ratio associated with the WFT was statistically indistinguishable from 1.

Table 4 contains the results obtained when the final models for the DWRT and the DSST were calculated for specific categories of deaths. Because the hazard ratios for the WFT did not vary by cause of death and were very similar to those reported in table 3, they were omitted from table 4. There was some variability in the strength of the association between each measure and the three mortality

TABLE 2. Means or proportions of study variables by survival status, Atherosclerosis Risk in Communities Study cohort, 1990–1997

	Alive (n = 10,962)		Dead (n = 482)		p value*
	Mean or %	SD†	Mean or %	SD	
Cognitive function measures					
Delayed Word Recall Test (mean score)	6.68	1.49	6.03	1.78	<0.001
Digit Symbol Substitution Test (mean score)	45.56	14.01	37.07	15.99	<0.001
Word Fluency Test (mean score)	33.59	12.46	30.10	13.07	<0.001
Age at visit 2 (mean score)	56.68	5.66	59.66	5.45	<0.001
Sex (% female)	54.63		44.81		<0.001
Race (% African American)	24.04		36.31		<0.001
Education (% in each category)					<0.001
Some college	38.56		28.27		
High school or vocational school graduate	42.16		35.34		
Less than 12 years	19.27		36.38		
Occupation (% in each category)					<0.001
Managerial/professional	24.97		15.35		
Technical	21.42		16.60		
Service occupations	10.19		11.20		
Farming, forestry, and fishing	0.78		0.62		
Precision, craft, and repair	8.29		8.92		
Operators, fabricators, laborers	9.76		9.54		
Homemakers	8.35		11.83		
Retired	13.26		22.61		
Missing code	2.97		3.32		
Center (% in each site)					<0.001
Forsyth County, NC	24.93		20.95		
Jackson, MS	21.19		33.61		
Minneapolis, MN	28.40		24.07		
Washington County, MD	25.48		21.37		
Body mass index (mean kg/m^2)	27.93	5.30	27.75	6.01	0.461
Waist/hip ratio (mean)	0.92	0.08	0.95	0.07	<0.001
Plasma fibrinogen (mean mg/dl)	298.52	61.48	328.07	79.00	<0.001
Total cholesterol (mean mg/dl)	209.06	38.51	211.77	46.27	0.136
Carotid intimal thickness (average μm from six sites)	23.69	3.76	23.97	4.00	0.109
Diagnosed hypertension (% yes)	32.99		50.31		<0.001
Diagnosed diabetes based on criterion of fasting plasma glucose of >126 mg/dl (% yes)	13.38		27.14		<0.001
History of coronary artery bypass surgery at visit 2 (% yes)	0.64		2.49		<0.001
Diagnosed cancer (% yes)	5.99		12.66		<0.001
Vital exhaustion (mean)	5.71	5.48	7.91	6.47	<0.001
Perceived health (% fair/poor)	12.40		31.64		<0.001
Leisure time sports participation index (mean)	2.47	0.80	2.25	0.75	<0.001
Ethanol intake >90th percentile (% reporting >130 g/week)	9.93		11.00		0.443
Smoking status (% in each category)					<0.001
Current smoker	21.14		38.17		
Former smoker	37.63		37.14		
Never smoker	41.23		24.69		

* p value for comparison of group means by analysis of variance or differences in proportions by chi-square test.

† SD, standard deviation.

endpoints. The point estimate for the association of the DWRT with each specific cause of death was of approximately the same magnitude (ranging from 0.89 to 0.92), although it achieved statistical significance only for cancer deaths. Conversely, the DSST was not associated with cancer deaths but remained strongly associated with both

TABLE 3. Unadjusted and adjusted mortality hazard ratios associated with three cognitive function scores, Atherosclerosis Risk in Communities Study cohort, 1990–1997*

	Cognitive function measure†								
	Delayed Word Recall Test (1-point score increments)			Digit Symbol Substitution Test (7-point score increments)			Word Fluency Test (6-point score increments)		
	Hazard ratio	95% CI‡	*p* value	Hazard ratio	95% CI	*p* value	Hazard ratio	95% CI	*p* value
Model 1 (cognitive function hazard ratios unadjusted for covariates)	0.77	0.73, 0.81	<0.001	0.76	0.73, 0.79	<0.001	0.87	0.84, 0.91	<0.001
Model 2 (cognitive function hazard ratios adjusted for sociodemographic variables)	0.88	0.83, 0.94	<0.001	0.82	0.77, 0.88	<0.001	0.98	0.93, 1.03	0.410
Model 3 (cognitive function hazard ratios adjusted for variables in model 2 plus biologic and psychologic variables)	0.90	0.84, 0.96	0.003	0.83	0.77, 0.90	<0.001	1.06	0.96, 1.07	0.693
Model 4 (cognitive function hazard ratios adjusted for variables in model 3 plus health-related behaviors)	0.90	0.84, 0.97	0.005	0.85	0.78, 0.92	<0.001	1.02	0.97, 1.09	0.416
Model 5 (cognitive function hazard ratios adjusted for all significant covariates found in model 4)§	0.90	0.84, 0.97	0.003	0.86	0.80, 0.93	<0.001	1.01	0.95, 1.06	0.824

* Sociodemographic variables included sex, race, education, and study field center. Biologic and psychologic variables included body mass index, waist/hip ratio, plasma fibrinogen, total cholesterol, carotid intimal wall thickness, diagnosed hypertension, diagnosed diabetes, diagnosed cancer, history of coronary artery bypass surgery at the visit 2 examination, vital exhaustion, and perceived health. Health-related behaviors included leisure time sports participation index, ethanol use, and smoking status.

† Higher scores on each cognitive function measurement reflect better performance. The score ranges for each measurement were 0–10 for the Delayed Word Recall Test, 0–93 for the Digit Symbol Substitution Test, and 0–99 for the Word Fluency Test.

‡ CI, confidence interval.

§ Variables that remained significant in the full multivariate model were age, sex, study field center, body mass index, plasma fibrinogen, diabetes, hypertension, history of coronary artery bypass surgery, self-rated health, vital exhaustion, smoking status, and leisure time activity index. Variables not significant ($p > 0.05$) in the full multivariate models: education, race, waist/hip ratio, total cholesterol, carotid intimal wall thickness, and ethanol intake.

cardiovascular deaths and all noncancer and noncardiovascular deaths.

DISCUSSION

Two of the three cognitive function measures in the ARIC Study cohort were independently predictive of all-cause mortality over an average follow-up time of 6.3 years. A statistically significant association was found even after adjustment for a large number of other variables associated with mortality. The present analysis indicates that cognitive function, measured in persons who are healthy enough to attend an extensive population cohort follow-up examination session and who are below the age when dementia is expected to be clinically apparent, is a significant, independent risk factor for all-cause mortality.

Comparisons of the results of this study with those of others are complicated by a lack of uniformity in the cognitive domains measured, the specific cognitive function instruments selected, or in the categorization of cognitive function measures for statistical analysis. Two of the three cognitive function measures administered to the ARIC Study cohort, the DSST and the WFT, are widely used as components of a comprehensive neuropsychologic assessment battery (16, 17) and are designed to tap specific domains of cognitive function that could be affected by vascular disease. Although it was developed more recently than the other two measures, the DWRT resembles other tests of verbal

TABLE 4. Association of Delayed Word Recall Test and Digit Symbol Substitution Test scores with specific causes of death, Atherosclerosis Risk in Communities Study cohort, 1990–1997

Causes of death	Delayed Word Recall Test (1-point increments)			Digit Symbol Substitution Test (7-point increments)		
	Adjusted hazard ratio*	95% CI†	*p* value	Adjusted hazard ratio	95% CI	*p* value
Malignant neoplasms ($n = 231$)	0.89	0.80, 0.98	0.020	0.99	0.89, 1.19	0.850
Cardiovascular disease, cerebrovascular disease, and diabetes ($n = 119$)	0.91	0.79, 1.04	0.157	0.77	0.66, 0.89	<0.001
All noncancer and noncardiovascular deaths ($n = 129$)	0.92	0.80, 1.04	0.180	0.76	0.67, 0.87	<0.001

* Hazard ratios adjusted for sociodemographic variables, biologic and pyschologic variables, health-related behaviors, and all significant covariates.

† CI, confidence interval.

memory that are typically included in neuropsychologic assessment batteries.

Of the cognitive function tests administered to the ARIC Study cohort, the DSST has the widest use in other epidemiologic studies. Some investigators have modeled performance on this test as a continuous variable and others as a categorical variable. In the Western Collaborative Study (3), performance on this measure was entered as a continuous variable in a Cox proportional hazards model and was found to be significantly associated with all-cause mortality after adjustment for age, education, and health-related variables. In the Cardiovascular Health Study, the DSST was summarized as a categorical variable with five levels based on score ranges selected by the study investigators (4). A statistically significant trend of increasing mortality risk with decreasing score was found over the five categories.

The DWRT has not been previously tested as a predictor of mortality in a population sample. However, the association of long-term verbal recall with mortality observed with DWRT performance is consistent with findings obtained in elderly cohorts when verbal learning and retrieval are assessed with other tests of this domain (28). We were not able to identify any studies in which the performance on an individual test comparable with the WFT was evaluated in relation to all-cause mortality.

Because of the exploratory nature of our analysis, the findings with regard to cause-specific mortality must be interpreted with caution. The ARIC Study cohort was relatively young at inception. Therefore, the number of mortality events observed over an average follow-up of 6 years was low, and the statistical power we had to study specific causes of death was limited. Nevertheless, based on the results shown in table 4, it appears that the DWRT is consistently associated with mortality, regardless of cause, whereas the DSST, a test that taps motor coordination and reaction time, does not appear to be related to mortality from cancer. The findings in the cause-specific analysis, when considered together with the results of the all-cause mortality analysis, suggest that it may be necessary to focus attention on specific cognitive domains rather than on global function measures, in order to advance our understanding of the role that cognitive function plays in health outcomes.

In interpreting the results of this study, one must keep in mind that the relations observed occurred throughout the normal range of performance on the measures. The average scores obtained by the ARIC Study cohort sample were similar to those of other noncognitively impaired population groups (2), and there was no evidence of a threshold effect for the decrease in mortality risk with increasing cognitive function scores.

The causal pathways by which cognitive function influences survival are not known. Because most of the deaths in the ARIC Study cohort were not due to major cardiovascular causes, and because most known risk factors for vascular disease were accounted for, it does not seem plausible that the association between cognitive function and mortality is due to subclinical cerebrovascular disease. The fact that cognitive function contributed additional mortality risk beyond that associated with health behaviors such as smoking calls into question the hypothesis that cognitive function is protective primarily via a behavioral pathway. Even though we excluded persons with known vascular disease and central nervous system dysfunction at the time the measures were administered, and even though we took into consideration a large number of potential confounders, including perceived health and mood, the possibility remains that unmeasured factors such as specific dietary patterns, health care utilization, or undetected underlying disease could account for the association of cognitive function with mortality. Furthermore, although we did not find a difference when we excluded deaths occurring in the first year of follow-up, it is possible that a longer "latency" interval should be allowed to eliminate confounding between cognitive performance and disease status at the time of the examination.

The strong potential for confounding of the association between cognitive function and mortality with traditional indicators of socioeconomic status is evident in this study. After adjustment for age and other sociodemographic variables, there was little additional attenuation of the hazard ratios associated with the cognitive function measures in the ARIC Study cohort when biologic and behavioral variables were added. It is also noteworthy that, except for the indicator variables representing field center, measures of socioeconomic status were not independently predictive of mortality in the models tested. Education, the single most consistent predictor of mortality in population studies (29), was not significant, either in the restricted model that accounted only for sociodemographic covariates or in the full model. The present analysis is consistent with that in other studies in which the influence of socioeconomic variables is greatly reduced when cognitive function is included as a prognostic variable (4, 12). In addition, the argument that the association of cognitive function with mortality merely represents residual confounding with socioeconomic status is not supported by our analysis in view of the inconsistency between the results for the WFT and those of the DWRT and the DSST. All of the association between WFT performance and mortality was accounted for by sociodemographic variables, including race, sex, and education, whereas adjustment for these same variables did not eliminate the association between the DWRT and the DSST with mortality. This implies, at least, that the contribution of socioeconomic status to measures of cognitive function varies with the cognitive domain being tested.

It was not possible to address the question of whether the increased mortality risk associated with lower cognitive function is related to premorbid cognitive decline from an earlier level of functioning or to a lower lifetime level of functioning in this study. Bassuk et al. (5) have obtained preliminary evidence that cognitive decline (expressed as downward movement in score category on the Mini-Mental State Examination) over 3 years 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 that analysis to precisely estimate increased relative risks in some strata of cognitive decline. As additional mortality experience accrues in the ARIC Study cohort, it will be possible to associate both baseline level and decline in cognitive performance at

follow-up examinations with survival. The present study does make clear that a single baseline measurement of cognitive function is a robust predictor of mortality over an extended follow-up period in both middle-aged and elderly cohorts. As such, there is a need both to understand the reasons for the observed relation and to routinely take cognitive function into account as a covariate in population-based epidemiologic studies.

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