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Low-fat, plant-based diet in multiple sclerosis: A randomized controlled trial

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ABSTRACT

Background: The role that dietary interventions can play in multiple sclerosis (MS) management is of huge interest amongst patients and researchers but data evaluating this is limited. Possible effects of a very-low-fat, plant-based dietary intervention on MS related progression and disease activity as measured by brain imaging and MS related symptoms have not been evaluated in a randomized-controlled trial. Despite use of disease modifying therapies (DMT), poor quality of life (QOL) in MS patients can be a significant problem with fatigue being one of the common disabling symptoms. Effective treatment options for fatigue remain limited. Emerging evidence suggests diet and vascular risk factors including obesity and hyperlipidemia may influence MS disease progression and improve QOL.

Objectives: To evaluate adherence, safety and effects of a very-low-fat, plant-based diet (Diet) on brain MRI, clinical [MS relapses and disability, body mass index (BMI)] and metabolic (blood lipids and insulin) outcomes, QOL [Short Form-36 (SF-36)], and fatigue [Fatigue Severity Scale (FSS) and Modified Fatigue Impact Scale (MFIS)], in relapsing-remitting MS (RRMS).

Methods: This was a randomized-controlled, assessor-blinded, one-year long study with 61 participants assigned to either Diet (N=32) or wait-listed (Control, N=29) group.

Results: The mean age (years) [Control -40.9 ± 8.48; Diet -40.8 ± 8.86] and the mean disease duration (years) [Control -5.3 ± 3.86; Diet -5.33 ± 3.63] were comparable between the two groups. There was a slight difference between the two study groups in the baseline mean expanded disability status scale (EDSS) score [Control -2.22 ± 0.90; Diet -2.72 ± 1.05]. Eight subjects withdrew (Diet, N=6; Control, N=2). Adherence to the study diet based on monthly Food Frequency Questionnaire (FFQ) was excellent with the diet group showing significant difference in the total fat caloric intake compared to the control group [total fat intake/total calories averaged ~15% (Diet) versus ~40% (Control)]. The two groups showed no differences in brain MRI outcomes, number of MS relapses or disability at 12 months. The diet group showed improvements at six months in low-density lipoprotein cholesterol ($\Delta = -11.99$ mg/dL; $p=0.031$), total cholesterol ($\Delta = -13.18$ mg/dL; $p=0.027$) and insulin ($\Delta = -2.82$ mg/dL; $p=0.0067$), mean monthly reductions in BMI (Rate $= -1.125$ kg/m2 per month; $p<0.001$) and fatigue [FSS (Rate $= -0.0639$ points/month; $p=0.0010$); MFIS (Rate $= -0.233$ points/month; $p=0.0011$)] during the 12-month period.

Conclusions: While a very-low fat, plant-based diet was well adhered to and tolerated, it resulted in no significant improvement on brain MRI, relapse rate or disability as assessed by EDSS scores in subjects with RRMS over one year. The diet group however showed significant improvements in measures of fatigue, BMI and metabolic biomarkers. The study was powered to detect only very large effects on MRI activity so smaller but clinically meaningful effects cannot be excluded. The diet intervention resulted in a beneficial effect on the self-reported outcome of fatigue but these results should be interpreted cautiously as a wait-list control group may not completely control for a placebo effect and there was a

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baseline imbalance on fatigue scores between the groups. If maintained, the improved lipid profile and BMI could yield long-term vascular health benefits. Longer studies with larger sample sizes are needed to better understand the long-term health benefits of this diet.

1. Introduction

The role of diet in ameliorating the severity of multiple sclerosis (MS) has been long debated, but there remains a paucity of relevant research. Observational studies by Dr. Roy Swank, published between 1953 and 2003, suggested significantly reduced MS disease activity and disability progression and longer survival in people following a diet low in total and saturated fat compared with those who did not (Swank, 1953; Swank and Goodwin, 2003; Swank, 1970). Swank's diet book, last published in 1987, remains popular among patients with MS. However, this approach to treating MS has never been subjected to a well-controlled clinical trial.

The supposed large clinical effect of the Swank low fat diet led to our hypothesis that a very-low-fat, plant-based diet might have a large effect on MRI activity. We conducted a pilot study to explore the tolerability and potential benefits of a very-low saturated fat, plant-based diet followed for 12 months by people with relapsing-remitting MS (RRMS) with the primary endpoint being brain MRI disease activity.

2. Methods

This study sought to determine whether people with MS can adhere to a very-low-fat, plant-based diet (Diet) and explore its effects on brain MRI and other MS disease-specific measures and metabolic measures. The outcomes of interest included 1) diet adherence, safety, and tolerability, 2) changes in brain MRI, MS clinical activity, fatigue and quality of life (QOL) and 3) blood lipids, insulin and high sensitivity C-reactive protein (hs-CRP) in those randomized to the Diet versus a wait-listed (Control) group. Oregon Health & Science University (OHSU) Institutional Review Board approved the study protocol. Written informed consent was obtained from all study participants. The study was registered at www.clinicaltrials.gov (NCT00852722).

2.1. Design

The study was a single-center, assessor-blinded clinical trial with subjects randomized to the Diet or Control group. After randomization, study participants, caring neurologists (VY, DB), study coordinators and the dietician knew group assignments. The blinded assessors in the study included the radiologists reviewing the MRI at the MS/MRI Research Group at the University of British Columbia, EDSS assessing neurologists and the statistician analyzing the primary and secondary outcomes. Randomization was stratified dependent upon DMT use, with random blocks of 2 and 4 generated using the Excel random number generator function. Subjects were considered to be “on treatment” if they were taking a Food and Drug Administration (FDA)-approved DMT (interferon beta-1a, interferon beta-1b, glatiramer acetate, or natalizumab) within 6 months of screening, or “off treatment” if they were on no DMT within 6 months of screening.

2.2. Participants

Subjects were recruited from the OHSU MS Center and through national advertisements by the National MS Society. Inclusion criteria were as follows: RRMS (McDonald criteria (McDonald et al., 2001; Polman et al., 2011)); abnormal brain MRI consistent with MS; MS duration < 15 years; EDSS ≤ 6.0 (Kurtzke, 1983); age 18–70 years; documented clinical relapse or active disease by MRI in the previous 2 years; baseline diet with over 30% of total daily caloric intake from fat as determined by the self-administered Nutrition Quest® Block 2005 Food Frequency Questionnaire (FFQ) (Block et al., 1994). Subjects were allowed to be on a DMT during the trial if they were on a stable dose for at least 6 months prior to screening and maintained stable treatment throughout the study. We excluded subjects who were pregnant or breastfeeding and those with any clinically significant MS exacerbation or systemic corticosteroid use within 30 days of screening.

2.3. Procedure

After enrollment, diet group subjects received residential diet training in Santa Rosa, California through the McDougall Program (Anonymous, 2014) and were then followed for 12 months. The control group received no diet training at study onset and continued their usual diet throughout the study. After study exit at 12 months, control group subjects were offered the 10-day residential diet training at no cost. The study required 6 clinic visits at OHSU. A telephone pre-screen was used to gauge interest and eligibility. Baseline visit included consent, blood draw [complete blood count (CBC), complete metabolic panel (CMP), vitamin B-12 (B12), thyroid-stimulating hormone (TSH); fasting lipid profile, serum insulin, and hs-CRP (Liposcience, Inc.®)], pregnancy test if indicated, vital signs, medical history, physical exam, EDSS, MS Functional Composite (MSFC) (Cutter et al., 1999), FFQ, Fatigue Severity Scale (FSS) (Krupp et al., 1989), MS QOL Inventory (MSQLI) (Cella et al., 1996), Beck Depression Inventory (BDI), Rapid Assessment of Physical Activity (RAPA) (Topolski et al., 2006), brain MRI, and concomitant medication check. After the baseline visit, subjects randomized to the diet group received the diet training and the control group received an exercise education seminar conducted by a licensed physical therapist within three weeks of the baseline visit. Subsequent visits occurred at months 1, 3, 6, 9, and 12 and included physical exams, MSFC, FFQ, FSS, MSQLI, BDI, RAPA, concomitant medications check, and adverse events (AEs) reporting. EDSS was completed at months 3, 6, 9 and 12. Fasting serum biomarkers including lipid profile were re-measured at months 6 and 12. The exit visit after 12 months included CBC, CMP, B12, TSH, brain MRI and blinding check.

2.4. The very-low-fat, plant-based study diet

The study diet was based on starchy plant foods (beans, breads, corn, pastas, potatoes, sweet potatoes, and rice with the addition of fruits and non-starchy vegetables). Approximately 10% of calories were derived from fat, 14% from protein and 76% from carbohydrate (Anonymous, 2014). Meat, fish, eggs, dairy products and vegetable oils (such as corn and olive oil) were prohibited.

We used monthly FFQ and telephone contact to assess diet adherence. Subjects were considered diet adherent if they consumed 20% or less of calories from fat at least 80% of the time during the study. Additional counseling in clinic or by telephone

by a trained dietician was used to help subject adherence. Diet group subjects were allowed to discuss dietary challenges with other diet group subjects or the un-blinded study team members via a secure, online discussion board or in-person meetings. The un-blinded study team members documented all correspondence between subjects. Subjects deemed to be having difficulty with diet adherence were not excluded or disqualified after consent.

2.5. Exercise

Subjects in both groups were encouraged to perform at least 30 min of moderate intensity activity at least five days a week, as recommended by the American Heart Association (Anonymous, 2014). Exercise activity (intensity, duration, and frequency) and adherence were assessed using the RAPA questionnaire completed at each clinic visit. Exercise adherence was defined as, "consistently active more than 30 min (RAPA score >5) for at least 80% of the clinic visits".

2.6. Outcomes

Study objectives were assessed through validated questionnaires or objective measures (Appendix A).

MRI was performed at OHSU and blinded MRI analysis was performed by the MS/MRI Research Group at the University of British Columbia. For each MRI visit, the following sequences were acquired in the axial plane: 3D T1 gradient echo, proton density (PD)/T2 weighted, Fluid Attenuated Inversion Recovery (FLAIR) and pre and post gadolinium-enhanced T1. MRI outcomes included a) number of new T2 lesions over 12 months, b) number of T1 gadolinium-enhancing lesions at baseline and month 12, c) number of enlarging T2 lesions over 12 months, d) change (%) in T2 lesion volume from baseline to month 12 and e) change (%) in brain volume from baseline to month 12 [Using SIENA with 3D T1 gradient echo scans and brain parenchymal fraction (BPF) with the PD/T2 scans].

2.7. Sample size and statistical analysis

The study was powered using the number of new T2 MRI brain lesions that develop over a year as the primary outcome based upon a pilot dataset of 22 subjects participating in a behavioral intervention clinical trial to reduce stress in MS (Mohr et al., 2012). Three effect sizes "small", "medium" and "large" corresponding to a reduction in the number of subjects with new T2 lesions by 44%, 78%, and 89% respectively, were simulated using bootstrapping. According to the study by Swank, subjects following his low fat diet had 70% reduction in relapse rate in the first year (baseline average relapse rate was 1.0/patient/year that decreased to 0.3/patient/year during the first year of following the diet (Swank, 1970)). Based upon the significant decrease in the MS relapses reported by Swank, we hypothesized a 90% reduction in new T2 lesion formation and thus a large effect size was plausible. With two-sided significance set at 0.05 and power of 80%, assuming the largest effect size, corresponding to a 90% reduction, after adjusting for 10% loss to follow-up and 10% non-adherence, we determined the required sample size to be 27 subjects per group.

The principal statistical analysis used linear mixed models in an intent-to-treat framework to determine the effect of the diet on the outcomes of interest. Exploratory data analysis included simple longitudinal regression of the outcome variables based on arm assignment and comparison of baseline demographics between groups using Student's *t*-tests. Final comparisons were corrected for age, gender, and MS disease severity (EDSS score). Given the large number of response variables and multiple comparisons utilizing the same regression model design, a Holm-Sidak stepwise correction was applied to the sets of model *p*-values within each of the major outcome domains (physical outcomes, serum biomarkers, MRI).

Model integrity was evaluated using standard diagnostic procedures for mixed-effect regression models. Potential outliers and leverage points were identified using Cook's Distance and visual inspection of the residual plots with outliers assessed on a subject-level basis. Outcome set normality was evaluated using quantile-quantile plots comparing the observed probability quantiles of the model residuals against the expected quantiles of the normal probability cumulative distribution function. Homogeneity of the error variance was evaluated visually using plots of model residuals against the predicted responses. All diagnostic procedures were done iteratively to verify consistency and robustness of the adjusted models.

Based on preliminary analyses, the relationship between diet and fatigue (MFIS) was further examined for causal mediation due to changes in BMI, total serum cholesterol, and insulin levels. We used models for mediation and outcome from the above described multivariate linear regression models. The analysis utilized time-dependent arm assignment as the independent variables, BMI, cholesterol, and insulin levels as the mediators and the MFIS score as the mediated outcome. Variance estimation of the average causal mediation was done using bootstrapping with 10,000 sampling iterations per model to guarantee robustness. Multiple-comparison adjusted *p*-values are indicated in the text. All analyses were carried out using R 3.1 (Anonymous) with additional utility from the 'lme4' (Bates et al., 2014),'influence. ME' (Nieuwenhuis et al., 2012), 'ggplot2' (Wickham, 2009), and 'mediation' (Tingley et al., 2014) packages.

3. Results

Subject enrollment began in July 2009 and the last subject completed the study in March 2013. Sixty-one subjects were randomized to either the Diet (N=32) or Control (N=29) intervention. Forty-four percent (27/61) of the study participants resided outside of Oregon and traveled to OHSU for the study visits (Appendix B). Among the thirty-four subjects from Oregon, twenty-five were patients referred from the OHSU MS Center. Eight subjects withdrew (Diet N=6; Control N=2). Details of subject disposition are provided in Fig. 1. The remaining subjects completed the study.

Table 1 describes the baseline characteristics of the study participants. Most subjects were on a DMT with 24/32 (75%) in the diet group and 20/29 (69%) in the control group taking a DMT. Groups were similar at baseline except for significant differences in fatigue, EDSS and gadolinium enhancing lesions on brain MRI. The groups also had similar dietary fat intake. At baseline, diet group subjects had 1) greater fatigue [Modified Fatigue Impact Scale–short version (MFIS) and FSS] than control group subjects (FSS–Control: 3.92 ± 1.51, Diet: 4.89 ± 1.39; $t=-3.56$, $p<0.001$; MFIS–Control: 6.10 ± 4.52, Diet: 9.87 ± 3.47; $t=-2.59$, $p=0.014$), 2) higher EDSS scores (Control: 2.22 ± 0.90, Diet: 2.72 ± 1.05, $t=2.36$, $p=0.043$) and 3) a higher proportion with enhancing lesions (Control: 2/29 (6.9%), Diet, 9/23 (28%); $p=0.045$) and a larger median number of enhancing lesions ($W=259$; $p=0.037$). There were no significant differences between the diet and control groups in pre-enrollment relapse rate, BMI, total cholesterol, LDL, fasting insulin levels and total brain T2 disease burden. Baseline differences were controlled for in subsequent analyses.

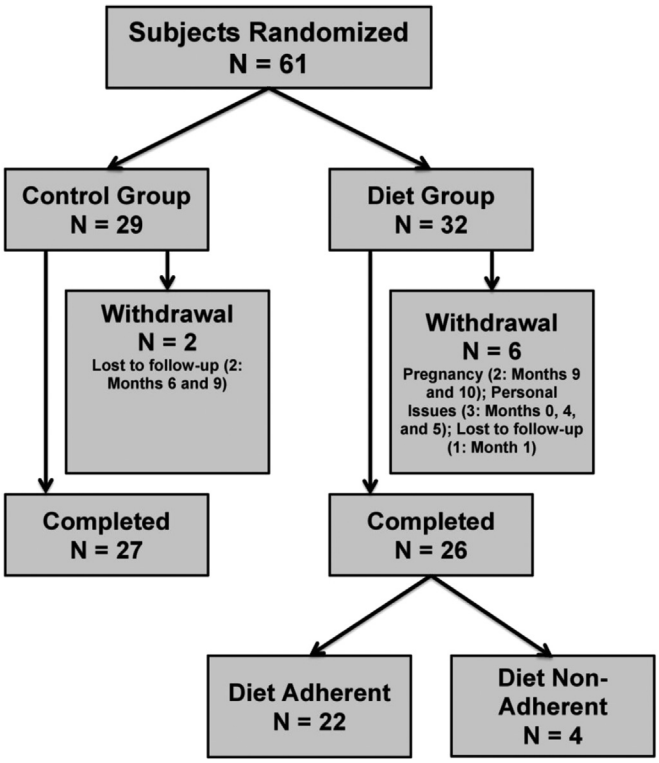


Fig. 1. Subject disposition.

3.1. Adherence, safety, and tolerability of the diet

A significant and sustained change in diet was observed in the majority of the diet group subjects during the 12 month study duration as measured by changes in the fat calories on the FFQ (Fig. 2). Importantly, 85% (22/26) of the diet group subjects were diet adherent during the 12 month study (% caloric intake as fat across 12 months: mean=14.4% ± 6.13%; median=12.8%; interquartile range [IQR=(10.6 − 16.7%); Fig. 2]. AEs were comparable between groups [76 total AEs (Diet, N=41; Control, N=35); Appendix C, D]. The groups had similar exercise adherence (Diet: 13/26; Control: 12/27) and showed no differences in RAPA scores at baseline [Controls: 6.17 ± 2.70, Diet: 6.0 ± 2.27; t=0.27, p=0.79) or at 12 months (Controls: 6.97 ± 2.80, Diet: 6.19 ± 3.98; t=0.89, p=0.38)]. Using mixed-effects modeling, neither the control group (Rate=0.037 points/month, t=0.79, p=0.27) nor the diet group (Rate= − 0.081 points/month, t= − 0.93, p=0.17) changed their activity (RAPA) significantly over the 12 month study period.

3.2. Brain MRI

After controlling for baseline MRI differences, the numbers of new T2, newly enlarging T2, T1 enhancing or combined unique active lesions revealed no differences between the two groups at 12 months (Table 2). We also found no significant changes between groups in T2 burden of disease and brain volume (for both SIENA and BPF) at 12 months. Exclusion of diet non-adherent subjects (N=4) did not change the MRI outcomes results.

3.3. Clinical MS activity (relapse rate and disability progression)

EDSS did not change significantly over the study course for either group. While MSFC performance of both groups improved significantly during the study (Standardized Rate=0.0211 SD per month; t=3.34; p_{adj}=0.0046), specifically the 9-Hole Peg Test (9HPT) (Rate= − 0.111 points/month; t= − 3.61; p_{adj}=0.0020) and Paced Auditory Serial Addition Test (PASAT) (Rate=0.380 points/month; t=5.20; p_{adj} < 0.001), these improvements did not differ between groups. Fifteen subjects (Diet, N=7; Control, N=8) had one or more relapses during the study. There was no difference between the groups in the number of relapses (χ2=1.04, p=0.59) or between arm assignment and having at least one relapse (χ2=0.00, p=1.0). Mean number of relapses over the 12-month study for the two groups were similar [Control: 0.47 (± 0.62); Diet: 0.37 (± 0.48), t=0.58, p=0.56).

Table 1
Baseline demographics of study participants.

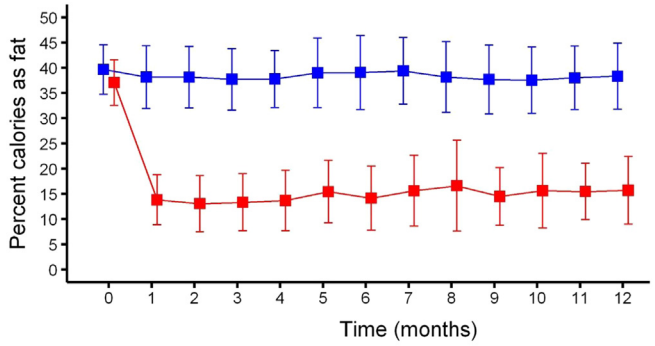
Demographic characteristics (mean ± s.d.)	Control N=29	Diet N=32
Age (years)	40.9 ± 8.48	40.8 ± 8.86
Gender		
Female, %	89.7	96.9
Male, %	10.3	3.10
Race - no. (%)		
Caucasian	25 (86.2)	26 (81.25)
African American	4 (13.8)	2 (6.25)
Hispanic/Latino	–	2 (6.25)
Other	–	2 (6.25)
EDSS score*	2.22 ± 0.90	2.72 ± 1.05
Disease duration (years)	5.30 ± 3.86	5.33 ± 3.63
Relapses in prior 2 years	1.38 ± 0.73	1.69 ± 1.33
Time since last relapse (months)	11.7 ± 5.82	12.0 ± 6.92
DMT		
None	9	8
Interferon beta-1a	9	8
Interferon beta-1b	1	3
Glatiramer acetate	10	12
Natalizumab	0	1
Blood pressure		
Systolic (mm Hg)	127 ± 16.1	124 ± 14.1
Diastolic (mm Hg)	75.4 ± 11.0	74.9 ± 11.3
BMI (kg/m^2)	28.4 ± 6.76	29.3 ± 7.42
MFIS Score*	6.10 ± 4.52	9.87 ± 3.47
FSS Score*	3.92 ± 1.51	4.89 ± 1.39
Insulin (mg/dL)	9.88 ± 6.09	12.7 ± 10.5
Total cholesterol (mg/dL)	172.8 ± 26.5	169.7 ± 34.9
LDL cholesterol (mg/dL)	114.0 ± 31.0	101.1 ± 34.1
Percent caloric intake from:		
Fat	39.67 ± 4.92	37.05 ± 4.54
Saturated fat	11.51 ± 2.15	10.58 ± 2.48
Protein	16.59 ± 3.13	15.31 ± 2.88
Carbohydrates*	43.82 ± 5.16	47.93 ± 5.87
MRI T2 disease burden (mm^3)		
Mean ± s.d.	2643.26 ± 2578.83	4959.97 ± 7279.03
Median {IQR}	1620 {1132,3100}	2662 {1418,4152}
Enhancing MRI lesions**		
Mean ± s.d.	0.11 ± 0.42	0.78 ± 2.23
Median {IQR}	0 {0,0}	0 {0,1}
N (%) Participants with baseline enhancing lesions***	2/29 (6.9)	9/32 (28)
MRI BPF	0.82 ± 0.04	0.83 ± 0.03

EDSS=expanded disability status scale, MFIS=modified fatigue impact scale–short version, FSS=Fatigue severity scale, BMI=body mass index, LDL=low density lipoprotein, DMT=disease modifying therapies, BPF=brain parenchymal fraction, s.d.=standard deviation.

* Mean arm differences seen at baseline by t-test, $p < 0.05$.
** Median arm differences seen at baseline by Wilcox test, $p < 0.05$.
*** Fisher's exact test p=0.045.

3.4. Fatigue and QOL

Fatigue (FSS and MFIS) improved significantly in the diet group over time with mean FSS improving by 0.06 points/month and MFIS by 0.23 points/month. These improvements were greater



Group sample size	0	1	2	3	4	5	6	7	8	9	10	11	12
Control	29	29	27	29	27	28	29	29	29	29	28	27	27
Low-fat diet	32	31	29	30	28	29	28	28	28	26	26	25	26

Fig. 2. Diet adherence and cohort retention. Adherence to the diet was determined by evaluating the fat content in subjects' caloric intake as recorded by monthly FFQ. Subjects in the intervention arm consistently showed reduced fat intake compared to controls throughout the entire study period.

than for the control group despite controlling for baseline differences (FSS $t=-3.88$; $p_{adj}=0.0010$, Fig. 3A; MFIS $t=-3.85$; $p_{adj}=0.0011$, Fig. 3B). After removing baseline values altogether, the MFIS rates of change (Control: 0.0654 points/month, Diet: −0.112 points/month; $t=-2.49$, $p_{adj}=0.041$) remained significantly greater in the diet group than for controls and there was a trend for a difference in FSS (Control: 0.0250 points/month; Diet: −0.245 points/month, $t=-2.37$, $p_{adj}=0.064$).

We found a trend for greater improvement in the Short Form-36 (SF-36) mental scale in the diet group compared to controls (Control: 0.0752 points/month, Diet: 0.298 points/month; $t=2.19$, $p_{adj}=0.077$) but found no improvements in other QOL and subjective measures including Pain Effects Scale (PES), Perceived Deficits Questionnaire (PDQ), Bowel Control Scale (BWCS) and the Physical SF-36.

3.5. Changes in BMI, serum markers of inflammation, and lipid metabolism

BMI reduced in the diet group significantly over the 12 month study course by an average of 0.18 kg/m^2 per month (0.5 kg/month) with most of the weight loss occurring during the first six months (Fig. 4A). This rate of weight loss for the diet group was significant after correction for their baseline weight ($t=-3.94$; $p_{adj}<0.001$) and was faster than for the control group (Control: 0.0172 points/month; Diet: −0.18 points/month; $t=-3.68$; $p_{adj}<0.001$).

Several serum metabolic biomarker levels changed in the diet group after 6 months (Fig. 4). These included reductions in LDL cholesterol (Control: −0.235 mg/dL, Diet: −11.99 mg/dL; $t=-2.79$; $p_{adj}=0.031$, Fig. 4B), total cholesterol (Control: 0.123 mg/dL, Diet: −13.18 mg/dL; $t=-2.88$; $p_{adj}=0.027$; Fig. 4C) and fasting insulin levels (Control: −0.235 mg/dL, Diet: −2.82 mg/dL; $t=-3.37$; $p_{adj}=0.0068$; Fig. 4D). Although the effect size of these changes was largely maintained after the full 12 months of intervention, the final on-treatment changes from baseline in the described biomarkers in the diet group were not significantly different from controls. The diet group showed a non-significant trend of hs-CRP reduction after 6 months compared to controls (Control: 2.20 mg/dL, Diet: −2.00 mg/dL; $t=-2.48$,

Table 2
Endpoint values of MRI parameters. The 12-month mean and median changes in brain volumes, white matter disease burden, and lesion volume were not significantly different between control and diet subjects. The counts of various lesions at 12 months also showed no difference in lesion pathology between study arms and analysis were adjusted for the baseline counts. The 95% confidence intervals for the group difference in mean/median outcomes was determined to identify the clinical upper boundary of potential outcome improvement due to the diet intervention.

MRI volume 12 month change	Control (N =27)	Diet (N=26)	Test stat	95% CI Clinical Improvement Upper Bound	*p*-value
Brain parenchymal fraction					
Mean (SE) (Control N =26)	−0.00419 (0.00197)	−0.00484 (0.00194)	t=0.24	0.00620	0.81
Median {IQR}	−0.004 {−0.011,0}	−0.002 {−0.0075,0.0035}	W=326	0.00502	0.84
SIENA brain volume % change					
Mean (SE)	−0.129 (0.213)	−0.313 (0.226)	t=0.59	0.809	0.56
Median {IQR}	−0.4 {−0.96,0.39}	−0.07 {−1.37,0.53}	W=379	0.850	0.62
T2 disease burden (mm(Swank, 1970))					
Mean (SE)[a]	275.7 (151.0)	30.5 (247.0)	t=0.85	829.6	0.40
Median {IQR}	23.7 {−104.1, 321.4}	104.1 {−400.4, 332.6}	W=369	442.5	0.76
% Change T2 disease burden					
Mean (SE)	11.1 (6.02)	10.7 (7.62)	t=0.04	19.9	0.97
Median {IQR}	1.6 {−7,18}	7.8 {−12,19}	W=358	13.9	0.91
Lesion pathology 12 month count	**Control (N =26)**	**Diet (N=26)**	**Test stat**		***p*-value**
New T2 lesions					
Mean (SE)	2.04 (1.11)	2.35 (1.19)	t=0.19	2.96	0.85
Median {IQR}	0 {0,1}	0 {0,2}	W=302	0	0.45
Newly enlarged T2 lesions					
Mean (SE)	0.423 (0.243)	0.923 (0.693)	t=0.68	0.997	0.50
Median {IQR}	0 {0,0}	0 {0,0}	W=325	0	0.73
Newly T1 enhancing lesions					
Mean (SE)	0.308 (0.206)	0.962 (0.692)	t=0.91	0.821	0.37
Median {IQR}	0 {0,0}	0 {0,0}	W=301	0	0.30
New unique lesions					
Mean (SE)	2.46 (1.33)	3.53 (2.19)	t=0.42	4.09	0.68
Median {IQR}	0 {0,1}	0 {0,2.75}	W=292	0	0.34

Mean (SE) tested using *t*-test; Median (IQR) tested using Wilcox test.

[a] Note: There was an extremely large lesion on the baseline MRI scan which had resolved considerably by the year 1 follow-up visit. All other lesions for this outlier subject were generally stable between the two scans so all of the lesion load changes can be attributed to this one very active resolving lesion.

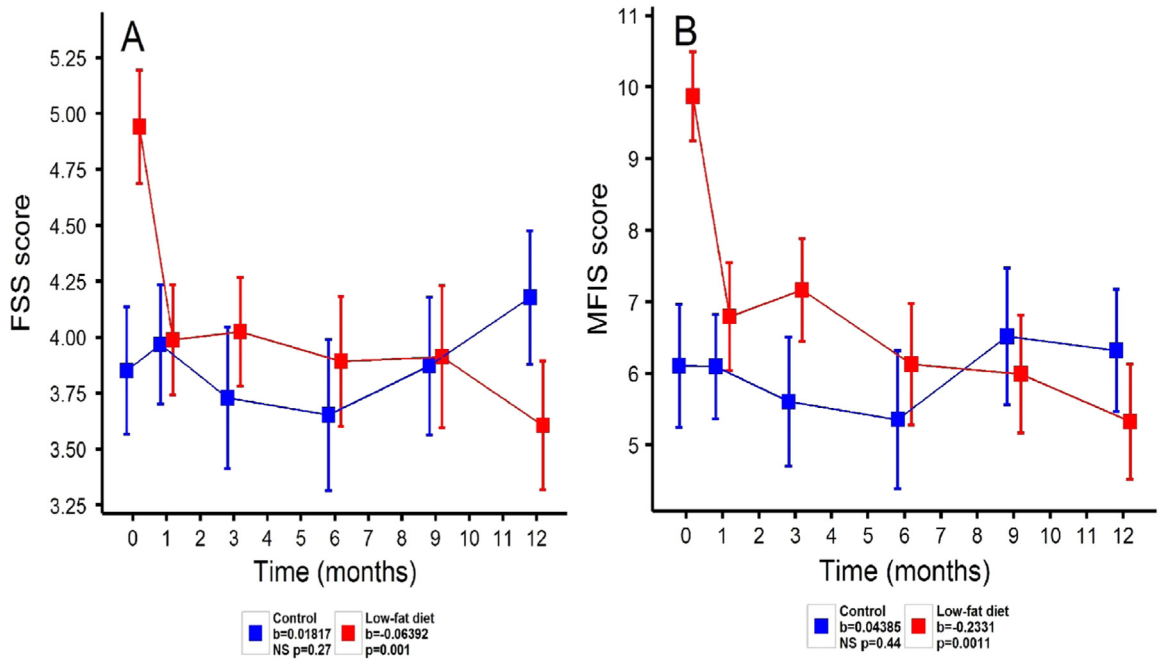


Fig. 3. Changes in fatigue. In addition to BMI, diet participants reported a significant decrease in fatigue as measured by both total FSS score (A) and MFIS score (B) when compared to controls. Over the 12 month study, intervention subjects showed an average decrease of 0.064 FSS points/month ($p_{adj}=0.0010$) and 0.23 MFIS points/month ($p_{adj}=0.0011$) even when explicitly controlling for baseline differences. Since the two arms showed a difference in fatigue at baseline, the models were rerun after removing the values at baseline. Even after baseline exclusion, the mean rates of fatigue score improvement were still significant in the intervention cohort as measured by MFIS ($p_{adj}=0.0041$) and trending in FSS ($p_{adj}=0.064$).

$p_{adj}=0.059$); however measurements after 12 months were not different. We found no group differences in the other biomarkers.

3.6. *Mediation of weight loss on fatigue and biomarkers*

We found no associative relationship between fatigue and LDL, total cholesterol or insulin levels, suggesting that the fatigue improvements and reduction in these biomarkers were independent. However, we found a significant relationship between diet intervention, weight loss and MFIS fatigue. Analysis of total effect size of diet on fatigue improvement [$d=-0.646$; CI=$(-1.389;-0.163)$; $p<0.01$] revealed a significant causal mediation that occurred through weight loss [$d=-0.201$; CI=$(-0.386,-0.061)$; $p<0.01$] while diet intervention was directly related with a non-significant trend [$d=-0.468$; CI=$(-1.016, 0.044)$, $p=0.08$]. Of the total effect of the diet on MFIS fatigue improvement, 42.5% was attributable to weight loss.

4. Discussion

This study investigated a very-low-fat, plant-based diet because prior studies by Swank suggested long-term benefits in people with MS following a low-fat diet. Based upon Swank's findings, we believed that, a large effect size on new lesion formation on brain MRI was possible and pursued this pilot trial. The current study was powered to detect a very large effect on new T2 lesions on MRI (Swank, 1953, 1970; Swank and Goodwin, 2003). We chose a "wait-list" group as a control as we were exploring the effects of the low-fat intervention as compared to a "standard American diet." In this exploratory pilot trial, we found no differences between the diet and control groups on the primary outcome of new brain T2 lesion formation, nor any of the other MRI endpoints. Additionally, MS clinical disability measured by EDSS and MSFC and relapses did not differ between the diet and control groups. The low relapse rate in both groups over the course of the study was expected since most subjects were on a DMT. However, this study showed that the diet was safe, most subjects in the diet group adhered to a very-low-fat, plant-based diet, and the diet group experienced reductions in BMI, serum LDL and total cholesterol, and fasting insulin levels. In hindsight, it was overly optimistic to power the study based on the Swank study, which was done before the availability of DMTs. Even if a low-fat, plant-based diet could reduce disease activity by 90%, this effect would be difficult to detect among patients on DMT, which reduces new brain MRI lesions and relapse rates tremendously.

Good diet adherence in this study likely reflected the effectiveness of the 10-day residential diet-training program and ongoing support from study staff and the online discussion board. Upon study completion, a majority (25/29) of the subjects in the control group attended the 10-day training program at no cost. During the diet training period, subjects in the diet group reported difficulty in limiting fat intake, but found elimination of animal products easier. Additionally, as the study progressed and the subjects reported beneficial changes in their energy levels, they appeared increasingly motivated to adhere to the diet.

Several challenges affected study recruitment. Reasons for slow recruitment of subjects were as follows: 1) stringent inclusion criteria that allowed only people with RRMS and evidence of active disease in the previous 2 years; 2) people interested in such a life style intervention were mostly clinically stable patients or patients with progressive MS; 3) people were concerned about protein intake in a plant-based and low-fat diet; 4) time commitment of the subjects for the study related visits; 5) patients eager to change their diet did not like the risk of being randomized to a wait-list group for a year. While future studies of this and other diets should follow this paradigm of participant training and support, challenges to study recruitment and retention need to be addressed.

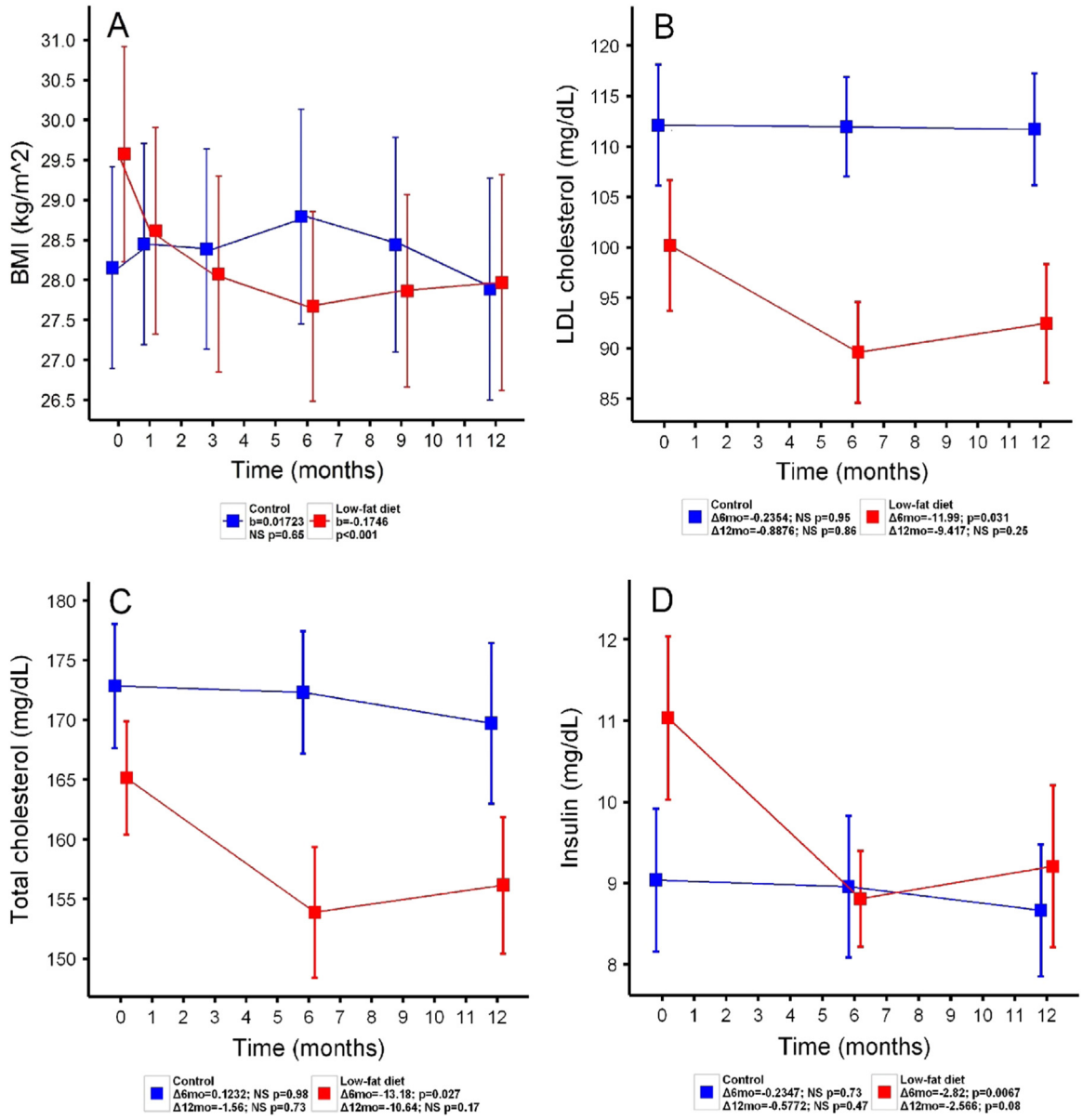


Fig. 4. Changes in BMI and biomarker profiles. Subjects in the diet group showed a significant reduction in BMI over the course of the study compared to controls (A). On average, intervention subjects had a reduction of 0.175 kg/m^2 per month (1.125 pounds per month) while no overall change was seen in control subjects. After six months of the diet, a significant reduction in LDL cholesterol (B), total cholesterol count (C), and insulin (D) was observed in intervention subjects when compared to measurements at baseline. Although these improvements were largely retained after 12 months, the biomarker profiles were not significantly different compared to baseline. Control subjects saw no changes in the biomarker profiles during the study period. All errors bars are SEM (standard error of the mean).

It is well known that despite the availability of FDA-approved therapies, MS remains a disabling disease (Noseworthy et al., 2000) and there is increasing interest in promoting healthy lifestyles in MS management (Wingerchuk and Carter, 2014; Marrie and Hanwell, 2013; Anonymous, 2015). Growing evidence suggests that vascular disease risk factors such as hyperlipidemia, hypertension, diabetes, and heart disease are common in people with MS, which may in turn, increase the risk of disability progression and increased lesion burden and brain atrophy (Marrie et al., 2010; Kappus et al., 2015). A recent 5 year study suggests that being overweight and obese significantly increases the risk of MS progression (Ben-Zacharia, 2015). Additionally, being overweight or obese increases the risk of diabetes mellitus, hypertension, hyperlipidemia and vascular disease (Pi-Sunyer, 1996; Prospective Studies Collaboration et al., 2009). Importantly, even a modest weight loss of 5–10% can lower the risk of developing obesity-associated diseases (Diabetes Prevention Program Research Group et al., 2009). Dietary intervention participants experienced reduction in weight, BMI, LDL and total cholesterol and insulin levels. These improvements would likely enhance their long-term general health if they remained on the diet. While unproven, the observation that vascular disease risk factors may accelerate MS progression, Swank's long-term follow-up of people with MS who followed his low fat diet is consistent with this possibility (Swank and Goodwin, 2003; Swank, 1970).

Fatigue is a major problem for people with MS and is difficult to treat (Kos et al., 2008). Notably, this study found fatigue improvement among participants following the dietary intervention. The effect of the active intervention on fatigue in our study was evident throughout the one-year period. While it is difficult to

predict the duration or impact of the placebo effect in clinical trials, some studies in Alzheimer's disease suggest this effect is likely short (Wilcock et al., 2000). Furthermore, the magnitude of the effect seen with diet in our study is a clinically relevant 2 points on the FSS implicating an effect beyond placebo. While comparing across trials is difficult, in a previous placebo controlled trial of modafinil (Moller et al., 2011) the placebo arm showed an improvement of 0.4 points on the FSS. Because of the subjective nature of fatigue, it is possible that the improvements resulted from increased socialization, participation in the dietary intervention, and the expectation of benefits that the wait-list control group did not have. Thus, our results suggesting that a low-fat, plant-based diet might reduce fatigue can only be considered a very preliminary, albeit interesting, observation that warrants additional investigation.

Recent studies suggest a possible link between higher BMI and fatigue in MS (Weiland et al., 2015). Exercise can also improve fatigue (Motl and Pilutti, 2012), but both groups in this study exercised to a similar extent. The causal influence analysis in the study suggested that 42.5% of the improvement in fatigue scores on the MFIS was explained by weight loss. The potential role of body weight in MS fatigue is unexplored and may be important in overweight or obese patients. These data suggest that future dietary intervention studies will need to include an isocaloric control group that does not experience weight loss.

Many people with MS are interested in dietary interventions to help manage their MS (Yadav et al., 2006). Unfortunately, due to a paucity of sound research, neurologists have little information to guide them in making dietary recommendations (Yadav et al., 2014; Farinotti et al., 2012). Furthermore, US medical schools and teaching hospitals lack adequate training to students and practitioners about healthy diets and their implementation in overall patient care. We believe this training can be an important opportunity to improve health (Lenders et al., 2013). Dietary research is inherently difficult as dietary interventions involve major modifications for the participants and methodology is challenging because although assessors can be blinded, subjects cannot, and identifying an appropriate control group can be difficult. However, sound clinical trials of dietary interventions can be performed, as illustrated by the extensive literature on the Dietary Approach to Stop Hypertension (DASH) diet (Appel et al., 1997) for cardiovascular risk factors.

5. Conclusion

This study demonstrates the practical feasibility of using a very-low-fat, plant-based diet in people with MS. While we saw no effect of the diet on MS disease activity (MRI and clinical) the study was limited by the small sample size, short duration and the use of DMT among most participants. Over the 12 month period, the diet was safe, reduced BMI, lipid and insulin levels and appeared to improve fatigue. Future larger studies should explore the potential beneficial effects of such a diet on fatigue. Presently, it remains uncertain whether a low-fat, plant-based diet will positively change the course of MS.

Disclosures

V. Yadav has served as a section editor for *Current Neurology and Neuroscience Reports*, as consultant for Bayer Healthcare Pharmaceutical, Teva Neurosciences, Biogen Idec, on the speakers' bureau of Novartis, and received research support from the McDougall Foundation, NIH, National Multiple Sclerosis Society (NMSS) Foundation, Nancy Davis Center Without Walls Foundation, and Biogen Idec.

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S. Overs has received personal compensation from Biogen Idec for travel and serving on an advisory board.

A. Riddehough is the Operations Director of the UBC MS/MRI Research Group which has been contracted to perform central analysis of MRI scans for therapeutic trials with Genzyme, Hoffmann-LaRoche, Merck-Serono, Nuron Biotech, Parexel and Sanofi-Aventis.

D. K. B. Li has received research funding from the Canadian Institute of Health Research and Multiple Sclerosis Society of Canada. He is the Director of the UBC MS/MRI Research Group which has been contracted to perform central analysis of MRI scans for therapeutic trials with Genzyme, Hoffmann-LaRoche, Merck-Serono, Nuron Biotech, Parexel and Sanofi-Aventis. He has also acted as a consultant to Vertex Pharmaceuticals and served on the Data and Safety Advisory Board for Opexa Therapeutics and Scientific Advisory Boards for Novartis, Nuron and Roche.

J. McDougall serves as the president of The McDougall Research and Education Foundation, Founder and Director of the McDougall's Health and Medical Center and served as 2010–2014) a member of the Whole Foods Market Science Advisory Board.

J. Lovera has received research support from NIH, the NMSS, and LaCats.

C. Murchison reports no relevant disclosures.

D. Bourdette has received speaker honoraria and consulting fees from Biogen Idec and Teva Neurosciences, consulting fees from Elan Pharmaceuticals, speaker honoraria from Genzyme, and research grants from the US Department of VA, NIH and NMSS.

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Appendix A. Outcome measures

FFQ: The 147-item FFQ is a modified version of the Block Questionnaire (Kurtzke, 1983). It is based on extensive population surveys and is validated by food records.

RAPA (Cella et al., 1996) was used to assess exercise adherence. The 9-item questionnaire defines activity types ranging from light to vigorous, and evaluates amount of physical activity through simple yes/no statements.

FSS (Cutter et al., 1999) and **MFIS** are well-validated scales to measure fatigue in MS. MFIS was administered as part of a larger questionnaire, the MSQLI (Krupp et al., 1989).

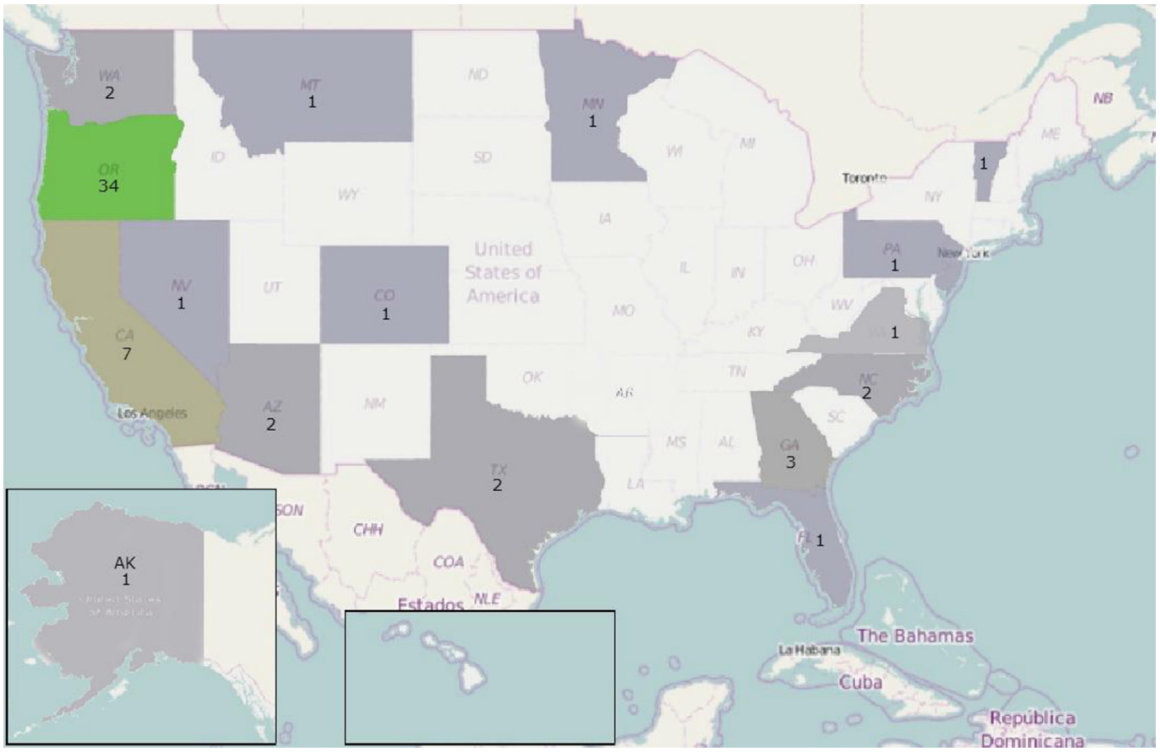
EDSS (Polman et al., 2011) and **MSFC** (Anonymous, 2014) are well-validated measures of disability and progression of disease in MS. EDSS assessment was performed by a blinded physician and MSFC by a trained study coordinator. MSFC comprises three measurements: Timed 25 Foot Walk (T25FW), 9HPT, and PASAT. Each measurement assesses MS progression based on lower extremity (T25FW), upper extremity (9HPT), and cognitive (PASAT) timed task completion.

QOL was measured using the SF-36 portion of the **MSQLI**, a 36-item questionnaire that assesses mental health and ability to perform tasks of daily living. Other QOL factors measured in MSQLI were PES, PDQ, and BWCS.

Serum biomarkers measured inflammation via hs-CRP and lipid metabolism via serum lipoprotein analysis (NMR spectroscopy) and insulin concentrations. Analysis of these biomarkers was performed at Liposcience, Inc.®, a company with expertise in advanced lipid analysis.

MS Relapse: We defined MS relapse as occurrence of new MS related neurologic symptoms or worsening of previous MS neurologic symptoms that lasted for more than 24 h in the absence of an illness/infection or unusual stress.

Appendix B. Geographical location of the residence of the study participants



Appendix C. Adverse events

Most AEs were neurologic (n=33, including relapses, fatigue, balance, and other sensory and motor phenomena) or infectious (n=25, including upper respiratory, urinary, gastrointestinal, systemic, and skin) in origin (Appendix D). Overall AEs included 2 dermatological (Control: 1; Diet: 1), 2 gastrointestinal (Control: 2; Diet: 0), 25 infectious (Control: 12; Diet: 13), 8 musculoskeletal (Control: 3; Diet: 5), 33 neurologic (Control: 15; Diet: 18), 1 psychiatric (Control: 1; Diet: 0), 2 pregnancies (Control: 0; Diet: 2) and 3 from other systems (Control: 1; Diet: 2). There was no significant association between arm assignment and type of organ system ($\chi^2=5.91$; $p=0.55$), nor an observed assignment difference in total number of AEs ($p=0.57$).

Appendix D. Adverse events by organ systems

AEs by organ system and relapses

Over the 12 month intervention period, 76 total AEs were recorded that were mainly neurologic or infectious in origin. There was no significant association between arm assignment and type of organ system ($\chi^2=5.91$; $p=0.55$) nor an observed assignment difference in total number of AEs ($p=0.57$). Additionally, no association was observed between arm assignment and number of relapses ($\chi^2=5.21$; $p=0.16$). No severe AEs were recorded in either group.

Adverse events and organ systems	Control	Diet
Dermatological		
Hives	–	1
Rash	1	–
Gastrointestinal		
Abdominal pain with constipation	1	–
Colonoscopy	1	–
Infectious		
Cold	5	1
Urinary tract	–	4
Flu	2	2
Sinus infection	3	2
Pneumonia	1	–
Shingles	–	1
Throat	–	3
Other upper respiratory	1	–
Musculoskeletal		
Total knee replacement	1	–
Dental crown lengthening	1	–
Shoulder injury	1	–
Bruised knee	–	1
Cheilectomy, surgery with osteotomy	–	1
Other musculoskeletal pain	–	3
Neurologic		
MS relapse	9	7
Fatigue	2	1
Numbness	1	3
Paresthesia	1	1
Migraine	1	–
Nonspecific visual disturbance	1	–
Weakness	–	1
Walking difficulty/imbalance	–	2
Lightheadedness	–	1
Fall	–	2
Other		
Pain	–	2
Sleep disturbance	1	–
Depression	1	–
Pregnancy	–	2

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