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Cognitive Impairment and Mortality in the Cardiovascular Health Study

Robert M. Shavelle, PhD, FAACPDM; David R. Paculdo, MPH; David J. Strauss, PhD, FASA; Scott J. Kush, MD, MPH

Cognitive impairment is associated with increased mortality, depending on the severity of impairment. We analyzed data from the Cardiovascular Health Study (CHS), using Cox proportional hazards regression models to quantify the effect of the impairment. After adjustment for age, sex, and medical risk factors, we found the resulting relative risks to range from 1.19 for mild impairment to 1.98 for severe.

Address: Life Expectancy Project, 1439 – 17th Avenue, San Francisco, CA 94122-3402; ph: 415-731-0240; Shavelle@LifeExpectancy.org.

Correspondent: Dr. Robert M. Shavelle.

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INTRODUCTION

Cognitive impairment and deficits in cognitive function are associated with increased mortality.[1–9] In part, this is because the impairment is in some cases a marker for serious medical conditions, such as cerebrovascular disease, atherosclerosis, diastolic hypertension, and vitamin C deficiency.[2] It may also signal the onset of Alzheimer's disease or other forms of dementia. Further reasons are that (1) cognitive impairment is a predictor of functional status,[13] especially motor function, which itself is known to affect mortality,[4] and (2) it may be a risk factor by itself, being associated with poor self-care and increased risk of accidents.[14,15]

Cognitive impairment is also associated with aging. As advances in medicine lead to longer life expectancies and thus an increasingly aging population, cognitive impairment may become a proportionally more significant factor in underwriting.

Our goals here are to quantify the association of cognitive impairment with mortality (1) in a broad population after adjustment for age, sex, race, and other medical risk factors, and (2) in an otherwise healthy sub-population after adjustment only for age, sex, and race.

MATERIALS AND METHODS

Study Population

The data are from the non-commercial limited-access data set of the Cardiovascular Health Study (CHS).[16] The CHS was designed to study the risk factors associated with the development and progression of coronary heart disease and stroke in people aged 65 years and older. There were 5888 persons in total during the study years from 1989 through 1999, comprising 5201 Caucasian participants in 1989 and a subsequent sample of 687 African-Americans in 1992. Study participants were recruited from 4 communities in the United States and underwent extensive clinic examinations for evaluation of markers of sub-clinical cardiovascular disease. These participants were sampled from Medicare eligibility lists. Those eligible were: 65 years or older at the time of examination; non-institutionalized; expected to remain in the area for the next 3 years; able to give informed consent; and did not require a proxy respondent at baseline. Potentially eligible individuals who were wheelchair-bound in the home at baseline or were receiving hospice treatment, radiation therapy or chemotherapy for cancer were excluded. Of the 5888 total persons, 93 declined to have their information shared in the non-commercial limited-access data set, leaving a total of 5795 persons.

Variable Definition

Cognitive impairment was determined using the 30-point Mini-Mental State Examination (MMSE). The MMSE is a widely used test of cognitive function among the elderly, and includes tests of orientation, registration, attention, calculation, recall, language and visual-spatial skills. Severe impairment is defined as a score of 0 to 17, moderate impairment a score of 18 to 23, mild impairment a score of 24 to 26, and normal a score of 27 or greater, as defined by the CHS study protocols.

Healthy Group

As noted at the outset, our second goal was to determine the effect of cognitive impairment on an otherwise healthy subpopulation. We defined this group in CHS to be persons who (1) never smoked, (2) were not overweight (body mass index less than 25), and (3) did not have a history of any of the medical conditions specified in Table 1 (other than, of course, some level of cognitive impairment).

Statistical Analyses

Analyses were performed using the statistical package SAS 9.1 for Windows.[17] Cox proportional hazards regression models[18] were developed using the ''PROC PHREG'' procedure in SAS.

We constructed 6 models. All 6 included adjustments for age, sex, race, and cognitive impairment. We used 2 different variables to account for cognitive impairment: (1) a single yes/no variable, indicating at least mild impairment, and (2) the 3 levels of impairment defined above (mild, moderate, and severe).

Two of the 6 models were further adjusted for smoking status, BMI, and the medical conditions specified in Table 1. The 6 models and the data they analyze are:

1. Model 1: Based on all data (n=5795; 2086 deaths), with terms for age, sex, race, and cognitive impairment (y/n).
2. Model 2: Based on all data (n=5795; 2086 deaths), with terms for age, sex, race, and cognitive levels (mild/moderate/severe).
3. Model 3: Based on all data (n=5795; 2086 deaths), with terms for age, sex, race, cognitive impairment (y/n), and all conditions in Table 1.
4. Model 4: Based on all data (n=5795; 2086 deaths), with terms for age, sex, race, cognitive levels (mild/moderate/severe) and all the medical conditions listed in Table 1.
5. Model 5: Based on data from ''healthy persons'' – those without any of the

Table 1. Characteristics of the CHS Population

	All	Cognitive Impairment Mild	Moderate	Severe
Sample size (n)	5795	893	386	73
Deaths	2086	395	203	49
Age, years	73±6	75±6	77±7	79±7
Male	43	47	47	59
White	84	70	58	36
College Education	43	28	13	3
Smoker	12	13	14	15
Former Smoker	41	38	34	32
Body Mass Index (BMI)	27±4	27±4	27±4	26±4
Overweight ($25 \leq BMI < 30$)	41	41	40	30
Obese ($BMI \geq 30$)	20	22	23	15
Percentage of persons with a history of the following medical conditions:				
Diabetes Mellitus	16	19	20	29
Hypertension	45	51	53	52
Coronary Heart Disease	19	24	22	16
Chronic Obstructive Pulmonary Disease	27	25	22	21
Congestive Heart Failure	5	7	9	10
Stroke / Cerebrovascular Accident	4	7	9	12
Transient Ischemic Attack	3	4	3	7
Intermittent Claudication	3	3	4	1
Cancer	14	11	11	3
Aneurysm	1	1	1	1
Atrial Fibrillation	4	4	3	0
Depression	22	27	33	36
Left Ventricular Hypertrophy	5	7	8	8
Chronic Renal Insufficiency	12	16	16	25

Sample size (n) and deaths are the observed frequencies. Age and body mass index are reported as the mean ± standard deviation. All other figures are column percentages.

medical conditions listed in Table 1 (n=154; 38 deaths) – with terms for age, sex, race, and cognitive impairment (y/n).

6. Model 6: Based on data from ''healthy persons'' – those without any of the medical conditions listed in Table 1 (n=154; 38 deaths) – with terms for age, sex, race, and cognitive levels (mild/moderate/severe).

Each model was then used to compute the 10-year mortality rates for a Caucasian male, 65 to 69 years old, who is a ''never smoker'' and is without any cognitive impairment or other medical condition. These are the ''baseline mortality rates'' provided by the models, and are given to allow comparisons to other sets of mortality rates. Because the models controlled for sex, it was not necessary to compute a sex-blended mortality rate.

RESULTS

Table 1 shows the demographic and medical breakdown of the CHS database. The average age of persons in the database was 73, and the more cognitively impaired groups tended to be older. Also, the more cognitively impaired groups had more males and fewer Caucasians, and tended to include persons with less education. For example, only 3% of the severely impaired had a

Table 2. Relative Risk of Death for Persons with Any Cognitive Impairment (Y/N) [Stratified by the severity of impairment (mild, moderate, or severe). Figures in parentheses are the associated 95% confidence interval for each estimated relative risk.]

	Model[a]					
Factor in the model	1	2	3	4	5	6
Cognitive Impairment (Y/N)	1.42 (1.28–1.57)	–	1.30 (1.17–1.44)	–	2.80 (1.34–5.85)	–
Mild Cognitive Impairment	–	1.31 (1.17–1.47)	–	1.19 (1.06–1.34)	–	2.01 (0.82–4.94)
Moderate Cognitive Impairment	–	1.59 (1.36–1.86)	–	1.50 (1.28–1.76)	–	5.25 (1.98–13.95)
Severe Cognitive Impairment	–	2.40 (1.78–3.23)	–	1.98 (1.47–2.68)	–	–[b]
Baseline Mortality Rate[c]	0.0273	0.0275	0.0156	0.0157	0.0077	0.0081
Excess Death Rate (EDR)[d]	0.0115	–	0.0047	–	0.0139	–

[a] For description of the models and data, see the text.

[b] There were no healthy persons with severe cognitive impairment.

[c] The baseline mortality rate is the 10-year annualized model-computed rate (deaths per person-year) for 65- to 69-year-old Caucasian males with no medical conditions and no cognitive impairment. That is, we used the model to compute the associated 10-year survival for the specified group, then found the associated 10-year annualized mortality rate. Because Models 1 and 2 did not control for any medical conditions, the associated baseline rates are higher than those of Models 3 and 4. Similarly, because Models 5 and 6 were based on data from persons with no medical conditions, it is not surprising that the baseline rates are lower than those of Models 3 and 4.

[d] The excess death rate (EDR; deaths per person-year) for cognitive impairment suggested by the respective model is 1 less than the estimate relative risk (that is, RR − 1) times the baseline mortality rate. For Model 1 it is computed as $(1.42-1)*0.0273 = 0.0115$.

college education, compared with 13% of the moderately impaired, 28% of the mildly impaired, and 43% overall.

Persons in the most severe cognitive impairment group appeared to suffer more from diabetes, congestive heart failure, stroke/TIA (transient ischemic attack), depression, and chronic renal insufficiency than the other groups. But most of the differences were not dramatic.

The healthy subset defined here contained 154 persons. It was rather different from the entire CHS database. The group had fewer males (29% vs 43%), more Caucasians (94% vs 84%), and more who were highly educated (48% vs 43%), but the average age was the same in both groups (73 years). In addition, it turned out that there were no persons with severe cognitive impairment within the healthy subset.

Table 2 shows the relative risk (RR) of mortality for persons with cognitive impairment. In Models 1 and 2, based on the entire database, adjustments were made only for age, sex, and race, in addition to cognitive impairment.

Models 3 and 4, also on the entire database, were further adjusted for smoking history, BMI, and all the medical conditions specified in Table 1. Models 5 and 6 were based on the healthy subset of 154 persons, and included adjustment for age, sex, and race, in addition to cognitive impairment.

As can be seen by comparing Models 1 and 3, the RR of mortality for persons with cognitive impairment decreased from 1.42 to 1.30 once the other factors (medical conditions) were taken into account. The finding that the RR for a given factor becomes smaller once additional factors are considered is typical of mortality studies. This is because cognitive impairment is correlated with those other factors. The same pattern is observed in comparing Models 2 and 4.

The overall RR of mortality for any cognitive impairment in Model 1 (1.42) is, as expected, within the range of the severity-specific RRs of Model 2 (1.31, 1.59, and 2.40). The same is observed in comparing the RRs of Models 3 (1.30) and 4 (1.19, 1.50, 1.98), and the RRs of Model 5 (2.80) and 6 (2.01, 5.25).

Table 2 also reports the baseline mortality rate for each model, along with the imputed excess death rate (EDR). As can be seen, the RRs are higher in Models 5 and 6 (2.80, 2.01, and 5.25) than in Models 1–4. But the 95% confidence intervals are very wide, reflecting the small sample size. Thus, these narrow results may be due to random error, rather than a reflection of a true increased risk of this magnitude.

DISCUSSION

We have seen that cognitive impairment is associated with increased mortality, and that the effect is correlated with the severity of impairment. The adjusted effects range from a relative risk of 1.19 in the mild case to 1.50 in the moderate and 1.98 in the severe.

These figures are consistent with, and expand upon, recent literature on the topic. For example:

- Arfken et al (1999),[1] in a study of medically ill adults aged 60 and over who were admitted to a rehabilitation hospital, and followed for 1 year, reported an adjusted odds ratio of 2.13 for mortality in severe cognitive impairment, after controlling for sex and depression. Given these 3 factors, others (such as age, race, education, ADLs, etiology of hospitalization, and Charleston index [a measure of the burden of medical illness]) were not statistically significant.
- Gale et al (1996)[2] undertook a 20-year follow-up of UK residents aged 65 and older. Cognitive impairment, as defined by a score of 7 or less on the Hodkinson mental test, was associated with an adjusted relative risk of 2.0, after controlling for age, sex, blood pressure, vitamin C intake, and diagnosis of cardiovascular disease.
- Langa et al (2008)[3] studied Health and Retirement Survey (HRS) data from 2002. They reported a hazard ratio for mortality in moderate/severe cognitive impairment of 3.11 after adjusting only for age and sex, and 1.88 after adjusting for age, race, sex, net worth, education, potential caregiver network, chronic conditions, and smoking.
- McGuire et al (2006)[4] examined the effect of deficits in cognitive functioning in diabetes. The authors excluded persons with any significant cognitive impairment, focussing instead on persons with very mild cognitive disabilities. They controlled for age, sex, race, marital status, educational level, duration of diabetes, cardiovascular disease, and self-rated health. They found that deficits in cognitive functioning were associated with increased mortality and disability, and noted a graded relationship therein, but did not report further details.
- Stump et al (2001)[5] reported an adjusted hazard ratio of 1.70 for mortality in moderate to severe cognitive impairment, after controlling for demographics (age, sex, race, and education) and 16 co-morbid health conditions (including diabetes, coronary artery disease, smoking, and cancer).
- Kelman et al (1994)[13] studied 1855 community residents age 65 and older who were participants in a longitudinal study of aging and health. The authors used the MMSE to assess cognitive function at baseline. After adjusting for age, gender, income, problems in daily activities, fair/poor self-assessed health, and social support, the relative risks for mortality in mild and severe impairment were 1.5 (95% ci: 1.12–1.82) and 2.2 (1.13–2.69), respectively.
- Dewey et al (2001)[14] identified 23 studies of cognitive impairment that provided information on the size of the mortality

effect. They reported that in the 11 studies that stratified by the severity of impairment, 10 showed an increase in mortality risk with increasing impairment.

- Lievre et al (2008)[15] analyzed data from a US nationally representative study of 7138 persons aged 70 and older. In their Figure 4, they plot mortality rates by age, education, and cognitive impairment. The effect of impairment was greater for those with higher educational attainment and did not appear to vary significantly with age.
- Most recently in this *Journal*, Vecchione and Golus (2007)[6] reported on data from 1995–2006 acquired from a long-term care insurance company. The company used the 10 delayed word recall (DWR) test in their underwriting, and the authors used the same test to define cognitive impairment. They stratified results by age, sex, and smoking status. Scores of 0–5 on the DWR test were associated with mortality ratios of 175% to 200% in persons aged 75 and older at time of underwriting, and 325% in persons aged 70 to 74.

The models used here to analyze the healthy subset – Models 5 and 6 – reported higher RRs than those of Models 1 through 4. This may be partly explained by their much lower baseline mortality rate (0.0077 compared with 0.0273 and 0.0156). That is, the effect of cognitive impairment might be viewed as unrelated to the baseline rate, so that a lower baseline rate would induce a comparably higher RR. On the other hand, as noted, the confidence interval is unduly wide. It would, therefore, be prudent to place comparably less weight on these results. Nevertheless, cognitive impairment in an otherwise healthy person could indicate a serious underlying medical condition. For example, as Alzheimer's disease could not be ruled out in the ''healthy group,'' cognitive impairment might represent this very factor. At present there is no clear answer. Additional analyses of this and other databases are required.

We estimated the effect of cognitive impairment on mortality in both (1) the entire CHS database, controlling for other factors, and (2) in a healthy subset. The former might reasonably be considered applicable to the general population of the United States, while the latter a surrogate for the insurance population. If so, the relative risks given in Table 2 can be applied to these populations.

A strength of the present study is that severity-specific relative risks are reported. As noted, even a mild cognitive impairment is associated with excess risk. Many prior studies did not report on the mild group, and the moderate and severe groups were combined.

A limitation of the present study is that the CHS database did not have variables for dementia, Alzheimer's, or other mental disorders. The cognitive variable might thus serve as a marker for these conditions. If so, the relative risks reported here are confounded by these other conditions, and thus are overestimates of the effect of cognitive impairment alone.

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