Decline in cognitive and functional skills increases mortality risk in nondemented elderly

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Abstract—*Objective:* To investigate the relation between rate of decline in cognitive and functional/physical abilities and risk of death in nondemented elderly. *Methods:* Data were included from individuals participating in a prospective study of aging and dementia in Medicare recipients, 65 years and older, residing in northern Manhattan. The authors included 878 members of the cohort who had measures of memory, cognitive, language, or functional scores over three study intervals, excluding all participants who were demented or had more than one problem in activity of daily living (ADL) skills at baseline. Participants were classified as showing no decline, slow, medium, or rapid rate of decline, based on the slope of change in cognitive and functional/physical factors. The authors used survival methods to examine the relation of rate of decline in cognitive and functional performance to subsequent mortality in younger and older nondemented elderly and across three ethnic groups, adjusting for potential confounders. *Results:* Nondemented elderly with preserved ADL skills who showed rapid rates of decline on measures of visuospatial reasoning/cognitive, language, ADL, and instrumental ADL functions were approximately twice as likely to die as nondemented elderly who showed no decline or slower rates of decline, while rate of decline in memory or in measures of extremity mobility was not related to risk of death. The association of the rate of decline to risk of death was stronger in relatively young (≤75 years) than in older participants. *Conclusions:* Rate of decline in cognitive and functional skills predicts mortality in nondemented elderly.

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The phenotypes that characterize successful aging are not fully established. Findings from elderly cohorts and from centenarian studies suggest that preservation of functional and cognitive ability is an important factor. In a retrospective study of New England centenarians, 100 to 109 years of age, 89% were still living independently at 93 years, 73% at 97 years, and 35% at 102 years.[1] Functional and cognitive impairment is a robust predictor of mortality in diverse populations. Increased risk of mortality has been found using self-reported measures of dependence in instrumental activities of daily living (IADL) and activities of daily living (ADL) or with reduced performance on measures of physical function such as lower extremity mobility measures of walking speed, time to complete chair stands, and low peak expiratory flow.[2-10] Cognitive impairment has been shown to be associated with mortality in both nondemented and demented elderly. In population-based cohorts of the elderly, those with mild as well as severe cognitive impairment have been found to have an increased risk of death.[3,11-20] Adjustment for a variety of health conditions, lifestyle factors, and sociodemographic characteristics did not decrease the mortality risk associated with poor cognitive function.[3,11-17,19-21] These findings suggest that decline in cognitive function with age is a predictor, not simply a surrogate, of rate of aging and mortality risk. Age-related decline in executive function has been associated with decline in functional status, reflecting the impairment in cognitive processes required to plan and execute goal directed IADL and ADL such as shopping, cooking, and dressing.[22-24]

The majority of published studies on cognition and mortality have used a global assessment of cognitive status, such as the Mini-Mental State Examination, as the measure of cognitive function, whereas only a few have used tests based on learning and memory, information processing, or fluid intelligence.[3,12,13,25] A number of studies of cognitive function and mortality have focused on age-related mortality risk associated with dementia rather than normal aging.[11,26-30] Thus, determination of the cognitive phenotypes associated with mortality risk requires fuller investigation with

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neuropsychological tests specifically targeted to processes affected by normal aging. In this study, we examined the relation of the rate of decline in cognitive and functional/physical performance to subsequent mortality in younger and older nondemented elderly across three ethnic groups. We focused our analysis on a group of participants who were not demented and had no more than one problem in ADL skills at baseline. Our results indicate that rates of declines in cognitive and functional ability are predictors of mortality and that the association of the rate of decline with mortality is stronger among younger elderly.

Methods. *Subjects and setting.* Data were included from individuals participating in a prospective study of aging and dementia in 2,126 Medicare recipients, 65 years and older, residing in northern Manhattan. The cohort was recruited in 1992 and has been followed at 18-month intervals since then. Data included in this analysis was gathered by 2002. A stratified random sample of 50% of all persons older than 65 years was obtained from the Health Care Finance Administration (HCFA).[31] All randomly selected persons received a letter from HCFA explaining that they had been selected to participate in a study of aging by investigators at Columbia University. The participation rate was 73% and did not differ by ethnic group. Each person received the same medical, neurologic, and neuropsychological evaluations at regular 18-month intervals. At the baseline examination, 327 participants (15%) were found to be demented, leaving 1,799 participants for the prospective study of incident Alzheimer disease (AD). Over the study period, the annual mortality rate has been 8.1%, the overall refusal rate has been 10%, and the annual incidence rate of AD has been 3%. To address the study aims, there were 961 of the 1,799 participants in the cohort at first follow-up (53.4%) who had measures of memory, cognitive, language, or physical function scores over three study intervals from which the slope of scores could be computed to characterize rate of change. For these analyses, we also excluded 81 participants with more than one problem in ADL skills, such as bathing or dressing, at baseline, leaving 880 participants to be included in the analysis. Of these 880, 878 had complete data. The average number of evaluations for the participants included in the analysis was 4.0 (range 3 to 5) and the average duration of follow-up was 6.5 years. Compared with those with one or two evaluations, participants included in the analysis were younger at baseline (75.9 vs 78.9 years), performed significantly better on cognitive tests, and had better functional skills but did not differ by ethnic group, level of education, sex, or in the frequency of self-reported medical conditions.

Ethnic group was determined by self-report. Participants were asked whether they considered themselves white, black, or other and then asked whether they were Hispanic. If Hispanic, the country in which they were born was queried. Most of those classified as Hispanic (84%) were of Caribbean origin, predominantly from the Dominican Republic, with the remainder from Mexico and Central America. Four participants had identified themselves as of "other" ethnic group, and they were excluded from the analysis. Recruitment, informed consent, and study procedures were approved by the Institutional Review Boards of Columbia Presbyterian Medical Center and Columbia University Health Sciences and the New York State Psychiatric Institute.

Clinical evaluation. All participants received structured neurologic and functional assessments by physicians. Spanish speakers were interviewed and tested in Spanish. Medical history was recorded with specific attention to stroke, trauma, medications, recreational drug use, and common age-related conditions such as heart disease, stroke, diabetes, thyroid disorders, or cancer; history of smoking and alcohol use (never, ever, current); and hearing and visual impairment. All participants underwent a standardized neuropsychological battery[32] that included orientation from the modified Mini-Mental State Examination,[33] language using the Boston Naming Test,[34] the Controlled Word Association test,[35] category naming, the Complex Ideational Material Subtest and the repetition of phrases from the Boston Diagnostic Aphasia Evaluation,[36] abstract reasoning from the Wechsler Adult Intelligence Scale-Revised (WAIS-R) Similarities subtest,[37] and the nonverbal Identities and Oddities subtest of the Mattis Dementia Rating Scale,[38] visuospatial ability using the Rosen Drawing Test,[39] and the Benton Visual Retention Test and a matching version of the Benton Visual Retention Test.[40] Memory was evaluated using the multiple-choice version of the Benton Visual Retention test and the seven subtests of the Selective Reminding Test.[41] Information from the neurologic, psychiatric, and neuropsychological assessments was reviewed in a consensus conference composed of neurologists, psychiatrists, and neuropsychologists. Based on this review, all participants were assigned to one of three categories: dementia, cognitive impairment, or normal cognitive function. For functional/physical domains, we used self-reported ability to perform basic and IADL, assessed at the time of interview and at time of the medical and neurologic examination by the physician. The field interview contained several functional assessment scales, including a modification of the Katz Index of Activities of Daily Living,[42] Lawton Instrumental Activities of Daily Living,[43] and Comprehensive Assessment and Referral Evaluation (CARE) Activity Limitation, Mobility, and Self-Perceived Health scales.[44] The physician administered the Blessed Dementia Rating Scale[45] and the Schwab and England Rating Scale.[46]

Classification of rate of change. A factor analysis was performed using data from the baseline assessment of the entire cohort with the 15 neuropsychological measures using a principal component analysis with varimax rotation and Kaiser normalization.[47] This analysis yielded three factors: 1) a memory factor, in which the seven subtests of the Selective Reminding Test were the main contributors;[41] 2) a visuospatial reasoning/cognitive factor (cognitive factor), in which visuospatial tests of reasoning were the main contributors (these included the Rosen Drawing Test,[39] matching and recognition components of the Benton Visual Retention Test,[40] and the Identities and Oddities of the Mattis Dementia Rating Scale;[38] 3) a language factor in which language measures were the main contributors (the Boston Naming Test,[34] the Controlled Oral Word Association test,[35] and the WAIS-R Similarities subtest[37]). Component scores for each subject at each visit were calculated by adding the loading weighted scores of the measures that contributed to each factor. We used the factor weights of the baseline factor scores and normalizing equations to calculate factor scores for the follow-up assessments. We used these weighted scores to calculate the slope of the memory, visuospatial reasoning/cognitive and language factor scores over three study intervals. Participants were classified as showing no decline if the slope of the factor scores were equal or greater than zero. Then we used tertiles of the slopes showing declines for each factor to classify the participants as showing slow, medium, or rapid rate of decline.

For functional/physical domains, we used self-reported ability to perform basic ADL and IADL, assessed at the interview and at time of the medical and neurologic examination by the physician. Classification of rate of change in functional/physical domains employed a similar procedure to that used for cognitive functions. Functional scores were based on the ability to carry out basic ADL and IADL. Physical factor measures included lower and upper extremity mobility. Preliminary analyses showed no difference in subsequent mortality risk by tertile of decline, and few participants showed decline in functional and physical factors after exclusion of those with two or more problems in ADL. Hence, participants were classified as showing no decline if the slopes of the functional or physical scores showed no change or improved and were classified as declining if the slopes showed decline.

Vital status. We obtained vital status from the follow-up interviews and from the National Death Index for those reported to be dead or who were lost to follow-up through 2002.

Statistical analysis. We investigated the associations between rate of change in cognitive and functional/physical ability in the participants and their total years of survival. We used χ^2 tests, *t* tests, and analysis of variance to compare the characteristics of participants with no decline or with slow, medium, or rapid rates of decline in cognitive factor scores and with no decline or decline in functional/physical scores. We compared the risk of mortality by risk categories using Cox proportional hazards modeling. We estimated the rate ratio (RR) of participant death associated with rate of change in cognitive or physical/function factors in the participant; first in models that adjusted for age at baseline, sex,

Table 1 *Participant demographic characteristics by cognitive factors*

Participant characteristics	No decline	Slow decline	Medium decline	Rapid decline
Memory factor				
Sample size	240	212	212	213
Age at entry, y, mean ± SD*	75.4 ± 5.8	75.2 ± 5.3	75.2 ± 5.4	77.0 ± 5.7
Sex, n (%)				
Female	174 (72.5)	147 (69.3)	142 (67.0)	148 (69.5)
Male	66 (27.5)	65 (30.7)	70 (33.0)	65 (30.5)
Ethnic group,* n (%)				
White/non-Hispanic	52 (21.7)	35 (16.5)	26 (12.3)	47 (22.1)
African American	63 (26.3)	64 (30.2)	66 (31.1)	78 (36.6)
Hispanic	125 (52.1)	113 (53.3)	120 (56.6)	88 (41.3)
Education, mean ± SD*	8.6 ± 4.9	7.8 ± 4.7	8.3 ± 4.3	9.2 ± 4.6
Cognitive factor				
Sample size	457	140	141	140
Age at entry, y, mean ± SD*	74.9 ± 5.2	76.0 ± 5.7	75.6 ± 5.8	78. ± 6.6
Sex, n (%)				
Female	306 (67.0)	100 (71.4)	105 (74.5)	101 (72.1)
Male	151 (33.0)	40 (28.6)	36 (25.5)	39 (27.9)
Ethnic group, n (%)				
White/non-Hispanic	96 (21.0)	15 (10.7)	23 (16.3)	26 (18.6)
African American	133 (29.1)	47 (33.6)	40 (28.4)	51 (36.4)
Hispanic	228 (49.9)	78 (55.7)	78 (55.3)	63 (45.0)
Education, mean ± SD*	8.8 ± 4.7	8.0 ± 4.8	7.3 ± 4.8	8.9 ± 4.4
Language factor				
Sample size	474	135	134	135
Age at entry, y, mean ± SD*	75.0 ± 5.3	75.2 ± 5.2	77.6 ± 6.2	77.6 ± 6.7
Sex, n (%)				
Female	319 (67.3)	96 (71.1)	96 (71.6)	101 (74.8)
Male	155 (32.7)	39 (28.9)	38 (28.4)	34 (25.2)
Ethnic group, n (%)				
White/non-Hispanic	99 (20.9)	17 (12.6)	18 (13.4)	26 (19.3)
African American	139 (29.3)	40 (29.6)	42 (31.3)	50 (37.0)
Hispanic	236 (49.8)	78 (57.8)	74 (55.3)	59 (43.7)
Education, mean ± SD*	8.8 ± 4.7	8.0 ± 4.9	7.5 ± 4.8	8.6 ± 4.2

* $p < 0.05$.

ethnic group, level of education, and baseline level of performance (Model A). We used time from baseline until death for deceased participants and time from baseline until last assessment for non-deceased participants as the time-to-event variable in the survival analysis. Baseline level of performance was included to account for the possibility that different change groups may have started at different levels at baseline. Then we estimated the rate ratio (RR) of participant death associated with the rate of change in cognitive or functional/physical factors in models with additional adjustment for the presence or absence of self-reported history of stroke, diabetes, heart disease, thyroid disorders, or cancer; history of smoking and alcohol use; hearing or visual impairment; and baseline level of performance (Model B).

To account for a possible healthy survivor bias and to investigate whether influences on survival were different at different ages, we repeated the Cox models in analyses stratified by the median participant age at entry into the study (≤75 vs >75 years). If healthy survival influenced mortality, estimated RRs might be differentially affected in younger compared with older participants.

Results. *Participant characteristics.* The mean age of the cohort was 75.9 years and the median age was 75.0 years. Overall, there were approximately twice as many women as men participating (70% vs 30%) and the difference in sex ratio was observed consistently across rate of change phenotypes. The largest number of participants identified themselves as Hispanic (51%), followed by African American (30.8%) and white (18.2%) Tables 1 and 2 show the distribution of demographic characteristics of the study participants within rate of change phenotypes. Participants were more likely to show declines in memory than in the visuospatial reasoning/cognitive or language

Table 2 *Participant demographic characteristics by physical/functional factors*

Participant characteristics	No decline	Decline
Activities of daily living		
Sample size	717	159
Age at entry, y, mean ± SD*	75.2 ± 5.5	77.8 ± 6.2
Sex, n (%)*		
Female	482 (67.2)	128 (80.5)
Male	235 (32.8)	31 (19.5)
Ethnic group, n (%)		
White/non-Hispanic	135 (18.8)	23 (14.5)
African American	219 (30.5)	51 (32.1)
Hispanic	363 (50.6)	85 (53.5)
Education, mean ± SD	8.6 ± 4.7	7.7 ± 4.8
Instrumental activities of daily living		
Sample size	491	387
Age at entry, y, mean ± SD*	74.5 ± 5.2	76.8 ± 6.2
Sex, n (%)*		
Female	317 (64.6)	295 (76.2)
Male	174 (35.4)	92 (23.8)
Ethnic group,* n (%)		
White/non-Hispanic	96 (19.6)	63 (16.3)
African American	163 (33.2)	108 (27.9)
Hispanic	232 (47.3)	216 (55.8)
Education, mean ± SD*	9.1 ± 4.6	7.6 ± 4.6
Lower extremity mobility		
Sample size	426	448
Age at entry, y, mean ± SD*	74.8 ± 5.2	76.5 ± 6.1
Sex, n (%)*		
Female	276 (64.8)	333 (74.3)
Male	150 (35.2)	115 (25.7)
Ethnic group, n (%)		
White/non-Hispanic	77 (18.1)	80 (17.9)
African American	138 (32.4)	132 (29.5)
Hispanic	211 (49.5)	236 (52.7)
Education, mean ± SD*	8.9 ± 4.7	8.1 ± 4.7
Upper extremity mobility		
Sample size	538	338
Age at entry, y, mean ± SD	75.6 ± 5.7	75.8 ± 5.8
Sex, n (%)*		
Female	359 (66.7)	251 (74.3)
Male	179 (33.3)	87 (25.7)
Ethnic group, n (%)		
White/non-Hispanic	91 (16.9)	76 (19.8)
African American	172 (32.8)	98 (29.0)
Hispanic	275 (51.1)	173 (51.1)
Education, mean ± SD	8.4 ± 4.6	8.5 ± 4.8

* $p < 0.05$.

measures (see table 1). Participants were also more likely to show declines in upper and lower extremity mobility and in IADL than in basic ADL (see table 2). Participants with rapid decline in cognitive factors were older than those who did not decline (see table 1). Participants with rapid decline in the memory factor were more likely to be white and African American than Hispanic. Participants with rapid decline in the memory factor, but not in the visuospatial reasoning/cognitive or language factors, were significantly better educated compared with those showing no or a slow rate of decline, whereas there was no difference in the distribution of sex across rate of change groups (see table 1). Participants with decline in ADL, IADL, and lower extremity mobility were older than those who did not decline on those factors, whereas no difference in age was observed among those with and without decline in upper extremity mobility. Women were more likely than men to show decline on all functional/physical factors (see table 2). Level of education did not differ among those with or without decline on functional/physical factors except for IAD and lower extremity mobility. Whites were less likely than African Americans or Hispanics to show decline in IADL skills (see table 2).

Correlations between slopes of factor score. We computed the correlation between the slopes of the factor scores to determine whether there was a generalized decline in all scores related to mortality or whether particular factors might have independent effects on mortality (table 3). The slopes of the cognitive factors were highly correlated with each other, but less so with the functional/physical factors (see table 3). The highest correlation was between the slope of the visuospatial/cognitive factor and the slope of the language factor ($r = 0.957$, $p < 0.001$). Similarly, the slopes of the functional/physical factors were correlated with each other (see table 3). The highest correlation in functional/physical factors was between the slopes of the ADL and IADL factors. ($r = 0.464$, $p < 0.01$).

Mortality risks in participants. In the initial model (Model A), adjusted for sex, education, ethnic group, and baseline level of performance, mortality risk was approximately twice as high among participants showing rapid decline in the visuospatial reasoning/cognitive factor (RR = 2.2, 95% CI: 1.5 to 3.2) compared with participants who did not decline and 2.6 times as high among those showing rapid decline in language skills (RR = 2.6, 95% CI: 1.8 to 3.6) (figure 1), while there was no consistent or significant pattern of mortality in relation to the rate of decline in memory (Model A, table 4). Decline in ADL, IADL, or upper extremity mobility was associated with increased mortality risk compared with those without decline (RR for ADL = 2.2, 95% CI: 1.7 to 4.0; RR for IADL = 1.7, 95% CI: 1.3 to 2.3 and RR for upper extremity mobility = 1.4, 95% CI: 1.1 to 1.9) (see Model A, table 4) (figure 2). Additional adjustment for a history of chronic disease (heart disease, stroke, thyroid disease, cancer), smoking and alcohol use, and hearing and visual impairment did not substantially modify these associations for cognitive factors (Model B: RR for the visuospatial reasoning/cognitive factor = 2.0, 95% CI: 1.4 to 2.9; RR for the language factor = 2.2, 95% CI: 1.6 to 3.3. Model B, table 4). The association of decline in performance of ADL and IADL skills with increased mortality persisted after additional adjustment for potential confounders (RR for ADL = 2.0,

Table 3 *Pearson correlations between slopes of factors*

	Memory	Visuospatial/ cognitive	Language	ADL	IADL	Lower extremity mobility	Upper extremity mobility
Memory	1.000	0.493*	0.352*	−0.038	−0.058	0.008	−0.026
Visuospatial/cognitive		1.000	0.957*	0.162*	0.206*	−0.088*	−0.055
Language			1.000	0.168*	0.204*	−0.080†	−0.039
ADL				1.000	0.464*	0.304*	0.240*
IADL					1.000	0.458*	0.266*
Lower extremity mobility						1.000	0.202*
Upper extremity mobility							1.000

* Correlation is significant at the 0.01 level (two tailed).
† Correlation is significant at the 0.05 level (two tailed).

ADL = activities of daily living; IADL = instrumental activities of daily living.

95% CI: 1.4 to 2.7; RR for IADL = 1.6, 95% CI: 1.2 to 2.1), while the association of decline in lower and upper extremity mortality with increased mortality failed to reach statistical significance (RR = 1.2, 95% CI: 0.9 to 1.7; and RR = 1.2, 95% CI: −0.9 to 1.6, respectively) (see Model B, table 4.)

To investigate whether rate of decline influenced survival differently at different ages, we repeated the Cox models within strata defined by participants' median age at enrollment (≤75 years or >75 years) adjusting for sex; education; ethnic group baseline level of performance; presence of a history of stroke, heart disease, diabetes, thyroid disorders, or cancer; past or current smoking and alcohol use; and hearing or visual impairment. The effect of rapid cognitive decline compared with no decline was stronger among younger participants. For the visuospatial reasoning/cognitive factor, the RR for rapid decline was 3.2 (95% CI: 1.8 to 6.0) for those 65 to 75 years and 1.4 (95% CI: 0.9 to 2.4) for those older than 75 years of age. For the language factor, the RR for rapid decline was 3.3 (95% CI: 1.8 to 6.0) for those 65 to 75 years and 1.8 (95% CI: 1.1 to 2.9) for those older than 75 years of age. Similarly, increased mortality among those showing decline in ADL skills was stronger for those 65 to 75 years than for those older than 75 years of age (RR = 3.5, 95% CI: 2.0 to 6.2 vs RR = 1.6, 95% CI: 1.1 to 2.3, respectively), but did not differ by age group for the other functional/physical factors (not shown).

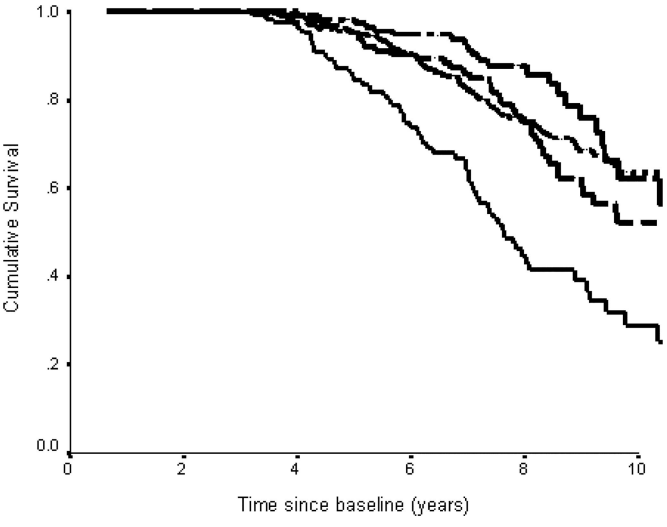

Figure 1. Cumulative survival by rate of decline in the language factor. No decline = - - -; slow decline = – – –; medium decline = — - — ; rapid decline = —.

To determine whether the association of the rate of decline in the cognitive and functional/physical factors with mortality risk varied among ethnic groups, we repeated the analyses within strata defined by ethnic group, adjusting for all covariates and baseline level of performance. The relation of the rapid rate of decline in measures of visuospatial reasoning/cognition and language functions to mortality was strongest among white participants (For visuospatial reasoning/cognition: RR for whites = 2.7, 95% CI: 1.2 to 6.0; RR for African Americans = 1.7, 95% CI: 0.9 to 3.2; RR for Hispanics = 1.9, 95% CI: 1.04 to 3.6. For language, RR for whites = 4.0, 95% CI: 1.8 to 9.1; RR for African Americans = 1.8, 95% CI: 1.02 to 3.3; RR for Hispanics = 2.1, 95% CI: 1.1 to 3.9) (not shown). The relation of decline in ADL skills to mortality was also stronger among white participants than among African-American or Hispanic participants (RR for whites = 4.3, 95% CI: 1.9 to 9.8; RR for African Americans = 1.7, 95% CI: 1.05 to 2.9; RR for Hispanics = 1.9, 95% CI: 1.2 to 3.2) (not shown). The association of rate of decline with mortality did not vary by ethnic group for memory or for IADL and extremity mobility measures.

We combined all variables into a single model to determine the relative strength of the factors in relation to mortality risk. Only the language factor remained a strong and significant predictor of mortality in this model. Those with rapid decline in measures of language function were 2.5 times more likely to die than those with no decline (RR = 2.5, 95% CI: 1.01 to 6.1) (not shown).

Discussion. Nondemented elderly with no more than one problem in ADL skills who showed rapid decline on measures of visuospatial reasoning/cognitive function, language, ADL, or IADL skills were approximately twice as likely to die as nondemented elderly who showed no decline or slow rates of de-

Table 4 *Participant survival by rate of decline in cognitive and physical/functional factors*

Participant characteristics	No. participants (% deceased)	Rate ratio: Model A (95% CI)	Rate ratio: Model B (95% CI)
Memory factor			
No decline	240 (24.6)	1.0 (reference)	1.0 (reference)
Slow decline	212 (24.1)	0.7 (0.5–1.0)	0.7 (0.5–1.1)
Medium decline	212 (23.6)	1.0 (0.7–1.4)	1.0 (0.7–1.5)
Rapid decline	213 (28.6)	1.2 (0.8–1.8)	1.1 (0.8–1.7)
Cognitive factor			
No decline	447 (19.0)	1.0 (reference)	1.0 (reference)
Slow decline	140 (22.1)	1.0 (0.6–1.5)	1.1 (0.7–1.6)
Medium decline	141 (25.5)	1.1 (0.7–1.6)	1.1 (0.7–1.6)
Rapid decline	140 (47.9)	2.2 (1.5–3.2)*	2.0 (1.4–2.9)*
Language factor			
No decline	474 (19.6)	1.0 (reference)	1.0 (reference)
Slow decline	135 (16.3)	0.9 (0.5–1.4)	0.9 (0.5–1.4)
Medium decline	134 (30.6)	1.1 (0.8–1.7)	1.1 (0.7–1.7)
Rapid decline	135 (48.1)	2.6 (1.8–3.6)*	2.2 (1.6–3.3)*
Activities of daily living (ADL)			
No decline	717 (19.1)	1.0 (reference)	1.0 (reference)
Decline	159 (51.6)	2.2 (1.7–3.0)*	2.0 (1.4–2.7)*
Instrumental ADL			
No decline	491 (16.7)	1.0 (reference)	1.0 (reference)
Decline	387 (35.9)	1.7 (1.3–2.3)*	1.6 (1.2–2.1)*
Lower extremity mobility			
No decline	426 (19.2)	1.0 (reference)	1.0 (reference)
Decline	448 (30.4)	1.4 (1.1–1.9)*	1.2 (0.9–1.7)
Upper extremity mobility			
No decline	538 (22.9)	1.0 (reference)	1.0 (reference)
Decline	338 (28.4)	1.2 (0.9–1.6)	1.2 (0.9–1.6)

Model A = Cox proportional hazards, adjusted for age, sex, ethnic group, education, and baseline level of performance; Model B = Cox proportional hazards, adjusted for age, sex, ethnic group, education, history of chronic disease (heart, stroke, diabetes, thyroid disease, cancer), smoking, alcohol use, hearing, visual impairment, and baseline level of performance.

* $p < 0.05$.

cline. In the initial models, decline in lower extremity mobility was also associated with increased risk of death, but the association did not persist after additional adjustment for a history of chronic disease, smoking, alcohol use, or sensory impairment. This suggests that the decline in lower extremity mobility was associated with the presence of comorbid conditions and was not an independent predictor of mortality. Rate of change in memory was not related to subsequent mortality. This finding contrasts with previous reports of increased mortality risk associated with impairment and decline in cognitive ability.[11-20] However, only a few studies have used tests based on learning and memory, information processing, or fluid intelligence.[3,12,13,25] It may be that memory decline is so common among elderly persons that the relation between decline and mortality risk is attenuated. Alternatively, decline in memory is strongly associated with dementia, and we excluded those with dementia at baseline from the analysis. Similarly, we excluded participants with more than one problem in ADL skills, and our sample had relatively few participants with functional deficits at baseline.

The relation of cognitive decline to likelihood of death was strongest and most robust for the language factor and was stronger among relatively young participants. Adjustment for the presence of common chronic diseases (a history of heart disease, stroke, diabetes, thyroid disorders, and cancer) that may affect cognitive performance did not modify these associations, as has been found by other investigators.[3,11-17,19-21] However, there was a high correlation between decline on the language factor and decline on the visuospatial/cognitive ($r = 0.957$) (see table 3). The substantial relation between these

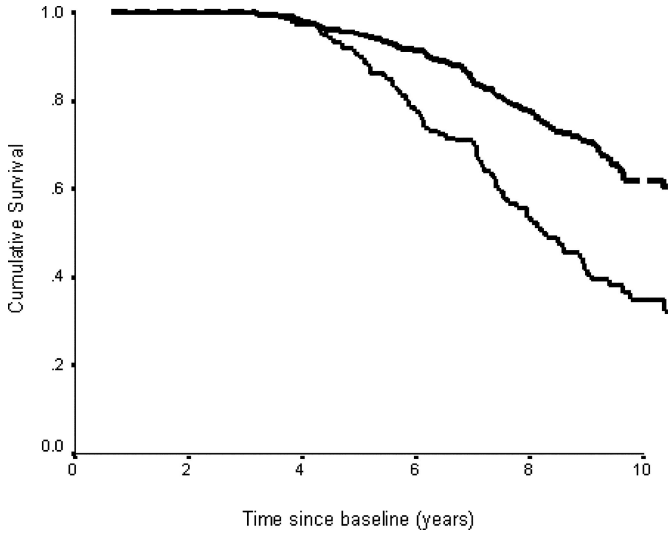

Figure 2. Cumulative survival by rate of decline in the activities of daily living factor (instrumental activities of daily living). No decline = ---; decline = —.

two factors suggests that a more general cognitive decline underlies this association. In contrast, the lack of strong correlation between decline on the cognitive factors and decline on the functional/physical factors suggests that the association of decline in cognitive or functional skill factors with increased risk of mortality is not simply a reflection of a generalized "frailty," but rather is related to specific aspects of cognitive and functional performance.

Our study adds to the growing literature demonstrating that cognitive decline and functional decline are strong independent predictors of subsequent mortality. The effect of rapid decline in cognitive and functional skills among cognitively normal elderly with few functional deficits at baseline may represent relatively recent decline compared with elderly participants whose cognitive or functional performance was low at the initial assessment but did not decline further.[17] To take this possibility into account, we included baseline level of performance as a covariate in all analytic models. Another study also found that incident cognitive decline was a better predictor of 2-year mortality than low cognitive function at baseline among persons younger than 80 years of age.[17] The pattern of these results suggests that the rate of cognitive and functional decline is an important risk factor for subsequent mortality, even among those who are relatively unimpaired.

The influence of decline in visuospatial reasoning/cognitive and language functions on mortality risk might be influenced by the presence of mild cognitive impairment in our nondemented participants. The term mild cognitive impairment (MCI) has been used to describe the transitional state between normal cognitive function and AD.[48] While general cognitive performance and function are well preserved, memory performance on standardized tests falls below expectations for age and education. Subsequent studies have confirmed MCI as a transitional state that progresses to AD at the rate of nearly 10% to 15% per year.[49] Other definitions of MCI include nonmemory MCI, which comprises deficits in abstract reasoning/executive function, language, and/or visuospatial function.[49]

Our results are consistent with previous studies that have reported increased risk of death associated with cognitive impairment or dementia[3,11-20] and have extended these findings to demonstrate that declines in specific cognitive domains, visuospatial reasoning/cognitive and language functions, are most strongly implicated in mortality risk. The visuospatial reasoning/cognitive factor includes the Rosen Drawing Test,[39] matching and recognition components of the Benton Visual Retention Test,[40] and the Identities and Oddities of the Mattis Dementia Rating Scale.[38] These tasks require skills in detecting spatial relations and in abstract reasoning. A number of other studies have found a significant association of the rate of decline on digit-symbol substitution tasks with subsequent mortality,[3,13,50] a measure that is highly sensitive to general brain dysfunction and is thought to mainly reflect speed of processing. The language factor that was most strongly related to elevated mortality risk includes the Boston Naming Test,[34] the Controlled Oral Word Association Test (letter fluency),[35] and WAIS-R Similarities subtest[37] as the main contributors. A common function assessed by these tests is word searching, which may be related to some aspects of executive function. Previous studies have shown that deficits in executive function are associated with the cognitive impairments found in mild cognitive impairment and AD[22,23] and can predict decline in functional status.[24] Thus, a component of the mortality risk associated with the language factor may be related to executive function.

We found that the association of cognitive or functional decline with the likelihood of death was stronger among relatively young participants ($\leq$75 years vs $>$75 years). Elevated mortality risk associated with cognitive or functional decline in the relatively young compared with old elderly is a consistent finding in studies of risk factors for mortality.[15,17,18,51-53] Cognitive or functional decline in participants younger than 75 years of age is less common than among those 75 and older and may be less likely to be associated with the presence of age-related common health conditions. Rather, decline in the relatively young elderly may reflect the effect of processes that are directly associated with increased mortality risk,[17] such as rate of biologic aging rather than chronologic aging.

A complex process such as aging is likely to involve several pathways with varying effects. To enhance power to detect contributing pathways with smaller effects, as in most complex traits, it is useful to examine intermediate phenotypes such as specific cognitive or functional skills, which are components

of the outcome of interest.[54] Our study is limited by the nature of the clinical variables and scales that we used, which may have determined how well change in participants could be measured. The measurement of memory and other cognitive functions by psychometric testing is more precise and yields scores that are more truly quantitative and more likely to indicate subtle change over time than is the assessment of ADL, IADL, or ratings of upper and lower extremity mobility. Further refinement of these and additional phenotypes will be required to support our hypothesis that preservation of cognitive and functional ability in old age represent key traits that contribute to the overall phenotype of longevity. Another limitation is that we did not evaluate nonlinear forms of decline. The rate of terminal cognitive decline can be highly variable but is likely to accelerate beginning about 3 years before death.[55] In sum, our findings are consistent with previous studies showing that risk of death is associated with cognitive or functional impairment primarily in participants with varying degrees of cognitive or functional impairment at baseline. Our study is noteworthy because we excluded participants with dementia and functional deficits at baseline and found a significant association of decline in cognitive or functional ability and mortality.

References

1. Hitt R, Young-Xu Y, Silver M, Perls T. Centenarians: the older you get, the healthier you have been. Lancet 1999;354:652–.
2. Guralnik JM, Simonsick EM, Ferrucci L, et al. A short physical performance battery assessing lower extremity function: association with self-reported disability and prediction of mortality and nursing home admission. J Gerontol 1994;49:M85–94.
3. Fried LP, Kronmal RA, Newman AB, et al. Risk factors for 5-year mortality in older adults: the Cardiovascular Health Study. JAMA 1998;279:585–592.
4. Fried TR, Pollack DM, Tinetti ME. Factors associated with six-month mortality in recipients of community-based long-term care. J Am Geriatr Soc 1998;46:193–197.
5. Melzer D, Lan TY, Guralnik JM. The predictive validity for mortality of the index of mobility-related limitation—results from the EPESE study. Age Ageing 2003;32:619–625.
6. Manton KG. A longitudinal study of functional change and mortality in the United States. J Gerontol 1988;43:S153–161.
7. Reuben DB, Siu AL, Kimpau S. The predictive validity of self-report and performance-based measures of function and health. J Gerontol 1992;47:M106–110.
8. Parker MG, Thorslund M, Nordstrom ML. Predictors of mortality for the oldest old. A 4-year follow-up of community-based elderly in Sweden. Arch Gerontol Geriatr 1992;14:227–237.
9. Shibata H, Haga H, Nagai H, et al. Predictors of all-cause mortality between ages 70 and 80: the Koganei study. Arch Gerontol Geriatr 1992;14:283–297.
10. Carey EC, Walter LC, Lindquist K, Covinsky KE. Development and validation of a functional morbidity index to predict mortality in community-dwelling elders. J Gen Intern Med 2004;19:1027–1033.
11. Liu IY, LaCroix AZ, White LR, Kittner SJ, Wolf PA. Cognitive impairment and mortality: a study of possible confounders. Am J Epidemiol 1990;132:136–143.
12. Smits CH, Deeg DJ, Kreigsman DMW, Schmand B. Cognitive functioning and health as determinants of mortality in an older population. Am J Epidemiol 1999;150:978–986.
13. Swan GE, Carmelli D, LaRue A. Performance on the digit symbol substitution test and 5-year mortality in the Western Collaborative Group Study. Am J Epidemiol 1995;141:32–40.
14. Kelman HR, Thomas C, Kennedy GJ, Cheng J. Cognitive impairment and mortality in older community residents. Am J Public Health 1994; 84:1255–1260.
15. Bruce ML, Hoff RA, Jacobs SC, Leaf PJ. The effects of cognitive impairment on 9-year mortality in a community sample. J Gerontol B Psychol Sci Soc Sci 1995;50:P289–296.
16. Gussekloo J, Westendorp RG, Remarque EJ, Lagaay AM, Heeren TJ, Knook DL. Impact of mild cognitive impairment on survival in very elderly people: cohort study. BMJ 1997;315:1053–1054.
17. Bassuk SS, Wypij D, Berkman LF. Cognitive impairment and mortality in the community-dwelling elderly. Am J Epidemiol 2000;151:676–688.
18. Dewey ME, Saz P. Dementia, cognitive impairment and mortality in persons aged 65 and over living in the community: a systematic review of the literature. Int J Geriatr Psychiatry 2001;16:751–761.
19. Neale R, Brayne C, Johnson AL. Cognition and survival: an exploration in a large multicentre study of the population aged 65 years and over. Int J Epidemiol 2001;30:1383–1388.
20. Nguyen HT, Black SA, Ray LA, Espino DV, Markides KS. Cognitive impairment and mortality in older Mexican Americans. J Am Geriatr Soc 2003;51:178–183.
21. Rozzini R, Franzoni S, Frisoni G, Trabucchi M. Cognitive impairment and survival in very elderly people. Decreased survival with cognitive impairment seems not be related to comorbidity. BMJ 1998;316:1674.
22. Boyle PA, Malloy PF, Salloway S, Cahn-Weiner DA, Cohen R, Cummings JL. Executive dysfunction and apathy predict functional impairment in Alzheimer disease. Am J Geriatr Psychiatry 2003;11:214–221.
23. Ready RE, Ott BR, Grace J, Cahn-Weiner DA. Apathy and executive dysfunction in mild cognitive impairment and Alzheimer disease. Am J Geriatr Psychiatry 2003;11:222–228.
24. Royall DR, Palmer R, Chiodo LK, Polk MJ. Declining executive control in normal aging predicts change in functional status: the Freedom House Study. J Am Geriatr Soc 2004;52:346–352.
25. Tuokko H, Frerichs R, Graham J, et al. Five-year follow-up of cognitive impairment with no dementia. Arch Neurol 2003;60:577–582.
26. Aronson M, Ooi WL, Geva DL. Dementia: age-dependent incidence, prevalence, and mortality in the oldest old. Arch Intern Med 1991;151: 989–992.
27. Evans DA, Smith LA, Scherr PA, Albert MS, Funkenstein HH, Hebert LE. Risk of death from Alzheimer's disease in a community population of older persons. Am J Epidemiol 1991;134:403–412.
28. Albert SM, Costa R, Merchant C, Small S, Jenders RA, Stern Y. Hospitalization and Alzheimer's disease: results from a community-based study. J Gerontol A Biol Sci Med Sci 1999;54:M267–271.
29. Jorm AF, A.SH, Kay DWK, et al. Mortality in relation to dementia, depression, and social integration in an elderly community sample. Int J Geriatr Psychiatry 1991;6:5–11.
30. Katzman R, Hill R, Yu E, et al. The malignancy of dementia: predictors of mortality in clinically diagnosed dementia in a population survey of Shanghai, China. Arch Neurol 1994;51:1220–1225.
31. Tang MX, Stern Y, Marder K, et al. The APOE-epsilon4 allele and the risk of Alzheimer disease among African Americans, whites, and Hispanics [see comments]. JAMA 1998;279:751–755.
32. Stern Y, Andrews H, Pittman J, et al. Diagnosis of dementia in a heterogeneous population. Development of a neuropsychological paradigm-based diagnosis of dementia and quantified correction for the effects of education. Arch Neurol 1992;49:453–460.
33. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state." A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 1975;12:189–198.
34. Kaplan E, Goodglass H, Weintraub S. Boston Naming Test. Philadelphia: Lea and Febiger, 1983.
35. Benton A, ed. FAS Test. Victoria, BC: University of Victoria, 1967.
36. Goodglass H, Kaplan D. The assessment of aphasia and related disorders, 2nd ed. Philadelphia: Lea and Febiger, 1983.
37. Wechsler D. Wechsler Adult Intelligence Scale-Revised. New York: The Psychological Corporation, 1981.
38. Mattis S. Mental status examination for organic mental syndrome in the elderly patient. New York: Grune and Stratton, 1976.
39. Rosen W. The Rosen Drawing Test. Bronx: Veterans Administration Medical Center, 1981.
40. Benton AL. The Benton Visual Retention Test. New York: The Psychological Corporation, 1955.
41. Buschke H, Fuld PA. Evaluating storage, retention, and retrieval in disordered memory and learning. Neurology 1974;24:1019–1025.
42. Katz S, Downs TD, Cash HR, Grotz RC. Progress in development of the index of ADL. Gerontologist 1970;10:20–30.
43. Lawton MP, Brody EM. Assessment of older people: self-maintaining and instrumental activities of daily living. Gerontologist 1969;9:179–186.
44. Golden RR, Teresi JA, Gurland BJ. Development of indicator scales for the Comprehensive Assessment and Referral Evaluation (CARE) interview schedule. J Gerontol 1984;39:138–146.
45. Blessed G, Tomlinson BE, Roth M. The association between quantitative measures of senile change in the cerebral grey matter of elderly subjects. Br J Psychol 1968;114:797–811.
46. Schwab JF, England AC, Gillingham FH, Donaldson MC Projection technique for evaluating surgery in Parkinson's disease. In: Third Symposium on Parkinson's Disease. New York: Churchill Livingstone, 1969: 152–157.
47. Kleinbaum DG, Kupper LL, Muller KE. Applied regression analysis and other multivariable methods. Boston: PWS-KENT Publishing, 1988.

48. Petersen RC, Smith GE, Waring SC, Ivnik RJ, Tangalos EG, Kokmen E. Mild cognitive impairment: clinical characterization and outcome. Arch Neurol 1999;56:303–308.
49. Petersen RC, Doody R, Kurz A, et al. Current concepts in mild cognitive impairment. Arch Neurol 2001;58:1985–1992.
50. 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;157:327–334.
51. Brayne C, Gill C, Paykel ES, Huppert F, O'Connor, DW. Cognitive decline in an elderly population—a two wave study of change. Psychol Med 1995;25:673–683.
52. Korten AE, Henderson AS, Christensen H, et al. A prospective study of cognitive function in the elderly. Psychol Med 1997;27:919–930.
53. Starr JM, Deary IJ, Inch S, Cross S, MacLennan WJ. Age-associated cognitive decline in healthy old people. Age Ageing 1997;26:295–300.
54. NIA. Genetic epidemiologic studies on age-specified traits. NIA Aging and Genetic Epidemiology Working Group. Am J Epidemiol 2000;152:1003–1008.
55. Wilson RS, Beckett LA, Bienas JL, Evans DA, Bennett DA. Terminal decline in cognitive function. Neurology 2003;60:1782–1787.