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ORIGINAL COMMUNICATION

Dietary and lifestyle factors in multiple sclerosis progression: results from a 5-year longitudinal MRI study

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Abstract

Background Evidence regarding the role, if any, of dietary and lifestyle factors in the pathogenesis of multiple sclerosis (MS) is poorly understood.

Objective To assess the effect of lifestyle-based risk factors linked to cardiovascular disease (CVD) on clinical and MRI-derived MS outcomes.

Methods The study enrolled 175 MS or clinically isolated syndrome (CIS) patients and 42 age- and sex-matched healthy controls (HCs) who were longitudinally followed for 5.5 years. The 20-year CVD risk was calculated by Healthy Heart Score (HHS) prediction model which includes age, smoking, body mass index, dietary intake, exercise, and alcohol consumption. Baseline and follow-up MRI scans were obtained and cross-sectional and longitudinal changes of T2-lesion volume (LV), whole brain volume (WBV), white matter volume (WMV), gray matter volume (GMV), and lateral ventricular volume (LVV) were calculated.

Results After correcting for disease duration, the baseline HHS values of the MS group were associated with baseline GMV ($r_s = -0.20$, $p = 0.01$), and longitudinal LVV change ($r_s = 0.19$, $p = 0.01$). The association with LVV remained significant after adjusting for baseline LVV volumes ($r_s = 0.2$, $p = 0.008$) in MS patients. The diet component of the HHS was associated with the 5-year T2-LV accrual ($r_s = -0.191$, $p = 0.04$) in MS. In the HC group, the HHS was associated with LVV ($r_s = 0.58$, $p < 0.001$), GMV ($r_s = -0.57$, $p < 0.001$), WBV ($r_s = -0.55$, $p = 0.001$), T2-LV ($r_s = 0.41$, $p = 0.027$), and WMV ($r_s = -0.38$, $p = 0.042$). Additionally, the HC HHS was associated with the 5-year change in LVV ($r_s = 0.54$, $p = 0.001$) and in WBV ($r_s = -0.45$, $p = 0.011$).

Conclusion Lifestyle risk factors contribute to accelerated central brain atrophy in MS patients, whereas unhealthier diet is associated with MS lesion accrual. Despite the lower overall effect when compared to HCs, lifestyle-based modifications may still provide a beneficial effect on reducing brain atrophy in MS patients.

Keywords MRI · MS · Lifestyle · Exercise · Smoking · Diet · Alcohol · T2-lesions · Central brain atrophy

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Introduction

Multiple sclerosis (MS) is a chronic inflammatory demyelinating disease of the central nervous system (CNS) that presents with heterogeneous pathology involving both the white matter (WM) and gray matter (GM) [1]. An increasing body of evidence has established the concomitant occurrence of neurodegenerative processes leading to widespread brain atrophy and progressive long-term disability accumulation [2]. The etiology and pathophysiology of MS is considered to be multifactorial and involves a complex interplay between environmental, infectious, and genetic factors [3].

The recent success in MS disease management has contributed to improving and extending the overall longevity and quality of life of these patients. Consequently, the epidemiological profile of MS patients is shifting towards an aging population with increasing comorbidities [4, 5]. Among other chronic diseases, the prevalence of cardiovascular diseases (CVD) have sharply increased from below 10% in patients aged 20–44 years old to more than 40% in MS patients older than 60 years old [6, 7].

Several environmental factors that are associated with increased MS susceptibility and severity are also risk factors shared with CVD and unhealthy aging [8]. Among those factors, obesity, active smoking, presence of hypertension, diabetes, heart disease, lack of exercise, increased salt intake, and poor diet have been associated with poorer MS clinical and MRI-derived outcomes [9–13]. The higher concurrence of MS and CVD has been additionally corroborated in several population-based studies, which indicates that MS patients have a higher prevalence of comorbidities than age-, sex, and geographical location-matched controls [14]. Furthermore, this increase in cardiovascular comorbidities was observed as early as 5 years before the MS diagnosis [14]. To address this potentially preventable cause of additional disability, current efforts in understanding the effect of environmental factors have been initiated and are ongoing [15, 16].

Based on this background, the aim of this study was to integrate several environmental factors associated with cardiovascular health and to examine their composite longitudinal effect on MS progression. Additionally, we aimed to further detect the effect of the aforementioned environmental factors on cross-sectional and longitudinal MRI-derived changes in both MS patients and healthy controls (HCs).

Materials and methods

Demographic and clinical characteristics

The MS patients and HCs included in this sub-analysis were part of a larger ongoing 5-year, longitudinal, case-controlled, cardiovascular, environmental, and genetic study in MS (CEG-MS) that were initially enrolled from years 2009–2012 and returned for a follow-up visit from years 2014–2017 [17, 18]. The inclusion criteria for this analysis were: (1) baseline and follow-up 3.0T MRI examination performed with the standard imaging protocol, (2) clinical assessment within 30 days of the MRI exam and completed lifestyle questionnaire, (3) baseline age of 18 to 75 years old, (4) MS or clinically isolated syndrome (CIS) patients defined by the 2010-revised McDonald criteria [19] and (5) HCs without any current or past neurological disease. The exclusion criteria were: (1) clinically-diagnosed relapse or steroid treatment within 30 days of the MRI examination, and (2) nursing or pregnant mothers.

The demographic, clinical, lifestyle-based, and diet-based information were acquired by in-person interview and by additional standardized questionnaires. The full questionnaire has been previously published elsewhere [20]. The history of previous CVD was collected during the interview and a further cross-reference with the patients' electronic medical records was performed. Positive smoking status was defined if the subject had consecutively smoked for a minimum of 6 months at any point in their past. Neurological assessment and Expanded Disability Status Scale (EDSS) scoring were performed by an experienced neurologist [21]. The study was approved by the University at Buffalo Institutional Review Board (IRB) and all participants signed written informed consent.

Lifestyle and diet score calculation

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 [22]. The only modification to the original HHS model was done to better utilize the collected dietary data. Based on the recommended American Heart Association (AHA), an ounce-equivalent serving of dietary fiber was replaced with the cereal fiber intake score, which was computed based on a previously acquired information of cumulative servings of whole wheat bread, whole wheat pasta, and brown rice consumption.

The gender-specific scores were calculated as follows:

$$\text{Female: } 20-\text{year CVD} \sim \text{risk } (\%) = \left[1 - 0.9660^{(\exp[F-6.57301])}\right] \times 100\%$$

$$\text{Where}: F = 0.10820 \times \text{age} + 0.15285\ (\text{past smoker}) + 0.90138\ (\text{current smoker}) + 0.04676 \times \text{BMI} - 0.01923 \times \text{grams/d alchohol} + 0.0004 \times (\text{grams/d of alchohol})^2 - 0.01755 \times \text{hours/week of exercise} - 0.06691 \times \text{diet score}$$

$$\text{Where: Diet score} = \begin{pmatrix} 0.03326 \times \text{grams/d of dietary fibers} + 0.18283\ [\text{if fruits} + \text{vegetables} \geq 3\ \text{servings/d}] \\ + 0.14522\ [\text{if nuts } 0.1 - 1\ \text{servings/d} + 0.244444\ [\text{if nuts} > 1\ \text{servings/d}] - 0.14631 \\ \times\ \text{servings/d of sugar sweetened bevarages} - 0.15624 \times \text{servings/d of red and processed meats} \end{pmatrix} \times 10$$

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

$$\text{Where: } M = 0.13580 \times \text{age} + 0.0005 \times \text{age}^2 + 0.06979\ (\text{past smoker}) + 0.42305\ (\text{current smoker}) + 0.07424 \times \text{BMI} - 0.00898 \times \text{grams/d alchohol} + 0.0001 \times (\text{grams/d of alchohol})^2 - 0.01755 \times \text{hours/week of exercise} - 0.06691 \times \text{diet score}$$

$$\text{Where}: \text{Diet score} = \begin{pmatrix} 0.01816 \times \text{grams/d of dietary fibers} + 0.08819\ [\text{if fruits} + \text{vegetables} \geq 3\ \text{servings/d}] \\ + 0.0.00535\ [\text{if nuts } 0.1 - 1\ \text{servings/d} + 0.14285\ [\text{if nuts} > 1\ \text{servings/d}] \\ - 0.14734 \times \text{servings/d of sugar sweetened beverages} - 0.07112 \times \text{servings/d of red and processed meats} \end{pmatrix} \times 10.$$

Greater 20-year CVD risk scores indicate worse cardiovascular-associated behavior and higher chances of future CVDs, whereas greater diet scores indicate healthier diet preferences.

In addition to the HHS calculation, the "hard" Framingham Coronary Heart Disease Risk Score, which is intended for non-diabetic patients aged 30–79 and no prior history of coronary heart disease or intermittent claudication, was additionally derived [23]. Patients without prior cardiovascular diseases and with available baseline cholesterol and blood pressure data were used for this secondary score analysis. EDTA plasma samples were obtained in non-fasted state. The total cholesterol and high-density lipoprotein cholesterol (HDL-C) were measured with diagnostic reagent kits from Sekisui Diagnostics (Lexington, MA, USA) and ABX Pentra 400 (Horiba Instruments, Irvine, CA) automated chemistry analyzer [24]. Similarly to HHS, a greater Framingham Coronary Heart Disease Risk Score indicates higher chances of a myocardial infarction in the following 10 years.

Magnetic resonance imaging (MRI) acquisition and analysis

The MRI scans were obtained using a 3T GE Signa Excite HD 12 Twin Speed 8-channel scanner (General Electric, Milwaukee, WI, USA) using an 8-channel head and neck (HDNV) coil. No MRI hardware or software changes occurred throughout the follow-up period. The T1- and T2-lesion volume (LV) were obtained by a semi-automated edge detection and contouring/thresholding technique. The cross-sectional analysis of whole brain volume (WBV), white matter volume (WMV), gray matter volume (GMV) and lateral ventricular volume (LVV) was derived using the SIENAX cross-sectional software (version 2.6) [25]. To reduce the impact of T1 hypointensities, lesions maps were filled prior to the SIENAX segmentation [26]. The percent longitudinal change of WBV, WMV, GMV, and LVV were calculated using SIENA and SIENAX multi-time-point algorithms [25, 27].

Statistical analysis

For demographic and clinical comparisons between MS patients and HCs, Student t test, χ^2 test, and Mann–Whitney U test were used. The associations between the 20-year CVD-based behavior risk score and diet score with clinical and MRI-derived variables were assessed using Spearman's ranked correlation and partial correlation adjusted for disease duration. Scatter plots were used to visualize the associations between the lifestyle-based scores and LVV in MS patients and HCs (Fig. 1); and between lifestyle-based scores with GMV and WMV in HCs (Supplement Fig. 1). In both figures, the lifestyle-based scores were transformed using the

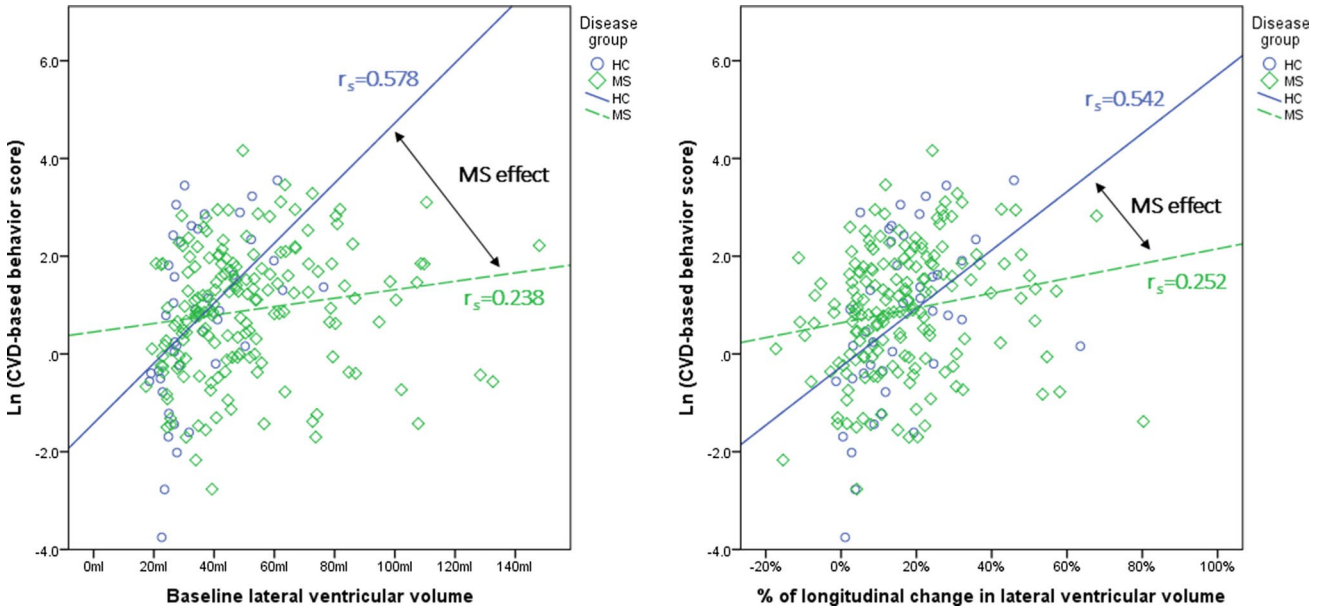

Fig. 1 Scatter plot representation of the lifestyle scores associations with the cross-sectional lateral ventricular volume and longitudinal lateral ventricular volume change for both multiple sclerosis patients and healthy controls. *MS* multiple sclerosis, *HC* healthy control, *CVD* cardiovascular disease. Spearman's ranked correlations were used to derive the correlation coefficient shown in the figure. For illustrative purposes, the CVD-associated behavior is depicted by using natural logarithmic transformation. The MS effect bar does not represent the actual effect size, but rather demonstrates the differences in slopes

natural logarithm. In a secondary analysis, MS patients were divided based on the HHS tertiles and the clinical and MRI-derived measures were compared using one-way ANOVA, Student's *t* test, Mann–Whitney *U* test, Kruskal–Wallis, and disease duration-adjusted ANCOVA tests, as appropriate. Bar plots illustrate the 5-year LVV atrophy differences seen between the different MS tertiles (Supplement Fig. 2).

The initial exploratory association analyses were corrected for disease group-specific multiple comparisons using the Benjamini–Hochberg procedure. The adjusted *p* values for the association analysis are shown as corrected *q* value. *Q* values < 0.05 were considered significant in two-tailed tests. Significant findings from the MS association analyses were further corroborated by the multivariate regression model. The model initially utilized force entered correction step with variables including disease duration, baseline MRI-derived volumes, baseline DMT, DMT switch and the different clinical phenotypes (CIS/relapsing-remitting (RRMS)/progressive MS). In the second step-wise step, the HHS score was added only if it provided additional explanatory power.

Results

Study population

The demographic and clinical characteristics of both the MS and HCs groups are shown in Table 1. The study included 175 CIS/MS patients (24 with CIS, 106 with RRMS), 45 with progressive MS, and 42 sex- and age-matched HCs that were followed over mean periods of 5.4 and 5.5 years, respectively (Table 1). Over the follow-up period, 16 CIS patients converted into clinically definite MS, and 12 RRMS patients converted into progressive phenotype. The baseline clinical phenotypes are hereafter used. There were no differences in sex ratio (73.1% females in MS vs. 71.4% females in HC, $p = 0.85$), mean age (46.9 years for MS vs. 46.8 years for HC, $p = 0.92$), and baseline BMI (27.3 kg/m^2 for MS vs. 25.9 kg/m^2 for HC, $p = 0.14$). The prevalence of hypertension (15.4% in MS vs. 9.5% in HC, $p = 0.46$), hyperlipidemia (14.9% in MS vs. 16.7% for HC, $p = 0.81$) and heart disease (9.1% in MS vs. 4.8% in HC, $p = 0.54$) were similar in the MS and HC groups, respectively. There was also no significant difference in the calculated 20-year CVD risk score between MS patients and HCs (4.9% vs. 6.3%, $p = 0.37$). Although not significantly different, the MS patients had numerically lower diet scores (0.13 in MS vs. 0.23 in HC, $p = 0.079$).

The MS group had a mean disease duration of 13.9 years and the treatment profile at baseline consisted of: interferon-β (41.1%), glatiramer acetate (19.4%), natalizumab (14.3%), and no current disease-modifying therapy (DMT) use (22.3%). Five patients (2.9%) were on off-label immunoglobulins, azathioprine, mitoxantrone, and mycophenolic acid. The median EDSS score at baseline was 2.5 (interquartile range (IQR) 1.5–4.5), the median EDSS

Table 1 Demographic and clinical characteristics of the multiple sclerosis patients and age- and sex-matched healthy controls

Demographic and clinical characteristics	CIS/MS ($n=175$)	HCs ($n=42$)	p value
Female, *n* (%)	128 (73.1)	30 (71.4)	0.85
Age at baseline, mean (SD)	46.9 (11.2)	46.8 (14.4)	0.92
Follow-up period, mean (SD)	5.4 (0.6)	5.5 (0.5)	0.52
BMI at baseline, mean (SD)	27.3 (5.6)	25.9 (5.8)	0.14
BMI at follow-up, mean (SD)	27.4 (5.8)	25.9 (5.8)	0.14
Diet score, mean (SD)	0.13 (0.3)	0.23 (0.3)	0.079
20 year CVD risk, mean (SD)	4.9 (7.1)	6.3 (8.8)	0.37
Framingham Risk Score, mean (SD)	2.4 (3.2)	–	–
Hypertension, *n* (%)	27 (15.4)	4 (9.5)	0.46
Hyperlipidemia, *n* (%)	26 (14.9)	7 (16.7)	0.81
Heart disease, *n* (%)	16 (9.1)	2 (4.8)	0.54
Disease duration, *n* (SD)	13.9 (10.2)	–	–
CIS/RRMS/PMS	24/106/45	–	–
EDSS at baseline, median (IQR)	2.5 (1.5–4.5)	–	–
EDSS at follow-up, median (IQR)	3.0 (2.0–5.6)	–	–
EDSS change, mean (SD)	0.4 (0.9)	–	–
Annualized relapse rate, mean (SD)	0.178 (0.37)	–	–
DMT use at baseline			
IFN-β, *n* (%)	72 (41.1)	–	–
Glatiramer acetate, *n* (%)	34 (19.4)	–	–
Natalizumab, *n* (%)	25 (14.3)	–	–
Other DMTs, *n* (%)	5 (2.9)	–	–
No DMT use, *n* (%)	39 (22.3)	–	–

Patients classified as other DMTs used immunoglobulins (2), azathioprine (1), mitoxantrone (1), mycophenolic acid (1)

The 20 year CVD risk and Framingham Risk Score are reported in percentages. Student t test, χ^2 test, and Mann–Whitney U test were used accordingly

MS multiple sclerosis, *HC* healthy controls, *BMI* body mass index, *CIS* clinically isolated syndrome, *RRMS* relapsing remitting multiple sclerosis, *PMS* progressive multiple sclerosis, *CVD* cardiovascular disease, *EDSS* Expanded Disability Status Scale, *DMT* disease-modifying therapy, *IFN-β* interferon-beta, *SD* standard deviation, *IQR* interquartile range

score at follow-up was 3.0 (IQR 2.0–5.6), and the 5-year annualized relapse rate (ARR) was 0.178.

Over the follow-up period, 96 MS/CIS patients remained on their baseline assigned DMT and 79 switched to a different medication. Out of the 79 switches, 17 patients switched to dimethyl fumarate, 13 switched to glatiramer-acetate, 12 to natalizumab, 10 to interferon-β, 9 stopped their medication, 6 switched to fingolimod, 7 switched to other off-label medications and 5 switched to teriflunomide.

Associations of CVD-associated behavior and diet scores with clinical and MRI variables in MS patients and HCs

The associations between the 20-year CVD and diet score with the clinical and MRI measures in both the MS and HC groups are summarized in Table 2.

Within the HC population, the 20-year CVD-based behavior scores exhibited strong correlations with multiple MRI-derived baseline volumes including LVV ($r_s = 0.58$, $q < 0.001$), GMV ($r_s = -0.57$, $q < 0.001$), WBV ($r_s = -0.55$, $q = 0.001$), T2-LV ($r_s = 0.41$, $q = 0.027$) and WMV ($r_s = -0.38$, $q = 0.042$). Additionally, the 20-year CVD score was associated with the 5-year change in LVV ($r_s = 0.54$, $q = 0.001$) and in WBV ($r_s = -0.45$, $q = 0.011$). The diet scores from the HCs did not correlate with any of the MRI-derived measures.

In the MS group, the 20-year CVD score of the MS patients was associated with the baseline GMV ($r_s = -0.455$, $q < 0.001$), baseline WBV ($r_s = -0.36$, $q < 0.001$), and baseline LVV ($r_s = 0.24$, $q = 0.007$). The CVD score also correlated with the 5-year longitudinal change in LVV ($r_s = 0.252$, $q = 0.004$). After disease duration correction, only baseline GMV ($r = -0.196$, $p = 0.01$) and the longitudinal 5-year LVV change ($r = 0.194$, $p = 0.01$) remained significant. Due to the potential influence of baseline brain volume on the longitudinal atrophy rate, MRI-derived variables were further corrected for their baseline volumes [28]. Even

Table 2 Association between 20-year cardiovascular disease risk score and diet with clinical and demographic characteristics of multiple sclerosis patients and healthy controls

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	r_S	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	–	–	–	–

Spearman's rank correlation (r_S) was used. q value is adjusted p value from the Benjamini–Hochberg procedure for multiple testing. Benjamini–Hochberg q values lower than 0.05 were considered as statistically significant

MS multiple sclerosis, *HCs* healthy controls, *CVD* cardiovascular disease, *BH* Benjamini–Hochberg, *EDSS* Expanded Disability Status Scale, *LV* lesion volume, *GMV* gray matter volume, *WMV* white matter volume, *WBV* whole brain volume, *LVV* lateral ventricular volume

after this adjustment, the association between higher CVD-based behavior scores and greater longitudinal 5-year LVV change remained significant (disease duration and baseline LVV-adjusted $r=0.202$, $p=0.008$). The association between HHS and longitudinal LVV change was further tested by the multivariate regression model, as previously described (Supplement Table 2). In the initial regression step, only baseline LVV had a significant effect to the longitudinal LVV change (t statistics = 2.034, standardized $\beta=0.166$, $p=0.044$). On the other hand, HHS showed an additional significant effect on the longitudinal LVV change (t statistics = 2.698, standardized $\beta=0.229$, $p=0.008$). Overall, step 1 was not able to predict the longitudinal LVV change ($F_{5,170}$ = 1.426, $p=0.217$), whereas step 2 (with addition of HHS) was able to significantly predict the longitudinal LVV change ($F_{6,169}$ = 2.447, $p=0.027$).

In the tertile analysis, the highest HHS tertile had lower baseline WBV (1462.9 ml vs. 1500.6 ml, $p<0.001$), lower GMV (713.5 ml vs. 769.4 ml, $p<0.001$) and greater longitudinal LVV change (20.8% vs. 14.7%, $p=0.045$) when compared to the lowest HHS tertile in MS patients. After correction for the differences in disease duration, the longitudinal LVV change remained significant (ANCOVA $p=0.027$). All tertile-based MRI-derived measures are also described in Supplement Table 1.

In regards to clinical outcomes, the MS patient CVD-associated behavior risk score was associated with both baseline and follow-up EDSS score ($r_s = 0.34$, $p<0.001$, $r_s = 0.39$, $p<0.001$, respectively) and inversely correlated with the 5-year ARR ($r_s = -0.27$, $p=0.002$). None of the clinical associations survived the adjustment for disease duration. Moreover, the standalone diet score of the MS patients was correlated with the longitudinal 5-year T2-LV accrual ($r_s = -0.19$, $p=0.04$).

Lastly, the Framingham Coronary Heart Disease Risk Score was calculated in a smaller MS subpopulation ($n=110$, with mean 2.4% risk for myocardial infarction in the next 10 years). The Framingham Risk Score was significantly associated with HHS ($r_s = 0.523$, $p<0.001$). In terms of MRI-derived associations, greater Framingham Risk Score was associated only with lower baseline GMV ($r_s = -0.225$, $p=0.018$). In terms of clinical associations, baseline Framingham Risk Score was associated only with follow-up EDSS score ($r_s = 0.224$, $p=0.02$).

Discussion

This study demonstrates that lifestyle-based behavior linked to higher CVD risk is associated with greater central brain atrophy over 5-year period in MS patients. However, the

discrepancy between the different effect size observed in MS and HCs, indirectly points to an MS-specific and lifestyle-independent neurodegenerative process. Despite the lower associations observed in the MS population, addressing the modifiable lifestyle-based risk factors may have the potential of further reducing overall development of MS-related brain atrophy.

Cardiovascular risk factors and CVDs have been increasingly associated with greater chance of future disability in MS patients, where the risk increases with each additional CVD reported [29]. Several population-wide studies have shown that MS patients are more likely to die due to a CVD complication when compared to the age-matched population [30]. Furthermore, the prevalence of cerebrovascular comorbidities changes from a low occurrence before the MS onset, into a higher occurrence after the MS onset [31]. This increased incidence and greater CVD burden in MS patients can be potentially explained by converging inflammatory pathways [31]. A recent MRI study utilized a large number of MS patients and age-, sex-, and CVD-matched HCs and showed that MS patients present with lower neck arterial vessels size relative to HCs, potentially indicative of larger atherosclerotic burden [32]. Moreover, the MS patients demonstrated higher longitudinal narrowing in these arteries, changes which were not directly associated with the prevalence of CVD [33].

Our study showed that MS patients with unhealthier diet preferences (lower diet scores) had higher T2-LV accrual over the 5-year follow-up period. The diet score utilized in this study follows food preference compatible with the Mediterranean diet which commonly includes high consumption of fruits, vegetables, whole grains and reduced consumption of sugary beverages and red meats [34]. The Mediterranean diet has a long documented beneficial effect on cardiovascular health and might counter the CVD effect on increased MS pathology [10]. Another clinical observation of this study is the association of higher 20-year CVD-associated risk score and lower relapse rate over the 5-year follow-up period. This finding may be explained by the age dependence of the CVD score itself. Older and more CVD-prevalent MS patients are entering the progressive phase of the disease and have a lower relapse rate when compared to the disease-active but CVD-healthier RRMS group. A limited number of studies have examined the relationship between cardiovascular comorbidity and MS relapses and one, in particular, has reported a 2.6-fold relapse increase in MS patients with obesity, hypertension, and diabetes when compared to healthier MS patients [7, 35]. Furthermore, the study employed exclusion criteria on MS patients with an active relapse, thus limiting interpretations regarding the association between the CVD-based behavior and relapse rate.

The CVD-based behavior scores also showed good correlations with the overall cross-sectional brain volumes, their longitudinal change, and the WM hyperintensities in HCs (correlation coefficients ranging from 0.4 to 0.6). These significant correlations imply high dependence of healthy brain loss on both the increasing age and the CVD-based behavior, which includes obesity, smoking, alcohol use, diet, and exercise. Therefore, the 5-year longitudinal WBV and LVV changes seen in the HCs were highly associated with the composite CVD risk scores. Our findings are in line with previous studies in healthy populations demonstrating that CVD risk factors and CVD-based behavior are associated with more WM hyperintensities, lower global, and central brain volumes [36–39]. On the contrary, the 20-year CVD scores had poorer associations with the MRI outcomes measured in the MS population, described by 2- to 10-fold lower correlation coefficients. We hypothesize that this lack of fidelity is a product of disease-specific brain atrophy that is not present in HCs, thus corroborating an independent neurodegenerative aspect of MS [40, 41]. On the other hand, we additionally calculated the more traditional measure of Framingham Coronary Heart Disease Risk score which did not show comparable associations with the MRI-derived outcomes. In line with our results, previous reports showed associations between the Framingham risk score and increased MS-based disability measures (EDSS and MS severity scale) [42].

Lastly, this work demonstrates that interventional studies aimed at cardiovascular and diet modifiable risk factors would require use of disease biomarkers that have the potential of demonstrating proper responsiveness. Obtaining MRI-derived WBV, GMV, and especially LVV can be highly valuable in detecting changes within the usually short timeframe employed in such trials. On the other hand, the classically-used T2-LV and WM volume changes were not as strongly associated with the lifestyle factors. Recent technological developments within the imaging field have increased the accessibility and reliability of routine MRI use in deriving brain volumes [43]. For example, a software tool developed to measure LVV has been demonstrated to yield accurate results even with clinically acquired T2-FLAIR images [44, 45]. Moreover, deep GM volume loss has been further proposed as an MRI marker for MS disease progression throughout the entire time course of the disease [46, 47].

The 20-year CVD-based risk score and its utilization in this paper has several limitations. The calculations derived from the proposed equation establish certain impact coefficients allocated for each risk factors. For example, the negative effect of being a current smoker can be negated by only 6 weekly hours of exercise. In a similar fashion, a person that on average consumes 3 alcoholic drinks per day can negate this negatively associated behavior with an average of 9 weekly hours of exercise. However, these coefficients have been calibrated and validated within large CVD cohorts that included more than 95,000 subjects that were

followed for up to 24 years [22]. Nonetheless, it is unknown whether CVD-based behavior has the same impact on the MS disease. Furthermore, a recent analysis also showed that the presence of already diagnosed CVD can additionally influence the rate of brain atrophy [10]. Secondly, both the 20-year CVD risk score and the Framingham Coronary Heart Disease Risk Score use age as a significant risk factor for predicting future cardiovascular events. Therefore, the correction for disease duration partially or fully eliminates this component from the association analysis. In a confirmatory multivariate regression model, we did demonstrate that CVD-based behavior is able to explain larger variance of longitudinal LVV change than disease duration, clinical phenotype, baseline medication, medication switch and baseline LVV alone. Lastly, it is reasonable to assume that individuals with unhealthier lifestyle would be more likely to drop out from a longitudinal study. This would potentially introduce a study selection bias towards healthier study participants. Despite the aforementioned limitations of the score, the 20-year CVD risk score provided a validated and structured method, enabling the analysis of multiple lifestyle-based factors and their influence on mid-term clinical and MRI progression in both MS patients and HCs. Lastly, we were not able to detect and implement lifestyle-based changes during the follow-up period. A recent study showed that a considerable portion of MS patients do make lifestyle-based change within the first year from their initial MS diagnosis [48]. The MS patients from this cohort had longer disease duration and may have already made that lifestyle change (MS patients had numerically lower baseline HHS when compared to the HC group).

In conclusion, overall lifestyle-based behavior and cardiovascular health contribute to accelerated central brain atrophy in MS patients. Additionally, poorer diet was associated with higher T2-LV accrual. The relatively weaker associations of HHS, a composite measure that incorporates age, sex, exercise, diet, alcohol, and tobacco use, with the MS brain volumes may imply an independent and MS-specific process which contributes to brain atrophy. However, lifestyle-based modifications may nevertheless contribute to lowering the overall brain atrophy rate observed in the MS population.

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Compliance with ethical standards

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