

Vascular risk factors' impact on motor performance and sensorimotor network structural integrity in multiple sclerosis

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Abstract

Background: Vascular risk factors (VRFs) are associated with diffuse brain damage in multiple sclerosis (MS). We investigated VRFs' impact on motor performance and sensorimotor network (SMN) structural integrity in MS patients.

Methods: In this retrospective cross-sectional study, 268 MS patients and 180 healthy controls were classified according to VRF presence (VRF[+]) or absence (VRF[-]). Clinical measures included Expanded Disability Status Scale (EDSS), Timed 25-Foot Walk test, and 9-Hole Peg Test. SMN integrity was assessed using white matter lesion volumes, cortical thickness of primary motor and somatosensory cortices, normalized deep gray matter volume (NDGMV), anterior (ACMA) and posterior cerebellar motor area volumes, mean upper cervical cord area, and diffusion metrics of the middle and superior cerebellar peduncles, medial lemniscus (ML), and corticospinal tracts. Group differences and MS-VRF interactions were examined. In MS, associations between clinical and magnetic resonance imaging (MRI) measures were explored, focusing on VRF influence.

Results: MS-VRF[+] patients showed higher EDSS scores and worse motor performance than MS-VRF[-] (false discovery rate p value [pFDR] ≤ 0.004). Significant MS-VRF interactions were observed for motor performance, ML mean diffusivity, NDGMV, and ACMA volumes (pFDR ≤ 0.039). In MS, EDSS was associated with the VRF $\times$ ML fractional anisotropy interaction term ($\beta = 1.931$, $p = 0.042$).

Conclusions: VRFs may contribute to increased disability, motor impairment, and region-specific SMN structural damage in MS patients.

Keywords: Multiple sclerosis, disability, walking capacity, manual dexterity, vascular risk factors, sensorimotor network, magnetic resonance imaging

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Introduction

Multiple sclerosis (MS) is a chronic immune-mediated disease of the central nervous system (CNS) characterized by inflammation, demyelination, axonal loss, and neurodegeneration, leading to irreversible disability.¹ Motor dysfunction is among the most disabling MS manifestations, with a major impact on quality of life.²

Beyond immune-mediated mechanisms, vascular risk factors (VRFs), including hypertension, diabetes, dyslipidemia, obesity, alcohol intake, and smoking, have been associated with worse MS progression and clinical outcomes.^{3,4} Through cerebral hypoperfusion,

endothelial dysfunction, impaired neurovascular coupling, blood-brain barrier disruption, and oxidative stress,^{3,5-14} VRFs may synergize with MS-related processes to exacerbate inflammation, demyelination, astrogliosis, and neurodegeneration. These mechanisms may result in increased T2-hyperintense white matter (WM) lesion volume (LV), accelerated brain atrophy, and earlier disability milestones.^{3,5-8,10,14-16}

Despite these associations, the biological substrates linking VRFs to MS manifestations remain poorly understood. In particular, it is unclear whether VRFs selectively affect structural networks such as the sensorimotor network (SMN), which comprises cortical

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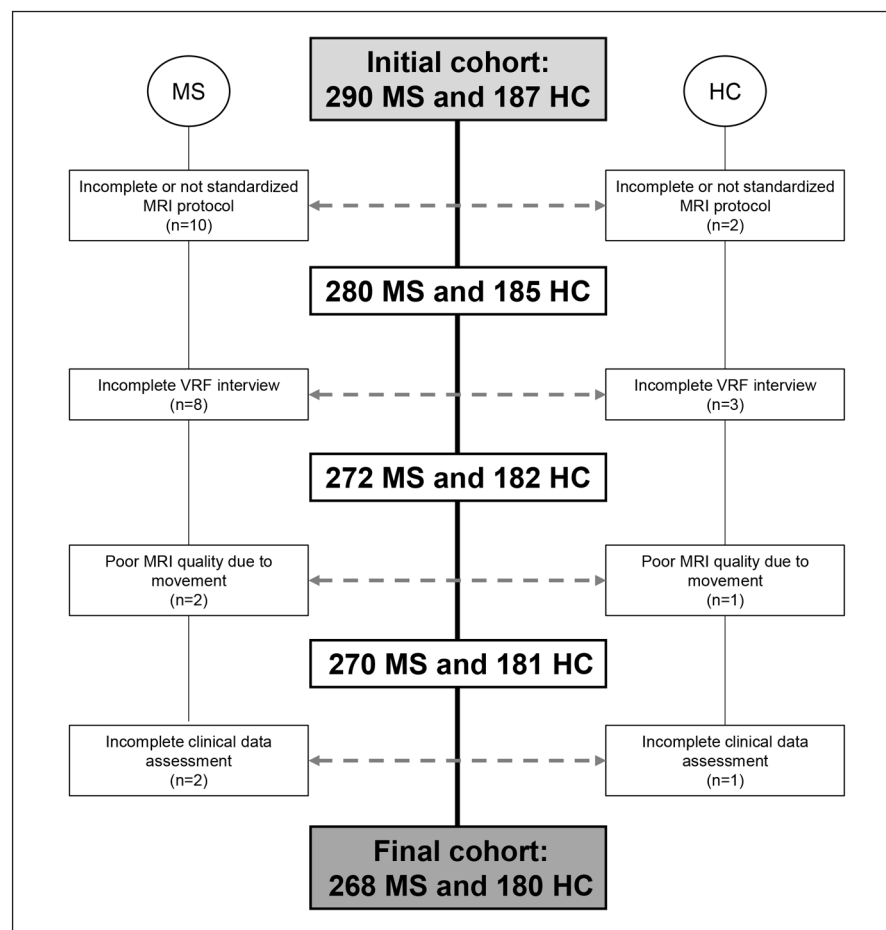


Figure 1. Study flow-diagram.

HC: healthy controls; MRI: magnetic resonance imaging; MS: multiple sclerosis.

(e.g. primary motor and somatosensory cortices), deep gray matter (GM) (e.g. thalamus, caudate nucleus, putamen, and globus pallidus), cerebellar, and spinal cord structures, interconnected *via* specific WM tracts.¹⁷ All these regions are essential for voluntary movements and motor control.

MS-related focal lesions, diffuse microstructural damage, and tissue loss frequently involve SMN components and strongly contribute to irreversible motor disability.^{2,18} Given the high prevalence of modifiable VRFs in MS, clarifying their impact on SMN integrity may provide mechanistic insight into vascular contributions to motor impairment and disability.

In this context, this study aimed to assess the effect of VRFs on disability, motor performance, and SMN structural integrity in a large MS cohort using advanced quantitative magnetic resonance imaging

(MRI) techniques and comprehensive clinical evaluation.

Material and methods

Study population

From our institutional database, we included patients with MS and healthy controls (HC) acquired between April 2017 and January 2024, satisfying specific inclusion and exclusion criteria (Supplemental Table 1). No sample size calculation was performed; all eligible subjects were included. The study flowchart is shown in Figure 1.

Clinical and VRF assessment

On the same day of MRI acquisition, patients with MS underwent a neurological evaluation, with assessment of Expanded Disability Status Scale (EDSS)

score, disease duration, clinical phenotype (relapsing-remitting [RR] or progressive [P]), and ongoing disease-modifying treatment (DMT). All subjects completed the Timed 25-Foot Walk test (T25FW), evaluating walking speed, and the 9-Hole Peg Test (9HPT), assessing manual dexterity. A structured interview evaluated VRFs: obesity, alcohol consumption, smoking, hypertension, cardiovascular disease, dyslipidemia, and hyperglycemia (classification details in Supplemental Table 2). Participants were stratified into four groups based on VRF presence: HC without VRFs (HC-VRF[−]), HC with one or more VRFs (HC-VRF[+]), MS patients without VRFs (MS-VRF[−]), and MS patients with one or more VRFs (MS-VRF[+]).

MRI acquisition

All participants underwent a 3T MRI scanning with the acquisition of the following brain MRI sequences: (1) sagittal three-dimensional (3D) fluid attenuation inversion recovery (FLAIR), (2) 3D T1-weighted Turbo Field Echo (TFE), and (3) axial diffusion-weighted (DW) pulsed-gradient spin echo single-shot echo-planar imaging sequence. The full list of sequence parameters is reported in Supplemental Table 3.

MRI analysis

We conducted a comprehensive set of advanced MRI analysis, which are described in detail in Supplemental Table 4 and Figure 2, to obtain measures of global structural integrity, as well as of specific regions of the SMN and area not directly involved in motor function as control regions. For each subject, we collected the following MRI outcomes: T2-hyperintense LV (Figure 2(a)), normalized brain volume (NBV), normalized cortical GM volume (NCGMV), normalized deep GM volume (NDGMV), including separate thalamic and basal ganglia volumes, and normalized WM volume (NWMV) (Figure 2(b)). We also extracted the volumes of the anterior and posterior cerebellar motor area (ACMA and PCMA) (Figure 2(c)); cortical thickness (CT) of the primary motor cortex (M1) and the primary somatosensory cortex (S1), as well as the middle and superior temporal gyrus (MTG and STG) (Figure 2(d)). We also obtained the fractional anisotropy (FA) and mean diffusivity (MD) of the middle and superior cerebellar peduncle (MCP and SCP), the medial lemniscus (ML), the corticospinal tract (CST), and of the superior longitudinal fasciculus (SLF) (Figure 2(e)). Finally, we also extracted the normalized mean upper cervical cord area (nMUCCA) (Figure 2(f)).

Statistical analysis

Differences in VRF prevalence between HCs and patients with MS were analyzed using Pearson's Chi-square test. The normality of clinical and MRI variables was verified with the Shapiro-Wilk test. To improve data distribution (i.e. reduce skewness), T25FW and 9HPT scores were inverted and converted to z-scores using the HC-VRF[−] group as the reference. We chose HCs as the reference group because they represent a more consistent benchmark and provide more clinically meaningful z-scores than using another group of patients with MS for the calculations. T2-hyperintense LV values were log-transformed.

Group differences in motor performance and MRI measures according to VRF, disease status, and their interaction were explored with age- and sex-adjusted linear models. Direct MS subgroups comparisons were not reported, as the disease status $\times$ VRF interaction more accurately captures the additional impact of VRFs within the MS population.

In MS patients, associations between EDSS, z-score of inverted Timed 25-Foot Walk test (zT25FW), and z-score of inverted 9-Hole Peg Test (z9HPT) with MRI measures were assessed using age- and sex-adjusted linear models, including MRI measure $\times$ VRF interaction terms to explore the potential moderating role of VRFs. Tract-specific T2-hyperintense LVs were excluded due to frequent zero values. Multiple mediation models were then performed to further investigate whether the associations between VRFs and disability/motor performance were mediated by MRI metrics.

Several supplementary analyses were conducted to improve quality of our results and their interpretability. A supplemental analysis was conducted considering only smoking status in order to isolate its contribution as a single, highly prevalent VRF. Within the MS cohort, another analysis was conducted to exclude the potential confounding effects of EDSS and clinical phenotype on the group differences found, using linear regression models for each outcome. For outcomes showing a significant disease status $\times$ VRF interaction at the group comparison, we further investigated the contribution of each VRF using linear models adjusted for age, sex, disease duration, and DMT efficacy within our MS population. Finally, to further explore the mechanistic contribution of vascular comorbidities, we performed an additional analysis in the whole cohort using a slightly different group division, defined as quantitative VRF classification (three levels: 0, 1, and 2 or more VRFs)

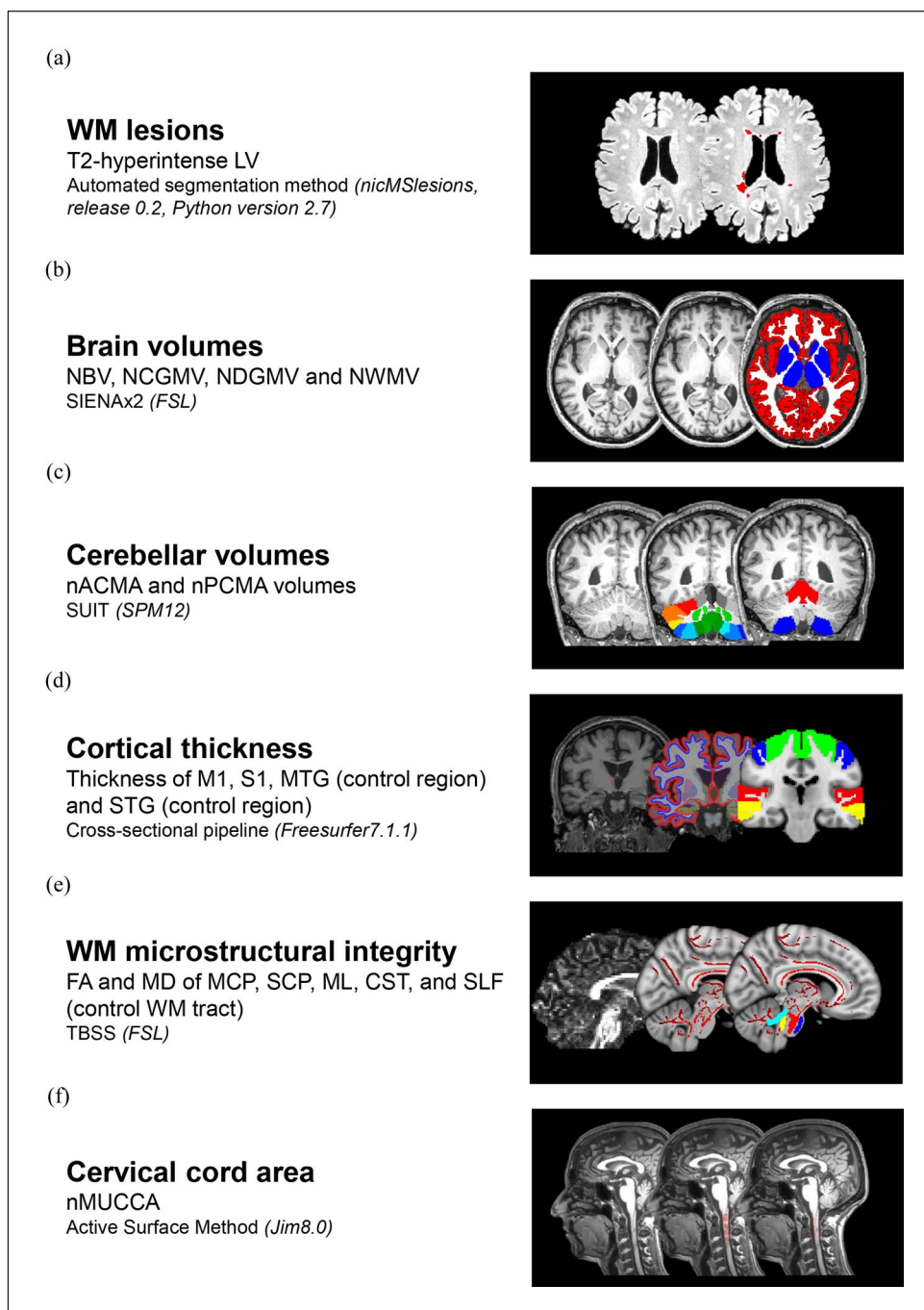


Figure 2. Analysis methods utilized in this study. (a) Fully automated segmentation method was used to identify focal T2-hyperintense WM lesions (red), from which the T2 hyperintense LV was derived. (b) SIENAx2 was employed to obtain NBV (not shown), NCGMV (red), NDGMV (blue), and NWMV (white). (c) SUIIT segmentation provided nACMA (red) and nPCMA (blue). (d) Cross-sectional Freesurfer pipeline was used to calculate cortical thickness of M1 (green), S1 (blue), MTG (yellow), and STG (red). (e) TBSS was applied to extract FA and MD measures of MCP (blue), SCP (light blue), ML (yellow), CST (red), and SLF (not shown). (f) The Active Surface Method was utilized to derive the nMUCCA measures based on cord markers and contours (red).

CST: corticospinal tract; FA: fractional anisotropy; FSL: FMRIB (functional magnetic resonance imaging of the brain) Center Software Library; LV: lesion volume; M1: primary motor cortex; MCP: middle cerebellar peduncle; MD: mean diffusivity; ML: medial lemniscus; MTG: middle temporal gyrus; nACMA: normalized anterior cerebellar motor area; NBV: normalized brain volume; NCGMV: normalized cortical gray matter volume; NDGMV: normalized deep gray matter volume; NWMV: normalized white matter volume; nMUCCA: normalized mean upper cervical cord area; nPCMA: normalized posterior cerebellar motor area; S1: primary somatosensory cortex; SCP: superior cerebellar peduncle; SLF: superior longitudinal fasciculus; SPM12: statistical parametric mapping version 12; STG: superior temporal gyrus; TBSS: tract-based spatial statistics; WM: white matter.

and a linear regression approach for each clinical and MRI outcomes.

Analyses were performed in SPSS v28.0 (IBM), with significance set at $p < 0.05$ and multiple comparisons corrected using the Benjamini–Hochberg false discovery rate (FDR) method.

Results

Demographic, clinical, and motor performance findings

A total of 268 MS patients, 179 of whom had VRFs, and 180 HCs, 74 of whom had VRFs, were included in this study. Between-group comparisons of demographic, clinical, and motor performance variables are presented in Table 1. Compared to MS-VRF[–], MS-VRF[+] more frequently had a progressive MS phenotype (42% vs 24%; FDR p value [pFDR] = 0.004) and a higher EDSS score (3.0 vs 1.5; pFDR = 0.003). A significant interaction effect between disease status and VRF presence for both motor outcomes was found (pFDR $\leq$ 0.027). No differences between MS-VRF[+] and MS-VRF[–] were found in terms of age, sex, disease duration, or ongoing DMT (pFDR $\geq$ 0.068).

VRFs findings

VRF prevalence in HCs and patients with MS is reported in Table 2. Compared to HCs, patients with MS were characterized by a higher prevalence of VRFs (pFDR = 0.003), with smoking being the most common VRF in both groups reported by 142 (53.0%) patients with MS.

MRI findings

Between-group comparisons of MRI measures are summarized in Table 3 and Figure 3. A significant interaction effect between VRFs and disease status was observed for NDGMV, basal ganglia volume, normalized anterior cerebellar motor area (nACMA) volume, and MD of the ML, suggesting a more severe structural damage of these areas among MS patients with VRFs (pFDR $\leq$ 0.036). No VRF $\times$ disease interaction was found for the other MRI measures (pFDR $\geq$ 0.083).

Associations between clinical and MRI measures in patients with MS

Associations between disability, motor performance, and MRI measures, as well as the VRF $\times$ MRI

measures interaction are provided in Supplemental Table 5 and Figure 4. Our results showed a statistically significant interaction effect only between VRF status and FA of the ML ($\beta = 1.931$, $p = 0.042$), indicating that the association between FA reduction in this tract and higher EDSS scores was significantly stronger in patients with VRFs.

Mediation analysis results

As shown in Supplemental Table 6, we found significant total effects of VRF on EDSS ($\beta = 0.625$, $p = 0.013$), z9HPT ($\beta = -0.609$, $p = 0.011$), and zT25FW ($\beta = -0.383$, $p = 0.015$). Significant indirect effects were consistently observed for basal ganglia volume and nACMA across all clinical outcomes. Specifically, basal ganglia volume significantly mediated the association between VRF and EDSS (indirect effect $\beta = 0.132$, 95% CI = 0.011; 0.304), z9HPT ($\beta = -0.181$, 95% CI = -0.367; -0.018), and zT25FW ($\beta = -0.059$, 95% CI = -0.144; -0.003). Similarly, nACMA significantly mediated associations between VRF and EDSS ($\beta = 0.117$, 95% CI = 0.015; 0.262), z9HPT ($\beta = -0.103$, 95% CI = -0.231; -0.012), and zT25FW ($\beta = -0.051$, 95% CI = -0.126; -0.003). No significant indirect effects were observed for remaining MRI metrics.

Analysis according to smoking status only

Complete results of the smoking-only VRF analysis are reported in Supplemental Tables 7–9. Smokers and non-smokers with MS were comparable in terms of age, sex, disease duration, phenotype, and DMT use (pFDR $\geq$ 0.437). Compared to non-smokers, smokers had higher EDSS scores and higher T2-hyperintense LV within the CST (pFDR $\leq$ 0.032). Consistent with the main analysis, a significant smoking $\times$ disease interaction was observed for NDGMV, nACMA, and MD of the ML (pFDR $\leq$ 0.042), but not for manual dexterity or walking capacity (pFDR $\geq$ 0.070).

Analysis of confounding factors

Complete results of an additional analysis on confounders are reported in Supplemental Table 10. Across all linear regression models, adjustment for clinical phenotype substantially attenuated the effect of VRFs on previously significant outcomes, except for z9HPT ($p = 0.039$) and nACMA ($p = 0.012$). Adjustment for EDSS consistently attenuated the effects of VRF presence, except for nACMA ($p = 0.012$).

Table 1. Comparison of demographic, clinical, and motor performance data between HC-VRF[−], MS-VRF[−], HC-VRF[+], MS-VRF[+], and MS-VRF[+].

Variables	HC		MS	HC-VRF[+] vs HC-VRF[-]		MS-VRF[-] vs HC-VRF[-]	MS-VRF[+] vs HC-VRF[+]	MS-VRF[+] vs MS-VRF[-]
	VRF[-] (106)	VRF[+] (74)		VRF[-] (89)	VRF[+] (179)			
Mean age (SD) [years]	31.44 (9.94)	37.75 (13.92)	41.03 (10.20)	44.88 (10.60)	0.001^a (0.003)	<0.001^a (0.003)	<0.001^a (0.003)	0.043 ^a (0.068)
Sex M/F (%)	44/62 (42/58)	42/32 (57/43)	32/57 (36/64)	81/98 (45/55)	0.044 ^b (0.068)	0.428 ^b (0.504)	0.096 ^b (0.137)	0.147 ^b (0.184)
Median disease duration (IQR) [years]	—	—	9.00 (1.27;17.88)	10.02 (2.17;19.91)	—	—	—	0.114 ^c (0.152)
Median EDSS (IQR)	—	—	1.5 (1.0;4.0)	3.0 (1.5;5.5)	—	—	—	<0.001^c (0.003)
Clinical phenotype: RRMS/PMS (%)	—	—	68/21 (76/24)	103/76 (58/42)	—	—	—	0.002^b (0.004)
DMT*: none/ME/HE (%)	—	—	11/46/32 (12/52/36)	29/87/63 (16/49/35)	—	—	—	0.701 ^b (0.701)
EM z9HPT (SE)	-0.32 (0.16)	-0.19 (0.18)	-1.56 (0.17)	-2.25 (0.12)	0.577 (0.607)	<0.001^d (0.003)	<0.001^d (0.003)	0.008^c (0.016)
EM zT25FW (SE)	-0.23 (0.12)	-0.12 (0.13)	-0.78 (0.12)	-1.23 (0.09)	0.540 (0.600)	0.001^d (0.003)	<0.001^d (0.003)	0.015^c (0.027)

Statistically significant comparisons are shown in bold. DMT: disease-modifying therapy; EDSS: Expanded Disability Status Scale; EM: estimated mean; F: female; MS: multiple sclerosis; HC: healthy controls; HC-VRF[−]: healthy control without any VRF; HC-VRF[+] : healthy control with one or more VRF; HE: high efficacy; IQR: interquartile range; M: male; ME: moderate efficacy; MS-VRF[−]: multiple sclerosis without any VRF; MS-VRF[+] : multiple sclerosis with one or more VRF; pFDR: false discovery rate *p*-value; PMS: progressive multiple sclerosis; RRMS: relapsing-remitting multiple sclerosis; SD: standard deviation; SE: standard error; VRF: vascular risk factor; zT25FW: z-score of inverted Timed 25-Foot Walk test; z9HPT: z-score of inverted 9-Hole Peg Test

^aTwo-sample *t*-test.

^bChi-square test.

^cMann-Whitney U test.

^dAge- and sex-adjusted linear models.

^e*p*-Value for significance of VRF × disease interaction effect.

*ME DMT: dimethyl fumarate, glatiramer acetate, interferon beta 1a, teriflunomide; HE DMT: alemtuzumab, azathioprine, cladribine, fingolimod, natalizumab, ocrelizumab, rituximab, siponimod.

Table 2. Prevalence of VRFs in HC and MS patients.

	HC (180)	MS (268)	<i>p</i> (pFDR)
Smoking, <i>n</i> (%)	63 (35.0)	142 (53.0)	<0.001 ^a (0.003)
Hypertension, <i>n</i> (%)	7 (3.9)	33 (12.3)	0.002 ^a (0.005)
Dyslipidemia, <i>n</i> (%)	12 (6.7)	33 (12.3)	0.051 ^a (0.102)
Obesity, <i>n</i> (%)	5 (2.8)	16 (6.0)	0.117 ^a (0.195)
Diabetes, <i>n</i> (%)	4 (2.2)	10 (3.7)	0.368 ^a (0.526)
Heart disease, <i>n</i> (%)	3 (1.7)	4 (1.5)	0.884 ^a (0.884)
Alcohol consumption, <i>n</i> (%)	1 (0.6)	3 (1.1)	0.534 ^a (0.668)
One or more VRFs, <i>n</i> (%)	74 (41.1)	179 (66.8)	<0.001 ^a (0.003)
Two VRFs, <i>n</i> (%)	8 (4.4)	37 (13.8)	0.001 ^a (0.003)
Three or more VRFs, <i>n</i> (%)	6 (3.3)	11 (4.1)	0.675 ^a (0.750)

Percentage values were calculated based on the total number of HC and MS subjects. HC: healthy control; MS: multiple sclerosis; *n*: number; VRF: vascular risk factor.

^aChi-square test.

Analysis of each VRF contribution. Complete results of these additional analyses are shown in Supplemental Table 11. Within MS patients, we found that smoking was the only predictor among all VRFs for z9HPT ($\beta = -0.148$, pFDR = 0.040), basal ganglia volume ($\beta = -0.159$, pFDR = 0.024), and nACMA ($\beta = -0.143$, pFDR = 0.041), while no other significant predictors were found for hypertension, dyslipidemia, and other VRFs.

Analysis according to quantitative classification of VRFs (0, 1, 2, or more)

Complete results of the additional analyses based on quantitative classification of VRFs are presented in Supplemental Table 12 and Figure 5. Consistent with the main analysis, a VRFs $\times$ disease status interaction was observed for z9HPT, NDGMV, nACMA, and MD of ML (all $p < 0.050$). As shown in Figure 5, z9HPT, zT25FW, and nACMA progressively worsened with increasing vascular comorbidities, whereas NDGMV and MD of ML plateaued after the first VRF.

Discussion

This large cross-sectional study suggests that VRFs in MS may contribute to greater disability, poorer motor performance, and more pronounced structural damage in key SMN regions. Speculating, these findings raise the possibility that vascular comorbidities can act as disease modifiers, exacerbating both brain damage and clinical outcomes in MS. However, despite the application of FDR correction, it is important to acknowledge the large number of measures included in our analyses and the relatively small number of significant

associations observed. Therefore, these findings should be replicated in independent datasets to assess their robustness and reproducibility.

Consistent with previous literature,^{3,5,13,15} we found that patients were characterized by a high prevalence of VRFs,¹⁹ which were associated with more severe disability and a higher prevalence of the PMS phenotype. Furthermore, we observed a significant interaction effect between disease status and VRF presence for both motor outcomes. These findings may reflect the minimal functional impairment observed in our sample of HCs, which may have limited our ability to detect the impact of VRFs on motor performance. Alternatively, they may indicate that VRFs exert a greater detrimental effect on motor performance in patients with MS than in HCs. If this hypothesis is correct, VRFs appear to exacerbate motor impairment, particularly affecting walking speed and manual dexterity.⁵ The association between VRFs and reduced walking speed may reflect systemic cardiovascular deterioration and reduced aerobic capacity, both known to influence physical performance in MS.²⁰ Yet, this explanation does not fully account for the additional impact on manual dexterity, which suggests the involvement of CNS-specific mechanisms. In line with this hypothesis and with previous studies showing that VRFs may increase focal WM lesion accumulation, WM microstructural damage, and brain atrophy,^{3,5-8,10,14-16} our findings suggest that VRFs may amplify MS-related damage in a clinically-relevant network such as the SMN. Specifically, the presence of VRFs in patients with MS was associated with more severe microstructural damage in the ML, lower NDGMV (in particular of the basal ganglia), and

(continued)

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Table 3. (continued)

	HC-VRF[-] (106)			HC-VRF[+] (74)			MS-VRF[-] (89)			MS-VRF[+] (179)			HC-VRF[-] vs HC-VRF[+] (pFDR)			MS-VRF[-] vs HC-VRF[+] (pFDR)			Interaction ^b MS-VRF[+] vs MS-VRF[-] (95% CI)		
	EM (SE)	EM (SE)	EM (SE)	EM (SE)	EM (SE)	EM (SE)	EM (SE)	EM (SE)	EM (SE)	EM (SE)	EM (SE)	EM (SE)	ES	p	ES	ES	p	ES	EMD (95% CI)	p	ES
MD	CST	0.63 (0.00)	0.62 (0.00)	0.62 (0.00)	0.62 (0.00)	0.61 (0.00)	0.62 (0.00)	0.62 (0.00)	0.62 (0.00)	0.61 (0.00)	0.62 (0.00)	0.62 (0.00)	0.279 (0.405)	0.001 (0.003)	0.03	0.04	0.001 (0.003)	0.04	0.00 (-0.01;0.01)	0.640 (0.786)	0.001
	SLF	0.51 (0.00)	0.51 (0.00)	0.51 (0.00)	0.51 (0.00)	0.49 (0.00)	0.49 (0.00)	0.49 (0.00)	0.49 (0.00)	0.49 (0.00)	0.49 (0.00)	0.49 (0.00)	0.302 (0.432)	0.001 (0.003)	0.05	0.05	0.001 (0.003)	0.05	0.00 (-0.01;0.01)	0.795 (0.913)	0.001
	MCP	0.71 (0.00)	0.70 (0.00)	0.70 (0.00)	0.70 (0.00)	0.72 (0.00)	0.72 (0.00)	0.72 (0.00)	0.72 (0.00)	0.72 (0.00)	0.72 (0.00)	0.72 (0.00)	0.185 (0.290)	0.001 (0.003)	0.03	0.03	0.001 (0.003)	0.03	0.01 (-0.01;0.01)	0.163 (0.266)	0.001
	SCP	0.80 (0.00)	0.79 (0.00)	0.79 (0.00)	0.79 (0.00)	0.81 (0.00)	0.81 (0.00)	0.81 (0.00)	0.81 (0.00)	0.81 (0.00)	0.81 (0.00)	0.81 (0.00)	0.204 (0.311)	0.001 (0.003)	0.02	0.02	0.001 (0.003)	0.02	0.02 (0.00;0.02)	0.097 (0.177)	0.001
	ML	0.74 (0.00)	0.73 (0.00)	0.73 (0.00)	0.73 (0.00)	0.75 (0.00)	0.75 (0.00)	0.75 (0.00)	0.75 (0.00)	0.75 (0.00)	0.75 (0.00)	0.75 (0.00)	0.099 (0.177)	0.001 (0.003)	0.01	0.01	0.001 (0.003)	0.01	0.02 (0.01;0.04)	0.009 (0.022)	0.001
	CST	0.71 (0.00)	0.70 (0.00)	0.70 (0.00)	0.70 (0.00)	0.72 (0.00)	0.72 (0.00)	0.72 (0.00)	0.72 (0.00)	0.72 (0.00)	0.72 (0.00)	0.72 (0.00)	0.217 (0.327)	0.001 (0.003)	0.01	0.01	0.001 (0.003)	0.01	0.03 (0.02;0.03)	0.040 (0.083)	0.001
T2 LV ^a [mL]	SLF	0.71 (0.00)	0.71 (0.00)	0.71 (0.00)	0.71 (0.00)	0.74 (0.00)	0.74 (0.00)	0.74 (0.00)	0.74 (0.00)	0.74 (0.00)	0.74 (0.00)	0.74 (0.00)	0.939 (1.000)	0.001 (0.003)	0.05	0.05	0.001 (0.003)	0.11	0.01 (-0.01;0.03)	0.176 (0.284)	0.001
	MCP	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)	1.000 (1.000)	0.001 (0.003)	0.00	0.00	0.001 (0.003)	0.00	0.00 (-0.01;0.01)	1.000 (1.000)	0.001
	SCP	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)	1.000 (1.000)	0.001 (0.003)	0.00	0.00	0.001 (0.003)	0.00	0.00 (-0.01;0.01)	1.000 (1.000)	0.001
	ML	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)	1.000 (1.000)	0.001 (0.003)	0.00	0.00	0.001 (0.003)	0.00	0.00 (-0.01;0.01)	1.000 (1.000)	0.001
	CST	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)	1.000 (1.000)	0.001 (0.003)	0.00	0.00	0.001 (0.003)	0.00	0.00 (-0.01;0.01)	1.000 (1.000)	0.001
	SLF	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)	1.000 (1.000)	0.001 (0.003)	0.00	0.00	0.001 (0.003)	0.00	0.00 (-0.01;0.01)	1.000 (1.000)	0.001

Statistically significant comparisons are shown in bold. MD is expressed in units of mm²/sec $\times 10^{-3}$; while FA is a dimensionless index. CI: confidence interval; CST: corticospinal tract; CT: cortical thickness; EM: estimated mean; EMD: estimated mean difference; ES: effect size; FA: fractional anisotropy; HC-VRF[-]: healthy control without any VRF; HC-VRF[+]: healthy control with one or more VRF; M1: primary motor cortex; MCP: middle cerebellar peduncle; MD: mean diffusivity; mL: milliliters; ML: medial lemniscus; mm: millimeter; MS-VRF[-]: multiple sclerosis without any VRF; MS-VRF[+]: multiple sclerosis with one or more VRF; MTG: middle temporal gyrus; nACMA: normalized anterior cerebellar motor area; NBV: normalized brain volume; NCGMV: normalized cortical gray matter volume; NDGMV: normalized deep gray matter volume; nMUCCA: normalized mean upper cervical cord area; nPCMA: normalized posterior cerebellar motor area; NWMV: normalized white matter volume; pFDR: false discovery rate *p*-value; S1: primary somatosensory cortex; SCP: superior cerebellar peduncle; SE: standard error; SLF: superior longitudinal fasciculus; STG: superior temporal gyrus; T2 LV: T2 hyperintense lesion volume; VRF: vascular risk factor

^aAnalyses were conducted on the log-transformed ranked data, while medians and interquartile ranges of the original values are presented descriptively.

^bVRF $\times$ disease status interaction.

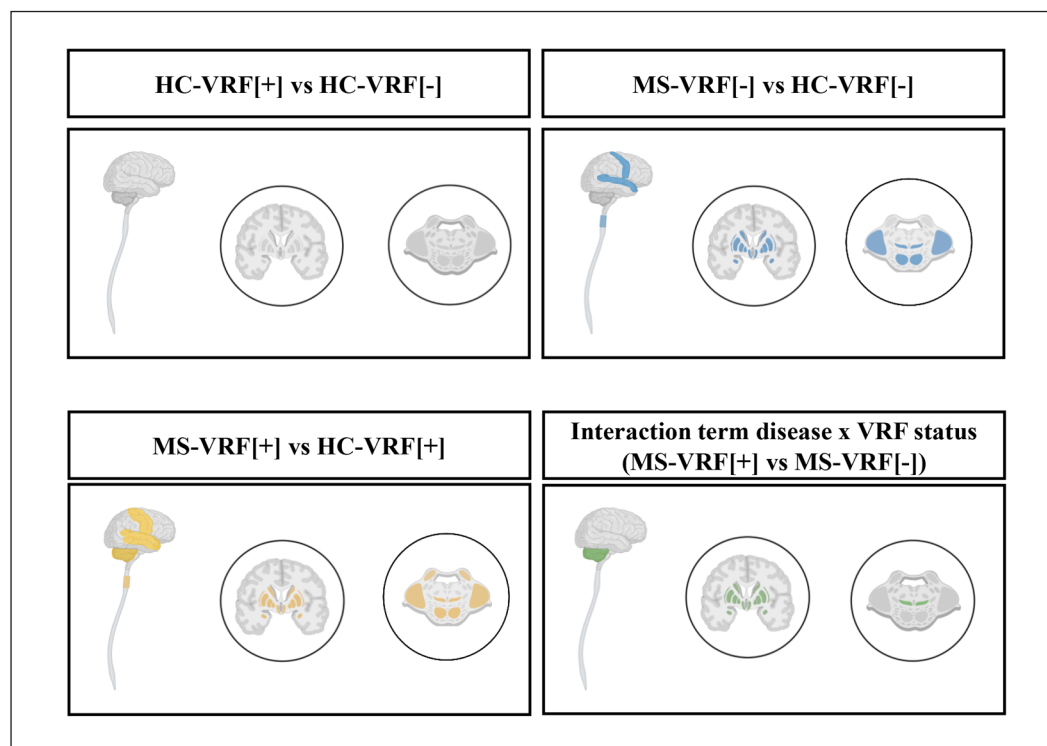


Figure 3. Comparison of MRI data between study groups.

Each square represents a specific group comparison and highlights MRI measures showing statistically significant differences. No significant differences were observed between the two healthy control groups. MRI metrics differing between MS-VRF[-] and HC-VRF[-] (blue) included CT of the primary motor cortex and superior temporal gyrus, normalized deep gray matter volume, and FA of the middle cerebellar peduncle, medial lemniscus, and corticospinal tract. MRI metrics differing between MS-VRF[+] and HC-VRF[+] (yellow) included CT of the primary motor cortex, primary somatosensory cortex, and superior and middle temporal gyri; normalized anterior and posterior cerebellar motor areas; normalized mean upper cervical cord area; normalized deep gray matter volume; and FA and MD of the middle and superior cerebellar peduncles, medial lemniscus, and corticospinal tract. Interaction effects (disease $\times$ VRF status; green) were observed for the normalized anterior cerebellar motor area, normalized deep gray matter volume, and MD of the medial lemniscus. CT: cortical thickness; FA: fractional anisotropy; HC-VRF[-]: healthy control without any VRF; HC-VRF[+]: healthy control with one or more VRF; MD: mean diffusivity; MS-VRF[-]: multiple sclerosis without any VRF; MS-VRF[+]: multiple sclerosis with one or more VRF.

reduced nACMA volume, all regions critical for sensory-motor integration and coordination.^{21–24} This interpretation is further supported by our mediation analyses, indicating that the effects of VRFs on disability and motor performance are mediated by basal ganglia volume and nACMA in patients with MS.

Within this framework, the ML emerged as a particularly vulnerable tract. Indeed, in our cohort, MS-VRF[+] showed disproportionately greater ML damage than MS-VRF[-], as evidenced by a significant VRF $\times$ MS status interaction. In addition, we observed a significant VRF $\times$ ML FA interaction in relation to EDSS scores, suggesting that this tract may represent a convergence point where vascular and MS-related damage act synergistically to accelerate structural injury and disability. These results resonate with evidence that central pontine lesions, where the ML is located, are more often linked to vascular

aging, whereas peripheral pontine lesions are more typical of MS pathology.^{9,10,13}

In addition, the deep GM and the ACMA, key regions for motor control and sensory inputs integrations, emerged as critical areas of vulnerability within the SMN. These results are in line with previous studies showing that specific VRFs such as alcohol consumption,²⁵ smoking,^{26,27} hypertension,²⁸ obesity,²⁹ and diabetes³⁰ adversely affect these structures.

Interestingly, not all SMN structures appeared equally susceptible to the combined effect of VRFs and MS. No significant VRF $\times$ disease interactions were observed for CST or spinal cord measures, suggesting that certain sensorimotor pathways may be more resilient or that longer disease duration is required for vascular effects to manifest in these regions.³¹ This heterogeneity underscores the need for longitudinal

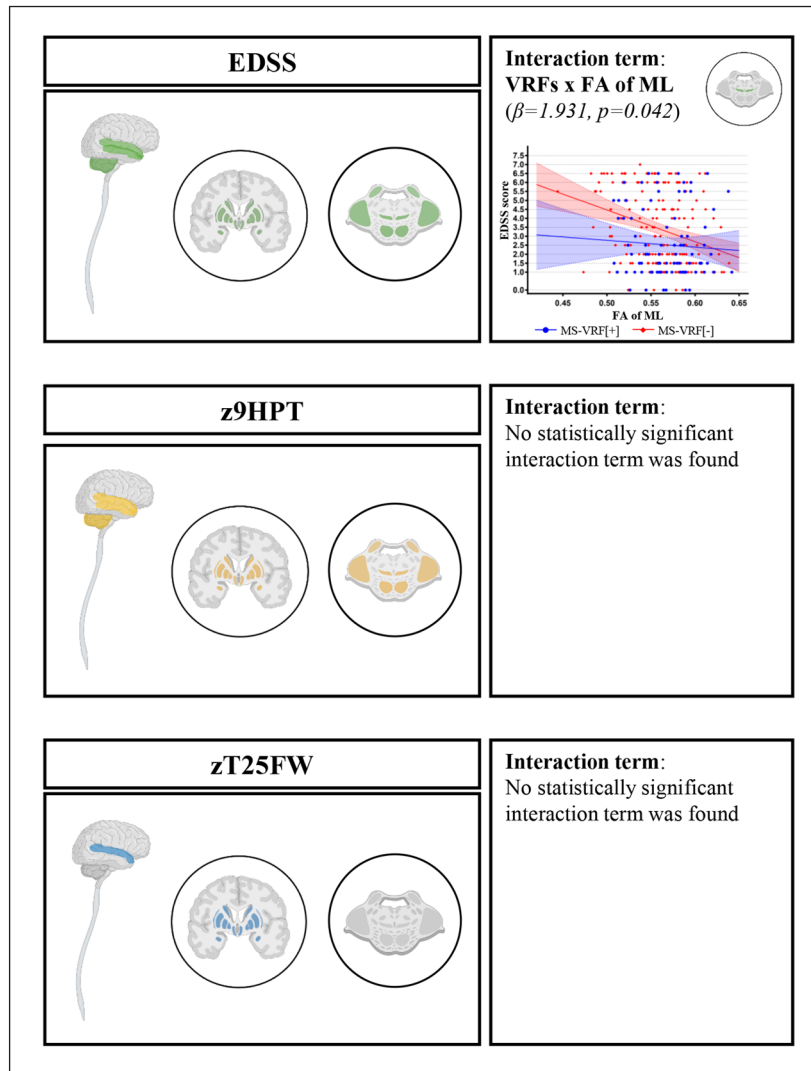


Figure 4. Association between clinical and MRI measures in MS patients, with the interaction term between VRFs and MRI variables.

Each square represents the association between a clinical variable with MRI metrics. Associations between EDSS and MRI metrics (green): normalized deep gray matter volume, CT of middle and superior temporal gyrus, normalized anterior and posterior cerebellar motor area, FA and MD of middle and superior cerebellar peduncles and corticospinal tract, and FA of medial lemniscus. Associations between z9HPT and MRI metrics (yellow): CT of middle and superior temporal gyrus, normalized anterior and posterior cerebellar motor area, FA and MD of middle and superior cerebellar peduncles, corticospinal tract and FA of medial lemniscus. Associations between zT25FW and MRI metrics (blue): normalized deep gray matter volume and CT of the superior temporal gyrus. In the scatter plot showing the association between FA of the ML and EDSS scores in patients with MS, patients with VRFs are shown in red diamond-shaped markers, while patients without VRFs are shown in blue circle-shaped markers. Higher EDSS values are associated with lower FA scores, especially in MS patients with VRFs, with a negative trendline observed. Shaded areas represent confidence intervals for each group's trendline. CT: cortical thickness; EDSS: Expanded Disability Status Scale; FA: fractional anisotropy; MD: mean diffusivity; MRI: magnetic resonance imaging; MS-VRF[-]: multiple sclerosis patients without VRFs; MS-VRF[+]: multiple sclerosis patients with VRFs; zT25FW: z-score Timed 25-Foot Walk test; z9HPT: z-score 9-Hole Peg Test.

studies to disentangle temporal and region-specific effects of VRFs on MS pathology. Moreover, despite evidence that VRFs are associated with higher accumulation of focal WM lesions in both healthy aging³² and patients with MS,¹² we did not observe significant differences in T2-hyperintense LV according to VRF status, possibly due to the relatively young age of our

cohort and the limited number of VRFs among participants in whom vascular-related lesion accumulation may not yet be evident. However, our findings may suggest that diffuse microstructural tissue abnormalities and atrophy, rather than focal lesion accumulation, may represent the critical pathway through which VRFs exacerbate disability in MS.

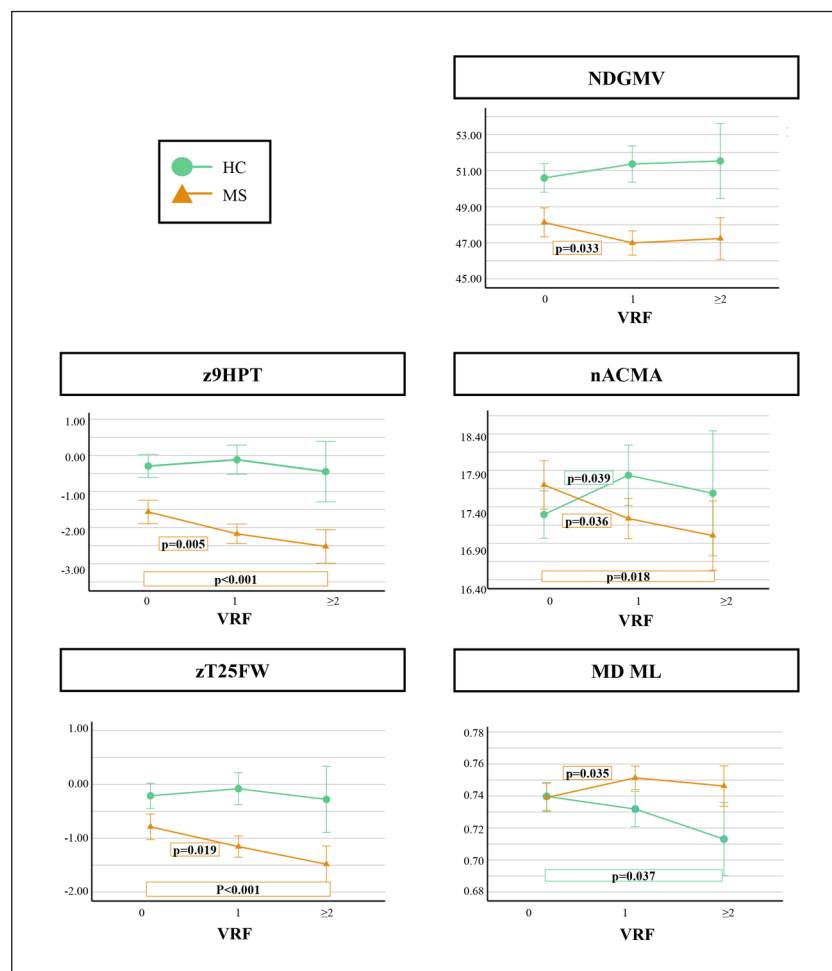


Figure 5. Results of linear regression analyses with clinical and MRI data as outcomes and MS, quantitative VRF classification, and their interaction as predictors.

Each plot shows the estimated marginal means (EMM) values of each variable across VRF categories and stratified by MS status. Values are adjusted for age and sex. Error bars represent 95% confidence intervals. Green lines with circular markers represent HC subjects, while orange lines with triangular markers represent MS patients. MRI: magnetic resonance imaging; MD: mean diffusivity; ML: medial lemniscus; MS: multiple sclerosis; nACMA: normalized anterior cerebellar motor area; NDGMV: normalized deep gray matter volume; *p*: *p*-value; VRF: vascular risk factor; zT25FW: z-score Timed 25-Foot Walk test; z9HPT: z-score 9-Hole Peg Test.

Although the mechanisms underlying the detrimental effects of VRFs on CNS integrity remain unclear, evidence suggests that VRFs may accelerate MS-related damage through additive effects of hypoperfusion, inflammation, and oxidative stress, thereby amplifying neurodegeneration.³³ These mechanisms may particularly affect metabolically demanding regions, such as deep GM nuclei and long, heavily myelinated WM tracts (e.g. ML), which rely on continuous energy supply for ionic balance and synaptic transmission.³⁴ This may explain the selective involvement of deep GM and sensorimotor tracts observed in our sample.

Despite these findings, several limitations should be acknowledged. First, HC and MS groups were not

perfectly age-matched, although age was included as a covariate in all analyses to reduce its potential confounding effect. In addition, the MS group with VRFs exhibited greater disability and a higher prevalence of progressive phenotypes, which may have influenced the other evaluated outcomes. These factors were not included as confounders in the main analyses because groups were stratified a priori by VRF status. Nevertheless, supplementary analyses adjusting for disability and phenotype partially attenuated the observed effects, indicating a potential contribution of these factors. Future studies should include larger and more balanced cohorts or stratified analysis to better disentangle the independent effects of VRFs, disability, and disease phenotype.

The cross-sectional design precludes causal or temporal inferences between VRFs and MS progression. Moreover, VRFs were self-reported and not confirmed by objective measures (i.e. medical records, laboratory or biometric data), potentially introducing misclassification bias. Smoking was the predominant VRF in our sample; therefore, we conducted a supplementary smoking-only analysis, which partially overlapped with the main findings, suggesting a major contribution of smoking to the observed effects, also supported by the analysis investigating the role of each VRF. However, combined VRFs appeared to exert a stronger impact on motor performance, whereas smoking alone showed no measurable clinical effect. Conversely, smoking was specifically associated with increased T2-weighted LV within the CST, an effect not observed when all VRFs were analyzed together. To investigate the potential cumulative effects of VRFs, additional analyses using a quantitative VRF classification showed that some MRI and clinical measures worsened with increasing vascular comorbidities, whereas others plateaued after a single VRF. Future studies with more balanced VRF distributions should clarify the individual and combined effects of vascular comorbidities, their biological mechanisms, and the potential modifying role of MS-DMT category on disability and MRI outcomes.

Finally, although standardized criteria were applied to define each VRF, differences in severity, chronicity, and exposure duration were not quantified. Similarly, we did not consistently collect data on VRF treatment. These limitations may have diluted the associations between individual VRFs and MRI or clinical outcomes and should be addressed in future studies.

In conclusion, this study provides preliminary evidence, which should be confirmed by future independent studies, that VRFs (in particular smoking) may be associated with greater structural damage in MS within critical sensorimotor regions, particularly the ML, deep GM, and cerebellar motor areas, as well as with worse disability and motor performance. Speculating on possible clinical implications, these results suggest that early identification and proactive management of modifiable VRFs should be integrated into standard care for patients with MS since they could represent a pragmatic and impactful strategy to slow disability progression.

Author Contributions

M.A., P.P., M.R., and M.A.R. contributed to the conception and design of the study. M.A., P.P., G.R.,

N.T., E.P., L.S., P.V., and M.R. contributed to the acquisition and analysis of data. M.A., P.P., and M.A.R. contributed to drafting the text and preparing the figures. M.A., P.P., G.R., N.T., E.P., L.S., P.V., M.R., M.F., and M.A.R. approved the final draft of the manuscript.

Declaration of Conflicting Interests

The authors declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: The authors declare that they have no competing interest in relation to this work. Potential conflicts of interest outside the submitted work are as follows: M. Albergoni has nothing to disclose. P. Preziosa received speaker honoraria from Roche, Biogen, Novartis, Merck, Bristol Myers Squibb, Horizon, and Sanofi. G. Ritroso, N. Tedone, E. Pagani, L. Storelli, P. Valsasina, and M. Rubin have nothing to disclose. M. Filippi is the Editor-in-Chief of the *Journal of Neurology* and an Associate Editor of *Human Brain Mapping*, *Neurological Sciences*, and *Radiology*; received compensation for consulting services from Almirall, Biogen, Bristol Myers Squibb, Eli Lilly, Merck, Novartis, Roche, and Sanofi; speaking activities from Amgen, Bayer, Biogen, Bristol Myers Squibb, Celgene, Chiesi Italia SpA, Eisai, Eli Lilly, Fujirebio, Genzyme, Janssen, Merck, Neopharmed Gentili, Neuraxpharm, Novartis, Novo Nordisk, Roche, Sanofi, and Takeda; participated in advisory boards for Alexion, Biogen, Bristol Myers Squibb, Eli Lilly, GE Healthcare Ltd, Merck, Neuraxpharm, Novartis, Roche, Sandoz, Sanofi, and Takeda; provided scientific direction of educational events for Biogen, Merck, Roche, Celgene, Bristol Myers Squibb, Lilly, Novartis, and Sanofi-Genzyme; and receives research support from Biogen Idec, Merck Serono, Novartis, Roche, the Italian Ministry of Health, the Italian Ministry of University and Research, and Fondazione Italiana Sclerosi Multipla. M.A. Rocca received consulting fees from Biogen, Bristol Myers Squibb, and Roche and speaker honoraria from Alexion, Biogen, Bristol Myers Squibb, Celgene, Horizon Therapeutics Italy, Merck Serono SpA, Mitsubishi-Tanabe Pharma, Neuraxpharm, Novartis, Roche, Sandoz, and Sanofi. She receives research support from the MS Society of Canada, the Italian Ministry of Health, the Italian Ministry of University and Research, and Fondazione Italiana Sclerosi Multipla. She is an Associate Editor for *Multiple Sclerosis and Related Disorders* and an Associate Co-Editor for Europe and Africa for the *Multiple Sclerosis Journal*.

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Ethical Approval and Patient Consents

This retrospective observational cross-sectional study involved human participants and was approved by the ethical standards committee on human experimentation of IRCCS Ospedale San Raffaele (Protocol ID: 2015-33). All participants provided informed consent to participate in the study before inclusion.

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Data Availability Statement

The dataset used and analyzed during the current study are available from the corresponding author on reasonable request.

Supplemental Material

Supplemental material for this article is available online.

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