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Education modulates the impact of white matter lesions on the risk of mild cognitive impairment and dementia

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Keywords : Alzheimer's disease, dementia, mild cognitive impairment (MCI), white matter lesions, Magnetic Resonance Imaging (MRI), cognitive reserve, cohort studies.

Abstract

Objectives: Conflicting results have been reported regarding the association between white matter lesions (WML) and cognitive impairment. We hypothesized that education, a marker of cognitive reserve (CR), could modulate the effects of WML on the risk of Mild Cognitive Impairment (MCI) or dementia.

Methods: We followed 500 healthy subjects from a cohort of community-dwelling persons aged 65 years and over (ESPRIT Project). At baseline, WML volume was measured using a semi-automatic method on T2-weighted MRI. Standardized cognitive and neurological evaluations were repeated after 2, 4 and 7 years. The sample was dichotomized according to education level into low (≤8 years) and high (>8 years) education groups. Cox proportional hazard models were constructed to study the association between WML and risk of MCI/dementia.

Results: The interaction between education level and WML volume reached significance (p=0.017). After adjustment for potential confounders, the association between severe WML and increased MCI/dementia risk was significant in the low education group (≤8 years) (p=0.02, HR= 3.77 [1.29-10.99]), but not in the high education group (>8 years) (p=0.82, HR=1.07 [0.61-1.87]).

Conclusions: Severe WML significantly increases the risk of developing MCI/dementia over a 7-year period in low educated participants. Subjects with higher education levels were seen to be more likely to be resilient to the deleterious effects of severe WML. The CR hypothesis suggests several avenues for dementia prevention.

Key words: Alzheimer's disease, dementia, mild cognitive impairment (MCI), white matter lesions, Magnetic Resonance Imaging (MRI), cognitive reserve, cohort studies.

INTRODUCTION

Cerebral white matter lesions (WML) are commonly found on magnetic resonance imaging (MRI) scans of elderly people. WML are thought to be the result of degenerative changes in small vessels (1, 2), and hypertension and arteriosclerosis are considered significant risk factors (3, 4). Although several studies indicate that WML is associated with cognitive decline and incident dementia (5), others suggest no relationship between WML and cognition (6, 7). The relationship of WML to cognitive impairment in normal aging and dementia is still not fully understood. Discrepant findings may be due in part to the heterogeneity of the cognitive domains assessed, differences in MRI methodologies and variability in the cognitive status of the subjects. Apart from differences in study design, there is also considerable variability in the density of WML in normal older adults, and the relationship of density to cognitive dysfunction: people may differ in their capacity to compensate for the deleterious effect of cerebral lesions, as has already been observed for some people with extensive Alzheimer disease (AD) pathology (senile plaques and neurofibrillary tangles) who do not exhibit cognitive impairment (8). Identifying factors associated with the ability to tolerate WML accumulation has important implications for promoting successful cognitive aging.

A concept which has been developed to explain how neurodegenerative changes that are similar in nature and extent, may give rise to considerable variation in terms of cognitive consequences, is the “cognitive reserve” that could be active or passive (9). This may be defined as individual ability to make flexible and efficient use of available neuronal networks in the active model (10), and as the capacity of the brain itself to cope with pathology better than others in the passive model. The reserve hypothesis

has been evoked in relation to many brain disorders, notably those which are ageing-related but also to head injury, schizophrenia, depression and multiple sclerosis (11). Patients with AD or mild cognitive impairment (MCI) with higher cognitive reserve (CR) showed an increased capacity to cope with reduced white matter integrity in diffusion tensor imaging (DTI) studies compared to patients with lower CR (12, 13). Although one study did not find direct evidence to support the CR hypothesis (14), several others volumetric MRI studies observed that CR could influence the relationship between WML and some cognitive domains (14-20), and dementia (21). CR could indeed balance the negative impact of pathological brain burden such as that of WML on late life cognitive ability in people without cognitive impairment acting through both protective and compensatory mechanisms. The most frequently used proxies for CR have been education, occupational attainment, premorbid intelligence quotient (IQ), head size, and mentally stimulating activities (22-25). The only study to date investigating the influence of CR on the relationship between WML and dementia was cross-sectional (21), and used head size as proxy of CR, which is assumed to reflect the passive model. Moreover, WML were estimated with CT scans that are less sensitive than MRI in detecting WML. To our knowledge, education, a proxy of the active model of CR, has not been considered as a possible moderating factor in the association between WML load and onset of dementia or MCI; outcomes that reflect a global cognitive disorder covering several cognitive domains.

We thus examined in a seven-year longitudinal population-based study whether education level could modulate the impact of WML on risk of MCI/dementia in cognitively non-impaired elderly persons.

METHODS

Study population

Between 1999 and 2001, 1863 people aged 65 years and over were recruited from the electoral rolls for the ESPRIT Project (Montpellier, France). The study design has been described elsewhere (26). The study protocol was approved by the Ethics Committee of the University Hospital of Bicêtre (France) and written informed consent was obtained from each participant. Examinations comprised a standardized interview, neuropsychological tests and a standardized neurological examination at baseline and after 2, 4 and 7 years. At baseline, 760 participants under the age of 80 years were randomly selected and invited to have a MRI brain scan. For the present study, we excluded 43 persons who did not have MRI images of sufficiently good quality to quantify the total WML volume and subjects who received a diagnosis of dementia (n=14) or MCI (n=127) at baseline. This group was further reduced by eliminating subjects with missing data for cognitive status at baseline (n=29) or covariates (total brain volume: n=23, hippocampal volume: n=3, Apolipoprotein E4 (APOE 4) genotype: n=4, depressive symptomatology: n=1), and without follow-up examination (n=16). These 76 excluded subjects were significantly older than the other participants, but did not differ with respect of gender, education level, and total WML volume. Of the remaining 500 participants, 53% were women and the median age was 71 years for men and 70 for women.

MR imaging

Estimation of white matter lesion volume

MRI structural imaging was carried out by transversal fast multislice double echo T2-weighted 2D axial acquisition, (TR=4400ms, TE1 and TE2= 16ms and 98ms, slice thickness = 4mm, gap= 0.4mm, matrix = 256x256, in-plane resolution = 0.98 x 0.98mm^2), that covered the whole brain. T1-weighted volumetric MR imaging was also obtained by using the spoiled gradient echo sequence (TR = 97ms, TE = 4ms)) which consisted of a set of 124 adjacent transverse sections parallel to the anterior commissure-posterior commissure line with a section thickness of 1.5mm (no gap). WML volume was estimated using a semi-automatic method (27-29). Areas of supratentorial WML appearing as hyperintensities were segmented on T2-weighted sequences using the MRIcro software (30). Assessment of infratentorial WML was not included in the present study. A first layer of regions of interest (ROIs) corresponding to WML was created by a semi-automated technique based on intensity thresholding. A second layer of ROIs was then manually outlined on each slide by roughly contouring all WML. The intersection between the first and second layer was then manually inspected and automatic total WML volume obtained. An experienced reader blind to follow-up outcome (EB) examined all scans. A neurologist (FP) examined 80 randomly chosen scans to assess inter-rater reliability. Inter-reader and intrareader-intraclass correlation coefficients showed good to excellent agreement (0.79 and 0.95 respectively).

Estimation of brain volume, brain atrophy, hippocampal volume and silent brain infarcts

T1-weighted anatomical images were segmented with SPM 5 (Wellcome Department of Cognitive Neurology) to derive grey matter and white matter volumes. Total brain volume was then calculated as the sum of volumes of grey and white matter, and used as covariate in order to minimize the effect due to global brain size differences.

Brain atrophy was determined as the percentage of the volume of cerebrospinal fluid (CSF) on the intracranial volume (sum of grey matter, WM and CSF volumes). Hippocampal ROIs were manually outlined on consecutive coronal slices and the axial and sagittal orientations verified (31). The complete method was described elsewhere (32). Presence of silent brain infarcts (SBI) was assessed visually by a neurologist (FP). SBI were defined as focal hyperintensities areas (≥ 3 mm in size) on T2-weighted images, measured using dedicated software (Myrian®, Intrasense).

Assessment of education level

Education level was assessed at baseline with a four-level variable: no formal education or primary school, lower secondary education, higher secondary education, and university degree. For the analyses, we defined a dichotomous variable: participants with no formal education or primary school (years of schooling ≤ 8) and participants with at least a lower secondary education level (years of schooling >8).

Diagnosis of dementia and MCI

Preliminary diagnoses of dementia made by a neurologist according to DSM IV criteria (33) at baseline and at each follow-up examination were validated by an independent national panel of neurologists to obtain consensus. Although type of dementia was

determined during the clinical interview, we did not distinguish between AD and other types of dementia in our analysis due to the low number of incident cases. MCI (which is considered a prodrome to dementia) was diagnosed according to the currently used, revised criteria for MCI (MCI-R algorithm), proposed by an international consensus group (34). We previously showed that the MCI-R algorithm allows a better prediction of the cognitive deficits that will progress towards dementia than the original MCI criteria (35). Briefly, MCI was diagnosed in the presence of a cognitive complaint and with a score within the 20^{th} percentile for the relevant age-matched and education-matched group in at least one of the tests from a short cognitive battery (Benton Visual Retention Test (36), Isaacs' Set Test of verbal fluency (37) and immediate and delayed recall of the 5 Word-Test of Dubois (38)). We used percentiles rather than standard deviations, given the non-normal distribution of the cognitive scores. Study participants with incident MCI are at high risk of developing dementia after the 7 year follow-up and therefore cannot be classified as normal subjects.

We chose to group together patients with dementia and MCI. Separate dementia and MCI groups may be preferable for analytical studies that sought to clarify causation, but in this context we consider both dementia and its prodrome state to constitute a common outcome of progressive cognitive deficit, both being relevant in a public health context.

The date of onset of dementia or MCI was set half way between the date of the last follow-up visit when the subject was classified as normal and the date of diagnosis.

Socio-demographic and clinical factors

The standardized interview included questions on socio-demographic characteristics regarding age, sex and smoking status (non smoker, ex-smoker and current smoker). Depressive symptomatology was assessed with the Center for Epidemiologic Studies-Depression Scale (CESD) (39) with a >16 cut-off point indicating a high level of symptomatology. Blood pressure was measured with a digital electronic OMRON M4 tensiometer twice during the interview. Subjects were considered hypertensive when the mean of the two measures was ≥ 160/90 mm Hg or if they were taking anti-hypertensive drugs. Vascular disease antecedents was composed of self-reported variables and included history of stroke, angina pectoris, myocardial infarction, coronary surgery, coronary angioplasty and arterial surgery of the legs for arteritis. APOE 4 genotype (presence or absence of the allele ε4) (http://www.genopole-lille.fr/spip/) and MMSE score (40), which was used as a dichotomized variable (24 < or ≥ 24), were also included in the statistical analyses.

Statistical analysis

WML volume was considered as a categorical variable to aid interpretation as in many studies (5) and divided in tertiles: severe (tertile 3 >1.5 ml), mild (0.3 ml< tertile 2 ≤ 1.5 ml) and low (0 ml ≤ tertile 1≤ 0.3ml). Univariate comparisons between subjects with low, mild or severe WML load were carried out using polytomous logistic regression adjusted for age and gender. To examine the relationship between WML and risk of MCI/dementia over the 7-year follow-up period, Cox proportional hazard regression models with delayed entry (41) were performed with age as the basic timescale and birth as the time origin.Participants who died or were lost to follow-up without

MCI/dementia were censored at their age of death or at the last cognitive examination respectively .To examine whether education level could modulate the influence of WML on the risk of MCI/dementia, we tested the interaction term for WML and education in a Cox proportional hazard ratio model using age, education level and WML volume as covariates. We stratified the analysis on education level. We first investigated the association between WML load and risk of MCI/dementia in a univariate model. Then a multivariate model adjusted for possible confounders (age, sex, total brain volume, brain atrophy, hippocampal volume, presence of SBI, APOE 4 genotype, depressive symptomatology, previous history of vascular pathology, and hypertension) was carried out.

Finally, we carried out supplementary analyses 1) excluding participants with a baseline MMSE score below 24, 2) to assess separately the association between WML volume and the risk of dementia and the association between WML volume and the risk of MCI. Results of proportional-hazard regression analyses were expressed as hazard ratios (HR) with 95% confidence intervals (CI). Statistical analyses were performed using the SAS software version 9.1 (SAS Institute, Inc., Cary, NC).

RESULTS

Participants' characteristics

Table 1 describes the demographic, clinical and MRI features of the 500 participants selected for this study, and comparison between tertiles of WML volume (low, mild and severe). WML volume was positively correlated with total brain volume, brain atrophy, and age. Severe WML (last tertile) was associated with hypertension and presence of SBI. We did not find any association between WML volume and gender, hippocampal volume, smoking status, history of stroke and variables known to influence cognitive performance, notably depressive symptomatology and APOE ε4 genotype.

Based on education level, participants were divided in two groups: a low education group (no formal education or primary school, ≤8 years) and a high education group (education level ≥ lower secondary education, >8 years). No significant differences in age, gender, smoking status, APOE ε4 genotype, depressive symptomatology, hypertension, vascular factors, WML volume or total brain volume were observed between the two groups. Conversely, frequency of participants with a MMSE score <24 at baseline was significantly higher in the low education group (table 2).

(Table 2 here)

Four hundred and ninety seven (99.4%) subjects had at least 1 follow-up examination. During 3175 persons-years of follow-up (mean per person, 5.4 years), 14 participants

developed dementia (incidence rate: 4.4/1000 person-years in the whole sample; 9.2/1000 person-years in the low education group; and 2.9 /1000 person-years in the high education group) and 121 MCI (incidence rate, 38.1/1000 person-years) (see flow chart in Figure 1). Of the 14 incident cases of dementia, AD was diagnosed in 11 subjects (79%), vascular dementia in 1 (7%), and another 2 (14%) were diagnosed as having other forms of dementia. Twenty participants died (4%), and 89 (18%) were lost to follow-up or refused to continue the study. Subjects who died or were lost to follow-up did not differ from the other participants with respect to gender and volume of WML. However, they were significantly older (mean (SD) age of 72 (4) years), had significantly lower score at MMSE at baseline (mean (SD) score of 27.3 (1.8)) and a lower education level.

(Figure 1, here)

Influence of education level on the relationship between WML and MCI/dementia

The interaction between education level and WML volume reached significance ($p=0.017$). In the univariate analysis, a severe WML load (tertile 3 versus 1) was significantly associated with the risk of MCI/dementia in the low education group ($p<0.01$; HR 4.90; 95% CI, 1.85-12.98), while this association was not significant in the high education group ($p=0.19$; HR 1.38; 95% CI, 0.86-2.23).The results of the Cox proportional-hazard regression analysis stratified according to education level and adjusted for all potential confounders are presented in Table 3. The increased risk of

transition to MCI/dementia in the presence of severe WML load (tertile 3 versus 1) was significant in the low education group (p=0.02; HR 3.77; 95% CI, 1.29-10.99), but was not significant in the high education group (p=0.82; HR 1.07; 95% CI, 0.61-1.87).

Supplementary analysis

Exclusion of subjects with a baseline MMSE score below 24 (n=15) did not modify the results, which suggests the association is not confined to subjects with cognitive deficit at baseline in low educated participants (data not shown).

When they were assessed separately, the association between WML volume and the risk of dementia and the association between WML volume and the risk of MCI remained significant in low educated participants (see tables 1 and 2 in supplemental material).

DISCUSSION

In our sample, education influenced the relationship between WML load and the risk of transition to MCI/dementia. Indeed, individuals with a high education level were more likely to be resilient to the deleterious effects of severe WML, whereas severe WML load increased the risk of transition to MCI/dementia in low educated people during the 7-year study period independently of potential confounders and other structural brain changes detected by MRI. WML volume is not directly associated with education in our sample suggesting that education lowering effect on MCI/dementia risk is thus independent from the WML load.

The observed association between WML severity and risk of MCI/dementia is in agreement with other recent reports (5). Several potential mechanisms may underlie this relationship. WML could cause cognitive impairment by disrupting cortical connections mediated by specific white matter tracts (42). Another hypothesis is the possible interaction between WML and pathological changes related to Alzheimer's disease, which could increase the likelihood of developing clinically significant cognitive decline (43). Finally, WML could be a biomarker of cerebrovascular disease (44). Compared with previous studies, our results show the effect of high WML load on the risk of MCI/dementia over a longer follow-up period (7 years). WML load is likely to progress over time. However, only severe lesion load at baseline (last tertile) was found to be significantly associated with higher risk of transition to MCI/dementia, probably due to a specific increased rate of progression in subjects with greater baseline WML burden

(45). It is therefore important to take this into account in future studies, these findings may be useful to researchers designing clinical trials and could help to identify individuals at higher risk of MCI/dementia.

Our findings suggest that subjects with higher education levels may tolerate more pathology than those with lower education, and that education mitigates the impact of WML on the risk of developing MCI/dementia. How CR is implemented is unclear. Both passive (head size)(21) and active model of CR (education) seem to modulate the effect of WML on dementia. Stronger myelination and more richly connected fiber tracts were observed in white matter of highly educated people (13), and education has been related to head size (46), suggesting a possible link between the two models. This study does not allow us to investigate the precise mechanisms by which education might influence the consequences of WML on the risk of developing MCI or dementia.

A previous study, in which most participants had high levels of education, did not find any influence of education on the relationship between WML and cognitive decline (14). In our population, the interaction between WML and education for risk of MCI/dementia reached significance when education level was defined as low for participants with no formal education or primary school (26% of participants), and high for participants with at least a lower secondary education level (74% of participants). However, if the cut off defining the two education level was changed to a higher secondary education level (55% of participants with education level < higher secondary education or years of schooling<12), the interaction term was no longer significant. This may suggest that education could be protective above a certain threshold which could be quite low (in our study the lower secondary education level). However, above this threshold, the

protective effect is probably not linear and thus difficult to investigate in well-educated samples. Education is related to higher socio-economic status and healthy lifestyle (47, 48), which may protect against vascular brain disease. However, WML load was not different between low and high education groups, suggesting that education might protect against the negative effects of WML, but not against WML development (49). Education could have a specific role in CR. Even if cognitive exercise training still provides protective effects in elderly (50), educational achievement probably occurs during critical periods of neurodevelopment (51).

Some limitations of our study should be considered. Our study sample shows a relative low incidence of dementia (4.4 per 1000 person-year) (52), certainly because it included only participants aged 80 years and younger. Our results might thus have been mainly due to the more numerous incident cases of MCI, but we showed in supplementary analyses (see Table 2 in Supplemental Material) that results did not differ when assessing dementia cases only. Some studies distinguish periventricular from deep WML, however, the different impact of these two locations on cognitive function being still controversial in the literature (53). We have not distinguished these two subtypes but have quantified the overall load of WML.

The strengths of our study include the large number of available MRI data and the length of the follow-up period (7 years). The chosen composite outcome (MCI/dementia), which includes several features and degrees of severity of cognitive disorders, is closer to the clinical reality.

In conclusion**,** our study highlights the impact of WML on the risk of MCI/dementia in healthy elderly people and supports the CR hypothesis by demonstrating that subjects with a high education level are more likely to better tolerate the deleterious effect of severe WML.

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Figure 1. Flow Chart.

Legend to Figure 1.
Study design and flow of participants through the study.

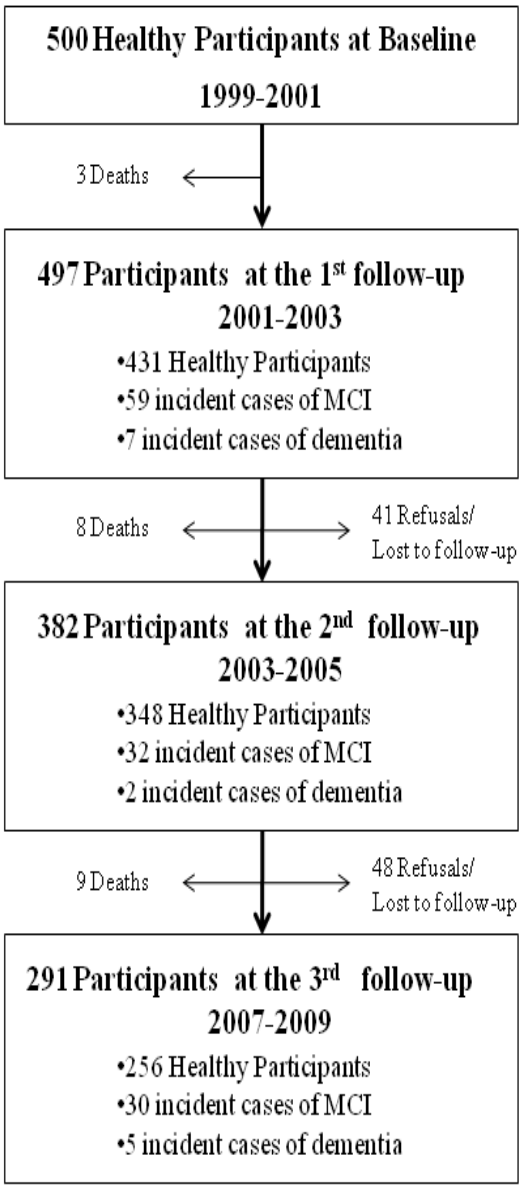

Table 1. Baseline characteristics of the study participants (n=500) and comparison between different levels of WML volume.

	Overall	**Volume of WML**		
		Low (1^{st} tertile) ≤ 0.3ml	Mild (2^{nd} tertile) 0.3-1.5ml	Severe (3^{rd} tertile) >1.5ml
n	500	172	171	157
	Median (10-90th)			
Volume of WML (ml)	0.65 (0.10-7.10)			
			Mean (SD)	
Age (years)	71(4)	70(4)	71(4)	72(4)*
Brain Atrophy (%)	15.2(2.5)	14.5(2.2)	15.2(2.3)*	15.8(2.8)*
Total brain volume (ml)	1020(101)	1004(90)	1018(104)	1038(109)*
Hippocampal volume (ml)	5.80(0.75)	5.77(0.68)	5.88(0.76)	5.75(0.80)
Duration of follow-up (years)	5.4(2.7)	5.5(2.5)	5.9(2.5)	4.8(3.0)
			n (%)	
MCI/dementia (7 years of follow-up)	135(27)	38(22)	38(22)	59(38)*
Female	265(53)	95(55)	85(50)	85(54)
Education level				
Low (≤8years)	129(26)	37(22)	44(26)	48(31)
High (>8years)	371(74)	135(78)	127(74)	109(69)
Smoking status				
Non smoker	277(55)	100(58)	94(55)	83(53)
Ex-smoker	184(37)	60(35)	63(37)	61(39)
Current smoker	39(8)	12(7)	14(8)	13(8)
Hypertension	223(45)	66(38)	70(41)	87(55)*
History of vascular pathology	33(7)	10(6)	10(6)	13(8)
History of stroke	11(2)	3(2)	1(1)	7(4)
Presence of silent brain infarcts	214(43)	35(20)	78(46)*	101(64)*
Apoe ε4 carriers	101(20)	27(16)	37(22)	37(24)
Depressive symptomatology	72(14)	23(13)	26(15)	23(15)
MMSE at baseline <24	15(3)	4(2)	4(2)	7(4)

*p value <0.05, referent=1^{st} tertile (polytomous logistic regression for WML tertile adjusted for sex and age).

Table 2. Comparison between high (>8years) and low (≤8 years) education groups.

	Education level	
	High (n=371)	**Low (n=129)**
	Mean (SD)	
Age at baseline (years)	71(4)	71(4)
Brain atrophy (%)	15.2(2.5)	15.1(2.5)
Total brain volume (ml)	1025(99)	1006(107)
Hippocampal volume (ml)	5.83(0.76)	5.73(0.71)
Duration of follow-up (years)	5.5 (2.6)	5.1 (2.9)
	n (%)	
Total WML volume		
Low (<0.3ml)	135 (37)	37 (29)
Mild (0.3-1.5ml)	127 (34)	44 (34)
Severe (>1.5ml)	109 (29)	48 (37)
MCI/dementia (7 years of follow-up)	99 (27)	36 (28)
Female	190 (51)	75 (58)
Smoking status		
Non smoker	195(53)	82(64)
Ex smoker	146(39)	38(29)
Current smoker	30(8)	9(7)
Hypertension	158 (43)	65 (50)
History of vascular pathology	22 (6)	11 (9)
History of stroke	7(2)	4(3)
Presence of silent brain infarcts	160(43)	54(42)
APOE ε4 carriers	77 (21)	24 (19)
Depressive symptomatology	57 (15)	15(12)
MMSE at baseline <24	4 (1)	11 (9)*

*p value < 0.05 (logistic regression for education level adjusted for sex and age)

Table 3. Influence of education level on the relationship between WML load and risk of MCI/dementia during the 7-year follow-up (multivariate Cox proportional hazard model).

	Education level			
Variables	**High** n=371 , n. of events=99		**Low** n=129, n. of events=36	
	HR (95% CI)	***p***	**HR (95% CI)**	***p***
WML volume				
1st tertile (<0.3ml)	1.0 (Referent)		1.0 (Referent)	
2nd tertile (0.3-1.5ml)	0.71(0.42-1.20)	0.20	0.90(0.25-3.19)	0.87
3rd tertile (>1.5ml)	1.07(0.61-1.87)	0.82	3.77(1.29-10.99)	0.02
Total brain volume (ml)	1.00(0.99-1.01)	0.35	1.00(0.99-1.01)	0.67
Brain atrophy(%)	1.11(1.03-1.21)	0.01	1.08(0.90-1.28)	0.42
Hippocampal volume (ml)	1.09(0.79-1.49)	0.60	0.64(0.34-1.19)	0.16
Presence of silent brain infarcts				
No	1.0 (Referent)		1.0 (Referent)	
Yes	1.08(0.68-1.72)	0.74	1.96(0.94-4.09)	0.07
Sex				
Male	1.0 (Referent)		1.0 (Referent)	
Female	0.75(0.46-1.23)	0.26	1.10(0.37-3.22)	0.87
Smoking status				
Non smoker	1.0 (Referent)		1.0 (Referent)	
Ex-smoker	0.64(0.39-1.05)	0.07	1.38(0.51-3.72)	0.53
Current smoker	1.02(0.50-2.09)	0.96	0.88(0.10-7.81)	0.91
APOE ε4 genotype				
No	1.0 (Referent)		1.0 (Referent)	
Yes	1.34(0.81-2.22)	0.26	1.24(0.54-2.81)	0.61
Depressive symptomatology				
No	1.0 (Referent)		1.0 (Referent)	
Yes	1.69(1.03-2.80)	0.04	1.95(0.69-5.55)	0.21
Previous history of vascular pathology				
No	1.0 (Referent)		1.0 (Referent)	
Yes	1.13(0.50-2.56)	0.77	0.87(0.21-3.55)	0.85
Hypertension				
No	1.0 (Referent)		1.0 (Referent)	
Yes	0.92(0.60-1.41)	0.69	1.62(0.72-3.66)	0.25

Cox proportional hazard regression models with delayed entry were performed with age as the basic timescale and birth as the time origin.

Education modulates the impact of white matter lesions on the risk of mold cognitive impairment and dementia

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Table 1, Supplemental Material. Influence of education on the relationship between WML load and risk of MCI during the 7-year follow-up (Cox proportional hazard model), n=486, n. of events=121.

In order to examine the influence of education on relationship between WML and MCI, the MCI baseline cases and the dementia cases were excluded.

	Education level			
Variables	**High***		**Low†**	
	HR (95% CI)	***p***	**HR (95% CI)**	***p***
WML volume				
1st tertile (<0.3ml)	1.0 (Referent)		1.0 (Referent)	
2nd tertile (0.3-1.5ml)	0.68(0.40-1.16)	0.16	0.75(0.19-2.89)	0.67
3rd tertile (>1.5ml)	1.02(0.58-1.81)	0.93	3.61(1.20-10.88)	0.02
Total brain volume (ml)	1.00(0.99-1.01)	0.40	1.00(0.99-1.01)	0.64
Brain atrophy(%)	1.13(1.04-1.23)	<0.01	1.05(0.86-1.27)	0.65
Hippocampal volume (ml)	1.11(0.81-1.54)	0.52	0.76(0.40-1.46)	0.41
Presence of silent brain infarcts				
No	1.0 (Referent)		1.0 (Referent)	
Yes	1.03(0.64-1.66)	0.90	1.74(0.77-3.91)	0.18
Sex				
Male	1.0 (Referent)		1.0 (Referent)	
Female	0.82(0.52-1.30)	0.41	1.12(0.40-3.10)	0.83
APOE ε4 genotype				
No	1.0 (Referent)		1.0 (Referent)	
Yes	1.26(0.74-2.14)	0.40	1.11(0.42-2.97)	0.83
Depressive symptomatology				
No	1.0 (Referent)		1.0 (Referent)	
Yes	1.76(1.06-2.93)	0.03	3.09(0.96-9.90)	0.06
Previous history of vascular pathology				
No	1.0 (Referent)		1.0 (Referent)	
Yes	1.10(0.49-2.47)	0.82	0.76(0.17-3.45)	0.72
Hypertension				
No	1.0 (Referent)		1.0 (Referent)	
Yes	0.94(0.60-1.46)	0.78	2.06(0.85-5.03)	0.11

* n=362 , n. of events=92.

† n=122, n. of events=29.

Cox proportional hazard regression models with delayed entry were performed with age as the basic timescale and birth as the time origin.

Table 2, Supplemental Material. Influence of education on the relationship between WML load and risk of dementia during the 7-year follow-up (Cox proportional hazard model), n=637, n. of events=30.

In order to examine the influence of education on relationship between WML and dementia, the MCI baseline cases were included. The results should be interpreted with caution, because of the low number of events in each group.

	Education level			
Variables	**High ***		**Low†**	
	HR (95% CI)	***p***	**HR (95% CI)**	***p***
WML volume (ml)	1.02(0.99-1.05)	0.19	1.04(1.01-1.07)	0.02
Total brain volume (ml)	1.005(1.001-1.008)	0.01	1.00(0.99-1.01)	0.17
Brain atrophy(%)	1.21(0.97-1.51)	0.09	1.28(0.90-1.84)	0.76
Hippocampal volume (ml)	0.49(0.20-1.16)	0.10	0.18(0.06-0.54)	<0.01
Presence of silent brain infarcts				
No	1.0 (Referent)		1.0 (Referent)	
Yes	1.50(0.39-5.79)	0.55	2.40(0.78-7.39)	0.13
Sex				
Male	1.0 (Referent)		1.0 (Referent)	
Female	1.82(0.54-6.08)	0.33	0.44(0.11-1.84)	0.26
APOE ε4 genotype				
No	1.0 (Referent)		1.0 (Referent)	
Yes	2.39(0.71-8.06)	0.16	5.98(1.61-22.3)	<0.01
Depressive symptomatology				
No	1.0 (Referent)		1.0 (Referent)	
Yes	0.59(0.11-3.31)	0.55	3.31(0.85-12.9)	0.08
Previous history of vascular pathology				
No	1.0 (Referent)		1.0 (Referent)	
Yes	0.63(0.07-5.64)	0.68	3.54(0.67-18.7)	0.14
Hypertension				
No	1.0 (Referent)		1.0 (Referent)	
Yes	0.97(0.30-3.15)	0.96	0.24(0.06-0.98)	0.05

* n=471 , n. of events=14.

† n=166, n. of events=16.

Cox proportional hazard regression models with delayed entry were performed with age as the basic timescale and birth as the time origin.