Cognitive reserve moderates long-term cognitive and functional outcome in cerebral small vessel disease

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ABSTRACT

Background: Cerebral small vessel disease (SVD) is characterized by progressive white matter hyperintensities (WMH), cognitive decline and loss of functional independence. The correspondence between neuroimaging findings and the severity of clinical symptoms has been modest, however, and thus the outcome may be affected by various host factors. We investigated the predictive value of educational and occupational attainments as proxy measures of cognitive reserve on long-term cognitive and functional outcome in subjects with different degrees of WMH.

Methods: In the Leukoraraiosis and Disability Study (LADIS), 615 older individuals with WMH were evaluated with brain MRI and detailed clinical and neuropsychological assessments in 3-year follow-up. A prolonged follow-up of functional and cognitive status was administered with a structured telephone interview after up to 7 years.

Results: Higher levels of educational and occupational attainment were strongly related to baseline cognitive scores and predicted slower rate of decline in 3-year follow-up in measures of processing speed, executive functions and memory independently of WMH volume and other confounders. The deleterious effect of WMH on processing speed and memory was moderated by education and occupation. Education mitigated the relation of WMH volume on 7-year cognitive status. Moreover, higher education and occupational attainments were related to favorable outcome in 7-year follow-up as defined by sustained functional independence and lower mortality.

Conclusion: The results support the presumption that cognitive reserve plays a significant role as a buffer against the clinical manifestations of SVD and may in part explain high individual variability in outcome.

INTRODUCTION

Cerebral small vessel disease (SVD) is the leading cause of vascular cognitive impairment and a considerable burden on public health. To date, there is no specific treatment for SVD, and the primary therapeutic goals are in early prevention and control of the risk factors.[1, 2] The core neuroimaging findings of SVD are white matter hyperintensities (WMH) of presumed vascular origin, which may occur together with lacunes or small subcortical infarcts, microbleeds, perivascular spaces and brain atrophy.[3] These changes are associated with cognitive decline and loss of independent functional abilities.[4-7] However, the correspondence between lesions and outcome has remained modest suggesting that the clinical manifestation of SVD is multifactorial and likely affected by various host features.

Cognitive reserve hypothesis provides one explanation for the individual differences in susceptibility to brain pathology. Life-long experiences such as educational and occupational attainment as well as participation in cognitively stimulating leisure activities may increase resilience to tolerate age-related and disease-related brain changes and sustain functional autonomy.[8] In recent years, the mitigating effect of cognitive reserve on cognitive dysfunction has been shown in progressive brain diseases such as Alzheimer's disease and multiple sclerosis, but its role in vascular cognitive impairment is not well known.[9] Cross-sectional studies have suggested that educational level or other measures of cognitive reserve have an intervening effect on the association between WMH and cognitive impairment,[10-12] but evidence on their significance on longitudinal change of cognitive functions is lacking.

This study aimed to examine how educational level and work history, as proxy measures of cognitive reserve, are related to cognitive performance and functional independence in subjects with age-related WMH. Specifically, we were interested to find out whether these features modulate the effect of WMH on cognitive and functional outcome in long-term follow-up.

METHODS

The LADIS cohort

The subjects were participants of the Leukoaraiosis and Disability (LADIS) study, a longitudinal multicenter study investigating the impact of SVD on the development of disability in older people.[4, 13] In all, 639 subjects, aged 65-84 years, were recruited between July 2001 and January 2003 in 11 European centers: Amsterdam (The Netherlands), Copenhagen (Denmark), Florence (Italy), Graz (Austria), Gothenburg (Sweden), Helsinki (Finland), Huddinge (Sweden), Lisbon (Portugal), Paris (France), Mannheim (Germany) and Newcastle-upon-Tyne (UK). At baseline, all subjects had mild to severe WMH on brain MRI according to the modified scale of Fazekas,[13] but they had no or mild disability as assessed by the Instrumental Activities of Daily Living (IADL) scale[14] (no impairment at all or only 1 item compromised). The study excluded subjects with severe unrelated neurological diseases, leukoencephalopathy of presumed nonvascular origin or severe psychiatric disorders, and those who were unable or refused to undergo cerebral MRI.

Informed written consent was obtained from all subjects. The ethics committees of each participating center approved the study.

Baseline evaluations

At study entry, the subjects underwent comprehensive clinical, functional, and neuropsychological assessments, and brain MRI as described in full detail before.[13, 15, 16] Information of the demographic characteristics, education (years of schooling), employment status, longest job in life, living conditions and lifestyle habits were recorded using a structured questionnaire.

The neuropsychological test battery of the LADIS study included the Mini-Mental State Examination (MMSE),[17] the Vascular Dementia Assessment Scale-Cognitive Subscale (VADAS),[18] and the Stroop and the Trail Making tests.[19] In the present study, we utilized detailed data of the individual test scores to demonstrate differences in cognitive performance for clinical implication. Cognitive domains most relevant for vascular cognitive impairment were studied. Processing speed was evaluated with the time scores of Stroop I (reading), Stroop part II (color naming) and Trail making A. Selective attention was assessed with the Symbol digit modalities test and Digit cancellation subtests of the VADAS. The subtraction scores of the Stroop test (III time-II time) and the Trail making (B time-A time) were used in assessing inhibition and flexible set shifting. Initiation and executive control were evaluated with the verbal fluency task of VADAS (animal category). Moreover, memory functions were assessed with the digit span backwards task (working memory) as well as VADAS immediate and delayed word recall tasks (verbal memory). Low values indicate better performance in the Stroop, Trail making and VADAS word recall, but poor performance in the digit span, symbol digit modalities, digit cancellation and verbal fluency tests.

Brain MRI was conducted using the same protocol at each center including T1-weighted magnetization-prepared rapid-acquisition gradient echo, T2-weighted fast spin echo, and fluid-attenuated inversion recovery (FLAIR) sequences.[16] Image analysis was performed centrally at the Department of Neurology, Vrije Universiteit Medical Center, Amsterdam, by raters blinded to the clinical details. Severity of WMH was evaluated on the axial FLAIR images with the modified visual rating scale of Fazekas[13] and with a semi-automatic volumetric measurement covering periventricular, subcortical and infratentorial regions.[16] In addition, lacunar and non-lacunar infarcts and brain atrophy were rated visually.[6, 20] For the purposes of the present study, WMH volume was used as the most sensitive single indicator of the severity of ischemic SVD. In further analysis, presence of lacunar infarcts was used as secondary marker of SVD.

Follow-up evaluations

The subjects were followed up for 3 years with annual repetitions of the complete clinical, functional and cognitive evaluations. Transition from functional independence to disability was determined as an increase of IADL scale score from 0-1 to ≥2.[14] At the 3-year follow-up visit, brain MRI was repeated. Progression of WMH was rated with the modified Rotterdam progression scale, in which absence or presence (0 vs. 1) of progression is rated separately in three periventricular, four subcortical white matter regions and infratentorial region (range 0–8).[20]

After up to 7 years from baseline, between April 2008 and June 2009, a prolonged follow-up of cognitive and functional status was administered by telephone interview. Cognitive status of the subjects was assessed by using the Telephone Interview for Cognitive Status (TICS), an 11-item screening test (range 0-41).[21] Evaluation of functional abilities was administered to the proxy/informant with the IADL scale[14] asking for activities in the last three months. Poor long-term functional outcome was defined by transition to disability (IADL≥2), or subject's death within the 7-year follow-up period.

Data analysis

Education and occupation were considered as the main predictor variables. Years of education was used in the statistical models as a continuous variable. Occupation was categorized into two groups on the basis of longest job in life into "white collar" (white collar, professional, managerial) vs. "blue collar" (all other occupations: blue collar, farmer, house wife, service employee, shop keeper). All analyses were controlled for age, gender, study center and WMH volume. Hypertension, diabetes and physical activeness (classified by the American Heart Association Scientific definition of at least 30 min of physical activity on at least 3 times/week)[22] were also considered as potential confounders. Since these factors had no or minimal effects on the results, they were excluded from the main analyses (see results for details).

Data analysis was conducted in five stages. Firstly, association of the predictor variables with baseline cognitive performance was studied with linear regression models using neuropsychological test scores as dependent variables. Secondly, the association of the predictor variables with longitudinal change in cognitive performance was evaluated with similar models, but using the third year follow-up scores as dependent variables and adding the corresponding baseline score as a covariate. Thirdly, interactions between predictor variables and WMH volume on longitudinal cognitive decline were inspected in separate models (education*WMH and occupation*WMH; centered were appropriate) adjusting for the confounders and main effects. Fourthly, the predictors of cognitive status at 7 years were examined with linear regression analyses using the TICS score as the dependent variable. Interactions were analyzed similarly as above. Finally, predictors of poor long-term functional outcome within 7 years of follow-up was investigated with Cox regression survival analyses.

Additional analysis were conducted replacing WMH volume with presence of lacunes as a surrogate of SVD in corresponding models as above to explore whether the pattern of results was similar for another major SVD feature.

All subjects with available data of baseline WMH volume (n=615) were included in the study. Due to missing data in outcome variables the number of cases varied between the analyses.

RESULTS

Characteristics

The baseline characteristics of the subjects are presented in table 1. Of the total 615 subjects, 275 (44.7%) had mild, 190 (30.9%) moderate and 150 (24.4%) severe WMH according to the modified Fazekas scale. Education was not significantly associated with age (Pearson's *r* -0.04, p=0.315), baseline WMH volume (*r* -0.05, p=0.219) or WMH progression as rated with the Rotterdam progression scale after 3-year follow-up (Spearman's rho -0.02, p=0.672). Nor was occupation related to these variables (p>0.05). WMH progression data was available for 387 subjects.

Baseline cognitive performance

Linear regression analyses controlling for age, gender, study center, and WMH volume revealed a strong relationship between education and cognitive performance at baseline across all tests (table 2). More years of education was associated with higher cognitive scores, as has been shown also in a previous report of the LADIS study.[15] White collar occupation was related to higher baseline scores in all cognitive variables except immediate word recall.

Table 1. Baseline characteristics of all subjects (n=615)

Age (mean SD)	73.6 (5.1)
Gender (male/female)	278/337
Education, years (mean, SD)	9.6 (3.8)
Employment status	
Employed	23 (3.8%)
Retired	587 (96.2%)
Longest job in life	
White collar, professional, managerial	276 (45.2%)
Other occupation	334 (54.8%)
MMSE (mean, SD)	27.4 (2.4)
Hypertension	429 (69.8%)
Diabetes	90 (14.6%)
Physically active[1]	387 (62.9%)
WMH volume, ml (mean,SD)	21.3 (22.7)
Number of lacunar infarcts	
0	321 (52.2%)
1-3	213 (34.6%)
>3	81 (13.2%)
Brain atrophy score, range 0-16 (mean, SD)	8.0 (2.4)

MMSE=Mini-Mental State Examination, SD=standard deviation, WMH=white matter hyperintensities. [1] At least 30 min of physical activity on at least 3 times/week.

Table 2. Association of educational and occupational attainment with cognitive performance at baseline and after 3-year follow-up

Cognitive scores		Education (years)	Occupation (white collar/professional vs. other)
Stroop I time			
	Baseline	-0.23 (<0.001)	-0.22 (<0.001)
	Follow-up	-0.14 (0.002)	ns
Stroop II time			
	Baseline	-0.20 (<0.001)	-0.16 (<0.001)
	Follow-up	ns	ns
Stroop III-II			
	Baseline	-0.16 (<0.001)	-0.11 (0.009)
	Follow-up	ns	ns
Trail making A time			
	Baseline	-0.24 (<0.001)	-0.21 (<0.001)
	Follow-up	ns	ns
Trail making B-A			
	Baseline	-0.31 (<0.001)	-0.25 (<0.001)
	Follow-up	-0.16 (<0.001)	ns
Digit cancellation			
	Baseline	0.26 (<0.001)	0.18 (<0.001)
	Follow-up	0.10 (0.004)	ns
Symbol digit modalities			
	Baseline	0.43 (<0.001)	0.32 (<0.001)
	Follow-up	ns	ns
Verbal fluency			
	Baseline	0.29 (<0.001)	0.23 (<0.001)
	Follow-up	0.13 (<0.001)	ns
Digit span backwards			
	Baseline	0.35 (<0.001)	0.18 (<0.001)
	Follow-up	0.10 (0.020)	0.09 (0.034)
Immediate word recall			
	Baseline	-0.16 (<0.001)	ns
	Follow-up	-0.16 (<0.001)	-0.10 (0.017)
Delayed word recall			
	Baseline	-0.20 (<0.001)	-0.10 (0.004)
	Follow-up	-0.12 (0.005)	ns

Values are standardized β (p) from linear regression models adjusted for age, gender, study center and WMH volume. Analyses of the follow-up cognitive scores were also adjusted for the corresponding baseline score to examine the role of the predictors of the rate of cognitive decline. Additional adjusting for hypertension, diabetes and physical activity had no effect on the results.

Rate of cognitive decline in 3-year follow-up

The contribution of the predictors on longitudinal change in cognitive scores was studied with similar linear regression models using the 3rd year cognitive scores as dependent variables and adding the corresponding baseline score as another independent variable (table 2). More years of education was significantly associated with slower rate of decline in Stroop I, Trail making B-A, digit cancellation, verbal fluency, digit span backwards, and immediate and delayed word recall independently of age, gender, center and WMH volume. White collar occupation was related to slower decline in digit span backwards and immediate word recall test.

The moderating effects of the predictors on the association between WMH volume and cognitive decline were examined by adding the predictor*WMH volume interaction terms in the models adjusted for the confounders and main effects. Education*WMH volume interaction was significant for longitudinal change in Stroop I (standardized β -0.09, p=0.024) and Stroop II (-0.08, p=0.043). In 3-year follow-up, higher education was related to weaker effect of WMH on the Stroop I and II time scores, whereas low education was associated with a steeper rate of decline over time as shown in figure 1 with categorical variables (education split into two groups according to median value and WMH evaluated with the 3-point Fazekas scale for illustrative purposes). Moreover, occupation*WMH volume interaction was significant for change in immediate word recall (0.11, p=0.039). Specifically, white collar occupation was related to weaker contribution of WMH on decline in memory performance over 3 years.

Cognitive status after 7-year follow-up

Prolonged follow-up data of cognitive status as evaluated with the TICS was available for 332 of the 615 subjects (54.0%) due to subject's death, drop-out from the follow-up, or inability or unwillingness to complete the test. In addition, one center was unable to accomplish this particular subpart of the study. The subjects taking part in the evaluation with TICS represented a somewhat selected subgroup, since they were younger and had lower WMH volume and higher MMSE scores at baseline as compared to the subjects without TICS data ($p<0.001$). There were no significant differences between these groups in gender, education or occupation.

In linear regression models adjusted for the confounders, years of education independently predicted the TICS score (total sample mean 29.6, SD 8.6; standardized β 0.30, $p<0.001$) together with age (-0.14, $p=0.004$) and WMH volume (-0.19, $p<0.001$). Additional controlling for baseline MMSE score did not change these results. However, occupation was not significantly related to the TICS score. The interaction term education*WMH volume reached significance (0.12, $p<0.015$). As illustrated in figure 2 with categorical variables, subjects with severe WMH and low education showed the lowest cognitive status, while WMH only had a mild effect on cognition in subjects with high education.

Long-term functional outcome

Follow-up functional outcome data was available for 609 (99%) subjects. During up to 7-years of follow-up, 217 (35.3%) subjects had converted to disability and 90 (14.6%) had died. Cox regression analyses adjusted for the confounders revealed that poor long-term functional outcome, as defined by transition to disability or subject's death during follow-up, was inversely associated with higher education (hazard ratio per year=0.93, CI 95%=0.90-0.96, $p<0.001$) and white collar occupation (hazard ratio=0.73, CI 95%=0.58-0.94, $p=0.013$). Age and WMH volume also remained as significant predictors of outcome in the adjusted models ($p<0.001$). The relationships are presented in figure 3 with categorical variables.

Vascular risk factors and physical activity as confounders

All analyses were repeated by additionally adjusting for a) hypertension and diabetes and b) hypertension, diabetes and physical activity. Hypertension and diabetes had no effect on the results. Controlling for physical activity slightly changed two of the observed longitudinal associations: the predictive value of occupation increased on the rate of decline in Trail making B-

A (standardized β -0.9, p=0.040), but decreased in the interaction with WMH volume on immediate word recall (p=0.062). All other results remained unchanged.

Lacunes as a surrogate of SVD

The results were also reanalyzed by replacing WMH volume with presence of lacunes (0 vs. ≥1) in otherwise similar models as above. All results presented in table 2 remained unchanged with the only exception that occupation was no longer significantly associated with longitudinal change in digit span backwards. Moreover, education*lacunes interaction was significant for change in delayed recall (standardized β -0.15, p=0.008), but not in Stroop. Occupation*lacunes interaction was significant for change in both immediate (F=6.1, p=0.014) and delayed word recall (F=6.17, p=0.013). Subjects with lacunes and low education or blue collar occupation showed a disproportionate decline in memory recall. Regarding prolonged follow-up and functional outcome data, the results analyzed with lacunes were otherwise identical to the ones with WMH volume, except for education*lacunes interaction on TICS, which did not reach significance.

DISCUSSION

This study explored how educational and occupational backgrounds, as proxy measures of cognitive reserve, predict and modulate longitudinal cognitive decline and loss of independent functional abilities in older individuals with different degrees of WMH. Follow-up of the subjects was conducted in two parts: comprehensive neuropsychological, clinical and functional evaluations were repeated within 3 years and a prolonged follow-up of cognitive and functional outcome was administered by telephone interview after up to 7 years from baseline.

The results suggested substantial effects of cognitive reserve measures on clinical outcome. As expected, higher educational and occupational attainments were strongly related to baseline cognitive scores across all evaluated cognitive domains. In addition, higher education predicted significantly slower rate of decline in measures of processing speed, attention, executive functions and memory independently of the demographic variables and WMH volume. Cognitively more demanding occupation (based on longest job in life: white collar, professional or managerial) was related to slower rate of decline in working memory and immediate memory recall.

Cognitive reserve measures significantly affected the strength of the relationship between WMH and cognitive change over time. Specifically, lower education was associated with stronger influence of WMH on processing speed, while high education attenuated this relationship. Similarly, cognitively challenging occupation was associated with a mitigating effect of WMH on decline in memory recall. These moderation effects were found only in part of the used neuropsychological tests, but importantly, they suggest a possibility of cognitive reserve to reduce individual's susceptibility to SVD-related brain changes. Education and occupation were not directly related to baseline or 3-year progression of WMH, but still they had a beneficial effect on the clinical manifestations of SVD. The significance of cognitive reserve measures on cognitive and functional outcome was confirmed in long-term follow-up for up to 7 years. Higher education predicted better cognitive status and moderated the effect of WMH on cognitive function. Moreover, higher educational and occupational attainments predicted favorable functional outcome as determined by sustained independent activities of daily living and lower mortality over 7 years. The pattern of the results was very similar using lacunes as a marker of SVD instead of WMH.

Previous research on cognitive reserve hypothesis has concentrated mostly on aging and Alzheimer's disease.[8] Recent cross-sectional studies have, however, suggested a protective effect of cognitive reserve against cognitive impairment in relation to vascular brain changes.[9] WMH has been more strongly associated with cognitive scores in the low-educated subjects as compared to the well-educated subjects.[10, 11] Brickman et al. reported subjects with higher estimates of cognitive reserve to have greater degrees of WMH for any given level of cognitive functions, suggesting that these individuals are better able to cope with brain pathology.[12]

Only a few studies have investigated the effect of cognitive reserve on the clinical outcome of vascular pathology in longitudinal settings. In a follow-up study of Mortamais et al. with community-dwelling older persons, WMH increased the risk of developing mild cognitive impairment or dementia only in the less-educated but not in the highly-educated group.[23] Ojala-Oksala et al. showed a protective effect of education on post-stroke cognitive impairment, dementia and long-term survival independently of the severity of WMH.[24] Moreover, a recent study of Vemuri et al. investigated cognitively normal subjects with amyloid and vascular pathologies (brain infarct and/or WMH) and found a beneficial influence of high cognitive reserve on cognitive performance at baseline in both groups, but no relationship between reserve variables and the rate of cognitive decline.[25]

Our results confirm previous findings that cognitive reserve has a beneficial effect on SVD-related cognitive impairment at a cross-sectional level. Adding to these observations, the present results suggest a considerable influence of cognitive reserve also on the longitudinal trajectories of cognitive function in terms of the rate of decline and the strength of the relation between clinical symptoms and WMH. In other words, cognitive reserve may substantially alter the course of the disease by slowing the cognitive and functional decline associated with SVD. Education and occupation are likely related to many lifestyle factors such as nutrition and overall health care, which may in part explain the association with increasing disability and mortality. However, we found no influence of the main vascular risk factors (hypertension and diabetes) on the present results. Nor did physical activity as the subjects own report of regular exercise explain the observed associations.

Limitations of the present study include some data loss in the cognitive follow-up measures due to subject’s inability or unwillingness to complete all elements of the extensive evaluations. In particular, 7-year follow-up of cognitive status (TICS) had the highest attrition rate (63% of the subjects alive at time of contact were evaluated), whereas disability and survival data was available even for 99% of the initially enrolled subjects. In addition, the measures of cognitive reserve were limited to education and occupation as proxies, and no other information of cognitively stimulating activities was available. Educational attainment has been most commonly used as a proxy measure of cognitive reserve, but it does not equally reflect later life experiences or leisure activities. Moreover, the subjects of the LADIS cohort were born mainly in the 1920’s and

1930's, and thus, their opportunities to gain higher education have been likely affected by societal situations in European countries, the World War II in particular. All analyses were controlled for study center, however, so regional differences did not explain the present results. Another limitation is that the possibility of mixed neurodegenerative and vascular pathologies cannot be ruled out on the basis of the available data. A proportion of the subjects had brain atrophy, which we have previously shown to accelerate cognitive decline in SVD.[6] Brain atrophy may reflect co-existing neurodegenerative disease such as Alzheimer's disease, but it can also result from SVD.

Strengths of the study include a large and well-characterized sample of subjects stratified into the different severity degrees of WMH representing clinical population with different stages of SVD, detailed neuropsychological and clinical assessments and a long follow-up of cognitive and functional outcome.

Our results point to three main conclusions. Firstly, cognitive reserve appears to substantially affect the individual ability to tolerate and compensate the deleterious effects of the accumulating brain changes of SVD, possibly as a result of greater intellectual enrichment. Secondly, educational and occupational attainments as active forms of reserve are useful proxy measures of cognitive reserve predicting resilience to SVD-pathology. Thirdly, variability related to cognitive reserve is important to take into account in clinical assessment of the patients, because it can seriously obscure tangible cognitive and functional symptoms. In fact, a highly educated person with severe WMH may perform equally well or even better in cognitive tasks after years of follow-up as compared to baseline performance of a low-educated person with mild WMH (Fig 1.). These substantial individual differences emphasize the fact that cognitive screening without an estimate of premorbid cognitive capacity may be unreliable. Future studies are needed to gain knowledge of the significance of later life cognitive stimulation and its prospects in prevention of cognitive decline and disability in SVD.

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Author contributions HJ, SM, JMW and TE were involved in the conception and design of the present study. JMF, FF, RS, PS, FB, DI, LP and TE planned and initiated the LADIS study. JMF, SM and AV constructed the cognitive test battery. FF, RS, PS and FB were responsible for the MRI methods. LP and DI coordinated the LADIS study. HJ conducted the statistical analyses, and drafted and finished the manuscript. All authors contributed in critically revising the manuscript. All authors approved the final version of the manuscript to be published.

Competing interests JMF reports personal fees from Boheringer Ingelheim and Daiichi Sankyo. FB serves on the editorial boards of Brain, European Radiology, Neuroradiology, Neurology, Multiple Sclerosis Journal, and Radiology, serves as a consultant for Bayer-Schering Pharma, Sanofi-Aventis, Genzyme, Biogen-Idec, Teva, Novartis, Roche, Synthon BV, Merck-Serono, and Jansen Research, and reports grants from Dutch MS Society, EU-FP7. JMW reports honorarium for expert advice from GlaxoSmithKline. DI reports grants from Bayer and Shire. All activities are outside the submitted work.

Patient consent Obtained.

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FIGURE LEGENDS

Figure 1. Relationship between educational background (low <9 years vs. high ≥9 years) and the degree of white matter hyperintensities (WMH; modified Fazekas scale, 1=mild, 2=moderate, 3=severe) on change in processing speed as evaluated with the Stroop reading (I) and color naming (II) subtasks at baseline and after 3-year follow-up. Pronounced slowing of processing speed is seen over time in subjects with low education and severe WMH, whereas in subjects with high education, the same degree of WMH only has a mild effect. Mean change between baseline and follow-up in subjects with low education was 0.3, 0.7 and 5.3 s in Stroop I and -0.5, 1.5, 6.3 s in Stroop II, while in subjects with high education, it was 0.7, 0.1 and 2.2 s in Stroop I and 1.0, 0.8, 3.0 s in Stroop II, by WMH degree 1, 2 and 3, respectively.

Figure 2. Interaction of education and the severity white matter hyperintensities (WMH; modified Fazekas scale, 1=mild, 2=moderate, 3=severe) on cognitive function as evaluated with the Telephone Interview for Cognitive Status (TICS, range 0-41) at 7-year follow-up. Subjects with low education and severe WMH at baseline show the poorest long-term cognitive outcome. The mean difference in TICS total score between the two educational groups is 4.3, 2.7 and 8.9 points, by WMH degrees 1, 2 and 3, respectively. Error bars indicate 95% confidence intervals.

Figure 3. Association of educational and occupational attainment with poor functional outcome in follow-up; endpoint transition from functional independence to disability or death. Cox regression analysis controlling for age, gender, study center and WMH volume (p-values <0.05).