Neurology Asia 2024; 29(3) : 737 – 748

Associations between the Framingham Risk Score and cognitive functions in people with multiple sclerosis

[1]Alevtina Ersoy *MD*, [2]Senanur Baloglu *MA*, [3]Ceyda Tanoglu *MD*, [4]Serhat Hayme *PhD*

[1]Department of Neurology, Erzincan Binali Yildirim University, Faculty of Medicine, Mengucek Gazi Training and Research Hospital, *Erzincan, Turkey; [2]Psycologist, Ankara Provincial Directorate of Youth and Sports, The Ministry of Youth and Sports, Ankara, Turkey; [3]Department of Neurology, İzmir University of Health Sciences, Tepecik Training and Research Hospital, Izmir, Turkey; [4]Department of Biostatistics and Medical Informatics, Erzincan Binali Yildirim University, Erzincan, Turkey*

Abstract

Background & Objective: Cognitive impairment is common in people with multiple sclerosis (MS). The Framingham Risk Score (FRS) is an algorithm used to estimate the 10-year risk of developing cardiovascular disease (CVDr). This study aimed to evaluate the possible associations between FRS and cognitive impairment in people with MS. *Methods:* Demographic characteristics, laboratory parameters, clinical findings, vascular risk factors, and Brief International Cognitive Assessment for MS (BICAMS) test results, FRS and CVDr scores were recorded for 110 MS patients. *Results:* FRS and CVDr scores exhibited a significant negative correlation with the number of correct responses in the Symbol Digit Modalities Test ($p < 0.001$ for all) and California Verbal Learning Test–Second UK Edition (CVLT-II) test ($p < 0.001$ for all), and significant positive correlation with the number of incorrect responses in the CVLT-II ($p < 0.001$ for all). The total score of the Brief Visuospatial Memory Test Revised had a negative correlation with FRS and CVDr ($p < 0.001$ for both). BICAMS scores showed no significant correlation with smoking status, homocysteine, and uric acid levels. *Conclusion:* We suppose that vascular risk factors and FRS and CVDr scores may be associated with the deterioration of working memory, information processing speed, verbal learning, and memory in people with MS. Based on the potential impact of vascular risk factors on cognitive functions, our findings suggest that lifestyle changes, appropriate treatment, and using a multidisciplinary approach toward vascular risk factors during MS management may exhibit a positive effect on cognition in people with MS.

Keywords: Multiple sclerosis, Framingham Risk Score, cognition, BICAMS, vascular risk factors.

INTRODUCTION

Cognitive impairment in multiple sclerosis (MS) was first mentioned by Charcot (1877), and subsequent studies have demonstrated that cognitive impairment is a common MS symptom.[1-3] The prevalence of cognitive impairment, which is observed in all types and periods of MS, ranges from 34% to 65%.[4] Moreover, cognitive dysfunction can be detected in the earliest stages of the disease, including in the clinically and radiologically isolated syndromes.[5,6] Although cognitive impairment is known to be important in MS, its exact pathophysiology has not yet been fully understood. MS pathogenesis involves both the gray and white matter; however, the vast majority of MS lesions occur in the white matter areas. Furthermore, plaque buildup, tissue destruction, or disrupted cortical–subcortical connections in the brain due to demyelination are considered to be associated with declining cognitive functions in MS, and gray matter atrophy has been postulated to be an early sign of possible future cognitive decline.[4,7,8] The most common cognitive functions affected in MS include visual memory, verbal memory, information processing speed, attention, visuospatial processing, verbal fluency, free recall from long-term memory, working memory, and abstract reasoning while

Address correspondence to: Dr. Alevtina Ersoy, Erzincan Binali Yildirim University, Department of Neurology, Mengucek Gazi Training and Research Hospital, Erzincan, Turkey. Tel: + 90 5332145569; E-mail: alevtina_ersoy@hotmail.com

Date of Submission: 31 March 2024; Date of Acceptance: 8 April 2024

https://doi.org/10.54029/2024rer

other functions, such as semantic memory, basic language, conceptual reasoning, and recognition memory are less affected.[3,4,9] De Meo *et al*. described five cognitive phenotypes in people with MS with cognitive impairment: mild–multidomain, severe–executive/attention, and severe–multidomain involvement and preserved cognition and mild–verbal memory/semantic fluency. The authors believed that this new classification could determine the cognitive status of people with MS in greater detail, complement the expanded disability status scale (EDSS) score, support clinicians in selecting treatment options, and help tailor cognitive rehabilitation strategies.[10] Furthermore, a direct relationship has been found among cognitive dysfunction, fatigue, quality of life, and depression in people with MS.[11,12]

Compared with the general population, people with MS harbor a greater risk of developing cerebrovascular and cardiovascular diseases in the first few years following diagnosis, after which this risk decreases but remains high for stroke and venous thromboembolism.[13] The prevalence of vascular risk factors, such as arterial hypertension and hyperlipidemia, exceeds 10% in the MS population and increases with age. Although the prevalence of coronary heart disease, congestive heart failure, and stroke is usually <5%, it is higher than in the general population.[14] Another study reported that the most common risk factor for atherosclerosis in MS was smoking and the least common risk factor was diabetes mellitus (DM). Dyslipidemia and hypertension are the second and third most frequently cited risk factors of atherosclerosis in MS, respectively. Male sex and advanced age have been associated with multiple risk factors for atherosclerosis.[15] Carotid intima–media thickness, an early indicator of atherosclerosis, appears to be related to disease prognosis and age in people with MS, and has been hypothesized to be an indicator of susceptibility to subclinical atherosclerosis.[16] Moreover, a study by Yang *et al*. found that genetic susceptibility to MS was associated with an increased risk of coronary artery disease (CAD), myocardial infarction, heart failure, all-cause stroke, and any type of ischemic stroke.[17]

A study by Lorefice *et al*. associated DM with a significant reduction in the whole brain and gray matter of the brain and cortex volumes. Similarly, reduced cortical gray matter volume was associated with hypertension. Furthermore, the co-occurrence of multiple vascular risk factors and lower cortical gray matter volume has been strongly correlated. Patients with at least one vascular risk factor have been found to exhibit a greater annualized brain volume loss compared with controls.[18] Vascular risk factors have been associated with lower brain volume already present in early MS but did not increase brain volume loss during 3.5 years of follow-up.[19]

Based on available literature data, we hypothesized that vascular risk factors in people with MS may lead to cognitive dysfunction. This study aimed to evaluate the association between vascular risk factors, the Framingham Risk Score (FRS), and cognitive function in patients with MS.

METHODS

Study design

This cross-sectional study included 110 people with MS who presented to the Neurology Outpatient Clinic and met the current McDonald criteria at the time of diagnosis. The patients were >18 years of age and had at least a primary school degree. Several parameters were recorded for all the patients, including demographic characteristics (age, sex, height, weight, education, and employment), laboratory parameters (total cholesterol [TC], low-density lipoprotein [LDL], high-density lipoprotein [HDL], triglyceride [TG], uric acid, and homocysteine levels), clinical findings (age at onset of MS, duration of disease, MS type, annualized rate of relapses, EDSS score, number of medications used, and last medication used), vascular risk factors (arterial hypertension [HT], DM, smoking, CAD, cerebrovascular disease [CVD], and peripheral vascular disease [PVD]), and Hamilton Depression Scale[20] and Brief International Cognitive Assessment for MS (BICAMS) battery test[21] results. Body mass index (BMI), TC/HDL ratio, FRS, and cardiovascular disease risk (CVDr) were calculated. The patients with depression according to the Hamilton Depression Scale (score > 13) were excluded from the study because of the potential impact on their cognitive functions. Other exclusion factors involved pregnancy or lactation, relapse, receiving intravenous methylprednisolone or plasmapheresis over the last 1-month, psychiatric diseases independent of MS, diagnoses of mental retardation, dementia, and minimal cognitive impairment, substance abuse, active infection, impaired liver, kidney, and thyroid functions, vitamin B12 deficiency, and impaired hearing, vision, speech, and upper extremity dysfunction at a degree that would prevent taking the tests.

Associations between the FRS, CVDr, vascular risk factors, and cognition were analyzed. The study was approved by the Clinical Research Ethics Committee of Erzincan Binali Yildirim University, Turkey (No.: 04/09 22.02.2021) and conducted in accordance with the Declaration of Helsinki. Informed consent was obtained from all the patients.

Calculating the Framingham Risk Score (FRS)

The FRS is a sex-specific estimate of the CVDr (CAD, stroke, peripheral vascular disease, congestive heart failure, and cardiac death).[22] The FRS is calculated using age, sex, diabetes (yes/no) and smoking (yes/no) statuses, systolic and diastolic blood pressures, and LDL and HDL levels. The sum of all the item scores comprises the total FRS, which is then converted into the CVDr score expressed in percentage. Higher FRS indicates higher CVDr.

Brief International Cognitive Assessment for MS (BICAMS)

All the patients received the BICAMS test validated for use in Turkey.[23] This test comprises three separate tests: the Symbol Digit Modalities Test (SDMT), California Verbal Learning Test–Second UK Edition (CVLT-II), and Brief Visuospatial Memory Test Revised (BVMT-R).[21]

The SDMT assesses working memory and information processing speed.[21,24] It is based on a series of nine symbols, each paired with a single digit in a key at the top of a standard sheet of paper. Below the key, there are several rows of the same symbols arranged in a random order. After a short matching trial, the patients were asked to match as many numbers and symbols as possible in 90 s. The short trial was performed with 10 pairs and the number of total, correct, and incorrect answers provided within 90 s were recorded. We used the written SDMT.

The CVLT-II measures verbal learning and memory in older adolescents and adults.[21,25] This test comprises a list of 16 words in 4 semantic categories. The examiner reads all the words in a sequence at a steady pace of ~20 s. After hearing the complete list, the patients were asked to repeat as many of the items as possible in any sequence and the examiner recorded the proportion of recall. Altogether, there were five learning trials, and in each trial, the patients were asked to recall the answers given in the previous trial. The final score constituted the total number of words recorded in all the trials. We recorded the total number of correct, incorrect, and repeated words after the five trials.

The BVMT-R is a test used to measure visuospatial learning and memory abilities in research and clinical settings.[21,26] It uses six abstract designs drawn on a standard sheet of paper. The designs were presented to the patients for 10 s and then removed from their view. The patients were then asked to render as many designs as possible in the given order via pencil on paper. Each design received 0–2 points based on accuracy and location. The total score was the sum of the scores from all the three attempts.

Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics version 22. Nominal variables were expressed as numbers and percentages. Normally distributed continuous variables were presented as mean and standard deviation and non-normally distributed variables as median and minimum-maximum. Intergroup comparisons were performed using chi-squared test for nominal variables, Student's t-test and analysis of variance for normally distributed continuous variables, and Mann–Whitney U and Kruskal–Wallis tests for non-normally distributed continuous variables. The correlation of continuous variables was analyzed using Pearson's correlation test when both variables were normally distributed and Spearman's correlation test when otherwise. Correlation with controlled variables was carried out using the partial correlation method. Statistical significance was considered $p < 0.05$.

RESULTS

Patient characteristics

Most patients were female (F:M = 2.5:1) and had completed primary, secondary, or high school education (67.3%); 32.7% of them had a associate's, bachelor's or master's degree. In terms of employment, 42.7% patients were employed or student, and 6.4% of unemployed patients were unemployed due to MS. The demographic characteristics of the patients are shown in Table 1.

In terms of clinical characteristics, 83.6% patients exhibited relapsing–remitting MS (RRMS) and 16.4% exhibited progressive MS. In 53.6% patients, the first attack manifested with optic neuritis and sensory findings, which are considered good prognostic indicators. Very few patients (4.6%) had two or more relapses per year (suggestive of active MS). Half the patients

Table 1: Demographic characteristics of the MS patients

Age (years)	39.7 ± 10.3
Sex	
Men	31 (28.2%)
Women	79 (71.8%)
BMI	25.6 (16.7–43.0)
Education	
Primary	35 (31.8%)
Secondary	12 (10.9%)
High school	27 (24.6%)
Associate's degree	7 (6.4%)
Bachelor's degree	25 (22.7%)
Master's degree	4 (3.6%)
Occupation	
Voluntarily unemployed	53 (48.2%)
Unemployed due to MS	7 (6.4%)
Pensioner	3 (2.7%)
Student	6 (5.4%)
Employed	41 (37.3%)

BMI, body mass index; MS, multiple sclerosis.

(50.8%) were receiving first-line treatment, 30.0% were receiving second-line treatment, and 19.2% were not receiving any treatment. The clinical characteristics of the patients are shown in Table 2.

The most common vascular risk factors included smoking (41.8%), hypertension (10.0%), and diabetes (8.2%). Table 3 shows the lipid panel, homocysteine levels, uric acid levels, blood pressure, and FRS and CVDr results.

The patients did not exhibit depression that could affect their cognitive performance. In the SDMT, the patients provided an average of 31.5 responses, of which 92.1% were correct. In the CVLT-II, an average of 40.4 correct answers was recorded out of a maximum of 80. In the BVMT-R test, an average of 20.1 out of 36 points was observed. BICAMS scores are shown in Table 4.

Associations between FRS and CVDr and demographic and MS characteristics

The correlation between FRS and CVDr and demographic and MS characteristics is shown in Table 5. As no patients had peripheral vascular disease and only one patient used statins and had cerebrovascular disease (0.9%), that patient was not included in the analysis. The FRS and CVDr were positively correlated with age ($p < 0.001$ for both), BMI ($p < 0.001$ and $p = 0.001$, respectively), EDSS score ($p < 0.001$ for both), and age at onset of MS ($p < 0.001$ for both).) These scores were observed to be lower in women ($p = 0.024$ and $p < 0.001$, respectively), patients with higher education levels ($p < 0.001$ for both), and those with RRMS ($p < 0.001$ for both). Only FRS score was lower in those who were employed ($p = 0.011$) and exhibited a positive correlation with disease duration ($p = 0.029$).

Associations between BICAMS scores and demographic and MS characteristics

Associations between demographic and MS characteristics and BICAMS scores are shown in Table 6. The BICAMS scores exhibited no significant correlation with the annual relapse rate and number of medications used.

Symbol Digit Modalities Test (SDMT)

The total number of answers and the number of correct answers in the SDMT exhibited a significant negative correlation with age, BMI, EDSS, MS treatment duration, onset age of MS, and disease duration ($p = 0.020$ for BMI, $p = 0.001$ for treatment duration, $p < 0.001$ for others). The patients who provided the highest number of correct answers either had a bachelor's or master's degree ($p < 0.001$), were employed ($p < 0.001$), and had RRMS ($p < 0.001$). Conversely, increased incidences of relapses was associated with fewer correct answers ($p = 0.048$).

California Verbal Learning Test–Second UK Edition (CVLT-II)

The number of correct answers in the CVLT-II was inversely correlated with age, onset age of MS, and EDSS score ($p = 0.002$, $p = 0.010$, and $p < 0.001$, respectively). Furthermore, women ($p = 0.002$), and those with RRMS ($p = 0.001$) provided more correct answers. In addition, the CVLT-II scores demonstrated no significant correlation with BMI, total number of relapses, and duration of MS.

Brief Visuospatial Memory Test Revised (BVMT-R)

The total BVMT-R score was negatively correlated with age, age at onset of MS, disease duration, treatment duration, and EDSS score ($p < 0.001$, $p < 0.001$, $p = 0.006$, $p = 0.004$ and $p < 0.001$, respectively). Furthermore, the patients who were employed, those with higher education levels, and those with RRMS achieved higher total scores ($p = 0.005$, $p = 0.002$, and $p = 0.015$, respectively).

Table 2: Clinical characteristics of MS

Type	
RRMS	92 (83.6%)
SPMS	6 (5.5%)
PPMS	12 (10.9%)
Age at onset of MS (years)	31.4 ± 9.43
MS duration (years)	7.0 (0.0–35.0)
First attack	
Motor	20 (18.2%)
Sensory	37 (33.6%)
Ataxia	10 (9.1%)
Optic neuritis	22 (20.0%)
Multisystem	13 (11.8%)
Brainstem	8 (7.3%)
ARRs	
0	68 (61.8%)
1	37 (33.6%)
≥ 2	5 (4.6%)
Total number of relapses	2.0 (0.0–14.0)
EDSS score	1.5 (0.0–6.5)
Duration of treatment	4.0 (0.0–24.0)
Number of DMT	
0	16 (14.5%)
1	37 (33.6%)
2	32 (29.2%)
≥ 3	25 (22.7%)
Last DMT used	
Glatiramer acetate	12 (10.9%)
Teriflunomide	16 (14.5%)
Dimethyl fumarate	16 (14.5%)
Fingolimod	16 (14.5%)
Ocrelizumab	15 (13.7%)
Natalizumab	2 (1.8%)
Interferon	12 (10.9%)
No DMT	21 (19.2%)
Last DMT exposure time	2.0 (0.0–16.0)

MS, multiple sclerosis; RRMS, relapsing–remitting multiple sclerosis; SPMS, secondary progressive MS; PPMS, primary progressive MS; ARR, annualized rate of relapses; EDSS, expanded disability status scale; DMT, disease-modifying therapy

Associations between BICAMS scores and vascular risk factors

The correlation between BICAMS scores and vascular risk factors is shown in Table 7. BICAMS scores exhibited no significant correlation with smoking status and homocysteine and uric acid levels.

SDMT: The total number of answers and correct answers in the SDMT exhibited a significant negative correlation with the values of TC ($p = 0.005$ and $p = 0.007$, respectively), LDL ($p = 0.012$ and $p = 0.017$, respectively), FRS, and CVDr ($p < 0.001$ for all). Furthermore, the total number of responses was lower in people with hypertension, diabetes, and CAD ($p = 0.018$, $p = 0.046$, and $p = 0.027$, respectively).

Table 3: Vascular risk factors of the MS patients

Arterial hypertension	11 (10.0%)
Diabetes	9 (8.2%)
Statin use	1 (0.9%)
Smoking	46 (41.8%)
Coronary artery disease	2 (1.8%)
Cerebrovascular disease	1 (0.9%)
Peripheral vascular disease	0 (0%)
Systolic blood pressure (mm/Hg)	120.0 (120.0–120.0)
Diastolic blood pressure (mm/Hg)	80.0 (70.0–80.0)
TC (mg/dL)	200.5 (105.0–398.0)
LDL (mg/dL)	130.0 (56.2–260.0)
HDL (mg/dL)	52.5 ± 11.8
Triglyceride (mg/dL)	121.5 (40.0–485.0)
TC/HDL	4.04 (1.98–8.83)
Homocysteine (mmol/L)	11.0 (5.82–42.5)
Uric Acid (mg/dL)	3.81 (1.40–7.40)
Framingham risk score	1.0 (-14.0–16.0)
CVDr	3.0 (0.0–27.0)

MS, multiple sclerosis; TC, total cholesterol; LDL, low-density lipoprotein; HDL, high-density lipoprotein; CVDr, 10-year cardiovascular disease risk

CVLT-II: TC/HDL ratio, FRS, and CVDr exhibited a significant negative correlation with the total number of correct answers in the CVLT-II ($p = 0.006$, $p < 0.001$, and $p < 0.001$, respectively) and a significant positive correlation with the number of incorrect answers ($p = 0.022$, $p = 0.032$, and $p = 0.046$, respectively). In addition, patients without hypertension and CAD provided more correct answers ($p = 0.029$ and $p = 0.014$, respectively) while those with hypertension provided more incorrect answers ($p = 0.019$). No correlation was observed between the number of repetitions and vascular risk factors.

BVMT-R: The total score of the BVMT-R test demonstrated a negative correlation with the FRS and CVDr ($p < 0.001$ for both). The total BVMT-R score exhibited no correlation with the other vascular risk factors.

Factors that are not included in the calculation of FRS but show a significant correlation with FRS and BICAMS may affect the relationship between FRS and BICAMS. When controlling for education, employment, BMI, MS type, ARR, and MS duration, a significant negative correlation was found between FRS and SDMT total responses, SDMT total correct responses, CVLT-II total correct responses, and BVMT-R total score ($p = 0.018$, $p = 0.035$, $p = 0.046$, $p = 0.007$, respectively) (Table 8).

DISCUSSION

This study investigated the possible associations

Table 4: BICAMS results of the MS patients

SDMT total responses	31.5 (3.00–85.0)
SDMT total correct responses	29.0 (0.0-84.0)
SDMT total incorrect responses	2.0 (0.0-8.0)
CVLT-II total correct responses	40.4 ± 10.6
CVLT-II total errors	1.0 (0.0–11.0)
CVLT-II total repetitions	2.0 (0.0–12.0)
BVMT-R total scores	20.1 ± 8.2

MS, multiple sclerosis; BICAMS, Brief International Cognitive Assessment for Multiple Sclerosis; SDMT, Symbol Digit Modalities Test; CVLT-II, California Verbal Learning Test–Second UK Edition; BVMT-R, Brief Visuospatial Memory Test Revised

Table 5: Associations between demographic characteristics, clinical MS characteristics, and Framingham Risk Score and 10-year cardiovascular disease risk in people with MS.

Variable			FRS	CVDr
Age	r		0.804	0.725
	p		**<0.001**	**<0.001**
BMI	r		0.381	0.302
	p		**<0.001**	**0.001**
Treatment duration	r		0.169	0.106
	p		0.079	0.275
Age at onset of MS	r		0.711	0.665
	p		**<0.001**	**<0.001**
MS duration	r		0.209	0.128
	p		**0.029**	0.186
EDSS	r		0.441	0.451
	p		**<0.001**	**<0.001**
ARR	r		-0.198	-0.200
	p		**0.039**	**0.037**
Total relapses	r		0.036	-0.029
	p		0.712	0.762
Number of medications	r		0.063	0.041
	p		0.512	0.670
Sex, (median (min-max))		Male	2.0 (-4-10)	4 (0-27)
		Female	-0.5 (-14-16)	1.5 (0-27)
			p = 0.024	**p < 0.001**
Education, (median (min-max))		Primary	4.5 (-8-9)[a]	4.5 (0-14)[a]
		Secondary	-1.0 (-14-10)[a, c]	1.5 (0-27)[a, c]
		High school	2.0 (-11-16)[a]	4.0 (0-27)[a]
		Associate's, Bachelor's ans Master's Degrees	-6.5 (-14-8)[b, c]	0.0 (0-11)[b, c]
			p < 0.001	**P < 0.001**
Occupation, (median (min-max))		Employed	0.0 (-14-10)	2.0 (0-14)
		Unemployed	2.0 (-14-16)	3.0 (0-27)
			p = 0.011	p = 0.189
MS type (median (min-max))		Relapsing	0.0 (-14-16)	2.0 (0-27)
		Progressive	6.0 (-11-10)	8.0 (0-27)
			p < 0.001	**p < 0.001**

MS, multiple sclerosis; BMI, body mass index; ARR, annualized rate of relapses; EDSS, expanded disability status scale; FRS, Framingham Risk Score, CVDr, 10-year cardiovascular disease risk.

[a, b, c]: Groups marked with the same letter are statistically similar, and there is a statistically significant difference ($p < 0.05$) between groups with different letters.

among vascular risk factors, FRS, and CVDr and cognitive functions in people with MS. The results showed that longer MS duration, higher EDSS scores, increased relapses, hyperlipidemia, and the presence of CAD, DM, hypertension, high FRS and CVDr values engendered impaired working memory and slower information processing speed. Verbal learning and memory were negatively affected by advanced age, dyslipidemia, hypertension, and high EDSS, FRS and CVDr values. Similarly, visuospatial learning and memory were found to be impaired with advanced age, longer disease and treatment durations, and high EDSS, FRS, and CVDr values. Furthermore, increased FRS and CVDr yielded higher EDSS scores.

Petruzzo *et al*. evaluated the possible association between the FRS and MS course over a 5-year follow-up and found that a one-

Table 6: Associations between demographic characteristics, clinical MS characteristics and BICAMS

			SDMT total responses	SDMT total correct responses	CVLT-II total correct responses	CVLT-II total errors	CVLT-II total repetitions	BVMT-R total score
Age	r		-0.620	-0.618	-0.295	0.148	-0.024	-0.531
	p		**<0.001**	**<0.001**	**0.002**	0.122	0.803	**<0.001**
BMI	r		-0.221	-0.231	-0.161	0.097	-0.058	-0.074
	p		**0.020**	**0.015**	0.092	0.314	0.549	0.445
Treatment duration	r		-0.323	-0.311	-0.052	0.102	0.063	-0.270
	p		**0.001**	**0.001**	0.589	0.290	0.516	**0.004**
Age at onset of MS	r		-0.394	-0.403	-0.245	0.100	-0.116	-0.331
	p		**<0.001**	**<0.001**	**0.010**	0.301	0.228	**<0.001**
MS duration	r		-0.327	-0.318	-0.049	0.049	0.090	-0.258
	p		**<0.001**	**0.001**	0.610	0.613	0.350	**0.006**
EDSS	r		-0.594	-0.586	-0.586	0.063	-0.017	-0.445
	p		**<0.001**	**<0.001**	**<0.001**	0.515	0.224	**<0.001**
ARR	r		0.140	0.101	0.160	-0.034	0.121	0.112
	p		0.144	0.291	0.094	0.725	0.209	0.245
Total relapses	r		-0.162	-0.189	-0.019	0.009	0.099	-0.073
	p		0.091	**0.048**	0.848	0.923	0.301	0.451
Number of medications	r		-0.153	-0.150	0.010	0.128	0.105	-0.085
	p		0.110	0.117	0.921	0.184	0.277	0.375
Sex, (median (min-max))		Male	32 (3-60)	30 (0-57)	36 (18-61)	0 (0-11)	1 (0-8)	19 (4-36)
		Female	31 (4-85)	29 (0-84)	43 (19-65)	1 (0-9)	2 (0-12)	21 (0-34)
			p = 0.928	p = 0.725	**p = 0.002**	p = 0.76	p = 0.210	p = 0.540
Education, (median (min-max))		Primary	21 (4-40)[a]	18 (0-40)[a]	37 (19-54)[a]	1 (0-6)[a]	1 (0-12)[a]	17 (0-29)[a]
		Secondary	27 (3-43)[a, b]	25 (0-39)[a, b]	31 (18-52)[a]	2 (0-5)[a]	1.5 (0-10)[a, b]	18.5 (2-26)[a]
		High school	30 (9-54)[b]	29 (9-52)[b]	39 (23-59)[a, b]	0 (0-11)[a]	3 (0-11)[a, b]	19 (4-33)[a, b]
		Associate's, Bachelor's ans Master's Degrees	45 (13-85)[c]	44 (13-84)[c]	50 (23-65)[b, c]	1 (0-9)[a]	3 (0-8)[b]	25 (13-36)[b]
			p = <0.001	**p = <0.001**	**p = <0.001**	**p = 0.046**	**p = 0.025**	**p = 0.002**
Occupation, (median (min-max))		Employed	42 (11-85)	41 (10-84)	42 (18-61)	1 (0-9	2.5 (0-8)	22.5 (4-36)
		Unemployed	22.5 (3-51)	20 (0-48)	38.5 (19-65)	1 (0-11)	2 (0-12)	19 (0-29)
			p = <0.001	**p = <0.001**	p = 0.456	p = 0.297	p = 0.848	**p = 0.005**
MS type (median (min-max))		Relapsing	35 (4-85)	33.5 (0-84)	42 (18-65)	1 (0-11)	2 (0-12)	22 (0-36)
		Progressive	19.5 (3-60)	16 (0-59)	35 (22-45)	1.5 (0-5)	1.5 (0-7)	16.5 (1-29)
			p = <0.001	**p = <0.001**	**p = 0.001**	p = 0.262	p = 0.216	**p = 0.015**

MS, multiple sclerosis; BICAMS, Brief International Cognitive Assessment for Multiple Sclerosis; SDMT, Symbol Digit Modalities Test; CVLT-II, California Verbal Learning Test–Second UK Edition; BVMT-R, Brief Visuospatial Memory Test Revised; BMI, body mass index; ARR, annualized rate of relapses; EDSS, expanded disability status scale.
[a, b, c]: Groups marked with the same letter are statistically similar, and there is a statistically significant difference ($p < 0.05$) between groups with different letters.

Table 7: Associations between vascular risk factors, FRS, CVDr, and BICAMS in people with MS

		SDMT total responses	SDMT total correct responses	CVLT-II total correct responses	CVLT-II total errors	CVLT-II total repetitions	BVMT-R total score
TC (mg/dL)	r	-0.267	-0.257	-0.069	0.126	0.092	-0.159
	p	**0.005**	**0.007**	0.476	0.190	0.339	0.097
HDL (mg/dL)	r	-0.057	-0.069	-0.216	-0.075	0.145	0.013
	p	0.552	0.476	**0.023**	0.434	0.130	0.889
LDL (mg/dL)	r	-0.238	-0.028	-0.079	0.157	0.097	-0.134
	p	**0.012**	**0.017**	0.411	0.101	0.312	0.164
Triglyceride (mg/dL)	r	-0.182	-0.168	-0.137	0.167	-0.042	-0.150
	p	0.058	0.080	0.152	0.081	0.665	0.117
TC/HDL	r	-0.197	-0.186	-0.262	0.218	-0.049	-0.152
	p	**0.039**	0.052	**0.006**	**0.022**	0.613	0.113
Homocysteine (mmol/L)	r	0.024	0.020	-0.043	-0.084	-0.169	-0.027
	p	0.810	0.838	0.662	0.392	0.085	0.782
Uric acid (mg/dL)	r	-0.022	-0.030	-0.120	0.350	0.062	-0.063
	p	0.825	0.758	0.217	0.108	0.522	0.516
FRS	r	-0.548	-0.538	-0.432	0.205	-0.110	-0.407
	p	**<0.001**	**<0.001**	**<0.001**	**0.032**	0.253	**<0.001**
FRS controlled for education, employment, BMI, MS type, ARR and MS duration	r	-0.231	-0.208	-0.197	0.127	0.076	-0.263
	p	**0.018**	**0.035**	**0.046**	0.200	0.443	**0.007**
CVDr	r	-0.494	-0.476	-0.446	0.192	-0.136	-0.363
	p	**<0.001**	**<0.001**	**<0.001**	**0.046**	0.160	**<0.001**
CVDr controlled for education, employment, BMI, MS type, ARR and MS duration	r	-0.173	-0.143	-1.163	0.144	0.032	-0.078
	p	0.08	0.150	0.100	0.147	0.748	0.431
HT, (median (min-max))	No	34 (3-85)	30 (0-84)	39 (18-65)	1 (0-11)	2 (0-12)	20 (0-36)
	Yes	19 (4-59)	18 (0-59)	33 (19-49)	3 (0-5)	1 (0-4)	23 (3-29)
		p = 0.018	**p = 0.025**	**p = 0.029**	**p = 0.019**	p = 0.128	p = 0.628
DM, (median (min-max))	No	33 (3-85)	30 (0-84)	39 (18-65)	1 (0-11)	2 (0-12)	21 (0-36)
	Yes	21 (15-38)	18 (12-38)	38 (24-43)	2 (0-5)	3 (0-7)	20 ().9-28
		p = 0.046	p = 0.060	p = 0.292	p = 0.060	p = 0.921	p = 0.596
Smoking, (median (min-max))	No	34 (4-59)	32 (0-59)	41.5 (18-59)	1 (0-9)	2.5 (0-11)	21.5 (1-33)
	Yes	28 (3-85)	26 (0-84)	36.5 (22-65)	1 (0-11)	2 (0-12)	20 (0-36)
		p = 0.785	p = 0.918	p = 0.201	p = 0.546	p = 0.314	p = 0.935
CAD, (median (min-max))	No	32 (3-85)	29.5 (0-84)	39 (18-65)	1 (0-11)	2 (0-12)	21 (0-36)
	Yes	14.5 (14-15)	14.5 (14-15)	23.5 (23-24)	1.5 (1-2)	0.5 (0-1)	11.5 (8-15)
		p = 0.027	p = 0.091	**p = 0.014**	p = 0.574	p = 0.133	p = 0.096

MS, multiple sclerosis; BICAMS, Brief International Cognitive Assessment for Multiple Sclerosis; SDMT, Symbol Digit Modalities Test; CVLT-II, California Verbal Learning Test–Second UK Edition; BVMT-R, Brief Visuospatial Memory Test Revised; TC, total cholesterol; HDL, high-density lipoprotein; LDL, low-density lipoprotein; FRS, Framingham Risk Score, CVDr, 10-year cardiovascular disease risk; HT, arterial hypertension; DM, diabetes mellitus; CAD, coronary artery disease.

point increase in the FRS was associated with 31% higher risk of relapse, 19% higher risk of achieving an EDSS score of 6.0, and 62% higher risk of disease-modifying therapy escalation.[27] CVDr was 36.8% in healthy individuals versus 43.8% in patients with MS with a stable course.[28] Another study found a significantly higher FRS in secondary progressive MS compared with RRMS and showed a direct correlation between the FRS and EDSS scores and MS Severity Score.[29] Likewise, our study detected an association between higher EDSS scores and advanced age and higher BMI, FRS, and CVDr.

Reia *et al*. investigated the association between cognitive functions and demographic characteristics and clinical features of MS and found that lower SDMT scores corresponded to longer disease duration and higher EDSS scores; however, SDMT scores were not correlated with demographic variables (age, sex, and education). Conversely, the CVLT-II and BVMT-R scores were unaffected by demographic variables and clinical features of MS.[30] Our study found a similar result: fewer correct and/or total responses in the SDMT were associated with higher EDSS scores and longer disease duration as well as with increased number of relapses. Conversely, our study found that younger age, higher education levels, employment, and RRMS may lead to higher BVMT-R and SDMT scores while longer disease and treatment durations and higher EDSS scores may decrease the aforementioned scores. Furthermore, the number of correct responses in the CVLT-II and SDMT tended to decrease with increased number of relapses.

Several studies have reported that vascular risk factors affect brain volume and various cognitive functions in patients with MS. For instance, Marrie et al. found that higher FRS was associated with lower brain volumes in patients with MS at baseline and with brain volume loss over time. This effect was the most pronounced in patients with higher brain volumes at baseline.[31] The same study reported that comorbid vascular disease was generally associated with lower cognitive functions and particularly associated with processing speed, fluency measures, verbal learning, and memory. These diseases affect thalamic and hippocampal volumes as well as mean gray matter diffusion and normal-appearing white matter, thereby supporting the hypothesis that comorbid vascular disease affects cognition in patients with MS through changes in the brain structure.[32] A study by Chow *et al*. found smoking to be significantly associated with lower SDMT scores following primary progressive MS onset. Moreover, the LDL receptor-related protein risk allele was associated with decreased performance in the CVLT-II.[33] Similarly, our study showed that hyperlipidemia and dyslipidemia adversely affected SDMT and CVLT-II sores. However, unlike other studies, smoking was not found to affect cognitive functions in the present study. Some studies showed that cognitive functions were significantly impaired in former smokers with MS.[34-36] Diabetes, another vascular risk factor, has been shown to reduce BVMT-R scores and impair verbal fluency.[37] However, our study found that diabetes primarily affected working memory and information processing speed. Moreover, cognitive impairment can be attributed to hypertension and CAD alongside diabetes. Numerous studies have associated high EDSS scores with cognitive dysfunction.[34,38] Likewise, our study found that increased EDSS scores were associated with decreased SDMT, CVLT-II, and BVMT-R scores.

The FRS, which evaluates global cardiovascular health via interactions among different risk factors, has been associated with MS disability, severity,

Table 8: Associations between FRS, CVDr, and BICAMS in people with MS controlled for education, employment, BMI, MS type, ARR and MS duration

		SDMT total responses	SDMT total correct responses	CVLT-II total correct responses	CVLT-II total errors	CVLT-II total repetitions	BVMT-R total score
FRS	r	-0.231	-0.208	-0.197	0.127	0.076	-0.263
	p	**0.018**	**0.035**	**0.046**	0.200	0.443	**0.007**
CVDr	r	-0.173	-0.143	-1.163	0.144	0.032	-0.078
	p	0.08	0.150	0.100	0.147	0.748	0.431

MS, multiple sclerosis; BICAMS, Brief International Cognitive Assessment for Multiple Sclerosis; SDMT, Symbol Digit Modalities Test; CVLT-II, California Verbal Learning Test–Second UK Edition; BVMT-R, Brief Visuospatial Memory Test Revised; BMI, body mass index; ARR, annualized rate of relapses; FRS, Framingham Risk Score, CVDr, 10-year cardiovascular disease risk.

and course.[29] The FRS is reportedly an important marker for managing CVDr in patients with MS.[28] A study by Reia *et al*. reported that each point increase of the FRS corresponded to 0.21 lower CVLT-II scores. With regard to FRS components, male sex and higher TC levels corresponded to lower CVLT-II scores. However, no associations were detected between CVDr and SDMT or BVMT-R scores.[30] Similarly, our study found that increased FRS and CVDr yielded lower SDMT, CVLT-II, and BVMT-R scores. Analyzing the FRS and vascular risk factors involved in calculating this score showed that FRS, CVDr, and the aforementioned risk factors affected SDMT scores the most and BVMT-R scores the least. Moreover, when controlling for other demographic and clinical factors, it was found that the FRS scores negatively affects all test included in the BICAMS.

In conclusion, our study supposes that vascular risk factors and high FRS and CVDr, showing the combined effects of these factors, may be responsible for impairing working memory, information processing speed, verbal learning, and memory in patients with MS. Conversely, visuospatial learning and memory function impairments appeared to be affected not by individual vascular risk factors but a combination of these factors. Based on the potential impact of vascular risk factors on cognitive functions, our findings suggest that lifestyle changes, appropriate treatment, and a multidisciplinary approach toward vascular risk factors in MS may induce a positive effect on cognition in patients with MS.

Evaluation of the association between FRS, vascular risk factors and cognitive function in people with MS only, without a control group; besides, due to the small number of patients with PPMS, considering all patients with MS as a single group, regardless of the type of MS, is a limitation of our study. Thus, we cannot conclude whether FRS and vascular risk factors influence cognitive function in people without MS, and if so, whether this influence differs from that in people with MS. This topic can be explored in future studies. In addition, by including a larger number of people with progressive forms of MS, it will be possible in the future to compare the impact of the aforementioned factors on cognitive function between people with relapsing and progressive forms of MS.

ACKNOWLEDGMENT

We would like to thank the translation bureau ENAGO for linguistic assistance in preparing the article.

DISCLOSURE

Financial support: None

Conflict of interest: None

REFERENCES

1. Hsu WY, Rowles W, Anguera JA, *et al.* Assessing Cognitive Function in Multiple Sclerosis With Digital Tools: Observational Study. *J Med Internet Res* 2021; 23:e25748. doi:10.2196/25748
2. Koutsouraki E, Kalatha T, Grosi E, Koukoulidis T, Michmizos D. Cognitive decline in Multiple Sclerosis patients. *Hell J Nucl Med* 2019; 22 Suppl:75-81.
3. Rogers JM, Panegyres PK. Cognitive impairment in multiple sclerosis: evidence-based analysis and recommendations. *J Clin Neurosci* 2007; 14:919-27. doi: 10.1016/j.jocn.2007.02.006
4. Benedict RHB, Amato MP, DeLuca J, Geurts JJG. Cognitive impairment in multiple sclerosis: clinical management, MRI, and therapeutic avenues. *Lancet Neurol* 2020; 19:860-71. doi: 10.1016/S1474-4422(20)30277-5
5. Baysal Kıraç L, Ekmekçi Ö, Yüceyar N, Sağduyu Kocaman A. Assessment of early cognitive impairment in patients with clinically isolated syndromes and multiple sclerosis. *Behav Neurol* 2014; 2014:637694. doi: 10.1155/2014/637694
6. Labiano-Fontcuberta A, Martínez-Ginés ML, Aladro Y, *et al.* A comparison study of cognitive deficits in radiologically and clinically isolated syndromes. *Mult Scler* 2016; 22:250-3. doi: 10.1177/1352458515591072
7. Lassmann H. Multiple sclerosis pathology. *Cold Spring Harb Perspect Med* 2018; 8. doi: 10.1101/cshperspect.a028936.
8. Rocca MA, Amato MP, De Stefano N, *et al.* Clinical and imaging assessment of cognitive dysfunction in multiple sclerosis. *Lancet Neurol* 2015; 14:302-17. doi: 10.1016/S1474-4422(14)70250-9.
9. Grzegorski T, Losy J. Cognitive impairment in multiple sclerosis - a review of current knowledge and recent research. *Rev Neurosci* 2017; 28:845-60. doi: 10.1515/revneuro-2017-0011.
10. De Meo E, Portaccio E, Giorgio A, *et al.* Identifying the distinct cognitive phenotypes in multiple sclerosis. *JAMA Neurol* 2021; 78:414-25. doi: 10.1001/jamaneurol.2020.4920.
11. Campbell J, Rashid W, Cercignani M, Langdon D. Cognitive impairment among patients with multiple sclerosis: associations with employment and quality of life. *Postgrad Med J* 2017; 93:143-7. doi: 10.1136/postgradmedj-2016-134071
12. Davenport L, Cogley C, Monaghan R, *et al*. Investigating the association of mood and fatigue with objective and subjective cognitive impairment in multiple sclerosis. *J Neuropsychol* 2022; 16:537-54. doi: 10.1111/jnp.12283.
13. Christiansen CF. Risk of vascular disease in patients with multiple sclerosis: a review. *Neurol Res* 2012;

34:746-53. doi: 10.1179/1743132812Y.0000000051.
14. Marrie RA, Reider N, Cohen J, *et al*. A systematic review of the incidence and prevalence of cardiac, cerebrovascular, and peripheral vascular disease in multiple sclerosis. *Mult Scler* 2015; 21:318-31. doi: 10.1177/1352458514564485.
15. Etemadifar M, Salari M, Esnaashari A, *et al*. Atherosclerosis and multiple sclerosis: An overview on the prevalence of risk factors. *Mult Scler Relat Disord* 2022; 58:103488. doi: 10.1016/j.msard.2022.103488.
16. Yuksel B, Koc P, Ozaydin Goksu E *et al*. Is multiple sclerosis a risk factor for atherosclerosis? *J Neuroradiol* 2021; 48:99-103. doi: 10.1016/j.neurad.2019.10.002.
17. Yang F, Hu T, He K, Ying J, Cui H. Multiple sclerosis and the risk of cardiovascular diseases: A Mendelian randomization study. *Front Immunol* 2022; 13:861885. doi: 10.3389/fimmu.2022.861885.
18. Lorefice L, Frau J, Coghe G, *et al*. Assessing the burden of vascular risk factors on brain atrophy in multiple sclerosis: A case- control MRI study. *Mult Scler Relat Disord* 2019; 27:74-78. doi: 10.1016/j.msard.2018.10.011.
19. Pichler A, Khalil M, Langkammer C, *et al*. The impact of vascular risk factors on brain volume and lesion load in patients with early multiple sclerosis. *Mult Scler* 2019; 25:48-54. doi: 10.1177/1352458517736149.
20. Hamilton M. Rating depressive patients. *J Clin Psychiatry* 1980; 41(12 Pt 2):21-4.
21. Langdon DW, Amato MP, Boringa J, *et al*. Recommendations for a Brief International Cognitive Assessment for Multiple Sclerosis (BICAMS). *Mult Scler* 2012; 18:891-8. doi: 10.1177/1352458511431076.
22. D'Agostino RB, Sr., Vasan RS, Pencina MJ, *et al*. General cardiovascular risk profile for use in primary care: the Framingham Heart Study. *Circulation* 2008; 117:743-53. doi: 10.1161/CIRCULATIONAHA.107.699579.
23. Ozakbas S, Yigit P, Cinar BP, Limoncu H, Kahraman T, Kösehasanoğulları G. The Turkish validation of the Brief International Cognitive Assessment for Multiple Sclerosis (BICAMS) battery. *BMC Neurol* 2017; 17:208. doi: 10.1186/s12883-017-0993-0.
24. Smith A. Symbol digit modalities test (SDMT) manual (revised) Western Psychological Services. Los Angeles 1982.
25. Delis D, Kramer J, Kaplan E, Ober B. California Verbal Learning Test. The Psychological Corporation. San Antonio, TX 2000.
26. Benedict RH. Brief Visuospatial Memory Test–Revised (BVMT-R™). Lutz, FL: Psychological Assessment Resources: Inc, 1997.
27. Petruzzo M, Reia A, Maniscalco GT, *et al*. The Framingham cardiovascular risk score and 5-year progression of multiple sclerosis. *Eur J Neurol* 2021; 28:893-900. doi: 10.1111/ene.14608.
28. Albuquerque LDS, Damasceno NRT, Maia FN, *et al*. Cardiovascular risk estimated in individuals with multiple sclerosis: A case-control study. *Mult Scler Relat Disord* 2021; 54:103133. doi: 10.1016/j.msard.2021.103133.
29. Moccia M, Lanzillo R, Palladino R, *et al*. The Framingham cardiovascular risk score in multiple sclerosis. *Eur J Neurol* 2015; 22:1176-83. doi: 10.1111/ene.12720.
30. Reia A, Petruzzo M, Falco F, *et al*. A retrospective exploratory analysis on cardiovascular risk and cognitive dysfunction in multiple sclerosis. *Brain Sci* 2021; 11(4):502. doi: 10.3390/brainsci11040502.
31. Marrie RA, Patel R, Figley CR, *et al*. Higher Framingham Risk Scores are associated with greater loss of brain volume over time in multiple sclerosis. *Mult Scler Relat Disord* 2021; 54:103088. doi: 10.1016/j.msard.2021.103088.
32. Marrie RA, Patel R, Figley CR, *et al*. Effects of vascular comorbidity on cognition in multiple sclerosis are partially mediated by changes in brain structure. *Front Neurol* 2022; 13:910014. doi: 10.3389/fneur.2022.910014.
33. Chow HH, Talbot J, Marstrand L, *et al*. Smoking, cardiovascular risk factors and LRP2 gene variation: Associations with disease severity, cognitive function and brain structure in primary progressive multiple sclerosis. *Mult Scler Relat Disord* 2021; 56:103296. doi: 10.1016/j.msard.2021.103296.
34. Alirezaei M, Forouzannia SM, Yarahmadi P, *et al*. Demographic features, behavioral measures, and clinical factors as predictors of cognitive function in patients with multiple sclerosis. *Mult Scler Relat Disord* 2021; 49:102758. doi: 10.1016/j.msard.2021.102758.
35. Cortese M, Munger KL, Martínez-Lapiscina EH, *et al*. Vitamin D, smoking, EBV, and long-term cognitive performance in MS: 11-year follow-up of BENEFIT. *Neurology* 2020; 94:e1950-e1960. doi: 10.1212/WNL.0000000000009371.
36. Ozcan ME, Ince B, Bingöl A, *et al*. Association between smoking and cognitive impairment in multiple sclerosis. *Neuropsychiatr Dis Treat* 2014; 10:1715-9. doi: 10.2147/NDT.S68389.
37. Marrie RA, Patel R, Figley CR, *et al*. Diabetes and anxiety adversely affect cognition in multiple sclerosis. *Mult Scler Relat Disord* 2019; 27:164-70. doi: 10.1016/j.msard.2018.10.018.
38. Amato MP, Prestipino E, Bellinvia A, *et al*. Cognitive impairment in multiple sclerosis: An exploratory analysis of environmental and lifestyle risk factors. *PLoS One* 2019; 14:e0222929. doi: 10.1371/journal.pone.0222929.