EPIDEMIOLOGY OF CARDIOVASCULAR COMORBIDITIES IN AGING OF MULTIPLE SCLEROSIS

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Disclosures

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Incidence vs. prevalence of MS

Figure 1 Age-standardized incidence of multiple sclerosis in Manitoba per 100,000 population from 1998 to 2006

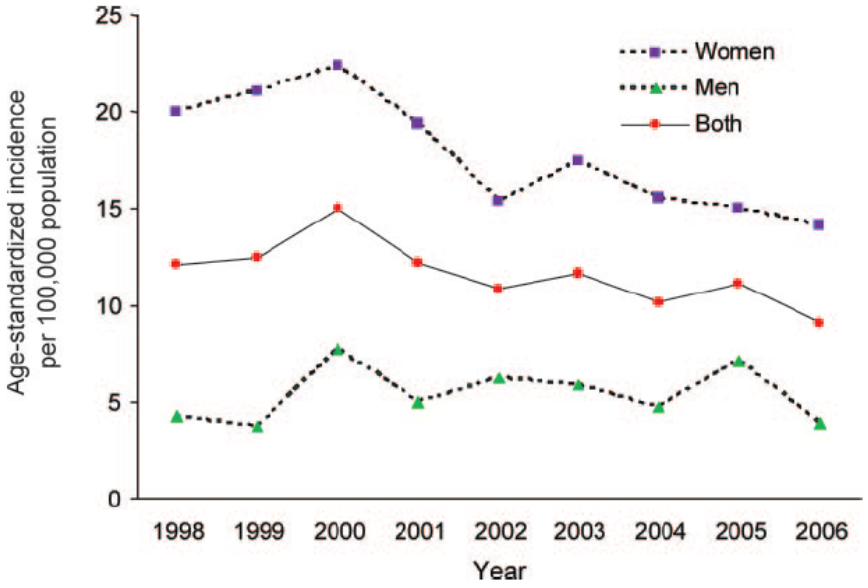
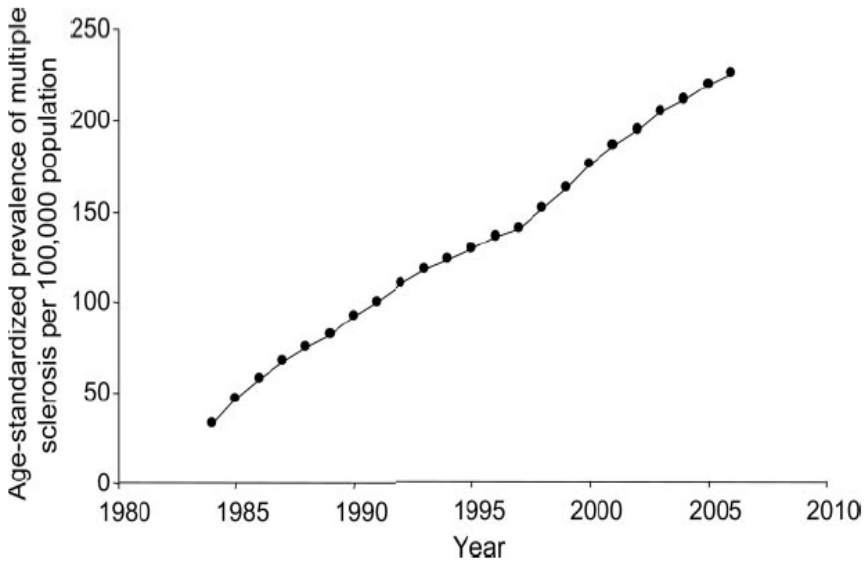
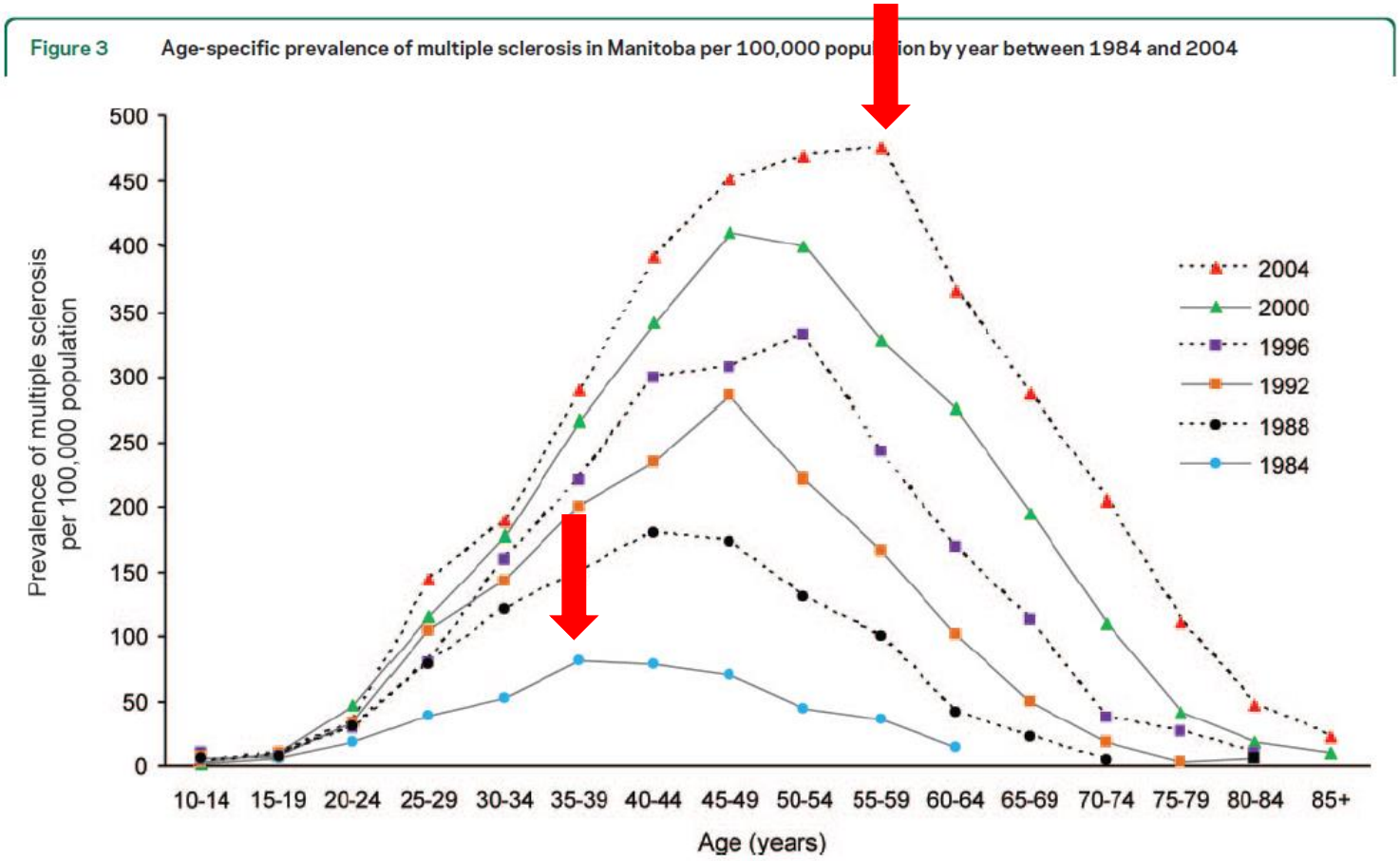


Figure 2 Age-standardized prevalence of multiple sclerosis in Manitoba per 100,000 population from 1984 to 2006



- The change in long-term outcomes and mortality rates have contributed to drastic increase in MS prevalence, despite the relatively stabilized incidence rate.
- Data from 1984 showed no MS patients older than 64 years when compared to the prevalent number of cases aged 65 to 85 years old twenty years later.

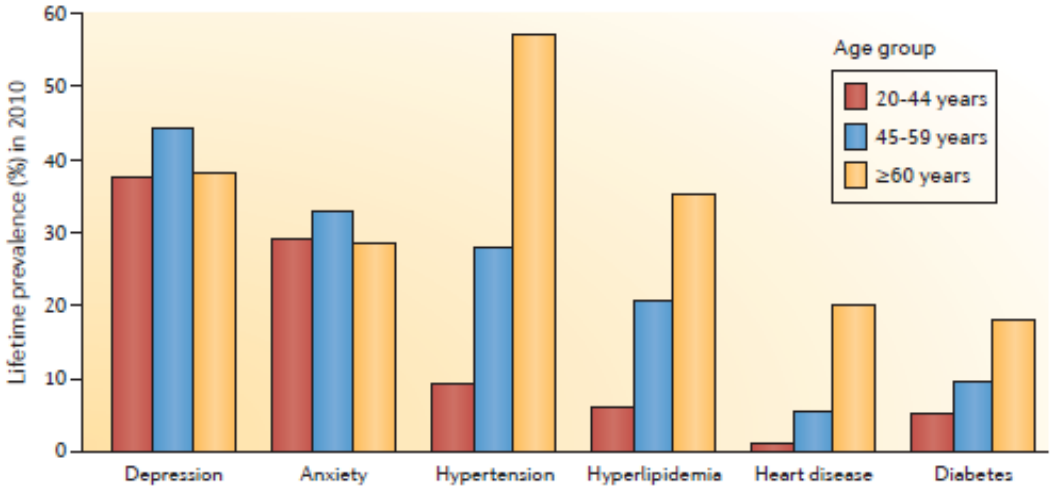
Marrie et al. Neurology 2010;74:465-471

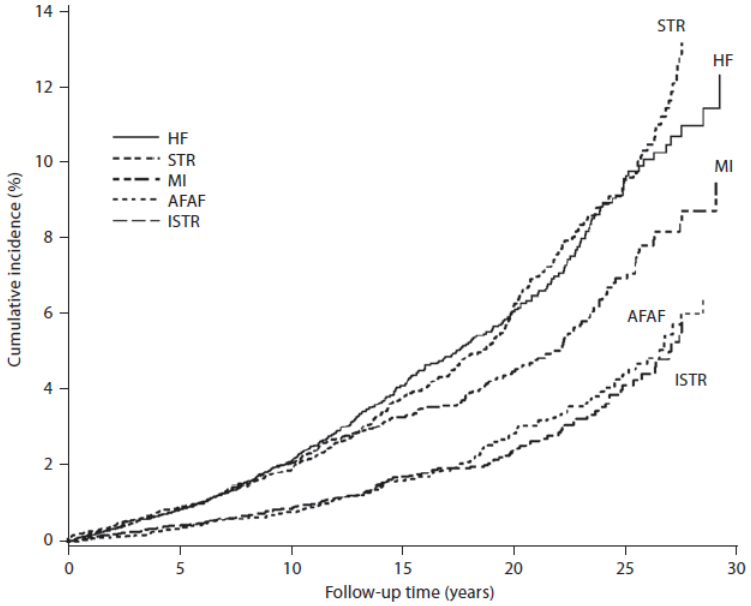


- Considerable shift from year 1984 where the MS peak prevalence was located within people aged 35 to 39 years, to peak prevalence among people within the 55-59 years old in 2004

Marrie et al. Neurology 2010;74:465-471

MS patients have high rate of comorbidities





- In comparison to the stable rate of psychiatric comorbidities, significantly higher prevalence of CVD comorbidities in noted.

E.g. hypertension:

- 7.7% in the 20-44 years old group
- 24.7% in 45-59 years old group
- 46.0% in >60 years old group

- MS diagnosis was associated with a markedly increased risk of stroke, MI and heart failure in the 1st year following diagnosis

Christiansen et al. Neuroepidemiology 2010;35:267-274;Marrie Nat Rev Neurol 2017;13:375

Comorbidities lead to worse disease outcomes

Kaarina Kowalec, PhD
Kyla A. McKay, PhD
Scott B. Patten, MD, PhD
John D. Fisk, PhD

Comorbidity increases the risk of relapse in multiple sclerosis

A prospective study

Neurology® 2017;89:2455-2461

Effects of physical comorbidities on disability progression in multiple sclerosis

Tingting Zhang, PhD, Helen Tremlett, PhD, Feng Zhu, MSc, Elaine Kingwell, PhD, John D. Fisk, PhD, Virender Bhan, MBBS, Trudy Campbell, MN, NP, Karen Stadnyk, MSc, Robert Carruthers, MD, Christina Wolfson, PhD, Sharon Warren, PhD, and Ruth Ann Marrie, MD, PhD, for the CIHR Team in the Epidemiology and Impact of Comorbidity on Multiple Sclerosis

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Neurology® 2018;90:e419-e427. doi:10.1212/WNL.0000000000004885

R.A. Marrie, MD, PhD
R. Horwitz, MD
G. Cutter, PhD
T. Tyry, PhD
D. Campagnolo, MD
T. Vollmer, MD

Comorbidity delays diagnosis and increases disability at diagnosis in MS

Neurology® 2009;72: 117-124

Anja Thormann, MD, PhD
Per Soelberg Sørensen, MD, DMSc
Nils Koch-Henriksen, MD, DMSc

Comorbidity in multiple sclerosis is associated with diagnostic delays and increased mortality

Neurology® 2017;89:1668-1675

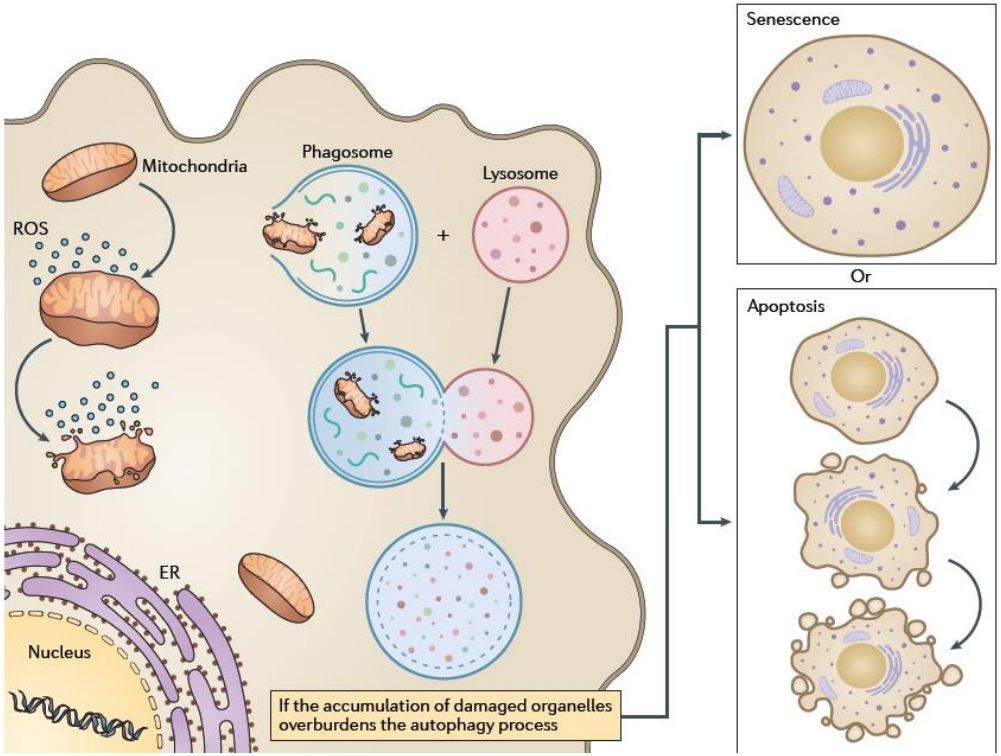
- Participants reporting ≥3 baseline comorbidities (relative to none) had a higher relapse rate over the subsequent 2 years (rate ratio 1.45)
- Physical comorbidity was associated with disability; with each additional comorbidity, there was a mean increase in the EDSS score of 0.18
- Higher mortality hazard ratios with psychiatric, cerebrovascular, and cardiovascular comorbidities

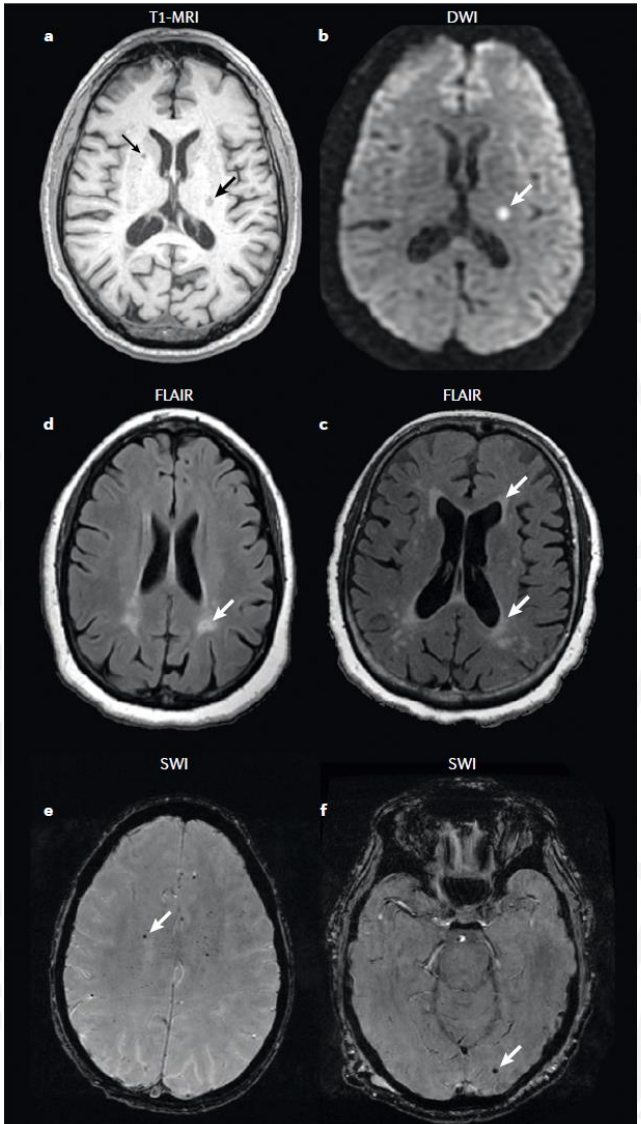
Kowalec et al. Neurology 2017; Zhang et al. Neurology 2018; Marrie et al Neurology 2009; Thormann et al. Neurology 2017

Nat Rev Neurol, 2019

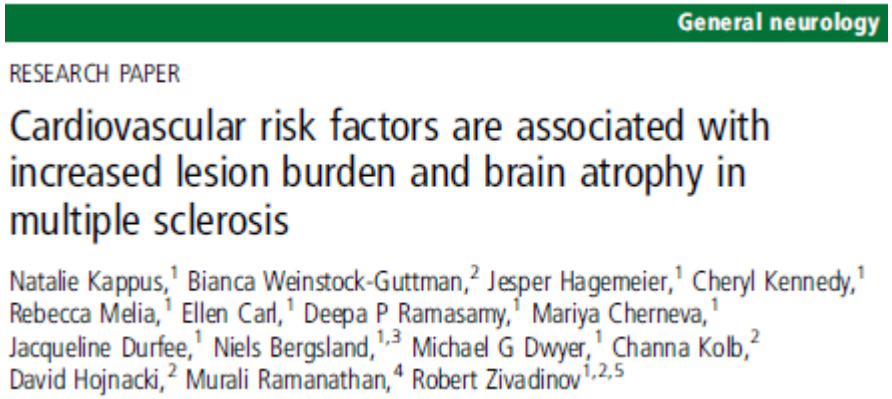
Epidemiology and treatment of multiple sclerosis in elderly populations

*Caila B. Vaughn[1], Dejan Jakimovski[2], Katelyn S. Kavak[1], Murali Ramanathan[3], Ralph H. B. Benedict[1], Robert Zivadinov[2,4] and Bianca Weinstock-Guttman[1]**





Comorbidities impact the MRI-derived outcomes



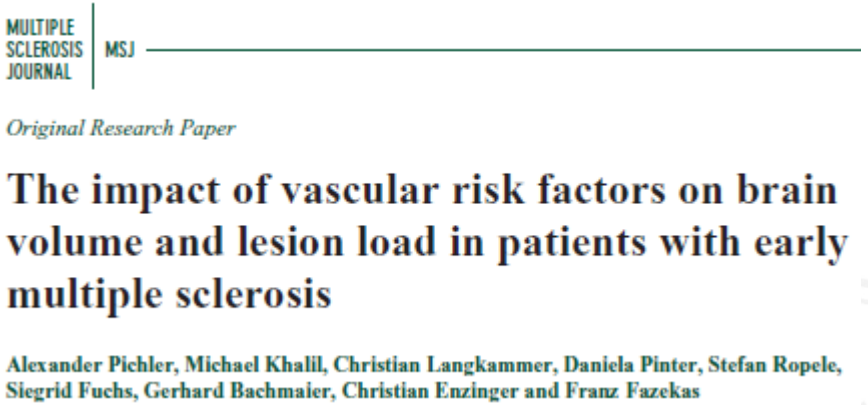
General neurology

RESEARCH PAPER

Cardiovascular risk factors are associated with increased lesion burden and brain atrophy in multiple sclerosis

Natalie Kappus,[1] Bianca Weinstock-Guttman,[2] Jesper Hagemeier,[1] Cheryl Kennedy,[1] Rebecca Melia,[1] Ellen Carl,[1] Deepa P Ramasamy,[1] Mariya Cherneva,[1] Jacqueline Durfee,[1] Niels Bergsland,[1,3] Michael G Dwyer,[1] Channa Kolb,[2] David Hojnacki,[2] Murali Ramanathan,[4] Robert Zivadinov[1,2,5]

- Confirmed higher CVD prevalence in MS
- Hypertension and heart disease were associated with decreased grey matter and cortical volumes
- Obesity with T1-lesions (black holes)
- Smoking with decreased whole brain volume



MULTIPLE SCLEROSIS JOURNAL | MSJ

Original Research Paper

The impact of vascular risk factors on brain volume and lesion load in patients with early multiple sclerosis

Alexander Pichler, Michael Khalil, Christian Langkammer, Daniela Pinter, Stefan Ropele, Siegrid Fuchs, Gerhard Bachmaier, Christian Enzinger and Franz Fazekas

- Confirmed cross-sectional findings of lower brain volumes
- Failed to demonstrate longitudinal differences between patients w and w/o vascular risk factors

Kappus et al. Neurol Neurosurg Psychiatry 2016;87:181-187; Pichler et al. Mult Scler 2017:1352458517736149

ORIGINAL ARTICLE

Hypertension and heart disease are associated with development of brain atrophy in multiple sclerosis: a 5-year longitudinal study

D. Jakimovski[a], S. Gandhi[a], I. Paunkoski[a], N. Bergsland[a], J. Hagemeier[a], D. P. Ramasamy[a], D. Hojnacki[b], C. Kolb[b], R. H. B. Benedict[b], B. Weinstock-Guttman[b] and R. Zivadinov[a,c]

- Patients with diagnosis of heart disease showed higher white matter and whole brain volume loss compared to those without (4.2% vs. 0.7% and 3.4% vs. 1.6%, respectively).
- The percentage lateral ventricle volume change in MS patients with hypertension was higher compared to non-hypertensive patients (24.5% vs. 14.1%).

ELSEVIER
Multiple Sclerosis and Related Disorders
Volume 27, January 2019, Pages 74-78

Assessing the burden of vascular risk factors on brain atrophy in multiple sclerosis: A case- control MRI study.

L. Lorefice [a], J. Frau [a], G. Coghe [a], R. Pitzalis [a], I. Gessa [a], F. Contu [b], M.A. Barracciu [b], M.G. Marrosu [a], E. Cocco [a, 1], G. Fenu [a, 1]

- Confirmed cross-sectional findings
- Greater annualized brain volume loss was found in those with at least one vascular risk factor than in the control group (−1.05% vs. −0.58%).

Ramifications:

Impacting clinical trials outcomes which heavily depend on MRI outcomes
Studying MS within the ever more aging and comorbid population

Jakimovski et al. Eur J Neurol 2019; 26:87-e88; Lorefice et al. Mult Scler Relat Disord 2019;27:74-78

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

American Heart Association | American Stroke Association

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**

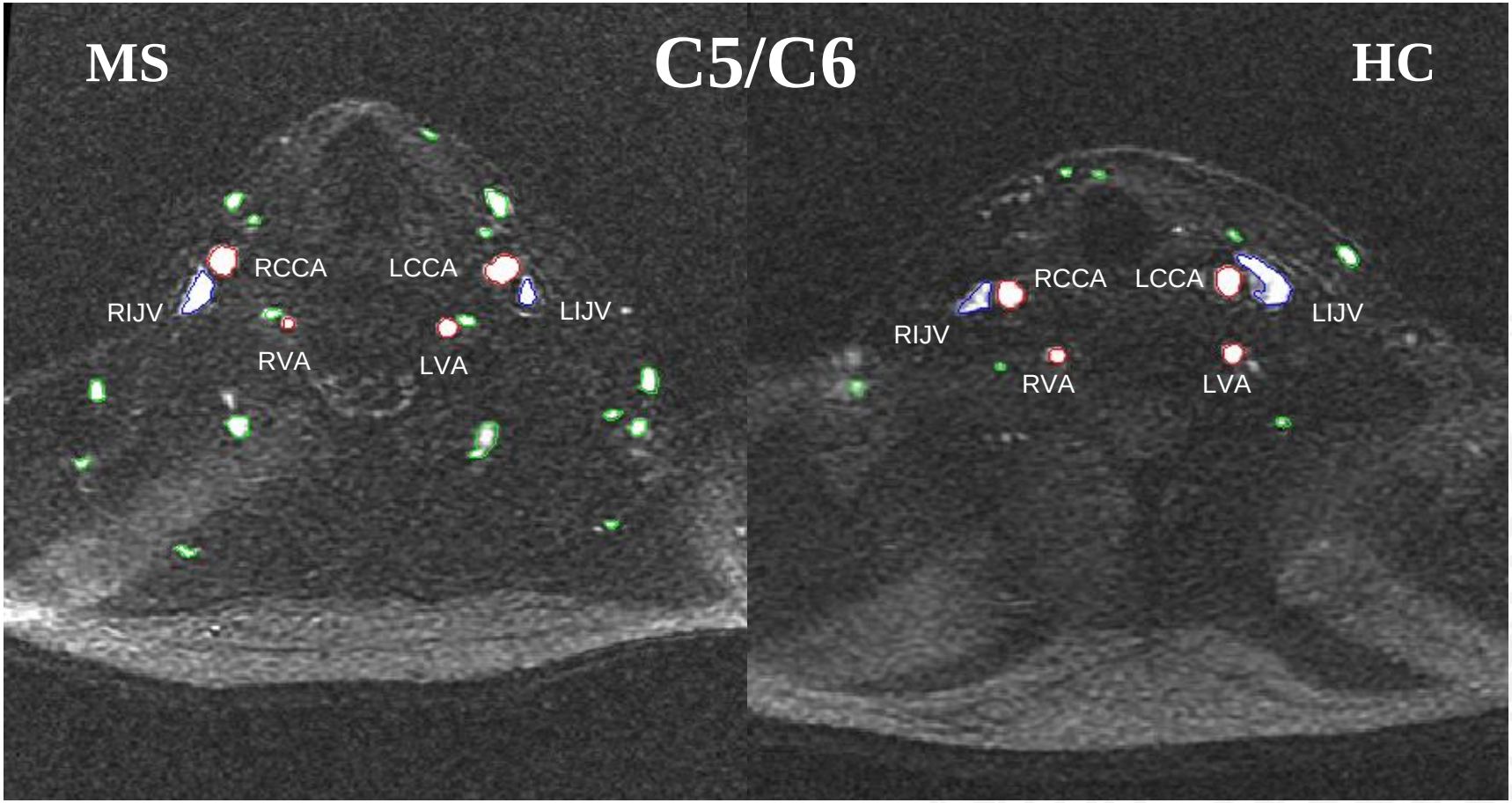
HC: healthy controls; MS: multiple sclerosis; CABF: cerebral arterial blood flow; SDMT: Symbol Digit Modalities Test; CVLT-II: California Verbal Learning Test—Second Edition; BVMT-R: Brief Visuospatial Memory Test—Revised.
Partial correction adjusted for age and years of education was used. False discovery 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.

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

Jakimovski et al. Mult Scler 2019;1352458518819608



Legend: MS - multiple sclerosis, HC – healthy control, IJV – internal jugular vein, CCA – common carotid artery, VA – vertebral artery, Green color represents the collateral vessels, red represents the CCAs, and VAs, while blue represents the IJVs

Belov et al. AJNR Am J Neuroradiol 2018 Jan;39(1):123-130.

Table 1: Demographic and clinical characteristics of patients with multiple sclerosis (n = 193) and healthy controls (n = 193)[a]

	MS (n = 193)	HC (n = 193)	P Value
Female (No.) (%)	130 (67.4)	130 (67.4)	1.000
Age (mean) (SD) (yr)	42.2 (13.9)	42.9 (17.5)	.676
BMI (mean) (SD)	26.8 (5.8)	26.8 (5.7)	.94
Disease duration (mean) (SD) (yr)	12.0 (9.4)	NA	–
EDSS (median) (range)	2 (0.0–6.5)	NA	–
Smoking history (No.) (%)	73 (46.8)	58 (32.4)	.005[b]
Heart disease (No.) (%)	30 (19.7)	20 (12.4)	.053
Hypertension (No.) (%)	38 (25.3)	19 (11.3)	.001[b]

Note:—EDSS indicates Expanded Disability Status Scale; IQR, interquartile range; NA, not applicable.
[a] χ^2 and Student t test were used for comparing variables between groups.
[b] An α level of .05 was considered significant.

- Perfectly matched large case-controlled study
- Confirmed the higher rate of cardiovascular diseases and risk factors in MS patients

Table 3: Arterial, venous, and secondary neck vessel frequency and the cross-sectional area in the study groups[a]

	Primary Vessel (CSA) (mm^2)					
	Arterial and Venous			Arterial (VAs)		
	MS (n = 193)	HC (n = 193)	P Value	MS (n = 193)	HC (n = 193)	P Value
Arterial (CCA/ICA/ECA)						
C2/C3	55.1 (16.4)	60.9 (17.9)	.030[b]	20.1 (4.4)	21.8 (5.8)	.02[b]
C4	60.8 (15.7)	63.4 (16.3)	.229	18.6 (4.2)	20.3 (5.0)	.012[b]
C5/C6	50.1 (10.1)	53.9 (12.5)	.026[b]	18.1 (6.9)	19.3 (4.7)	.341
C7/T1	47.6 (9.8)	52 (9.9)	.005[b]	16.3 (4.5)	18.4 (5.9)	.006[b]

- The MS patients had a smaller arterial CSA of the main and secondary arterial vessels (CCA, ICA, ECA, and VA, respectively).
- Findings were reconfirmed in a subgroup of subjects (70%) without the presence of cardiovascular comorbidities.

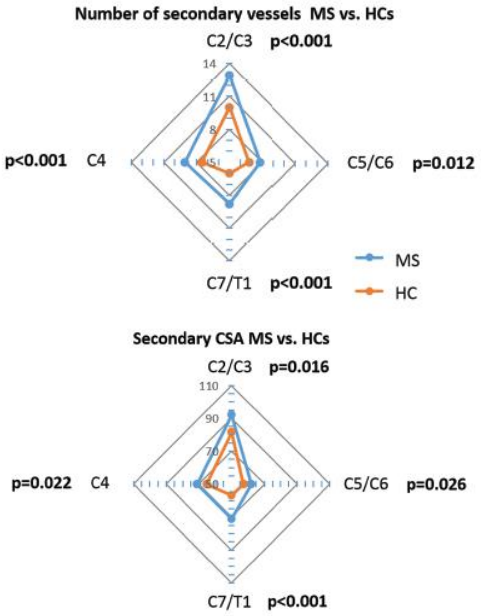
Belov et al. AJNR Am J Neuroradiol 2018 Jan;39(1):123-130.

Larger number and size of secondary vessels

Table 4: Secondary neck vessel frequency and the cross-sectional area in the study groups[a]

	No. of Vessels			CSA (mm^2)		
	MS (n = 193)	HC (n = 193)	P Value	MS (n = 193)	HC (n = 193)	P Value
Secondary vessels						
C2/C3	12.9 (5.4)	10 (4.2)	<.001[b]	92.1 (40.6)	81.6 (35.5)	.016[b]
C4	9.1 (4.2)	7.5 (3.3)	<.001[b]	71.0 (33.7)	65.3 (28.7)	.022[b]
C5/C6	7.8 (3.9)	6.8 (3.4)	.012[b]	61.9 (32.2)	57.2 (28.2)	.028[b]
C7/T1	8.8 (4.9)	6 (3.5)	<.001[b]	71.1 (40.5)	56.7 (32.5)	<.001[b]

[a] Analysis of covariance adjusted for age and BMI, smoking history, heart disease, and hypertension was used. In the ANCOVA for frequency of vessels, ranked variables were used.
[b] An α level of .05 was considered significant.



- A higher frequency of secondary neck vessels was found at all 4 levels
  - Limitation: We don't know the directionality of the flow
  - Conformation with phase imaging is needed
- Future longitudinal analysis of secondary vessels is planned

Belov et al. AJNR Am J Neuroradiol 2018 Jan;39(1):123-130.

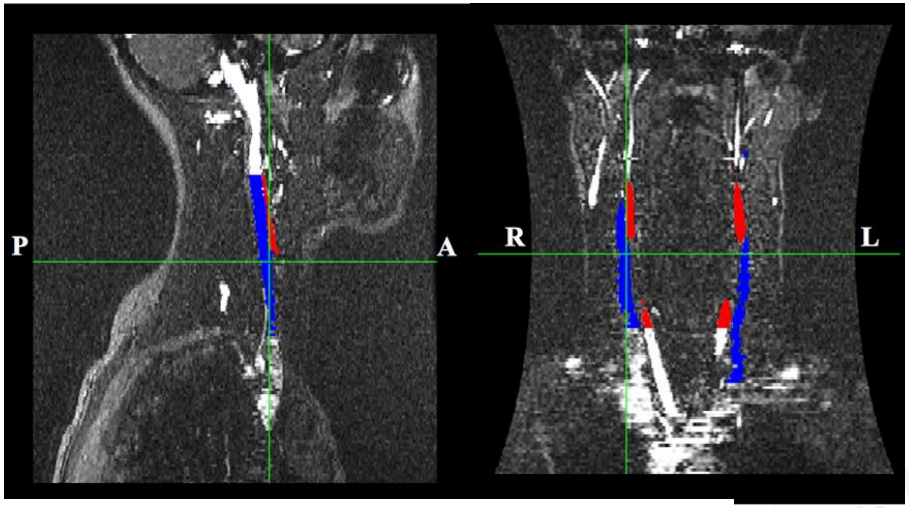
Journal of Neuroimaging
Official Journal of the American Society of Neuroimaging

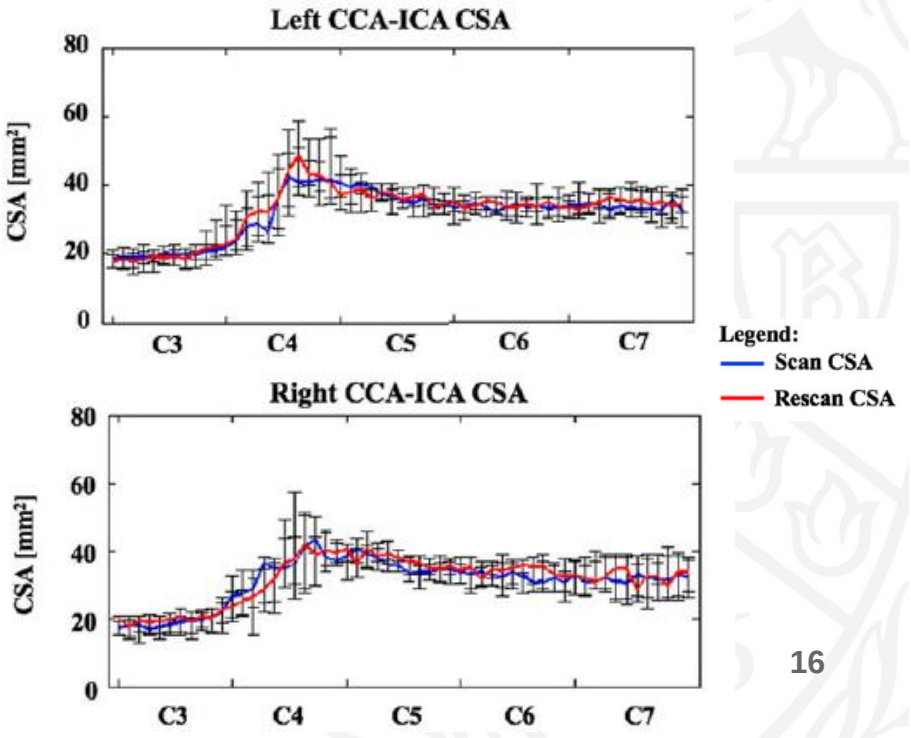
Technology Update | Free Access

Neck Vessel Cross-Sectional Area Measured with MRI: Scan-Rescan Reproducibility for Longitudinal Evaluations

Laura Pelizzari, Maria Marcella Laganà, Dejan Jakimovski, Niels Bergsland, Jesper Hagemeier, Giuseppe Baselli, Robert Zivadinov

- 9 HCs scanned 5 days apart and 12 HCs scanned 5 years apart
- No significant CSA differences were found for the scan-rescan and baseline-follow-up CSA comparisons, using the whole vessel length or single cervical level measurements
- Interclass correlation coefficient analysis showed good degree of scan-rescan reproducibility



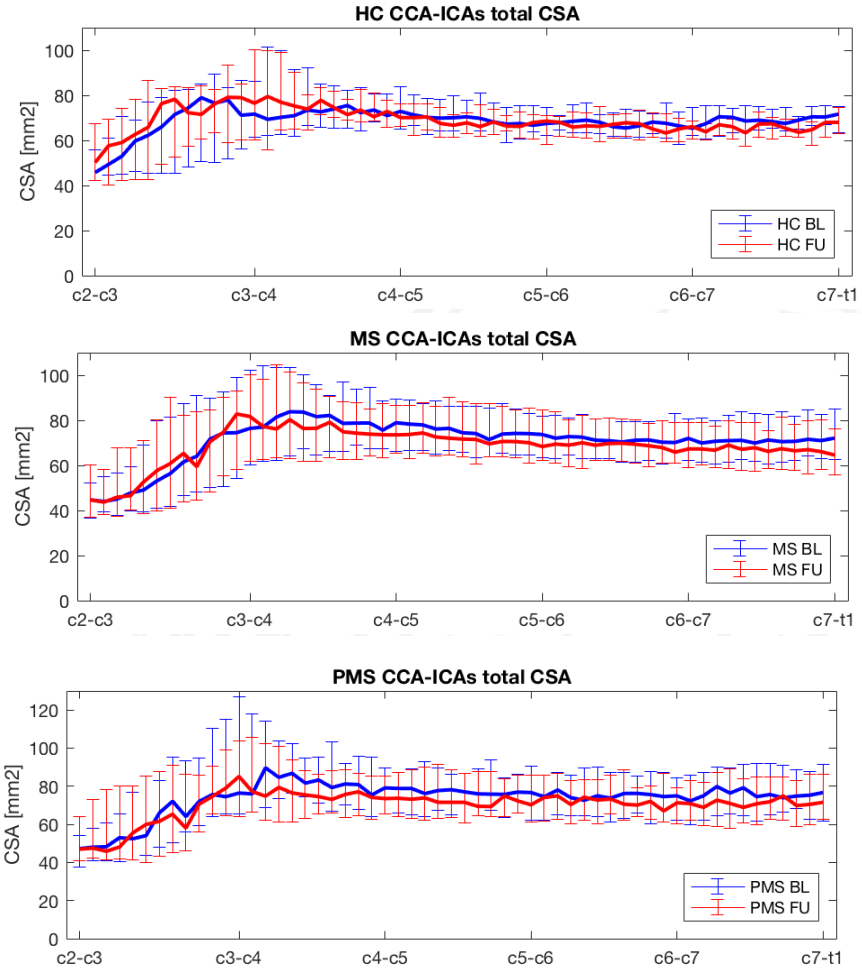


ORIGINAL RESEARCH
EXTRACRANIAL VASCULAR

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 arterial CSA at follow-up was seen independent of disease phenotype and vascular comorbidity



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

Decrease in secondary neck vessels in multiple sclerosis: a 5-year longitudinal magnetic resonance angiography study

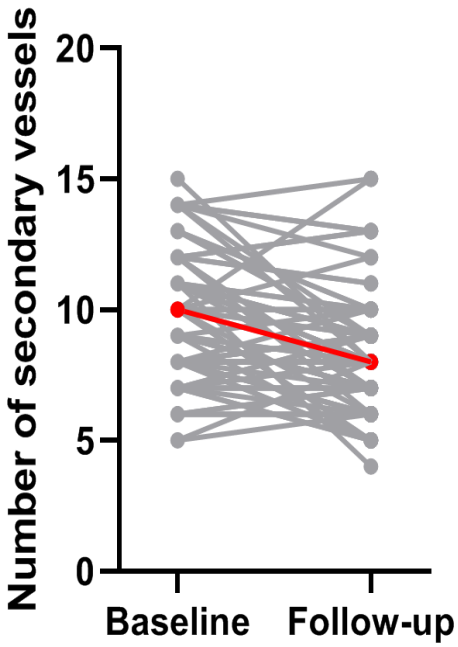
Dejan Jakimovski[1], Matthew Topolski[1], Kana Kimura[1], Virja Pandya[1], Bianca Weinstock-Guttman[2], Robert Zivadinov[1,3]

Table 4. The number and size of secondary neck vessels in the HCs and MS patients.

	PwMS (n=83)	HCs (n=25)	p-value	PwMS (n=83)	HCs (n=25)	p-value
	At baseline MRA			At follow-up MRA		
Number of secondary neck vessels						
C2-C3	12 (10-15)	13 (11-17)	0.068	11 (9-12)	12 (9.5-14)	**0.022**
C3-C4	10 (8-12)	10 (10-15)	**0.033**	8 (7-11)	10 (8-13)	**0.029**
C4	10 (8-12)	10 (8-13)	0.406	8 (7-10)	9 (8-12)	0.071
C4-C5	10 (8-11)	10 (8.5-13)	0.168	8 (7-9)	10 (7.5-12)	**0.019**
C5-C6	8 (7-10)	10 (7.5-11.5)	**0.046**	7 (6-9)	9 (7-11)	**0.02**
C6-C7	8 (7-10)	11 (8-12)	**0.018**	7 (6-9)	9 (7-11)	**0.002**
C7-T1	9 (8-11)	11 (9-13.5)	**0.004**	8 (7-9)	9 (8-11.5)	**0.015**
Cross-sectional area of secondary neck vessels						
C2-C3	102.5 (83.4-124.3)	107.7 (82.7-162.1)	0.276	82.9 (62.3-113.1)	96.7 (72.3-138.4)	0.134
C3-C4	98.9 (71.8-1021.4)	101.8 (73.1-145.0)	0.376	79.2 (58.9-110.9)	88.4 (55.7-113.7)	0.361
C4	88.1 (65.6-121.6)	81.8 (59.7-130.5)	0.567	75.9 (53.8-105.0)	75.3 (55.7-113.7)	0.841
C4-C5	90.2 (67.7-121.5)	85.6 (60.6-125.1)	0.724	75.4 (50-7-98.9)	76.0 (54.5-115.1)	0.567
C5-C6	74.9 (57.4-110.4)	71.3 (49.8-95.7)	0.538	65.4 (43.2-95.2)	63.5 (43.5-107.2)	0.807
C6-C7	73.1 (53.4-104.3)	69.9 (54.5-105.2)	0.962	62.9 (41.9-89.8)	65.1 (44.0-77.8)	0.997
C7-T1	89.1 (70.7-120.9)	95.9 (55.3-132.9)	0.774	79.7 (55.6-109.1)	73.3 (47.8-123.8)	0.881

Legend: PwMS – persons with multiple sclerosis, HCs – healthy controls, MRA – magnetic resonance angiography

Mann Whitney U tests was used to compare the number and size of the secondary vessels. P-value lower than 0.05 was considered statistically significant and shown in bold.



Jakimovski et al. Curr Neurovasc Res, in press

- CV comorbidities are associated with higher susceptibility of neurodegenerative disorders and aging
- CV comorbidities are associated with disease progression, as measured by range of clinical and MRI outcomes in MS
- Preliminary studies show a modest to strong link between CSA of neck vessels and CV risk factors
  - ✓ Arterial and venous
  - ✓ Secondary vessels
- Future studies should investigate association between CSA of neck vessels and hypoperfusion in the brain from earliest disease stages
- Heart-brain axis should be better investigated in neurodegenerative disorders and aging

Legend: CV- cardiovascular risks; MS- multiple sclerosis; AD – Alzheimer's disease; PD – Parkinson's disease; IJV – internal jugular vein; CSA – cross-sectional area; CSF – cerebrospinal fluid; MS – multiple sclerosis

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