

# Higher Education Is Associated with a Lower Risk of Dementia after a Stroke or TIA. The Rotterdam Study

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## Key Words

Stroke · Transient ischemic attack · Dementia · Education · Cognitive reserve · Epidemiology · Population-based

## Abstract

**Background:** Higher education is associated with a lower risk of dementia, possibly because of a higher tolerance to subclinical neurodegenerative pathology. Whether higher education also protects against dementia after clinical stroke or transient ischemic attack (TIA) remains unknown. **Methods:** Within the population-based Rotterdam Study, 12,561 participants free of stroke, TIA and dementia were followed for occurrence of stroke, TIA and dementia. Across the levels of education, associations of incident stroke or TIA with subsequent development of dementia and differences in cognitive decline following stroke or TIA were investigated. **Results:** During 124,862 person-years, 1,463 persons suffered a stroke or TIA, 1,158 persons developed dementia, of whom 186 developed dementia after stroke or TIA. Risk of dementia after a stroke or TIA, compared to no stroke or TIA, was highest in the low education category (hazards ratio [HR] 1.46, 95% CI 1.18–1.81) followed by intermediate education category (HR 1.36, 95% CI 1.03–1.81). No significant association

was observed in the high education category (HR 0.62, 95% CI 0.25–1.54). In gender stratified analyses, decrease in risk of dementia with increasing education was significant only in men. **Conclusion:** Higher education is associated with a lower risk of dementia after stroke or TIA, particularly in men, which might be explained by a higher cognitive reserve.

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## Introduction

Higher education is associated with a lower risk of dementia, which is thought to be explained by a higher cognitive reserve [1, 2]. The cognitive reserve hypothesis postulates that people with a higher reserve can tolerate more neurodegenerative pathology and maintain brain function for longer than people with low reserve, before the damage manifests clinically as dementia [3–5]. In the context of Alzheimer’s disease, people with higher cognitive reserve can have more senile plaques and amyloid- $\beta$  deposits before the disease manifests clinically [6–9].

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Although vascular disease is also an important risk factor for dementia including Alzheimer's disease [10], it is less known if people with higher education, and thus more cognitive reserve, can also tolerate more cerebrovascular damage before dementia occurs. Evidence does suggest, however, that subclinical vascular lesions such as white matter lesions [11] or silent brain infarcts [12] result in less cognitive decline in people with higher education. Since clinical cerebrovascular events such as stroke and transient ischemic attack (TIA) are related to more tissue damage than silent lesions [13], it remains to be established whether higher education also protects against dementia after clinical events. More importantly, stroke and TIA have a high clinical impact and may lead to considerable morbidity, which is further aggravated by sequelae like dementia [14, 15]. Hence, identification of (modifiable) factors that act as protectors against dementia following a stroke or TIA is of major public health and clinical importance. Finally, given the differences in risk factors [16], education categories [17] and incidence of stroke and dementia in men and women [18, 19], the association between stroke or TIA and consequent dementia across education categories needs to be explored for sex differences.

Therefore, in this population-based study, we investigated whether educational level used as a marker of cognitive reserve, is associated with a lower risk of dementia after a stroke or TIA. We also examined differences in cognitive decline after a stroke or TIA across levels of education.

## Materials and Methods

### *Setting and Study Population*

This study was part of the population-based Rotterdam Study [20]. In 1990, 7,983 persons aged 55 years and older were recruited. In 2000, the cohort was expanded by 3,011 persons aged 55 and older, and in 2006, in a second expansion wave, an additional 3,932 persons aged 45 and older were added. Of these total 14,926 participants, 527 with prevalent dementia and 902 with insufficient baseline information for dementia or no consent for the follow-up of stroke, TIA or dementia were excluded. We also excluded 354 persons with prevalent stroke, 324 with prevalent TIA and 258 with missing education information, resulting in 12,561 participants eligible for the analyses of incident dementia.

For the analyses of cognition, only participants who had suffered a stroke or TIA between the 2 follow-up rounds in 2004–2008 and 2009–2013 were eligible, as these rounds comprised the most comprehensive cognitive test battery. In these examination rounds, 7,039 persons participated, of which 34 participants with no consent for collection of follow-up data, 435 participants with prevalent stroke or TIA at the first test date, 3 participants with prevalent

dementia, 80 participants with insufficient information for dementia at the first test date, and 83 with missing data on education were excluded. Of the remaining 6,404 participants, 5,588 had at least one cognitive test in both follow-up rounds. Two hundred and five of these participants suffered a stroke or TIA between the 2 follow-up rounds and were therefore eligible for analyses.

### *Standard Protocol Approvals, Registrations, and Patient Consents*

The Rotterdam Study is approved by the Medical Ethics Committee of the Erasmus MC and by the Ministry of Health, Welfare and Sport of the Netherlands, implementing the 'Wet Bevolkingsonderzoek: ERGO (Population Studies Act: Rotterdam Study)'. A written informed consent was obtained from all participants.

### *Educational Level as a Measure of Cognitive Reserve*

Educational level as marker of cognitive reserve can be measured based on years of education or degree of literacy. We used the latter since it measures educational attainment more directly and might therefore be a better marker of cognitive reserve [21]. Participants were classified as having low (primary, unfinished secondary and lower vocational), intermediate (secondary or intermediate vocational) or high education (higher vocational or university).

### *Assessment of Stroke and TIA*

At baseline, history of stroke and TIA was assessed using home interviews and verified using medical records. From baseline onward, participants were continuously followed up for occurrence of stroke and TIA through a computerized linkage between the study database and medical records of general practitioners (GPs). This data linkage system is highly efficient in the Dutch situation where the GPs receive all medical information about their patients if they contact any medical caregiver or professional, including specialists. Additionally, nursing home physicians' files and files from GPs of participants that moved out of the study area were checked on a regular basis. Information from GPs and hospital records was collected from participants with a potential stroke or TIA. Research physicians reviewed the information and an experienced vascular neurologist verified the strokes according to World Health Organization criteria [22, 23]. We defined TIAs as temporary attacks with presence of focal symptoms, which are attributable to dysfunction of one arterial territory of the brain [24]. Follow-up for stroke and TIA was complete until 2013 for 98.5% of potential person-years [25].

### *Assessment of Dementia*

Participants were screened for dementia at baseline and follow-up examinations using a 3-step protocol [26]. First, screening was done using the Mini-Mental State Examination (MMSE) [27] and the Geriatric Mental Schedule (GMS) organic level. Second, screen-positives (MMSE <26 or GMS organic level >0) subsequently underwent an examination and informant interview with the Cambridge Examination for Mental Disorders in the Elderly. Participants who were suspected of having dementia underwent further neuropsychological testing if necessary. Additionally, the total cohort was continuously monitored for dementia through computerized linkage between the study database and digitized medical records from GPs and the Regional Institute for Outpatient Mental Health Care. Third, a consensus pan-

el led by a neurologist decided on the final diagnosis in accordance with standard criteria using the DSM-III-R criteria for dementia, the NINCDS-ADRD for Alzheimer disease [28] and the NINCDS-AIREN criteria for vascular dementia [29]. Follow-up for dementia was complete until 2013 for 98.4% of potential person-years.

#### *Cognitive Tests*

From 2004 to 2008 and 2009–2013, participants underwent extensive cognitive testing. Executive function was assessed by the Stroop test (interference task) which tests attention and concentration, letter-digit substitution task (LDST) which tests processing speed and verbal fluency test (VFT) which assesses verbal fluency. Memory was assessed by the 15-word verbal learning test (WLT) including both immediate and delayed recall. Fine motor skills and coordination was assessed by the Purdue pegboard test for both hands [30]. A higher score indicates a better cognitive performance for all tests, except the Stroop test in which a higher score indicates a worse performance as it measures time to complete the task.

#### *Covariates*

Smoking habits and medication use were assessed during the home interview. Participants were categorized into current, former and never smokers. Body mass index was calculated as weight in kilograms per height in meters squared. Total cholesterol and high-density lipoprotein cholesterol were measured in serum in mmol/l. Blood pressure was measured twice at the right arm in sitting position at the research center and the average of 2 blood pressure readings was used. Diabetes mellitus type 2 was diagnosed as fasting blood glucose  $\geq 7.00$  mmol/l or the use of anti-diabetic medication was evaluated by interview and pharmacy records [31]. Cognitive score was assessed using the MMSE [27]. Since the study population included 3 cohorts from the Rotterdam Study, cohort was also used as a covariate.

#### *Statistical Analyses*

We examined the risk of dementia in people with stroke or TIA as compared to people without stroke or TIA using Cox proportional hazard models. Adherence to the proportional hazards assumption was tested by plotting smoothed Schoenfeld residuals against time; no violations of the assumption were identified. Stroke or TIA was used as time varying exposure, which took into account the incident cases of stroke or TIA as they occurred during follow-up. Participants were censored at the date of dementia, date of death or last date of follow-up, whichever came first. Subsequently, we examined this association across levels of education by stratifying on educational level as well as by including an interaction term. In secondary analyses, we examined this association in men and women separately since levels of education differ between older men and women, as well as their risk factors for stroke [16].

Subsequently, we tested whether education is associated with change in cognitive test scores after a stroke or TIA using linear regression models. This was conducted in a subgroup of participants with stroke or TIA for which cognitive test scores were available both before and after the stroke or TIA. Using low education level as the reference, we first examined the association of education with cognitive test scores before stroke or TIA. Second, we examined the association of education with cognitive test scores after stroke or TIA. Third, the association of education with the

change in cognitive tests scores after stroke or TIA was examined. This was tested by performing linear regression of education with cognitive test scores after stroke or TIA, adjusting for the test score before stroke or TIA. In these analyses, an interaction between cognitive performance and sex was also tested.

Finally, we tested cognitive decline in persons with a stroke or TIA altogether, as compared to persons without a stroke or TIA, across levels of education.

As sensitivity analyses, we repeated the dementia analyses combining the intermediate and high education categories.

For all analyses, 2 models were fitted. Model 1 was adjusted for age and sex only (where applicable). Model 2 was additionally adjusted for education level (where applicable), body mass index, smoking, total and high-density lipoprotein cholesterol, systolic and diastolic blood pressure, lipid- and blood pressure-lowering medication, diabetes mellitus type 2, MMSE and study cohort. The analyses of change in cognition were additionally adjusted for time between the 2 cognitive examinations. The dementia analyses were adjusted for covariates using their baseline values, while cognition analyses were adjusted using the values of covariates from the first visit of cognition assessment. Missing values on covariates (<6%) were handled by multiple imputations.

Data were analyzed using the Stata software version 13 (Stata-Corp, College Station, Tex., USA) and IBM SPSS statistics version 21.0 (IBM Corp., Armonk, N.Y., USA).

## **Results**

This study included 12,561 dementia-, TIA- and stroke-free participants at baseline. Table 1 summarizes baseline characteristics of the study population. People with higher education were younger and more frequently men. During a mean follow-up of  $9.9 \pm 5.2$  years, 1,463 persons suffered a stroke or TIA and 1,158 persons were diagnosed with dementia. Of these 1,158, 186 persons developed dementia after a stroke or TIA.

Differences in baseline characteristics of persons excluded and included in the analyses are summarized in online supplementary table 1 (for all online suppl. material, see [www.karger.com/doi/10.1159/000443649](http://www.karger.com/doi/10.1159/000443649)).

Of the total 1,463 stroke cases or TIAs, the low education category had 449 (8.5%) stroke cases and 300 (5.7%) TIAs. The intermediate education category suffered 331 (6.2%) strokes and 245 (4.6%) TIAs, whereas the high education category had 64 (3.3%) stroke cases and 74 (3.8%) TIAs.

People with a stroke or TIA had an increased risk of dementia compared to participants without stroke or TIA (multivariable adjusted hazards ratio [HR] 1.42, 95% CI 1.20–1.67). In analyses stratified for education, this risk was highest in persons with low education (HR 1.46, 95% CI 1.18–1.81), followed by those with intermediate education (HR 1.36, 95% CI 1.03–1.81). In the high education group, people with a stroke or TIA did not

**Table 1.** Baseline characteristics of the study population (n = 12,561)

Characteristics	Levels of education		
	low (n = 5,299)	intermediate (n = 5,342)	high (n = 1,920)
Age, years	67.8 (9.9) <sup>b, c</sup>	63.3 (8.8) <sup>a, c</sup>	60.0 (8.2) <sup>a, b</sup>
Women	3,754 (70.8) <sup>b, c</sup>	2,838 (53.1) <sup>a, c</sup>	735 (38.3) <sup>a, b</sup>
Study cohort			
First cohort	3,463 (65.4) <sup>b, c</sup>	2,402 (45.0) <sup>a, c</sup>	532 (27.7) <sup>a, b</sup>
Second cohort	910 (17.2) <sup>b, c</sup>	1,344 (25.2) <sup>a, c</sup>	470 (24.5) <sup>a, b</sup>
Third cohort	926 (17.5) <sup>b, c</sup>	1,596 (29.9) <sup>a, c</sup>	918 (47.8) <sup>a, b</sup>
Body mass index, kg/m <sup>2</sup>	27.2 (4.2) <sup>b, c</sup>	26.8 (4.1) <sup>a, c</sup>	26.5 (3.9) <sup>a, b</sup>
Smoking			
Never	1,993 (37.9) <sup>c</sup>	1,558 (29.3) <sup>c</sup>	539 (28.1) <sup>a, b</sup>
Former	2,018 (38.4) <sup>b, c</sup>	2,459 (46.2) <sup>a</sup>	950 (49.6) <sup>a</sup>
Current	1,247 (23.7) <sup>b, c</sup>	1,301 (24.5) <sup>a, c</sup>	428 (22.3) <sup>a, b</sup>
Total cholesterol, mmol/l	6.4 (1.3) <sup>b, c</sup>	6.1 (1.2) <sup>a, c</sup>	5.8 (1.2) <sup>a, b</sup>
High-density lipoprotein cholesterol, mmol/l	1.4 (0.4) <sup>b, c</sup>	1.4 (0.4) <sup>a, c</sup>	1.4 (0.4) <sup>a, b</sup>
Lipid lowering medication	409 (7.7)	556 (10.4)	222 (11.6)
Systolic blood pressure, mm Hg	139.8 (22.2)	137.3 (20.9)	135.3 (21.1)
Diastolic blood pressure, mm Hg	76.0 (12.0) <sup>b, c</sup>	78.0 (11.6) <sup>a, c</sup>	79.8 (11.7) <sup>a, b</sup>
Blood pressure lowering medication	1,313 (24.8) <sup>c</sup>	1,131 (21.2)	350 (18.3) <sup>a</sup>
MMSE, points	27.2 (2.1) <sup>b, c</sup>	28.2 (1.5) <sup>a, c</sup>	28.6 (1.4) <sup>a, b</sup>
Diabetes mellitus type 2	417 (8.6)	390 (7.7)	107 (5.8)

Values are means (SD) or counts (%).

n = Number of persons included in study.

<sup>a</sup> Significantly different from people with low education (p < 0.05), after age and sex adjustment – if applicable.

<sup>b</sup> Significantly different from people with intermediate education (p < 0.05), after age and sex adjustment – if applicable.

<sup>c</sup> Significantly different from people with high education (p < 0.05), after age and sex adjustment – if applicable.

**Table 2.** Risk of dementia after stroke or TIA by levels of education

	HRs (95% CIs) of dementia			
	n/N <sup>a</sup>	n/N <sup>b</sup>	Model 1	Model 2
Total population	1,158/12,561	186/1,463	1.40 (1.19–1.65)	1.42 (1.20–1.67)
Strata of education				
Low education	732/5,299	112/749 <sup>c</sup>	1.47 (1.19–1.81)	1.46 (1.18–1.81)
Intermediate education	364/5,342	68/576 <sup>c</sup>	1.38 (1.04–1.82)	1.36 (1.03–1.81)
High education	62/1,920	6/138 <sup>c</sup>	0.74 (0.31–1.77)	0.62 (0.25–1.54)
p value for interaction <sup>d</sup>			0.65	0.65

<sup>a</sup> n/N: number of dementia cases/total number of participants at risk for dementia.

<sup>b</sup> n/N: number of dementia cases after stroke or TIA/total number of stroke or TIA.

<sup>c</sup> Low education: 300 TIAs, 449 strokes; intermediate education: 245 TIAs, 331 strokes; high education: 64 TIAs, 74 strokes.

<sup>d</sup> Interaction between presence of stroke or TIA and educational level for the risk of dementia.

Model 1: adjusted for age and sex.

Model 2: adjusted for age, sex, education (where applicable), study cohort, MMSE score, body mass index, smoking, total cholesterol, high-density lipoprotein cholesterol, lipid-lowering medication use, systolic blood pressure, diastolic blood pressure, blood pressure-lowering medication use and diabetes mellitus type 2.

**Table 3.** Risk of dementia after a stroke or TIA by levels of education in men and women

	HRs (95% CIs) of dementia							
	men				women			
	n/N <sup>a</sup>	n/N <sup>b</sup>	Model 1	Model 2	n/N <sup>a</sup>	n/N <sup>b</sup>	Model 1	Model 2
Total population	360/5,234	70/618	1.56 (1.18–2.06)	1.66 (1.25–2.20)	798/7,327	116/845	1.33 (1.08–1.63)	1.32 (1.08–1.62)
Strata of education								
Low education	147/1,545	29/202	2.10 (1.36–3.23)	2.21 (1.43–3.43)	585/3,754	83/547	1.33 (1.04–1.70)	1.32 (1.03–1.69)
Intermediate education	172/2,504	36/320	1.36 (0.91–2.03)	1.45 (0.97–2.17)	192/2,838	32/256	1.41 (0.95–2.09)	1.40 (0.94–2.08)
High education	41/1,185	5/96	0.87 (0.33–2.30)	0.72 (0.25–2.06)	21/735	1/42	0.33 (0.04–2.61)	0.24 (0.03–2.37)
p value for interaction <sup>c</sup>			0.08	0.05			0.85	0.82

<sup>a</sup> n/N: number of dementia cases/total number of participants at risk for dementia.

<sup>b</sup> n/N: number of dementia cases after stroke or TIA/total number of stroke or TIA.

<sup>c</sup> Interaction between presence of stroke or TIA and educational level for the risk of dementia.

Model 1: adjusted for age.

Model 2: adjusted for age, education (where applicable), study cohort, MMSE score, body mass index, smoking, total cholesterol, high-density lipoprotein cholesterol, lipid-lowering medication use, systolic blood pressure, diastolic blood pressure, blood pressure-lowering medication use and diabetes mellitus type 2.

have an increased risk of dementia compared to people without a stroke or TIA (HR 0.62, 95% CI 0.25–1.54; table 2). Stratification by gender showed a similar pattern of associations, which was more pronounced in men than in women (table 3). Interaction testing of educational level with stroke or TIA on the risk of dementia yielded p value 0.65 in the overall population, 0.05 in men and 0.82 in women.

People with high education scored better on 15-WLT (both immediate and delayed recall), VFT and LDST both before and after stroke or TIA (table 4). When we studied the change in cognitive test scores from before to after stroke or TIA, we found that that people with high education declined less in delayed recall compared to people with low education ( $\beta$  1.33, 95% CI 0.24–2.43). Effect sizes of the Stroop interference task and VFT also suggested a lower decline in the higher education group, although only borderline significant. We did not observe an interaction between cognitive performance and sex, which is why we did not stratify on sex in these analyses.

When comparing cognitive decline in those with a stroke or TIA to those without, we found that people with a stroke or TIA had a stronger decline on the Stroop test, immediate recall and delayed recall than people without stroke or TIA in low and intermediate education categories (online suppl. table 2). This difference was not observed in the high education category. However, interaction testing of educational level with stroke or TIA on

cognitive decline only gave a borderline significant interaction for the Stroop test ( $p = 0.08$ ).

In the sensitivity analyses for risk of dementia, our results did not change after combining the intermediate and high education categories (data not shown).

## Discussion

This population-based study showed that stroke or TIA increased the risk of subsequent dementia in persons with low and intermediate education but not in those with high education. Additionally, as compared to people with low education, those with high education not only scored better on cognitive tests both before and after stroke or TIA, but also declined less in memory and executive function after a stroke or TIA.

It is known that people with stroke or TIA have an increased risk of dementia compared to those without stroke or TIA [24, 32], but we showed that this effect was dependent upon the level of education.

Previously, clinical studies have identified low education as a risk factor for dementia in patients with stroke, but because of the clinical setting, a comparison to risk of dementia in persons without stroke was lacking [15, 33–35]. It is specifically this comparison with persons without stroke that provides evidence for higher education to be protective against post-stroke dementia. Therefore, a major novelty of our study is that we were

**Table 4.** Change in cognitive test scores after stroke or TIA by levels of education

	n <sup>a</sup>	Stroopinterference task, s	LDST (correct answers)	VFT (animal names)	15-WLT immediate recall (correct answers)	15-WLT delayed recall (correct answers)	Purdue pegboard (number of pins placed)
<i>Difference (95% CIs)</i>							
Before stroke or TIA							
Low education	73	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Intermediate education	89	-0.12 (-6.54 to 6.30)	3.88 (1.62 to 6.15)	1.32 (-0.41 to 3.04)	2.52 (0.42 to 4.62)	1.33 (0.32 to 2.35)	0.55 (0.01 to 1.08)
High education	43	-3.93 (-11.88 to 4.02)	5.77 (2.98 to 8.57)	5.11 (3.01 to 7.21)	4.61 (2.07 to 7.16)	2.03 (0.80 to 3.25)	0.32 (-0.33 to 0.97)
After stroke or TIA							
Low education	73	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Intermediate education	89	-3.04 (-11.19 to 5.11)	3.28 (1.07 to 5.48)	1.60 (-0.21 to 3.41)	3.46 (1.33 to 5.60)	1.30 (0.30 to 2.29)	0.18 (-0.42 to 0.78)
High education	43	-11.40 (-21.51 to -1.30)	4.82 (2.10 to 7.55)	4.72 (2.51 to 6.92)	4.87 (2.29 to 7.44)	2.39 (1.19 to 3.60)	-0.09 (-0.82 to 0.64)
<i>Difference in change in cognition (95% CIs)</i>							
Decline after stroke or TIA							
Low education	73	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Intermediate education	89	-3.07 (-9.84 to 3.70)	0.64 (-1.01 to 2.29)	0.88 (-0.68 to 2.45)	2.06 (0.20 to 3.92)	0.63 (-0.26 to 1.52)	0.01 (-0.57 to 0.59)
High education	43	-9.13 (-17.64 to -0.63)	0.93 (-1.14 to 3.01)	1.94 (-0.09 to 3.96)	2.13 (-0.20 to 4.46)	1.33 (0.24 to 2.43)	-0.22 (-0.92 to 0.48)

Estimates represent differences in test score and differences in change in cognitive test scores as compared to the low education category, with 95% CIs. A higher score indicates a better cognitive performance for all tests (scores), except the Stroop test (time taken to finish the task, in seconds) in which a higher score indicates a worse performance.

Change in cognition is defined as cognition after stroke or TIA, adjusted for cognition before stroke or TIA.

Estimates are adjusted for age, sex, study cohort, body mass index, smoking, total cholesterol, high-density lipoprotein cholesterol, lipid-lowering medication use, systolic blood pressure, diastolic blood pressure, blood pressure-lowering medication use and diabetes mellitus type 2.

Estimates for change in cognition are additionally adjusted for time between the 2 examination dates.

LDST = Letter-digit substitution task; VFT = verbal fluency test; 15-WLT = 15-word learning test; n = number of persons with at least one cognitive test.

<sup>a</sup> Low education: 42 TIAs, 26 strokes, 5 both stroke and TIA; intermediate education: 50 TIAs, 35 strokes, 4 both stroke and TIA; high education: 26 TIA, 16 strokes, 1 both stroke and TIA.

able to make this comparison and, importantly, showed that in persons with high education, stroke or TIA did not increase the risk of dementia. This differing effect across levels of education has 2 major probable explanations.

One likely explanation is the cognitive reserve, which is an established concept and has been shown to protect against Alzheimer pathology. Cognitive reserve is thought to be built by cognitively enduring activities such as education and occupation complexity. Our results are novel as they demonstrate the protective role of cognitive reserve against clinical cerebrovascular pathology. Perhaps people with higher education and, consequently, higher cognitive reserve are more resilient to the damage caused by a stroke or TIA either due to better efficiency or more capacity or flexibility of brain networks already present before the damage (neural reserve) or because of better compensation for the damage (neural compensation). Neural compensation pertains to the ability of persons with higher cognitive reserve, to form collateral networks in the brain, when the usual neuronal networks are compromised by the vascular damage [4, 36, 37]. Studies have

suggested that cognitively stimulating activities, which are mostly experienced during education, not only promote neurogenesis but also upregulate brain-derived neurotrophic factor, which in turn promotes plasticity [3, 37].

However, an alternative explanation is that people with higher education have a more favorable environment including a healthier lifestyle, better compliance to treatment and better access to healthcare. Such a favorable environment might lead to less severe strokes, perhaps better detection of less severe strokes and, more importantly, early hospitalization and thus fewer complications after stroke. In our study, we adjusted for the potential cardiovascular risk factors. Although associations did not change meaningfully, these adjustments might not fully address every aspect of a favorable environment as pointed out above. This was also reflected in our data, as we found relatively fewer strokes compared to TIAs with increasing educational level.

In analyses stratified on gender, we found that the decrease in the risk of dementia after a stroke or TIA with

increasing education was only significant in men. This suggests a stronger protective effect of cognitive reserve against dementia following stroke in men. However, only few women had dementia after a stroke or TIA in the high education group, which could have affected our power, and might explain the findings. For both men and women, we did not observe a higher risk in the high education category. Alternatively, perhaps in women from older generation birth cohorts, education is less representative of their cognitive reserve than in men, particularly for West European populations. In our study, many women were born in a period when girls were not equally encouraged for education as boys and often only completed limited years of education, which was not reflective of their potential. Instead, they quit school to work at home. Therefore, in this group, educational level might not be the best proxy for cognitive reserve and thus obscured any associations in women. The time spent on leisure activities including social, physical and recreational activities might have been a better proxy for cognitive reserve, but we did not have that information in our study.

The finding in our study of less cognitive decline in the high education category in people with stroke or TIA further supports the role of cognitive reserve. Unlike previous studies which only had information on cognitive decline after stroke or TIA [34, 35], we had cognition assessments both before and after the stroke or TIA. This allowed to demonstrate that the impact of a stroke or TIA on executive function and memory was smaller in people with high education, suggesting that persons with higher education not only have a better cognition in the first place, they can also adapt better to the cerebrovascular damage, indicating cognitive reserve.

Strengths of this study include a large population-based sample representative of different levels of education, a long and robust follow-up of incident TIA, stroke and dementia and the availability of cognitive tests before and after stroke or TIA. However, there are certain limitations. First, only education as a measure of cognitive reserve was available. Activities in later life, such as occupational complexity or leisure activities including recreation, physical and social engagements could not be taken into account, which might be important particularly in older adults. Education might also reflect a better socioeconomic status and thus a better access to healthcare. Nevertheless, these other markers of cognitive reserve might have the same limitations as the educational level, and education remains the most used measure of cognitive reserve in existing literature [36–38]. Second, we

could not adjust for brain reserve in our study, since brain volumes were not available in this population. This might have led to an overestimation of results, as the observed associations could partly be explained by brain reserve. Another limitation is that we did not have information about the severity of stroke. It is possible that people with higher education had less severe strokes leading to less brain damage and therefore a smaller risk of dementia. Third, we did not have enough cases of dementia in the high education category for women and therefore the effect estimates might be underpowered. Finally, complete cognitive testing was available in a subgroup of our study population only; therefore, the results might be influenced by selection. Since people with severe strokes primarily stop attending the research center, our results are only applicable to those with less severe stroke or TIA.

## Conclusions

These results suggest that higher education is associated with a lower risk of dementia after cerebrovascular events, particularly in men. Future studies should explore the mechanisms underlying this protective effect as well as investigate whether improvement of cognitive reserve later in life, for instance using cognitively stimulating activities, might delay or prevent dementia in stroke patients.

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## Disclosure Statement

No conflicts of interest.

## References

- 1 Caamano-Isorna F, Corral M, Montes-Martinez A, Takkouche B: Education and dementia: a meta-analytic study. *Neuroepidemiology* 2006;26:226–232.
- 2 Meng X, D'Arcy C: Education and dementia in the context of the cognitive reserve hypothesis: a systematic review with meta-analyses and qualitative analyses. *PLoS One* 2012; 7:e38268.
- 3 Lenehan ME, Summers MJ, Saunders NL, Summers JJ, Vickers JC: Relationship between education and age-related cognitive decline: a review of recent research. *Psychogeriatrics* 2014, Epub ahead of print.
- 4 Stern Y: What is cognitive reserve? Theory and research application of the reserve concept. *J Int Neuropsychol Soc* 2002;8:448–460.
- 5 Jones RN, Manly J, Glymour MM, Rentz DM, Jefferson AL, Stern Y: Conceptual and measurement challenges in research on cognitive reserve. *J Int Neuropsychol Soc* 2011;17:593–601.
- 6 Bennett DA, Wilson RS, Schneider JA, Evans DA, Mendes de Leon CF, Arnold SE, Barnes LL, Bienias JL: Education modifies the relation of AD pathology to level of cognitive function in older persons. *Neurology* 2003;60: 1909–1915.
- 7 Bennett DA, Schneider JA, Wilson RS, Bienias JL, Arnold SE: Education modifies the association of amyloid but not tangles with cognitive function. *Neurology* 2005;65:953–955.
- 8 Rentz DM, Locascio JJ, Becker JA, Moran EK, Eng E, Buckner RL, Sperling RA, Johnson KA: Cognition, reserve, and amyloid deposition in normal aging. *Ann Neurol* 2010;67:353–364.
- 9 Roe CM, Xiong C, Miller JP, Morris JC: Education and Alzheimer disease without dementia: support for the cognitive reserve hypothesis. *Neurology* 2007;68:223–228.
- 10 de la Torre JC: Is Alzheimer's disease a neurodegenerative or a vascular disorder? Data, dogma, and dialectics. *Lancet Neurol* 2004;3: 184–190.
- 11 Dufouil C, Alperovitch A, Tzourio C: Influence of education on the relationship between white matter lesions and cognition. *Neurology* 2003;60:831–836.
- 12 Elkins JS, Longstreth WT Jr, Manolio TA, Newman AB, Bhadrelia RA, Johnston SC: Education and the cognitive decline associated with MRI-defined brain infarct. *Neurology* 2006;67:435–440.
- 13 Vermeer SE, Longstreth WT Jr, Koudstaal PJ: Silent brain infarcts: a systematic review. *Lancet Neurol* 2007;6:611–619.
- 14 Murray CJ, Vos T, Lozano R, Naghavi M, Flaxman AD, Michaud C, et al: Disability-adjusted life years (DALYs) for 291 diseases and injuries in 21 regions, 1990–2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet* 2012;380:2197–2223.
- 15 Pendlebury ST: Stroke-related dementia: rates, risk factors and implications for future research. *Maturitas* 2009;64:165–171.
- 16 Mosca L, Barrett-Connor E, Wenger NK: Sex/gender differences in cardiovascular disease prevention: what a difference a decade makes. *Circulation* 2011;124:2145–2154.
- 17 de Bruijn RF, Bos MJ, Portegies ML, Hofman A, Franco OH, Koudstaal PJ, Ikram MA: The potential for prevention of dementia across two decades: the prospective, population-based Rotterdam study. *BMC Med* 2015;13: 132.
- 18 Reeves MJ, Bushnell CD, Howard G, Gargano JW, Duncan PW, Lynch G, Khatiwoda A, Lisabeth L: Sex differences in stroke: epidemiology, clinical presentation, medical care, and outcomes. *Lancet Neurol* 2008;7:915–926.
- 19 Seshadri S, Wolf PA: Lifetime risk of stroke and dementia: current concepts, and estimates from the Framingham study. *Lancet Neurol* 2007;6:1106–1114.
- 20 Hofman A, Brusselle GG, Darwish Murad S, van Duijn CM, Franco OH, Goedegebuure A, Ikram MA, Klaver CC, Nijsten TE, Peeters RP, Stricker BH, Tiemeier HW, Uitterlinden AG, Vernooij MW: The Rotterdam study: 2016 objectives and design update. *Eur J Epidemiol* 2015;30:661–708.
- 21 Stern Y: Cognitive reserve and Alzheimer disease. *Alzheimer Dis Assoc Disord* 2006;20: 112–117.
- 22 Bos MJ, Koudstaal PJ, Hofman A, Ikram MA: Modifiable etiological factors and the burden of stroke from the Rotterdam study: a population-based cohort study. *PLoS Med* 2014; 11:e1001634.
- 23 Wieberdink RG, Ikram MA, Hofman A, Koudstaal PJ, Breteler MM: Trends in stroke incidence rates and stroke risk factors in Rotterdam, the Netherlands from 1990 to 2008. *Eur J Epidemiol* 2012;27:287–295.
- 24 Bos MJ, van Rijn MJ, Witteman JC, Hofman A, Koudstaal PJ, Breteler MM: Incidence and prognosis of transient neurological attacks. *JAMA* 2007;298:2877–2885.
- 25 Clark TG, Altman DG, De Stavola BL: Quantification of the completeness of follow-up. *Lancet* 2002;359:1309–1310.
- 26 Schrijvers EM, Verhaaren BF, Koudstaal PJ, Hofman A, Ikram MA, Breteler MM: Is dementia incidence declining?: trends in dementia incidence since 1990 in the Rotterdam study. *Neurology* 2012;78:1456–1463.
- 27 Folstein MF, Folstein SE, McHugh PR: 'Minimal state'. A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res* 1975;12:189–198.
- 28 McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM: Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA work group under the auspices of department of health and human services task force on Alzheimer's disease. *Neurology* 1984;34:939–944.
- 29 Roman GC, Tatemichi TK, Erkinjuntti T, Cummings JL, Masdeu JC, Garcia JH, Amaducci L, Orgogozo JM, Brun A, Hofman A, et al: Vascular dementia: diagnostic criteria for research studies. Report of the NINDS-AIREN international workshop. *Neurology* 1993;43:250–260.
- 30 Hoogendam YY, Hofman A, Van der Geest JN, van der Lugt A, Ikram MA: Patterns of cognitive function in aging: the Rotterdam study. *Eur J Epidemiol* 2014;29:133–140.
- 31 Alberti KG, Zimmet PZ: Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus provisional report of a WHO consultation. *Diabet Med* 1998;15: 539–553.
- 32 Savva GM, Stephan BC; Alzheimer's Society Vascular Dementia Systematic Review Group: Epidemiological studies of the effect of stroke on incident dementia: a systematic review. *Stroke* 2010;41:e41–e46.
- 33 Jacquin A, Binquet C, Rouaud O, Graule-Petot A, Daubail B, Osseby GV, Bonithon-Kopp C, Giroud M, Bejot Y: Post-stroke cognitive impairment: high prevalence and determining factors in a cohort of mild stroke. *J Alzheimers Dis* 2014;40:1029–1038.
- 34 Ojala-Oksala J, Jokinen H, Kopsi V, Lehtonen K, Luukkonen L, Paukkunen A, Seeck L, Melkas S, Pohjasvaara T, Karhunen P, Hietanen M, Erkinjuntti T, Oksala N: Educational history is an independent predictor of cognitive deficits and long-term survival in postacute patients with mild to moderate ischemic stroke. *Stroke* 2010;43:2931–2935.
- 35 Sachdev PS, Brodaty H, Valenzuela MJ, Lorentz LM, Koschera A: Progression of cognitive impairment in stroke patients. *Neurology* 2004;63:1618–1623.
- 36 Harrison SL, Sajjad A, Bramer WM, Ikram MA, Tiemeier H, Stephan BC: Exploring strategies to operationalize cognitive reserve: a systematic review of reviews. *J Clin Exp Neuropsychol* 2015;37:253–264.
- 37 Stern Y: Cognitive reserve. *Neuropsychologia* 2009;47:2015–2028.
- 38 Valenzuela MJ: Brain reserve and the prevention of dementia. *Curr Opin Psychiatry* 2008; 21:296–302.