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A Multimodal, Nonpharmacologic Intervention Improves Mood and Cognitive Function in People with Multiple Sclerosis

Jennifer E. Lee, PhD, MA[a,b], Babita Bisht, PhD, BPT[c], Michael J. Hall, PhD[d,e], Linda M. Rubenstein, PhD, MS[f], Rebecca Louison, BS[a], Danielle T. Klein, BS[c], and Terry L. Wahls, MD[c,g]

[a]Department of Psychology, Mount Mercy University, Cedar Rapids, Iowa; [b]College of Nursing, The University of Iowa, Iowa City, Iowa; [c]Department of Internal Medicine, Carver College of Medicine, The University of Iowa, Iowa City, Iowa; [d]Department of Psychiatry, Iowa City VA Health Care System, Iowa City, Iowa; [e]Department of Psychiatry, Carver College of Medicine, University of Iowa, Iowa City, Iowa; [f]College of Public Health, The University of Iowa, Iowa City, Iowa; [g]Extended Care and Rehabilitation Service Line, Iowa City VA Health Care System, Iowa City, Iowa

ABSTRACT

Objective: The objective of this study was to examine whether participation in a 12-month multimodal intervention would improve mood and cognitive function in adults with progressive multiple sclerosis (MS).

Methods: In this one-arm, open-label feasibility trial, participants were prescribed a home-based multimodal intervention, including (1) a modified Paleolithic diet; (2) an exercise program (stretching and strengthening of the trunk and lower limb muscles); (3) neuromuscular electrical stimulation (EStim) of trunk and lower limb muscles; and (4) stress management (meditation and self-massage). Individuals completed measures of mood (Beck Anxiety and Depression Inventories) and cognitive (Cognitive Stability Index, Cognitive Screening Test, Delis–Kaplan Executive Function System) and executive function (Wechsler Adult Intelligence Scale) at baseline and 3, 6, 9, and 12 months after the start of the intervention. Dosage of the multimodal intervention was assessed at 3, 6, 9, and 12 months.

Results: The more individuals participated in the intervention activities, the greater improvements they had from baseline to 12 months on self-report measures of anxiety (Beck Anxiety Inventory [BAI]; *ps* = 0.001 to 0.02), depression (Beck Depression Inventory [BDI]; *ps* = <0.0001 to 0.09), cognitive function (Cognitive Stability Index [CSI/T], Delis-Kaplan Executive Function System [DKEFS]; *ps* = 0.001 to 0.06), and executive function (Wechsler Adult Intelligence Scale [WAIS]; *ps* = <0.0001 to 0.09). Mood and cognitive improvements were more closely related to a higher intake of the modified Paleolithic diet than to exercise and stress management dosage. Anxiety and depression changes were evident after just a few months, whereas changes in cognitive function were generally not observed until later in the intervention period. Mood and cognitive function changes from baseline to 12 months were significantly associated with fatigue improvements (*ps* = <0.0001 to 0.03).

Conclusions: A modified Paleolithic diet, exercise, EStim, and stress management intervention like this one has the potential to improve the mood and cognitive symptoms that can lead to considerable suffering in people with MS, potentially improving quality of life and function for people with progressive MS.

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Introduction

Cognitive impairment is a debilitating feature of multiple sclerosis (MS) that affects up to 60% of individuals [1] and occurs independent of physical decline [2]. The cognitive abilities most affected by MS are processing speed, attention, learning, and memory [2–4], making everyday tasks challenging. There is also a 35 to 50% lifetime prevalence of anxiety or depression in people with MS [5,6], worsening the cognitive deficits [7]. These cognitive and mood impairments intensify the physical symptoms, leading to further decreased function and quality of life. Unfortunately, current therapy decreases (but does not eliminate) the relapses in relapsing–remitting MS (RRMS) and may slow the decline of secondary progressive MS (SPMS) but is ineffective at treating progressive disability associated with MS [8,9]. Furthermore, disease-modifying drugs have undesirable side effects [10] and are cost-prohibitive (thousands of dollars per month) [11]. Cost-effective therapies that alter the MS disease are needed.

At present, there are no therapies to counteract the mood impairment or cognitive damage resulting from MS, so many patients use complementary, nonpharmacologic approaches. Non-drug treatments such as psychotherapy, neuropsychological rehabilitation, and relaxation training are generally effective for cognitive and mood symptoms in people diagnosed with MS [12–14]. Diet changes are also recommended; the dietary approaches of MS are varied and may consist of allergen-free (gluten, milk) and/or polyunsaturated fatty acids (PUFA) supplements, vitamins (e.g., vitamin D), micronutrients, and/or or

CONTACT Jennifer E. Lee jlee@mtmercy.edu Mount Mercy University, Department of Psychology, 1330 Elmhurst Dr NE, Cedar Rapids, IA 52402.
Dr. Terry Wahls is currently affiliated only with the University of Iowa.

antioxidants (e.g., selenium, *Gingko biloba*, coenzyme Q10) [15]. Specific diets can include the Swank, McDougall, and Paleolithic diets. Emerging data suggest that environmental factors such as diet quality (i.e., total daily vegetable servings) have a greater influence on the development and severity of MS than genetics [16], and diet quality is inversely correlated with the risk of developing MS and obesity [16]. A higher intake of greens, sulfur-rich vegetables, and brightly colored vegetables and fruits also provides more helpful dietary molecules (e.g., flavonoids, polyphenols, thiols) that may impact multiple molecular pathways influencing MS disease activity (e.g., sirtuins, AMP-activated protein kinase (AMPK), nuclear transcription factor kappa B, peroxime proliferator–activated receptors) [17,18], possibly setting the stage for reduced disease activity. Gluten sensitivity is also associated with neurologic dysfunction and white matter changes in the brain and spinal cord [19]. Thus, a diet that is maximally nutrient dense and avoids foods linked to white matter damage and neurological symptoms in genetically predisposed individuals is likely beneficial for MS and associated with less risk than traditional pharmacological approaches.

A second environmental factor affecting MS development is physical activity [16]. Among people diagnosed with MS, systematic reviews reported that exercise interventions and increased physical activity are associated with improved cardiorespiratory function, quality of life, muscle strength, body composition, fitness, disability, fatigue, and mood [20–22]. Despite the potential usefulness and rationale for MS diet and exercise approaches, only a handful of high-quality studies examined the efficacy of diet and/or exercise interventions for people with MS. In a 2009 case report [23], a neuromuscular electrical stimulation (EStim) and nutritional intervention led to significant improvements in physical function. A follow-up pilot feasibility study [24,25] assessed whether this case report intervention could be adopted and tolerated by others with progressive MS. The pilot trial found that a multimodal intervention (diet, exercise, EStim, stress management) was feasible in a larger sample and significantly improved quality of life and fatigue in people with progressive MS. This nonpharamacologic approach may also benefit mood and cognitive function in people with MS and be associated with less risk than traditional interventions, but the case report and pilot trial did not report mood and cognitive outcomes. Indeed, studies found that an 8-week exercise intervention improved cognitive scores in people with MS [26], and 12 weeks of resistance training led to significantly improved mood and cognition in another MS sample [27]. Though no known studies examined the efficacy of the case report intervention on mood and cognition in people with MS, collectively these studies suggest that a multimodal intervention may benefit the symptoms and prognosis of MS.

The aim of this study was to examine the efficacy and effectiveness of this multimodal intervention on mood (anxiety, depression) and cognitive function (learning/memory, attention, language, speed, complex verbal fluency, and verbal and visual reasoning) in people diagnosed with progressive MS. This investigation extends prior findings on non-drug interventions for MS and fills a gap in the literature by addressing the mood and cognitive symptoms of progressive MS in a single study. We chose progressive MS patients because spontaneous remissions do not occur with SPMS or primary progressive MS (PPMS), so if improvements were observed, they would be attributed to remission. Specifically, we prescribed a home-based, 12-month individualized intervention that included a modified Paleolithic diet, exercise, EStim, and stress management. We hypothesized that a higher dosage of this multimodal intervention between baseline and 12 months would lead to greater improvements in mood and cognitive function. Establishing this association in people with MS is a critical first step toward identifying an effective, nonpharmacologic intervention for MS.

Materials and methods

Study design

This pilot, one-group, quasi-experimental with multiple time points study design was described previously [24,25]. Briefly, it was a one-arm, open-label trial, and potential participants with PPMS and SPMS were informed about the study by physicians in the spinal cord injury clinic at the Iowa City Veteran's Affairs Medical Center and the University of Iowa Neurology Department. Eligible patients from the University of Iowa Neurology Department were also sent invitation letters, and some participants contacted the research team after they heard about the study from other sources. Enrollment of participants started on October 6, 2010, and the last 12-month study visit was completed on December 2, 2013.

Participants were first enrolled into a 2-week "run-in" period to determine who would meet the adherence requirements and thus would be included in the year-long study. During this run-in, participants were asked to follow the study diet and stretching exercise intervention (see below), and people who adhered with the diet for 7 consecutive days were enrolled in the 12-month study. The study design was approved by the University of Iowa Institutional Review Board (#200911781) and informed consent was obtained from all participants according to the Declaration of Helsinki (ClinicalTrials.gov Identifier: NCT01381354; https://clinicaltrials.gov/ct2/show/NCT01381354?term=wahls&rank=2).

Inclusion and exclusion criteria

Inclusion criteria included (1) SPMS or PPMS diagnosis (confirmed by a neurologist, clinical presentation, brain and spinal magnetic resonance imaging, and spinal fluid examination); (2) 18–65 years; and (3) a minimum of mild gait disability. Exclusion criteria included (1) unable to walk 25 feet with or without an assistive device; (2) no adult companion to assist with the exercise intervention; (3) change in MS status in the past 3 months; (4) abnormal renal or hepatic functions; (5) current diagnosis of cancer, psychotic disorder, significant cognitive dysfunction, seizure disorder, heart block or abnormal rhythm, unstable heart disease, lung disease, and/or diabetes (requiring medication change in the past 3 months); (6) implanted electronic device; (7) antiplatelet or blood thinner medication; and (8) vitamin D level $>$ 150 ng/mL (or a vitamin D level $>$ 100 ng/mL combined with a blood calcium abnormal elevation $>$ 10.2 mg/dL).

Table 1. Study Diet.[a]

Food Item	Instructions	Recommended Daily Intake
Green leafy vegetables	Recommended	3 cups cooked/6 cups raw (3 servings)
Sulfur-rich vegetables	Recommended	3 cups raw or cooked (3 servings)
Intensely colored fruits or vegetables	Recommended	3 cups raw or cooked (3 servings)
Omega-3 oils	Encouraged	2 tablespoons
Animal protein	Encouraged	4 ounces or more
Plant protein	Encouraged	4 ounces or more
Nutritional yeast	Encouraged	1 tablespoon
Milks (soy, almond, peanut, rice, coconut)	Encouraged	According to participant choice
Kelp	Encouraged	1/4 teaspoon powder or 2 capsules
Algae (spirulina/chlorella/klamath blue green)	Encouraged	1/4 to 1 teaspoon or 4 to 8 capsules
Gluten-free grains/starchy food	Allowed	2 servings per week
Gluten-containing grain	Excluded	
Dairy	Excluded	
Eggs	Excluded	

[a]If participants were not able to consume 9 total servings daily of the recommended foods, they were asked to consume equal proportions from each category.

Intervention

The study intervention was described previously [24,25] and the diet is described in Table 1. This intervention has no serious side effects and is feasible for people with MS [24,25].

Diet

Participants were taught the study diet by a team member (T.W.). All participants were required to have at least one adult companion to support them with implementing and adhering to the diet. Briefly, individuals were instructed to adopt the modified Paleolithic study diet consisting of (1) "recommended" foods (9 total cups of leafy green vegetables, sulfur-rich vegetables, and/or deeply colored fruits and vegetables; that is, "vegetables/fruits"); (2) "encouraged" foods (plant and animal protein, seaweed, nondairy milks); and (3) "excluded" foods (gluten, eggs, dairy; i.e., "gluten/dairy/eggs"). We recommended that foods be prepared at home and organic (when possible). The Paleolithic diet removes foods like grains and dairy that may cause undiagnosed food sensitivity (mediated by immunoglobulin [Ig] A or IgG antibodies or the innate immune system) and encourages the consumption of meat, organ meat, vegetables, fruits, nuts, and seeds. The Paleolithic diet was modified to provide key nutrients for brain function [28,29] and have a favorable impact on multiple molecular pathways contributing to MS disease severity [17,18]. The diet prescribed specific types of vegetables and fruits (and to increase the amount daily) and encouraged moderating meat intake. Participants received recipes and menus to encourage diet adherence. Nutritional supplements were initially provided (Table 1; *e.g.*, green algae) [24,25], but there was high interindividual variability in their use for the first 9 participants, so the last 11 people did not receive supplements. Instead, participants were supplemented with vitamin D, methyl folate, and methylcobolamin based on blood levels, and they were referred to a primary care physician/neurologist if they had suboptimal vitamin D, folate, cobalamin, or homocysteine.

Exercises, EStim, and stress management

Briefly, at the first run-in visit, each participant and adult companion were provided with instructions by a team member (B.B.) for a home-based stretching exercise intervention. After enrollment into the main study, at visit 2, the following were added to the intervention: (1) individualized strengthening exercises of the trunk and lower limb muscles 5 days per week; (2) EStim (using the electrical therapy device EMPI 300 PV, DJO Inc., Vista, CA) of the lower limbs and trunk muscles; and two daily stress management activities: (3) meditation; and (4) self-massage of the face, feet, and hands. Participants were asked to complete 10 to 20 exercise repetitions of each muscle group within 10 minutes of EStim daily, allowing time to perform exercises with stimulation and rest between repetitions, and to complete a minimum of 20 minutes of meditation and/or massage daily.

Participant support

Research assistants called participants twice during the 2-week run-in period to provide support and answer intervention questions. After enrolling in the 12-month main study, research assistants continued to call participants weekly for the first 2 months and thereafter participants were encouraged to call the research team with any questions. Research assistants were trained to use motivational interviewing techniques (e.g., open-ended questions and reflective statements) [30] to encourage adherence.

Dosage measures

Participants completed daily home record logs documenting their food intake, exercises, EStim use, meditation, and self-massage. These logs were submitted at the study visits and used to measure intervention dosage for each 3-month assessment period. Vegetable/fruit intake was obtained by calculating the mean daily amount of servings that participants consumed of the recommended foods (green leafy vegetables, sulfur-rich vegetables, intensely colored fruits or vegetables). Gluten/dairy/egg consumption (excluded or 2 servings maximum per week gluten-free/starchy foods) was obtained by calculating the mean daily amount of servings that participants consumed of the excluded foods. A participant was considered adherent with the study diet on a particular day if he or she consumed any recommended foods and did not consume any excluded food. Exercise dosage was obtained by calculating the mean length of time (in minutes) per day that participants completed any exercises. EStim dosage was obtained by calculating the mean length of time (in minutes) per day that participants applied EStim. A participant was considered adherent with exercise/EStim on a particular day if he or she performed any exercise and/or applied EStim. Stretches (per muscle) were calculated by adding up the total time per day (in seconds) doing any of the prescribed stretches and dividing that by the number of muscles exercised to obtain a mean daily dose of stretching per muscle. Massage and meditation dosage was obtained by calculating the mean length of time (in minutes) per day that participants completed each activity. Vegetable/fruit and gluten/dairy/

eggs intake was manually calculated at baseline based on responses to the Harvard food frequency questionnaire [31,32] and based on daily food logs at 3, 6, 9, and 12 months (5 times total). Dosages of the other intervention variables were assessed at visits 2 through 5 (starting at 3 months) using the daily logs (4 times total).

Side effects measures

A monthly side effects questionnaire and blood analyses (complete blood count, creatinine, calcium, magnesium, and alanine aminotransferase, conducted at the Iowa City Veteran's Affairs Medical Center) were used to assess potential intervention side effects. Participants documented: (1) perceived side effects of nutritional supplements; (2) burns following EStim use; and (3) rated the following symptoms on a 0 to 3 scale (0 = none, 1 = mild, 2 = moderate, 3 = severe): palpitations, joint pain, abdominal pain, chest pain, bruising, easy bleeding, diarrhea, constipation, nausea, headache, and skin rash. We also recorded each participant's height and weight at each of their 5 study visits to measure any weight loss due to the intervention.

Outcome measures

Mood

The Beck Anxiety Inventory (BAI) [33] is a 21-item self-report measure of common anxiety symptoms (e.g., restless) during the past week. Participants rate the degree to which each symptom bothers them on a 4-point scale from 0 (*not at all*) to 3 (*severely*). The BAI has excellent internal consistency (Cronbach's alpha = 0.92), a 1-week test–retest reliability of 0.75 [34], and good convergent validity ($r = 0.58$ with the State-Trait Anxiety Inventory) [35].

The Beck Depression Inventory–II (BDI) [36] is a 21-item self-report measure of depressive symptoms (e.g., hopelessness). Participants rate the degree to which they experience each symptom on a 4-point scale from 0 (*minimal*) to 3 (*severe*) in the past 2 weeks. The BDI can be reported as one total score (range 0 to 63) and/or as 2 subscales: (1) Cognitive (8 items: 2, 3, 5, 6, 7, 8, 9, 14; range 0 to 24) and (2) Somatic–Affective (13 items; 1, 4, 10–13, 15–21; range 0 to 39) [37]. The BDI-II has a 1-week reliability of 0.93, an internal consistency of 0.92 (outpatients), and 93% diagnostic accuracy [36].

Cognitive function

The Cognitive Stability Index (CSI; <55 years) and Cognitive Screening Test (CST; >55 years; Headminder Inc., New York, NY) are Internet-based cognitive screening tools for healthy, at-risk, and affected populations. There are 4 domains measured by both the CST (Learning, Recall, Speed, and Accuracy) and the CSI (Attention, Learning/Memory, Response Speed, and Processing Speed). Daily to 3-month test–retest reliability scores for the CSI range from 0.68 to 0.80 [38], and the domains are validated against traditional neuropsychological tests [38]. Based on expertise from a neuropsychologist (M.H.), the CSI/T was reduced to a smaller number of meaningful variables by collapsing across subscales: (1) Memory (mean of CSI Learning/Memory and CST Learning and Recall subscales); (2) Speed (mean of CSI Processing Speed and Response Speed subscales and CST Speed subscale); and (3) Attention (mean of CSI Attention and CST Accuracy subscales). Standardized scores were used.

The Delis-Kaplan Executive Function System (DKEFS) [39] is a neuropsychological test of verbal and nonverbal executive functions and consists of 9 subtests (e.g., Trail Making, Verbal Fluency) that can be used alone or in combination with other DKEFS tests. The DKEFS tests are sensitive to the assessment of executive function deficits in numerous clinical populations, including MS [40,41]. The DKEFS tests have moderately good internal consistency coefficients and good test–retest reliability [39]. For the current study, 2 DKEFS domains were created for analysis: (1) Language (mean of the scores on the Semantic Verbal Category and Phonemic Verbal Fluency subscales) and (2) Complex Verbal Fluency (Switch Verbal Fluency Trial). Standardized scores were used.

The Wechsler Adult Intelligence Scale (WAIS-III) [42] is a measure of general cognitive ability. There are 14 subtests, with 4 index scores calculated from 11 of these subtests. In the current study, only the Matrix Reasoning and Similarities subtests were administered. The Similarities subtest measures verbal reasoning by asking the examinee to describe how 2 words are alike (19 word pairs; each pair has a general property pertinent to both words). The Matrix Reasoning test measures visual reasoning by asking the examinee to look at a picture of geometric shapes with a section missing and identify the missing piece from 5 response options (26 items) [42]. The WAIS-III is a reliable measure, with subtest test–retest reliability scores ranging from 0.70 to 0.93 and an interrater agreement > 0.90 for most of the subtests [42]. Internal consistencies (Fisher's z) of the Similarities and Matrix Reasoning subtests are 0.86 and 0.90, respectively. Standardized scores were used for analysis.

Full-Scale IQ (FSIQ) was assessed as a potential covariate using the Wechsler Test of Adult Reading (WTAR) [43], a measure of premorbid intellectual functioning. The WTAR includes 50 irregularly spelled words on cards (with atypical grapheme to phoneme translations) and participants pronounce each one aloud. The total raw score is calculated as the number of correct pronunciations (maximum score of 50) and then converted to a standard score that is compared to a "predicted" score. The predicted WTAR is derived from demographic data based on a normative sample and then subtracted from the obtained WTAR score to assess the difference magnitude. The WTAR has very good convergent validity, with mean correlations between the WTAR and the WAIS-III Verbal and Full-Scale IQ of $r = 0.75$ and 0.73, respectively [43]. The WTAR has good discriminant and convergent validity in people with Alzheimer's disease, distinguishing between people with no or minimal cognitive impairment and mild cognitive decline [44]. Standard scores were used.

Disability

The Expanded Disability Status Scale (EDSS) [45] is a measure of physical disability within the MS population and was used as a potential covariate. A neurologist with MS expertise completed all EDSS assessments, taking into account patients' motor function/mobility, neurological exam, and medical history/symptoms (e.g., fatigue, urinary urgency, ability to perform activities of daily living). EDSS scores range from 0 (normal) to 10 (death), with

0.5-point increments representing progressively more impaired ambulation. Scores between 0.0 and 5.0 indicate full ambulatory ability and scores greater than 5.5 indicate the loss of ambulatory ability. The EDSS has an interrater score of 96% (≤1.0 difference), a repeatability coefficient of 0.90, and an intraclass coefficient of 0.99 [46].

Fatigue

The Fatigue Severity Scale-9 (FSS) [47] is a 9-item measure of fatigue severity and how fatigue affects activities of daily living the past week. Each statement is rated on a 7-point Likert scale ranging from 1 (*completely disagree*) to 7 (*completely agree*), with higher scores indicating elevated fatigue. The total score is a mean of all 7 items (range 1 to 7). The FSS has excellent reliability, with a test–retest intraclass correlation coefficient of 0.91 [48]. The FSS also has internal consistency scores (Cronbach's alpha) of 0.81 to 0.89 and good convergent and discriminant validity [47]. Researchers suggest that an FSS score of 4 indicates clinically meaningful fatigue [47].

Procedures

Baseline assessments of the mood (BAI, BDI), cognitive (CSI/T, DKEFS), and executive function (WAIS) outcome measures and the potential covariates (WTAR, FSS, EDSS) were completed during the run-in period (visit 1). We also recorded diet data (i.e., vegetables/fruits, and gluten/dairy/eggs) during the run-in phase and explained the individualized intervention (diet, exercise, EStim, and stress management). Participants returned for their postintervention assessments at 3, 6, 9, and 12 months after the start of the intervention (visits 2 through 5), at which time their mood, cognitive function, and intervention dosage (i.e., diet, exercise, EStim, and stress reduction) were assessed using the home record logs. Thus, all mood, cognitive, and diet variables were measured 5 times (at baseline and at 3, 6, 9, and 12 months), and exercise, EStim, and stress reduction dosage were assessed 4 times (3, 6, 9, and 12 months).

Analyses

No missing data were imputed because <2.0% of the data was missing and data were not missing at random. An intent-to-treat analytical approach was not applicable to this study because intent-to-treat analyses require randomizing to 2 or more groups with sufficient sample size for imputation and robust sensitivity analyses. Descriptive statistics were calculated for every variable at all study visits using frequencies (percentage), means (±SD), and medians (25th and 75th interquartile ranges). Outliers were checked for accuracy and possible data entry errors. Distributions of continuous variables were evaluated for normality by graphical observation and the Shapiro-Wilk test. Collinearity among variables was examined using the variance inflation factor method. To determine whether there were associations between categorical variables at baseline, Fisher's exact tests for small sample sizes were used. The BDI can be assigned one total score or using its 2 subscales (Cognitive and Somatic–Affective) [36]. To determine whether scores on the subscales differed in the sample, paired samples *t* tests were used. If the Cognitive and Somatic–Affective scales had significantly different means from another and/or the total score at any visit, they were reported separately in the results.

To determine whether the a priori selected baseline variables (age, disability, fatigue, and FSIQ; i.e., potential covariates) were significantly related to the outcomes, generalized linear models were used to test univariate associations between these 4 baseline variables and the outcome measures. If a baseline variable was significantly associated with 2 or more outcome measures, it was included in the subsequent models as a covariate. To identify whether any changes in weight or BMI from the intervention affected the outcomes, Spearman's correlation coefficients were used to measure associations among changes from baseline to 12 months in the 7 mood and cognitive measures, and change in (1) BMI (%) or weight (%).

Patterns of change from baseline to 3, 6, 9, and 12 months were examined with graphical representations of the data by plotting the means of the mood and cognitive outcome measures and 7 dosage variables against each study visit time point (i.e., 4 or 5 study visits, depending on the variable). Change in the mood and cognitive outcome measures was assessed in 2 ways: (1) To assess change over time for each outcome, linear mixed models for repeated measures were used, with the study visit number variable included; and (2) to assess the effect of change in intervention dosage (e.g., exercise) over the study period on change in the outcome measures, the dosage covariates were modeled as fixed effects using 4 study visits for all variables (except vegetables/fruits and gluten/dairy/eggs, which were assessed 5 times). The repeated option in these models included study visit as a categorical variable and participants as a random effect and specified a heterogeneous compound-symmetry covariance structure. All models were assessed for potential significant baseline covariates in the models, but due to the relatively small sample size and lack of significant change in mean outcomes estimates, all final models included either study visit or the dosage covariate.

Mean changes in the outcome measures between visits were assessed by creating change variables between each study visit (i.e., *p* value difference) and overall changes from baseline across the study visits (i.e., *p* value over time). The mean differences (*p* value difference) provided the magnitude and direction of changes and were assessed with *t* tests or signed rank tests depending on the normality of the change variable. The overall change (*p* value over time) provided information regarding whether there was a change in the variable over time/visits. Corrections for multiple comparisons were not used because this was an exploratory study to examine whether a multimodal intervention would be associated with changes in mood and cognition. There is no consensus in the literature regarding whether and when corrections (e.g., Bonferroni) should be used for multiplicity [49]. In this study, correcting for multiple testing could result in too many false negatives [50], and potential important areas for future research would be missed. Thus, these findings will need to be confirmed in additional, larger studies.

To determine whether any changes in the cognitive scores were due to practice effects (versus real improvement in

cognitive functioning), reliable change values were calculated using the Jacobson and Traux model [51]. First, the standard error of the measurement was calculated using test–retest reliability to calculate scores for each outcome measure and study visit. Next, the standard error of difference for each outcome measure and study visit was calculated. Finally, the reliable change score was calculated, providing a reliable change value for each outcome measure and study visit that took into account potential practice effects [52]. A reliable change value that increased or decreased by $\geq$1.65 indicates that scores on that measure were due to practice effects [52].

The data analysis was generated using SAS software, Version 9.4, of the SAS System (SAS Institute Inc., Cary, NC). All data were analyzed using 2-tailed tests, alpha $\leq$ 0.10 due to the relatively small sample size to decrease the likelihood of type II error.

Results

Participants

The Consolidated Standards of Reporting Trials diagram is shown in Fig. 1. Of the 67 people assessed for eligibility, 41 were eligible for participation in the run-in phase, and 26 were eligible for the main study. Five people were ineligible prior to the main study ($N = 21$ to start the main study), and 2 were excluded thereafter: one had clinically significant cognitive decline by 6 months, and one dropped out for unknown reasons before 3 months, thus only completing the baseline assessments), leaving 19 people in the analyses.

Sample characteristics

Table 2 shows the participants' demographic and clinical characteristics. The mean age was 51 ± 6.5 years and most individuals were female (73.7%), Caucasian (94.7%), and college educated or higher (63.1%). The mean diagnosis length was 13.6 ± 7.5 years and most of the sample had SPMS (89.5%). The mean disability (EDSS) score was 6.2 ± 1.0 out of 10, meaning a loss of ambulatory ability [45]; fatigue scores (FSS) had a mean score of 5.5 ± 1.3 out of 7, suggesting clinically significant fatigue [47]. At baseline, participants' overall BAI anxiety and BDI depression mean scores were 10.8 ± 9.1 and 9.9 ± 8.0, respectively. From baseline to 12 months, participants' mean weight changed from 68.5 ± 11.4 kg to 62.5 ± 10.1 kg

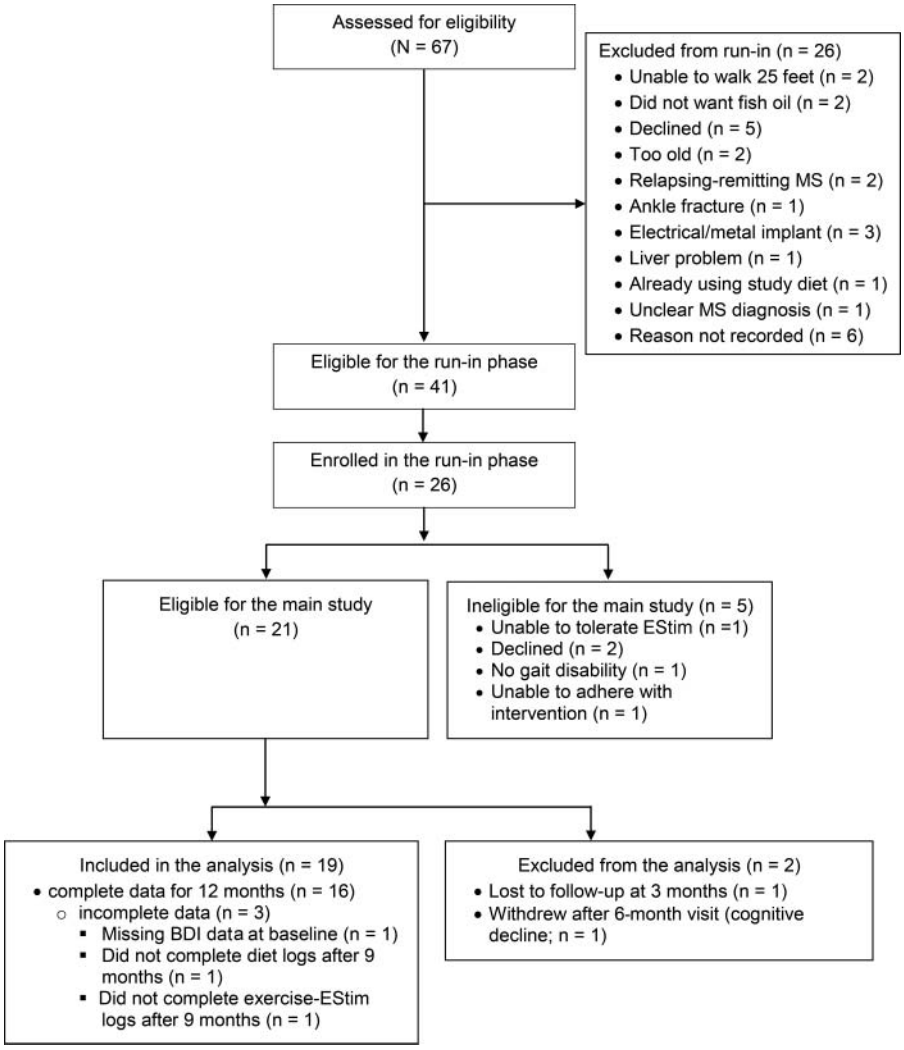

Figure 1. Assessment and assignment of patients in a multimodal, nonpharmacologic intervention to improve mood and cognitive function in people with multiple sclerosis.

Table 2. Participant Demographic and Baseline Clinical Characteristics.

Baseline Characteristic	*n*	Mean ± SD or *n* (%)	Observed Data Range	Median (25th to 75th Percentile Interquartile Range)
Age	19	51 ± 6.5	37 to 65	52 (47 to 54)
Female	19	14 (73.7)		
Weight (kg)	19	68.5 (11.4)	46.3 to 83.6	
BMI	19	24.4 (3.0)	20 to 30	
Race	19			
Caucasian		18 (94.7)		
Hispanic		1 (5.3)		
Marital status	19			
Married		18 (95)		
Widowed		1 (5)		
Education				
High school		1 (5.3)		
Some college		6 (31.6)		
4-Year degree		4 (21.0)		
>College		8 (42.1)		
Diagnosis	19			
Secondary progressive MS		17 (89.5)		
Primary progressive MS		2 (10.5)		
Years with MS		13.6 ± 7.5	3 to 27	11 (8 to 20)
Disability (EDSS; possible range 0–10)	19	6.2 ± 1.0	3.5 to 8	6.5 (6 to 6.5)
Fatigue (FSS; possible range 1–7)	19	5.5 ± 1.3	3.1 to 7	5.6 (4.4 to 6.7)
Disease-modifying drugs	19	9 (47.4)		
Walking aid	19	14 (73.7)		
Anxiety (BAI; range 0–63)	19	10.8 ± 9.1	1 to 42	9 (6 to 14)
Depression (BDI; range 0–63)				
Total score	18	9.9 ± 8.0	2 to 29	7 (4 to 13)
Cognitive (range 0–24)	18	2.9 ± 3.3	0 to 12	2 (1 to 4)
Somatic–Affective (range 0–39)	18	6.9 ± 5.3	2 to 19	5 (3 to 9)
CSI/T				
Learning and Memory (range 50–140)	19	94 ± 23.7	40 to 122	102 (80.5 to 111)
Speed (range 50–140)	19	89.4 ± 24.1	23 to 115	96.0 (82 to 107)
Attention (range 50–140)	19	98.6 ± 10.4	70 to 117	100 (94 to 105)
DKEFS				
Language (range 1–19)	18	10.0 ± 2.9	3.5 to 14	11.0 (8.5 to 12)
Complex Verbal Fluency (range 1–19)	18	9.7 ± 3.3	4.0 to 16	11.0 (8 to11)
WAIS-III				
Similarities (Verbal Reasoning; range 1–19)	19	11.7 ± 2.5	7 to 17	12 (11 to 13)
Matrix (Visual Reasoning; range 1–19)	19	12.3 ± 2.9	6 to 17	13 (10 to 14)
Full-Scale IQ (WTAR; range 50–140)	19	109.4 ± 6.5	95 to 118	112 (106 to 114)

Note: bold values p ≤ 0.05. BMI = body mass index, MS = multiple sclerosis, EDSS = Expanded Disability Status Scale, FSS = Fatigue Severity Scale, BAI = Beck Anxiety Inventory, BDI = Beck Depression Inventory, CSI/T = Cognitive Stability Index/Cognitive Screening Test, DKEFS = Delis-Kaplan Executive Function System, WAIS-III = Wechsler Adult Intelligence Scale–III, WTAR = Wechsler Test of Adult Reading.

(mean change = 8.4%), and mean BMI changed from 24.4 ± 3.0 to 21.9 ± 2.1 (mean change = 9.7%).

Intervention dosage

A detailed description of the study intervention doses is reported elsewhere [24,25]. Briefly, 12-month mean daily diet adherence scores ranged from 94.5 to 98% of days, and exercises/EStim adherence ranged from 78.8 to 82.8% of days. Home record logs were completed on 96% of days.

Figs. 2a and 2b show the pattern of change in the diet and exercise/EStim dosage variables over the 12-month study (mean scores in Supplemental Table 2). Participants appeared to change their diets substantially following the start of the intervention. From baseline to 12 months, gluten consumption decreased significantly ($p < 0.0001$; Fig. 2a), and vegetable/fruit intake increased significantly ($p < 0.0001$; Fig. 2a). From 3 to 12 months (exercise and EStim were not measured until the 3-month visit), we saw significant increases in exercise ($p = 0.02$) and EStim dosage ($p = 0.10$; Fig. 2b). Stretching, massage, and meditation dosage were not significantly different between 3 and 12 months (all ps > 0.50; data not shown in figures).

Because the majority of significant changes in the outcome measures occurred during the first 3 months (baseline/visit 1 and visit 2), between 3 and 12 months (visits 2 and 5), and over the entire study period (between baseline and visit 5), the subsequent analyses are limited to examining study-related changes between (1) baseline and 3 months; (2) 3 and 12 months; and (3) baseline and 12 months (fruits/vegetables and gluten/eggs/dairy only dosage variables assessed at baseline/visit 1). This also allowed us to limit the number of analyses, particularly given the small sample size in the current pilot study.

Side effects

No serious side effects were reported. The following side effects (number of participants) were perceived as being due to the intake of nutritional supplements by the first 9 participants (note that one of these 9 participants was excluded from the data analyses due to withdrawing prior to 3 months): 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. Overall, during

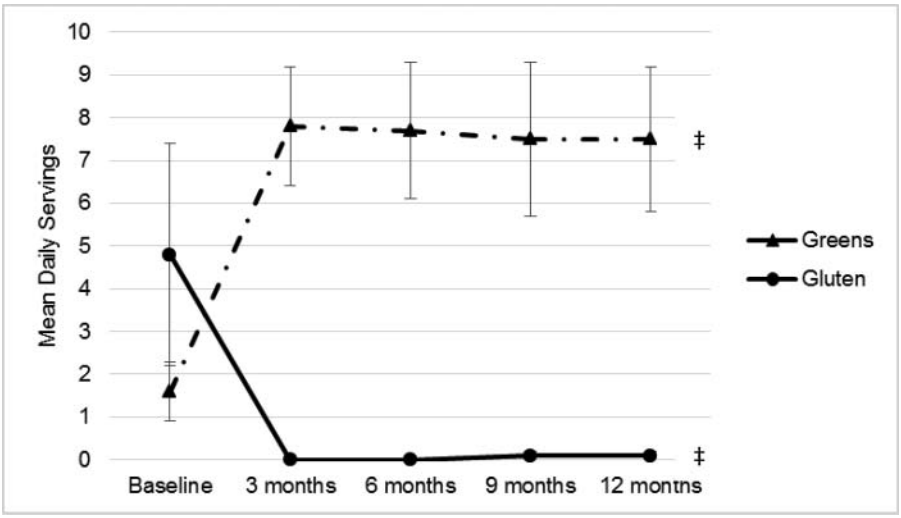

Figure 2a. Mean (SD) daily servings of the study diet's recommended (vegetables/fruits) and excluded (gluten/dairy/eggs) foods calculated from food frequency questionnaire (baseline) and daily food logs (3, 6, 9, 12 months). ‡$p < 0.0001$ difference from baseline to 12 months.

the 12-month intervention, participants reported these symptoms (number of participants) as "mild" in 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). These side effects were rated as "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 were reported by one participant. It was not clear whether these symptoms were due to the intervention or associated with the participant's disease because we did not assess symptom frequency at baseline. Following EStim, 2 participants reported skin burn one time, 2 participants reported skin burn twice, and one participant reported skin burn 3 times. However, none of the participants called the study physical therapist to discuss skin burns and no abnormal changes in skin were observed during study visits. Thus, the burns were presumably minor. No participants discontinued any component of the intervention due to side effects. All safety blood biomarkers remained within normal limits during the study period, except in 3 participants whose alanine aminotransferase levels were higher than normal at a study visit but decreased to normal limits during the subsequent visits.

Mood

In paired samples *t* tests, the mean BDI Cognitive scores were significantly different than the Somatic–Affective scores at all 5 visits ($ps = >0.0001$ to 0.08), suggesting that they were measuring distinct symptoms in this MS sample. The BDI Total scores were also significantly different from the subscale scores at all 5 visits ($ps = >0.0001$ to 0.02). Thus, all subsequent analyses examined the BDI Total score and the Cognitive and Somatic–Affective subscales separately.

Figure 3 shows the patterns of change in the BAI and BDI mood variables over the 12-month intervention (mean scores presented in Supplemental Table 1), and Table 3 shows the mean differences between visits (i.e., *p* value difference), and across the study (i.e., repeated measures, *p* value over time).

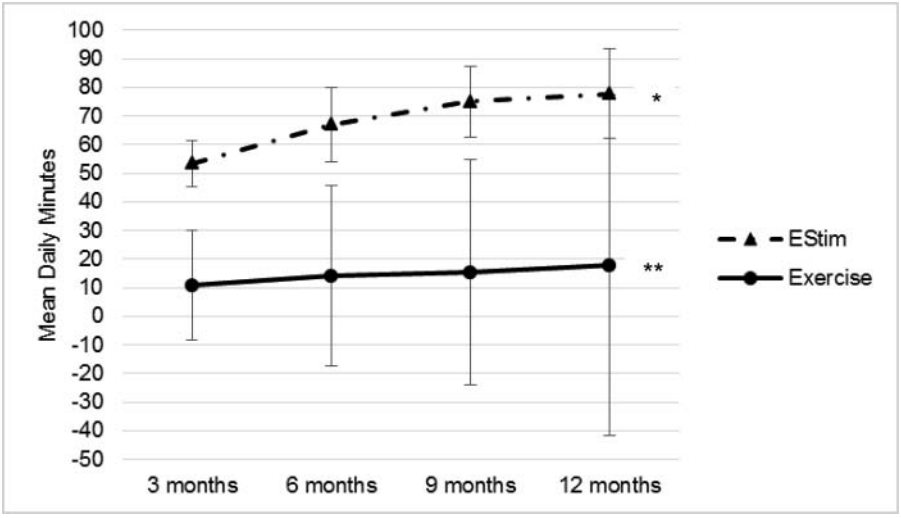

Figure 2b. Mean (SD) daily minutes of exercise and EStim. $^{**}p < 0.05$; $^{*}p \leq 0.10$ difference from 3 to 12 months.

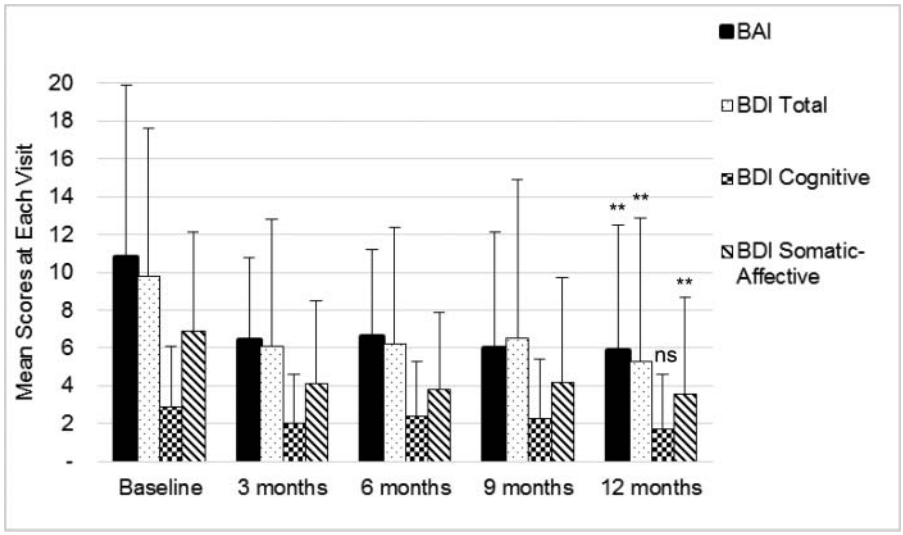

Figure 3. Mean scores on the mood measures at each study visit. The *p* value is over time and included the entire study period. It was generated from a repeated measures mixed model that included all study visits for that variable (2 to 5 study visits) as the outcome and visit number as a covariate (i.e., tests whether there is change in the variable from baseline to 12 months). $^{**}p < 0.05$ difference from baseline to 12 months; ns = not significant.

With the exception of the BDI Cognitive subscale, individuals self-reported improvements in mood during the course of the intervention, particularly within the first 3 months. From baseline to 3 months (*p* value over time and *p* value difference), there were significant decreases (i.e., improvements) in all 4 BAI and BDI mood outcomes (*p*s = 0.002 to 0.05). Overall, BAI anxiety mean scores decreased 4.4 ± 8.7, and total BDI depression scores decreased by 3.9 ± 5.5 in the first 3 months. None of the mood scores changed significantly (*p* value over time or *p* value difference) between 3 to 12 months (*p*s = 0.40 to 0.99). In the repeated measures mixed model (*p* value time), the BAI, BDI Total, and BDI Somatic–Affective scores decreased significantly (i.e., improved) from baseline to 12 months (all *p*s = 0.04), but the BDI Cognitive scores did not change ($p = 0.29$; Table 3). Similarly, *p* value difference scores showed that BAI, BDI Total, and BDI Somatic–Affective variable scored differed significantly from baseline (*p*s = 0.02 to 0.03), but BDI Cognitive did not ($p = 0.13$).

Cognition

Figures 4 and 5 show the patterns of change in the CSI/T, DKEFS, and WAIS cognitive variables over the 12-month intervention (mean scores presented in Supplemental Table 1), and Table 3 shows the mean differences between visits (i.e., *p* value difference) and across the study (i.e., repeated measures, *p* value over time). In general, the cognitive scores did not improve from baseline to 3 months of the intervention, but the majority of the mean scores improved from baseline to 12 months (*p* value difference ranged from 0.0001 to

Table 3. Mean Changes (SD) in the Mood and Cognitive Scores over the Study Period.[a]

	Mood Variables				Cognitive Variables						
	BAI	BDI			CSI/T			DKEFS		WAIS	
Variable	Anxiety (0 to 63)	Total (0 to 63)	Cognitive (0 to 24)	Somatic–Affective (0 to 39)	Learning/ Memory	Speed	Attention	Language	Switch (Complex Verbal Fluency)	Similarities (Verbal Reasoning)	Matrix (Visual Reasoning)
Baseline to 3 months	−4.4 ± 8.7	−3.9 ± 5.5	−0.9 ± 1.9	−3.0 ± 4.4	3.8 ± 10.4	2.2 ± 19.6	3.1 ± 14.6	0.6 ± 1.7	0.1 ± 2.9	1.5 ± 2.3	0.4 ± 2.6
p Value over time	**0.03**	**0.006**	**0.04**	**0.009**	0.12	0.62	0.80	0.12	0.89	**0.01**	0.53
p Value difference	**0.007**	**0.002**	**0.05**	**0.003**	0.13	0.35	0.42	0.14	0.87	**0.01**	0.28
3 to 12 months	−0.5 ± 5.9	−0.5 ± 4.7	−0.1 ± 1.7	−0.4 ± 3.7	3.9 ± 12.1	−4.1 ± 19.0	3.1 ± 9.3	1.0 ± 1.7	1.9 ± 3.9	1.1 ± 2.1	1.7 ± 2.1
p Value over time	0.60	0.97	0.94	0.99	0.13	0.32	0.43	**0.002**	**0.002**	**0.02**	**0.003**
p Value difference	0.41	0.66	0.79	0.66	0.17	0.34	0.21	**0.02**	**0.05**	**0.04**	**0.002**
Baseline to 12 months	−4.9 ± 7.9	−3.3 ± 5.4	−0.7 ± 1.8	−2.6 ± 4.0	7.7 ± 13.7	−1.9 ± 19.1	5.0 ± 10.0	1.6 ± 2.0	2.1 ± 3.5	2.6 ± 2.3	2.1 ± 2.6
p Value over time	**0.04**	**0.04**	0.29	**0.04**	**0.003**	0.50	0.11	**<0.0001**	**<0.0001**	**<0.0001**	**0.0001**
p Value difference	**0.02**	**0.02**	0.13	**0.03**	**0.02**	0.67	**0.05**	**0.003**	**0.02**	**0.0001**	**0.002**

Note: bold values p < 0.10. BAI = Beck Anxiety Inventory, BDI = Beck Depression Inventory, CSI/T = Cognitive Stability Index/Cognitive Screening Test, DKEFS = Delis-Kaplan Executive Function System, WAIS = Wechsler Adult Intelligence Scale.

[a]*p* Value over time was generated from a repeated measures mixed model that includes from 2 to 5 observations (2 to 5 study visits) as the outcome and visit number as a covariate (i.e., tests whether there is change in the variable over time/visits). *p* Value difference shows the direction and magnitude of change from baseline to 3 months (3-month value minus baseline value), 3 months to 12 months (12-month value minus 3-month value), and baseline to 12 months (12-month value minus baseline value). The *p* value for difference was generated from a *t* test for normal distribution or a signed-rank test for nonnormal distributions (i.e., test whether the changes are statistically significant).

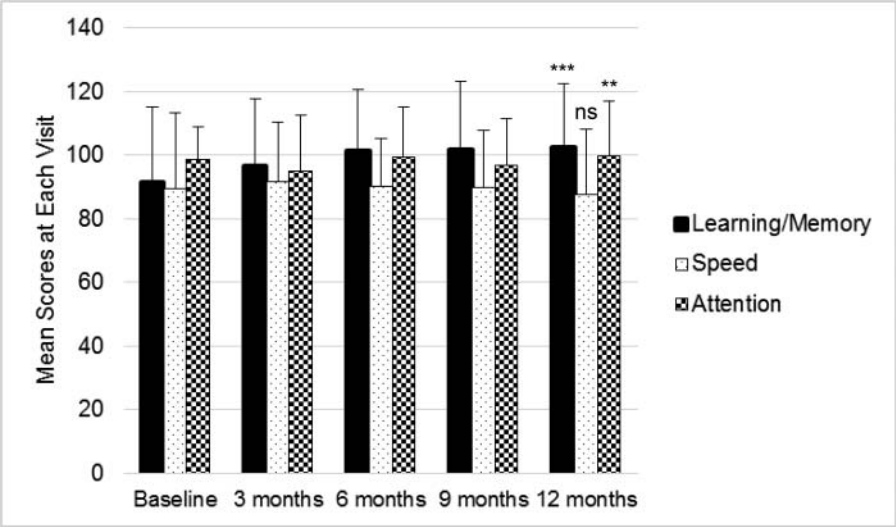

Figure 4. Mean scores on the Cognitive Stability Index/Cognitive Screening Test (CSI/CST) subscales at each study visit. The *p* value reported here is over time and included the entire study period. It was generated from a repeated measures mixed model that included all study visits for that variable (2 to 5 study visits) as the outcome and visit number as a covariate (i.e., tests whether there is change in the variable from baseline to 12 months). $^{***}p < 0.01$ difference from baseline to 12 months; $^{**}p \leq 0.05$ difference from baseline to 12 months; ns = not significant.

0.05), with the exception of CSI/T Speed (*p* value difference = 0.67). The only cognitive score that improved significantly from baseline to 3 months was WAIS Similarities (*p*s over time and difference = 0.01). From 3 to 12 months, there were significant improvements in 3 of the 8 cognitive scale scores in the repeated measures and mean differences analyses: DKEFS Language (*p*s = 0.002 to 0.02), DKEFS Switch (*p*s = 0.002 to 0.05), WAIS Similarities (*p*s from 0.02 to 0.04), and WAIS Matrix Reasoning (*p*s from 0.002 to 0.003). In the repeated measures mixed model (*p* value time), there were significant increases (i.e., improvements) from baseline to 12 months in the CSI/T Memory/Learning (*p*s = 0.003) score but not the Attention ($p = 0.11$) or Speed scores ($p = 0.50$). CSI/T *p* value mean difference scores showed that Learning/Memory ($p = 0.02$) and Attention ($p = 0.05$) differed from baseline, but Speed again did not ($p = 0.67$). From baseline to 12 months, in both the *p* value time repeated measures and *p* value difference analyses, all 4 of the DKEFS and WAIS scores improved significantly (*p*s = <0.0001 to 0.02). The reliable change analysis (to determine whether cognitive score changes were due to practice effects) indicated no practice effects (i.e., there were no values that increased or decreased by ≥1.65; thus changes were not due to practice effects) [52].

Associations among baseline characteristics and the outcome measures

To determine whether any baseline characteristics were related to outcome measure changes (and thus to include as a potential control variables in the analyses), Table 4 shows associations

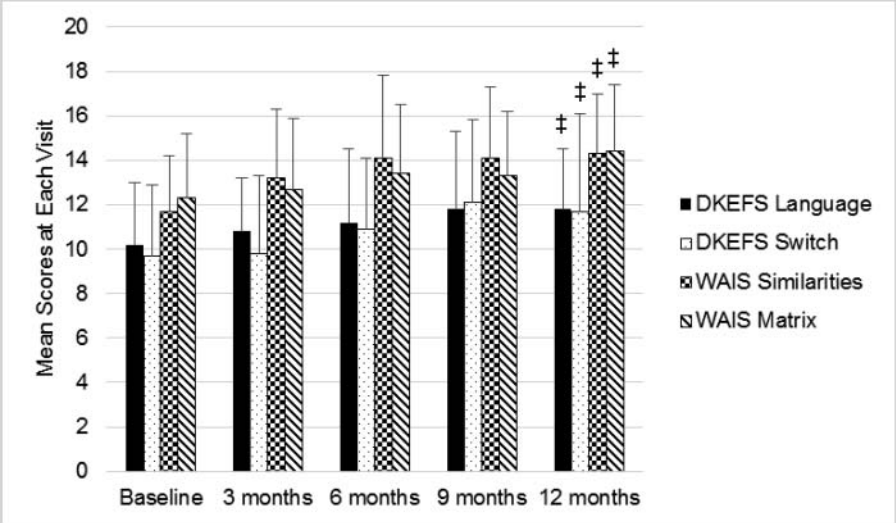

Figure 5. Mean scores on the DKEFS and WAIS subscales at each study visit. The *p* value reported here is over time and included the entire study period. It was generated from a repeated measures mixed model that included all study visits for that variable (2 to 5 study visits) as the outcome and visit number as a covariate (i.e., tests whether there is change in the variable from baseline to 12 months). ‡$p < 0.0001$ difference from baseline to 12 months in all 4 DKEFS and WAIS variables.

Table 4. *p* Values for Associations among Potential Covariates at Baseline and Changes (Baseline to 12 Months) in Mood and Cognitive Function.

	Mood				Cognitive Function						
		BDI			CSI/T			DKEFS		WAIS	
Variable	BAI Anxiety	Total	Cognitive	Somatic–Affective	Memory/Learning	Speed	Attention	Language	Switch (Complex Verbal Fluency)	Similarities (Verbal Reasoning)	Matrix (Visual Reasoning)
Age	0.66	0.74	0.73	0.39	**0.005**	**0.09**	**0.06**	0.17	0.52	0.40	0.51
Disability (EDSS)	**0.09**	**0.07**	0.22	**0.06**	0.30	**0.007**	0.45	0.27	**0.03**	0.97	0.14
FSIQ (WTAR)	**0.02**	**0.05**	**0.02**	**0.09**	**0.03**	**0.01**	0.90	**0.008**	**0.25**	**0.04**	**0.008**
Baseline fatigue (FSS)	0.79	0.12	0.53	**0.03**	0.30	0.34	**0.06**	0.98	0.91	**0.09**	0.31
Fatigue baseline to 3 months	**0.10**	**0.003**	**0.04**	**0.003**	0.28	0.19	0.50	**0.09**	0.75	**0.002**	0.13
Fatigue 3 to 12 months	**0.0002**	**<0.0001**	**0.004**	**<0.0001**	**0.06**	0.15	**0.0002**	**0.02**	**0.01**	0.16	0.22
Fatigue baseline to 12 months	**<0.0001**	**<0.0001**	**0.0004**	**<0.0001**	**0.03**	0.41	**0.0002**	**<0.0001**	**0.001**	**<0.0001**	**0.02**

Note: bold values p < 0.10. BAI = Beck Anxiety Inventory, BDI = Beck Depression Inventory, CSI/T = Cognitive Stability Index/Cognitive Screening Test, DKEFS = Delis-Kaplan Executive Function System, WAIS = Wechsler Adult Intelligence Scale, EDSS = Expanded Disability Status Scale, FSIQ = Full-Scale IQ, WTAR = Wechsler Test of Adult Reading, FSS = Fatigue Severity Scale.

among changes in the outcomes over time (from baseline to 12 months; i.e., 5 study visits) and the a priori selected possible baseline covariates: age, disability (EDSS), Full-Scale IQ (WTAR), and fatigue (FSS). Each of the baseline covariates was significantly associated with 2 or more outcome variables, so we included all 4 potential covariates in the intervention dosage and outcome measure models. We also analyzed associations among changes in fatigue and the outcome measures (Table 4) due to prior results indicating significant fatigue changes during this intervention [24,25]. From baseline to 3 months, fatigue change was significantly associated with 3 of the 4 mood variables (*p*s 0.003 to 0.04) and only 2 of the 7 cognitive variables (*p*s = 0.002 to 0.09). From 3 to 12 months, fatigue change was associated with all of the mood variables (*p*s < 0.0001 to 0.004) and 4 of the 7 cognitive variables (*p*s = 0.0002 to 0.06). Finally, fatigue changes from baseline to 12 months were significantly associated with all of the outcomes measures (*p*s < 0.0001 to 0.03) except CSI/T Speed ($p = 0.41$), suggesting that as fatigue decreased, the mood and cognitive outcome measures improved. Thus, associations among fatigue changes and mood and cognitive scores were more common during the last 9 months of the study. Finally, we analyzed associations between baseline to 12-month changes in weight (%), BMI (%), and the outcomes measures (data not shown). There were no significant correlations between weight or BMI and the mood (*p*s = 0.43 to 0.84) or cognitive outcome (*p*s = 0.22 to 0.98) measures.

Associations among intervention dosage and the outcome measures

Table 5 shows the baseline to 3-month associations (unadjusted models) among the 3-month dosage scores and changes in the mood and cognition variables between baseline and 3 months (between visits 1 and 2). In general, higher participation (dosage) in the study intervention led to greater improvements in the self-reported mood and cognitive outcomes. At 3 months, there were 7 significant associations (of a potential 77) observed between dosage changes in the outcome variables exercise and DKEFS Complex Verbal Fluency ($p = 0.05$); EStim and CSI/T Speed ($p = 0.02$); stretches and DKEFS Language ($p = 0.03$); massage and BAI Anxiety ($p = 0.08$); and meditation and BDI Cognitive ($p = 0.08$), CSI/T Speed ($p = 0.07$), and DKEFS Complex Verbal Fluency ($p = 0.08$). Thus, meditation was related to the most outcome measures after 3 months of the intervention. Also in Table 5 are associations among 3- to 12-month changes in dosage and the outcome measures (all values are 12-month minus 3-month values). The number of significant associations doubled from the 3-month visit (visit 2), with 17 of the 77 possible associations now significant when comparing changes from visit 2 to visit 5. Three- to 12-month exercise dosage changes were associated with the most outcome measure changes (4 of 11 possible), including BAI Anxiety ($p = 0.02$), BDI Cognitive ($p = 0.03$), CSI/T Attention ($p = 0.03$), and WAIS Similarities ($p = 0.06$). Gluten/dairy/eggs and meditation dosage changes were each significantly associated with 3 outcome measure changes from 3 to 12 months. Of the 7 outcome measures, change in CSI/T Attention scores was associated with the most dosage change scores (4 of 7 possible; *p*s = 0.002 to 0.03). From baseline to 12 months, changes in intake of the study diet were significantly associated with 18 of the 22 possible outcome measure changes (*p*s = < 0.0001 to 0.06; only diet was assessed at visit 1/baseline), suggesting that diet was an important contributor to improvements in mood and cognitive function in this MS sample. Specifically, 7 of the 8 mood variables were related to study diet intake (*p*s = <0.0001 to 0.06), and 11 of the 14 cognitive–diet dosage associations were significant (*p*s < 0.0001 to 0.06). Only CSI/T Speed was not related to diet over the 12-month study period.

We also examined the data to identify which outcome measures changed more in response to the intervention over the course of the entire 12-month intervention (Table 5; from the first assessment to 12 months; i.e., 3 to 12 months for exercise/EStim/stress management and baseline to 12 months for the study diet). Interestingly, 7 out of 8 possible mood–study diet associations were significant (*p*s = <0.0001 to 0.06), whereas only 3/20 mood–exercise/EStim/stress management associations were significant (*p*s = 0.02 to 0.09). Similarly, 12-month improvements in cognitive function were more associated with the study diet intake than the home exercise/EStim/stress management activities: 11 of the 14 cognitive–study diet associations

Table 5. Associations (*p* Values) among Changes in Intervention Dosage and Changes in Mood and Cognitive Function (Unadjusted Models).

	Mood Changes				Cognitive Function Changes						
		BDI			CSI/T			DKEFS		WAIS	
Variable	BAI Anxiety	Total	Cognitive	Somatic–Affective	Memory/Learning	Speed	Attention	Language	Switch (Complex Verbal Fluency)	Similarities (Verbal Reasoning)	Matrix (Visual Reasoning)
					Baseline to 3 months[a]						
Vegetables/fruits	0.62	0.29	0.87	0.16	0.70	0.92	0.50	0.35	0.92	0.43	0.91
Gluten/dairy/eggs	0.97	0.51	0.22	0.75	0.48	0.75	0.41	0.18	0.93	0.17	0.73
Exercise	0.61	0.93	0.78	0.90	0.58	0.96	0.52	0.21	**0.05**	0.29	0.20
EStim	0.84	0.95	0.87	0.99	0.87	**0.02**	0.36	0.67	0.42	0.62	0.42
Stretches	0.74	0.45	0.31	0.60	0.54	0.46	0.33	**0.03**	0.92	0.66	0.65
Massage	**0.08**	0.26	0.26	0.36	0.49	0.93	0.64	0.92	0.34	0.93	0.49
Meditation	0.62	0.11	**0.08**	0.20	0.57	**0.07**	0.66	0.56	**0.08**	0.49	0.95
					3 to 12 Months[b]						
Vegetables/fruits	0.89	0.53	0.58	0.21	0.23	0.76	0.54	0.89	0.61	**0.006**	**0.10**
Gluten/dairy/eggs	0.78	**0.05**	0.36	**0.03**	0.94	0.34	0.46	0.19	0.22	0.88	**0.002**
Exercise	**0.02**	0.47	**0.03**	0.85	0.78	0.74	**0.03**	0.31	0.79	**0.06**	0.96
EStim	0.13	0.83	0.83	0.76	0.11	0.86	0.53	0.70	**0.03**	**0.09**	0.17
Stretches	0.54	0.93	0.13	0.48	0.59	0.33	**0.002**	0.16	0.11	0.17	0.41
Massage	0.90	0.39	**0.09**	0.86	0.33	0.62	**0.03**	0.40	0.14	0.56	0.73
Meditation	>0.99	0.38	>0.99	0.23	0.73	0.14	**0.007**	0.46	**0.004**	0.33	**0.08**
					Baseline to 12 months[c]						
Vegetables/fruits	**0.008**	**0.0001**	0.12	<**0.0001**	**0.006**	0.74	**0.04**	**0.005**	**0.01**	<**0.0001**	**0.003**
Gluten/dairy/eggs	**0.001**	**0.001**	**0.06**	**0.001**	**0.001**	0.63	0.21	**0.001**	**0.06**	**0.005**	**0.001**

Note: bold values p ≤ 0.10. BAI = Beck Anxiety Inventory, BDI = Beck Depression Inventory, CSI/T = Cognitive Stability Index/Cognitive Screening Test, DKEFS = Delis-Kaplan Executive Function System, WAIS = Wechsler Adult Intelligence Scale, EStim = neuromuscular electrical stimulation.

[a]Baseline to 3-month values represent *changes* from baseline to 3 months in the outcome measures (visit 2 minus visit 1) and a *single mean* 3-month value for each of the dosage variables (because most dosage variables were not assessed at baseline but at 3 months).

[b]Three- to 12-month values represent changes over time when analyzing 4 time points (visits 2, 3, 4, and 5).

[c]Vegetables/fruits and gluten/dairy/eggs are the only dosage data collected 5 times; thus, baseline to 12-month data represent changes over time in dosage to the vegetables/fruits and gluten/dairy/eggs prescriptions when analyzing 5 time points (visits 1, 2, 3, 4, and 5); all other dosage variables were first assessed at 3 months (visit 2). Vegetables/fruits and gluten/dairy/eggs calculated from food frequency questionnaire (baseline) and daily food logs (3 and 12 months).

were significant (*p*s < 0.0001 to 0.06), whereas 9 of the 35 cognitive–exercise/EStim/stress management associations were significant (*p*s < 0.002 to 0.09). Thus, the majority of the improvements in the mood and cognitive outcome measures were related to the study diet (increased vegetables/fruits and decreased gluten/dairy/eggs).

To examine the unique effects of fatigue on the outcome variable–dosage associations, Table 6 shows *p* values among changes in dosage and mood and cognitive function, controlling for baseline FSS scores (baseline covariate). When controlling for fatigue, the diet–mood significant associations decrease from 7 out of 8 to 2 out of 8; for exercise/EStim/stress management and mood, the number of significant associations changed from 3 out of 20 to 4 out of 20. Regarding cognitive function, the number of significant associations for diet changed from 11 out of 14 to 5 out of 14, and for exercise/EStim/stress management from 9 out of 35 to 8 out of 35. Thus, fatigue contributed to the association between intake of the study diet and improvements in mood and cognitive function, suggesting that it is an important factor in this relationship. As for exercise/EStim/stress management, fatigue appears not to play as much of a role in its relationship with mood and cognitive changes because the estimates of results generally did not change when controlling for baseline fatigue.

To determine whether the additional potential baseline covariates contributed to the intervention and outcome measure changes, additional analyses controlled for age, baseline disability (EDSS), and FSIQ (WTAR) in 3 separate models. Results (data not shown) indicated that these 3 variables did not change the model results, suggesting that they were not unique contributors to the findings. We also included time (visit number) in the models and adding time to the models did not increase the effects of the intervention components on the outcomes.

Discussion

These results support the efficacy and effectiveness of a multimodal intervention (exercise, a modified Paleolithic diet, EStim, and stress management) for improving mood and cognitive function in people with progressive MS. Specifically, the more individuals participated in the intervention activities, the greater improvements they had on self-report measures of anxiety (BAI), depression (BDI), cognitive function (CSI/T, DKEFS), and executive function (WAIS). For the most part, a higher intake of the modified Paleolithic diet was more closely related to mood and cognitive improvements than dosage of the exercise and stress management components. Whereas improvements in anxiety and depression were evident after just a few months (i.e., from baseline to 3 months), significant improvements in cognitive function were generally not observed until later (between 3 and 12 months). Thus, a modified Paleolithic diet, exercise, and stress management intervention may produce mood changes relatively quickly, whereas the benefits for cognition take longer to be observed. Enhanced mood and cognitive function were related to improvements in fatigue, suggesting that changes in fatigue translate to benefits

Table 6. Associations (*p* Values) among Baseline to 12-Month Intervention Dosage Changes and Changes In Mood and Cognitive Function (Controlling for FSS Scores).[a]

	Mood				Cognitive Function						
		BDI			CSI/T			DKEFS		WAIS	
Variable	BAI Anxiety	Total	Cognitive	Somatic–Affective	Memory/Learning	Speed	Attention	Language	Complex Verbal Fluency	Similarities (Verbal Reasoning)	Matrix (Visual Reasoning)
Vegetables/fruits	0.24	0.27	0.88	**0.07**	**0.07**	0.92	0.73	0.42	0.61	0.11	**0.03**
Gluten/dairy/eggs	**0.08**	0.45	0.57	0.32	**0.007**	0.87	0.80	**0.08**	0.84	0.84	**0.007**
Exercise	**0.03**	0.54	**0.02**	0.67	0.98	0.84	0.19	0.21	0.59	0.11	0.80
EStim	0.22	0.33	0.56	0.26	0.17	0.99	>0.99	**0.09**	**0.05**	0.13	0.20
Stretches	0.75	0.93	**0.03**	0.36	0.69	0.64	**0.03**	0.12	0.44	0.29	0.29
Massage	0.74	0.29	**0.09**	0.72	0.43	0.46	**0.03**	0.36	0.16	0.49	0.70
Meditation	0.97	0.38	0.79	0.15	0.69	**0.10**	**0.04**	0.69	**0.007**	0.34	**0.09**

Note: bold values p ≤ 0.10. FSS = Fatigue Severity Scale, BAI = Beck Anxiety Inventory, BDI = Beck Depression Inventory, CSI/T = Cognitive Stability Index/Cognitive Screening Test, DKEFS = Delis-Kaplan Executive Function System, WAIS = Wechsler Adult Intelligence Scale, EStim = neuromuscular electrical stimulation.
[a]Changes in vegetables/fruits and gluten/dairy/eggs are from baseline (visit 1) to 12 months (visit 5); all other dosage variable changes are from 3 (visit 2) to 12 months (visit 5) because they were first assessed at 3 months (visit 2). Vegetables/fruits and gluten/dairy/eggs calculated from food frequency questionnaire (baseline) and daily food logs (3 and 12 months).

in other areas of function. Altogether, these findings suggest that this multimodal approach may benefit other people with progressive MS. Larger, randomized control trials are needed to determine whether these results can be replicated in a larger group, particularly when compared to individuals not partaking in the intervention.

Diet

In the first 3 months of the intervention, participants drastically increased their intake of the recommended vegetables and fruits and all but eliminated their intake of gluten, dairy, and egg products. Many participants reported verbally that once they developed a daily dietary routine, the diet was not difficult to follow, and the reduction in fatigue motivated them to continue with the diet. Indeed, study diet intake was impressive, with participants adhering to the food guidelines 94.5 to 98% of days during the 12-month intervention. The nutritional approaches for MS are varied and may include reducing saturated fat in combination with omega-3 fat supplements [53,54], the use of dietary supplements (e.g., vitamin D, fish oil, lipoic acid), and/or eliminating allergens (e.g., gluten). Despite decades of nutritional recommendations for people with MS, their efficacy and safety are not well understood and there are surprisingly few nutrition and MS clinical trials. In a 2012 *Cochrane Review* [55], the majority were poor in quality and/or did not have clear results. All 6 of the 923 papers that met inclusion criteria in the *Review* examined PUFA diets (no studies on vitamins, antioxidants, or other dietary interventions met criteria), and the data were insufficient to assess potential benefits or harms from PUFA supplementation. In another *Cochrane Review* from 2010 [56], a phase I/II trial [57] reported that 12 months of high-dose vitamin D improved MS outcomes (i.e., relapse rate, disability, T-cell reactivity and proliferation) and had no adverse side effects. This was the only one of 12 trials that met inclusion criteria, and it was low-powered with a high bias risk (not blinded), possibly limiting generalizability. In another study on vitamins and MS, 6 months of riboflavin supplementation (involved in myelin formation in nerve cells) did not improve disability scores (EDSS) versus a placebo control [58]. However, vitamin A derivatives (retinoic acids) decreased inflammatory T-helper cell populations and activation in MS patients [59,60]. Sedel et al. found that high-dose biotin, also involved in myelin production, was associated with improved outcomes (i.e., changes in visual acuity, visual-evoked potentials, proton magnetic resonance spectroscopy, and homonymous hemianopsia) in a progressive MS pilot study [61]. Thus, evidence on the safety and efficacy of nutritional approaches for MS is limited despite 33.7 to 52.4% of people with MS reporting using dietary regimens and supplements [62].

Diet and mood

In general, higher adherence to the modified Paleolithic diet led to greater improvements in mood scores. The benefits of the diet on mood were evident within 3 months and maintained their effectiveness through 12 months. In particular, when we examined changes in mood and diet intake over the entire study period, all of the mood variables were significantly related to increasing vegetable and fruit intake and decreasing or eliminating consumption of gluten, dairy, and eggs (BDI Cognitive was the only exception, $p = 0.12$). Although most of the mood–diet change associations were not significant at 3 months, it is likely that the effects were already taking place, because we saw significant improvements in all of the mood variables from baseline to 3 months.

This is the first known study to investigate a multimodal diet and lifestyle program for mood in people with MS, and very few investigated the impact of a unimodal diet or lifestyle intervention despite a high lifetime prevalence of anxiety or depression in people with MS [5,6]. In one article [63], MS patients who received zinc sulfate had reduced depression scores compared to the placebo group. In another placebo-controlled randomized controlled trial (RCT) [64], vitamin A for 12 months significantly improved fatigue and depression due to the modulation of inflammatory conditions. Participants in the current study initially received supplements (e.g., coenzyme Q10), but high interindividual variation and nonadherence in the first 9 participants led to the remaining people not receiving them [24,25], so the findings cannot be compared. In a separate pilot study [65], MS patients were randomized to 6 months of (1) "whole-practice" naturopathic

plus conventional care; (2) MS education plus conventional care; or (3) conventional care. There were no group differences in depression or fatigue but trends (*ps* = 0.07 to 0.11) toward improved quality of life (SF36), walking ability, and disability (EDSS) in the naturopathic group; the education group had a trend toward improved attention (Stroop test). However, the small sample size ($n = 15$ per group) limits generalizability of the results. Moreover, the majority of their naturopathic group followed a moderately simple diet (they chose from increasingly limited diet options), which involved a less restrictive approach than the current study and was shorter in duration. In the current study, participants received precise instructions for which foods to eat and how much, foods to avoid, and menu ideas, and higher intake of this diet was positively associated with improvements in mood. Thus, a more restrictive diet for a longer duration might be critical to seeing long-lasting mood effects in people with MS.

Despite very few studies on mood and dietary interventions for people with MS, there are investigations on nutrition and mood in healthy and other medical populations. Diets rich in fruits, vegetables, fish, olive oil, nuts, and legumes are protective against depression [66,67], whereas processed food and high-sugar diets increase the risk of depression [66,68]. In a recent review of RCTs examining diets for depression and anxiety [69], 17 of 1274 studies met eligibility criteria, and in half (8/17), depression scores improved significantly more for the treatment than the control group; only 20% reported significant anxiety improvements (2/10; not all assessed anxiety). This RCT included a heterogeneous set of dietary interventions, ranging from individualized nutritional education to group sessions but, in general, the most mood benefits came from including an individualized diet education by a registered dietician. Thus, prior studies and the present investigation provide preliminary evidence of the efficacy of improved nutrition for improving mood, including people with MS.

Diet and cognitive function

Increased intake of the modified Paleolithic diet led to significant improvements in memory/learning, attention, language, complex verbal fluency, and verbal and visual reasoning but not cognitive processing/response speed. The effects of diet intake on cognitive function were not observed at 3 months, but by 12 months, study diet intake was significantly associated with improvements in almost all of the cognitive measures. Along these lines, though very few changes in the cognitive outcomes were significantly different from baseline to 3 months (only WAIS Similarities improved), by 12 months, the majority of cognitive scores improved significantly from baseline. This is the only study we are aware of that examined the effects of a modified Paleolithic diet on cognitive function in people with progressive MS, but there are data to show the benefits that diet has on cognitive function in general. Diets with more dark and leafy greens, fruit, and fish, and less red meats, dairy, and trans-fats are beneficial for overall cognitive health [29], whereas higher trans-fat diets are related to lower cognitive performance [29]. Indeed, the Mediterranean diet (i.e., fruits, vegetables, fish, whole grains, healthy fats) is protective against cognitive decline, potentially due to an association between the nutritional components and brain physiology [70]. Because the modified Paleolithic diet stressed 9 cups of vegetables and fruit per day, it has some shared attributes (increased vegetables and fruits and low glycemic content) with the Mediterranean diet.

Exercise

Despite prior recommendations that people with MS limit activity due to fatigue and pain, exercise and physical activity are now promising intervention strategies for managing the physical symptoms of MS [71]. A meta-analysis reported that exercise training improved quality of life and fatigue, particularly aerobic exercise 90+ minutes per week [20]. A *Cochrane Review* [22] and systematic reviews concluded that exercise therapy was related to improvements in cardiorespiratory function, quality of life, muscle strength, body composition, fitness, disability, fatigue, and mood [20–22]. Indeed, prior studies also found that the current multimodal intervention significantly improved quality of life and fatigue in people with MS [24,25]. Though not as commonly studied as the physical symptoms of MS, psychological symptoms (e.g., anxiety, depression) also respond positively to exercise in people with MS [72,73], and these changes may last longer than the physical benefits [74]. Despite prior studies examining an exercise intervention for the physical and psychological symptoms of MS, this is the first to examine the effects of a long-term, multimodal intervention including diet, exercise, Estim, and stress management.

Exercise and mood

Increased exercise dosage was related to significant improvements in BAI Anxiety and BDI Depression (Cognitive) scores (but not BDI Total or Somatic–Affective scores). EStim and muscle stretches were not related to any mood changes. In a similar study by Swank and colleagues [75], the BDI Total and Cognitive scores did not change after their 8-week aerobic exercise intervention, but BDI "Somato–Affective" scores improved significantly, with benefits lasting 3 months. In the present study, exercise was not related to BDI Total scores, and the opposite of what Swank et al. reported was found for the subscales (exercise dosage was associated with the BDI Cognitive but not Somatic–Affective scores). This discrepancy may be due to methodological differences, with the current intervention lasting one year, including EStim and stress management, and a larger sample size (9 vs 19 participants). That said, both studies provide promising results for people with MS. Garrett et al. [76] also reported longer-term positive effects of exercise on mood, with a 10-week MS exercise intervention leading to significantly improved psychological symptoms (MSIS-29v2), even after 3 months. Similarly, recent MS studies reported that physical activity/exercise was related to decreased depression and anxiety symptoms [72,77]; relaxation training (yoga) also improved depression and anxiety scores [77]. This emerging research collectively provides evidence supporting the use of exercise or physical activity, as well as stress management (e.g.,

meditation, relaxation), for improving mood among individuals diagnosed with MS.

Exercise and cognitive function

Increased dosage of the exercise/EStim/stress management intervention led to more changes in cognitive function than mood, with Speed (CSI/T) the only exception. Attention showed the greatest improvement in relation to exercise dosage: CSI/T Attention change scores were significantly associated with increased participation in exercises, stretches, meditation, and massage. Thus, attention appears to respond well to exercise and stress management activities and may benefit the most from future multimodal interventions. Previous MS research found that physical activity was positively associated with cognitive processing speed (e.g., Paced Auditory Serial Addition Test) but not learning and memory (e.g., Selective Reminding Test) [78]. This is different from the current study, which found that Learning/Memory was related to EStim and Speed was not related to exercise, but there are 2 main differences between studies. First, the current study's CSI/T Speed score was a combined measure of response and processing speed, so it is possible that response speed is not related to exercise, whereas processing speed is. Further, this study included EStim and the comparison study did not, so we cannot compare the EStim outcomes. Swank et al. [75] did not find improvements in working memory or verbal learning cognitive domains after an 8-week aerobic exercise intervention, but as they indicated, the short duration of their intervention (8 weeks) may not be sufficient for cognitive changes. The present study's authors agree with this, because most of the cognitive improvements observed with increased exercise dosage were not significant until 3 to 12 months after the start of the current intervention. Indeed, Baker et al. [79] reported that cognitive function improvements in people with mild impairment were not evident until after 6 months of an exercise intervention (no effects at 3 months), and Colcombe and Kramer [80] indicated that 6 months of exercise is necessary for cognitive improvements in older individuals, particularly for executive control processes (e.g., coordination, inhibition, scheduling, planning, and working memory). Intensity of the aerobic exercise intervention appears to be an important feature. Moreover, in prior MS studies, exercise improved more than just cognitive test scores: Aerobic exercise is associated with improvement in brain activation and less brain matter density declines (both white and grey) [81]. Collectively, these findings highlight the positive effects of exercise on cognitive ability, as well as improved brain functioning and structure, in patients with MS [78,81].

Fatigue, mood, and cognition

In this study, fatigue improvements were significantly related to changes in mood (on all 4 mood measures). It is unclear whether decreased fatigue led to improved mood or vice versa (chicken or the egg). This association might also depend on the person; for some, improved mood leads to reduced fatigue, whereas for others mood changes decrease fatigue severity, or the process may act simultaneously. Although fatigue is one of the most disabling symptoms of MS, its association with other symptoms (e.g., mood) is not well understood, making the symptoms challenging to treat. That said, research shows promising steps toward elucidating the link, with fatigue significantly correlated with mood disorders in MS patients [82]. Immune dysfunction and psychosocial stressors also relate to depression in MS [83], and inflammatory cytokines appear to play a role in the development of MS fatigue [84]. Further, disease processes in MS result in diffuse gamma-aminobutyric acid-ergic (GABAergic) alteration in neurons, and depression is linked to GABAergic neurotransmission [85]. In support of this association, Bakshi et al. [86] reported that MS fatigue correlated significantly with depression, and those common mechanisms may play a role in the pathogenesis of these related conditions. The current study found that changes in fatigue were also significantly related to cognitive improvements (on all cognitive measures, except CSI/T Speed) but, like the mood changes, it is unclear whether improvements in fatigue led to cognitive changes or vice versa. Adding to the complexity, the association between mood and cognitive improvements is unknown. Prior studies reported mixed results [87], suggesting that moderate or severe depression is correlated with effortful aspects of cognition but not automatic information processing [88–90]. In subsequent analyses of the current study's data (data not shown), changes over time (from baseline to 12 months) in the cognitive scores were not significantly associated with changes in BAI anxiety ($ps > 0.31$) or BDI depression scores ($ps > 0.18$; with the exception of CSI/T Attention, $p = 0.03$). Thus, it appears that there is a complex interplay among fatigue, mood, and cognitive function in people with MS. Though the associations among these 3 important symptoms are not discernable using the current study design, they will be important to assess in future studies.

Complexity of the intervention

Multiple interventions were used simultaneously to target different MS symptoms, making it difficult to discern the effects of a specific intervention or outcome. No known prior studies used an exercise, diet, and stress management multimodal intervention; thus, the improvements we found in MS-related mood and cognition likely resulted from synergistic effects. This comprehensive approach, though challenging, might be needed to receive optimal outcomes. Studies comparing the individual components to their combined effects would clarify whether certain components have a greater impact, but given the progressive nature of the disease, it could be challenging to enroll participants in a unimodal trial arm. To increase the feasibility of the intervention, (1) participants were required to have an adult companion to assist and support them and (2) the run-in phase provided an opportunity to practice the intervention and experience potential challenges. Of the 26 who enrolled in the run-in phase, 21 enrolled in the main study (i.e., 19% withdrew or were ineligible), and 2 did not complete the study. Though one of them became ineligible due to cognitive decline, the other only completed baseline data before dropping out for unknown reasons, leaving 19 out of 26 (73%) participants eligible for the main study. Thus, adhering to this complex multimodal intervention may be difficult for some people with MS, particularly those with more disability. Moreover, the

prescribed diet may be challenging (e.g., 9 daily cups of fruits/vegetable, and no gluten, eggs, dairy), time-consuming, and expensive (we recommended organics), particularly for an extended period of time. For these reasons, participants needed an adult companion to support them with adherence and we provided recipes and menus. Many participants reported that once they developed a daily dietary routine, the diet was not difficult to follow, and the reduction in fatigue motivated them to continue with the diet and increased their ability to complete everyday tasks such as food preparation, providing evidence for its feasibility in this sample. That said, these results should be verified by other researchers and a follow-up study is needed to verify the nutritional adequacy of the diet and to assess its feasibility and safety over 2 to 3 years.

Limitations and strengths of the study

This exploratory pilot study has several limitations. First, the sample size was small, limiting its generalizability and necessitating that the results be interpreted with caution. However, a small feasibility study was needed to determine whether the prior case report interventions [23] would (1) be adopted and well tolerated by others with progressive MS and (2) influence mood and cognitive function in a small sample. Second, the study lacked randomization and a control or placebo group. Due to the nature of the intervention, a placebo group was not possible because individuals are active participants and well educated about each intervention component (unlike taking a pill). Given the progressive nature of the disease, persons with MS tend not to agree to participate in a control group, especially for a long period of 12 months. Further, the current sample was SPMS and PPMS patients (most with moderate to severe disability) who are anticipated to have a steady worsening of disability and gait scores each year [91,92] and would not be anticipated to experience a spontaneous reduction in MS symptoms. The current study population instead showed enhanced mood and cognition; thus, improvements cannot be solely due to placebo effects or performance bias. Further, the first 9 participants received supplements but the last 10 did not, so this makes a comparison between supplement and non-supplement participants and the intervention's statistical significance challenging to determine. Finally, we did not measure the nutritional adequacy of the diet. As part of the study approval process, the diet's nutritional adequacy was analyzed using 3-day food records and nutrient data software, and the diet had >90% probability of exceeding the recommended daily allowances for vitamins with recommended daily allowances. The nutritional adequacy of the study diet is important and needs to be analyzed and reported (and over a longer study period) to ensure the long-term safety of this nutritional approach. In summary, additional, larger studies are needed to further assess the safety, feasibility, and efficacy of this multimodal intervention for mood and cognitive function in a larger sample of people with MS and over a longer study period.

Conclusion

The multimodal intervention, consisting of a modified Paleolithic diet, exercise, EStim, and stress management, improved mood and cognitive function in people with progressive MS. Specifically, the more individuals participated in the intervention, the greater improvements they had on measures of anxiety, depression, and cognitive and executive function. Changes in the mood and cognitive outcomes were related to changes in fatigue, suggesting that improvements in fatigue are associated with mood and cognitive function improvements. These findings have the potential to improve quality of life and function for people with progressive forms of MS. Pharmacologic therapies may cause significant side effects, be cost-prohibitive, and/or not benefit a significant number of MS patients [65], so this study offers a novel approach to treating MS-related mood and cognitive function. This is clinically significant because up to half of MS patients will be diagnosed with anxiety and/or depression [5,6], which can exacerbate cognitive deficits [7], highlighting the necessity of including psychological factors in MS assessment and treatment plans. In summary, a modified Paleolithic diet, stress management practices, and exercise interventions like this one have the potential to improve the MS disease course by improving the deleterious mood and cognitive symptoms that can lead to considerable suffering in people with 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 of the other authors report no conflicts of interest in this work.

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