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DOES COGNITIVE STATUS MODIFY THE RELATIONSHIP BETWEEN EDUCATION AND MORTALITY? EVIDENCE FROM THE CANADIAN STUDY OF HEALTH AND AGING

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Abstract:

Background. There is compelling evidence of an inverse relationship between level of education and increased mortality. In contrast to this, one study showed that among subjects with Alzheimer's Disease, those with high education are more than twice as likely to die earlier; however, this result has proven difficult to replicate. We examine the relationship between education and mortality by cognitive status using a large, nationally representative sample of elderly.

Methods. A representative sample of 10,263 people aged 65 or over from the 10 Canadian provinces participated in the Canadian Study of Health and Aging in 1991. Information about age, gender, education, and an initial screening for cognitive impairment were collected; those who screened positive for cognitive impairment were referred for a complete clinical and neuropsychological examination, from which cognitive status and clinical severity of dementia were assessed. Vital status and date of death were collected at follow-up in 1996. The analysis was conducted using survival analysis.

Findings. Cognitive status modifies the relationship between education and mortality. For those with no cognitive impairment, an inverse relationship between education and mortality exists. Elderly with cognitive impairment but no dementia, or those with dementia, are more likely to die early than the cognitively normal at baseline, but no relationship exists between education and mortality.

Interpretation. These findings do not support previous work that showed a higher risk of mortality among highly educated dementia subjects.

Keywords. Alzheimer disease, cognition, dementia, education, epidemiology, etiology, mortality

Introduction

There is compelling evidence that an inverse relationship exists between level of education and risk of increased mortality. People with more years of education have a reduced risk of death in general (1) as well as from disease-specific causes such as cardiovascular disease, cancer, and others (2;3). This pattern between education and mortality is consistent throughout the lifespan. While strongest for young and middle-aged adults (4), the association holds for mortality among children of parents with lower education (7) and among the elderly (6;4). The association is consistent across different countries and over different time periods (7;8).

An exception to the observed pattern of higher education and lower mortality has been argued to exist in subjects with dementia. One study (9) showed that highly educated subjects with Alzheimer's Disease (AD) not only did not show a reduced risk of mortality, but were actually almost twice as likely to die than those with less education over the measured 4-year period. This finding implies that dementia status modifies the effect of education on mortality. Specifically, for non-demented individuals higher education is associated with reduced mortality, while for demented subjects higher education is associated with increased mortality. The underlying mechanism of this result has been the topic of considerable discussion (6;9;10;11).

The modifying effect of dementia status on the relationship between education and mortality has not been demonstrated within the context of a single study. Two studies have tried (6;9), but have generated conflicting results. One

(9) showed higher mortality among more highly educated subjects with dementia, but no association among non-demented individuals. The other (6), in an explicit attempt to replicate these findings, showed lower mortality among more highly educated non-demented individuals, but no relationship among demented subjects. The relative analytical power of both studies has been cited to explain the apparently contradictory findings. The first study involved a relatively large sample of demented subjects (n=246), but a small control group of non-demented individuals (n=292) relative to other studies in the literature. In contrast, the second had a large sample of non-demented individuals (n=4022), but relatively few dementia subjects (n=66). A single study with large numbers of both demented and non-demented individuals is required to address the question of how dementia status modifies the effect of education on mortality.

While many studies have compared subjects with dementia to non-demented elderly, relatively few have examined intermediate stages of cognitive decline (12). Recent attention has focused on clinically identifiable cognitive impairment, which does not meet criteria for dementia (13). Cognitive impairment, no dementia (CIND) has been shown to be at least twice as prevalent as dementia at ages over 65, and is associated with more functional impairment and institutionalization than with healthy elderly (14). As research into methods of slowing the progression of dementia focuses attention on early detection, knowledge about CIND and its correlates becomes more important (14). Indeed, the nature of early stages of cognitive decline has been identified by the Lancet as one of the key epidemiological questions in the study of the dementias (15).

It is an open question whether education is also associated with mortality among subjects with CIND. To an extent, the answer to this question hinges on the nature of CIND itself (15). If CIND amounts to the early stages of progressive dementia, as indicated by the finding that nearly half of subjects with CIND progress to dementia over a five-year period (16), one might expect a similar relationship between education and mortality as with dementia subjects. Such an effect might be smaller than for dementia subjects, given that CIND subjects are less far along the progression of cognitive decline than dementia subjects. If CIND is best considered an extension of the healthy aging process (12) , one might expect the association between education and mortality to mimic that of non-demented people. If CIND amounts to a heterogeneous diagnosis that includes some who progress to dementia and others who do not, one may expect no relationship between education and mortality.

The current study will examine the relationship between education and mortality in light of the spectrum of cognitive decline ranging from no cognitive impairment (NCI), through CIND, to dementia. This study is the first to examine this issue within the context of a single population-based study involving large numbers from each of these three groups.

Methods

The methods employed in the first phase of the Canadian Study of Health and Aging (CSHA-1), conducted in 1991, are described in detail elsewhere (17;18). In brief, representative samples of people aged 65 or over from 36 urban and surrounding rural areas in the 10 Canadian provinces completed an initial screening interview. As part of this interview, participants were screened for cognitive impairment using the Modified Mini-Mental State Examination (3MS) (19). Those who screened positive for cognitive impairment (i.e. scored < 78 on the 3MS), as well as a random sample of those who screened negative, were referred for a complete clinical and neuropsychological examination, where a diagnosis of dementia could occur. In all, 10,263 people participated in the study, including 9008 from the community and 1255 from institutions. Of the 10,263 in the original CSHA-1 sample, 248 were excluded from the current analysis because they lacked education information. An additional 334 were excluded because they did not have reliable information on time of death or vital status, leaving a sample of 9681 for the current analyses.

Diagnostic decisions about dementia and CIND were carried out on the basis of information collected in the clinical examination. This four to five hour examination included an initial interview by a nurse, a neuropsychological exam by a psychometrician, physical and neurological exams by a physician, and a series of hematological and biochemical tests (17). Diagnoses of Alzheimer's Disease were made according to NINCDS-ADRDA criteria (20), while diagnoses of vascular dementia was made according to ICD-10 criteria (21). When a

diagnosis of dementia was made, it was categorized as mild, moderate, or severe, as indicated by guidelines in the DSM-III-R (22). Diagnoses of CIND were made when a clinical diagnosis of dementia was excluded, but there was evidence of one or more types of cognitive impairment, including delirium, chronic alcohol and drug abuse, depression, psychiatric illness, mental retardation, circumscribed memory impairment, and unclassified other impairments (14). Of the 9681 included in the current analyses, 918 were diagnosed with dementia, 812 with CIND, and 7951 were considered to be cognitively normal.

The original participants were followed up in 1996. Those who had been diagnosed with dementia at CSHA-1 were re-examined to study the progression of the disease, while all other survivors proceeded through a screening and referral process as in CSHA-1 (18). The primary outcome for the present study was time to death. Information about those who had died between 1991 and 1996 was collected from two sources. First, both the date and cause of death were obtained from the Provincial Registrars of Vital Statistics. In addition, a relative or other informant was interviewed to assess the decedent's health and cognitive status three months before their death. In cases in which vital statistics data about the decedent were not available, this information was taken from the decedent questionnaire.

The predictors of mortality in this study included cognitive status (NCI, CIND, dementia), severity of dementia (mild, moderate, severe), education, gender, and age. Cognitive status and severity of dementia were determined according to the criteria used at CSHA-1 (discussed above). The other

demographic variables were collected at the time of the initial screening interview. Age (at time of initial contact, CSHA-1) was categorized into three groups: 65-74 years, 75 - 84 years, and 85 years and over. We also categorized years of education into three categories: less than 8 years, 8-12 years, and more than 12 years. We chose to trichotomize education because while studies with smaller samples generally dichotomize into less than 8 and 8 or more years of education (2;23), evidence suggests that effects of education on mortality may be more pronounced at higher levels of education (24). This 3-level categorization of education has been employed in other large-scale studies (25).

Analysis

Initial descriptive analyses took the form of cross-tabulations and correlations between all relevant variables. Analysis of the relationship between education and mortality and whether it differs by cognitive status, was carried out through survival analysis and Cox proportional hazards regression. Time to death was measured in months from the beginning of the study (February 1991). Those still alive at the end of follow-up (December 1996) were treated as censored observations. All variables to be included in the model were tested against the proportional hazards assumption by the graphics test (26). None violated this assumption. Variables included in the model were added in 3 steps. Model 1 consisted of only the demographic variables of age and gender. Model 2 added education and cognitive status, while Model 3 also included the interaction between education and cognitive status. At each step, a log likelihood χ^2 test

indicated whether the addition of the new variables to the model contributed significantly to the explanatory power of the model.

We further examined the extent to which cognitive status modifies the relationship between education and mortality by calculating hazard ratios for eight separate groups differing by cognitive status and education, in comparison to a single reference category (high education, no cognitive impairment). This method provides a clear comparison of the risk of mortality among different subgroups of the sample, within the context of a single analysis. Significance of between-group differences was determined by overlap of the 95% confidence intervals.

Finally, we conducted further analysis on a subsample of dementia subjects for whom the diagnosis was possible or probable AD. A Cox regression entering age, gender, and education into the equation allowed us to evaluate if a relationship exists between education and mortality in this subsample of AD-diagnosed individuals. We then added clinical severity of the dementia to the model as a covariate to examine whether it changes the observed association between education and mortality.

Results

Table 1 describes the distribution of the total sample and those who died according to age, gender, education and cognitive status. Of this sample of 9681, 2719 had died by the time of follow-up, for an overall mortality rate of 28.1%. Mortality was more common among the higher age groups ($\chi^2_{(1)} = 1025.2$, $p < .001$), among males ($\chi^2_{(1)} = 31.5$, $p < .001$), among those with lower levels of education ($\chi^2_{(1)} = 100.3$, $p < .001$), and among those with increasing cognitive impairment ($\chi^2_{(1)} = 1204.1$, $p < .001$).

Table 2 describes the associations between cognitive status and each of the other three predictors. Results show a significant association between cognitive status and age group $\chi^2_{(4)} = 903.4$, $p < .001$. Further analysis shows that people in the CIND category were older than those in the NCI group, $\chi^2_{(1)} = 301.5$, $p < .001$, while those in the dementia category were even older than those in the CIND group $\chi^2_{(1)} = 28.78$, $p < .001$. Results also show a significant association with gender $\chi^2_{(2)} = 24.0$, $p < .001$. Further analysis shows that while the NCI group does not differ from CIND $\chi^2_{(2)} = 0.63$, $p < .85$, people in the dementia group are more likely to be female than in either of the other groups (vs. NCI: $\chi^2_{(2)} = 24.48$, $p < .001$; vs. CIND: $\chi^2_{(2)} = 8.98$, $p < .005$). Finally, there was a significant association with education $\chi^2_{(4)} = 327.9$, $p < .001$. Further analysis shows that the NCI group were more highly educated than either the CIND group ($\chi^2_{(2)} = 193.64$, $p < .001$) or the dementia group ($\chi^2_{(2)} = 166.12$, $p < .001$), while the latter two groups did not differ on education $\chi^2_{(2)} = 3.98$, $p = 0.27$.

Table 3 describes the hazard ratios (HR) and 95% confidence intervals associated with three proportional hazards models. The first of these models includes only the demographic characteristics of age and gender in the model, while the second adds education and cognitive status. The final model includes the interaction between education and cognitive status. Both demographic factors of age and gender were significant predictors of time to mortality, as indicated in Model 1. Those in the 75-84 year old category were more than twice as likely to die than the 65-74 year age group (HR = 2.39, CI 2.16 - 2.64), while the 85+ age group was more likely to die than either of the other groups (HR = 5.76, CI 5.18 - 6.40). Gender was significantly associated with mortality, with males being more likely to die than females (HR = 1.49, CI 1.38 - 1.61). These factors remained significant with the addition of the other factors into later models.

Both education and cognitive status were associated with mortality, as indicated in Model 2. Both low education (HR = 1.18, CI 1.06 -1.32) and medium education (HR = 1.17, CI 1.05 - 1.31) participants were more likely to die than high education participants, and did not differ from one another. Cognitive status was also highly related to mortality, with those with CIND being approximately twice as likely to die as NCIs (HR = 2.01, CI 1.80 - 2.26), and those with dementia being more than three times more likely to die (HR = 3.57, CI 3.24 - 3.94).

The primary objective of this analysis was to examine whether cognitive status modifies the relationship between education and mortality. A significant interaction between education and cognitive status in Table 3 shows this to be true (Wald statistic = 12.87, p = .012). Table 4 clarifies this interaction by

comparing the mortality hazard of eight subgroups to a single reference category (high education, NCI). Among those with no cognitive impairment, those in the low and medium education categories were more likely to die than the reference category. People with CIND were more than twice as likely to die than the reference category; however, this risk did not vary with education. Similarly, subjects with dementia were more than four times more likely to die than the reference category; however, risk did not vary significantly with education.

The data reported in Tables 3 and 4 therefore show evidence that cognitive status modifies the relationship between education and mortality. This stems from a significant inverse relationship between education and mortality for NCI subjects (lower education, increased mortality), but no significant relationship between education and mortality among subjects with CIND or dementia. Our data do not show a positive association between education and mortality for subjects with dementia, a result at odds with previous findings (9). We wondered whether differences in sample characteristics might explain these conflicting results. To more closely mimic previous work, we conducted an analysis on a sub-sample of subjects with AD, and explicitly evaluated the importance of severity of dementia in modifying the relationship between education and mortality. Table 5 shows the results of this analysis. Of the 918 individuals in our sample diagnosed with dementia, a total of 591 had possible or probable AD. Eight of these lacked information on clinical severity of dementia, leaving a sample of 583 to be included in the analysis. For this sample of AD subjects, there remained no significant relationship between education and mortality. This

remained true even when severity of the dementia was included in the model. As with previous analyses, we could find no evidence of a positive association between education and mortality for subjects with dementia.

Discussion

Data from the current study show that cognitive status modifies the relationship between education and mortality. Our data support the findings of Geerlings et al. (6) in showing that for elderly with no cognitive impairment, higher education is associated with lower mortality, while among cognitively impaired elderly, there is no association between education and mortality. The findings do not support those of Stern et al. (9), who reported higher mortality among demented elderly with higher education.

Reserve Hypothesis

Stern's finding of higher mortality among more highly educated subjects with AD was surprising in light of the literature that typically shows a benefit for higher education. Stern employed the "reserve hypothesis" to explain the effect. This hypothesis argues that people with higher education are able, either through physiological (10) or cognitive (9;23) means, to delay the clinical expression of dementia. In the case of AD, the underlying pathology associated with the disease is likely to progress despite the subject's ability to delay or prevent its clinical expression. Stern et al. (9) argued that subjects with higher education are likely to have more advanced pathology by the time they are clinically diagnosed with dementia, and consequently will die sooner after diagnosis. In essence, the reserve hypothesis states that subjects with higher education are closer to death by the time they are diagnosed.

Prior to the current work, the only two studies to have tested this prediction of the reserve hypothesis yielded conflicting findings. These contradictory

findings may have stemmed from methodological or sample differences. Indeed, a number of such differences have been cited to explain these findings (9;6;11). First, dementia subjects in the Geerlings study were younger than those in the latter (mean age 78.9 years vs. 83.9 years), and were limited to non-institutionalized elderly, while the Stern study examined both those in and outside of institutions. The age difference may also have meant that the Geerlings sample was limited to relatively mild cases of dementia, reducing any effect of more severe cases on the data (11). Alternatively, the findings of the Stern study (9) may have stemmed from selective mortality, in which the less educated members of the sample die at relatively young ages, leaving only a subsample of healthy, lesser educated people who tend to outlive a more heterogeneous sub-sample of more highly educated people. These selection issues might also explain why this study failed to find an association between education and mortality for healthy individuals (6).

Second, lack of power of the analyses may have contributed to the different conclusions. As discussed earlier, the Geerlings study had a relatively large non-demented sample, while the Stern study had a relatively large sample of dementia subjects. Stern (11) argued that the effect size for the non-dementia subjects was similar in size for the two studies, but was non-significant in the Stern study because of lack of power. Indeed, it may be that both the association between education and mortality among healthy individuals and the opposite relationship among demented individuals are both small effects that require large samples to be statistically significant.

Finally, it has been argued that knowledge of the cause of death is critical to obtaining the finding of increased mortality among dementia subjects with higher education. Stern (11) argues that “using time of death as a test of the reserve hypothesis assumes that there is a relation between death and the severity of AD pathology, and that subjects die of AD." (p 1238). While this argument is not made in detail, presumably it would proceed as follows. Given that risks for death from non-AD causes are more highly associated with lower (rather than higher) education, any measure of mortality that includes deaths from these causes will tend to push the survival curves of people with high and low education together, resulting in a reduced likelihood of finding a difference in mortality between the two groups. If the Geerlings study somehow violated this assumption (and the Stern study had not) it might explain the conflicting results. However, AD is rarely cited as the underlying cause of death on death certificates. Indeed, Stern (9) reports only one subject out of 39 (~2%) for which they had cause of death information cited AD as the cause. In our case, 21 out of 655 (~3%) of our demented cohort who died had AD listed as the primary cause. Data as to whether AD was the cause of death is therefore not available in any of the studies, so all must deal with the additional variance stemming from non AD-related deaths. It therefore seems unlikely that this variance would account for the different findings among the studies in question.

It is possible that sample differences could explain our failure to replicate the findings of the Stern study. The most obvious difference between the two samples is that while the current study included all forms of dementia, the Stern

study included only subjects with AD. No justification for expecting these findings to be limited to AD has been offered in the literature. Indeed, there is mounting evidence of a much closer relationship between AD and vascular dementia than had previously been suspected. Evidence has shown that factors such as hypertension, coronary heart disease, and atherosclerosis, normally associated with vascular dementia, are also associated with AD (27;28). This blurring of the boundary between different forms of dementia led us to consider these issues in the context of all dementias, rather than AD in particular. However, it may have been that a heterogeneous sample including multiple forms of dementia was insensitive to the effect reported in the Stern study.

Nevertheless, we believe that such sample differences cannot explain our failure to replicate Stern's findings. First, although differing in racial composition, our sample is similar to that of the Stern study, having similar mean ages of dementia subjects (83.9 vs. our 82.6), and includes both institutionalized and non-institutionalized individuals. Second, the current study involved a nationally representative sample of people over 65, bringing a level of statistical power and representativeness unique to this literature. Most importantly, our results did not change when we limited our analyses to only those with AD, and while controlling for clinical severity of the dementia.

It should be noted that finding no association between education and mortality for subjects with dementia does not refute the reserve hypothesis. Physiological evidence suggests that when matched for clinical severity of AD, subjects with greater education or occupational attainment show greater

progression of the disease than do those with less (9;29) . The current data speak only to the prediction that more highly educated people will die sooner post-diagnosis than those with less education.

Our data show that subjects with cognitive impairment (CIND or dementia) differ from elderly who have no impairment in that they demonstrate no association between education and mortality. This difference between groups is not the result of age or gender differences. One explanation may stem from education differences; both groups with cognitive impairment were less educated than the NCI group (Table 2). Given that education affects mortality more at higher levels of education (24), the greater proportion of lower educated people among the cognitively impaired groups may have resulted in the non-significant association between education and mortality. Alternatively, in the face of a serious, progressive condition such as AD the mechanisms by which those with higher education are usually afforded an advantage (e.g. better nutrition) may no longer matter. Future research, perhaps in the form of a longitudinal study examining the progression of dementia, may shed light on the complex relationship between education and mortality as cognitive status changes.

CIND

The current study examined the risk of mortality among subjects with CIND. This subgroup was more than twice as likely to die over a five-year period than a baseline sample of NCI, highly educated individuals. Elderly people with CIND show no association between education and mortality.

There is debate in the literature as to what level of cognitive decline may be considered 'normal' in the elderly population. Mild cognitive decline is often viewed as an inevitable byproduct of aging, and CIND could simply reflect this normal cognitive decline. However, studies have shown that when sampling biases are controlled for, 'normal' elderly show considerable stability in cognitive function over time (12;30). In addition, evidence that approximately half of those with CIND go on to develop dementia (18) suggests that CIND might be better described as an early manifestation of a disorder, rather than normal cognitive decline. While the current study presents no conclusive data about this issue, it seems that our sample of elderly with CIND had more in common with our dementia sample than with our sample of NCI elderly. Both the CIND and dementia groups were more likely to die than the cognitively normal at baseline, even after controlling for age, gender, and education. Both the CIND and dementia groups were significantly less educated than the NCI group, while the two groups did not differ. Neither the CIND nor the dementia group showed an association between education and mortality, in contrast with our NCI group.

Implications

The question of whether education is related to mortality after diagnosis of CIND or dementia is important because it has clear implications for allocation of research resources. One might infer from the findings of Stern (9) that resources should be devoted to early detection of dementias particularly among those with high education backgrounds, given that their findings indicate this group is closer to death upon diagnosis. In contrast, the findings of the current study, along with

those of Geerlings (6), imply that once diagnosis of dementia is made, educational background is irrelevant in predicting mortality. This places priority of future research squarely on the task of early detection of dementia in general, regardless of educational background, with the goals not only of preventing mortality, but also of delaying the progression of cognitive impairment.

As research focuses attention on early detection of dementia, examination of subjects with cognitive impairment but no dementia becomes more important. Data from the CSHA provided the first conservative estimate of CIND prevalence in an elderly population (14). They showed that CIND in this sample was more than twice as prevalent as all dementias combined (16.8% vs. 8%). Seniors with CIND were more than three times more likely than cognitively unimpaired seniors to be living in institutions, while half reported some degree of functional impairment. The current study shows that people with CIND are more than twice as likely to die over a five-year period than the highly educated, cognitively normal, elderly. Clearly, CIND amounts to an important public health issue that warrants further investigation and discussion.

Table 1: Proportion of elderly who died during the 5-year follow-up period by age, gender, education, and cognitive status.

	Total (n=9681)	Dead by Follow-up (n=2719)	% Dead at Follow-up	χ^2 statistics *
Age Group				
65 - 74	4015	572	14.2	
75 - 84	4021	1215	30.2	
85+	1645	932	56.6	$\chi^2_{(1)} = 1025.2$, p<.001
Gender				
Female	5851	1522	26.0	
Male	3830	1197	31.3	$\chi^2_{(1)} = 31.5$, p<.001
Education				
Low (< 8 years)	3567	1204	33.8	
Medium (8-12 years)	4005	1053	26.3	
High (> 12 years)	2109	462	21.9	$\chi^2_{(1)} = 100.3$, p<.001
Cognitive Status				
NCI	7951	1674	21.0	
CIND	812	390	48.0	
Demented	918	655	71.4	$\chi^2_{(1)} = 1204.1$,p<.001

* For Age Group, Education, and cognitive status, χ^2 reported is test for linear trend. For gender, Pearson χ^2 is reported.

Table 2: Association between cognitive status, age, gender, and education.

	NCI	CIND	Dementia	
	n (%)	n (%)	n (%)	χ^2 statistics *
Age Group				
65 - 74	3719 (46.8)	176 (21.7)	120 (13.1)	
75 - 84	3251 (40.9)	365 (45.0)	405 (44.1)	
85+	981 (12.3)	271 (33.4)	393 (42.8)	$\chi^2_{(4)} = 903.5$, $p < .001$
Gender				
Female	4733 (59.5)	495 (61.0)	623 (67.9)	
Male	3218 (40.5)	317 (39.0)	295 (32.1)	$\chi^2_{(2)} = 24.0$, $p < .001$
Education				
Low (< 8 years)	2612 (32.9)	457 (56.3)	498 (54.2)	
Medium (8-12 years)	3433 (43.2)	273 (33.6)	299 (32.6)	
High (> 12 years)	1906 (24.0)	82 (10.1)	121 (13.2)	$\chi^2_{(4)} = 327.9$, $p < .001$
Total	**7951**	**812**	**918**	

* Pearson χ^2 reported in this table. Further analysis of the overall χ^2 reported in the text.

Table 3: Proportional Hazard model of cognitive status, education on mortality over 5 year follow-up period among elderly over 65 years. *

	Model 1		Model 2		Model 3	
	Beta (S.E.)	Hazard Ratio (95% C.I.)	Beta (S.E.)	Hazard Ratio 95% C.I.	Beta (S.E.)	Hazard Ratio 95% C.I.
Age Group						
65-74	reference	1	reference	1	reference	1
75- 84	0.72 (0.05)	2.39 (2.16-2.64)	0.74 (0.06)	2.05 (1.85-2.27)	0.72 (0.05)	2.05 (1.85-2.26)
85+	1.37 (0.05)	5.76 (5.18-6.40)	1.44 (0.07)	3.93 (3.52-4.40)	1.36 (0.06)	3.90 (3.49-4.36)
Gender						
Female	reference	1	reference	1	reference	1
Male	0.40 (0.04)	1.49 (1.38-1.61)	0.43 (0.04)	1.54 (1.43-1.66)	0.43 (0.04)	1.54 (1.43-1.67)
Education						
Low (< 8 years)			0.16 (0.06)	1.18 (1.06-1.32)	0.28 (0.07)	
Medium (8-12 years)			0.15 (0.06)	1.17 (1.05-1.31)	0.19 (0.07)	
High (> 12 years)			reference	1	reference	
Cognitive Status						
NCI			reference	1	reference	
CIND			0.70 (0.06)	2.01 (1.80-2.26)	0.80 (0.17)	
Demented			1.27 (0.05)	3.57 (3.24-3.94)	1.55 (0.12)	
Education x Cognitive Status (vs. NCI, High Education)					**Wald test of interaction (4) = 12.87, p = .012**	
Low Ed., CIND					-0.18 (0.19)	
Low Ed., Demented					-0.43 (0.14)	
Medium Ed., CIND					-0.06 (0.20)	
Medium Ed., Demented					-0.17 (0.14)	
Likelihood χ^2	χ^2 (3 df) = 1127.2 p < .001		χ^2 (4 df) = 647.7 p < .001		χ^2 (4 df) = 12.65 p = .013	

* Note: Hazard ratios for education, cognitive status, and their interaction are excluded in Model 3 because inclusion of the interaction makes these ratios difficult to interpret.

Table 4: The relationship between education and mortality by cognitive status over 5-year follow-up among elderly over 65 years. *

	NCI		CIND		Demented	
	Hazard ratio	**95% C.I.**	**Hazard ratio**	**95% C.I.**	**Hazard ratio**	**95% C.I.**
Education						
Low (< 8 years)	1.32	(1.16, 1.51)	2.47	(2.08, 2.94)	4.06	(3.48, 4.74)
Medium (8-12 years)	1.21	(1.06, 1.37)	2.54	(2.08, 3.11)	4.79	(4.03, 5.70)
High (> 12 years)	1	Reference	2.23	(1.59, 3.14)	4.72	(3.73, 5.97)

Note: Hazard ratios associated with each of the nine cells of the interaction between education and cognitive status, predicting time to mortality using Cox regression. Although age and gender were also included in this model, the analysis shows identical estimates to those of Table 3, and are not repeated here.

Table 5: Predictors of mortality during a 5 year follow-up period for a sub-sample of 583 participants diagnosed with possible or probable Alzheimer's disease

	Model 1		Model 2	
	Hazard Ratio	**95% C.I.**	**Hazard ratio**	**95% C.I.**
Age Group				
65-74	1	reference	1	reference
75-84	1.20	(0.80, 1.80)	1.33	(0.88, 2.01)
85+	2.07	(1.38, 3.09)	2.26	(1.51, 3.39)
Gender				
Female	1	reference	1	reference
Male	1.38	(1.11, .171)	1.57	(1.26, 1.96)
Education				
Low (< 8 years)	0.89	(0.66, 1.20)	0.90	(0.67, 1.22)
Medium (8-12 years)	1.06	(0.78, 1.45)	1.08	(0.79, 1.48)
High (> 12 years)	1	reference	1	reference
Clinical Severity of Dementia				
Mild			1	reference
Moderate			1.86	(1.41, 2.45)
Severe			3.06	(2.30, 4.06)

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