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Diet, lifestyle, and cerebral inflow effects on neuroinflammation-neurodegeneration in MS patients

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Disclosures

- Dejan Jakimovski has nothing to disclose.

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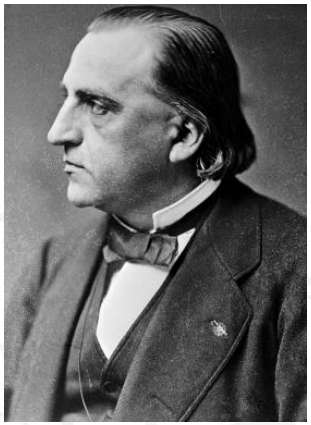
Multiple Sclerosis

- Multiple sclerosis (MS) was initially described as a disseminated plaque-like sclerosis and still today we need to demonstrate dissemination in space and time for an MS diagnosis.
- Histological studies and technological innovations (MRI) have contributed to greater understanding of the MS neuroinflammation and neurodegeneration.
- Cardiovascular health has been recently recognized as important factor within the processes of MS disease.



Jean-Martin Charcot (1825-93)

Fig. 1. — Elle représente une préparation fraîche, provenant du centre d'une plaque scléreuse, coloriée par le carmin et traitée par dilacération.

MS –multiple sclerosis

Charcot JM. Histologie de la sclerose en plaque. Gazette des hopitaux 1868; Thompson et al. Lancet Neurol 2018;17:162-173

Dietary intake and MS

- As early as the 1950s, Swank et al. hypothesized that the amount of consumed dietary fat can potentially explain the geographical variation of the MS prevalence.[1]
- Paleolithic diet (emphasis on intake of vegetables, fruit and their dietary fiber, with an avoidance of meat, milk and cereal grains).[2]
- A recent large study, which included almost 7000 MS patients, calculated such composite healthy diet scores and showed associations with lower patient-reported disability and lower depression scores.[3]
- Being randomized to any caloric restriction group within controlled study design has resulted in lowering of body weight and in improvement of the patient-reported outcomes of well-being and depression.[4]

MS –multiple sclerosis

[1]Swank et al. N Engl. J. Med. 1952; [2]Wahls et al. Trails 2018; [3]Fitzgerald et al. Neurology 2018l; [4]Choi et al. Cell Rep 2016

CVD-associated behavior and MRI-outcomes in MS

- For determining the overall CVD-associated behavior we used the Healthy Heart Score (HHS), a 20-year CVD risk prediction model which includes smoking status, BMI, physical activity, dietary intake, and alcohol consumption

- Alternatively, we calculated the Framingham Coronary Heart Disease Risk Score

Women

20-year CVD risk (%) = $[1 - 0.9660^{(\exp[W - 6.57301])}] \times 100\%$

where W = 0.10820 × age + 0.15285 (if past smoker) + 0.90138 (if current smoker) + 0.04676 × BMI – 0.01923 × grams/d of alcohol + 0.0004 × (grams/d of alcohol)^2 – 0.02951 × hours/week of exercise - 0.05113 × diet score*

*Diet score (women) = (0.03326 × grams/d of cereal fiber + 0.18283 [if fruits + vegetables ≥3 servings/d] + 0.14522 [if nuts 0.1-1 servings/d + 0.24444 [if nuts >1 servings/d] - 0.14631 × servings/d of sugar-sweetened beverages - 0.15624 × servings/d of red and processed meats)*10

Men

20-year CVD risk (%) = $[1 - 0.96368^{(\exp[M - 7.2437])}] \times 100\%$

where M = 0.13580 × age – 0.0005 × (age)^2 + 0.06979 (if past smoker) + 0.42305 (if current smoker) + 0.07424× BMI – 0.00898 × grams/d of alcohol + 0.0001 × (grams/d of alcohol)^2– 0.01755 × hours/week of exercise - 0.06691 × diet score†

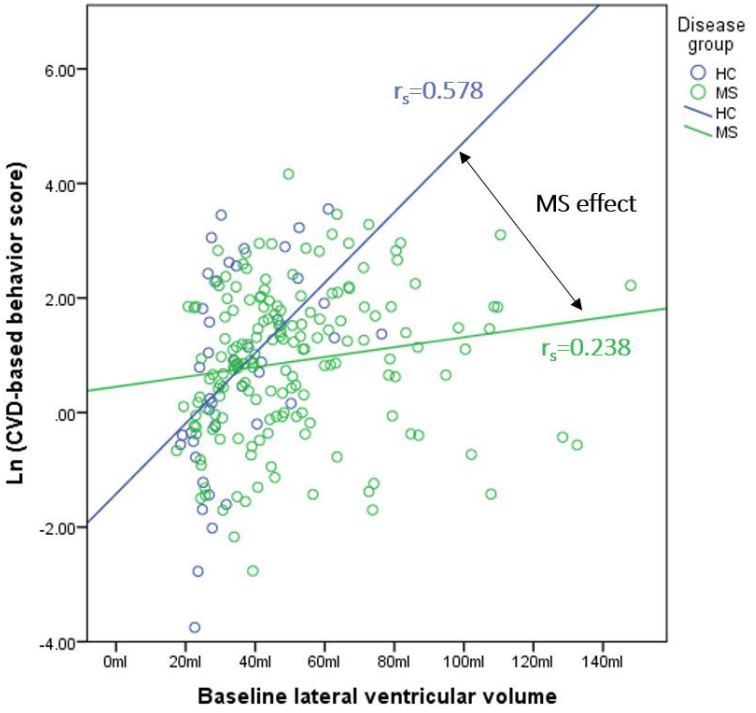
†Diet score (men) = (0.01816 × grams/d of cereal fiber + 0.08819 [if fruits + vegetables ≥3 servings/d] – 0.00535 [if nuts 0.1-1 servings/d] + 0.14285 [if nuts >1 servings/d] - 0.14734 × servings/d of sugar-sweetened beverages - 0.07112 × servings/d of red and processed meats)*10

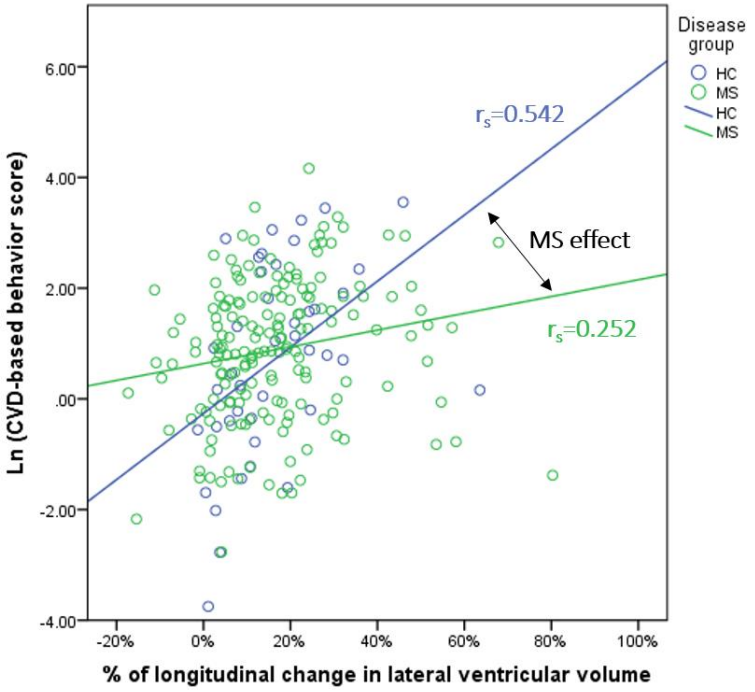
Demographic and MRI characteristic	CIS/MS patients (n=175)				HCs (n=42)			
	20-year CVD risk score		Diet score		20-year CVD risk score		Diet score	
	r_s	q-value	r_s	q-value	r_s	q-value	rs	q-value
EDSS at baseline	**0.34**	**<0.001**	-0.080	0.76	-	-	-	-
T2-LV at baseline	0.18	0.057	0.004	0.98	**0.41**	**0.027**	-0.040	0.92
GMV at baseline	**-0.46**	**<0.001**	-0.330	0.91	**-0.57**	**<0.001**	-0.082	0.94
WMV at baseline	-0.11	0.39	-0.029	0.89	**-0.38**	**0.042**	-0.034	0.89
WBV at baseline	**-0.36**	**<0.001**	-0.038	0.93	**-0.55**	**0.001**	-0.069	0.89
LVV at baseline	**0.24**	**0.007**	0.041	0.94	**0.58**	**<0.001**	0.041	0.99
T2-LV change	0.121	0.32	**-0.191**	**0.04**	0.11	0.90	-0.18	0.90
GMV change	0.061	0.88	-0.075	0.80	-0.15	0.83	0.095	0.94
WMV change	-0.053	0.87	-0.005	0.99	0.13	0.88	-0.23	0.41
WBV change	-0.003	0.97	-0.270	0.89	**-0.45**	**0.011**	0.036	0.90
LVV change	**0.25**	**0.004**	0.035	0.91	**0.54**	**0.001**	-0.11	0.89
EDSS at follow-up	**0.39**	**<0.001**	-0.058	0.87	-	-	-	-
EDSS change	0.020	0.90	-0.039	0.91	-	-	-	-
Relapse rate	**-0.27**	**0.002**	0.026	0.88	-	-	-	-

Chiuve et al. J Am Heart Asso 2014;3:e000954
Jakimovski et al. J Neurol 2019 266: 866.

American Heart Association | American Stroke Association

CVD-associated behavior is induces brain atrophy regardless of MS





- Overall lifestyle-based behavior and cardiovascular health does contributes to central brain atrophy in MS patients.

- Poorer diet was associated with higher T2 lesion accrual
- Simultaneously confirms a CVD-independent MS brain atrophy

MS –multiple sclerosis, CVD – cardiovascular disease

Jakimovski et al. J Neurol 2019 266: 866.

Clinical points for neurologist and patients alike

Review
For reprint orders, please contact: reprints@futuremedicine.com

Lifestyle-based modifiable risk factors in multiple sclerosis: review of experimental and clinical findings

Dejan Jakimovski*,[1], Yi Guan[1], Murali Ramanathan[2], Bianca Weinstock-Guttman[3] & Robert Zivadinov[1,4]

- The MS healthcare providers should engage, participate and provide lifestyle-based behavioral changes as part of their day-to-day practice.
- To promote smoking cessation and body weight control can significantly improve long-term clinical outcomes.
- Promoting exercise and rehabilitative protocols can significantly impact the physical and cognitive performance of the MS patients.
- Early and preventive adoption of healthy lifestyle may potentially reduce the worldwide incidence of new MS cases.

Jakimovski et al. Neurodegener Dis Manag 2019

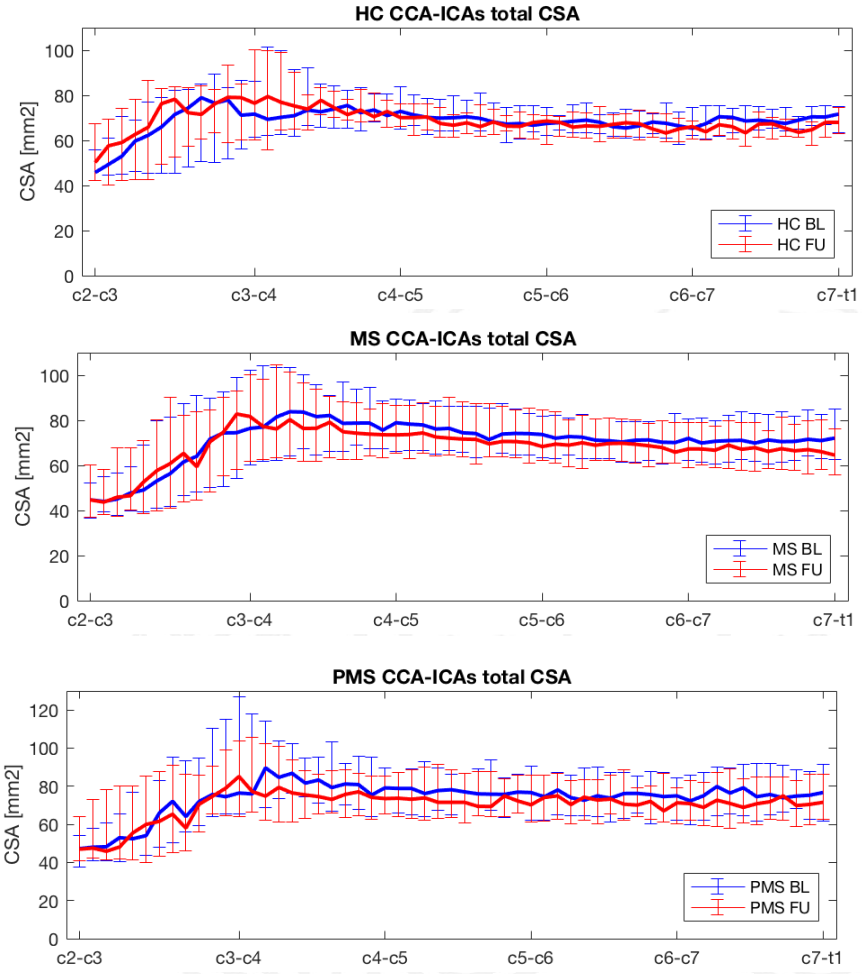
MS –multiple sclerosis

ORIGINAL RESEARCH
EXTRACRANIAL VASCULAR

Five-Year Longitudinal Study of Neck Vessel Cross-Sectional Area in Multiple Sclerosis

L. Pelizzari, D. Jakimovski, M.M. Laganà, N. Bergsland, J. Hagemeier, G. Baselli, B. Weinstock-Guttman, and R. Zivadinov

- 69 MS patients and 22 age- and sex-matched HCs were followed for 5 years.
- Significant cross-sectional area decrease in patients with MS for the CCA and VA at both baseline and follow-up
- The smaller CSA at follow-up was seen independent of disease phenotype and vascular comorbidity



MS –multiple sclerosis, HCs – healthy controls, CCA – common carotid artery, VA – vertebral artery, CSA – cross-sectional area

Pelizzari et al. AJNR Am J Neuroradiol 2018; 39:1703-1709

MULTIPLE SCLEROSIS JOURNAL | MSJ

Original Research Paper

Lower total cerebral arterial flow contributes to cognitive performance in multiple sclerosis patients

Dejan Jakimovski, Ralph HB Benedict, Karen Marr, Sirin Gandhi, Niels Bergsland, Bianca Weinstock-Guttman and Robert Zivadinov

Multiple Sclerosis Journal
1–9
DOI: 10.1177/1352458518819608

- Multimodal assessment of 132 MS patients and 47 HCs utilizing US Doppler, MRI and neuropsychological examination
- Association between lower total CABF and the lower cognitive performance was observed only in MS patients

Table 2. Correlation between the total cerebral arterial blood flow and neuropsychological tests in multiple sclerosis patients and healthy controls.

Correlations between arterial blood flow and neuropsychological tests				SDMT	CVLT-II	BVMT-R
HC	$N=47$	Total CABF	r-value	0.065	−0.002	0.151
			q-value	0.716	0.989	0.369
MS	$N=132$	Total CABF	r-value	**0.318**	0.094	**0.244**
			q-value	**0.001**	0.357	**0.012**

HC: healthy controls; MS: multiple sclerosis; CABF: cerebral arterial blood flow; SDMT: Symbol Digit Modalities Test; CVLT-II: California Verbal Learning Test—Second Edition; BVMT-R: Brief Visuospatial Memory Test—Revised.
Partial correction adjusted for age and years of education was used. False discovery rate was adjusted using Benjamini–Hochberg procedure and q-values are reported; q-values less than 0.05 were considered significant and are shown in bold.

Jakimovski et al. Mult Scler 2019;1352458518819608

MS –multiple sclerosis, HCs – healthy controls, CABF – cerebral arterial blood flow, SDMT – Symbol Digit Modalities Test, CVLT – California Verbal Learning Test, BVMT-R – Brief Visiospatial Memory Test - Revised

Table 3. Regression models analyzing the explanatory and predictive value of sex, age, years of education, total arterial cerebral blood arterial flow, lesion volume, and gray matter brain volume on the neuropsychological performance in multiple sclerosis patients.

	R^2	Adj. R^2	*t*-statistics	Standardized β	*p*-value
SDMT					
Block 1	0.149	0.127			
Sex			−0.781	−0.062	0.437
Patients' age			−1.457	−0.138	0.148
Years of education			1.064	0.083	0.289
Block 2					
Step 1: GMV	0.256	0.230	2.714	0.279	**0.016**[a]
Step 2: GMV + T2-LV	0.292	0.261	−2.666	−0.223	**0.016**[a]
Step 3: GMV + T2-LV + total CABF	0.331	0.295	2.538	0.203	**0.020**[a]

- The total CABF remained as a significant predictor of variance within the neuropsychological test performance associated with processing information speed even after correcting for sex, age, years of education, gray matter volume, T2 lesion volume

MS –multiple sclerosis, SDMT – Symbol Digit Modalities Test, GMV – gray matter volume, LV – lesion volume, CABF – cerebral arterial blood flow

Jakimovski et al. Mult Scler 2019;1352458518819608

Lower total arterial blood flow in cognitive impaired MS patients

- The post hoc comparison between the cognitively impaired (CI) and cognitively preserved (CP) MS patients was derived using the ⩾ -1.5 *z*-score classification (equivalent to 1.5 standard deviations) when compared to the performance of the HCs.

	MS patients		*p*-value
	CI ($n=57$)	CP ($n=75$)	
Female, *n* (%)	39 (68.4)	53 (70.7)	0.849
Age, mean (SD)	55.6 (11.1)	51.7 (11.2)	0.057
Disease duration, mean (SD)	21.8 (11.2)	19.3 (9.9)	0.180
EDSS, median (IQR)	3.5 (2.5–6.5)	2.5 (1.5–4.88)	**0.004**
RRMS vs PMS	29/28	53/22	**0.029**
Body mass index, mean (SD)	27.2 (6.1)	27.9 (5.9)	0.495
Hypertension, *n* (%)	10 (17.5)	15 (20.0)	0.824
Hyperlipidemia, *n* (%)	11 (19.3)	16 (21.3)	0.830
Heart disease, *n* (%)	5 (8.8)	18 (24.0)	**0.035**
Years of education, mean (SD)	14.6 (2.5)	15.2 (2.2)	0.189
Raw CVLT-II total, mean (SD)	43.5 (12.1)	58.2 (8.6)	**<0.001**[a]
Raw BVMT-R total, mean (SD)	15.7 (6.7)	26.5 (5.1)	**<0.001**[a]
Raw SDMT total, mean (SD)	40.2 (14.5)	56.6 (10.2)	**<0.001**[a]
Total CBAF (mL/min)	884.5 (234.3)	1020.2 (260.9)	**0.008**[a]
T2-LV, mean (SD)	18.1 (17.9)	10.1 (13.6)	**0.015**[a]
GMV, mean (SD)	721.1 (67.7)	746.6 (50.5)	**0.039**[a]

- Total CABF: (CI-MS < CP-MS ≈ HC)
- 20% reduction of total blood flow in CI
- Bigger implication in aging MS population

MS –multiple sclerosis, CI – cognitively impairment, cognitively preserved, HCs – healthy controls, CABF – cerebral arterial blood flow

Jakimovski et al. Mult Scler 2019;1352458518819608

Limitations

- Inability to differentiate CVD-based from MS based lesional pathology.
- Better understanding of dietary and other lifestyle changes and their link with gut microbiota dysbiosis is needed.

Conclusion

- The chronic nature of the MS disease allows influences from multiple interacting genetic and environmental factors which ultimately affect the long-term disability outcomes.
- Lifestyle-based interventions may have their place in improving overall MS care

MS –multiple sclerosis, CVD – cardiovascular disease

Part of a larger cardiovascular study

Perfusion abnormalities and cardiovascular comorbidities in neurological disorders.

Niels Bergsland Ph.D.

31st May 8:26am

Epidemiology of cardiovascular comorbidities in aging of multiple sclerosis.

Robert Zivadinov M.D. Ph.D.

31st May 9:59am

Decrease in secondary neck vessels and cerebral aqueduct enlargement in multiple sclerosis: a 5-year longitudinal MRI study.

Dejan Jakimovski M.D. Ph.Dc
31st May 12:22pm

Stay tuned!

Thank you! Any questions?

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