

Multimodal intervention improves fatigue and quality of life in subjects with progressive multiple sclerosis: a pilot study

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Background: Fatigue is a disabling symptom of multiple sclerosis (MS) and reduces quality of life. The aim of this study was to investigate the effects of a multimodal intervention, including a modified Paleolithic diet, nutritional supplements, stretching, strengthening exercises with electrical stimulation of trunk and lower limb muscles, and stress management on perceived fatigue and quality of life of persons with progressive MS.

Methods: Twenty subjects with progressive MS and average Expanded Disability Status Scale (EDSS) score of 6.2 (range: 3.5–8.0) participated in the 12-month phase of the study. Assessments were completed at baseline and at 3 months, 6 months, 9 months, and 12 months. Safety analyses were based on monthly side effects questionnaires and blood analyses at 1 month, 3 months, 6 months, 9 months, and 12 months.

Results: Subjects showed good adherence (assessed from subjects' daily logs) with this intervention and did not report any serious side effects. Fatigue Severity Scale (FSS) and Performance Scales-fatigue subscale scores decreased in 12 months ($P<0.0005$). Average FSS scores of eleven subjects showed clinically significant reduction (more than two points, high response) at 3 months, and this improvement was sustained until 12 months. Remaining subjects ($n=9$, low responders) either showed inconsistent or less than one point decrease in average FSS scores in the 12 months. Energy and general health scores of RAND 36-item Health Survey (Short Form-36) increased during the study ($P<0.05$). Decrease in FSS scores during the 12 months was associated with shorter disease duration ($r=0.511$, $P=0.011$), and lower baseline Patient Determined Disease Steps score ($r_s=0.563$, $P=0.005$) and EDSS scores ($r_s=0.501$, $P=0.012$). Compared to low responders, high responders had lower level of physical disability ($P<0.05$) and lower intake of gluten, dairy products, and eggs ($P=0.036$) at baseline. High responders undertook longer duration of massage and stretches per muscle ($P<0.05$) in 12 months.

Conclusion: A multimodal intervention may reduce fatigue and improve quality of life of subjects with progressive MS. Larger randomized controlled trials with blinded raters are needed to prove efficacy of this intervention on MS-related fatigue.

Keywords: modified Paleolithic diet, exercise, neuromuscular electrical stimulation, stress management, lifestyle changes, vitamins, supplements

Background

Approximately 74% of persons with multiple sclerosis (pwMSs) experience severe fatigue¹ and 28%–55% describe fatigue as one of their most disabling symptoms.^{2,3} Fatigue has been shown to negatively impact quality of life of pwMSs. Fatigue scores are significantly associated with impaired health perception ($P=0.03$) and role limitations due to physical dysfunction ($P=0.008$),⁴ as well as reduced vitality (adjusted $R^2=0.52$), general health (adjusted $R^2=0.21$), and mental health scores (adjusted $R^2=0.21$).⁵ In a

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survey of 6,691 subjects recruited from the North American Research Committee on Multiple Sclerosis (NARCOMS) registry, subjects with severe fatigue reported higher levels of perceived disability, as assessed with Patient Determined Disease Steps (PDDS) scale, than subjects with mild/moderate fatigue ($P < 0.0001$).¹ The most commonly utilized pharmacological agents to treat MS-related fatigue are amantadine and modafinil. However, a Cochrane Database review concluded that efficacy of amantadine on MS-related fatigue and its tolerability have been poorly documented.⁶ Similarly, a recent systemic review on amantadine and modafinil reported that there is insufficient evidence to support use of these agents for management of MS-related fatigue.⁷ Thus, the effects of fatigue are widespread and treatments that can effectively reduce this disabling symptom of MS are warranted.

Previous studies suggest that nonpharmacological interventions such as diet, exercise, and stress reduction can provide a safe and potentially beneficial treatment for MS symptoms, including fatigue.^{8–11} A recent cross-sectional study in individuals with relapsing–remitting MS (RRMS) showed that intake of vitamin D, folate, calcium, and magnesium were significantly lower than dietary reference intake values in these pwMSs.¹² Furthermore, higher fatigue scores on the modified fatigue impact scale and lower daily intake of folate ($P = 0.02$) and magnesium ($P = 0.03$) were significantly correlated. In a randomized controlled trial, significant improvements were reported in fatigue ($P = 0.0005$) and quality of life ($P = 0.0001$) for subjects in a mindfulness-based intervention, compared to usual care, over a period of 6 months.⁹ Similarly, a recent meta-analysis indicated that exercise training, especially with a resistance-training component, may be effective in reducing MS-related fatigue.¹³ In a randomized, controlled trial, progressive resistance training of the lower limbs for 12 weeks resulted in a 0.6-point reduction of Fatigue Severity Scale (FSS) scores and improved mood and quality of life in pwMSs with moderate disability.¹¹

Given the complex, multifactorial nature of MS-related fatigue, use of multiple interventions, including disease-modifying drugs, symptomatic pharmacological therapy, exercises, energy conservation, and stress management techniques, are recommended.¹⁴ An 8-week multidisciplinary program educating pwMSs about health-promoting activities, such as physical activities, fatigue, stress management, and nutritional awareness, resulted in significant improvement in mental and general health, as assessed with RAND 36-item Health Survey (Short Form-36), in the treatment group compared to the control ($P < 0.01$).¹⁵ These improvements

in mental and general health of the treatment group were maintained at the 3-month follow-up. Similarly, improvement in health-related quality of life (physical and mental health composite scores of MS quality of life-54 questionnaire; $P < 0.001$) were reported by pwMSs at 1 year and 5 years following a 5-day residential retreat, which included recommendations regarding diet, medications, exercise, and stress-reducing activities.¹⁶ A case report of a subject with secondary progressive MS showed improvement in fatigue and walking ability (transition from wheelchair dependence to mild gait disability) following the use of a multimodal intervention (as used in the current study) consisting of a modified Paleolithic diet, nutritional supplements, stretching and strengthening exercises, neuromuscular electrical stimulation (NMES), and stress management techniques.¹⁰ These findings provide preliminary evidence regarding benefits of a multidisciplinary approach for MS.

Recently, we published preliminary results on a subset of nine subjects from the current pilot study assessing the feasibility, safety, and effects on fatigue of a multimodal intervention in subjects with secondary progressive MS (SPMS) over a period of 12 months.¹⁷ This multimodal intervention consisted of a modified Paleolithic diet, nutritional supplements, stretching and strengthening exercises, NMES, and stress management techniques. Results showed that most of the subjects were able to adhere to this intervention over 12 months and no adverse side effects were reported. Moreover, these subjects showed significant reduction in their perceived fatigue within 3 months from initiation of the intervention. Here, we are reporting the effects of this multimodal intervention on perceived fatigue and health-related quality of life on all 20 subjects who participated in the study. We hypothesized that a multimodal intervention will decrease fatigue and improve quality of life. We also expected that decreased perception of fatigue would be positively correlated with increase in quality of life.

Materials and methods

Participants

Subjects with SPMS or primary progressive MS (PPMS) participated in this single-arm, open-label, pilot study. Inclusion and exclusion criteria have been described in detail previously.¹⁷ In short, subjects with confirmed diagnosis of PPMS or SPMS by a neurologist (ETS) who specializes in treating pwMSs, who had stable medical status in the previous 3 months and at least mild gait disability were recruited. Subjects with abnormal kidney or liver functions, clinically significant cognitive dysfunction, unstable heart or lung

disease, and with any implanted electronic device were excluded from the study. Subjects were recruited in two steps. The first phase of recruitment continued until ten subjects were enrolled into the 12-month main study. After this group completed 6 months of study participation, a safety report was submitted to the University of Iowa Institutional Review Board. Following the safety report review, we recruited the second group of subjects in the study. This study was approved by University of Iowa Institutional Review Board and informed consent was obtained from all subjects according to the Declaration of Helsinki. The clinical trials protocol registration number for this study is NCT01381354.

Study design

This was an open-label, single-arm, prospective, cohort study. We investigated the effects of a multimodal intervention on fatigue and quality of life of subjects with progressive MS over 12 months. Subjects were first enrolled into a 2-week run-in period, during which they were asked to follow the study diet and a stretching exercise program. At the end of the run-in period, dietary adherence of the subjects was analyzed and subjects who adhered with the study diet for 7 consecutive days during the run-in period were enrolled into the 12-month main study. All baseline assessments were completed over these first two visits. All postintervention assessments were performed at 3 months, 6 months, 9 months, and 12 months from enrollment into the main study, except safety blood analyses, which were performed at 1 month, 3 months, 6 months, 9 months, and 12 months.

Intervention

We used a multimodal intervention consisting of a modified Paleolithic diet, a home exercise program including stretching and strengthening exercises of trunk and lower limb muscles, neuromuscular electrical stimulation, stress reduction techniques, and nutritional supplements to address specific deficiencies. All components of this multimodal intervention have been described in detail previously.¹⁷ Each component of the intervention is briefly described as follows.

Study diet

A Paleolithic diet was modified to increase nutrient density and remove foods that may cause unrecognized food sensitivity issues (mediated by immunoglobulin (Ig) A or IgG antibodies or the innate immune system). The diet consisted of leafy green and sulfur-containing vegetables, intensely colored fruits and vegetables, plant and animal

proteins, seaweeds, and nondairy milks. Gluten-containing grains, eggs, and dairy products were excluded from the diet. Detailed description of the diet is provided in Table 1. Each subject's baseline food intake during the previous year was assessed with the 2007 Harvard semiquantitative food frequency questionnaire.¹⁸

Stretching exercises

A regimen focusing on gastrocnemius, hamstrings, quadriceps, and erector spinae muscles was designed for each subject during the first run-in visit. Subjects were asked to perform stretches at least 5 days per week.

Strengthening exercise and NMES

After enrollment into the main study, a home-based program was designed for each subject, which included strengthening exercises of lower limb and trunk muscles (dorsiflexors, quadriceps, hamstrings, gluteus maximus, abdominals, and back extensors) that varied in level of difficulty according to each subject's abilities (Table S1). Exercises used in the personalized program for each subject were mainly chosen from Table S1; however, modifications were made, if needed, for any subject. Most exercises were performed with concomitant use of NMES applied using a portable

Table 1 Study diet developed by T Wahls

Food item	Instruction	Recommended daily intake
Green leafy vegetables	Recommended*	Three cups cooked/six cups raw = three servings
Sulfur-rich vegetables	Recommended*	Three cups, raw or cooked = three servings
Intensely colored fruits or vegetables	Recommended*	Three cups, raw or cooked = three servings
Omega-3 oils	Encouraged	Two tablespoons
Animal protein	Encouraged	4 ounces or more
Plant protein	Encouraged	4 ounces or more
Nutritional yeast	Encouraged	One tablespoon
Milks of soy, almond, peanut, rice, and coconut	Encouraged	According to subject choice
Kelp	Encouraged	¼ teaspoon powder or two capsules
Spirulina/chlorella/klamath blue green algae	Encouraged	¼–1 teaspoon or 4–8 capsules
Gluten-free grains/starchy food	Allowed	Only two servings per week
Gluten-containing grain	Excluded	
Dairy products	Excluded	
Eggs	Excluded	

Notes: *If not able to take total nine servings of the recommended food, subjects were asked to take equal proportions of each category. Copyright © 2014. Reprinted with permission from Mary Ann Liebert, Inc. Bisht B, Darling WG, Grossmann RE, et al. A multimodal intervention for patients with secondary progressive multiple sclerosis: feasibility and effect on fatigue. *J Altern Complement Med.* 2014;20(5):347–355.¹⁷

stimulator (EMPI 300 PV). Subjects were asked to voluntarily contract the muscle as they start feeling electrical stimulation and hold the muscle contraction for 10 seconds (duration of one cycle of electrical stimulation) and then relax. Subjects were instructed to perform the exercise–NMES program 5 days per week. The first group of subjects (S1–S14) was given the option of NMES at submotor intensity during activities of daily living, but this stimulation was used by only three subjects. To simplify the intervention regimen, we removed this option from the intervention for the second group of subjects (S15–S28).

Stress management

Self-massage and meditation were added to the intervention after enrollment into the main study. We recommended 20 minutes of stress management per day.

Nutritional supplements

The first group of nine subjects was provided with several nutritional supplements¹⁷ (Table S1), which were introduced one at a time. Subjects could choose to discontinue a supplement if they experienced side effects. Large variations among subjects in supplement use was observed, and only one subject followed the whole regimen, thus making it difficult to determine any potential effects of nutritional supplementation on the first group of subjects. Given the variation and nonadherence with intake of supplements, we did not provide any nutritional supplements to the second group of eleven subjects. We referred the subjects to their primary care physician/treating neurologist for additional vitamin D supplementation for suboptimal vitamin D levels (target: 50–100 ng/mL) and for methyl folate, methyl B12, and B complex supplementation if folate and B12 were below normal range or if homocysteine was elevated beyond 7.5 μ M/L.

Outcome measures

Adherence and safety measures

Percentage of intervention adherent days was measured from subject's daily logs. Adherence with only the main components of the intervention, diet, exercises, and NMES was assessed. Subjects were considered adherent to study diet on a particular day if they consumed study-compliant food and did not consume any foods excluded from diet. If subjects performed either exercises or NMES, or both together, on a day, they were considered to have adhered to exercise–NMES. A monthly side effects questionnaire and blood analyses (complete blood count, creatinine, calcium, magnesium, and alanine aminotransferase, conducted at Iowa

City Veteran Affairs Medical Center) were used to assess any potential side effects of the intervention. Subjects were asked to record any perceived side effects of nutritional supplements, number of burns following use of NMES, and rate (0= none, 1= mild, 2= moderate, 3= severe) the following symptoms, if they experienced any, in the monthly side effects questionnaire: palpitations, joint pain, abdominal pain, chest pain, bruising, easy bleeding, diarrhea, constipation, nausea, headache, and skin rash.

Perceived fatigue

Perceived fatigue was measured with two self-reported questionnaires: 1) FSS and 2) Performance scales fatigue subscale (PS-Fatigue).^{19,20} FSS is a nine-item questionnaire in which subjects are asked to rate how fatigue affects their activities of daily life. Subjects with a mean value of ≥ 4 are considered fatigued.^{21,22} FSS is a reliable and sensitive measure and has demonstrated internal consistency and discriminative properties in pwMSs.²¹ Changes in FSS scores were considered the primary outcome. Reliability, precision, and clinically important changes of FSS were recently assessed by comparing the FSS scores at two time points separated by 6 months in subjects with MS, which suggested that a minimal detectable change of >2 points should be considered clinically significant.²³ Recently, use of either seven²⁴ or five²⁵ questions of FSS was shown to have better psychometric properties than using all nine questions (FSS-9). Thus, assessment of changes in FSS scores of seven (FSS-7) and five questions (FSS-5) was also performed. PS-Fatigue is a self-reported measure of disability associated with MS provided for use by the NARCOMS Registry. This scale assesses disability on eight domains including fatigue. On the fatigue subscale, subjects rate their fatigue compared to the level before they developed MS on a scale of 0–5 (0= normal fatigue; 5= total fatigue disability). Both criterion validity and construct validity of the fatigue subscale of PS have been demonstrated in pwMSs.^{19,20}

Health-related quality of life

Health-related quality of life was measured with the RAND 36-item Health Survey (also known as Short Form-36), a validated tool used widely to assess quality of life in pwMSs.^{26,27} This questionnaire provides the index of physical, mental, and social health for eight different outcomes: general health perceptions, physical functioning, role limitations due to physical dysfunction, energy/fatigue, emotional well-being, social function, bodily pain, and role limitations due to emotional problems. Responses to a Likert-type scale

for each item in the questionnaire were transformed to a scale of 0–100, where 100 indicated most favorable health state. Scores for each of the eight domains were calculated by averaging the scores of those items within that dimension which range from 0 (the worst score) to 100 (the best possible score).

Statistical analysis

In this intent-to-treat analysis, we used all available data and considered missing values as missing at random. A priori analyses included assessment of changes in FSS and PS-Fatigue scores over time, changes of RAND 36-item Health Survey scores over time, and relationship between FSS changes and RAND 36-item Health Survey score changes over time. Normality of the data was tested using the Shapiro–Wilk test. For normally distributed data, linear mixed model analyses with repeated measures were performed to assess changes from the baseline. Visits were modeled as fixed effect and subjects as random effect. An unstructured covariance matrix was used. Estimated means at months 3, 6, 9, and 12 were compared to the baseline values using Bonferroni correction. Correlation analyses were performed using Pearson's correlation. For nonnormally distributed data, missing values were replaced using the multiple imputations method. Friedman's tests were performed to check overall change and then pairwise comparisons were performed using the Wilcoxon signed rank test or exact sign test (as appropriate) to assess changes at each visit from the baseline. As this was an exploratory study, corrections for multiple comparisons were not performed. Spearman's correlations were derived for correlation analyses. Furthermore, subjects were divided into two groups based on their fatigue level changes during the study: high responders (>2-point decrease in average FSS-9 scores) and low responders (inconsistent or <1-point decrease in average FSS-9). Post hoc analyses were performed to compare the two groups in terms of baseline characteristics and the average adherence and dosage of different components of the interventions during the 12-month study period. Baseline characteristics of these groups were compared using the independent *t*-test (for normally distributed data) and Mann–Whitney *U*-test (for nonnormally distributed data). Average adherence and dosage of different components of the interventions during the 12-month period were compared between the two groups using independent *t*-test or Mann–Whitney *U*-test. To analyze if there were any associations between subjects' response to the intervention and their baseline characteristics, we performed correlation analyses between changes in

FSS-9 scores over 12 months and baseline characteristics of the subjects (age, duration since MS diagnosis, highly sensitive C-reactive protein level, Expanded Disability Status Scale [EDSS] scores, PDDS scores, intake of recommended [greens, sulfur-containing, and colored] and excluded foods [gluten, dairy products, and eggs]). As subject 8 was withdrawn from the study at 6 months, only the changes in her FSS-9 scores over 6 months were used for this analysis. All analyses were performed using SPSS version 22 software (IBM Corp, Armonk, NY, USA).

Results

Participants

Twenty-six subjects participated in the run-in phase, of whom 21 subjects met eligibility criteria for the main study. One subject (S10) withdrew from the study within 3 months for unknown reasons. One subject (S8) was withdrawn from the study at 6 months due to clinically significant cognitive decline. Thus, 20 subjects (18 SPMS, 2 PPMS) continued in the study for 6 months, 19 of whom completed 12 months in the study. Subjects' screening, enrollment, and follow-up during the study are shown in Figure 1. Mean age of the 20 subjects was 51.7 (standard deviation [SD]: 6.4) years and average disease duration was 14.7 (SD: 8.7) years. Demographics and baseline clinical characteristics of the subjects are presented in Table 2.

Intervention

Study diet

On average, there were 92 days between visits, and subjects completed food logs for an average of 88 days (96%). Analysis of food logs showed that subjects adhered with study diet on an average of 98%, 97%, 95%, and 94.5% days at 3 months, 6 months, 9 months, and 12 months, respectively. Average daily consumption of green, sulfur-containing, and colored fruits and vegetables was 7.8, 7.7, 7.5, and 7.3 servings at 3 months, 6 months, 9 months, and 12 months, respectively. Average daily consumption of gluten, dairy products, and eggs was 0.02, 0.03, 0.06, and 0.08 servings at 3 months, 6 months, 9 months, and 12 months, respectively.

Exercise and NMES program

Subjects completed exercise–NMES logs for an average of 90 days (97%) between visits. Exercise–NMES logs showed that subjects adhered with the program for an average of 81.6%, 81%, 78.8%, and 82.8% days at 3 months, 6 months, 9 months, and 12 months, respectively. Mean daily duration of stretches per muscle were 85 seconds, 89 seconds,

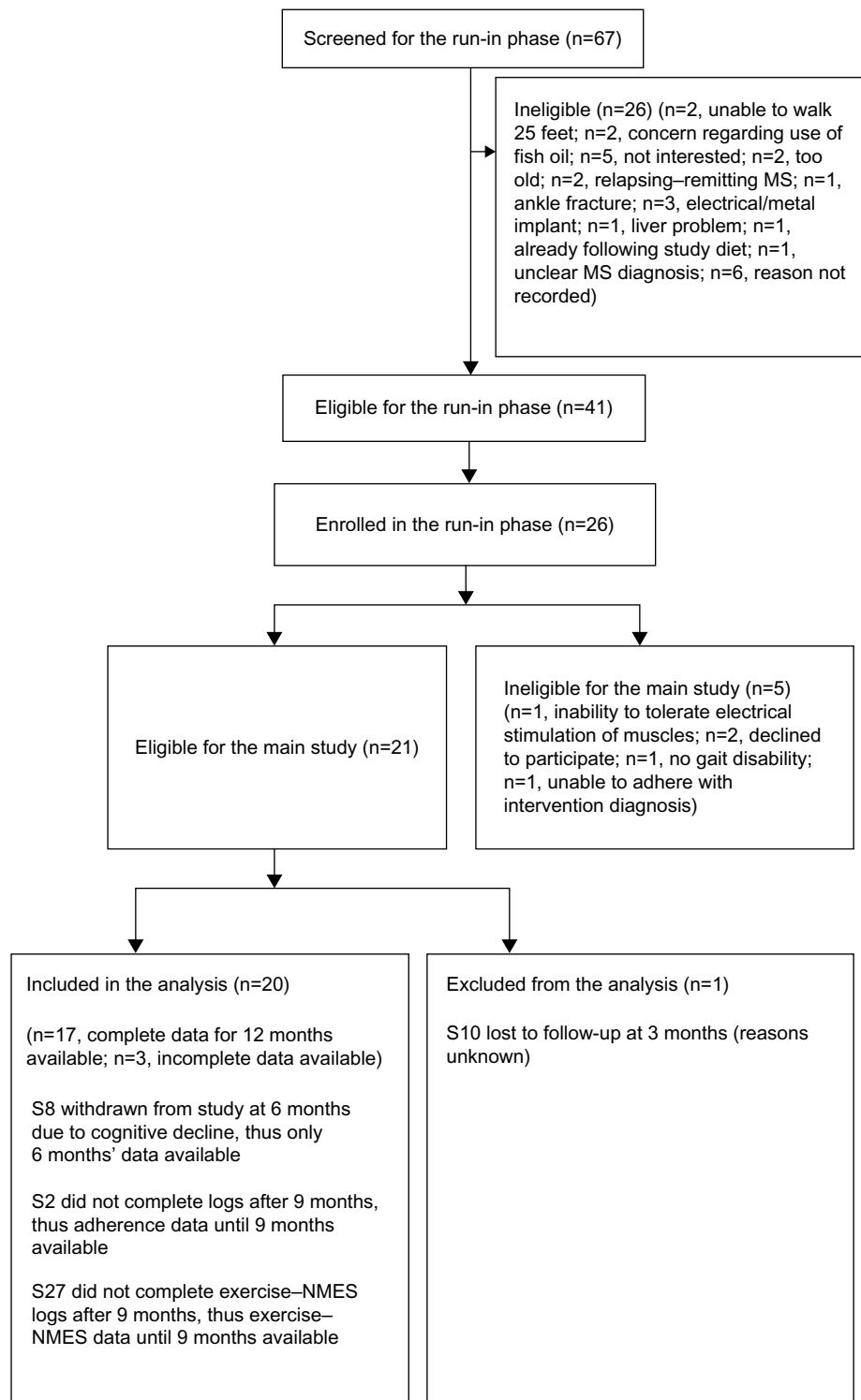


Figure 1 Flowchart of the screening, enrollment, and follow-up of participants in the study.

Abbreviations: S, subject; NMES, neuromuscular electrical stimulation; MS, multiple sclerosis.

99 seconds, and 89 seconds at 3 months, 6 months, 9 months, and 12 months, respectively. Subjects applied NMES for an average total daily duration of 52.5 minutes, 65.1 minutes, 69.2 minutes, and 64.6 minutes at 3 months, 6 months, 9 months, and 12 months, respectively.

Median duration of total daily exercises was 9.2 minutes, 8.9 minutes, 13.6 minutes, and 17 minutes at 3 months, 6 months, 9 months, and 12 months, respectively. Although subjects applied electrical stimulation for 5–60 minutes on a particular muscle group, they performed exercises only for

Table 2 Demographics and baseline characteristics of the subjects in the main study

Subject ID	Age (years)	Sex/race	MS duration (years)	MS type	Baseline EDSS	Walking aid	Education	DMDs ^a	FSS-9 (scores)
S1	45.6	F/C	10	SPMS	6	–	High school	Interferon beta-1a	5.9
S2	53.8	F/C	14	SPMS	6	Cane	Some college		7.0
S3	54.2	F/C	20	SPMS	6.5	Walker	Masters		5.6
S5	57.3	F/C	11	SPMS	6.5	Walker	Masters	Interferon beta-1a	6.4
S6	52.5	F/C	3	SPMS	6	–	Some college		6.9
S8	55.2	F/C	35	SPMS	6.5	Walker	Masters		5.2
S9	52.2	F/C	25	SPMS	6	Cane	2-year associate	Glatiramer acetate	3.1
S11	54.8	F/C	11	SPMS	6	–	Bachelor		5.3
S14	45.9	M/H	13	SPMS	6.5	Poles	Doctorate (MD)	Interferon beta-1b	7.0
S15	54.8	F/C	10	SPMS	6.5	Walker	Bachelor		4.4
S16	39.6	F/C	4	SPMS	7	Walker	Bachelor		7.0
S17	66.0	F/C	4		6.5	Brace + cane	2-year associate		6.7
S18	57.7	M/C	6	PPMS	8	FES + walker	2-year associate		4.4
S19	55.4	M/C	27	SPMS	7	Walker	Masters		3.1
S20	47.3	F/C	19	SPMS	7	Walker	Masters		5.4
S21	53.7	F/C	10	SPMS	6.5	Cane	Masters	Natalizumab	6.6
S22	47.8	F/C	17	SPMS	6	Cane	Masters	Naltrexone hydrochloride	5.8
S26	37.6	M/C	8	SPMS	3.5	–	2-year associate		4.6
S27	52.9	M/C	21	SPMS	6.5	Cane	Masters	Glatiramer acetate	4.0
S28	50.3	F/C	25	SPMS	4	–	Bachelor	Interferon beta-1a	5.4
Mean	51.7		14.7		6.2				5.5
SD	6.4		8.7		1.0				1.2

Notes: ^aSubjects chose to take DMDs although they understood that DMDs are not considered effective therapy for SPMS. Copyright © 2014. Adapted with permission from Mary Ann Liebert, Inc. Bisht B, Darling WG, Grossmann RE, et al. A multimodal intervention for patients with secondary progressive multiple sclerosis: feasibility and effect on fatigue. *J Altern Complement Med.* 2014;20(5):347–355.¹⁷

Abbreviations: Brace, ankle brace; C, Caucasian; DMDs, disease-modifying drugs; EDSS, Expanded Disability Status Scale; F, female; FES, dorsiflexion assist functional electrical stimulation; FSS-9, nine-item Fatigue Severity Scale; H, Hispanic; M, male; MS, multiple sclerosis; PPMS, primary progressive MS; SD, standard deviation; SPMS, secondary progressive MS; MD, Doctor of Medicine.

a part of that time and took rest between exercise repetitions to prevent muscle fatigue.

Meditation and massage

Subjects meditated each day for a median duration of 9.4 minutes, 12.9 minutes, 9.2 minutes, and 9.5 minutes at 3 months, 6 months, 9 months, and 12 months, respectively. Average daily duration of massage was 7.7 minutes, 7.7 minutes, 9.8 minutes, and 6.8 minutes at 3 months, 6 months, 9 months, and 12 months, respectively.

Side effects

No serious side effects were reported. The following side effects (number of subjects) were perceived as being due to the intake of nutritional supplements by the first nine subjects (S1–S14): bloating (1), nausea (3), stomach upset (1), diarrhea (2), constipation (1), intestinal problem (1), irritability (1), fatigue (1), headache (1), and flushing with rash (1). These symptoms were resolved by reducing/eliminating nutritional supplements that were suspected to be the cause of the side effect. Overall, during the 12-month intervention, subjects reported the following symptoms (number of subjects) in mild intensity: joint pain (6),

abdominal pain (4), chest pain (2), bruising (6), easy bleeding (3), diarrhea (5), constipation (11), nausea (6), headache (11), palpitations (1), and skin rash (2), with the following side effects at moderate intensity: joint pain (3), abdominal pain (2), chest pain (3), bruising (3), diarrhea (3), constipation (5), nausea (6), and headache (1). Severe constipation and diarrhea, each in one subject, were also reported. It was not clear whether these symptoms were due to the intervention or were associated with the subject's disease as we did not assess frequency of such symptoms at baseline. S5 and S11 reported experiencing skin burn once, S3 and S19 twice, and S27 thrice following use of NMES during the study. Subjects were asked to call the study physical therapist if they experienced any problem or if they had any questions. However, none of the subjects called the physical therapist to talk about skin burns. These subjects informed the physical therapist about the skin burns only during their subsequent visit. No abnormal changes in subjects' skin were observed during any of the study visits. Thus, the skin burns experienced by subjects were presumably minor. None of the subjects discontinued any component of the intervention due to side effects. All subjects' safety blood biomarkers remained within normal limits during the study period, except in three subjects, who

had higher-than-normal alanine aminotransferase levels at some time point during the study, which decreased to normal limits during subsequent visits.

Perceived fatigue and quality of life

Fatigue

Perceived severity of fatigue decreased substantially in the entire group. The primary outcome measure, mean FSS-9 scores decreased by 1 point or more from baseline to assessments at 3 months, 6 months, 9 months, and 12 months ($P < 0.0005$, Figure 2). Average baseline score of FSS-9 was 5.5, which suggests that on average subjects were severely fatigued. Out of 20 subjects, 18 (90%) had severe fatigue (FSS-9: ≥ 4) and only two (10%) subjects had mild/moderate fatigue reported as < 4 on FSS-9 at baseline (Table 2).^{21,28} Mean FSS-9 scores of eleven subjects (55%) showed clinically significant decrease (> 2 points) from baseline to each time point of the study. These subjects were considered high responders. These subjects had mean FSS-9 scores of 5.5 at baseline, which decreased by 2.2 (95% confidence interval [CI]: -3.0 to -1.4), 2.3 (95% CI: -3.2 to -1.3), 3.0 (95% CI: -3.8 to -2.2), and 3.1 (95% CI: -4.2 to -2.0) at 3 months, 6 months, 9 months, and 12 months, respectively. The remaining subjects ($n=9$) were considered low responders as they either showed inconsistent or < 1 point decrease in mean FSS-9 scores during the 12 months. These subjects had mean FSS-9 scores of 5.5 at baseline and showed an average decrease by 0.8 (95% CI: -1.7 to $+0.1$), 0.4 (95% CI: -0.8 to 0), 1.1 (95% CI: -2 to -0.2), and 1.3 (95% CI: -2.8 to $+0.2$)

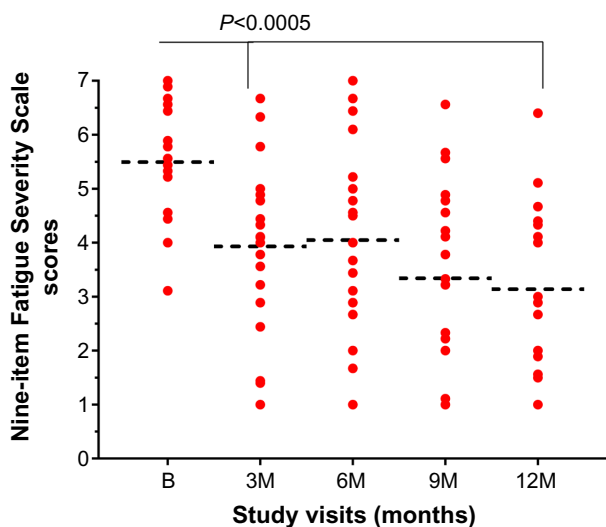


Figure 2 Subject's nine-item Fatigue Severity Scale scores during the study.
Notes: Red dots represent individual subject scores and dotted lines represent mean scores. $P < 0.0005$, statistical significant change from baseline to 3, 6, 9 and 12 months.
Abbreviations: B, baseline; 3M, 3 months; 6M, 6 months; 9M, 9 months; 12M, 12 months.

at 3 months, 6 months, 9 months, and 12 months, respectively. Fatigue scores of the entire cohort on FSS-7 and FSS-5 showed a significant decrease by 1 point or more from baseline to 3 months, 6 months, 9 months, and 12 months ($P < 0.0005$ at each time point). Perceived fatigue of the entire cohort, as measured by the PS-Fatigue subscale, also decreased at 3 months, 6 months, 9 months, and 12 months compared to baseline ($P < 0.05$ at each time point) (Figure S1). Median (interquartile) values of PS-Fatigue subscale scores were 3 (2–3) at baseline, which decreased to 2 (1–2.75) at 3 months, 1.5 (1–3) at 6 months, 1.2 (0–2) at 9 months, and 0.82 (0–2) at 12 months after the intervention.

Health-related quality of life

Scores on the Short Form-36 energy and general health scores increased significantly ($P < 0.05$) during the study (Figure 3). Average general health scores (95% CI) increased from baseline by 11.3 (3.8–18.7, $P=0.002$), 12 (2.5–21.5, $P=0.01$), 13.8 (2.1–25.5, $P=0.017$), and 13.8 (1.7–25.8, $P=0.021$) at 3 months, 6 months, 9 months, and 12 months, respectively. Average energy scores (95% CI) showed an increase from baseline by 13 (-0.8 to 26.8, $P=0.072$), 16.8 (2.0 to 31.5, $P=0.022$), 21.7 (5.6 to 37.9, $P=0.006$), and 20 (4.5 to 35.6, $P=0.008$) at 3 months, 6 months, 9 months, and 12 months, respectively. Friedman's test showed no significant change in other Short Form-36 subscale scores; however, median scores of physical functioning, role physical, pain, and social functioning showed a trend toward increase (improvement) from baseline during the 12 months (Figure S2).

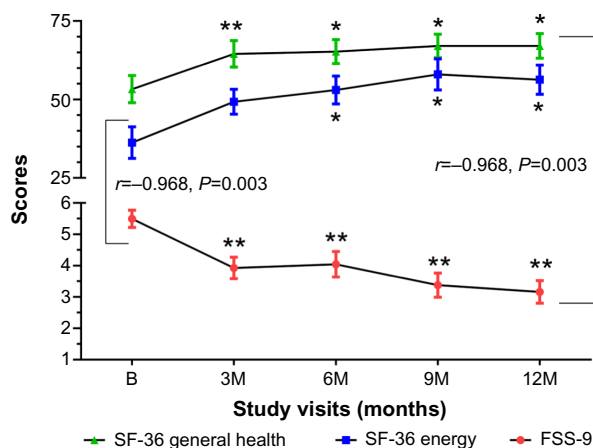


Figure 3 SF-36 energy, SF-36 general health and FSS-9 scores during the study, and correlation of mean SF-36 energy and mean SF-36 general health scores with mean FSS-9 scores at different time-points during the study.

Notes: Data is shown as mean \pm SE. $r =$ Pearson's correlation coefficient. $**P < 0.005$, $*P < 0.05$ for significant difference from baseline.

Abbreviations: B, baseline; 3M, 3 months; 6M, 6 months; 9M, 9 months; 12M, 12 months; SF-36, Short Form-36; FSS-9, nine-item Fatigue Severity Scale; SE, standard error.

Association of FSS-9 scores with health-related quality-of-life outcome scores

The primary outcome measure, FSS-9 score, showed strong negative correlations with Short Form-36 energy scores at baseline ($r=-0.649$, $P=0.001$), 3 months ($r=-0.623$, $P=0.001$), 6 months ($r=-0.705$, $P<0.0005$), 9 months ($r=-0.764$, $P<0.0005$), and 12 months ($r=-0.790$, $P<0.0005$). Similarly, Short Form-36 general health scores were negatively correlated with FSS-9 scores at baseline ($r=-0.400$, $P=0.040$), 3 months ($r=-0.475$, $P=0.017$), 6 months ($r=-0.566$, $P=0.004$), and 12 months ($r=-0.790$, $P=0.007$) of the study. In addition, mean FSS-9 scores at baseline, 3 months, 6 months, 9 months, and 12 months correlated very strongly with mean energy ($r=-0.968$, $P=0.003$) and mean general health scores ($r=-0.968$, $P=0.003$) at baseline, 3 months, 6 months, 9 months, and 12 months, respectively (Figure 3).

High responders vs low responders

Comparison of baseline characteristics of the high responders and low responders showed that they differed significantly in terms of physical disability (EDSS, PDDS, and Short

Form-36 physical functioning scores) and intake of gluten, dairy products, and eggs (Figure S3). EDSS scores (median, interquartile range) of high responders were significantly lower (6, 6–6.5) than those of low responders (6.5, 6.5–7); $U=7.5$, $Z=-3.35$, $P<0.0005$ (Figure S3A). Similarly, high responders reported significantly lower PDDS scores (median: 5 vs 6, $P=0.009$; Figure S3B) and higher level of SF-physical functioning scores (median: 15 vs 5, $P=0.031$; Figure S3C) compared to low responders. Additionally, high responders were taking fewer mean (\pm SD) daily servings of gluten, dairy products, and eggs (3.58 ± 1.6) compared to low responders (6.15 ± 2.93) at baseline ($t_{11,84}=-2.36$, $P=0.036$, Figure S3D). Other baseline characteristics (age, duration of MS, mean daily servings of green, sulfur-containing, and colored fruits and vegetables, vitamin D, and highly sensitive C-reactive protein level and all Short Form-36 subscale scores except physical functioning) were not significantly different, and each group reported on average high fatigue scores at baseline (high responders: 5.51, and low responders: 5.46).

Over the 12-month intervention, average daily duration of massage (median: 8.7 minutes vs 4.7 minutes, $P=0.006$)

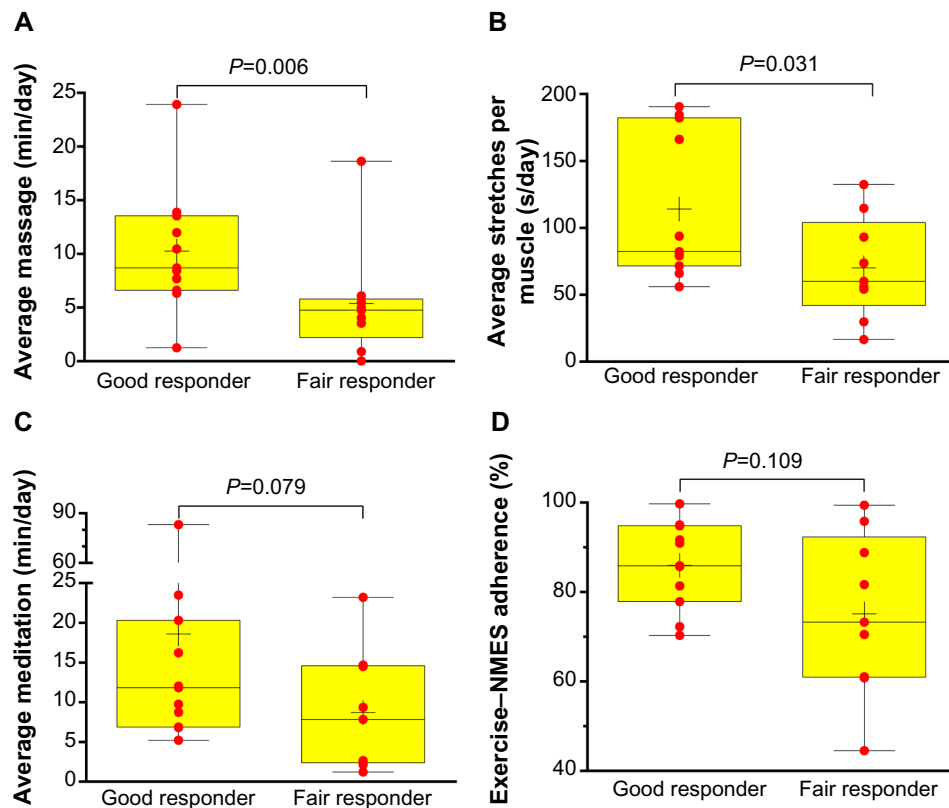


Figure 4 Comparison of good- and fair-responders' dosage of (A) average massage duration, (B) average duration of stretch per muscle, (C) average duration of meditation per day and (D) average exercise-NMES adherence during 12 months.

Notes: Upper and lower borders of the boxes represent 25th and 75th percentiles respectively. The line within the boxes represents median and + sign represents mean. The whisker error bars represent minimum and maximum values. Red dots represent each subject's score.

Abbreviation: NMES, neuromuscular electrical stimulation.

and stretches per muscle (median: 82 seconds vs 60 seconds, $P=0.031$) were comparatively higher in high responders than in low responders (Figure 4A and B). High responders also showed a strong trend toward longer average daily duration of meditation (median: 11.8 minutes vs 7.9 minutes, $P=0.079$) and higher average exercise–NMES adherence (median: 85.9% vs 73.3%, $P=0.109$) than low responders (Figure 4C and D). Dosage of other components of the intervention during the study period did not differ significantly between the two groups.

Associations between changes in FSS-9 scores over 12 months and baseline characteristics

Decrease in FSS-9 scores from baseline to 12 months showed moderate associations with shorter duration of MS ($r=0.511$, $P=0.011$), lower baseline PDDS scores ($r_s=0.563$, $P=0.005$), and lower baseline EDSS scores ($r_s=0.501$, $P=0.012$) (Figure 5). After excluding data from two subjects (S26, S28), who had much lower EDSS scores than other subjects (circled values in Figure 5C), the correlation between changes in FSS scores in 12 months and baseline EDSS scores stayed moderately positive ($r_s=0.482$, $P=0.022$). Other baseline characteristics showed weak associations ($r<0.300$) with changes in FSS scores over 12 months.

Discussion

This study suggests that a multimodal intervention is safe and may reduce fatigue and improve health-related quality of life of subjects with progressive MS. However, larger randomized controlled trials with blinded raters are needed to prove the efficacy of this intervention on MS-related fatigue. Baseline characteristics modulated the responses to this multimodal intervention; subjects with moderate disability and, on average, consuming <4 servings of excluded food (gluten, dairy products, and eggs) per day at baseline showed clinically significant reduction in fatigue at 3 months and sustained that improvement for 12 months. Longer durations of stretching and massage were also significant factors related to improving subject's fatigue during the study.

We used self-reported measures of fatigue because subjects' self-reports are considered the most appropriate method to assess such fatigue.²⁹ We observed statistically significant improvement in perceived fatigue at all time points of the study regardless of the instrument used. In the current study, average reduction of >1 point in FSS-9 scores was observed at 3 months and further reduction in fatigue was reported by most subjects during subsequent visits. These results indicate larger beneficial effects of this multimodal intervention on MS-related fatigue compared

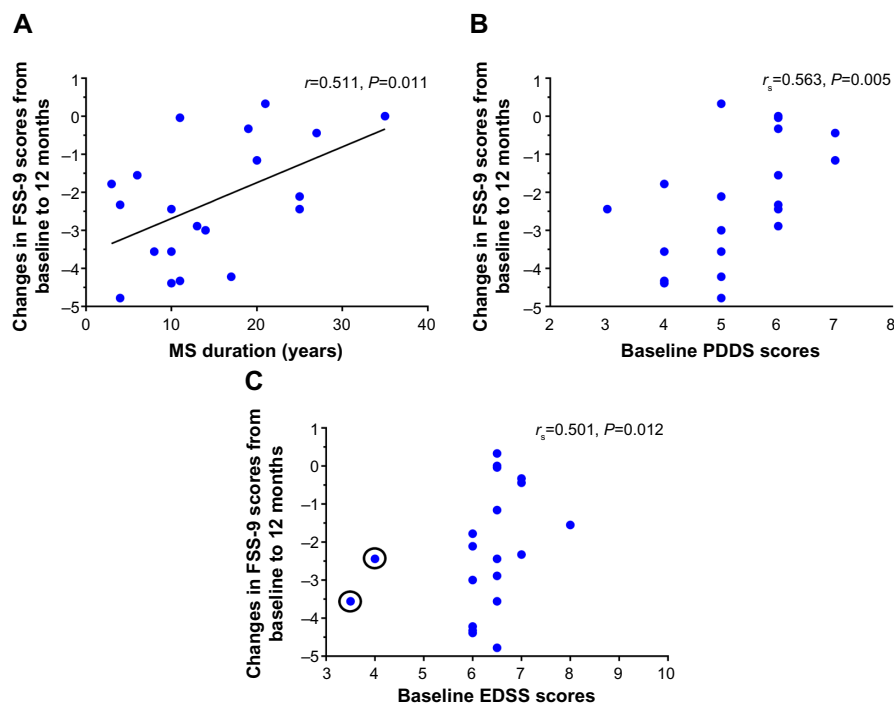


Figure 5 Correlations between changes in FSS-9 scores and (A) duration since MS diagnosis, (B) baseline PDDS scale scores, (C) baseline EDSS scores.

Notes: r , Pearson's correlation coefficient; r_s , Spearman's correlation coefficient. After excluding data of two subjects (circled dots in C) with much lower baseline EDSS scores than other subjects, correlation stayed moderately positive ($r_s=0.482$, $P=0.022$).

Abbreviations: EDSS, Expanded Disability Status Scale; MS, multiple sclerosis; PDDS, Patient Determined Disease Steps; FSS-9, nine-item Fatigue Severity Scale.

to pharmacological agents, such as amantadine, modafinil, and aminopyridine, which are usually prescribed but have shown only suboptimal and inconsistent effects and troublesome side effects.^{30–32} It is worth noting that eleven out of 20 subjects in the current study showed clinically significant improvement (≥ 2) from baseline at 3 months and sustained that improvement until 12 months. Moreover, subjects in this study were in the progressive phase of MS, and most had moderate to severe disability; thus, it is unlikely that subjects would show spontaneous improvement during the 12-month study period. It is doubtful that the robust improvement in perceived fatigue we observed is solely due to a placebo effect, although a major contribution of placebo effect cannot be denied. Thus, results of this study should be interpreted with caution. In summary, this multimodal intervention is probably a beneficial treatment for MS-related fatigue. Further studies are needed to fully assess the efficacy of this multimodal intervention on MS-related fatigue.

Although to date no other study has investigated the effects of a multimodal intervention that included diet, exercise, NMES, and stress management on perceived fatigue, previous studies discussed earlier have reported some beneficial effects of exercise, diet, NMES, relaxation, and energy conservation techniques on MS-related fatigue^{9,11,33,34} and thus support our findings. Notably, the above-mentioned studies included subjects with 1) RRMS and 2) less disability than those in the present work, and some used a modified fatigue impact scale, which is positively correlated with FSS ($r=0.66$).³⁵ The robust improvement in fatigue observed in the current study may have been due to the combined effects of all the intervention components, but studies comparing the effects of the individual components to their combined effect are needed to elucidate whether improved fatigue is primarily due to a single component of the intervention or due to the synergic interactions of multiple components.

As fatigue decreased, the energy and general health scores improved throughout the study, suggesting that fatigue affected the quality of life, which is consistent with results from previous studies.^{4,5} Although the above studies also included subjects with RRMS and most subjects had lower physical disability than those in the present study, they suggest that fatigue affects different domains of health-related quality of life. It is reasonable to suggest that reduction of fatigue following this multimodal intervention may lead to improved quality of life.

Although there was high variability in subjects' baseline characteristics, the results indicate that subjects with

lower level of physical disability, shorter duration since MS diagnosis, and lower consumption of gluten, dairy products, and eggs at baseline responded better to this multimodal intervention. Similarly, a study reporting beneficial effects of a low-fat diet on mortality and disability in pwMSS showed that greater benefits were experienced by subjects with minimal disability at baseline compared to those with severe disability.³⁶ Subjects with severe disability and longer disease duration may have greater disease burden and may need a longer intervention period than 12 months to show improvement. Further studies investigating the role of gluten, dairy products, and eggs on MS pathophysiology may shed some light on these questions.

High responders reported higher duration of daily massage and stretches per muscle during the 12-month intervention period and also showed a strong trend toward higher duration of meditation and adherence with the exercise–NMES program compared to low responders. These findings underscore the potential importance of these components of the intervention and also show that high responders were following the intervention more closely than low responders. We did not include duration of stretches, massage, and meditation into the adherence data and did not emphasize these components as much as diet and exercise–NMES because of the effort and time required to complete all components of the intervention each day. Our findings suggest that high responders were following all individual components of the intervention more often than low responders. A recent study showed that 5 weeks of massage therapy, exercise therapy, and combined massage–exercise therapy produced similar effects on fatigue (mean FSS-9 score reduction: 1.2 to 1.5) which were better than the results in controls (mean increase by 0.4 points).³⁷ Thus, it is not clear whether any one component or a combination of treatments is more effective in reducing fatigue.

Importantly, this complex combination of interventions was safe as mostly mild-to-moderate side effects were observed in a small number of subjects. Five subjects experienced skin burns following use of NMES. This raises concerns about unsupervised use of NMES by these subjects. Several factors, such as type of electrodes (pregelled vs with no gel) and subjects' skin condition could have contributed to the burns. Because most of the subjects were able to use NMES at home without any side effects and also because the reported side effects appeared to be minor, we think that NMES can be recommended for home use in subjects with MS, but detailed instructions should be provided.

Currently available pharmacological treatments for MS-related fatigue can potentially result in side effects such as

anxiety, blurred vision, anorexia, epileptic seizures and so on.⁶ Safer options to treat MS-related fatigue are needed and the current work shows that nonpharmacological treatments may improve perceived fatigue and quality of life with minimal side effects.

Conclusion

A multimodal intervention including modified Paleolithic diet, nutritional supplements, stretching and strengthening exercises, NMES, and stress management techniques can be safely implemented by subjects with progressive MS. This intervention decreased perception of fatigue and improved health-related quality of life, particularly in subjects with mild-to-moderate disability and relatively lower baseline consumption of gluten, dairy products, and eggs. Randomized controlled studies are needed to fully establish the efficacy of this multimodal intervention on MS and to elucidate mechanisms underlying its effects on MS.

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Disclosure

Dr Terry Wahls has equity interest in the following companies: Dr Terry Wahls LLC; TZ Press LLC; Xcellerator LLC; RDT LLC; and the website <http://www.terrywahls.com>. She also owns the copyright to the books *Minding My Mitochondria (2nd Edition)* and *The Wahls Protocol*, and the trademarks The Wahls Protocol and Wahls Diet. She receives royalty payments from Penguin Random House. Dr Wahls

has conflict of interest management plans in place with both the University of Iowa and the Veterans Affairs Iowa City Healthcare System. All the other authors report no conflicts of interest in this work.

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Supplementary materials

Table S1 List of exercises and the muscle group stimulated during the particular exercise

Exercises	Muscle group stimulated
Supine dorsiflexion	Dorsiflexors
Sitting dorsiflexion	
Dorsiflexion with weight	
Standing toe raise	
Sit/prone plantar flex	No neuromuscular electrical stimulation
Plantar flex with weight	
Standing heel raise	
Hip flexion in sitting	Quadriceps
Supine hip flexion without/with weight	
Isometric quadriceps	
Terminal knee extension	
Sitting knee extension without/with weight	
Hamstrings sets	
Supine hip and knee flexion	
Prone knee flexion without/with weight	
Isometric gluteal contraction	Gluteus maximus
Hip abduction in supine position	
Hip abduction without/with weight	
Hip extension without/with weight	
Bridging/single leg bridging	Erector spinae
Back extension with elbow support	
Back extension	
Pelvic tilt	Abdominals
Crunch	
Side crunch	
Right angle bridge	
Wall slides/squatting	No neuromuscular electrical stimulation
Four-point kneeling with upper and/or lower limb lift	No neuromuscular electrical stimulation

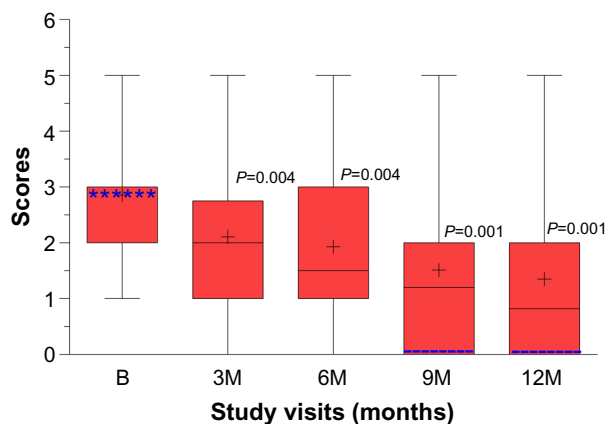


Figure S1 Subject's Performance Scales-fatigue scores during the study.
Notes: Upper and lower borders of the boxes represent 25th and 75th percentiles respectively. The line within the boxes represents median and + sign represents mean. The whisker error bars represent minimum and maximum values. **** represent median values overlapping with upper quartile values. ----- represent lower quartile values overlapping with minimum values. *P*= significant difference from baseline.
Abbreviations: B, baseline; 3M, 3 months; 6M, 6 months; 9M, 9 months; 12M, 12 months.

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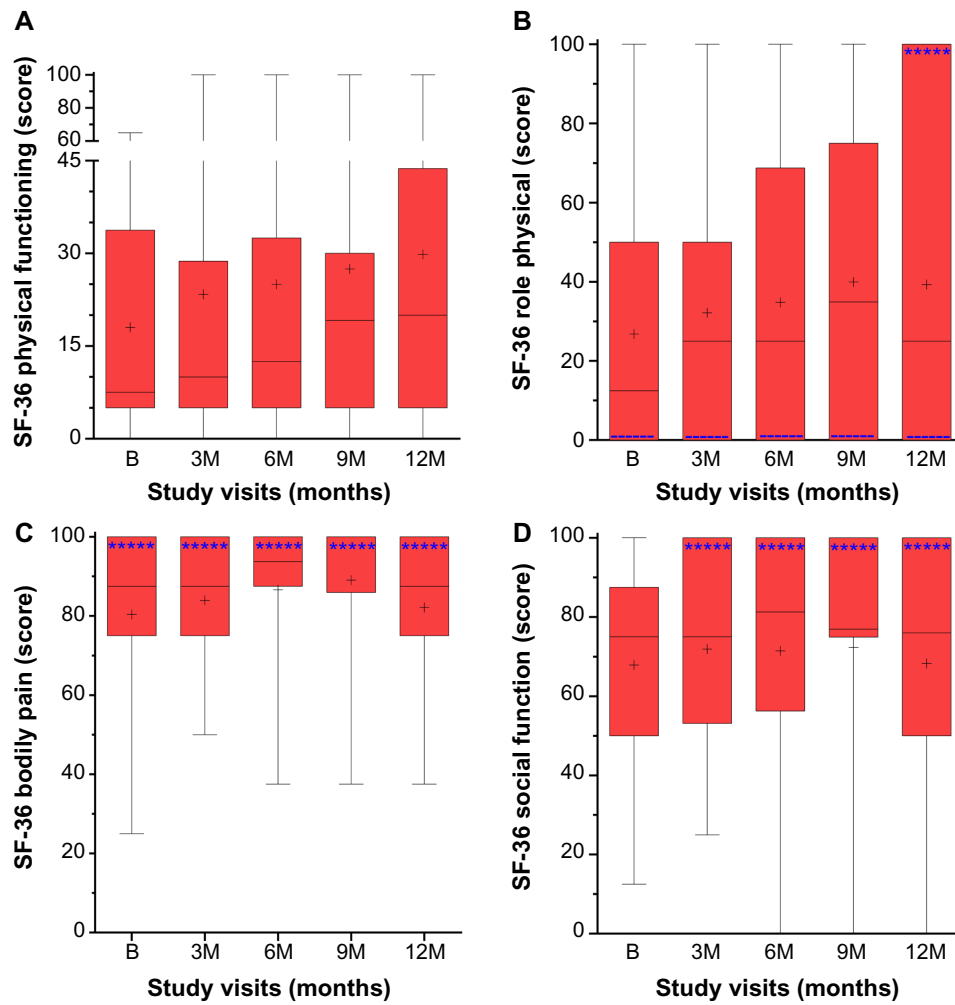


Figure S2 Health related quality of life scores: (A) SF-36 physical functioning, (B) role physical, (C) bodily pain and (D) social function scores during the study.

Notes: Upper and lower borders of the boxes represent 25th and 75th percentiles respectively. The line within the boxes represents median and + sign represents mean. The whisker error bars represent minimum and maximum values. **** represent median values overlapping with upper quartile values. ----- represent lower quartile values overlapping with minimum values.

Abbreviations: B, baseline; 3M, 3 months; 6M, 6 months; 9M, 9 months; 12M, 12 months, SF-36, Short Form-36.

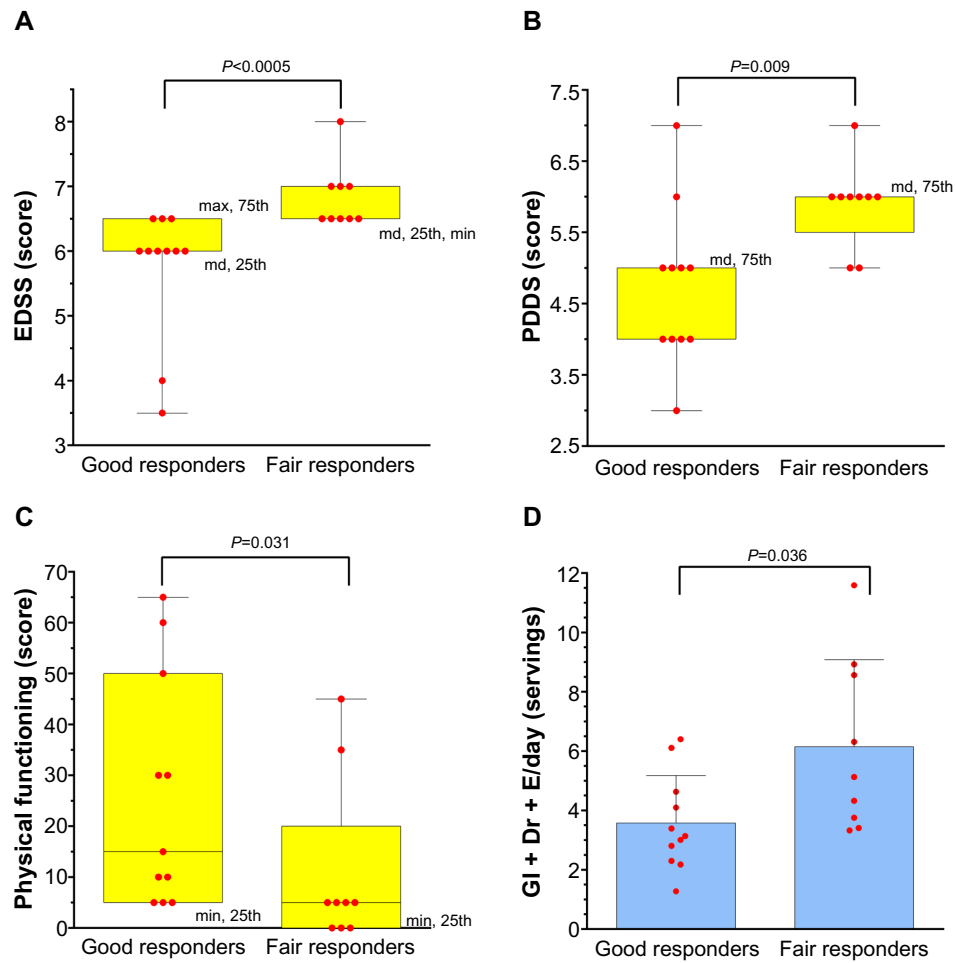


Figure S3 Comparison of baseline characteristics of good- and fair-responders in terms of (A) EDSS scores, (B) PDDS scores, (C) Sf-36 physical functioning scores and (D) mean daily serving of GI + D + E.

Notes: Red dots represent each subject's score. In figures A–C, upper and lower borders of the boxes represent 25th and 75th percentiles respectively. The line within the boxes represents median. The whisker error bars represent minimum and maximum values. Overlapping values are indicated in the figure. In figure D, values are mean + SD.

Abbreviations: EDSS, Expanded Disability Status Scale; GI + Dr + E, gluten-containing grains + dairy products + eggs; max, maximum; md, median; min, minimum; PDDS, Patient Determined Disease Steps; SD, standard deviation.

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