

Diet-induced changes in functional disability are mediated by fatigue in relapsing-remitting multiple sclerosis: A secondary analysis of the WAVES randomized parallel-arm trial

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Abstract

Background: People with multiple sclerosis (MS) often report dietary modifications; however, evidence on functional outcomes remains sparse.

Objective: Evaluate the impact of the low-saturated fat (Swank) and modified Paleolithic elimination (Wahls) diets on functional disability among people with relapsing-remitting MS.

Methods: Baseline-referenced MS functional composite (MSFC) scores were calculated from nine-hole peg-test (NHPT), timed 25-foot walk, and oral symbol digit modalities test (SDMT-O) collected at four study visits: (a) run-in, (b) baseline, (c) 12 weeks, and (d) 24 weeks. Participants were observed at run-in and then randomized at baseline to either the Swank ($n = 44$) or Wahls ($n = 43$) diets.

Results: Among the Swank group, MSFC scores significantly increased from -0.13 ± 0.14 at baseline to 0.10 ± 0.11 at 12 weeks ($p = 0.04$) and 0.14 ± 0.11 at 24 weeks ($p = 0.02$). Among the Wahls group, no change in MSFC scores was observed at 12 weeks from 0.10 ± 0.11 at baseline but increased to 0.28 ± 0.13 at 24 weeks ($p = 0.002$). In both groups, NHPT and SDMT-O z-scores increased at 24 weeks. Changes in MSFC and NHPT were mediated by fatigue.

Discussion: Both diets reduced functional disability as mediated by fatigue.

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Introduction

People with multiple sclerosis (MS) express interest in using dietary strategies to improve their wellness,¹ with approximately half reporting modifying their diets.² However, clinicians are reluctant to provide dietary information to their patients with MS³ due, in part, to a lack of evidence for the effect of diet on MRI-based disease activity and progression and unknown mechanisms by which diet impacts the disease course.^{4–6} This has led to people with MS not receiving the clinical resources and support they

desire for improving their diets.⁷ Instead, people with MS likely rely on dietary information obtained from online sources⁸ which may not be based on evidence.⁹

Recently, two meta-analyses of randomized dietary intervention trials found a significant impact of dietary interventions on fatigue and quality of life among people with MS.^{10,11} One of these meta-analyses¹⁰ resulted in members of the Nutrition Workgroup of the National MS Society recommending a healthy diet as an adjunct therapy for people with MS.¹² However,

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significant questions remain as the other recent meta-analysis additionally investigated the effect of dietary interventions on disability status and observed a standardized mean difference (95% confidence interval (CI)) of -0.19 ($-0.40, 0.03$) for the effect of dietary interventions on Expanded Disability Status Scale (EDSS) values.¹¹ Given this null finding, more research is needed to fully elucidate the impact of dietary interventions on disability among people with MS.

Two popular diets in the MS community are the low-saturated fat (Swank) and modified Paleolithic elimination (Wahls) diets.^{2,13} In a randomized parallel-arm (WAVES) trial comparing these two diets among people with relapsing-remitting MS (RRMS), both diet groups experienced statistically and clinically significant reductions in fatigue and improvements in quality of life.¹⁴ Participants also completed the nine-hole peg-test (NHPT), timed 25-foot walk (T25FW), and oral symbol digit modalities test (SDMT-O),¹⁵ which are components of the MS functional composite (MSFC),¹⁶ an objective measure of functional disability in MS¹⁷ that correlates well with the EDSS.¹⁸ A recent retrospective analysis observed an association between higher Mediterranean diet adherence and decreased functional disability as assessed by the MSFC¹⁹; however, prospective studies investigating the effect of dietary intervention on the MSFC are sparse and limited by methodological or reporting issues.^{20–24} Therefore, the objectives of this secondary analysis of the WAVES trial were to evaluate the effects of the Swank and Wahls diets on functional disability and explore the influence of fatigue on changes in functional disability among individuals with RRMS.

Participants and methods

Participants

This is a secondary analysis of a 36-week, randomized, parallel-arm, single-blinded trial conducted at the University of Iowa showing that both the Swank and Wahls diets cause significant improvements in quality of life and reductions in fatigue.¹⁴ Study activities took place from August 2016 to January 2020. The University of Iowa Institutional Review Board approved the trial which followed the Consolidated Standards of Reporting Trials (CONSORT) reporting guidelines. Written and informed consent was obtained from all participants.

Participants aged 18–70 years were recruited from Iowa City, IA and the surrounding area. Briefly,

participants were eligible for the trial if they: (a) had neurologist-confirmed RRMS based on the 2010 McDonald Criteria,²⁵ (b) had fatigue severity scale (FSS) ≥ 4.0 , (c) were able to walk 25 feet with unilateral or no support, (d) were not pregnant nor planning to become pregnant, and (e) were willing to comply with all study procedures. Major exclusion criteria included: (a) MS relapse, change in disease-modifying drug therapy, or change medication for symptom management within the previous 12 weeks; (b) BMI <19 kg/m²; (c) severe cognitive impairment as determined by the short portable mental health questionnaire²⁶; (d) self-reported adverse reactions to gluten-containing foods; (e) diagnosed with or treated for major comorbidities as detailed in the trial protocol.¹⁵

Study procedures

Data collection occurred during four study visits, each spaced 12 weeks apart: (a) run-in, (b) baseline, (c) 12 weeks, and (d) 24 weeks. Participants were randomized 1:1 at baseline to either the Swank or Wahls diets using password-protected randomization tables, which were accessible only by the study registered dietitian nutritionists (RDNs) who randomized participants. Study diet behavioral theory-based education was provided by the study RDNs, who also provided support consisting of two in-person and five telephone behavioral theory-based nutrition counseling sessions for the first 12 weeks of the intervention. During the second half of follow-up, RDN support was discontinued, but participants could still contact the RDNs any time for support or assistance.

Study diets

The composition of both diets has been reviewed in detail elsewhere.¹³ Briefly, the Swank diet limits saturated fat to ≤ 15 g per day and provides 20–50 g of unsaturated fat, four servings of grains, and four servings of fruits and vegetables (FV) per day. The Wahls diet recommends 6–9 servings of FV and 6–12 ounces of meat per day. All grains, legumes, eggs, and dairy foods are excluded from the Wahls diet. Nightshade vegetables were also excluded between the baseline and the 12-week timepoint, and then reintroduced between the 12-week and 24-week timepoints. Participants were emailed personalized feedback on their diet-specific checklists every 4 weeks from the study RDN to encourage adherence to their assigned study diet, which was previously reported as 80% adherence among the Wahls diet group and 87% among the Swank group based on analysis of 3-day weighed food records at 12 weeks.¹⁴ Participants in both groups were instructed to maintain the same level of physical activity and provided

the same supplement regimen to eliminate potential confounding effects from differing regimens.¹⁵

Outcomes

The results for the FSS, 6-min walk test (6MWT), and SDMT-O have been published previously.^{14,27} For this secondary analysis, the MSFC was used as a quantitative objective assessment of functional disability.²⁸ The MSFC is comprised of the T25FW, NHPT, and SDMT-O. The T25FW evaluates ambulation and the NHPT evaluates manual dexterity.²⁹ The SDMT-O was included in the MSFC as it is easier to administer and has similar reliability and better validity over the paced auditory serial addition test.¹⁶ All outcomes were collected using standardized procedures by masked assessors. MSFC scores were determined for all participants using standard scoring procedures²⁸ with the modification to include the SDMT-O.¹⁶ Baseline-referenced z-scores were calculated for each MSFC component using the baseline mean and standard deviation values of the entire study sample and averaged into an MSFC score. Increases in MSFC scores indicate reductions in functional disability. Clinically meaningful changes were defined as a ≥ 8 -point increase in the number correct for the SDMT-O,³⁰ $\geq 20\%$ reductions in time for the NHPT and T25FW,²⁹ and a ≥ 0.5 -point increase in MSFC score.³¹

Statistical analysis

The trial was powered to detect within- and between-group differences in FSS (the primary outcome) which also provided 90% power for secondary outcomes including the NHPT, T25FW, and SDMT-O¹⁵; however, no *a priori* power calculation was conducted for the MSFC. Descriptive statistics were calculated for every variable at enrollment using frequencies, means \pm standard error, and medians (interquartile range). Distributions of continuous variables were evaluated for normality by graphical observation, and outliers were checked for accuracy.

Generalized linear mixed models (GLMMs)³² were used to estimate and test the interacting effects of diet and time on outcome measures while accounting for repeated measures for each participant using a random effect. Models for outcomes with normal and right-skewed distributions specified identity and log link functions, respectively. Other potentially important variables (age, sex, BMI, smoking status, alcohol consumption, walking assistance, years since MS diagnosis, disease-modifying drug use, baseline vitamin D, baseline 6MWT distance, educational attainment) were considered for inclusion in

each model to assess their relationship with the outcome and obtain the modified estimates for the diet and time effects. For each unique model (outcome and predictor set combination), the Akaike information criterion (AIC)³³ was calculated for model selection. For each outcome, the model with the smallest AIC was deemed the optimal predictor set for estimating each adjusted relationship. Point estimates, 95% CIs, and *p*-values of the group-specific mean changes in outcome measures over visits were generated for each optimal model.

Due to the use of baseline values for z-score calculations, the run-in visit was excluded from analyses of MSFC scores and component z-scores. For primary MSFC analysis, data from all participants completing 12- and 24-week assessments were included. Additional analyses were conducted for the NHPT, T25FW, and SDMT-O z-scores and raw values. The two-item MSFC (MSFC-2), which excludes the SDMT-O, was also assessed to confirm findings while limiting bias from potential practice effects due to the frequent SDMT-O assessments.³⁴ Furthermore, a sensitivity analysis including only participants who were adherent to their assigned diet was conducted. The proportion of participants in each group exceeding thresholds for clinically significant changes was compared using Fisher's exact tests. The relationship between fatigue and functional outcomes was explored with additional GLMM models, spearman's rank correlation analyses, and causal mediation analyses.

All analyses were conducted with two-sided tests ($\alpha = 0.05$) using SAS software (version 9.4, SAS Institute, Inc.).

Results

This secondary analysis included 77 participants (39 Wahls and 38 Swank) who completed the primary study endpoint at 12 weeks and 72 participants (35 Wahls and 37 Swank) who completed follow-up to 24 weeks (Figure 1). At baseline, no differences in demographics, disease status, or lifestyle characteristics were observed between groups (Table 1).

There were no significant differences between groups at any time point for any outcome. The increase in MSFC scores from baseline values (-0.13 ± 0.14) to values at 12 weeks (0.10 ± 0.11) and 24 weeks (0.14 ± 0.11) were significant ($p = 0.04$ and $p = 0.02$, respectively) in the Swank group (Table 2). For the Wahls group, no changes in MSFC scores from baseline values (0.10 ± 0.11) were observed at 12 weeks (0.16 ± 0.10) but were at 24 weeks (0.28 ± 0.13 ; $p = 0.002$).

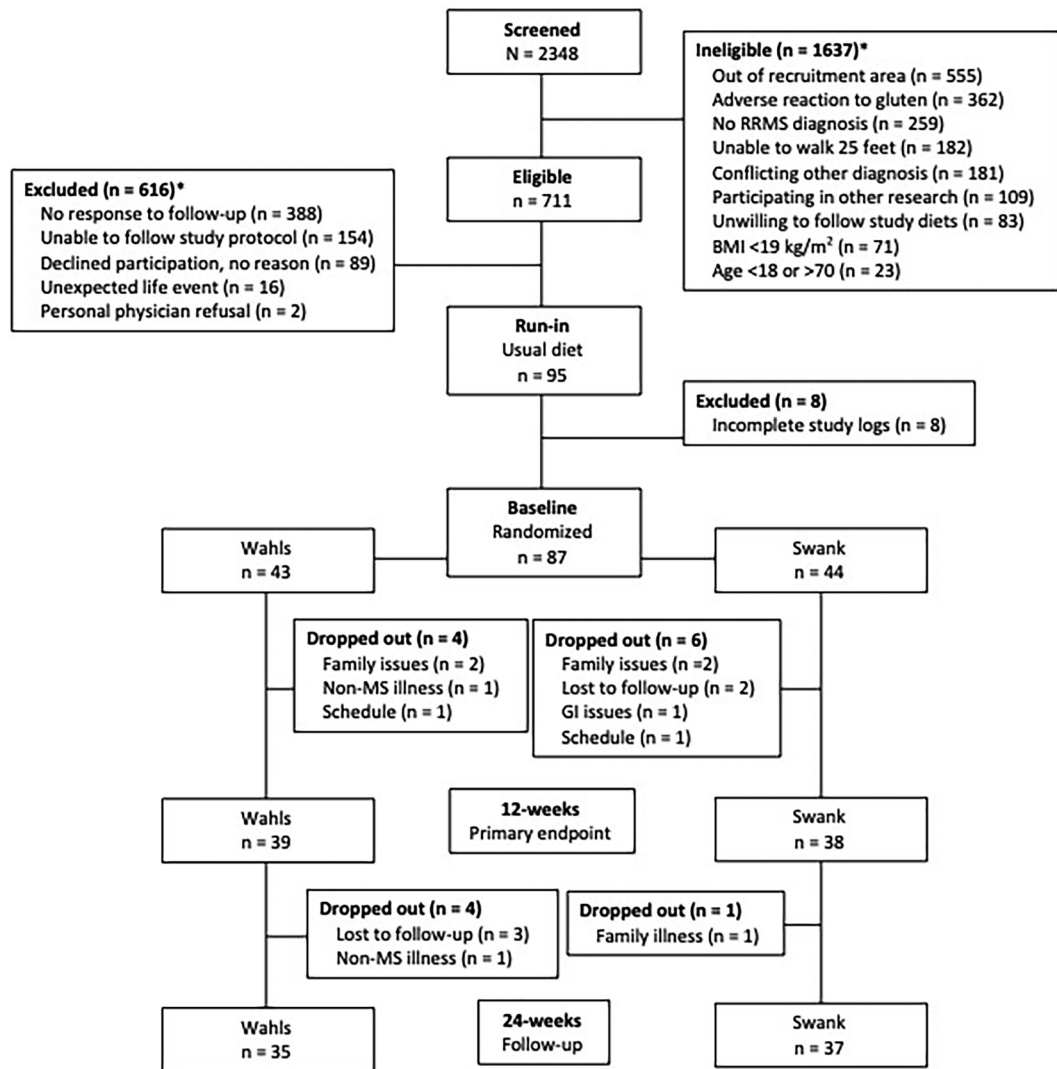


Figure 1. Study recruitment and participant flow diagram. Ineligibility or exclusion counts may not add up to the sum of ineligible or excluded because some participants were found ineligible or were excluded for multiple reasons. Adapted with permission.¹⁵

Findings for the MSFC-2 were attenuated in the Swank group but values were significantly higher in the Wahls group at 12 and 24 weeks compared to baseline. For the individual components of the MSFC, NHPT z-scores increased from -0.19 ± 0.16 at baseline to 0.07 ± 0.17 at 24 weeks in the Swank diet group ($p < 0.001$). Similarly, NHPT z-scores increased from 0.20 ± 0.15 at baseline to 0.47 ± 0.18 at 24 weeks in the Wahls diet group ($p = 0.003$). No changes in NHPT z-scores were observed at 12 weeks. Among the Swank diet group, SDMT-O z-scores increased from -0.08 ± 0.16 at baseline to 0.26 ± 0.16 at 12 weeks ($p < 0.001$) and 0.22 ± 0.17 at 24 weeks ($p = 0.009$). No changes in SDMT-O z-scores from baseline values (0.04 ± 0.16) were observed at 12 weeks (0.13 ± 0.16) but were at

24 weeks (0.28 ± 0.19 ; $p = 0.02$) among the Wahls group. There were no significant within-group changes observed for T25FW z-scores at 12 or 24 weeks for either group.

The interpretation of findings did not differ in analyses of raw values other than the statistically significant improvement in NHPT at 24 weeks that was no longer observed in the Swank group (Table 2). No differences were observed between run-in and baseline values among the Wahls diet group, but the Swank diet group had a statistically significant pre-intervention increase in SDMT-O correct responses. Interpretation of unadjusted results did not change for variables with covariates included in the optimal

Table 1. Baseline characteristics of participants who completed a 12-week intervention of the LSF or MPE diets^a.

Characteristics	LSF	MPE	<i>P</i> -value ^b
<i>N</i>	38	39	-
Age (years)	46.9 ± 1.7	46.4 ± 1.5	0.84
Sex (female)	35 (92.1)	32 (82.1)	0.31
MS duration (years)	12.1 ± 1.6	9.3 ± 1.0	0.14
Disease-modifying drug use			0.83
None	13	10	
Oral	11	11	
Injectable	10	12	
Infused	4	6	
Race (Caucasian)	36 (94.7)	38 (97.4)	0.99
Education			0.32
High school	0 (0.0)	3 (7.7)	-
Some college	12 (31.6)	10 (25.6)	-
4-year degree	11 (28.9)	8 (20.5)	-
Advanced degree	15 (39.5)	18 (46.2)	-
Smoking status			0.13
Never	29 (76.3)	23 (59.0)	-
Former	3 (7.9)	2 (5.1)	-
Current	6 (15.8)	14 (35.9)	-
Alcohol drinks per month ^c			0.99
None	6 (15.8)	7 (17.9)	-
Within recommendations	29 (76.3)	29 (74.4)	-
Above recommendations	3 (7.9)	3 (7.7)	-
BMI (kg/m ²)	27.6 ± 0.94	30.2 ± 1.3	0.11
6-min walk distance (meters)	481 ± 16.3	459 ± 10.3	0.40
Walking assistive device used (y)	5 (13.2)	4 (10.3)	0.73
Serum vitamin D (nmol/L)	47.9 ± 3.9	50.9 ± 3.2	0.55

^aData are shown as mean ± SEM or *N* (%). There were no significant differences in baseline values between groups. Adapted with permission.¹⁵

^bSignificance determined by Fisher's exact or two-sample t-tests.

^cAlcohol recommendations defined as ≤ 1 standard drink per day for females and ≤ 2 standard drinks per day for males.

model (Supplemental Table 1). Findings for the MSFC, NHPT, SDMT-O, and T25FW were consistent in a sensitivity analysis excluding participants who were not adherent to their assigned diet (Supplemental Table 2). Inclusion of walking assistance device use as a covariate in models did not change the interpretation of results for T25FW z-scores or raw values (data not shown).

MSFC 24-week changes were significantly correlated with 24-week changes in the NHPT ($r_s = -0.61$; $p < 0.001$), SDMT-O ($r_s = 0.74$; $p < 0.001$), T25FW ($r_s = -0.34$; $p = 0.004$), and 6MWT ($r_s = 0.32$; $p = 0.007$) but not with FSS ($r_s = -0.08$; $p = 0.48$; Table 3). In addition, 24-week changes in the 6MWT were correlated with 24-week changes in the T25FW ($r_s = -0.54$; $p < 0.001$). Inclusion of FSS values as a covariate in

models completely attenuated all significant results for all outcomes (data not shown). Causal mediation analysis showed that 24-week changes in FSS significantly mediated the effect of the dietary interventions on MSFC, NHPT, 6MWT with significant indirect effects (95% CIs) of 0.16 (0.02, 0.31) for MSFC, -2.03 (-3.55, -0.50) for NHPT, and 34.9 (12.3, 57.5) for 6MWT (Table 4).

At 24 weeks, 8.3% participants in the Swank group and 8.8% in the Wahls group had MSFC scores increases that exceeded the threshold of ≥0.5 points for clinical significance ($p > 0.99$). Furthermore, 11.1% participants in the Swank group and 8.8% in the Wahls group had improvements in the SDMT-O that exceeded the threshold of ≥8.0 points for clinical

Table 2. Optimal model multiple sclerosis functional composite scores among participants with RRMS assigned to the Swank low-saturated fat and Wahls modified Paleolithic elimination dietary interventions^{a,b}.

Outcome	Unit	Study visit			
		Run-in	Baseline	12 weeks	24 weeks
Swank					
MSFC	score	NA ^c	-0.13 ± 0.14	0.10 ± 0.11*	0.14 ± 0.11*
-NHPT	z-score	NA ^c	-0.19 ± 0.16	-0.06 ± 0.17	0.07 ± 0.17***
-SDMT-O	z-score	NA ^c	-0.08 ± 0.16	0.26 ± 0.16***	0.22 ± 0.17**
-T25FW ^d	z-score	NA ^c	-0.14 ± 0.23	0.06 ± 0.06	0.09 ± 0.06
MSFC-2	score	NA ^c	-0.15 ± 0.17	0.02 ± 0.11	0.10 ± 0.11
NHPT ^e	seconds	20.9 ± 0.14	20.6 ± 0.15	20.3 ± 0.14	20.0 ± 0.14
SDMT-O	number correct	57.8 ± 1.61*	60.4 ± 1.51	63.3 ± 1.52***	62.9 ± 1.60**
T25FW ^f	seconds	3.95 ± 0.30	4.48 ± 0.40	3.68 ± 0.25	3.64 ± 0.25
6MWT	meters	460 ± 19.1	481 ± 16.3	485 ± 15.7	491 ± 16.6
Wahls					
MSFC	score	NA ^c	0.10 ± 0.11	0.16 ± 0.10	0.28 ± 0.13**
-NHPT	z-score	NA ^c	0.20 ± 0.15	0.26 ± 0.14	0.47 ± 0.18**
-SDMT-O	z-score	NA ^c	0.04 ± 0.16	0.13 ± 0.16	0.28 ± 0.19*
-T25FW ^d	z-score	NA ^c	0.04 ± 0.09	0.09 ± 0.08	0.06 ± 0.11
MSFC-2	score	NA ^c	0.13 ± 0.10	0.19 ± 0.09*	0.28 ± 0.12*
NHPT ^e	seconds	18.9 ± 0.17	18.3 ± 0.17	18.1 ± 0.16	17.5 ± 0.16*
SDMT-O	number correct	60.2 ± 1.43	61.2 ± 1.53	62.0 ± 1.55	63.5 ± 1.83*
T25FW ^f	seconds	3.84 ± 0.27	3.90 ± 0.27	3.71 ± 0.26	3.80 ± 0.26
6MWT	meters	468 ± 19.3	459 ± 10.3	468 ± 20.3	495 ± 18.7**

^aAll values mean ± SEM with z-scores referenced to the full sample at baseline. * indicates statistical significance compared to baseline values ($p \leq 0.05$), ** indicates statistical significance compared to baseline values ($p \leq 0.01$), *** indicates statistical significance compared to baseline values ($p \leq 0.001$) as determined by optimal general linear mixed models according to AIC. Optimal models for outcomes without superscript letters did not include covariate adjustment based on AIC values.

^bAbbreviations: MSFC = multiple sclerosis functional composite; MSFC-2 = 2-item MSFC; NA = not applicable; NHPT = nine-hole peg test; SDMT-O = symbol digit modalities test – oral; T25FW = timed 25-foot walk; 6MWT = 6-min walk test.

^cRun-in values omitted as MSFC scores and component z-scores were calculated using baseline values.

^dModel adjusted for alcohol consumption.

^eModel adjusted for age and BMI.

^fModel adjusted for age, years with MS, and alcohol consumption.

significance ($p > 0.99$). In addition, no participants in either group had clinically meaningful improvements in T25FW or NHPT values. Clinically significant thresholds corresponded to baseline-referenced z-scores of 0.82 for SDMT-O, 1.02 for T25FW, and 1.04 for NHPT.

Discussion

In this secondary analysis of the WAVES trial, both the Swank and Wahls diets were shown to statistically reduce functional disability, as assessed by the MSFC,¹⁷ after 24 weeks. In addition, both groups also had statistically significant improvements in NHPT and SDMT-O z-scores at 24 weeks; however,

there was no change in T25FW for either group. The effect of the dietary interventions on MSFC, NHPT, and 6MWT values was significantly mediated by fatigue.

Five previous dietary intervention trials assessed functional disability using the MSFC. One reported only baseline values despite reporting that assessments occurred throughout follow-up.²¹ Three reported each of the three assessments used for MSFC calculations but did not report MSFC scores.^{20,22,23} The fifth reported that significant within-group MSFC improvements occurred in the plant-based low-fat intervention group over 12 months, but no differences were observed

Table 3. Spearman rank correlation between 24-week changes from baseline for fatigue and functional outcomes^{a,b}.

	FSS	MSFC	NHPT	SDMT-O	T25FW	6MWT
FSS	1.00	-0.08 (0.48)	-0.01 (0.91)	-0.20 (0.11)	0.09 (0.46)	-0.23 (0.07)
MSFC		1.00	-0.61 (<0.001)	0.74 (<0.001)	-0.34 (0.004)	0.32 (0.007)
NHPT			1.00	-0.07 (0.59)	0.19 (0.12)	-0.18 (0.15)
SDMT-O				1.00	-0.08 (0.53)	0.19 (0.13)
T25FW					1.00	-0.54 (<0.001)
6MWT						1.00

^aSpearman rank correlation coefficients shown as r_s (p -value).

^bAbbreviations: FSS = fatigue severity scale; MSFC = multiple sclerosis functional composite; NHPT = nine-hole peg-test; SDMT-O = oral symbol digit modalities test; T25FW = timed 25-foot walk; 6MWT = 6-min walk test.

compared to the control group.²⁴ Due to the potential effect of exercise on MSFC, the findings from the fifth trial are confounded due to the inclusion of an exercise intervention in both groups.²⁴ Therefore, the findings from the present study are the first known to report on dietary intervention-specific changes in MSFC scores.

In the WAVES trial, the Swank and Wahls diets were previously shown to reduce fatigue and increase quality of life after 12 weeks¹⁴; whereas the present secondary analysis indicates that reductions in functional disability occur at 24 weeks. This discrepancy in time between improvement in patient-reported outcomes and functional disability suggests that potential diet-induced changes in MS-specific functional outcomes require a longer duration intervention than changes in patient-reported outcomes. This observation is supported by previous findings from the WAVES trial showing that both groups had statistically significant improvements in the 6MWT at 24 weeks,¹⁴ which seemingly contradicts the lack of observed change in T25FW in the present study. Therefore, other factors are associated with improvements in the 6MWT. Indeed, the present analysis indicates that changes in the 6MWT are mediated by fatigue whereas the T25FW is not mediated by fatigue.

The observation in the present study, that functional disability was statistically reduced in both diet groups at 24 weeks, is encouraging as it suggests that the potential effects of diet on functional disability are modulated by similar diet components rather than the unique composition of each diet. Corroborating this suggestion are results of a recent network meta-analysis that found only diets recommending high intake of fruits and vegetables and avoidance of ultra-processed foods significantly reduced fatigue and improved quality of life.¹⁰

These recommendations are consistent across both the Swank and Wahls diets investigated in the present study.¹³ Furthermore, these recommendations are consistent with the Mediterranean diet, for which adherence is linked to less functional disability¹⁹ and greater brain volume³⁵ among people with MS.

The strengths of this study include the use of an objective measure of functional disability, masked assessors, repeated measures, and robust analytical methods. Additionally, there was high-diet adherence ($\geq 80\%$) among both groups as evidenced by analysis of weighed food records.¹⁴ This secondary analysis is limited by lack of a usual diet control group, no *a priori* power calculation for the MSFC, lack of diversity among the study participants, short duration of intervention, significant pre-intervention improvements among the Swank diet group, the reintroduction of nightshade vegetables among the Wahls group, and the wide range of exclusion criteria which limit the generalizability of the findings. Furthermore, the use of a single version of the SDMT-O necessitates caution due to the potential for practice effects³⁴; accordingly, results for the MSFC2, which excludes the SDMT-O, were attenuated in the Swank group. The low proportion of participants with clinically significant improvements limits the utility of recommendations for either of these diets investigated for short-term disability management among individuals with MS. However, it is worth noting that the low proportion with clinically meaningful SDMT-O changes are partially explained by the use of the recently recommended SDMT-O threshold of clinical significance which is twice the previous threshold.³⁰

This study provides preliminary evidence for the effect of dietary interventions on functional disability,

Table 4. Causal mediation analysis for the effect of 24-week changes in fatigue on 24-week changes in functional outcomes.

	Total effect		Direct effect		Indirect effect		Percentage mediated
	Effect size (95% CI)	p-value	Effect size (95% CI)	p-value	Effect size (95% CI)	p-value	
MSFC	0.22 (-0.03, 0.46)	0.09	0.05 (-0.22, 0.32)	0.98	0.16 (0.02, 0.31)	0.02	76.2%
NHPT	-0.82 (-3.31, 1.68)	0.52	1.21 (-1.51, 3.93)	0.38	-2.03 (-3.55, -0.50)	0.009	249%
SDMT-O	2.44 (-0.72, 5.61)	0.13	0.60 (-2.95, 4.16)	0.74	1.84 (-0.03, 3.71)	0.06	75.3%
T25FW	-0.62 (-1.86, 0.62)	0.33	-0.33 (-1.72, 1.06)	0.64	-0.29 (-0.96, 0.38)	0.40	46.8%
6MWT	22.7 (-13.2, 58.4)	0.22	-12.2 (-50.1, 25.6)	0.35	34.9 (12.3, 57.5)	0.003	154%

Abbreviations: MSFC = multiple sclerosis functional composite; NHPT = nine-hole peg-test; SDMT-O = oral symbol digit modalities test; T25FW = timed 25-foot walk; 6MWT = 6-min walk test.

as assessed by the MSFC, in RRMS and shows that fatigue mediates this effect largely through the NHPT. The observation that functional disability was reduced in both diet groups suggests that the benefits of dietary intervention in MS are driven by similar diet components, allowing patients to choose to follow dietary patterns based on their individual preferences.¹² Due to the limitations of the present study, future well-designed randomized controlled trials with an *a priori* defined objective to explore the impact of diet on functional disability are needed to confirm these findings and better understand the clinical usefulness of dietary interventions for disability management among people with MS.

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Data availability

The data presented in this study are available on request from the corresponding author. The data are not publicly available due to the privacy of the study participants.

Conflict of interests

TLW personally follows and promotes the Wahls™ diet. She has equity interest in the following companies: Terry Wahls LLC; TZ Press LLC; The Wahls Institute, PLC; FBB Biomed Inc; and the website: <http://www.terrywahls.com>. She also owns the copyright to the books *Minding My Mitochondria* (2nd Edition) and *The Wahls Protocol*, *The Wahls Protocol Cooking for Life*, and the trademarks The Wahls Protocol® and Wahls™, Wahls Paleo™, and Wahls Paleo Plus™ diets. She has completed grant funding from the National Multiple Sclerosis Society for the Dietary Approaches to Treating Multiple Sclerosis Related Fatigue Study. She has financial relationships with Vibrant America LLC, Standard Process Inc., MasterHealth Technologies Inc., Foogal Inc., Levels Health Inc., and the Institute for Functional Medicine. She receives royalty payments from Penguin Random House. TLW has conflict of interest management plans in place with the University of Iowa and the Iowa City Veteran's Affairs Medical Center.

Disclosures

Aspects of this work were presented at the 2020 ACTRIMS Forum and 2023 CMSC annual meetings.


Author contributions

LJ Crippes wrote the first draft of the manuscript with revisions from SMS, FS, and TJT. TJT cleaned and analyzed the data with supervision from LMR and PTE. LMR managed unblinded data. JK and CG were the study team neurologists. LJ Carr, WGD, KFH, BB, and JK trained study staff on assessment methods, assisted in data acquisition and interpretation, and oversaw study procedures. TJT planned the present analysis. TLW and LGS designed the trial and oversaw all study procedures. All authors have read and approved the final version of the manuscript.

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Supplemental material

Supplemental material for this article is available online.

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