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# Education and Literacy as Risk Factors of Dementia after Stroke and Transient Ischemic Attack: NEDICES study.

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## ABSTRACT

**Background:** A protective effect of education on cognitive decline after stroke has been claimed, but evidence from prospective population-based cohorts is very limited. The differential role of literacy and education on dementia after stroke remains unexplored.

**Objective:** This research addresses the role of education and literacy in dementia incidence after stroke and transient ischemic attack (TIA).

**Methods:** 131 participants with stroke or TIA were identified within the population-based NEDICES study (N = 5,278 persons). Participants were fully assessed at baseline (1994–1995) and incident dementia diagnosis was made by expert neurologists (DSM-IV criteria) after a mean follow-up of 3.4 years. Adjusted Cox regression analyses were applied to test the association between education, literacy and dementia risk.

**Results:** Within the 131 subjects with stroke or TIA, 19 (14%) developed dementia at follow-up. The Cox's regression model (age and sex ajusted) showed that low education (HR = 3.48, 95% CI = 1.28, 9.42, p = 0.014) and literacy (HR = 3.16, 95% CI = 1.08, 9.22, p = 0.035) were significantly associated with a higher dementia risk. Low education was also associated with dementia when main confounders (i.e., cognitive/functional performance) were considered in the Cox's model. However, after including stroke recurrence, only low/null literacy (vs. education) remained as significant predictor of dementia. Finally, low/null literacy showed an effect over-and-above education on dementia risk when both factors were introduced in the adjusted Cox's regression. **Conclusions:** These findings underline the importance of literacy to estimate cognitive decline after stroke in low-educated populations.



**Keywords:** stroke, transient ischemic attack, illiteracy, low education, cognitive reserve

## INTRODUCTION

Stroke is a leading cause of disability-adjusted life years (116.4 million) worldwide [1]. Due to the advances in intervention strategies, more people survive after stroke and live with its long-term motor, sensitive and cognitive consequences [2]. Thus, stroke often leads to cognitive decline, even in stroke patients who underwent revascularization therapies [3], ranging from subjective cognitive decline to dementia [4,5]. Cerebrovascular lesions, frequently associated with Alzheimer's disease (AD) and other neurodegenerative pathologies, are the most important treatable and preventable causes of dementia [6,7]. In fact, there is up to a ninefold excess risk of dementia in the first year after stroke, and the incidence rate increase thereafter [8]. However, the clinical heterogeneity in the occurrence, progression or recovery from cognitive impairment after stroke remains unexplained [5,9].

Typically, research on post-stroke dementia has been focused on risk factors (e.g., hypertension, diabetes, stroke severity, white matter lesions) [10], whereas the explanatory role of protective factors, such as cognitive reserve (CR), has barely been considered [9]. CR refers to individual differences in cognitive processes and/or compensatory abilities of the brain to cope with neuronal damage and explain differential susceptibility to functional impairment [11]. Basically, CR implies that some aspects of genetics and, mainly, life experience impart differential susceptibility to disease-related brain changes. In this context, education is a well-known CR proxy and there is robust evidence that the prevalence and incidence of AD, vascular dementia (VD), or unspecified dementia are significantly lower in individuals with higher educational level [12]. Nevertheless, it has been claimed that the protective effect of education on cognitive decline may be limited after stroke in comparison with other aging conditions [13]. Thus, different studies indicate that vascular events (i.e., leukaraiosis, strokes, and/or lesion load) modulate the effect of education (CR proxy) on an individual's cognitive prognosis due to the decrease in the brain's compensation capacity [14-16].

In this context, longitudinal population-based studies on post-stroke dementia are very scarce, and most data come from studies of hospital-based cohorts with short-term (less than one year) follow-up [16]. To our knowledge, only three longitudinal cohort studies have addressed the influence of education on dementia after stroke [16-18]. Moreover, it is known that even a few years of formal education contribute to CR [19], but it has been claimed that literacy is a better proxy of CR than education in populations with limited access to formal schooling [20-22]. Beyond that, the differential effect of education and literacy has not been tested in post-stroke dementia.

The main objective of this study is to examine the influence of education and literacy on the incidence of dementia (3-year follow-up) in a low-educated population-based sample of patients with stroke or TIA. To achieve this aim, different predictive models, controlling the effects for critical covariates associated with the outcome, were implemented.

## METHODS

### *Study Population*

This research is part of the Neurologic Disorders in Central Spain (NEDICES), a longitudinal population census-based study of major age-associated conditions in older Spanish adults (aged 65 years and older). The NEDICES cohort (N = 5,278) includes three samples from a working-class neighborhood (Las Margaritas, Greater Madrid), a professional-class neighborhood (Lista, Central Madrid) and a rural area (Arévalo,125 km northwest of Madrid). The protocol of the study was approved by two ethical committees (University Hospital “12 de Octubre” and ‘La Princesa’, Madrid, Spain) and written (signed) informed consent was obtained from all participants. Detailed background, study population, and methods of the study are reported elsewhere [23].

*Protocol Evaluation*

Essentially, the NEDICES study was developed in two phases: a door-to-door screening questionnaire performed by lay trained interviewers (i.e., student nurses; Phase 1) and a neurological examination at a health center (Phase 2) of those individuals who screened positive for cognitive decline, cerebrovascular disorders (CVD), and/or other neurological disorders (i.e., parkinsonism/Parkinson's disease and essential tremor). The screening questionnaire comprised 500 items to assess demographic characteristics, health status (e.g., medical and neurological disorders), depressive symptoms, complaints of cognitive decline, medication, and lifestyle (e.g., consumption of ethanol, smoking habits).

*Screening and diagnosis procedure: stroke and dementia.*

Four questions based on the questionnaire of the MONICA project (World Health Organization, WHO), were used to screen for stroke and TIA [24]: (1) Have you ever been diagnosed by a physician as having suffered a stroke? (2) Have you ever had slurred speech or problems talking to somebody? (3) Have you ever felt mouth deviation? (4) Have you ever felt weakness in an arm or a leg?. The screening for dementia was based on the 37-item version of the Mini-Mental State Examination (MMSE), and an 11-item Spanish version of Pfeffer's Functional Activities Questionnaire (FAQ) [25].

All participants who screened positive for dementia (i.e., a score of 23 points or lower on the 37-MMSE, >5 points on the FAQ, missing values in the dementia screening protocol [in-person interview] or available information about cognitive decline), stroke or TIA (positive response to at least one of the four questions) underwent a neurological examination at a National Health Service clinic or at home. If any participants could not attend the neurological examination, medical records from general practitioners, inpatient hospitalizations or specialists were reviewed to obtain the information for diagnosis. All diagnoses of dementia and stroke were made by consensus of two experienced neurologists based on a clinical interview

and/or the review of medical records. The diagnoses of stroke and TIA were considered definite if: (1) physicians had already diagnosed stroke or TIA, and the study neurologists agreed; or (2) the neurologists of the survey found present sequelae consistent with the diagnosis of stroke.

*Clinical Diagnoses of Cerebrovascular Disorders: Stroke and TIA*

The WHO clinical definition of a stroke (i.e., 'rapid development of clinical signs –focal or global- due to a cerebral disturbance, lasting more than 24 h unless interrupted by surgery or death, with no apparent cause other than a vascular origin') was applied. Hemorrhagic stroke included the categories of intraparenchymal hemorrhage, intraventricular hemorrhage and subarachnoid hemorrhage, whereas extradural and subdural hematomas and traumatic hemorrhages were excluded. Ischemic stroke was diagnosed if there was clinical evidence of focal brain dysfunction and absence of any brain hemorrhage. Conversely, TIA was defined as a disturbance of cerebral function during less than 24 h, no evidence of infarction (focal lesions) in neuroimaging (CT or MRI), and complete recovery of the symptoms [26].

According to the guidelines of the Ad Hoc Committee for the Classification and Outline of Cerebrovascular Disease [27], these key symptoms were considered for diagnosis: (1) weakness, clumsiness, or sensory alteration in one or both limbs on the same side, speech or language disturbance, loss of vision in one eye or part of the eye, or homonymous hemianopsia for symptoms that pertain to the carotid territory, (2) weakness or clumsiness (sometimes changing from one side to another), sensory alteration, complete blindness or homonymous hemianopsia, ataxia, imbalance, or unsteadiness not associated with vertigo, and/or (3) two or more of the following: diplopia, dysphagia, dysarthria or vertigo for symptoms that pertain to the vertebrobasilar territory.

The observed prevalence rates on May 1, 1994, were 4.9% for CVD (95% confidence interval [CI] = 4.3, 5.4), 3.4% for stroke (95% CI = 2.9, 3.9) and 1.3% for TIA (95% CI = 1.0, 1.6) in the total population [28].

*Dementia Diagnosis: Three-year follow-up.*

The clinical diagnosis of dementia was established according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV), using a standardized protocol, which included extensive information from medical records, clinical interviews, a brief mental examination, information of relatives, and functional state [25,29]. Cognitive and functional impairments were determined using standardized instruments (i.e., MMSE-37 and FAQ) and confirmed by the neurologists in the clinical interview.

*Level of Education and Literacy*

Years of schooling were registered by self-report (i.e., how many years did you attend school?). In addition, individuals were classified into four categories: illiteracy, can read and write, primary studies, and secondary or higher studies, according to the information of the municipal registry office. The illiteracy category included people with null reading and writing abilities or only able to read and write simple words or sentences, although they could sign the informed consent after a detailed explanation of the study aims (i.e., null/low literacy condition).

*Index of Comorbidity*

The number of comorbidities, including the main cardiovascular risk factors, was calculated by adding the presence (1) or absence (0) of: hypertension, diabetes mellitus, hyperlipidemia, heart disease, cancer, anaemia, chronic obstructive pulmonary disease, psychiatric disorders, osteoarthritis, osteoporosis, hypoacusis, cataracts and peripheral vascular disease [30].

*Statistical Analysis.*

The SPSS, version 25.0 (IBM Corp., NY, USA) was used for all statistical analyses. Means ± standard deviations (SD), median, ranges and frequencies were used to describe sociodemographic and clinical characteristics of the sample. Since most quantitative variables were not normal according to Kolmogorov-Smirnoff test, non-parametric contrasts (Mann-Whitney U test) were used to compare the individuals with versus those without incident dementia, whereas chi-square ($\chi 2$) test was used for categorical comparisons. The association between variables was tested with Spearman's correlation coefficient. The significance threshold (alpha) was set to 0.05, whereas no corrections were made for multiple comparisons because they were complementary and very limited [31].

Cox proportional-hazards models (95% confidence intervals, CIs) were carried out to estimate the relative risk of dementia associated with education (years) and level of literacy (low/null literacy vs. 'literates'). Regarding years of education, individuals were stratified in groups according to the median (Mdn = 6): 0-5 years (low education) vs. 6 years and over (high education). Cox's models were adjusted for several potential confounders associated with the risk of dementia (i.e., age, sex, comorbidities, depressive symptoms, stroke recurrence, MMSE, and FAQ scores). The following successive steps were implemented to complete the adjustments of the predictive models: 1) Essential regression models adjusted by age and sex; 2) Adjusted models by main factors associated with dementia (univariate analyses); 3) Fully adjusted model considering all potential confounders. The variable person-time of observation (in years) for individuals who did not develop dementia was calculated as the time between the baseline screening and the follow-up survey or their demise. In contrast, the person-time for participants who developed dementia was calculated as the time between the baseline screening and the reported onset of cognitive complaints. This estimation procedure was based on the assumption that dementia usually begin many

years before the clinical diagnosis, which is usually established at long-term follow-ups in population based studies [32]. Deceased participants at follow-up were considered as censored cases at the date of their demise, whereas living participants were considered as censored observations at the time of their follow-up screening. The proportional hazards assumption and Harrell C-test were tested on each model to confirm the goodness of fit. Finally, Kaplan-Meier curves were used to represent the differences between the probabilities of an event at the established follow-up. Log-rank tests were performed to compare the distribution of time until the occurrence of an event of interest in independent groups (i.e., low or null literacy vs. literates).

## RESULTS

Of the 5,278 participants who were screened, 678 (12.8%) were positive for CVD and were invited to attend Phase 2. In Phase 2, face-to-face examinations were administered to 630 (92.9%) by neurologists, whereas 47 (6.9%) were diagnosed by reviewing their medical records. Only one subject (0.1%) could not be traced. Of the 677 subjects investigated, 239 (36.2%) were found to be affected either by stroke or TIA. As this survey was part of a large-scale epidemiological survey of neurological diseases, we also detected 18 patients with symptoms/signs of CVD when evaluating subjects who had screened positive for other neurological disorders (dementia, parkinsonism or essential tremor), despite the fact that they had screened negatively for stroke. Finally, we detected in total 257 patients with CVD, of whom 186 (72.4%) patients had suffered a stroke and 71 (27.6%) had received a TIA diagnosis. 50 of them received the diagnosis of dementia at baseline, leaving a sample of 207 individuals with CVD.

[INSERT FIGURE 1]

Out of the 207 eligible subjects with CVD, 44 provided no data about education (years) and 32 were lost in the follow-up phase (1997/1998) due to changes in living area, rejections, or

deceases. Therefore, the final sample (see Figure 1) consists of 131 population-based participants with CVD (87 stroke and 44 TIA; mean age = 74.80 ± 6.92). The mean age at the first reported stroke was 65.37±9.91 (mean of evolution = 9.11 ± 8.63 years). 60.3% of the sample did not achieve a certificate of formal education (i.e., 12.2% were illiterate and 48.1% were only able to read and write). In comparison with the selected sample (N = 131), excluded participants (N = 126) with CVDs were older (Median (M) = 79.00 vs. 74.00, p <. 001) and showed lower scores in the MMSE-37 at baseline (M = 22.00 vs 29.00, p <.001), but no significant differences emerged in years of education (M = 6.00 vs. 6.00, p = 0.70) or number of comorbidities (M = 3.00 vs. 4.00, p = 0.57).

During the incidence period (Mean = 3.40 years, range: 0.04-4.75), 19 participants (14%) developed dementia (47% AD and 52.6% VD). Table 1 depicts the characteristics of the sample and the statistical differences between groups of participants who developed dementia or not at follow-up.

[INSERT TABLE 1]

Individuals with dementia at follow-up (1997/1998) showed significantly lower education (years) and, in turn, higher percentages of individuals with null/low literacy than those who did not develop dementia. Their MMSE-37 and Pfeffer's FAQ scores at baseline were also significantly lower versus those without dementia. Moreover, CVD individuals with incident dementia showed higher stroke recurrence than those without dementia at follow-up. However, no significant differences were found between these groups (with vs. without incident dementia) in age, sex distribution, comorbidities or depressive symptoms (see Table 1).

*Education and Risk of Dementia at three-year follow-up.*

The Cox regression model (adjusted for age and sex) showed that low education (years) (HR = 3.48, 95% CI = 1.28, 9.42, p = 0.014) and literacy (HR = 3.16, 95% CI = 1.08, 9.22, p = .035) were risk factors for dementia in patients with stroke. The effect of education (HR =

2.99, 95% CI = 1.13, 7.90, p = 0.027) remained significant after controlling the effects of significant confounders (i.e., MMSE and FAQ; Table 1) associated with dementia. However, when the stroke recurrence was included, only the FAQ scores and stroke recurrence itself were significant (see Table 2, Model 1). Otherwise, it is remarkable that the effect of literacy was significant even after adjusting for stroke recurrence (see Table 2, Model 2). Moreover, literacy remained significant (HR= 3.76, CI =1.03, 13.63, p =0.044) after including education in this model.

[INSERT TABLE 2]

To confirm the robustness of our findings, we carried out different secondary analyses (see supplemental material). It is worth mentioning that education was not associated with stroke recurrence or its severity. Moreover, the interaction effect between the groups (stroke vs. TIA) and education on dementia risk was not significant. Finally, the adjusted Cox models were consistent even after completing a full adjustment for all covariates (age, sex, comorbidities, depressive symptoms, stroke recurrence, MMSE, and FAQ). The proportional hazards assumption was confirmed in both models, whereas Harrell's test showed that the goodness of fit of the models is adequate.

## DISCUSSION

This study extends previous scientific evidence showing that education and literacy, as CR proxies, have a protective effect against post-stroke dementia. Our findings show that 14% (N = 19) of individuals with stroke/TIA developed dementia at follow-up, a percentage significantly higher in comparison with the 4.1% (N = 161) in the general cohort [25]. These findings are congruent with a recent review and meta-analyses showing stroke as a risk factor for dementia [32]. Noteworthy, individuals with lower education (years) and null/low literacy were more likely to develop dementia at the three-year follow-up after controlling the effect of critical covariates. Our results are consistent with previous longitudinal cohort studies,

indicating that lower educational attainment is associated with a more frequent diagnosis of dementia after stroke [16-18], but none of them addressed the importance of literacy. Although the association between low/null literacy and higher dementia rates (prevalence and incidence) was previously described in different populations [25,33], we found that literacy has an effect over-and-above education to predict dementia after stroke.

It is well-known that stroke and TIA are heterogeneous and complex conditions that often lead to cognitive impairment and dementia [34]. However, recent studies claim that there is high inter-individual variability in cognitive performance after stroke, which cannot be accounted for only through the location or severity of the lesion, and the CR theory may offer a better perspective to explain this fact [13,14]. Interestingly, the education effect in years was removed after including the recurrence of strokes at follow-up. In fact, these results suggest that the capacity of education (in years) to compensate for cognitive decline after stroke may be depleted by the accumulation of different brain insults or the progression of brain degeneration, respectively [13,15]. However, this mediation effect was not consistent for literacy, which remained as a significant predictor of dementia even after including stroke recurrence in the model. This scenario underlines the critical role of literacy in the building of CR, which may be a more robust indicator of CR than education (years) in populations with a low level of education [20-22]. In fact, the interaction analysis showed that the literacy effect on dementia is limited in those with higher education. It is important to consider that many older Spanish adults had to leave school (i.e., without achieving any formal certificate) due to the Spanish Civil War (1936–1939) and they used to have difficulties for recall how many years they attended school accurately [21].

This population-based study has some limitations. First, people with missing information about education (years), or lost at follow-up (36%), were excluded from the statistical analyses. Consequently, the number of eligible cases with CVD and, particularly, those with inci-

dent dementia (i.e., events; N=19) is limited. This fact may diminish the external validity (i.e., generalization) of the study and increase the risk of overfitting (i.e., inflation of risk estimates), particularly after including different confounders [35]. However, according to the algorithm for calculating the minimum sample size in Cox's models [36], our supplementary analyses indicate that it is adequate for 1.5 years (follow-up) and four parameters, whereas generalization over extended time-periods or parameters should be taken with caution. Secondly, we only consider education and literacy as the main CR proxies. Nevertheless, education and reading capacity are possibly the most effective component of CR concerning late-life cognition [37]. Third, it is known that education/literacy are indicators of socioeconomic status. Thus, it is difficult to assess whether the education effect is independent of other confounders such as socioeconomic status or stroke severity [38]. However, the supplementary analysis showed that education is not associated with the recurrence of stroke or its severity. Current evidence also indicates that both associated CR proxies (socioeconomic status and education) make independent contributions to cognitive performance in later life [39]. Consistently, education effects on dementia risk were significant, independently of the living (rural vs. urban) area, at different lifetime periods (childhood and adulthood) [40]. In spite of these facts, residual confounding effects (i.e., stroke severity or socioeconomic status) cannot be discarded. Finally, the lack of clinical information about stroke types and location (absence of neuroimaging data) prevents determining how CR could impact the relation between vascular lesions (type or extension) and cognitive performance. However, it should be noted that no interaction was found between the groups (TIA or stroke) and education in dementia risk, nor were education or literacy associated with stroke recurrence. As the main strength, NEDICES is a longitudinal population cohort including stroke/TIA cases followed during three years. All participants were diagnosed by expert neurologists using a comprehensive standardized protocol.

The findings of this study support the impact of education and literacy on dementia incidence in stroke or TIA patients. As the main novelty, this research highlights that literacy may be a more robust CR proxy than education (years) in populations with scarce access to formal schooling. Currently, it is essential to understand how different CR proxies, which are usually related to each other (i.e., SES and education), modify cognitive trajectories differentially. Future research should continue investigating their weighted role in post-stroke dementia. In particular, the incorporation of neuroimaging data will help to understand how these CR proxies influence the relationship between brain damage (i.e., vascular lesions) and the clinical outcomes in stroke patients.

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**Conflict of interest/ Disclosure Statement:**

Israel Contador declares no conflict of interest.

Patricia Alzola declares no conflict of interest.

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## TABLES

Table 1. Baseline characteristics of the sample stratified by evolution to dementia at follow-up.

| Variables | Without incident dementia (N=112) | With incident dementia (N=19) | Statistical contrast ($\chi^2$ / U) | P value |
|---|---|---|---|---|
| Age | 72.50 (65-93) | 77.00 (65-91) | 1308.00 | .110 |
| Sex (n, % women) | 54 (48.2) | 10 (52.6) | 0.12 | .722 |
| Education | 6.00 (0-20) | 2.00 (0-15) | 717.00 | .022* |
| % illiterates | 9.8% | 26.3% | 4.12 | .042* |
| Index of Comorbidity | 4.00 (0-8) | 4.00 (1-8) | 1123.50 | .693 |
| Stroke recurrence[¥] | 0.16 (0-3) | 0.73 (0-4) | 1016.00 | <.001 |
| MMSE-37 | 29.00 ($0^{T}$-37) | 26.00 (10-33) | 647.50 | .007** |
| Pfeffer's FAQ | 2 (0-32) | 9 (0-26) | 1537.50 | .001** |
| Depressive symptoms (n, %) | 36 (32.1%) | 9 (47.4%) | 1.67 | .196 |

Median and range scores (between parentheses) are shown for quantitative variables. [¥]Numbers represent means due to the median values were 0 for both groups. Stroke recurrence was missed in sixteen participants and two subjects did not complete MMSE-37 or FAQ (Functional Assessment Questionnaire). *p<.05; p<.01**.

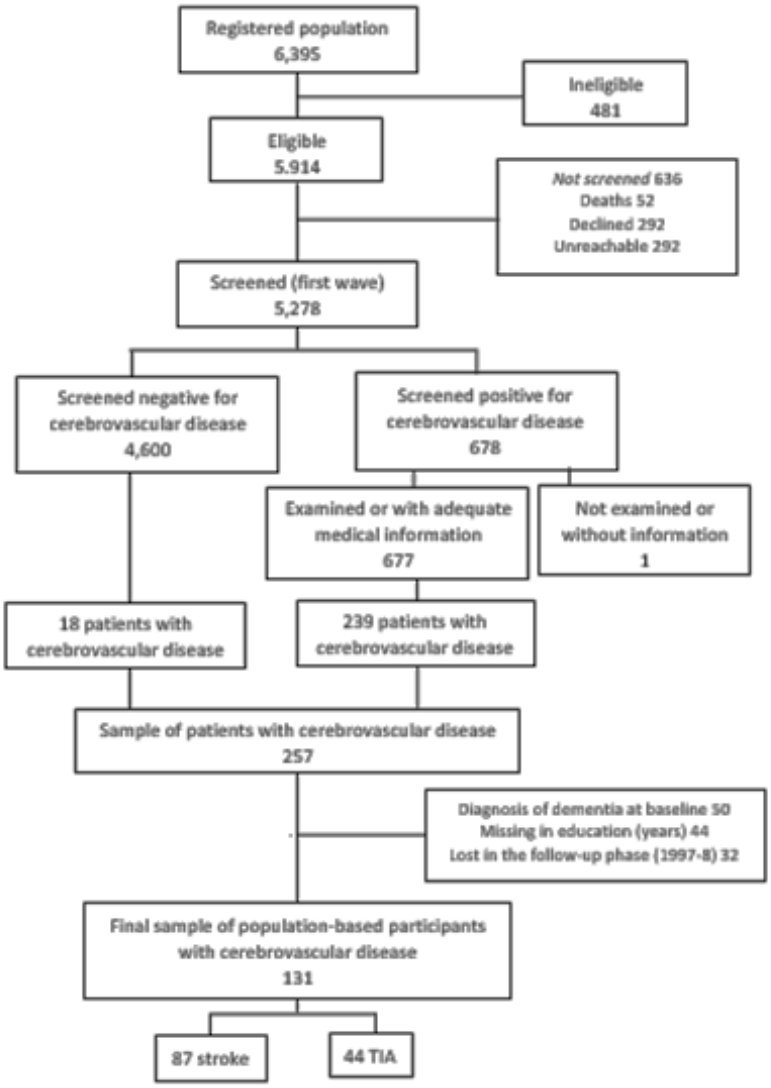
Table 2. Adjusted Cox proportional hazard models predicting incident dementia by education (years) and literacy.

| **Model 1.** | **Hazard Ratio** | **95% Confidence Interval** | **P Value** |
|---|---|---|---|
| Stroke (recurrence) | 1.68 | 1.02-2.78 | .041* |
| MMSE-37 (baseline) | 1.00 | 0.92-1.09 | .882 |
| FAQ (baseline) | 1.08 | 1.02-1.14 | .006** |
| Low education (0-5 years)[T] | 1.80 | 0.61-5.26 | .283 |
| **Model 2** | **Hazard Ratio** | **95% Confidence Interval** | **P Value** |
| Stroke (recurrence) | 2.03 | 1.23-3.34 | .005** |
| MMSE-37 (baseline) | 1.02 | 0.93-1.11 | .625 |
| FAQ (baseline) | 1.08 | 1.03-1.14 | .002** |
| Null/low literacy | 4.14 | 1.18-14.42 | .026* |

Note. Four parameters models, including the main confounders (see table 1), are shown to avoid overfitting effects. Essentially, these regression models were consistent even after applying a full adjusted model with all covariates (data shown in supplementary analyses). FAQ = Functional Assessment Questionnaire. *p<.05. p<.01**

## FIGURES LEGENDS

Figure 1. Flow chart of the study



## SUPPLEMENTAL MATERIAL

*Supplemental Analyses*

Firstly, no significant correlations (Spearman) were found between education (years) and number of strokes. Moreover, stroke subgroups (low vs. high education) did not show significant differences on FAQ (U= 2072,5, p = 0.998). Secondly, no interaction effect was found between the groups (stroke vs. TIA) and education on dementia risk (HR = 0.97, 95% CI = 0.65, 1.44, p = 0.88), but the interaction between education and literacy achieved significance for the main outcome (HR = 0.83, 95% CI = 0.73, 0.95, p <.01). Thirdly, education (HR = 2.29, 95% CI = 0.66, 7.94, p = 0.190) and literacy (HR = 3.91, 95% CI = 1.04, 14.58, p = 0.042) showed consistent effect after controlling all confounders in the models (Harrell's C index (range) = 0.769, 0.824). Finally, the Kaplan–Meier curves confirmed that low educated individuals (log-rank p = 0.019) and illiterates (log-rank p = 0.03) have a higher probability of suffering dementia at the 3-year follow-up (see figure 2s and 3s).

*Sample Size Estimation*

To minimize the effect of overfitting and guarantee an accurate estimation of the parameters, the minimum sample size required to develop a multivariable prediction model (Cox's model) was calculated with the package pmsampsize in R (https://cran. r-project.org/web/packages/pmsampsize/index.html). This model was calculated using 4 parameters, according to the main confounding variables associated with dementia (MMSE, FAQ, stroke recurrence and education/literacy). Considering an existing prediction model (Cox Regression: adjusted R-squared = 0.157; mean follow-up = 1.5 years; overall event rate 10.6), with an expected shrinkage (overfitting) of predictor effects by 15% or less, the minimum sample size required for the predictive model is 133 subjects with 21 events.

*Supplemental Figures*

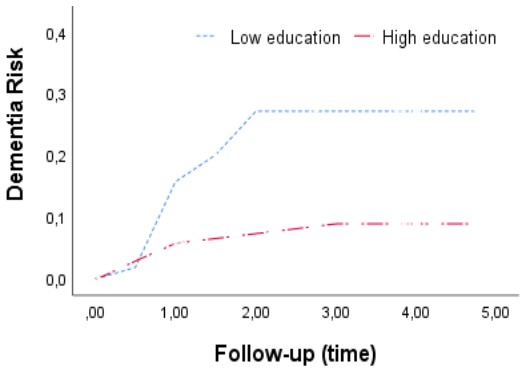



Figure 2s. Kaplan Meier Curves: comparison of dementia risk among those with low education (0-5 years) versus high education (6 years and over) at three years

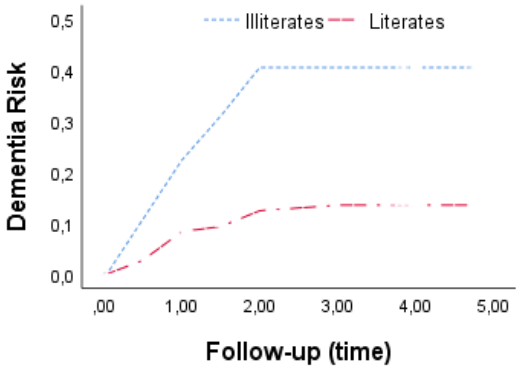



Figure 3s. Kaplan Meier Curves: comparison of dementia risk among illiterates versus literates.