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Influence of education on the relationship between white matter lesions and cognition

C. Dufouil, PhD; A. Alpérovitch, MD; and C. Tzourio, MD, PhD

Abstract—*Objective:* To test the hypothesis that education level modulates the effects of cerebral white matter hyperintensities (WMH) on cognition in a large population-based study. *Methods:* A total of 845 elderly subjects aged 64 to 76 years who enrolled in a longitudinal study on cognitive decline and vascular aging had an MRI examination. Cognitive functions were assessed by Mini-Mental State Examination, Trail Making Test Part B, Digit Symbol Substitution Test of the Wechsler Adult Intelligence Scale–Revised, Finger Tapping Test, Word Fluency Test, and Raven Progressive Matrix. MRI scans were interpreted visually using a standardized scale for rating WMH. *Results:* Severe WMH were present in 17% of the participants who had lower performances on tests involving attention tasks. In participants with a lower level of education, presence of severe WMH was significantly associated with lower cognitive performances. This was found for all cognitive tests. Conversely, in participants with a high level of education, there was no significant association between severity of WMH and level of cognitive functions. *Conclusion:* Education modulates the consequences of WMH on cognition. Participants with a high level of education were protected against the cognitive deterioration related to vascular insults of the brain.

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Cerebral white matter hyperintensities (WMH) are commonly observed on MRI of the brain of elderly persons. These hyperintensities are usually interpreted as small brain lesions related to age and vascular risk factors.[1]

The consequences of WMH on cognition have been investigated in clinical series of demented and nondemented patients and community-based samples.[2-17] Most studies have shown a significant association between WMH and cognitive impairment or severity of dementia.[2,5-11] However, a majority of these studies are based on small samples[3,5,6,9-11,14,15] and none of them has studied the possible role of education on the association between WMH and cognition.

There is substantial evidence of an association between higher educational level and decreased incidence of dementia in various populations and study settings.[18-20] Different hypotheses have been raised to explain this association, which remains intriguing and regularly debated.[21-30] The main hypothesis is that clinical manifestations of cognitive disorders related to brain lesions are delayed in more highly educated people. This putative protective effect of education on the risk of dementia or cognitive impairment could also be explored when evaluating the cognitive alterations related to WMH.

In the current study, we examined the relationship between WMH and cognitive performances by level of education in a large population-based cohort of elderly individuals.

Materials and methods. *Study population.* The Epidemiology of Vascular Ageing (EVA) study is a longitudinal study on vascular aging and cognitive decline. The EVA study sample consists of 1,389 subjects, born between 1922 and 1932, recruited between June 1991 and June 1993 from electoral rolls in Nantes, west of France. The 4-year follow-up (June 1995 through June 1997) was completed by 86% of the initial sample (n = 1,188); 31 subjects died and 170 refused to be re-examined.

Data collected. At each wave of the study, during a face-to-face interview at the examination center, data on demographic characteristics, medical history, and current medication intake were collected. A complete assessment of cognitive functions was performed using a battery of neuropsychological tests designed to cover multiple areas of cognitive functioning.[31] The tests were administered by trained psychologists. The Mini-Mental State Examination (MMSE) provided a global assessment of cognitive functioning.[32,33] Attention was assessed using two tests: the Trail Making Test part B (TMT B)[34] and the Digit Symbol Substitution Test (DSST) of the Wechsler Adult Intelligence Scale–Revised.[35] The battery also included assessment of general skills such as logical intelligence and reasoning (Raven Progressive Matrices [RPM][36]) and verbal fluency (Word Fluency Test [WFT][37]). Assessment of psychomotor speed by the Finger Tapping Test (FTT)[38] was also included in this battery.

MRI. At 4-year follow-up, MRI examination was proposed to all subjects and 88% of them agreed to participate. Owing to financial limitations, 845 MRI examinations were performed.

Exclusion criteria were conventional: 1) cardiac pacemaker, valvular prosthesis, or other internal electrical device; 2) history of neurosurgery or aneurysm; 3) metal fragments in the eyes, brain, or spinal cord.

MRI was performed using a 1.0 T scanner (Siemens, Erlangen,

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Germany). Details of image acquisition procedure are described elsewhere.[39] The proton density and T2-weighted MR images were rated visually with respect to the presence of hyperintensities in the white matter using a modified version of the scale developed by Scheltens et al.[40] It provided an overall four-class WMH grade ranging from A to D according to the following criteria: A = no lesion; B (mild WMH) = deep white matter hyperintensities (DWMH) ≤3 mm or periventricular hyperintensities (PH) ≤5 mm; C (moderate WMH) = 1 to 10 DWMH of 4 to 10 mm or PH of 6 to 10 mm; D (severe WMH) = more than 10 DWMH of 4 to 10 mm or confluent DWMH or PH ≥ 11 mm.

All the ratings were done by a single trained doctor who was blind to any clinical data or diagnoses. Among the 845 MRI examinations performed, 841 were read (four scans were not interpreted because of poor technical quality). The intraobserver variability was estimated on a random sample of 100 of the 841 scans. For the four-category grading of WMH, the intrareader kappa coefficient was 0.78.

The distribution of WMH in this sample showed that only 12 subjects had no WMH (grade A). These 12 subjects have therefore been pooled with those having mild WMH in the analyses.

Covariates. The following covariates were selected on the basis of their known association with cerebral WMH or cognition or both: age, sex, education, occupation, smoking status, alcohol consumption, history of vascular disease, hypertension, and depressive symptoms. For covariates changing over time—i.e., hypertension, depressive symptoms, smoking status, and alcohol use—values measured at the 4-year time point were studied.

Educational level was assessed at baseline by recording number of years of schooling. Two educational levels were defined based on median of the distribution for stratified analysis: low educational level (less than 11 years of schooling) or high education level (11 years of schooling or more). The quartiles of years of education distribution were also considered.

Occupation history was recorded during baseline interview. For the purpose of this study, we used the occupation with the longest duration, classified by the seven categories defined by the "Institut National des Statistiques et Etudes Economiques (INSEE)": farmers, domestic service employees, blue-collar workers, other employees, craftsmen and shopkeepers, professionals and managerials, housewives.

With respect to smoking behavior, subjects were classified as never smoked, former smoker, or current smoker. Total daily intake of alcohol was estimated in milliliters according to the average number of milliliters of ethanol in a glass of each type of alcoholic beverage. History of vascular disease was defined as self-reported history of myocardial infarction or angina pectoris or arteritis or stroke. At each wave of the study, two separate measurements of systolic and diastolic blood pressure were made using a digital electronic tensiometer after a 10-minute rest. We used the mean of the two measurements in the analysis. We defined high blood pressure as systolic blood pressure ≥ 160 mm Hg or diastolic blood pressure ≥ 95 mm Hg. Hypertension was defined as either high blood pressure or intake of antihypertensive medication. Depressive symptoms were assessed by the Center of Epidemiologic Studies–Depression scale (CES-D).[41] Evaluation of the CES-D in a French population has shown that men scoring more than 16 and women scoring more than 22 should be considered at high risk for clinical depression.[42]

Among subjects who were followed up at 4 years, subjects who participated (n = 845) in the MRI study were not statistically different from nonparticipants (n = 343) for age (68.9 years [SD = 2.9] vs 69.1 years [SD = 3.1], p = 0.53), female sex (58.0% vs 59.9%, p = 0.55), or mean number of years of schooling (10.7

Table 1 *Description of the EVA-MRI cohort**

	Grade of white matter hyperintensities (WMH)			*p* Values†			
Characteristics	I, mild, n = 320	II, moderate, n = 378	III, severe, n = 143	Global‡	I/II§	I/III¶	II/III‖
Mean (SD) age at MRI examination, y	68.5 (3.0)	69.1 (2.8)	69.7 (3.1)	0.0001	0.003	0.001	0.06
Female, %	54.7	60.6	59.4	0.27	0.12	0.35	0.82
Mean (SD) education level, y	10.6 (3.4)	10.8 (3.5)	10.6 (3.5)	0.74	0.55	0.85	0.51
Occupation, %							
Farmers, blue-collar workers	13.1	11.1	9.8	0.76	0.34	0.88	0.90
Employees	50.3	46.8	50.3				
Craftsmen and shopkeepers	7.5	7.9	7.0				
Professionals and managerials	17.5	17.5	18.2				
Housewives	11.6	16.7	14.7				
History of vascular disease,** %	10.3	11.9	21.0	0.005	0.51	0.002	0.009
Hypertension,†† %	21.3	23.9	41.3	0.0001	0.32	0.0001	0.002
Mean (SD) daily alcohol consumption, mL	16.3 (18.9)	13.3 (16.7)	12.9 (15.8)	0.04	0.02	0.05	0.85
Current smoker, %	6.9	9.0	9.8	0.47	0.30	0.28	0.48
High depressive symptoms,‡‡ %	13.5	16.4	15.5	0.56	0.29	0.57	0.81
At least one e4 allele of APO E, %	28.7	25.6	18.7	0.09	0.37	0.07	0.11

* Characteristics at 4-year follow-up.

† *p* Value from chi-square test for percentages comparisons, analysis of variance for means comparisons.

‡ Significance for global test.

§ Significance for test comparing subjects with mild WMH to those with moderate WMH.

¶ Significance for test comparing subjects with mild WMH to those with severe WMH.

‖ Significance for test comparing subjects with moderate WMH to those with severe WMH.

** Self-reported history of myocardial infarction or angina pectoris or arteritis or stroke.

†† Systolic blood pressure ≥160 mm Hg or diastolic blood pressure ≥ 95 mm Hg or intake of antihypertensive drugs.

‡‡ Depressive symptoms assessed by the Center of Epidemiological Studies–Depression scale.

EVA = Epidemiology of Vascular Aging study.

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[SD = 3.5] vs 10.8 [SD = 3.5], $p = 0.52$). Frequency of hypertension at 4-year follow-up was higher in MRI examination nonparticipants than in participants (43.5% vs 36.7%, $p = 0.03$). Participants and nonparticipants had similar frequency of positive history of vascular disease (13.0% vs 12.9%, $p = 0.81$), as well as smoking (42.0% vs 39.8% of ever smokers, $p = 0.81$) and alcohol consumption habits (mean daily alcohol consumption 17.9 [SD = 17.4] mL vs 18.4 [SD = 17.8] mL, $p = 0.76$). MRI study participants and nonparticipants also had similar mean MMSE scores at 4-year follow-up (27.53 [SD = 2.1] vs 27.48 [SD = 2.3], $p = 0.69$), and similar levels of performances on other psychometric tests (data not shown).

Statistical methods. The outcome variables consisted of the cognitive test scores at 4-year follow-up. We first assessed the effect of WMH on cognition using analysis of covariance methods. Age, sex, education, occupation, smoking status, alcohol consumption, history of vascular diseases, hypertension, and depressive symptoms were also added to the models as potential confounders. To test the hypothesis that the level of education may modify the relationship between WMH and cognition, we added the interaction term for WMH and education to the above model and tested for its significance. This was done using level of education both as a dichotomous variable and as a four-level variable.

Results. *Demographic and health characteristics.* Mean age of the 841 EVA-MRI participants was 69 years (SD = 2.9). Fifty-eight percent were women and the mean education attainment was 10.6 years. One percent of the participants had no WMH and 17% of them had severe WMH. Characteristics of participants by severity of WMH are shown in table 1. Subjects with severe WMH were older than those with mild or moderate WMH. Prevalence of moderate or severe WMH was higher in women, but the difference between men and women was not significant. Severity of WMH was not associated with education level or occupation. There was no significant relationship between WMH severity and variables known to influence cognitive performances like depressive symptomatology and apolipoprotein E polymorphism. Prevalence of vascular disease history and hypertension increased with increasing severity of WMH whereas mean alcohol consumption decreased with increasing severity of WMH.

WMH and cognition. Table 2 shows the age-adjusted relationship between WMH and cognitive performances. Global cognitive performances assessed by MMSE were not associated with severity of WMH. Subjects with severe WMH consistently performed worse than those with mild or moderate WMH across all tests assessing attention and speed (DSST, TMT B, RPM, and FTT).

Further adjustment on sex, education level, occupation, hypertension, alcohol consumption, smoking status, depressive symptoms, and history of vascular disease did not modify those relationships.

Excluding subjects with a history of stroke during the follow-up (n = 33) did not change our findings.

Interaction with education. Table 3 shows adjusted mean cognitive test scores by grade of severity of WMH in subjects with low education attainment and in those with high education attainment. Overall, there was a clear relationship between severe WMH and lower cognitive performances in lower educated people whereas no or weaker association between WMH and cognition was observed in those with higher education level. In lower educated people, subjects with severe WMH consistently performed worse than those with mild or moderate WMH on all neuropsychological tests. The interaction between education and WMH reached significance for MMSE, RPM, and WFT.

For tests assessing attention and psychomotor speed (TMT B, DSST, and FTT), the interaction term was not significant: subjects with severe WMH had lower cognitive performances than those with mild WMH whatever the education attainment (as shown in table 2).

The figure illustrates the influence of the interaction between education level and WMH grade on MMSE performances using quartiles of education rather than median. This analysis suggests a "dose effect": the lower the education level, the stronger the relationship between severity of WMH and lower cognition. We also performed similar analysis for the other tests but the results were not as clearly in favor of a dose-effect relationship (p value of test for interaction between quartile of education and severity of WMH was 0.86 for TMT B, 0.77 for DSST, 0.06 for RPM, 0.07 for WFT, and 0.19 for FTT).

Discussion. In this population-based study with a large number of MRI, we found that education level

Table 2 *Cross-sectional relationship between white matter hyperintensities (WMH) and cognitive performances*

Test	Grade of WMH, mean (SE)*			p Values				
	I, mild, n = 320	II, moderate, n = 378	III, severe, n = 143	Global†	Global‡	I/II§	I/III¶	II/III‖
MMSE	27.6 (0.1)	27.5 (0.1)	27.6 (0.2)	0.68	0.49	0.45	0.92	0.49
DSST	48.4 (0.7)	47.6 (0.6)	45.9 (1.0)	0.04	0.01	0.34	0.04	0.17
TMT B	105 (42)	108 (44)	114 (53)	0.10	0.05	0.51	0.08	0.19
RPM	15.1 (3.0)	15.0 (3.1)	14.4 (4.2)	0.07	0.10	0.61	0.05	0.10
WFT	17.9 (6.2)	17.9 (6.4)	17.4 (6.3)	0.41	0.54	0.98	0.46	0.44
FTT	142 (20)	139 (22)	135 (22)	0.003	0.01	0.08	0.003	0.08

* Age-adjusted means. SE = standard error.

† Significance for test comparing mean scores according to severity of WMH after adjusting for age.

‡ Significance for test comparing mean scores according to severity of WMH after adjusting for age, sex, years of education, occupation, hypertension at concurrent examination, alcohol consumption at concurrent examination, history of vascular disease.

§ Significance for test comparing mean scores between subjects with mild WMH and subjects with moderate WMH after adjusting for age, sex, years of education, occupation, hypertension at concurrent examination, alcohol consumption at concurrent examination, history of vascular disease.

¶ Significance for test comparing mean scores between subjects with mild WMH and subjects with severe WMH after adjusting for age, sex, years of education, occupation, hypertension at concurrent examination, alcohol consumption at concurrent examination, history of vascular disease.

‖ Significance for test comparing mean scores between subjects with moderate WMH and subjects with severe WMH after adjusting for age, sex, years of education, occupation, hypertension at concurrent examination, alcohol consumption at concurrent examination, history of vascular disease.

MMSE = Mini-Mental State Examination; DSST = Digit Symbol Substitution Test of the Wechsler Adult Intelligence Scale–Revised; TMT B = Trail Making Test part B; RPM = Raven Progressive Matrices; WFT = Word Fluency Test; FTT = Finger Tapping Test.

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Table 3 Adjusted* mean scores on neuropsychological tests by grade of white matter hyperintensities (WMH) and education attainment†

Test	Lower education attainment, Grade of WMH: Mild, n = 166	Moderate, n = 194	Severe, n = 80	Higher education attainment, Grade of WMH: Mild, n = 154	Moderate, n = 182	Severe, n = 63	p For interaction
MMSE	27.2 (0.2)	26.9 (0.2)	26.6 (0.2)	28.0 (0.2)	28.0 (0.2)	28.5 (0.3)	0.003
DSST	45.3 (1.0)	43.7 (0.9)	42.2 (1.4)	52.5 (1.0)	51.2 (0.9)	49.8 (1.5)	0.75
TMT B	115 (3.9)	119 (3.6)	125 (5.2)	94 (3.8)	96 (3.5)	101 (5.6)	0.31
RPM	14.4 (0.3)	14.2 (0.3)	13.6 (0.4)	15.8 (0.3)	15.8 (0.3)	15.7 (0.4)	0.04
WFT	16.7 (0.5)	16.2 (0.5)	15.2 (0.7)	19.2 (0.5)	19.7 (0.5)	19.8 (0.8)	0.03
FTT	139 (2)	135 (2)	131 (2)	143 (2)	143 (2)	139 (2)	0.13

Values are mean (SE).

* Estimated from analysis of covariance adjusting for the effects of age at MRI examination, sex, occupation, hypertension at concurrent examination, alcohol consumption at concurrent examination, history of vascular disease, grade of WMH, education attainment, and interaction between WMH and education attainment.

† Education attainment was treated as a binary variable based on median threshold.

MMSE = Mini-Mental State Examination; DSST = Digit Symbol Substitution Test of the Wechsler Adult Intelligence Scale–Revised; TMT B = Trail Making Test part B; RPM = Raven Progressive Matrices; WFT = Word Fluency Test; FTT = Finger Tapping Test.

modified the relationship between WMH and cognition. In individuals with lower education level, severe WMH were associated with lower cognitive performances. Conversely, in more educated people, there was no relationship between WMH severity and cognitive performances.

There have been relatively few population-based studies on the relationship between WMH and cognition. These studies generally reported that severe WMH were significantly associated with lower scores on cognitive tests assessing mainly attention and psychomotor speed.[2,5,7,43] Interestingly, we observed the same relationship when education was not taken into account. However, after stratification on education level, we found that WMH were associated with lower performances in all areas of cognition in participants with a low level of education.

These results reinforce the view that a higher educational level might protect against the consequences of brain lesions on cognition. Interestingly, the load of WMH was not associated with educational level, which suggests that, in this sample, education had no effect on the impact of vascular risk factors on the brain.

The EVA-MRI study has strengths and limitations. Its strengths include the large number of MRI examinations performed and the high rate of participation at both 4-year follow-up and MRI substudy (82%), the homogeneous reading of the scan by a single trained rater, the complete assessment of multiple areas of cognitive functioning, and the well-documented medical conditions of subjects. Some methodologic issues also must be raised. As mentioned above, although the acceptance rate of MRI study was high, MRI was performed on a subsample of those who agreed to participate owing to financial

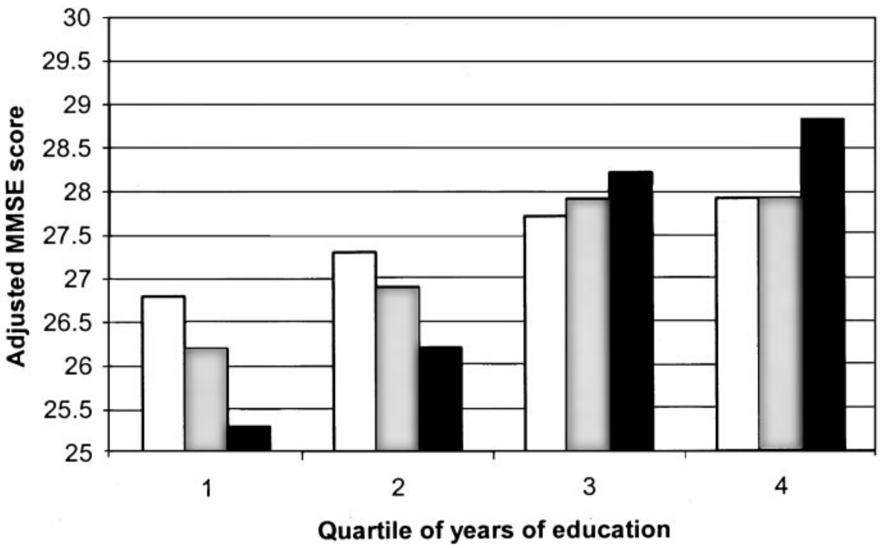

Figure. Relationship between grade of white matter hyperintensities (WMH) and Mini-Mental State Examination score by quartile of years of education. □ *= mild WMH,* ▨ *= moderate WMH;* ■ *= severe WMH.*

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restrictions. The fact that subjects who had the MRI were not different from those who did not have the examination for cognitive performances indicates that our findings based on a restricted sample of the original EVA sample are not biased. A second issue is related to the nature of the sample. The EVA subjects volunteered to participate and compared to the general population of the same age, they belong to higher social class and are globally healthier. To illustrate this, only 3.3% of the participants had a history of myocardial infarction in this cohort compared to 8% in the Rotterdam Study.[44] This selection might lead to an under-representation of people with the most severe WMH. Likewise, subjects with severe cognitive impairment might have been under-represented and people with high educational attainment are likely to be over-represented. This selection can be viewed as an advantage. Because the EVA study participants had fewer diseases and health problems than the general population of same age, it is unlikely that unmeasured factors confound the relationship between WMH and cognition.

The fact that the relationship between WMH and cognition is weaker in higher educated people could be due to psychometric properties of the tests used and especially ceiling effect. This is particularly true for the MMSE as the maximum score of 30 is often reached. It could be due as well to the fact that those tests are not sensitive enough to subtle changes that could occur in higher educated people.

Another limitation of our findings is that we performed multiple tests simultaneously and one cannot reject that some of the significant results are attributable to random. The fact that our results are in the same direction for most neuropsychological tests is reassuring in that regard.

We demonstrate that education is a strong effect modifier in the relationship between WMH and cognition. This finding suggests that the level of education must be taken into account in the analysis of the consequences of WMH on cognition. This could help to clarify some of the discrepancies found in previous studies.

More broadly, our findings reinforce the view that education is associated with an increased cognitive reserve. The cognitive reserve hypothesis speculates that individuals manifest different thresholds for symptom occurrence related to brain dysfunction.[23,45-48] Those with a greater reserve can sustain more brain disturbance before manifesting symptoms, whereas those with little cognitive reserve become symptomatic with more limited functional insults. Thus, if higher education increases cognitive reserve,[25] it might contribute to preventing or deferring the consequences of WMH on cognition. Alternatively, lower education would increase the likelihood of manifesting cognitive deterioration due to WMH. The concept of cognitive reserve could be interpreted in two nonexclusive ways. The reserve could be an acquired set of skills (qualitative scenario) or an increase of synaptic density (quantitative scenario). Our data are consistent with the reserve hypothesis in the relationship between vascular lesions and cognition. However, they do not allow us to decide in favor of either of the two scenarios. Both genetic factors and early life environmental factors might influence education attainment and contribute to cognitive reserve but we have not collected such data.[22,23,49-51] This study does not allow us to investigate more deeply the mechanisms by which education levels might influence the consequences of WMH on cognition. Other surrogates of general well-being like occupation or incomes were similarly studied but did not lead to similar results, suggesting a specific role of education.

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