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Cognitive Decline and Mortality in a Community-Based Cohort: The Movies Project

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Abstract

OBJECTIVES—In a longitudinal cohort study, we compared declines in specific cognitive domains on their ability to predict time to death, in the presence and absence of dementia, and explored an explanatory role for vascular disease.

DESIGN—Prospective population-based epidemiologic study.

SETTING—The mid-Monongahela valley of southwestern Pennsylvania from 1987 to 2002.

PARTICIPANTS—989 community-dwelling adults, aged =65, enrolled in The Monongahela Valley Independent Elders Survey (MoVIES project).

MEASUREMENTS—Biennial assessments of a range of cognitive domains for up to 12 years. Mortality was modeled as a function of decline in each domain, adjusting for vascular diseases and stratified by age [aged ≤75 (younger-old) and those aged >75 years (older-old)], using Cox Proportional Hazards modeling.

RESULTS—Average annual declines in almost all cognitive domains were significant predictors of mortality in the cohort as a whole. However, after adjustment for dementia, only general cognition, processing speed, the language composite and the executive function composite remained significant. Adjustment for vascular diseases did not alter the results. In the younger-old group, memory (HR 21.4) and executive function (HR 25.5) decline remained strong predictors after adjustment for dementia and vascular disease. In the older-old group, decline in processing

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speed was a strong mortality predictor both before (HR 7.4) and after (HR 5.3) controlling for dementia and vascular diseases.

CONCLUSION—Decline in most cognitive domains predicted mortality across the cohort, but declines in memory and learning were not independent of dementia. Different domains predicted mortality in younger and older subgroups.

Keywords

older adults; community-dwelling; terminal decline; cognitive domains; dementia

INTRODUCTION

The promotion of “healthy aging” has become an increasing priority at both individual and population levels. An improved understanding of the relationship between cognition and longevity may help in this quest, since preserved cognitive functioning is a central component of healthy aging. Alzheimer’s disease (AD), the leading cause of dementia, is ranked as the seventh leading cause of death in the US (1) and a well-recognized risk factor for mortality (2). However, impaired cognitive functioning, even in the absence of dementia, also appears to be associated with mortality.(3,4)

Cognition is not a unitary function. Understanding its relationship to mortality requires attention to the potentially varying effects of different cognitive domains. However, several previous studies examined only one cognitive measure.(5,6) In particular, memory deficits are associated with mortality (7), raising the question of whether this relationship simply reflects an incipient dementia such as AD in which memory deficits are prominent. Decline in other cognitive domains may suggest that other brain disorders are developing, or may reflect an independent “aging” process. Aging itself is associated with increasing comorbidity that could contribute to cognitive impairment. Studies of health measures and comorbidity as potential mediators in the relationship between cognition and mortality have yielded mixed results.(3,4,6,8) Vascular diseases in particular are associated with both mortality (9) and cognitive impairment (10), and could thus confound the association between cognitive decline and mortality.

We evaluated the relationship between cognitive decline and mortality in a rural, community-based older adult population followed with repeated cognitive assessments over 12 years. We examined declines in specific domains of cognitive functioning and decline in a global general mental status measure on their ability to predict time to death, in our cohort as a whole and between age strata, with and without adjustment for the presence of dementia. We also explored the role of vascular disease in the relationship between cognition and mortality.

METHODS

Participants

The Monongahela Valley Independent Elders Survey (MoVIES) project was a population-based epidemiologic study of cognitive impairment and dementia, conducted from 1987 to 2002 in the mid-Monongahela valley of southwestern Pennsylvania.(11,12) The original cohort of 1681 participants aged 65+ comprised an age-stratified random sample of 1422 older adults drawn from voter registration lists, and 259 volunteers from the same communities meeting same inclusion criteria. All participants were community-dwelling at enrollment, and fluent in English with at least 6th grade education. The assessments were conducted primarily in participants’ homes and repeated biennially over 12 years. Dropout/

attrition not due to mortality was 2.8% between data collection “waves.” The study was approved by the University of Pittsburgh Institutional Review Board.

For analyses reported here, Wave 3 (1993–1996), when key variables regarding specific health conditions were first collected, was established as study baseline. At this wave, 1166 participants underwent assessment. We excluded 177 with no follow-up assessments beyond Wave 3; they were significantly older (t-test, $p < 0.001$), more likely to be men (chi-square test, $p = 0.03$), to have lower than high school education (chi-square test, $p = 0.002$), and less likely to be volunteers (chi-square, $p = 0.01$) than randomly selected, than the 989 participants included in these analyses.

Cognitive Measures

The MoVIES cognitive test battery incorporated the neuropsychological panel established by the Consortium to Establish a Registry for Alzheimer Disease (CERAD). (13) Tests included the Mini-Mental State Exam (MMSE) (14), Trail Making Tests A and B (15), CERAD 10-word Word List Learning and Delayed Recall (13), Story Immediate Retell and Delayed Recall (16), Initial Letter Fluency (P and S) and Category Fluency (Fruits and Animals) (17), 15-item CERAD version of the Boston Naming Test (18), CERAD Constructional Praxis (19), and Clock Drawing (20).(11)

Composite scores were created to represent specific cognitive domains, with groupings based on conceptual grounds and/or factor analysis. Individual test scores were first z-transformed based on their distribution at baseline (wave 3), combined as shown below, and averaged to create composite scores. In addition to global cognitive function (MMSE), the domains examined in this study were:

- a. Learning (Word List Learning Test and Story, Immediate Retell),
- b. Memory (Word List Delayed Recall and Story Delayed Recall),
- c. Visuospatial (Clock Drawing and CERAD Constructional Praxis),
- d. Language (Verbal Fluency for Categories and Boston Naming Test),
- e. Processing Speed (Trail Making Test A),
- f. Executive function (Verbal Fluency for Initial Letters and Trail Making Test B).

Diagnosis of Dementia

At each wave, participants with operationally-defined cognitive impairment (12) or decline (21), and a randomly selected comparison group of individuals with normal cognitive scores, were selected to undergo a clinical assessment for dementia. This assessment used a field modification of the protocols of CERAD (13) and the University of Pittsburgh Alzheimer Disease Research Center. Diagnosis of dementia was based on the criteria of the *Diagnostic and Statistical Manual of Mental Disorders, 3rd ed., revised*.(22). A date of onset for dementia, when present, was estimated based on all available data.(21)

Defining Vascular Disease

Presence of these conditions was ascertained by self-report at all waves; participants were asked “has a doctor or nurse ever told you that you had...”: cardiovascular (coronary artery disease and congestive heart failure), cerebrovascular diseases (stroke and TIA), hypertension, and diabetes mellitus. Coronary artery disease was defined by angina, previous myocardial infarction or history of bypassing grafting or angioplasty.

Other Covariates

Demographic characteristics (age, sex, and education) were included. Given the established association of depression with mortality (23), depressive symptoms were included using the modified Center for Epidemiologic Studies-Depression Scale (mCES-D) (24,25) in which higher scores reflect more depressive symptoms. We used a threshold score of 5 or more symptoms (capturing the 90th percentile, i.e. the most depressed 10% of the sample) to indicate depression.(25)

Mortality

Mortality was determined from baseline until death or end of the study (December 31, 2001), whichever came first. Date of death was obtained from obituaries and confirmed by obtaining death certificate information. The geographic stability of this population allowed complete ascertainment of mortality to be achieved.(2)

Analysis

Average annual decline was calculated for each cognitive domain by dividing the difference in standardized scores observed between the first score (at baseline for all participants) and the last score (varied by participant) by duration of follow-up for that participant. Mortality during the follow-up period was modeled as a function of decline in each domain, adjusting for baseline performance in that domain and general cognitive function, using Cox Proportional Hazards modeling. All analyses also include a covariate “recruitment status” indicating whether the participant was from the random or volunteer subsample.

For the MMSE and for each of the six cognitive domains, we fit 3 models for average annual decline for the entire sample. To determine whether the relationship between cognitive decline and mortality was consistent across age groups, we divided the cohort into two roughly equal-sized groups aged 65–74 and 75+ years and fit the same models in the two age groups.

Model 1 covariates included age, sex, education, recruitment status, baseline MMSE and mCES-D scores and baseline score in that specific cognitive domain. In Model 2, dementia was included as a time-dependent variable based on estimated date of onset. Participants with date of onset at any time before Wave 3 were classified as prevalent dementia at baseline. In Model 3, self-reported vascular disease was added. Proportionality assumptions were examined through visual inspection of survival curves ($-\ln(-\ln S(t))$) as well as statistical assessments.(26)

RESULTS

Cohort Characteristics

The mean ($\pm$ SD) baseline age of the 989 participants was 76.3 (5.0) years. Women made up 64% of the cohort and 62.4% had at least high school education. The two age groups aged 65–74 and 75+ years, comprised 459 and 530 participants, with mean ($\pm$ SD) age 72.1 (1.7) years and 80.1 (3.9) years respectively. The mean ($\pm$ SD) MMSE score at baseline was 27.8 (1.9) in the younger group and 26.4 (3.1) in the older group. The mean ($\pm$ SD) MMSE score at the final evaluation was 26.8(4.6) in the younger group and 23.9 (6.1) in the older group. These data should be interpreted with the understanding that the interval between the final MMSE and death/dropout/ end of study ranged from 2.3–10.4 in the younger group and 2.4–10.4 in the older group.

Cohort Mortality and Overall Duration

Mean ($\pm$ SD) duration of follow-up beyond Wave 3 was 7.9 (2.0) years with a range from 2.3 to 10.4 years in the cohort as a whole, 8.6 (1.7) years in the younger group and 7.4 (2.2) years in the older group. Among the 989 participants included, 377 (38.1%) died during follow-up. Baseline characteristics of those who survived and those who died are shown in Table 1. Mean scores on all cognitive scores and composites were significantly different between the two groups at $p < 0.001$, using the Wilcoxon Rank Sum test for the MMSE and chi-square for all others (data not shown).

Dementia

Among the 264 participants with dementia, 90 developed dementia before study baseline of Wave 3 (prevalent cases) and 174 developed dementia during follow-up (incident cases). The 65–74 age group had 16 (3.5%) prevalent cases of dementia at baseline and a cumulative 60 cases (prevalent plus incident) over the course of the study. The corresponding figures for the 75–84 age group, were 74 (13.9%) prevalent cases and cumulatively 204 cases.

Vascular Disease

At baseline, 325 (32.9%) participants reported having been told by a doctor or nurse that they had cardiovascular disease, 90 (9.1%) reported cerebrovascular disease, 103 (10.4%) reported diabetes mellitus, and 446 (45.1%) reported hypertension. (Table 1)

Prediction of Mortality

Overall Cohort

Model 1: Decline over time in all cognitive domains, except visuospatial function, predicted mortality after adjusting for age, sex, education, volunteer status, MMSE score, and depression. (Table 2, first column). Executive function and processing speed were the most strongly associated with mortality. A one point average decline in the standardized executive function score was associated with a 7.5 times higher hazard of dying during the study period, for processing speed, the corresponding figure was 6.6.

Model 2: After adjustment for dementia, average annual declines in memory and learning were no longer significant predictors of mortality (Table 3, first column). Decline in scores on the MMSE (HR 1.9), language composite, (HR 2.6), processing speed, (HR 4.2) and executive function composite (HR 4.5) remained significant predictors of mortality.

Model 3: Inclusion of vascular diseases into the preceding model did not alter the results, indicating that these variables did not explain or confound the relationship between cognitive decline and mortality. (Model 2 vs. Model 3, not in Table)

Age Comparisons

In the 75+ group, declines in memory, learning, executive functions, and visuospatial functions did not significantly predict mortality even before dementia was included as a covariate. Only processing speed significantly predicted mortality in the older group both before (HR 7.4) and after (HR 5.3) controlling for dementia, and after (HR 4.3) controlling for vascular diseases. In the 65–74 group, memory (HR 23.5) and executive function (HR 21.8) were strong predictors even after adjustment for dementia. In both age groups, the MMSE was an independent predictor albeit with a weaker effect. (Table 2 and 3)

DISCUSSION

The results of this large, prospective, population-based study provide further support for the positive association of cognitive decline with mortality, even after adjustment for dementia and self-reported vascular diseases. Decline in processing speed and executive functions were the strongest predictors overall, and adjustment for dementia removed the significance of memory and learning. However, the most striking finding was the effect of age on this relationship. Specifically, in younger-old compared to older-old age groups, different cognitive domains more strongly predicted mortality.

The weight of current evidence supports the impact of impaired cognitive functioning on mortality.(3–6,8) Cognitive decline over time is also associated with mortality even in the absence of an underlying dementia (4) or preclinical dementia (27) suggesting that this association is not simply a reflection of underlying dementia.

The concept of “terminal decline,” first proposed by Kleemeier (28) suggests that a precipitous drop in cognitive function occurs in the years preceding death. Although “precipitous” is not defined consistently in the literature, subsequent studies have supported this observation (27,29) and attempted to identify its determinants. Brain aging may simply reflect overall age-related deterioration or the effects of specific biological or disease processes. In younger-old populations, the association between cognition and mortality may reflect underlying disease such as preclinical AD. In older populations, poorer cognitive functioning may reflect greater general morbidity and also itself affect health behaviors, medication compliance, and attention to care needs, leading to further cognitive decline. Although dementia appears to contribute to terminal decline (29), the relative roles played by comorbid illness versus “cognitive aging” in terminal decline are not clear.

As regard specific cognitive domains, impairments in memory (5) and processing speed (6) are associated with mortality. In one study, declines in visuospatial reasoning and language functions, but not in memory, were associated with increased risk of death.(4) In our cohort as a whole, declines in processing speed, language and executive function were strong predictors of mortality after adjusting for dementia, whereas memory decline was not. However, in the younger-old group, memory decline and also executive function, which did not predict mortality in older-old participants, were very strong mortality predictors even after adjustment for dementia. Our findings do not suggest that the relationship between overall cognitive decline and mortality is solely due to underlying dementia like AD, in which memory deficits are central. On the other hand, the measures of learning and visuospatial functioning in the younger-old group lost their significance after adjustment for dementia, suggesting that these measures only predict mortality insofar as they are related to dementia.

Current literature may support a stronger relationship between impaired cognitive functioning and mortality in younger than in older adults.(4) In general, young adults have more intact and resilient cognition and are perhaps less likely to experience cognitive consequences of mild illness than older adults. Cognitive decline in a younger adult may therefore have greater clinical significance than in an older adult, and be more likely reflect underlying brain disease of any etiology. It has been suggested that normal age-related memory decline may attenuate the relationship between memory decline and mortality.(4)

If dementia is not the sole mechanism, what other factors could be contributing? Many common conditions are associated both with cognitive impairment and mortality, in particular cardiovascular diseases.(9,10) Comorbid illness, as a potential explanation of this relationship, is therefore a compelling possibility. Surprisingly, current findings do not strongly support this hypothesis. Like Schupf et al (4) we found that vascular disease did not

explain the association between cognitive decline and mortality. The consistency of this finding suggests that cognitive impairment associated with mortality is not necessarily just a reflection of underlying disease but may also be a marker of biological aging.

What is the clinical relevance of our findings? Expected length of survival is an often-difficult factor to determine for many patients, especially those with high comorbidity. The clinician's ability to estimate the imminence of death can have a profound impact on medical decision-making, especially regarding treatments and medications with preventative or primarily long-term benefits, and on counseling of patients and families. Cognitive decline, in the absence of dementia, appears to be a strong predictor of mortality. Recognition of cognitive decline is in any case clinically warranted, to determine its cause and potentially to slow its progression. Impaired or declining cognition can draw the clinician's attention to a modifiable cause that may even improve survival. This may be especially true in younger adults, where declines in memory seem to herald poor outcomes. Remarkably, decline on the MMSE predicted mortality for both age groups even after adjustment for dementia and specific diseases. Given that the MMSE is probably the brief mental status screen most commonly used by primary care physicians, and despite its limitations, it might in fact also have some utility in estimating survival.

As regards study limitations, the presence of comorbid illness was determined by self-report, which is standard practice in population studies and has been shown to be accurate in this setting.⁽³⁰⁾ We could not assess severity of illness or include measures of subclinical disease. There is always the possibility of inaccurate self-report, both under and over-reporting, particularly in cognitively impaired individuals. Our findings have limited generalizability to dissimilar populations, such as African American individuals who have different vascular profiles. Further, as assessments were only conducted in alternate years, events immediately preceding death could not be determined when participants died several months after being assessed.

Our results further support the broad terminal decline hypothesis and, in a sense, help to further "deconstruct" it. The differential impact of specific cognitive domains on mortality has implications for understanding brain functions in late life, and suggests that multiple mechanisms likely underlie the relationship between cognitive functioning and mortality. The role of comorbid illness deserves further exploration. Most importantly, there is marked heterogeneity across age strata that should be taken into account in future research as well as clinical practice.

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Table 1

Cohort Characteristics at Baseline Stratified by Subsequent Mortality.

Baseline Characteristics	Died n = 377	Survived n = 612	p-value
Age (mean) [$\pm$ SD]	78.7 [5.5]	74.9 [4.1]	<0.001* [‡]
Women (%)	58.0	68.1	0.304 [‡]
High school or higher education (%)	52.5	68.5	0.001* [‡]
Recruitment status (volunteer %)	11.9	25.3	<0.001* [‡]
MMSE (mean) [$\pm$ SD]	26.1 [3.3]	27.7 [2.0]	<0.001 [‡]
Depressive symptoms (mCES-D $\geq$ 5 %)	8.1	6.1	<0.001* [‡]
Dementia prevalent and incident cases (%)	44.0	16.0	<0.001* [‡]
Cardiovascular disease (%)	41.1	27.8	<0.001* [‡]
Cerebrovascular disease (%)	14.1	6.1	<0.001* [‡]
Diabetes mellitus (%)	15.9	7.0	<0.001* [‡]
Hypertension (%)	44.4	45.7	0.700 [‡]

* Significant at $p < 0.01$;[‡] chi-square test;[‡] Wilcoxon Rank Sums non-parametric test

Table 2

Model 1. Cognitive Decline as Predictors of Mortality, without Adjustment for Dementia (covariates include: age, sex, education, depression, recruitment status [volunteer vs. random], general and a specific cognitive function at baseline).

Cognitive Domains*	Overall		Age 65 – 74		Age 75 – 84	
	HR (95% CI)	Significant covariates	HR (95% CI)	Significant covariates	HR (95% CI)	Significant covariates
General cognition decline	2.2 [§] (1.7–2.8)	Age [§]	2.6 [§] (1.6–4.4)	Volunteer [†]	2.2 [§] (1.7–2.8)	Age [§]
		Female [‡]		Baseline general cognition [†]		Female [§]
		Volunteer [§]				
Memory composite decline	2.6 [†] (1.2–5.9)	Age [§]	31.9 [§] (6.3–160.9)	Volunteer [†]	NS	Age [§] , female [‡]
		Volunteer [†]		Baseline memory [†]		Higher education [†]
		Baseline memory [§]				Baseline memory [§]
Learning composite decline	2.4 [†] (1.1–4.7)	Age [§]	8.5 [†] (1.9–37.4)	Volunteer [†]	NS	Age [§] , female [‡]
		Volunteer [†]		Baseline learning [†]		Higher education [†]
		Baseline learning [§]				Baseline learning [§]
Visuospatial composite decline	NS	Age [§]	3.2 [†] (1.1–9.5)	Volunteer [†]	NS	Age [§] , female [§]
		Female [§]		Baseline visuospatial [†]		Higher education [†]
		Volunteer [†]				Baseline visuospatial [§]
		Baseline visuospatial [§]				
Language composite decline	4.1 [§] (2.3–7.3)	Age [§]	6.5 [†] (1.9–22.9)	Volunteer [†]	3.1 [§] (1.6–6.0)	Age [§]
		Female [‡]		Baseline language [†]		Female [§]
		Volunteer [†]				
		Baseline language [†]				
Executive composite decline	7.5 [§] (2.6–20.8)	Age [§]	35.1 [§] (5.9–206.9)	Volunteer [†]	NS	Age [§]
		Female [‡]		Baseline executive [§]		Female [§]
		Higher education [†]				Higher education [†]
		Volunteer [†]				Baseline executive [†]

Cognitive Domains*	Overall		Age 65 – 74		Age 75 – 84	
	HR (95% CI)	Significant covariates	HR (95% CI)	Significant covariates	HR (95% CI)	Significant covariates
		Baseline executive§				
Processing speed decline	6.6§ (3.1–13.4)	Age§	NS	Volunteer‡	7.4§ (3.3–16.4)	Age§
		Female‡				Female‡
		Volunteer‡				Baseline speed§
		Baseline speed§				

* Separate model fit for average annual decline in each domain; model also adjusts for baseline score in that domain.

‡ p<0.05;

‡ p<0.01;

§ p<0.001; Bonferroni correction for multiple comparisons p < 0.005

Table 3

Model 2. Cognitive Decline as Predictors of Mortality, with Adjustment for Dementia (additional covariates include: age, sex, education, depression, recruitment status [volunteer vs. random], general and specific cognitive function at baseline).

Cognitive Domains*	Overall		Age 65 – 74		Age 75 – 84	
	HR (95% CI)	Significant covariates	HR (95% CI)	Significant covariates	HR (95% CI)	Significant covariates
General cognition decline	1.9 [†] (1.5–2.4)	Age [§] , Female [‡]	2.0 [†] (1.1–3.6)	Volunteer [‡]	1.8 [§] (1.4–2.4)	Age [§]
		Volunteer [‡]		Baseline general cognition [†]		Female [§]
		Dementia [‡]				Dementia [‡]
Memory composite decline	NS	Age [§]	23.5 [‡] (3.6–153.6)	Volunteer [‡]	NS	Age [§] , female [‡]
		Female [‡]				Higher education [†]
		Volunteer [‡]				Dementia [§]
		Dementia [§]				Baseline memory [†]
Learning composite decline	NS	Age [§]	NS	Volunteer [‡]	NS	Age [§] , female [‡]
		Volunteer [‡]		Baseline learning [†]		Higher education [†]
		Dementia [§]				Dementia [§]
		Baseline learning [‡]				Baseline learning [†]
Visuospatial composite decline	NS	Age [§]	NS	Volunteer [‡]	NS	Age [§] , female [§]
		Female [§]		Dementia [†]		Higher education [†]
		Volunteer [‡]		Baseline visuospatial [†]		Dementia [§]
		Baseline visuospatial [§]				Baseline visuospatial [§]
Language composite decline	2.6 [†] (1.4–5.1)	Age [§]	NS	Volunteer [‡]	NS	Age [§]
		Female [‡]		Baseline language [†]		Female [§]
		Volunteer [‡]				Dementia [§]
		Dementia [‡]				
		Baseline language [†]				
Executive composite decline	4.5 [†] (1.5–13.4)	Age [§] , Female [‡]	21.8 [†] (3.2–147.8)	Volunteer [‡]	NS	Age [§]

Cognitive Domains*	Overall		Age 65 – 74		Age 75 – 84	
	HR (95% CI)	Significant covariates	HR (95% CI)	Significant covariates	HR (95% CI)	Significant covariates
		Higher education [†]		Baseline executive [†]		Female [§]
		Volunteer [†]				Higher education [†]
		Dementia [†]				Dementia [†]
		Baseline executive [§]				Baseline executive [†]
Processing speed decline	4.2 [§] (2.0–9.2)	Age [§]	NS	Volunteer [†]	5.3 [§] (2.2–12.6)	Age [§]
		Female [†]		Baseline speed [†]		Female [†]
		Volunteer [†]				Dementia [†]
		Dementia [†]				Baseline speed [§]
		Baseline speed [§]				

* Separate model fit for average annual decline in each domain; model also adjusts for baseline score in that domain.

[†] p<0.05;

[‡] p<0.01;

[§] p<0.001; Bonferroni correction for multiple comparisons p < 0.005