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RESEARCH ARTICLE

Is Educational Attainment Associated with Increased Risk of Mortality in People with Dementia? A Population-based Study

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Abstract: ***Objective:*** The association between higher education and increased mortality in Alzheimer's disease (AD) is controversial. Further it is unknown whether education predicts survival in all dementia subtypes. We assessed mortality rates and death causes of persons with dementia compared to participants without dementia.

Methods: Participants derive from the Neurological Disorders in Central Spain, a prospective population-based cohort study of older adults. We compared 269 persons with dementia to 2944 participants without dementia. We carried out Cox regression models to predict the risk of mortality dependent on the educational attainment adjusting for covariates. Reasons of death were obtained from the National Population Register.

Results: During a median follow-up of 5.4 years, 400 individuals died (171 with dementia, 229 without dementia). Among the participants with dementia, those with higher educational attainment had an increased risk of death than those with lower education; the adjusted hazard ratio (HRa) was 1.40 (95% confidence interval [CI], 1.01 to 1.94). When the analysis was restricted to patients with AD the HRa increased to 1.51 (95% CI = 1.01-2.24). By contrast, educational attainment was not associated with increased mortality among participants without dementia (HRa = 0.92, 95% CI = 0.71-1.20, p = 0.55), whereas education did not influence mortality in QD.

Conclusion: Our findings suggest that high educational attainment is associated with increased mortality risk in people with dementia. This observation implies that neuropathology is more advanced in patients with higher education at any level of clinical severity, leading these individuals to an earlier death after diagnosis.

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INTRODUCTION

Dementia and mild cognitive impairment are associated with a lower life expectancy in older adults [1-2]. However, lifetime survival in both conditions is variable, depending on different factors [3]. It is well known that higher age and clinical severity decrease the survival of people with dementia [4], but the educational level has offered controversial results. In this context, the systematic review of Paradise, Cooper & Livingston [5] concludes that no relationship exists between education and mortality in dementia because only one out of eleven high-quality studies found a significant association in which higher education predicted an earlier death. Nevertheless, only three of the eleven high-quality studies they reviewed were population-based, and they showed conflicting results [6-8].

The cognitive reserve (CR) hypothesis suggests that individuals with higher levels of education may compensate better for the neuropathology associated with Alzheimer's disease (AD) and delay the onset of symptoms [9]. Consequently, once the diagnosis is reached, people with higher education will show a higher neuropathological changes than lower educated individuals for any level of clinical severity [10, 11]. Hence, high education has been associated with faster cognitive decline [12, 13] and increased mortality in patients with

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dementia [14]. The underlying mechanism implicated in the early death of highly educated individuals with dementia has created a controversial debate [4, 14-16].

We examined whether higher educational attainment is associated with an increased mortality rate over a five-year follow-up period in a representative, population-based sample of people with dementia. Respectively, we compared the findings of this group with those obtained in individuals without dementia from the same cohort. Moreover, reasons of death were found in all individuals to understand the differential mechanisms involved in the mortality of people who differed in educational attainment. This research contributes to the understanding of risk factors for mortality in dementia, particularly education, and collaterally may improve strategies for prevention and diagnosis.

MATERIAL AND METHODS

Study Population

The Neurological Disorders in Central Spain" (NEDICES) is a population-based survey for detecting the prevalence and incidence of dementia [17, 18], and other main age-related health conditions of older adults (aged 65 years or older) in Spain [19]. All participants were selected from updated population registers in three areas of central Spain with different socio-economic status [20]: two urban communities (Lista and Margaritas) and one rural (Arévalo). Institutionalized participants (*i.e.,* nursing homes) were taken into account in each area. Detailed information about the study methods and demographic findings are mentioned elsewhere [21].

Two independent ethical standards committees on human research at the University Hospitals "12 de Octubre" (Madrid) and "La Princesa" (Madrid) approved the protocol. The study complies with the principles of the Declaration of Helsinki. Participants signed a written informed consent before their enrolment in the study.

The initial cohort evaluated at baseline (1994-1995) included 5278 participants. There were 306 (5.8%) prevalent dementia cases and 4972 (94.2%) participants without dementia. The majority of persons with dementia were of the AD subtype (N = 206, 63.2% of all demented participants). Vascular dementia together with mixed dementia cases were the second most common cause (N = 57; 18.6%), and dementia with associated parkinsonism was the third (N = 14; 3.9%). Finally, the less frequent categories were the secondary dementias with five cases (*i.e.,* those where a specific cause is found or probable such as B12 vitamin deficiency) and undetermined dementia with 24 cases (*i.e.,* clinical information was insufficient to determine the etiology). Out of 4972 individuals without dementia, 83 cases were classified as questionable dementia (analogous to the 0.5 stage of Clinical Dementia Rating) in accordance with the World Health Organization (WHO) program for ageing research [22, 23] were excluded for the analyses.

Diagnosis of Dementia

The NEDICES study was developed in two phases: door-to-door screening of eligible people (Phase 1) and neurological examination of those individuals who screened positive (Phase 2). At baseline (1994–1995), 5278 older citizens were assessed using a screening questionnaire to collect data on demographics, medical conditions and current medication. Furthermore, the presence of dementia was screened using the WHO protocol [24, 25], including a 37-item version of the Mini-Mental State Examination [26], and an eleven-item Spanish version of Pfeffer's Functional Activities Questionnaire (FAQ) [27]. A brief form of the questionnaire was mailed to individuals who refused, or were unavailable for face-to-face or telephone interviews.

Participants who screened positive for dementia underwent a full neurological examination at National Health Service clinic or in their own homes [17, 18]. The final diagnosis of dementia was subsequently made by consensus of expert neurologists according to the Diagnostic and Statistical Manual of Mental Disorders (DSM–IV; American Psychiatric Association, 2000) and different subtypes were determined according the following criteria: AD according to NINCDS-ADRDA criteria (including both possible and probable categories), vascular dementia (VaD), using DSM-IV criteria; dementia associated with Parkinson's disease (PD), dementia with Lewy bodies or longstanding Parkinsonism (more than six months); and secondary dementia. Severity of dementia was established following the Diagnostic and Statistical Manual of Mental Disorders (third edition-revised) criteria (American Psychiatric Association, 1989).

Outcome: Vital Status

In Spain, a doctor completes a death certificate on all individuals at the time of death in accordance with the recommendations of the WHO. The certificate is later sent to the local authority and the information is collected in the Spanish National Population Register, through which time and death cause were obtained. The assignment of any death cause is based on the major illness or injury which started the chain of pathological events that directly led to death (http://www.who.int/topics/mortality/en/). Using the International Classification of Diseases – ICD (9th Revision for deaths), we classified the cause of death into 6 main categories: dementia, cerebrovascular disorders, cardiovascular disorders (pulmonary embolism, congestive heart failure, myocardial infarction, heart or aortic rupture, and asystole), respiratory diseases, cancer, and other causes (infections, trauma, genitourinary or gastrointestinal disorders). Death information was censored on May 1, 1999.

Statistical Analyses

All statistical analyses were performed using SPSS, version 21.0 (IBM Corp., NY, USA). Means, standard deviations (SD) and frequencies were used to describe sociodemographic and clinical characteristics of the sample. Student's T-tests for independent samples were applied to analyze statistical differences of continuous variables, whereas chi-square test (χ^2). was used for the categorical ones. Additionally, Cox proportional-hazards models (95% confidence intervals, CIs) were carried out to estimate the relative risk of mortality at five-year follow-up in all dementia cases and the AD subtype. The predictive variable was educational attainment categorized as follows: low education (illiterates or subjects who were capable of reading and writing) vs. high

education (individuals with certificate of primary school or higher). The time variable was measured in person-years of observation, defined as the interval between the screening date at baseline evaluation (1994–1995) and the date of death censored on May 1, 1999 (five-year mortality). Several potential confounding variables known to affect survival (baseline age, gender, subtype of dementia, dementia severity and other comorbidities) were considered to adjust the models [3]. None of the regression regression models show any deviation of the proportional hazards assumption. The Charlson comorbidity index was calculated based on an adaptation of Romano, Roos & Jollis [28]; only those variables that showed a relationship with the vital status in the univariate analyses ($p < 0.10$) were entered in the adjusted models. Finally, the influence of education on mortality was also tested in a broad cohort of non-demented individuals without dementia or other neurological condition. Moreover, the distributions of causes of death were compared between these groups to avoid counterfactual inferences, that is, to rule out differential mechanisms involved in the mortality of people who differed in educational attainment.

RESULTS

All subjects with the diagnosis of dementia (N = 306) at baseline (1994-5) had available mortality information at five-year interval (May 1, 1999). Eligible participants who did not have information (*i.e.,* missing values) about educational attainment (N = 8) or dementia severity (N = 29) were excluded from further analyses. Therefore, the sample consisted of 269 persons with dementia (87.9 % of the participants with dementia); 189 of them had AD (70.3%), 56 VD (20.8%) and 24 other dementia subtypes (8.9%). Those individuals with dementia (N = 37) who were excluded did not differ from the selected sample (N = 265) with regard to age (83.3 vs. 82.5, t = 0.66, $p = 0.50$). However, the percentage of men (45.9% vs. 29.7 %, χ^2=3.94, $p < 0.05$), participants with high educational attainment (51.7% vs. 29% χ^2=16.07, p <0.01) and the non-AD dementia subtypes (54.1% vs. 29.7%, χ^2=8.74, p <0.01) was higher in the excluded sample compared to the selected individuals. Table **1** depicts the socio-demographic and clinical characteristics of the sample.

Out of 269 selected subjects, 171 (63.6%) died within five years follow-up. Deceased individuals were older (84.0 vs. 79.9, t = -4.52, p <0.001) and showed a greater dementia severity (74.3% moderate-severe *vs.* 53.1%, χ^2 = 13.89, p <0.001) compared to living subjects. In addition, the association between educational attainment and mortality showed a significant trend in the univariate analyses (χ^2 = 7.03, p = 0.07), indicating that deceased individuals had higher educational level than those who were alive at follow-up. However, no other differences emerged between these two groups in terms of sex (χ^2 = 1.32, p = 0.25), comorbidity (t = -1.20, p = 0.23) or dementia subtypes (χ^2 = 1.81, p = 0.17).

Risk of Mortality of All Demented Individuals and those with the AD Subtype

In the Cox regression model, demented people with a high educational attainment showed a higher mortality rate compared to the group with low educational attainment (HR = 1.40, 95% confidence interval [CI] = 1.01-1.94, p<0.05), after controlling the effect of age and severity of dementia. When the analysis was limited to people with AD, the mortality risk associated with a high educational attainment was slightly increased compared to the all dementia subtypes (HR = 1.51, 95% CI = 1.01-2.24, p <0.05). Figs. (**1** and **2**) show the survival curves of all individuals with dementia and those with AD respectively.

Table 1. Characteristics of participants with dementia.

	Persons with dementia (N = 269)
Age (years)	82.53±7.34
Sex (% women)	189 (70.2)
Educational Level	
Illiterates	92 (34.2)
Read-write	99 (36.8)
Primary school	58 (21.6)
Secondary school or higher	20 (7.4)
Dementia type	
Alzheimer's disease	189 (70.3)
Vascular	56 (20.8)
Parkinson's disease	14 (5.2)
Secondary	5 (1.9)
Undetermined cause	5 (1.9)
Dementia severity	
Mild	90 (33.5)
Moderate	101 (37.5)
Severe	78 (29.0)
Comorbidity index*	4.18±1.42

Numbers between parentheses are percentages.
*Adaptation of Charlson's index.

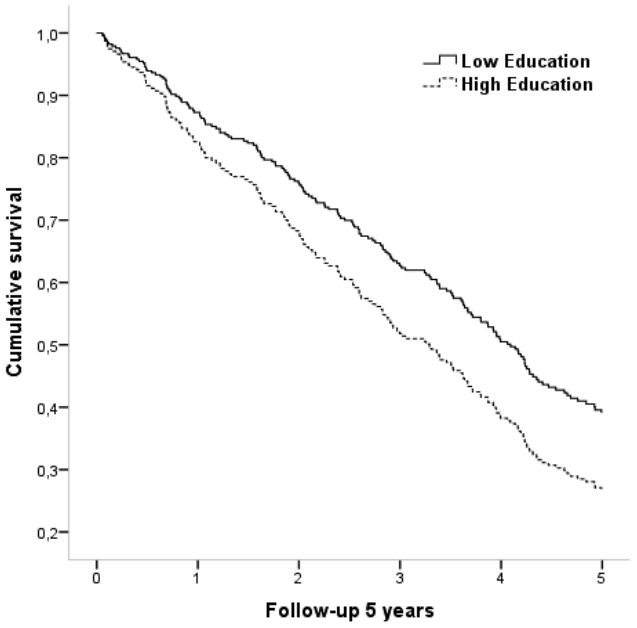

Fig. (1). Survival curve comparing demented individuals with high and low educational attainment.

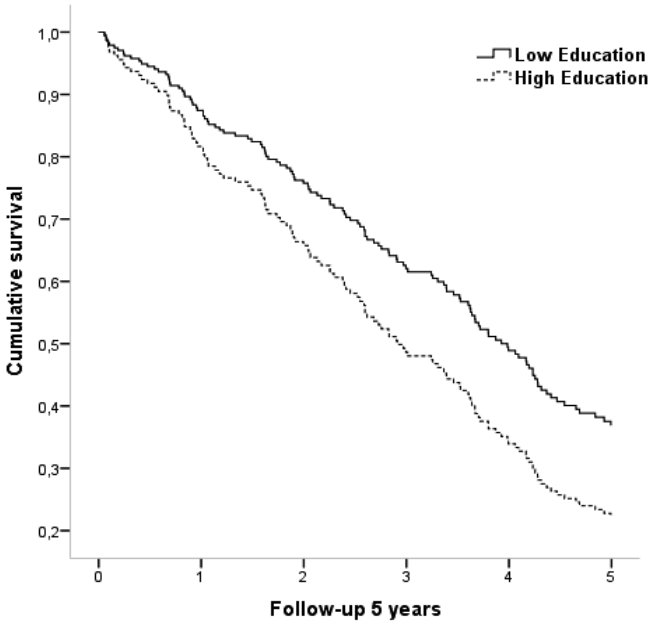

Fig. (2). Survival curve comparing Alzheimer's disease individuals with high and low educational attainment.

To rule out a possible effect of the severity of dementia, a t-student test for independent samples indicated no significant differences in terms of grade of severity between those with high vs. low educational level (t = 0.42, p = 0.66).

Primary Cause of Mortality in People with Dementia

The death causes of 171 deceased individuals with dementia are shown in Table **2**. In this regard, the distribution of mortality causes was not significantly different between high vs. low education subgroups (χ^2=1.25, p = 0.94).

People without Dementia: Group of Comparison

Out of 4889 individuals without dementia or QD at baseline, we selected for this analysis reachable subjects who did not suffered any neurological disorder (Parkinson's disease, essential tremor, stroke, dementia) at baseline or follow-up (incident cohort 1997-8). Therefore, five-year mortality risk was analysed in 2944 individuals free of dementia (mean age = 72.4 ± 5.9). There were 1690 women (57.4%), 53.2% of the population showed a low educational attainment (10.6% illiterates and 42.6% read and write) and comorbidity index was 0.93±1.13. 229 deaths (7.7%) occurred over 5 years of follow-up. Cox analyses indicated that high educational attainment was not associated with an increased risk of mortality adjusted for age, sex and comorbidity index (HR = 0.92 95% CI = 0.71-1.20, p = 0.55).

Primary Cause of Mortality in the Non-Demented Cohort

The distributions of death causes among dementia-free individuals are shown in Table **2**. Cause of death did not differ based on educational level among individuals free of dementia (χ^2 = 4.70, p = 0.45). Differences in cause of death were also tested using Yates' correction in 2 x 2 models for each group; but none of them was significant.

Table 2. Primary five-year cause of mortality by diagnostic groups.

	Free dementia cohort N (%)	Dementia N (%)
Dementia	2 (0.9)	30 (17.5)
Cerebrovascular disorders	9 (3.9)	23 (13.5)
Cardiovascular diseases	60 (26.2)	61 (35.7)
Respiratory diseases	35 (15.3)	26 (15.2)
Cancer	85 (37.1)	9 (5.3)
Other causes	38 (16.6)	22 (12.9)
Total	229 (100%)	171 (100%)

DISCUSSION

The current study found that higher educational attainment in people with dementia was associated with an increased five-year mortality rate. This outcome was significant, even after adjusting for covariates such as age and dementia severity. Our findings are consistent with the original community-based study of Stern *et al.* [14], in which a higher level of education was associated with an increased four-year mortality risk in 246 patients with probable AD. Several high quality prognostic cohort studies (level 1b) have confirmed this association [7, 29, 30]. Freels *et al.* [29] described similar results in African-Americans with AD over a seven-year follow-up, and Qiu *et al.* [7] found the same relationship in a four-year interval, although the association was no longer significant after controlling for covariates due to the small sample size. According to the CR hypothesis, highly educated individuals undergo greater neuropathological changes than individuals with low education for any clinical stage of dementia [10, 11], which results in a shorter interval from the diagnosis date to death.

The present study supports those findings in a larger and diverse population-based sample, which complies with the Level 2 requirements (follow-up > 80%) established by the Oxford Centre for Evidence-Based Medicine [31]. In contrast, the Canadian Study of Health and Aging (CSHA) found that education did not influence mortality rates in people with dementia [8]. There might be several reasons for this discrepancy in the findings. Firstly, 16% of the cohort was older than 85 in the CSHA cohort, whereas this only occurred in 8% of the NEDICES cohort. These differences persisted in the dementia subgroups (people +85 years = 42.8% vs. 37.9%). Furthermore, the proportion of people with low education was higher in NEDICES (33.8 vs. 53.6%), and the different thresholds chosen to classify low-educated individuals may produce conflicting evidence [30, 32]. Indeed, Brehaut *et al.* [8] found that the HRs for mortality in the group with low education (<8 years) was considerably smaller compared to the highly educated group (HRs = 4.06 vs. 4.72) after controlling for covariates such as gen-

der. Finally, the stage of dementia and causes of death were not described in the CHAS and this limits the assessment of the impact of the two factors on the CHAS findings [8].

It should be noted that both (CHSA and NEDICES) are the population-based studies with the largest sample sizes (N = 5278 in NEDICES vs. 9681 in CSHA), similar methodologies (screening and expert clinical assessment) for dementia diagnosis were followed, and they have covered broad populations (*i.e.,* urban-rural; institutionalized vs. outpatients). Therefore, studies carried out in specialized settings are not directly comparable when considering that people who seek advice are usually more educated (*i.e.,* higher CR) due to an early awareness of symptoms [33, 34], and educational attainment may not approach CR as well as it does in population-based studies. Additionally, some studies have linked the effect of education to more severe dementia cases [4], but the study of Geerlings *et al.* [4] collected a younger sample and did not cover the institutionalized population, in comparison with NEDICES data. Interestingly, Villarejo *et al.* have also reported that education was no longer significant on dementia mortality at 13 years [1], which indicates that education effects might have diminished as the disease progressed [35]. Finally, it is often assumed that comorbidity predicts survival, but we did not find this association, which is confirmed by other studies [36]. Presumably, this may be explained by the length bias or the lack of data on the severity of comorbidity [37].

The interpretation of the obtained findings suggests that there is a relationship between the severity of dementia pathology and mortality. Apparently, other underlying conditions may influence mortality rates among individuals with dementia. However, we observed that there are no significant differences in cause of death among demented individuals with low and high level of education, which makes an alternative mechanism unlikely. This possibility is further minimized considering that the comorbidity index does not predict mortality in people with dementia. Moreover, causes of death were also similar between high and low education groups. Consistent with our results, other studies have shown that there is no relationship between education and survival in people without dementia [2, 14, 38].

To conclude, this research advises that dementia could modify the influence of education on mortality. Therefore, at any level of clinical expression, individuals with higher educational attainment will likely present a greater neuropathological damage, which leads them to an earlier death. These postulations imply that people with higher education, who are usually diagnosed later due to the lesser manifestation of the symptoms, require an accurate diagnostic protocol to detect dementia in the earliest stages in order to promote specific intervention strategies for a better prognosis.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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