Cognitive Impairment and Mortality in the Community-dwelling Elderly

Shari S. Bassuk, David Wypij, and Lisa F. Berkman

The effects on mortality of cognitive impairment and 3-year declines in cognitive function were examined among community-dwelling adults aged 68 years or more. Data were taken from a population-based cohort study that enrolled noninstitutionalized elderly residents of New Haven, Connecticut, and followed them by conducting in-home interviews in 1982, 1985, 1988, and 1994. The cognitive function of 1,997 respondents was assessed by using the 30-point Mini-Mental State Examination in 1985; 1,372 respondents (86% of those alive) were retested in 1988. Responses were classified as high normal (28-30), low normal (24-27), mild impairment (18-23), or severe impairment (0-17); cognitive decline was defined as a transition to a lower category. After control for multiple potential confounders, both severe and mild cognitive impairment were strongly predictive of subsequent mortality among respondents aged less than 80 years. Upon closer examination, the elevated mortality risk was observed primarily among respondents whose cognitive decline was recent rather than among those whose cognitive performance was compromised but stable. Among respondents aged 80 years or more, declines to severe cognitive impairment were predictive of mortality, but it was not clear whether the decline per se signaled an unfavorable prognosis not accounted for by the resulting impairment level. Cognitive declines, especially those in the young elderly, have a marked adverse impact on survival. Am J Epidemiol 2000; 151:676-88.

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Abbreviation: MMSE, Mini-Mental State Examination.

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Approximately 15 percent of the US population aged more than 65 years suffers from dementia, defined as global cognitive deterioration sufficient to interfere significantly with social and occupational function (1). Milder cognitive dysfunction is estimated to be at least two to three times as prevalent (2, 3). Cognitive impairment represents a major public health burden: it has adverse psychosocial and economic consequences for affected persons and their families (4–6) and is a risk factor for increased home health care use (7), hospitalization (8–10), nursing home entry (11–15), and mortality.

Most of the data demonstrating an association between cognitive impairment and mortality have been gathered in studies that compared persons with and without dementing disorders. In population-based investigations, dementia diagnoses confer an increased mortality risk (16–23). In some studies, the elevated risk is observed primarily or exclusively among those respondents with the most marked cognitive deficits (19, 23). These findings are consistent with observations of clinical samples, which have found significant associations between indicators of dementia severity and shortened survival among patients with Alzheimer’s disease (24–27).

These results raise the question of whether variations in cognitive performance among the elderly who are not necessarily suffering from dementia have any prognostic significance with respect to survival. In population-based studies of representative elderly cohorts that have addressed the issue, aged persons evincing severe cognitive deficits do appear to have an elevated mortality risk when compared with cognitively intact persons (13, 28–34). However, it is not clear whether less severe cognitive dysfunction is also predictive of impending death. Some investigators have reported that mild but measurable cognitive difficulties are strongly associated with a shortened life span (31, 33, 34), but others have found either no association (13, 28, 32) or modest associations only (29, 30). Moreover, the issue of whether variation within the upper range of the cognitive spectrum is related to mortality generally has not been addressed. One exception is the report by Liu et al. (30), which, in a 10-year follow-up of a subsample of participants in the population-based Framingham Heart Study, did
not find that superior performance on a battery of neuropsychological tests conferred any survival advantage.

In most of these studies, which ranged in length of follow-up from 2 to 20 years, the authors either did not consider the possibility of or did not find evidence of diminishing relative mortality risks over time since the cognitive assessment. Given the expected decline in cognitive performance of many elderly persons, the apparent lack of attenuation in relative risks as time elapses from a single assessment of cognitive function is counterintuitive. Instead, it is reasonable to expect that the mortality risk associated with poor cognitive performance at one time point would weaken over long follow-up intervals. This phenomenon may account for some of the null findings reported above; studies with follow-up intervals exceeding 5 years did not detect associations between mild cognitive impairment and mortality.

In addition, although recent research has focused on severity of cognitive impairment rather than on change in cognitive function as a predictor of death, it has long been suggested that a critical rate of decline may distinguish survivors from nonsurvivors (35, 36). However, two population-based investigations that adequately controlled for potential confounders reported contradictory results. In a sample of middle-aged and elderly persons, Bruce et al. (37) detected no effect on mortality of a 1-year decline in performance on the Mini-Mental State Examination (MMSE) (38) beyond the test score attained. On the other hand, Deeg et al. (39) found that decline in performance on a modified version of the Wechsler Memory Scale (40) over an 8-year period strongly predicted subsequent mortality status among an elderly Dutch cohort; a weak association persisted even after adjustment for the resulting test score. Unfortunately, this study’s high nonparticipation rate renders the validity of its findings uncertain (less than 20 percent of respondents who were tested at baseline and survived 8 years were reexamined).

In this report, we examine the impact of the degree of severity of cognitive impairment and a history of cognitive decline on subsequent all-cause mortality in a large population-based cohort of urban elderly followed for 9 years. The following questions are addressed: 1) Is the relation between cognitive status and mortality best characterized as a threshold or as a gradient? In other words, must a critical level of impairment be present to confer an increased mortality risk, or does a lesser degree of cognitive difficulty also confer some risk? Is “high-end” variation among ostensibly unimpaired persons related to survival? 2) Is a recent history of cognitive decline a stronger predictor of mortality than cognitive impairment per se? 3) Does accounting for the time-dependent nature of cognitive function among aging cohorts bring these associations into clearer focus?

MATERIALS AND METHODS
Respondents

The study population was drawn from the New Haven, Connecticut, site of the Established Populations for Epidemiologic Studies of the Elderly program, initiated in 1980 by the National Institute on Aging to assess the health of four geographically defined populations of older persons. This cohort is a multistage probability sample of noninstitutionalized men and women aged 65 years or more who were living in New Haven in 1982. Details of the sampling design are provided elsewhere (41). Samples were drawn from three housing strata: 1) public elderly housing, which is age and income restricted; 2) private elderly housing, which is age restricted; and 3) community housing (all other houses and apartments). In public housing, all eligible persons were sampled; in other strata, women were subsampled randomly to achieve roughly equal representation of both genders. Of those eligible, 82 percent (n = 2,812) were enrolled. Trained lay examiners interviewed the cohort at home in 1982, 1985, 1988, and 1994 and by telephone in intervening years. The dates and circumstances of death were obtained from proxy informants, most often family members, and by continuous monitoring of local newspaper obituaries. Cohort records were also matched to the National Death Index, and death certificates were obtained for all deaths.

Measures

Cognitive function. Cognitive performance was measured during the 1985 and 1988 interviews by using the 30-point MMSE (38), which assesses orientation, memory, concentration, language, and praxis. Respondents were asked to spell the word “world” backward and to count backward from 100 in blocks of 7; the better score of the two was used to compute the total MMSE score. If 10 or more items were refused or missing, the MMSE was not scored. Otherwise, refusals were scored as incorrect, and scores for missing items were imputed by assigning the mean of nonmissing items. Scores were categorized into four groups: high normal (28–30), low normal (24–27), mild impairment (18–23), and severe impairment (0–17). Cognitive decline was defined as a transition to a lower MMSE category from the 1985 to the 1988 interview. Maintenance of cognitive function was defined as the absence of cognitive decline; that is,
respondents in the same cognitive category at both
time points and those who transitioned to higher cate-
gories were classified as having maintained cognitive
function. In this report, the 1985 MMSE is hereafter
referred to as the “baseline” cognitive test. At baseline
cognitive testing, the cohort consisted of persons aged
68 years or more.

Covariates. The following self-reported variables
were selected as potential confounders because of their
associations with cognitive status or mortality in the
New Haven cohort. Unless otherwise indicated, covariate information was assessed during the 1985
interview. When data were missing, values from the
1982 interview were substituted. Sociodemographic
variables included age (measured in 5-year groups),
gender, housing strata (public, private, or community),
race (White or non-White), education (≥12 or <12
years), and 1982 annual income (<$10,000, ≥$10,000,
or missing).

Health and social behaviors included smoking sta-
tus (current, former, or never), alcohol consumption
(current or not), regular physical activity (yes or no),
and level of “social disengagement.” Regular physical
activity was measured by asking respondents how
often (0 = never, 1 = sometimes, 2 = often) during
the past month they had participated in each of the fol-
lowing: active sports or swimming, taking walks, gar-
dening or yard work, and physical exercises. Persons
whose mean response was 1 or more were coded as
engaging in regular physical activity. Level of social
disengagement was constructed from six indicators:
1) presence of a spouse, 2) monthly visual contact with
three or more relatives or close friends, 3) yearly non-
visual contact (i.e., telephone calls or letters) with 10
or more relatives or close friends, 4) frequent attend-
ance at religious services (i.e., at least once per
month), 5) membership in other groups, and 6) regular
participation in recreational social activities (attending
movies, restaurants, or sporting events; playing cards,
bingo, or other games; taking day or overnight trips;
shopping; doing volunteer work; doing paid commu-
nity work). The social disengagement index was
scored as follows: 1 = 5–6 ties, 2 = 3–4 ties, 3 = 1–2
ties, 4 = 0 ties.

Health status indicators included the presence of
functional disability (requiring assistance with one or
more activities of daily living (42): walking across a
room, dressing, eating, bed-to-chair transferring,
bathing, using the toilet); a cardiovascular profile (low
vs. high risk, where the latter was defined as a history
of physician-diagnosed stroke, diabetes, or myocardial
infarction or a measured sitting blood pressure of
160/95 or higher); history of physician-diagnosed can-
cer; visual impairment (difficulty in reading ordinary
newspaper print); and depressive symptomatology (a
score of 16 or more on the Center for Epidemiologic
Studies Depression Scale (43)). With the exception of
visual impairment, health status assessments were
repeated in 1988. Declines in health were defined as
the onset of new health problems between 1985 and
1988 (i.e., four binary indicators for the onset of func-
tional disability, cardiovascular conditions, cancer, or
an elevated level of depressive symptoms not reported
at or by the 1985 interview but reported at or by the
1988 interview).

Analyses

The outcome of interest was survival time, which
was the time from the 1985 interview date to the date
of death or December 31, 1994, whichever was earlier.
The Kaplan-Meier product limit estimator (44) was
used to plot the unadjusted survivor function by base-
line MMSE category. Survival curves were tested for
homogeneity by using the log-rank test (45). Cox
regression models (46, 47) were used to quantify the
impact of cognitive function on mortality while adjust-
ing for sociodemographic and health-related covari-
ates. This adjustment was accomplished via a series of
four nested models that offered increasing control and
insight into the robustness of the cognition-mortality
relation. The initial step included only age, gender, and
housing type; the second added race, education, and
income; the third, health and social behaviors; and the
fourth, health status. In assessing the effect of cogni-
tive decline, we also adjusted for concomitant declines
in physical and mental health in a fifth step. Because
of space constraints, this report presents results from
only step two (sociodemographic-adjusted models)
and step four or five (fully adjusted models). Evidence
for nonproportionality (i.e., a change in relative haz-
ard's over time) was determined by using three proce-
dures: 1) visual examination of adjusted log(−log(sur-
rvival)) plots evaluated at the sample means for age,
gender, and housing status; 2) analysis of Schoenfeld
residuals (48) from the proportional hazards regression
model; and 3) significance testing of the coefficients of
interaction terms between time and cognitive function
categories in an extended Cox model. Because previ-
ous studies have provided limited data on cognitive
function in the oldest old, we also stratified the data by
age at the 1985 interview (<80 vs. ≥80 years) to deter-
mine whether this factor modified the cognition-mortality
relation.

Computing was done by using version 6.11 of the
statistical package SAS (49). Hazard ratio estimates
and confidence intervals were not weighted but were
adjusted for variables used to construct the sampling
weights (gender and housing status); this method min-
imizes bias in point estimates while maintaining optimal efficiency in the analysis of survey data (50). We also replicated the analyses by using the sampling weights and adjusting for clustering with the estimating equations approach (51). These analyses, carried out by using version 7.11 of SUDAAN software (52), did not yield substantively different findings from the results that follow.

RESULTS

In 1985, 2,322 of the original 2,812 respondents were alive; 1,997 respondents (86 percent of those alive) completed the MMSE. The vital status of 18 persons with valid 1985 MMSE scores was unknown at the end of follow-up. In addition, death dates could not be confirmed for 9 persons reported by proxies to have died during follow-up. These 27 persons (1.4 percent of the analytical sample) were censored at the last date on which they were known to be alive. The median censoring time for respondents who survived to the end of the observation period (December 31, 1994) was 9.6 years (5th–95th percentile: 9.1–9.8 years).

In 1985, the distribution of MMSE scores was as follows: high normal, 44 percent; low normal, 28 percent; mild impairment, 20 percent; and severe impairment, 8 percent. Sociodemographic and health characteristics of persons in the four cognitive groups are shown in table 1. Compared with those who scored in the normal range, cognitively impaired respondents were more likely to be older, female, non-White, less educated, poorer, socially disengaged, and functionally disabled and to have a high-risk cardiovascular profile, vision problems, and an elevated level of depressive symptoms. Impaired respondents were less likely to have consumed alcohol recently, to have ever smoked cigarettes, and to have a history of cancer.

Over half of the analytical sample (55 percent) had died by the end of the observation period. Figure 1 displays the unadjusted Kaplan-Meier survival curves, by

| TABLE 1. Characteristics* of the study sample,† by Mini-Mental State Examination category: New Haven, Connecticut site, Established Populations for Epidemiologic Studies of the Elderly, 1985 |
|---------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|
|                                 | Severe impairment (n = 167)     | Mild impairment (n = 366)       | Low normal (n = 556)           | High normal (n = 875)           | Total (n = 1,997)               |
| Mean (SD) age (years)           | 80.1 (7.3)                      | 78.1 (7.1)                      | 76.4 (6.2)                      | 75.4 (5.7)                      | 77.6 (6.9)                     |
| Gender: male                    | 29.3                            | 37.6                            | 39.9                            | 41.1                            | 39.1                            |
| Housing type                    |                                 |                                 |                                 |                                 |                                 |
| Public elderly                  | 48.5                            | 36.3                            | 21.0                            | 17.9                            | 25.0                            |
| Private elderly                 | 20.3                            | 28.7                            | 31.7                            | 31.4                            | 29.9                            |
| Community                       | 31.1                            | 35.6                            | 47.3                            | 50.6                            | 45.1                            |
| Race: non-White                 | 43.1                            | 39.4                            | 17.8                            | 11.4                            | 21.4                            |
| Education: ≥12 years            | 8.4                             | 13.8                            | 33.3                            | 45.5                            | 32.7                            |
| Income: ≥$10,000§               | 5.3                             | 6.6                             | 21.6                            | 31.7                            | 22.0                            |
| Smoking status                  |                                 |                                 |                                 |                                 |                                 |
| Never                           | 66.5                            | 56.9                            | 49.6                            | 47.8                            | 51.7                            |
| Former                          | 22.7                            | 26.8                            | 33.8                            | 34.9                            | 31.9                            |
| Current                         | 10.8                            | 16.5                            | 16.6                            | 17.3                            | 16.4                            |
| No alcohol consumption in past month | 80.8                            | 67.4                            | 56.8                            | 54.9                            | 60.1                            |
| Regular physical activity in past month | 10.8                            | 14.2                            | 19.6                            | 21.5                            | 18.6                            |
| Social disengagement (0–2 social ties) | 79.0                            | 62.4                            | 55.6                            | 43.9                            | 53.8                            |
| Functional disability           | 40.1                            | 31.3                            | 17.8                            | 11.1                            | 19.4                            |
| High-risk cardiovascular profile | 55.1                            | 40.1                            | 42.8                            | 34.3                            | 39.6                            |
| Cancer history                  | 9.6                             | 15.3                            | 18.7                            | 19.8                            | 17.7                            |
| Visual impairment               | 30.5                            | 20.6                            | 10.6                            | 5.9                             | 12.2                            |
| Depressive symptoms             | 27.5                            | 25.3                            | 17.5                            | 8.9                             | 16.1                            |

* The association of all characteristics with cognitive status was statistically significant (p < 0.05) when the chi-square test (for categorical covariates) or analysis of variance (for age) was used.
† All characteristics except age are expressed as percentages.
‡ SD, standard deviation.
§ 1982 annual income of the 1,514 respondents who reported income.
level of baseline cognitive function. The global log-rank test was significant (chi-square = 78.9, 3 df, \( p < 0.001 \)), and pairwise comparisons showed that each of the four survival trajectories was significantly different (at \( p < 0.02 \)) from the other three. Forty-six percent of respondents aged less than 80 years died during the course of follow-up, whereas 77 percent of those aged 80 years or more died during this period.

**Baseline cognitive function and mortality**

Proportional hazards regression was used to examine the relation between baseline cognitive function and mortality while adjusting for age and other potential sociodemographic confounders (table 2). We found that both severe and mild impairment were associated with an elevated mortality risk. Those persons categorized as low normal were also at a somewhat increased risk in comparison to their higher scoring counterparts, although the association did not reach statistical significance. Contrary to expectation, the hazard ratios associated with baseline cognitive performance did not appear to vary over time in the sample as a whole.

Stratification by age (<80 vs. \( \geq 80 \) years) revealed that associations between cognitive deficits and mortality were more pronounced among younger than among older respondents. Moreover, the diagnostic procedures used to evaluate the validity of the proportional hazards assumption within each age group clearly indicated that the association between cognitive function and mortality was time dependent. That is, 1) there was evident nonparallelism between at least two of the four log(−log(survival)) curves associated with the MMSE groups, 2) Schoenfeld residuals from proportional hazards models exhibited statistically significant \( (p < 0.05) \) associations with time in linear regression modeling, and 3) interaction terms between baseline MMSE category and time period were statistically significant in extended (i.e., nonproportional hazards) Cox models. (Detailed diagnostic findings are not shown.) Therefore, this report also presents results from time-stratified models, in which time was coded as 0–2 versus 2–9 years.

Among respondents in their sixties and seventies, mortality rates for those categorized as severely impaired, mildly impaired, and low normal were each higher during the first 2 years of follow-up than for those persons with the highest MMSE scores. Beyond 2 years, severe impairment continued to carry an unfavorable prognosis, but milder cognitive deficits were no longer predictive of mortality. (A more detailed specification of the time function revealed that the hazard ratios associated with each cognitive group peaked during the second year of observation and then declined for the next 7 years.) Among those aged 80 years or more, severe impairment was related to reduced survival (the association was observed only after 2 years), but there was little evidence that MMSE
scores in the mild impairment or low normal range were associated with mortality at any time during follow-up.

Although adjustment for health behaviors and health status attenuated the observed associations (table 3), the pronounced early elevation in the mortality rate associated with both severe and mild impairment persisted among younger respondents. Among older persons, severe impairment remained significantly predictive of death after a 2-year lag.

### Table 2. Baseline cognitive status as a predictor of mortality over a follow-up period of ≥9 years, after adjustment for sociodemographic covariates: New Haven, Connecticut site, Established Populations for Epidemiologic Studies of the Elderly, 1985-1994

<table>
<thead>
<tr>
<th>No.</th>
<th>0-9 years</th>
<th>Time-stratified analyses†</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>HR‡</td>
<td>95% CI‡</td>
</tr>
<tr>
<td>All ages</td>
<td>1,997</td>
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<tr>
<td>Severe impairment</td>
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<td>Mild impairment</td>
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<td>556</td>
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<tr>
<td>Low normal</td>
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<tr>
<td>High normal</td>
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<td>1.00</td>
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<tr>
<td>Age ≥80 years</td>
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<tr>
<td>Severe impairment</td>
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<td>Mild impairment</td>
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<tr>
<td>Low normal</td>
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<tr>
<td>High normal</td>
<td>205</td>
<td>1.00</td>
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</table>

* p < 0.10; ** p < 0.05; *** p < 0.01; **** p < 0.005; ***** p < 0.001.
† Hazards are assumed to be proportional within but not across time period.
‡ HR, hazard ratio; CI, confidence interval.

### Table 3. Baseline cognitive status as a predictor of mortality over a follow-up period of ≥9 years, after adjustment for sociodemographic covariates, health and social behaviors, and health status: New Haven, Connecticut site, Established Populations for Epidemiologic Studies of the Elderly, 1985-1994

<table>
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<tr>
<th>No.</th>
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<tr>
<td>All ages</td>
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<tr>
<td>High normal</td>
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<td>1.00</td>
</tr>
<tr>
<td>Age &lt;80 years</td>
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</tr>
<tr>
<td>Severe impairment</td>
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<td>Mild impairment</td>
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<td>1.02</td>
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<td>Low normal</td>
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<td>1.11</td>
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<td>High normal</td>
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<td>1.00</td>
</tr>
<tr>
<td>Age ≥80 years</td>
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<tr>
<td>Severe impairment</td>
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<td>Mild impairment</td>
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<td>0.86</td>
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<tr>
<td>High normal</td>
<td>205</td>
<td>1.00</td>
</tr>
</tbody>
</table>

* p < 0.10; ** p < 0.05; *** p < 0.01; **** p < 0.005.
† Hazards are assumed to be proportional within but not across time period.
‡ HR, hazard ratio; CI, confidence interval.
Decline in cognitive function and mortality

We also examined transitions in cognitive status over a 3-year interval (1985–1988) as predictors of mortality during the subsequent 6-year period (1988–1994). Of the 1,997 respondents with valid MMSE scores in 1985, 406 died before their 1988 assessment, and 1,372 (86 percent of those alive) were retested in 1988. One-half (52 percent) of high normal, one-third (32 percent) of low normal, and one-fifth (18 percent) of mildly impaired persons had transitioned to a lower MMSE category. Persons who scored in the low normal range were twice as likely to decline to a category indicating impairment than were those categorized as high normal (32 vs. 15 percent, \( p < 0.001 \)). Declines to severe impairment were significantly more common among the mildly impaired (18 percent) than among either low normal (5 percent, \( p < 0.001 \)) or high normal (4 percent, \( p < 0.001 \)) persons.

As shown in model 1 of table 4, cognitive decline was associated with a significantly higher hazard of death. The relation was strongest in the 2-year interval immediately following the second cognitive assessment. Control for initial (1985) cognitive category had little effect on the results (model 2). Adjustment for the final (1988) cognitive category did not dilute the association between decline and death observed during the first 2 years of follow-up, although it eliminated the association in the subsequent 4 years (model 3). The adverse effect of cognitive decline was observed in both age strata. Among respondents in their sixties and seventies, cognitive decline more than doubled the mortality rate in the 2-year period immediately following the assessment but had no subsequent effect among those who survived at least 2 years. On the other hand, among respondents in their eighties and nineties, cognitive decline was associated with a modest but consistent elevation in mortality during the entire 6-year follow-up period. Estimates were minimally affected after adjustment for health-related covariates and concurrent declines in health status (table 5).

Cognitive decline versus cognitive impairment as predictors of mortality

We next examined in more detail the mortality risks associated with cognitive decline. For persons aged less than 80 years (tables 6 and 7), the data were stratified by year of follow-up; small cell counts precluded similar stratification for persons aged 80 years or more.

<table>
<thead>
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<tr>
<td></td>
<td>0–26 years</td>
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<tr>
<td></td>
<td>HR§ 95% CI</td>
<td>0–2 years</td>
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<tr>
<td>All ages (n = 1,301)</td>
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<tr>
<td>Model 1: decline only</td>
<td>1.30 1.09, 1.55****</td>
<td>1.80 1.29, 2.40****</td>
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<tr>
<td>Model 2: decline and</td>
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<tr>
<td>initial MMSE category</td>
<td>1.37 1.14, 1.65****</td>
<td>1.89 1.33, 2.60****</td>
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<tr>
<td>Model 3: decline and</td>
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<td>final MMSE category</td>
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<td>1.82 1.13, 2.94****</td>
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<tr>
<td>Model 1: decline only</td>
<td>1.26 1.02, 1.57**</td>
<td>2.21 1.44, 3.37****</td>
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<tr>
<td>Model 2: decline and</td>
<td></td>
<td></td>
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<tr>
<td>initial MMSE category</td>
<td>1.36 1.08, 1.73***</td>
<td>2.51 1.59, 3.94****</td>
</tr>
<tr>
<td>Model 3: decline and</td>
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<tr>
<td>final MMSE category</td>
<td>1.10 0.62, 1.49</td>
<td>2.06 1.07, 3.96**</td>
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<tr>
<td>Age ≥80 years (n = 292)</td>
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<tr>
<td>Model 1: decline only</td>
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<td>1.28 0.77, 2.15</td>
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<td>Model 2: decline and</td>
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<td>1.21 0.70, 2.08</td>
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<td>1.13 0.77, 1.67</td>
<td>1.40 0.68, 2.88</td>
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* \( p \leq 0.10 \); ** \( p \leq 0.05 \); *** \( p \leq 0.01 \); **** \( p \leq 0.005 \); ***** \( p \leq 0.001 \).
† Cognitive decline: transition to a lower Mini-Mental State Examination (MMSE) category (high normal to low normal or mild or severe impairment, low normal to mild or severe impairment, or mild to severe impairment); respondents with severe impairment in 1985 (n = 71) not included here as they were not at risk of decline.
‡ Hazards are assumed to be proportional within but not across time period.
§ HR, hazard ratio; CI, confidence interval.

<table>
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<tr>
<th>Age &lt;80 years (n = 1,009)</th>
<th>Model 1: decline only</th>
<th>Model 2: decline and initial MMSE category</th>
<th>Model 3: decline and final MMSE category</th>
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<td>High normal to low normal</td>
<td>1.22, 0.98, 1.52*</td>
<td>2.12, 1.37, 3.27******</td>
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<td>High normal to mild impairment</td>
<td>1.25, 0.99, 1.58*</td>
<td>2.25, 1.42, 3.56******</td>
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<td>1.20, 0.88, 1.65</td>
<td>2.22, 1.13, 4.37**</td>
<td>0.98, 0.69, 1.40</td>
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<th>Age ≥80 years (n = 292)</th>
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<th>Model 2: decline and initial MMSE category</th>
<th>Model 3: decline and final MMSE category</th>
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<td>High normal, maintain function</td>
<td>1.35, 0.99, 1.85*</td>
<td>1.17, 0.66, 2.08</td>
<td>1.41, 0.94, 2.12*</td>
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* p ≤ 0.10; ** p ≤ 0.05; *** p ≤ 0.01; **** p ≤ 0.005; ***** p ≤ 0.001.
† Cognitive decline: transition to a lower Mini-Mental State Examination (MMSE) category (high normal to low normal or mild or severe impairment, low normal to mild or severe impairment, or mild to severe impairment); respondents with severe impairment in 1985 (n = 71) not included here as they were not at risk of decline.
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§ HR, hazard ratio; CI, confidence interval.


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somewhat higher mortality rate than those who scored low normal at baseline but did not decline cognitively between the two assessments. Likewise, respondents who transitioned to mild impairment from a high or low normal baseline score had a higher mortality rate than did persons with mild impairment at baseline who did not decline subsequently. Finally, persons with incident severe impairment tended to have higher mortality rates than persons already severely impaired at baseline. Although the large confidence intervals suggest inadequate power for some comparisons, these data nevertheless indicate that a recent history of cognitive decline confers an added mortality risk beyond the resulting impairment level among the young elderly, a finding in accordance with model 3 of tables 4 and 5. Among respondents in their eighties and nineties, a steep decline from a score in the normal range to one indicative of severe impairment was predictive of mortality, but more modest declines were not.

Among both younger and older respondents whose cognitive status did not decline, there was no indica-
tion of an association between baseline cognitive performance and survival. That is, neither mildly impaired nor low normal persons with a stable 3-year cognitive status were significantly more likely to die than their higher-scoring counterparts. This finding suggests that the elevated mortality rates observed among younger respondents with mild cognitive deficits at baseline (table 2) may have been due to a subgroup of persons in the midst of a decline to a more impaired state. It is also possible that these findings could be explained by the fact that some persons with initial scores in the low normal or mildly impaired range had improved upon retesting, with a subsequent decrease in their mortality risk. However, when we subdivided the respondents whose status had not declined into those who had improved (transitioned to a higher MMSE category) versus those who had not, the persons whose status had improved did not have a significantly reduced risk of death compared with those whose cognitive status was unchanged (among persons aged less than 80 years: hazard ratio = 0.80, 95 percent confidence interval: 0.51, 1.24; among persons aged more than 80 years: hazard ratio = 1.00, 95 percent confidence interval: 0.52, 1.91; analyses adjusted for sociodemographic covariates).

DISCUSSION

Among elderly men and women, a recent history of cognitive decline appeared to confer an additional mortality risk that was independent of the resulting level of impairment. Indeed, detailed analyses of transitions in MMSE scores over a 3-year interval suggest that incident cognitive decline is a better predictor of 2-year mortality than is compromised but stable cognitive performance among respondents in their sixties and seventies. While MMSE scores indicating both low normal and mild impairment at baseline were predictive of 2-year mortality in this age group, our findings imply that these associations could be accounted for by a subgroup of respondents in the midst of a decline to a more impaired state. Declines to severe impairment were more common among low normal and mildly impaired than among high normal persons, and such declines might be responsible for the striking short-term gradient characterizing the relation between baseline cognitive function and mortality in persons aged less than 80 years.

Cognitive decline also was associated with higher mortality among persons in their eighties and nineties. However, the increase in risk occurred primarily among unimpaired persons who had transitioned to severe impairment, and it is not clear whether the decline per se signaled an unfavorable prognosis not accounted for by the resulting impairment level in this age group.

Use of the MMSE, a well-validated measure of cognitive impairment (53), along with minimal attrition between the two cognitive assessments and virtually complete follow-up in a large population-based cohort, are arguments for the validity of our findings. In addition, adjustment for multiple sociodemographic and health-related covariates reduced the possibility that observed associations were confounded by these factors.

In light of recent concerns about uncontrolled confounding by educational level (30, 54), it is of interest to note that our series of nested models revealed that adjustments for education, income, and race had virtually no effect on any of the estimated hazard ratios (data not shown). On the other hand, adjustment for health and social behaviors produced measurable decrements in the magnitude of associations between baseline cognitive status and mortality, and further adjustment for indicators of physical and mental health caused the most marked attenuations. However, it is unclear whether health-related variables are confounders or intermediates in the pathway(s) between cognitive impairment and mortality. For example, an elevated level of depressive symptoms appears to be a consequence rather than a cause of cognitive deterioration in this cohort (55); physical functional decline also has been shown to result from cognitive difficulties (56). Because the possibility of overcontrolling cannot be excluded, our fully adjusted models may have underestimated the adverse effect of cognitive dysfunction on mortality.

Few previous population-based investigations have examined the cognition-mortality relation among very aged persons. However, our results are consistent with a report by Bruce et al. (37); in a 9-year follow-up of middle-aged and elderly participants in the New Haven Epidemiologic Catchment Area Study, these authors found that the adverse effect of cognitive impairment weakened with advancing age. (There was no respondent overlap between that study and ours.) On the other hand, Johansson et al. (34, 57) reported that mild impairment predicted reduced 2-year survival in a sample of Swedish octogenarians, but analyses were not adjusted for age or other potential confounders.

For several reasons, cognitive dysfunction may have had less prognostic significance among older versus younger respondents in our sample. In very old people, cognitive performance may be more susceptible to random variation regardless of true underlying cognitive capacity. That is, scores for aged persons may be influenced more by external factors such as motivation, sleep deprivation, transient sensory or motor difficulties, or hour of testing than those of their younger counterparts. The resulting measurement error may
differentially attenuate the cognition-mortality relation at older ages. Another possible explanation is that whereas some true diminution in cognitive capacity is nearly universal in the extremely old (58, 59), cognitive decline in younger persons occurs less commonly and may be linked more closely to an underlying disease that carries an increased mortality risk (37, 60). Although control for multiple indicators of incident disease (including physician-diagnosed stroke, diabetes, myocardial infarction, and cancer) did not eliminate the observed association between cognitive decline and mortality in this age group, our health measures are imperfect or incomplete reflections of covert (or manifest but undiagnosed) health problems. Adjustment for more precise and/or detailed indicators of disease status than are available in the data set (e.g., illness severity) would be desirable to reduce the likelihood of residual confounding.

No discussion of potential differences in the etiology of cognitive impairment between the young and old respondents in our sample would be complete without mention of Alzheimer’s disease, which accounts for at least 50 percent of dementia cases among the US elderly (61). The incidence of Alzheimer’s disease rises sharply with age (62). It is therefore likely that this disease is responsible for a significantly higher percentage of the observed cognitive dysfunction among older than among younger respondents. (In a recent population-based sample of elderly Australians, Korten et al. (59) reported that a low MMSE score was a much stronger predictor of incident dementia among persons aged 85 years or more than among those aged 70–84 years.) Evidence from a 5-year follow-up of a subsample of respondents from the East Boston Established Populations for Epidemiologic Studies of the Elderly site (19) suggests that the elevation in mortality risk associated with Alzheimer’s disease, which has an insidious onset and gradual course, is confined primarily to late-stage disease (i.e., when severe cognitive impairment and/or cachexia are present). Thus, the relation between early-stage Alzheimer’s disease, as manifested by, say, a decline from a high MMSE score to one in the low normal or mild impairment range, and mortality would not become evident until the disease had progressed to a severe state. This is consistent with the pattern of associations observed among the very elderly in our sample—that is, only severe impairment (or declines to severe impairment) was significantly related to mortality in this age group.

It is also possible that observed differences in the effects of cognitive impairment between younger and older subgroups may be due to the fact that octo- and nonagenarians represent a hardy survivor cohort able to adapt successfully to mild cognitive deficits. Yet another explanation is that the death rate for those aged more than 80 years is much higher than that for their younger counterparts, rendering it more difficult to detect an association between cognitive impairment and mortality in the older age group. Moreover, while one advantage of using rate rather than risk measures to quantify epidemiologic associations is to circumvent the problem of competing risks, it is conceivable that noncognitive causes of death (e.g., pneumonia) are more virulent in the very elderly than is, for example, Alzheimer’s disease. Thus, the difficulty of detecting an association between cognitive impairment and mortality in the presence of other competing causes of death is reduced but not entirely eliminated by using rate rather than risk measures.

Although cognitive declines are likely to be symptomatic of either dementia or other nonbrain systemic pathologies that increase mortality risk, it also has been postulated that cognitive impairment itself may play a causal role in promoting death. Poor cognitive function of either long-standing or recent origin may interfere with the ability to recognize signs and symptoms of disease, to seek timely medical assistance, to adhere to a medication regimen, to prepare adequate meals, and to engage in other preventive health care behaviors (30, 31, 54). To the extent that this is true, the observed lack of an association between prevalent mild impairment and mortality (tables 6–9) is somewhat puzzling. However, it is possible that the health care needs of persons with prevalent (as opposed to incident) cognitive impairment may have been managed more effectively by family or other caregivers who were long aware of the need for such intervention, thus forestalling an adverse outcome.

In conclusion, the data from this population-based longitudinal study indicate that even small declines in cognitive function are significantly associated with subsequent mortality among the community-dwelling elderly. Our findings suggest that periodic screening for cognitive impairment among older patients is warranted. Establishment of a baseline level of cognitive performance in the medical record should enhance the ability to detect subsequent cognitive declines. Especially in the young elderly, such declines should alert health care providers and other caregivers to the possibility of an underlying illness and to explore potential interventions to reduce mortality risk.

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REFERENCES


45. Mantel N. Evaluation of survival data and two new rank-order


