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Research Report

Vascular Brain Lesions, Cognitive Reserve, and Their Association with Cognitive Profile in Persons with Early-Stage Cognitive Decline

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Abstract.
Background: Cognitive reserve may protect against the effects of brain pathology, but few studies have looked at whether cognitive reserve modifies the adverse effects of vascular brain pathology.
Objective: We determined if cognitive reserve attenuates the associations of vascular brain lesions with worse cognition in persons with subjective concerns or mild impairment.

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Methods: We analyzed 200 participants aged 50–90 years from the Comprehensive Assessment of Neurodegeneration and Dementia (COMPASS-ND) study. Cognition was measured using the Montreal Cognitive Assessment and a neuropsychological test battery. High vascular lesion burden was defined as two or more supratentorial infarcts or beginning confluent or confluent white matter hyperintensity. Cognitive reserve proxies included education, occupational attainment, marital status, social activities, physical activity, household income, and multilingualism.

Results: Mean age was 72.8 years and 48% were female; 73.5% had mild cognitive impairment and 26.5% had subjective concerns. Professional/managerial occupations, annual household income≥\$60,000 per year, not being married/common law, and high physical activity were independently associated with higher cognition. Higher vascular lesion burden was associated with lower executive function, but the association was not modified by cognitive reserve.

Conclusion: Markers of cognitive reserve are associated with higher cognition. Vascular lesion burden is associated with lower executive function. However, cognitive reserve does not mitigate the effects of vascular lesion burden on executive function. Public health efforts should focus on preventing vascular brain injury as well as promoting lifestyle factors related to cognitive reserve, as cognitive reserve alone may not mitigate the effects of vascular brain injury.

Keywords: Brain vascular disorders, cerebral small vessel disease, cerebrovascular disease, cognitive dysfunction, cognitive reserve, infarct, white matter disease

INTRODUCTION

The cognitive reserve hypothesis postulates that markers of enhanced brain development and function, such as greater early-life education, can mitigate the cognitive effects of brain pathologies [1]. Compared to individuals with lower cognitive reserve, when individuals with higher reserve develop cognitive disorders studies show that their brain pathology is more severe [1–4]. This suggests that higher reserve conferred some resistance to the deleterious effects of the pathology [1]. This is often cited as a motivating factor for public health efforts to promote higher education, reduce social isolation, and increase engagement in cognitively demanding leisure activities to reduce risk of later-life dementia.

A limitation of literature on cognitive reserve is that it has mostly been tested in the context of Alzheimer's disease (AD) pathology, where the hypothesis has gained some support. There are few studies on whether cognitive reserve can mitigate the adverse effects of vascular brain pathology, such as white matter hyperintensities (WMHs) [5]. This is important because vascular pathology is the second biggest contributor to dementia, present in the brain of most persons with AD, mild cognitive impairment (MCI), and dementia. Furthermore, most studies of cognitive reserve focus on global cognition or memory. There is relatively little information about the impact of cognitive reserve on executive functions—the most common cognitive domain affected by cerebrovascular disease.

We analyzed data from patients with early stage impairment in the Comprehensive Assessment of Neurodegeneration and Dementia (COMPASS-ND) study [6] to test the hypothesis that cognitive reserve attenuates the associations of vascular brain lesions, such as WMHs and brain infarcts, with the degree of cognitive impairment. First, we examined the association of proxies of cognitive reserve with cognition. We then tested if vascular brain lesions were associated with cognition, divided into domains of memory, executive function, and processing speed. Lastly, we determined whether a composite cognitive reserve score modifies the association between vascular brain lesions and the cognitive profile.

METHODS

Study population

COMPASS-ND is a multi-site longitudinal cohort study recruiting participants with MCI, AD, vascular MCI (V-MCI), mixed dementia, Lewy body dementia, Parkinson's disease dementia, Parkinson's disease MCI, frontotemporal dementia, primary progressive aphasia, subjective cognitive impairment (SCI), and cognitively intact elderly [6]. Participants in this study were recruited from 22 participating memory clinics across Canada. Data from the first 409 participants were analyzed.

For this analysis, we used cross-sectional data from participants with either MCI, V-MCI, or SCI. Participants were 50–90 years old, proficient in English or French (measured by the Language Experience and Proficiency Questionnaire (LEAP-Q) [7, 8]), lived within 1 h of the study site, and had a study partner who saw the participant at least weekly. Participants were recruited from 2016 to 2019. According to COMPASS-ND inclusion and exclusion criteria, participants were required to have a Montreal Cognitive Assessment (MoCA) score greater than 12, no history of ongoing drug or alcohol misuse, and no other significant chronic brain diseases. For the purpose of this study, patients with MCI were recruited into the V-MCI group if clinical CT or MRI neuroimaging showed two or more supratentorial infarcts [9]. Of 409 participants, we excluded 223 participants that had diagnoses other than SCI, MCI, or V-MCI, 1 participant with missing data on ethnicity, 1 participant with missing data on the vascular lesion burden score, 1 participant with missing data on infarcts, and 20 participants with missing data on cognitive reserve, leaving 200 total participants for our analysis. All 200 participants had MRI data and at least one cognitive assessment (all 200 had MoCA, memory, and executive function measures, and 199 had processing speed measures).

Participants provided written consent. The study received local ethical approval from the participating centers' Institutional Review Boards.

Assessment

Demographic information, medical history, lifestyle, and cognitive reserve factors were collected through extensive self-reported questionnaires. Clinical assessments and physical exams were completed by a clinician [6].

We defined these variables as potential proxies of cognitive reserve: education, occupational attainment, physical activity, social activity, marital status, multilingualism, and annual household income. They were selected *a priori* based on literature searches [1, 10–16].

All cognitive reserve variables were dichotomized. High education was defined as having a university degree (undergraduate degree, some graduate school, or graduate degree) versus technical school/community college, some university, high school or less. High occupational attainment was defined as professional, managerial, or qualified non-manual occupations, marital status was married/common-law versus other, participation in social activities was defined as engagement in social activities once a month or more, high annual household income was defined based on the median income ($\geq$\$60,000 per year), and the language variable was defined as multilingual (one or more language) versus monolingual. High physical activity was defined as a z-score in the 75% percentile (top quartile) on the Physical Activity Scale for the Elderly (PASE) [17]. This z-score was obtained by standardizing the PASE score to previously published normative data (1993) [17].

Cognition was assessed using a cognitive screening tool (MoCA) [18] and neuropsychological assessments. All neuropsychological assessments were first converted to z-scores based on the means and standard deviations of the total study population. A memory composite z-score was then created by using the mean between the total recall z-score component of the Brief Visuospatial Memory Test and the trial raw z-score of the Rey Auditory Verbal Learning Test [19, 20]. An executive function composite z-score was created by using the mean between the trail making part B z-score component of the Reitan Trail Making Test (A & B) and the Letter Fluency total raw z-score of the Delis-Kaplan Executive Function System [21, 22]. A processing speed composite z-score was created by using the mean between the trail making part A z-score of the Reitan Trail Making Test (A & B) and the digit symbol raw z-score of the Wechsler Adult Intelligence Scale-III Digit Symbol-Coding [21, 23].

A 3T MRI was used in this study and sequences were standardized across MRI machines [6, 24]. The following sequences were used: 3D T1, PD/T2, FLAIR, gradient echo, resting state fMRI, and DTI [6]. MRI vascular lesions were identified visually centrally by readers at either the University of Calgary and Sunnybrook Hospital, Toronto [6, 9] according to Standards for Reporting Vascular Changes on Neuroimaging [25]. WMH was grade according to the Fazekas scale [26], summing the periventricular and subcortical scores to give a total range of 0-6. High WMH was defined as total Fazekas score 4-6.

Vascular brain injury was defined as the presence of either brain infarcts or high WMH. Additionally, we analyzed a combined variable, termed "high vascular lesion burden", defined as the presence of two or more supratentorial brain infarcts or beginning confluent or confluent WMH on the Age-Related White Matter Changes scale [27], which was hypothesized to be a threshold for a potential vascular contribution to cognitive impairment [9].

Statistical analysis

Total MoCA score was treated as a continuous variable. Memory, executive function, and processing speed variables were converted to z-scores and treated as continuous variables.

We first tested the association between each of the seven cognitive reserve variables, MoCA, and the three cognitive domains. To test this, we built separate multiple linear regression models for each cognitive reserve variable and each individual cognitive domain, adjusting each model for age, sex, and education. We then ran the same analysis in a fully adjusted model, adjusting for age, sex, and all cognitive reserve predictor variables. Collinearity between cognitive reserve variables was assessed by calculating variation inflation factors, and variables with inflation factor > 5 were removed from the model. An analysis was also performed to determine if the association between marital status and cognition was modified by sex. After finding that multilingualism was associated with worse, not better, MoCA we performed a secondary analysis on a revised total MoCA score removing 3 items that are more heavily dependent on language (naming, letter fluency, and sentence repetition).

A single cognitive reserve score was calculated based on the cognitive reserve candidate variables that were associated with either memory, executive function, or processing speed in the previous fully-adjusted analysis. Based on the relative size of the beta coefficients, a cognitive reserve composite score was created by allocating 3 points for professional/managerial/qualified non-manual occupations, and 2 points each for annual household income ≥ $60,000 per year, not being married/common law, and high physical activity. These four variables were used in the composite because they were the only four variables associated with any of the cognitive domains during our initial fully-adjusted analysis.

We tested the association between markers of vascular brain injury (infarcts, WMH, and high vascular lesion burden) and cognitive outcomes by building separate linear regression models for each exposure and outcome, adjusting for age, sex, and education. We also tested whether cognitive reserve predicts infarcts, high WMH, or high vascular lesion burden using separate multiple logistic regression models, adjusted for age and sex.

We then tested for effect modification to determine if cognitive reserve modifies the association between markers of VBI and cognitive outcomes. We analyzed only the markers of VBI that were associated with cognition in previously analyses. The models for effect modification included terms for age, sex, VBI variable, cognitive reserve, and the interaction of VBI with cognitive reserve. Education was not included as a separate term because it was included in the cognitive reserve score. Separate models were created for each cognitive outcome (MoCA total score, memory, processing speed, and executive functions).

Sensitivity analyses were performed to test the robustness of our results. We tested the impact of: a) creating a cognitive reserve score without dichotomizing any of the variables, b) stratifying or controlling for SCI and MCI status, c) using education alone as a proxy of cognitive reserve, and d) removing marital status from the cognitive reserve score.

A *p*-value of less than 0.05 was considered significant; because these analyses were considered exploratory, no adjustment was made for multiple hypothesis testing. Statistical analyses were conducted using SAS v9.4 (SAS Institute, Cary, NC).

RESULTS

Table 1 shows the characteristics of the study population. Of the 200 participants, 48% were

Table 1
Characteristics of the study population

Characteristic	% Mean (SD)	n/N
Female	48.0%	96/200
Age, y	72.8 (6.8)	200
Ethnicity	—	—
White	88.0%	176/200
Asian	4.5%	9/200
South Asian	2.5%	5/200
Black and Other	5.0%	10/200
Diagnosis	—	—-
Mild Cognitive Impairment	67.5%	135/200
Subjective Cognitive Impairment	26.5%	53/200
Vascular Mild Cognitive Impairment	6.0%	12/200
MoCA score	24.5 (3.3)	200
Brain Infarcts	19.5%	39/200
WMH Fazekas Score 4 to 6	22.0%	44/200
Vascular Lesion Burden	36.0%	72/200
Diabetes	11.0%	22/200
Hypertension	36.5%	73/200
Stroke	2.01%	4/199
Vascular Risk Factors	50.5%	101/200
University Degree	51.0%	102/200
Professional/Managerial Occupation	86.0%	172/200
Annual Household Income ≥ 60K	60.0%	120/200
Married/Common-Law	74.0%	148/200
Multilingual (2 or More)	57.5%	115/200
Normal/High Social Activity	65.0%	130/200
High Physical Activity	25.5%	51/200

WMH, white matter hyperintensity; MoCA, Montreal Cognitive Assessment; Vascular Risk Factors: Having one or more diagnoses of Diabetes, Hypertension, Stroke, Transient Ischemic Attack, Heart Attack or Congestive Heart Failure, Atrial Fibrillation, or Angina. High physical activity was defined as ≥ 75^{Th} Percentile z-score on the Physical Activity Scale for the Elderly.

female, 6% had V-MCI, 67.5% had MCI, and 26.5% had SCI. The mean age was 72.8 with standard deviation 6.8, 51% had a university degree, 86% had professional/managerial occupations or qualified non-manual occupations, 60% had an annual household income $\geq$ 60K, 57.5% were multilingual, and 74% were married/common law. Brain infarcts were seen in 19.5% of participants had brain infarcts, high WMH in 22%, and vascular brain lesions (either infarcts or high WMH) in 36%. The mean MoCA score was 24.5 ± 3.3.

Table 2 shows the associations of individual cognitive reserve variables with cognitive profile, adjusting for age, sex, and education. Table 3 shows the associations of these cognitive reserve variables with cognition in a fully adjusted model, adjusting for age, sex, and all cognitive reserve predictor variables. In this fully adjusted model, a total of five cognitive reserve variables were independently associated with cognition. Having a professional/managerial occupation was associated with higher MoCA scores ($p = 0.0006$), higher executive function ($p = 0.002$), and higher processing speed ($p = 0.004$). High annual household income was associated with high executive function ($p = 0.002$). Being married was associated with lower MoCA scores ($p = 0.002$), lower memory scores ($p = 0.02$), and low executive function scores ($p = 0.008$). High physical activity was associated with higher executive function ($p = 0.02$) and higher processing speed ($p = 0.02$). There was no evidence of interaction between marital status and sex (beta coefficient -0.08, 95% CI –2.28 to 2.13, interaction $p = 0.95$ for MoCA; beta coefficient -0.10, 95% CI –0.67 to 0.47, interaction $p = 0.73$ for memory; beta coefficient 0.40, 95% CI –0.17 to 0.98, interaction $p = 0.17$ for executive function; beta coefficient 0.39, 95% CI –0.16 to 0.94, interaction $p = 0.16$ for processing speed). Multilingualism was associated with lower score on the MoCA but not with lower performance in any of the neuropsychological domain scores (Table 2). However, after removing three MoCA items that depend heavily on language the association was no longer significant (β=-0.68, 95% CI -1.46 to 0.10, $p = 0.10$) and therefore multilingualism was not considered a candidate for the cognitive reserve composite score.

Table 4 shows the association between vascular brain lesions and cognitive profile. High vascular lesion burden, but not infarcts or WMH alone, was associated with lower executive function (beta coefficient -0.36, 95% CI -0.63 to -0.09, $p = 0.01$). Higher composite cognitive reserve score was associated with lower odds of high vascular lesion burden (OR 0.82 per additional point, 95% CI 0.68 to 0.996), but was not associated with WMH alone (OR 0.84, per additional point, 95% CI 0.68 to 1.03) or brain infarcts

Table 2
Association of cognitive reserve proxies with cognition

	MoCA		Memory		Executive function		Processing speed	
	β	95% CL	β	95% CL	β	95% CL	β	95% CL
University Degree	**1.17**	**0.27, 2.06**	0.05	–0.18, 0.28	0.17	–0.06, 0.40	0.14	–0.08, 0.36
Occupation	**2.72**	**1.42, 4.01**	0.23	–0.10, 0.57	**0.61**	**0.27, 0.94**	**0.52**	**0.19, 0.85**
Household Income	0.78	–0.14, 1.71	0.00	–0.23, 0.24	**0.41**	**0.17, 0.64**	**0.23**	**0.00, 0.45**
Multilingual	**–0.77**	**–1.69, 0.15**	–0.14	–0.37, 0.09	–0.00	–0.24, 0.24	0.08	–0.14, 0.31
Married	**–1.52**	**–2.58, –0.45**	**–0.32**	**–0.59, –0.06**	–0.27	–0.54, 0.01	–0.13	–0.40, 0.14
Social Activities	–0.23	–1.19, 0.73	0.05	–0.19, 0.29	0.18	–0.06, 0.43	0.20	–0.03, 0.44
Physical Activity	0.73	–0.33, 1.79	0.08	–0.19, 0.35	**0.30**	**0.03, 0.57**	**0.26**	**0.00, 0.52**

Beta coefficient for MoCA is the estimated different in points, otherwise it represents the estimated difference in z score. Adjusted for age, and education. MoCA, Montreal Cognitive Assessment.

Table 3
Association of predictors with cognition; fully adjusted model

	MoCA		Memory		Executive function		Processing speed	
	β	95% CL	β	95% CL	β	95% CL	β	95% CL
University Degree	0.90	–0.02, 1.82	0.04	–0.21, 0.29	0.05	–0.19, 0.28	0.02	–0.21, 0.25
Occupation	**2.38**	**1.03, 3.73**	0.24	–0.13, 0.60	**0.56**	**0.21, 0.90**	**0.51**	**0.16, 0.86**
Household Income	0.87	–0.03, 1.77	0.03	–0.21, 0.28	**0.37**	**0.14, 0.61**	0.16	–0.07, 0.39
Multilingual	**–1.04**	**–1.92, –0.16**	–0.15	–0.39, 0.09	–0.04	–0.27, 0.19	0.05	–0.17, 0.28
Married	**–1.67**	**–2.70, –0.65**	**–0.32**	**–0.60, –0.05**	**–0.36**	**–0.63, –0.10**	–0.16	–0.43, 0.10
Social Activities	–0.36	–1.26, 0.53	0.05	–0.19, 0.30	0.12	–0.11, 0.35	0.18	–0.05, 0.41
High Physical Activity	0.78	–0.23, 1.78	0.08	–0.19, 0.36	**0.31**	**0.05, 0.57**	**0.31**	**0.05, 0.56**

Adjusted for age, sex, and all predictor variables. MoCA, Montreal Cognitive Assessment.

Table 4
Association of vascular brain lesions (Multiple Infarcts or High WMH) with cognition

MRI brain measures	MoCA		Memory		Executive function		Processing speed	
	β	95% CL	β	95% CL	β	95% CL	β	95% CL
Infarcts	–0.75	–1.92, 0.41	0.04	–0.26, 0.34	–0.08	–0.38, 0.23	–0.06	–0.35, 0.23
WMH	–0.989	–2.16, 0.18	–0.08	–0.38, 0.22	–0.30	–0.60, 0.007	–0.13	–0.42, 0.16
Vascular Lesion Burden	–0.99	–2.04, 0.06	–0.03	–0.30, 0.24	**–0.36**	**–0.63, –0.09**	–0.23	–0.49, 0.03

Adjusted for age, sex, and education. MoCA, Montreal Cognitive Assessment; WMH, white matter hyperintensity.

Table 5
Modifying effect of cognitive reserve composite score on the association between vascular lesion burden and cognitive scores

	Interaction between cognitive reserve and vascular lesion burden			
Predictors of executive function	Without interaction		With interaction	
	Beta (95% CI)	*p*	Beta (95% CI)	*p*
Cognitive reserve	**0.18 (0.12, 0.23)**	**<0.0001**	**0.17 (0.10, 0.25)**	**<0.0001**
Vascular lesion burden	**–0.26 (–0.51, –0.004)**	**0.04**	–0.29 (–0.93, 0.34)	0.36
Interaction	—	—	0.008 (–0.11, 0.13)	0.90
Predictors of processing speed	Without interaction		With interaction	
beta (95% CI)	*p*	Beta (95% CI)	*p*	
Cognitive reserve	**0.12 (0.06, 0.18)**	**<0.0001**	**0.11 (0.04, 0.19)**	**0.003**
Vascular lesion burden	–0.16 (–0.41, 0.09)	0.21	–0.27 (–0.91, 0.36)	0.40
Interaction	—	—	0.02 (–0.10, 0.14)	0.71
Predictors of memory	Without interaction		With interaction	
	Beta (95% CI)	*p*	Beta (95% CI)	*p*
Cognitive reserve	**0.07 (0.005, 0.13)**	**0.03**	**0.09 (0.01, 0.17)**	**0.02**
Vascular lesion burden	0.006 (–0.26, 0.28)	0.97	0.31 (–0.37, 0.99)	0.36
Interaction	—	—	–0.06 (–0.19, 0.07)	0.33
Predictors of MoCA	Without interaction		With interaction	
	Beta (95% CI)	*p*	Beta (95% CI)	*p*
Cognitive reserve	**0.61 (0.38, 0.85)**	**<0.0001**	**0.70 (0.40, 0.996)**	**<0.0001**
Vascular lesion burden	–0.67 (–1.68, 0.35)	0.20	0.38 (–2.17, 2.92)	0.77
Interaction:	—	—	–0.22 (–0.70, 0.27)	0.38

Adjusted for age and sex. MoCA, Montreal Cognitive Assessment. The Cognitive Reserve Composite Score consists of 3 points for professional/managerial/qualified non-manual occupations, and 2 points each for annual household income ≥ 60K, not being married/common law, and high physical activity. Association between cognitive reserve and cognition (executive functioning (A), processing speed (B), memory (C), and MoCA (D)), in the presence (dotted line) or absence (solid line) of vascular lesion burden. Shaded regions display 95% confidence intervals, *p*-values represent the interaction between vascular lesion burden and cognitive reserve score. Participants with high vascular lesion burden had lower mean executive function, processing speed, and MoCA scores. However, there was no interaction between vascular lesion burden and cognitive reserve on cognitive function, as shown by the overlapping confidence intervals and non-significant interaction *p*-values.

alone (OR 0.93, per additional point, 95% CI 0.77 to 1.14) in analyses adjusted for age and sex. Considering marital status alone, being married or in a common law partnership was associated with higher odds of high vascular lesion burden (adjusted OR 2.50, 95% CI 1.08 to 5.80) controlling for age and sex.

Table 5 and Fig. 1 show the modifying effects of the composite cognitive reserve score on the association between vascular lesion burden and cognitive profile. When adjusted for each other in the same model, higher cognitive reserve composite score was associated with higher executive function ($p < 0.001$) and high vascular lesion burden was associated with lower executive function ($p = 0.046$). Higher cognitive reserve composite score was associated higher processing speed ($p < 0.001$), memory ($p = 0.03$), and MoCA ($p < 0.001$), but high vascular lesion burden was not associated with these cognitive domains. There was no evidence of an interaction between the cognitive reserve composite score and vascular lesion burden on any of the cognitive domains or MoCA (memory: beta coefficient -0.06, 95% CI -0.19 to 0.07, interaction 0.33; executive function: beta coefficient 0.008, 95% CI -0.11 to 0.13, interaction 0.90; processing speed: beta coefficient 0.02, 95% CI –0.10

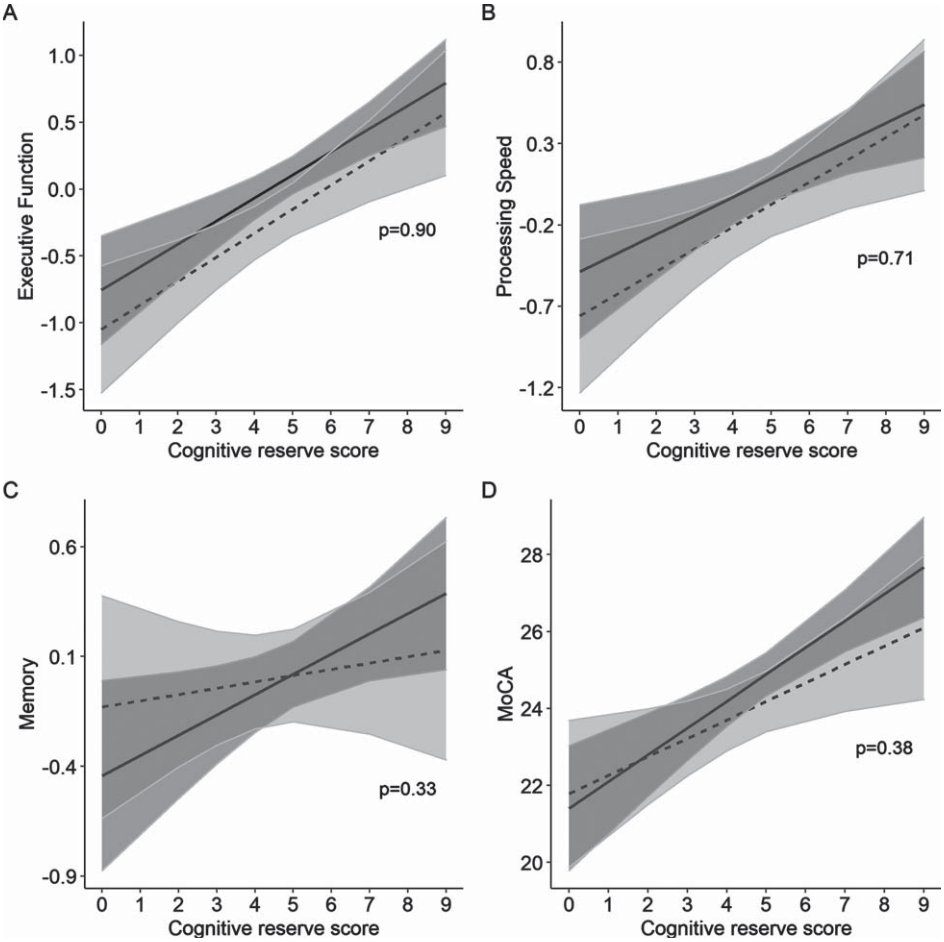

Fig. 1. Association of vascular lesion burden with cognition, across cognitive reserve composite scores.

to 0.14, interaction $p = 0.71$; MoCA: beta coefficient -0.22, 95% CI -0.70 to 0.27, interaction $p = 0.38$).

The results were similar in sensitivity analyses using variables without dichotomizing them (Supplementary Table 1), controlling for SCI and MCI status (Supplementary Table 2), using education alone was used as the cognitive reserve proxy (Supplementary Table 3), and when marital status was removed from the cognitive reserve score (Supplementary Table 4).

DISCUSSION

In this population with early, mild symptoms or impaired cognition, we found that vascular lesion burden was associated with a cognitive profile featuring poor executive function. We found that occupational attainment, income, marital status, and physical activity were independently associated with a milder cognitive profile. However, we found that both vascular lesion burden and cognitive reserve score had independent, non-interactive effects on cognition. The results were similar when education alone was used as the cognitive reserve proxy. Thus, we found that in this population the effects of vascular lesion burden on the cognitive profile were not mitigated by higher cognitive reserve.

Vascular lesion burden was associated with a cognitive profile marked by lower executive function. This is consistent with other studies showing that in vascular cognitive impairment, executive function is often affected out of proportion to memory [28]. However, we found only trends, without significant associations, when analyzing brain infarcts alone or WMH alone. This probably reflects limitations of the sample size and suggests that infarcts and WMH have additive effects when present in combination. Our findings are only relevant to the influence of vascular lesions on cognitive profile in persons with early-stage cognitive symptoms and impairment, whereas in the general population it is known that brain infarcts and WMH are also associated with impaired processing speed and global cognition, too [29].

Associations between cognitive reserve proxies and cognition were consistent with prior literature with the exception that multilingualism was associated with worse MoCA and marital status was associated with worse cognition rather than better cognition. Lower MoCA scores in multilingual persons may have reflected difficulty with language related MoCA items, as neuropsychological scores on tests of executive function and processing speed, which are less dependent on language, did not differ from unilingual persons. Indeed, after removing three of the more language dependent MoCA items the association was no longer significant. The association of marital status with lower cognition was unexpected and differs from what has been observed in studies in the general population, where being in a martial partnership is associated with higher cognition [30]. We explored whether there were sex-specific effects of marital status on cognition and did not find any. However, marital status was associated with higher odds of having high vascular lesion burden, suggesting that married persons may be presenting at a later stage of impairment, with higher levels of brain pathology, because their spouse helps them compensate for earlier impairments.

Some prior studies suggest that cognitive reserve modifies the association between vascular pathology and cognition [2, 4, 31–34] while others do not [30, 35]. Variable findings across studies may reflect differences in study populations. Our study was composed of participants that have high occupational attainment (85.3%), the majority were married or in a common-law partnership (73.1%), almost half had a university degree (48.7%), many participants had high annual household income (60.0%) and a high proportion were multilingual (57.5%). Thus, our study participants may have had unusually high cognitive reserve, with less heterogeneity in reserve than other studies. One recently published study found that cognitive reserve did not modify the association between WMH and cognition, which is consistent with our findings [35]. The participants in that study also had a relatively high mean years of education (13.0 ± 4.5) [35], which exceeded that reported in older studies of WMH and cognitive reserve (e.g., mean 9.6 ± 3.8 years in the Leukoaraiosis and Disability (LADIS) study) [2]. Other studies included participants with dementia, whereas our study only included persons with SCI or MCI. Because eligibility for our study required cognitive symptoms, which are related to the study outcome (neuropsychological function), the findings may be influenced by reasons why patients presented to the clinic or the presence of other cognitive brain pathologies, and associations with risk factors may differ from what would be observed in the general population. However, the study findings are applicable to the setting in which they were observed, i.e., patients presenting to a memory clinic with cognitive symptoms without dementia.

When individuals with higher cognitive reserve develop a cognitive disorder their brain pathology may be more severe, because the additional reserve capacity has allowed the brain to compensate for some of the effects of the pathology [1]. In other words, it takes more pathology to cause cognitive impairment in persons with higher reserve. If that were the case, then in persons with a cognitive disorder and high cognitive reserve one might expect to find *higher* levels of brain pathology. However, in our study we found the opposite–that in mildly impaired participants, higher cognitive reserve composite score was associated with *lower* vascular lesion burden. This finding may be because higher socioeconomic status and higher physical activity, which are proxy variables for cognitive reserve, are also associated with lower risk of cardiovascular disease and vascular brain injury in the general population [36, 37]. However, we did find that one component of the composite score, being married or in a common law partnership, was associated with higher burden of vascular brain lesions at presentation with SCI or MCI.

Limitations of our study include the cross-sectional nature of our cohort, which does not allow us to test temporality of relationships. However, future COMPASS-ND analyses plan to include longitudinal data to better determine the temporal association of vascular brain injury with cognitive profile. The COMPASS-ND study cohort is predominantly white and well educated with high occupational attainment; it is increasingly recognized that the dementia research field requires more studies targeting patient populations that previously have been under-represented [38]. Another potential limitation of our study is that we dichotomized our cognitive reserve variables for simplicity of interpretation, which may have some impact on statistical power. However, a sensitivity analysis using the original variable categories without dichotomization showed similar associations. Our analysis of social participation was based on a simple frequency of social interactions in three categories, and it is possible that the effect of social participation would have been greater if it had been captured in greater detail. Because our study was not done in the general population, it does not provide definitive evidence on whether cognitive reserve modifies the effect of vascular brain lesions in that setting.

Findings from our study suggest that high occupational attainment, high physical activity, high annual household income, and being unmarried or not being in a common-law partnership are lifestyle factors associated with a milder cognitive profile in persons with subjective cognitive concerns or mild cognitive impairment. However, these lifestyle factors did not mitigate the effects of vascular brain injury on executive function in this study population with early-stage cognitive concerns and impairments. Targeting vascular risk factors to prevent vascular brain injury, as well as promoting cognitive reserve, will be necessary to reduce the risk for vascular cognitive impairment.

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CONFLICT OF INTEREST

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SUPPLEMENTARY MATERIAL

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