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Original article

Modified Mediterranean Diet VS. Traditional Iranian Diet: Efficacy of Dietary Interventions on Dietary Inflammatory Index Score, Fatigue Severity and Disability in Multiple Sclerosis Patients

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Running head: Mediterranean diet and multiple sclerosis

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Iman Namjoo: Visualization, Project administration

Mohammad Borzoo-Isfahani: Data Curation, Resources

Fariborz Poorbaferani: Formal analysis

Amir Reza Moravejolahkami: Conceptualization, Methodology, Software, Validation, Formal analysis, Writing - Review & Editing, Supervision

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Abstract

Background

Current evidence suggests that adherence to the Mediterranean Diet (MeD) can reduce inflammation in chronic diseases; however, studies pertaining to Relapsing-Remitting Multiple Sclerosis (RRMS) are limited. Therefore, the aim of this study was to investigate the potential of the modified MeD (mMeD) in improving Dietary Inflammatory Index (DII) scores, disability, and fatigue severity, compared to Traditional Iranian Diet (TID), in RRMS patients.

Methods

After initial screening (n=261), 180 RRMS patients were randomized to receive mMeD or TID (as control) for six months. DII score, Expanded Disability Status Scale (EDSS) and 21-item Modified Fatigue Impact Scale (MFIS) were evaluated at baseline and trial cessation. Multivariate analysis of covariance was conducted and adjusted for age, gender, body weight, body mass index, education level, supplement use, family history and duration of MS.

Results

Of the 180 patients enrolled, 147 participants were included in the final analysis (n of mMeD=68; n of TID=79). Self-reported adherence was good (~81%). Dietary intakes of 45 food parameters were assessed through the food frequency questionnaire. The mMeD significantly reduced DII scores after six months (2.38 ± 0.21 to -1.87 ± 0.86 , $P < 0.001$), but TID did not elicit any changes (2.21 ± 0.44 to 2.14 ± 1.01 , $P = 0.771$). Additionally, MFIS total score decreased significantly (72.4 ± 17.2 to 63.9 ± 14.2 , $P < 0.001$), whereas there was no considerable improvement for EDSS in the mMeD group.

Conclusion

Adherence to mMeD, for six months, improved dietary inflammatory status and fatigue severity in RRMS patients, however, the traditional Iranian diet did not positively impact dietary inflammation and MFIS score.

Keywords: Dietary inflammatory index; Mediterranean diet; fatigue; multiple sclerosis; randomized controlled trial

1. Introduction

Multiple Sclerosis (MS) is an autoimmune disease of the central nervous system, with unknown etiology, characterized by chronic inflammation, demyelination, and neuronal loss [1]. Around 2.5 million individuals, worldwide, are affected by this disease [2], although young adults and females are more susceptible [3]. Relapsing-Remitting MS (RRMS), the most common type of MS, is indicated in, roughly, 85% of patients [4].

Contentions in the literature regarding the relationship between some dietary components and MS progression are evident. For example, dietary polyphenols have been reported to mitigate demyelination [5], whereas, resveratrol - a polyphenol compound found in a variety of foods and beverages - reportedly exacerbated both autoimmune and viral models of MS [6]. Milk proteins and gluten may worsen the clinical manifestations in MS patients [7], however, milk consumption more than once per week was found to decrease the risk of developing MS [8]. Furthermore, high doses of vitamin C have been shown to worsen MS conditions [9], while some authors have reported that vitamin C promotes oligodendrocytes generation and remyelination [10]. Indeed, more nutrition-based research is required to clarify these conflicting findings.

Among the most advocated healthy diets, the Mediterranean Diet (MeD) has the strongest evidence for improvement in inflammatory status [11]. This diet is characterized by high intake of vegetables, legumes, fruits, whole grains, and unsaturated fatty acids (mostly in the form of olive oil), a moderately high intake of fish, and low to moderate intake of dairy products, meat, and poultry [12]. Indeed, previous studies have shown the potential effects of anti-inflammatory diets, such as Mediterranean-style diets, in reducing fatigue severity in MS patients [12-14].

Dietary Inflammatory Index (DII), a literature-based scoring system, is a tool used to classify forty-five pro or anti-inflammatory dietary items into an overall score [15]. Previous studies have reported that several foods and nutrients used in the DII calculation, such as whole grains, fruits, vegetables, fish, onion, and ginger possess anti-inflammatory effects [16, 17]. In contrast, refined grains, red meat, high-fat dairy products, and sweets have been routinely related to systemic inflammation [18]. In previous studies, MeD reportedly yielded a strong anti-inflammatory DII score [19] and greater MeD adherence has been negatively associated with DII scores [20, 21]. On the other hand, some findings suggest that higher DII scores during adolescence might be an important risk factor for MS onset [22].

Therefore, given the equivocality present within the literature, we sought to determine the effect of mMeD vs. TID, on DII, disease disability, and fatigue severity in RRMS patients. We hypothesized that the modified form of MeD (mMeD; mainly by elimination of alcohol-containing foods and beverages) would yield a lower DII score (i.e., greater dietary anti-inflammatory potential) in comparison with the Traditional Iranian Diet (TID).

2. Materials & Methods

2.1. Study design and sample size determination

In this single-center, two parallel arms, single-blind, randomized clinical trial, 180 RRMS patients were recruited, according to the Extended Disability Status Scale (EDSS 0-3, mild to moderate disability as diagnostic criteria) [23]. Intervention delivery was performed from July 2018 to February 2019.

The study protocol was approved by ethics committee located in the University Medical Sciences, and WHO-related Registry of Clinical Trials (IRCT20181113041641N1). The Helsinki ethical principles [24] were well observed throughout the trial. Study objectives were explained, and voluntary informed consent was taken prior to data collection.

Fatigue Severity Scale (FSS), a tool for measuring fatigue in MS, was used to calculate the sample size based on previous reports [25].

$$n = \frac{(z_1 + z_2)^2(s_1^2 + s_2^2)}{(\bar{x}_1 - \bar{x}_2)^2} \cong \frac{594/80}{9} \cong 66/08$$

By the use of sample size determination formula (S_1 , SEM for FSS in control group=4.73; S_2 , SEM for FSS in intervention group=4.85; $\bar{x}_1 - \bar{x}_2$, mean changes for FSS=3), with a confidence level of 95% ($z_1=1.96$), power of 80% ($z_2=1.64$), and drop-out rate of 35 % in the number of participants, the total sample size was estimated to be 180.

2.2. Inclusion and exclusion criteria

Eligible patients had mild to moderate RRMS (defined as EDSS up to 3, and who received dimethyl fumarate 240 mg twice daily in the last year), aged between 20-60 years old, and ability to write or recall dietary history. Subjects were excluded if they had any of the following: other forms of MS and disease duration of less than one year with active relapses, viral infections such as Epstein Barr, major medical illnesses (such as cancer, allergy, other autoimmune diseases,

anticoagulant or antiplatelet use, and psychiatric disorders), and current smokers (one or more cigarette per day). Subjects were also excluded if they left more than 40% blank items on the Food Frequency Questionnaire (FFQ) at baseline or were prescribed high dose corticosteroid therapy (greater than 30 mg/day methylprednisolone).

2.3. Interventions and control groups

The main composition of each diet has been described briefly in *Table 1*. The intervention group followed a modified version of MeD (mMeD; 17 % protein, 51 % carbohydrate and 32 % fat [26]), based on higher intake of fresh fruits and vegetables, whole grains, monounsaturated fatty acids, fish, and low to moderate consumption of dairy products, meat, and poultry. In practice, the prescribed mMeD was individualized based on cultural and personal preferences, and the elimination of any alcohol-containing foods and beverages. The control group followed the TID (*low in low-fat dairy products, whole grains; high in red meats, solid oils, refined grains, and moderate intakes of legumes, fruits and vegetables*); based on prior investigations, this diet consisted of 13 % protein, 58 % carbohydrate and 29 % fat [27]. It must be noted that the TID group (as control) did not continue their normal eating pattern, i.e., the original dietary principles in the control group were maintained, however, the TID plan was adjusted for energy intake to avoid unexpected body weight changes.

Ideal body weight and the Harris-Benedict equation [28] were utilized to calculate the Basal Energy Expenditure (BEE) for each participant in both diets (mMeD and TID). Next, the above percentages were used to discern the macronutrient requirements in both diets. All the participants received an individualized diet plan, which had been designed according to the above principles. Dietary adherence was also measured with weekly with phone calls, and face-to-face interviewing every month.

2.4. Recruitment and randomization methods

Participants were recruited using advertisements in local media outlets and clinicians' invitation. Participants were randomly assigned into either the modified Mediterranean Diet (mMeD; intervention) or Traditional Iranian Diet (TID; control) group, with a computerized random sequence generator. Randomization was performed by a research assistant who did not participate in either the follow-up assessments or analysis.

2.5. Blinding

In this trial, blinding of participants and dietitians is not possible because of obvious differences between the intervention and control diets; however, where appropriate, trial personnel (research assistant who enrolled participants, outcome assessors and data analysts) remained blind to group allocation throughout the study period.

2.6. Outcome measurements

The primary outcome was the diet-induced change in DII. The secondary outcomes were change in disease disability (measured by EDSS) and fatigue severity (measured by MFIS). Sociodemographic and clinical characteristics were collected through a self-report survey completed at baseline, which included details on participants' age, body weight and height, Body Mass Index (BMI), education level, family history of MS, and supplement use. Baseline DII scores were also assessed in two states: dietary only and dietary plus supplements. However, the statistical analysis was conducted based on dietary DII scores.

2.6.1. Dietary assessment

Food intake of individuals during the previous year was assessed using a validated 168-item semi-quantitative FFQ [29], which included a list of foods with standard serving sizes commonly consumed [30-32]. Nutritionist IV software (N-squared Computing, Salam, OR, USA) was used to analyze the composition of consumed foods. Some DII parameters such as ginger, saffron, turmeric, thyme/oregano, and rosemary were additionally added to the FFQ. For calculation of flavonoids (flavan-3-ol, flavones, flavonols, flavonones, anthocyanidins and isoflavones), the USDA Databases for the Flavonoid Content of Selected Foods (Release 3.3, March 2018) [33] and Isoflavone Content of Selected Foods (Release 2.0, September 2008) [34] were used. Dietary intake of eugenol was estimated according to Phenol-Explorer database (latest version 3.6; released on December 2016) [35]. There were two timepoints for dietary assessment: one before the dietary intervention and one 6 months after the start of the study.

2.6.2. DII calculation

Shivappa et al. [36], after evaluation of 1943 articles (were published between 1950 and 2010), examined the association between inflammation and 45 food and nutrient parameters; this resulted in the development and validation of DII, where the score ranged from 7.98 (i.e.,

strongly pro-inflammatory) to -8.87 (i.e. strongly anti-inflammatory). In the present study, we calculated the DII scores at baseline and after 6 months of intervention. Estimated dietary intake data were adjusted against a reference global daily mean and standard deviation intake (from 11 countries) [36] for each parameter to obtain a Z-score; each Z-score was converted to percentile, and this value was multiplied by 2 and then subtracted from 1. This number for each intake parameter was multiplied by its respective parameter-specific inflammatory effect score to obtain the parameter-specific DII score. Each of these 45 scores were then summed to obtain an overall DII score.

2.6.3. Fatigue Severity Assessment

The Modified Fatigue Impact Scale (MFIS) was used to determine the MS-related fatigue [37] at baseline and 6 months after the intervention. This standard 21-item questionnaire has three subscales (Physical, ranges from 0-36; Cognitive, 0-40; and Psychosocial, 0-8). The total score is computed by summing scores from the three subscales and ranges from 0-84, where higher scores represent greater fatigue severity. In the present study, the validated Persian version of MFIS [38], with excellent test-retest reliability [39], was utilized.

2.6.4. Disability Assessment

A trained neurologist measured EDSS to assess MS-related disability [23, 40] at baseline and 6 months after the intervention. Scales for the total EDSS in the current study ranged from 0 (no disability at all) to 3 (mild to moderate disability).

2.7. Statistical analysis

Data were presented as means \pm Standard Deviation (SD) for continuous variables and number (percent) for categorical variables. The Kolmogorov–Smirnov test was used to assess the normality of continuous variables. In addition, independent student t and paired t tests (or non-parametric Mann–Whitney U and Wilcoxon tests) were used to compare the continuous variables. Categorical variables were compared using the χ^2 or Fisher's Exact test. Multivariate Analysis of Covariance (MANCOVA) was performed to evaluate the differences for change in DII scores, where the related values were adjusted for age, gender, body weight, BMI, education level, supplement use, family history, and duration of MS. The mean changes (Δ) were

calculated by subtracting the baseline and 6 months (end) values. To identify the relationship between DII (and other covariates) and fatigue severity/ disease activity scores at end of trial, multiple regression analysis was performed. All statistical analyses were conducted using Statistical Package for the Social Sciences (SPSS), version 24 (SPSS Inc.). $P < 0.05$ was considered to represent statistical significance.

3. Results

3.1. Enrollment and adherence

Between July 2018 and February 2019, we screened 261 RRMS patients, however, sixty-seven subjects were excluded as they did not meet the inclusion criteria, and fourteen patients declined to participate (*Figure 1*). 180 patients were dichotomized to the mMeD or TID group. Thirty subjects dropped out during the study follow-up: twenty due to lack of compliance, two due to lack of willingness to continue the study, one due to a driving accident, and ten subjects due to incomplete questionnaires. Overall, 147 participant-related data (intervention=68; control=79) were analyzed (based on per-protocol analysis). No side effects (diarrhea, abdomen pain, constipation, and appetite changes) were reported during the study period.

3.2. Baseline characteristics

Sociodemographic and medical characteristics, between the groups at baseline, are reported in *Table 2*. Overall, the participants were middle-aged adults (with mean age 39.3 ± 9.2 years old; ~83% female). More than 40 % were overweight and obese, 15 % had family history of MS, and the majority had already completed a degree to diploma level. More than 80 % of the study population were taking at least one type of nutritional supplement, of which vitamin D (~83 %) and omega-3 (~33%) were the most common. Additionally, ~20 % of subjects had consumed L-carnitine or caffeine-containing supplements during the past six months. A small number of male participants (13 %) were irregular smokers (average 1-2 cigarettes in a week). Mean EDSS score was slightly higher in the control group (2.0 vs. 1.7), although there were no significant differences between the study groups for EDSS and DII scores.

3.3. Clinical outcomes

3.3.1. Impact of diet interventions on DII

Table 3 details the mean daily intake for 45 DII parameters and overall DII score for each diet. Within the mMeD group, there was a significant decrease from 2.38 ± 0.21 to -1.87 ± 0.86 at 6 months for overall DII score ($P < 0.001$). Compared with control group (TID), the mean changes for overall DII score were also statistically significant (-4.25 ± 1.54 vs. -0.07 ± 0.62 ; $P < 0.001$).

For mean daily intake of DII food/nutrient parameters after 6 months (**Table 3**), there was a significantly higher intake of protein, n-6 Fatty acids, Monounsaturated Fatty Acids (MUFA), Polyunsaturated Fatty Acids (PUFA), selenium, beta carotene, vitamin E, riboflavin, garlic, onion, ginger, turmeric, pepper, thyme/oregano, rosemary, flavan-3-ol, anthocyanidins, isoflavones; in addition to lower intake of energy, carbohydrate, total fat, saturated fat, trans fat, iron, and caffeine in the mMeD group compared to TID group ($P < 0.05$).

3.3.2. Impact of diet interventions on fatigue

Table 4 details the results for fatigue severity. At the end of the study period, MANCOVA revealed a significant difference between the groups for MFIS total score (Δ for mMeD = -8.5 ± 2.74 vs. Δ for TID = 6.4 ± 1.62 , $P < 0.001$). These findings were adjusted for age, gender, body weight, BMI, education level, supplement use, family history, and duration of MS.

Participants who received mMeD had a statistically significant improvement in physical and cognitive MFIS subscales. After six months, there was a 2.7 and 5.6 points reduction in physical ($P < 0.001$) and cognitive ($P = 0.027$) MFIS subscales, respectively. However, no significant change in the psychosocial subscale of MFIS was evident.

3.3.3. Impact of diet interventions on disability

There was a non-significant reduction in EDSS at the end of the study period in the mMeD group ($\Delta = -0.02 \pm 0.07$, $P = 0.334$). Contrastingly, a non-significant rising trend in EDSS was seen in the TID group. MANCOVA, adjusted for age, gender, body weight, BMI, education level, supplement use, family history, and duration of MS, did not indicate any significant change for EDSS, in mMeD vs. TID ($P = 0.065$) (**Table 4**).

3.3.4. Relationship between DII and the fatigue severity/disease disability

Significant predictors and covariates for MFIS total score and EDSS are presented in *Table 5*. DII score significantly predicted fatigue severity in the intervention group ($B= 1.701$, $P= 0.041$; adjusted $R^2= 0.098$), however, age, gender, body weight, BMI, education level, supplement use, family history, and duration of MS had no significant association with MFIS total score.

In addition, regression analysis revealed that DII score does not predict disease disability in mMeD group ($B= 3.809$, $P= 0.067$; adjusted $R^2= 0.157$). Other covariates (age, gender, body weight, BMI, education level, supplement use, family history, and duration of MS) did not show any significant association with EDSS.

4. Discussion

This study assessed the effects of dietary intervention on DII score in Iranian RRMS patients. Our findings showed that the mMeD possesses significant anti-inflammatory properties, whereas the Traditional Iranian Diet (TID) had no significant effect on overall DII score. The key components of DII i.e., MUFA and polyphenols, increased significantly after six months adherence to the mMeD group. Moreover, mMeD also reduced fatigue severity (MFIS score); however, the effect on disease disability (measured by EDSS) was not significant.

Iranian dietary intervention studies typically use TID as the control diet [11, 41, 42]. TID (low in low-fat dairy products, whole grains; high in red meats, solid oils, refined grains, and moderate legumes, fruits and vegetables) is the most prevalent diet in Iran, and has both positive and negative health-related aspects [43]. In a case-control study, conducted by Jahromi et al. [44], the traditional dietary pattern was inversely related to the risk of RRMS; however, high amounts of red/organ meat in the TID can lead to both neurodegeneration and autoimmune disorders [45]. Indeed, it must be noted that nutritional transition in Iran has resulted in a change in TID, which must be considered in further research [43, 46]; however, the control group adhered to the prescribed TID, as defined in the present study.

In this research, DII was considered as an index that effectively represents dietary inflammatory status, based on several previous studies that have verified by the significant association of DII with inflammatory markers [47]. This index presents an alternative assessment tool for inflammation, as opposed to the laboratory-based techniques which are obtained through invasive methods and economically prohibitive [48]. Moreover, some previous studies have

indicated that the DII may also be correlated with other dietary indices i.e., Healthy Eating Index-2010 (HEI-2010), the Alternative Healthy Eating Index (AHEI), and the Dietary Approaches to Stop Hypertension Index (DASH) [49].

Regardless of the pro-inflammatory DII score for the TID, the mMeD elicited a reduction in the total DII score in the present study. Indeed, the association between MeD and DII score has been evaluated in previous research; for instance, in a Spanish cross-sectional study, adherence to the MeD was higher in the lowest quintile of DII scores [20]. Moreover, an inverse correlation was also observed between the DII and Mediterranean Diet Score [21], whilst Mayr et al. [19] showed that six months MeD adherence, compared with a low-fat diet, elicited an improvement in DII scores in patients with coronary heart disease. Interestingly, Mayr et al. evaluated 45 parameters of DII and reported an anti-inflammatory DII score of -1.74, which is comparable to the total score of -1.87 in the present study. Although we removed the alcohol-containing foods and beverages from our intervention, the current findings were comparable to the intact versions of the MeD reported in the literature.

Recently, it was reported that DII was not significantly associated with the clinical condition of individuals with MS [50]. Moreover, Silva et al. [51], in a cross-sectional study, reported that DII does not correlate to waist circumference, waist-hip ratio, body roundness index, body shape index, body shape z score index, and percentage of body fat among MS patients. In contrast, Shivappa et al. [52] observed that a pro-inflammatory diet (with a higher DII score) may be associated with an increased risk of MS in an Iranian population. In the current study, an anti-inflammatory diet was prescribed to assess the possible effects on DII in RRMS patients. The link between diet and chronic inflammation has been well established [53, 54], and the association between inflammation and neurodegeneration in MS is generally well-supported [55]. According to previous work, the Mediterranean diet is inversely associated with biomarkers of inflammation [56, 57].

The MUFA and PUFA content of mMeD appears to be responsible for the anti-inflammatory DII score in the current study. Omega-3 PUFAs inhibit NF- κ B signaling through activation of SIRT1-mediated pathway [58] and the reduction of pro-inflammatory cytokines (e.g., IL-12, IL-23) [59]. Olive oil polyphenols, which are a major part of the mMeD, also have an inhibitory effect on endothelial Nitric Oxide Synthase (eNOS) and Brain-Derived Neurotrophic Factor

(BDNF) expression [60]. However, two systematic reviews in 2012 and 2020, respectively, reported that PUFAs do not elicit any significant effect on MS-related outcomes [61, 62].

In the present study, flavonoids intake increased after six months adherence to the mMeD; moreover, flavan-3-ol, anthocyanidins, and isoflavones levels were significantly greater in comparison with the TID group. Flavan-3-ols, mainly extracted from green tea, have previously been advocated as neuroprotective compounds [63]. Furthermore, anthocyanidins possess anti-inflammatory and anti-proliferative effects through inhibition of the cyclooxygenase-2 expression in LPS-evoked macrophages [64]. Recently, Freedman et al. [65] found that a high-isoflavone diet ameliorates Experimental Autoimmune Encephalomyelitis (EAE) through modulation of gut microbiota in MS patients.

In the present study, fatigue severity was reduced by 12 percent (measured by MFIS total score). In a 12-week randomized trial, Mousavi-Shirazi-Fard et al. [13] observed the fatigue-modulatory effect of an anti-inflammatory diet among 100 RRMS patients. Another study, conducted by Yadav et al. [66], reported that a plant-based, low-fat diet, can reduce the MFIS by ~0.2 points per month in RRMS patients. Indeed, it seems that the bioactive components of mMeD are responsible for fatigue improvement.

The mMeD administration in the present study did not elicit any improvement in disease-related disability in RRMS participants. We hypothesized that the mMeD may have improved the level of disability from moderate (~3) to mild disability (≤ 2); however, in this study, and our previous work, there was no association between a Mediterranean-like dietary pattern and disability (measured by EDSS) [14]. EDSS is the most important secondary endpoint in MS trials addressing RRMS patients; this instrument is suitable for detecting the efficacy of clinical interventions, to monitor disease progression, and is internationally utilized [67].

While our study provides initial insights into understanding the potential role of dietary interventions in the management of MS, it has some limitations that should be considered. The current study is representative of patients with RRMS undergoing intensive pharmacotherapy, and who are potentially motivated and health-conscious. Therefore, the current findings are not necessarily pertinent to healthy subjects, or other disease populations. The sample size for the present study was calculated based on a secondary variable, i.e., FSS. Furthermore, incumbent findings could have been affected by insufficient statistical power, relative to DII score, small sample size, short follow-up period, and high drop-out rate (>18%). Moreover, there was an

imbalance between groups at follow-up in the drop-out rate (more than 22% in the intervention group versus 3.3 % in the control group). The nature of this study was single-blind and was vulnerable to selection and recall biases. The lack of neuroimaging data, which may be useful in evaluating the effect of diet on neurodegeneration, was the most important clinical limitation. The calculation of trans fat intake was predominantly based on high-fat dairy and meat products; thus, underestimation was possible. Finally, EDSS was used to measure disease disability in the current research; however, this tool may not be sensitive to clinical change, especially in short-term studies (≤ 6 months) and milder levels of disability [68].

However, despite the aforementioned limitations, the present study has several strengths worth mentioning. The MS participants recruited were relatively homogenous, allowing pertinent inferences to be drawn. Furthermore, adjustment in the final analysis allowed detailed consideration of potential confounding variables. In this trial, all 45 parameters of the DII were measured and a non-invasive method was used for evaluating inflammatory condition; these strategies helped to improve the accuracy and precision of our findings. Finally, although current evidence suggests that adherence to a Mediterranean-style diet can reduce inflammation in chronic diseases, studies pertaining to Relapsing-Remitting Multiple Sclerosis (RRMS) are limited; therefore, the present study provides a novel and important addition to the literature.

5. Conclusion

Our results demonstrated that adherence to the mMeD for 6-months can reduce DII score in RRMS participants. Indeed, the mMeD improved fatigue severity, without any significant change on disability. Comparatively, adherence to the Traditional Iranian Diet did not impact DII scores. Additional studies are required to evaluate the long-term safety and immunomodulatory properties of the MeD, and TID in progressive forms of MS, as well as in patients with other autoimmune diseases.

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Conflicts of interest

The Authors declare that there is no conflict of interest.

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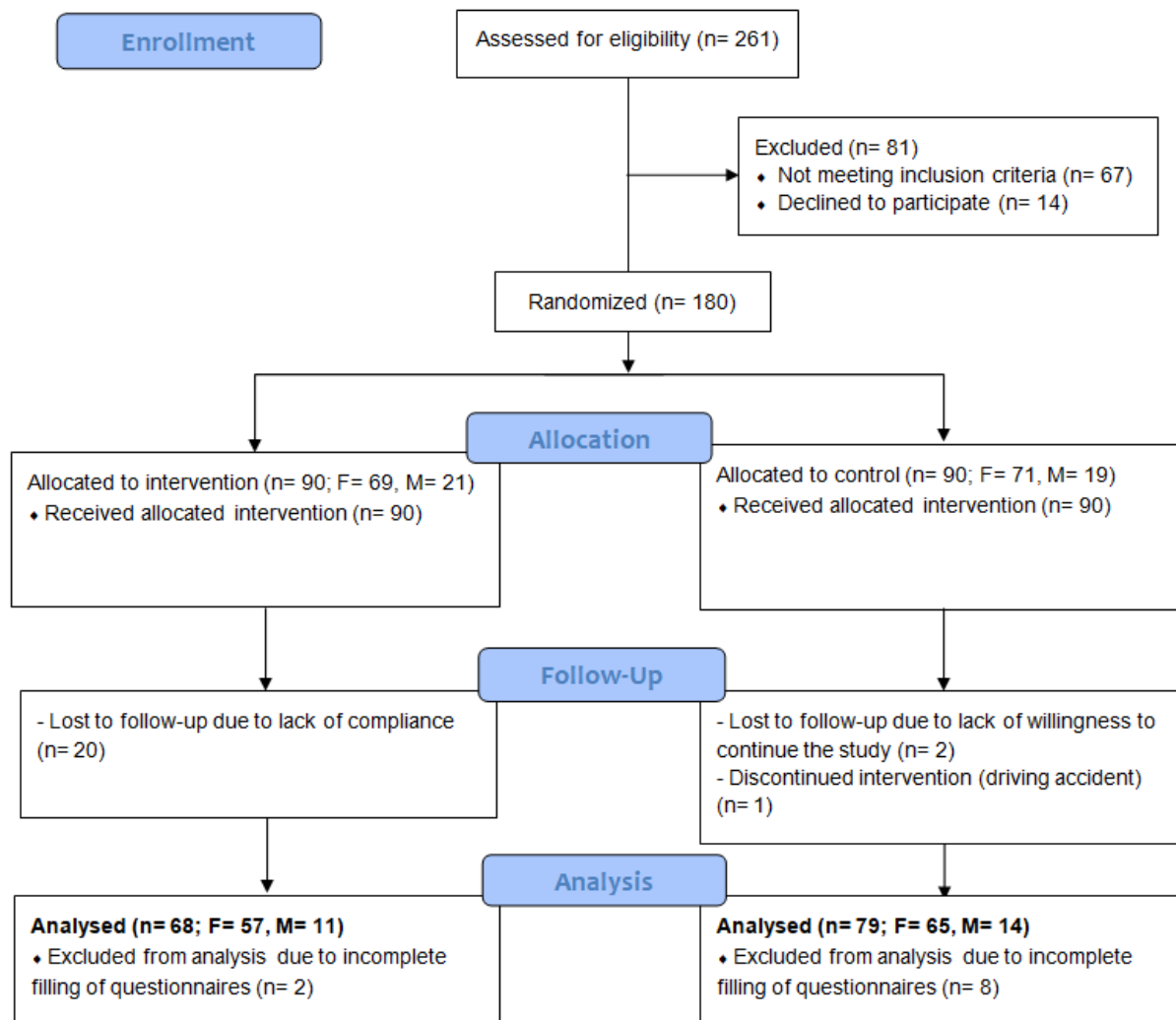


Figure 1. Flow diagram representing study plan.

Table 1. The main composition of modified Mediterranean (mMeD) and Traditional Iranian (control) diets.

Major nutrients	mMeD	Control†
	% of calories	% of calories
Protein	17 ^{1*}	13
Carbohydrate	51 ¹	58
Fat	32 ¹	29
	% of total fat	
Saturated	21 ¹	32
Monounsaturated	56 ¹	33
polyunsaturated	15 ¹	14
ω6/ω3 Fatty Acids	2.1-3/1 ²	3.8/1
Cholesterol mg/Cal	0.16 ¹	0.12
Fiber g/Cal	0.03 ³	0.005
Sodium mg/Cal	1.3 ^{1,3}	1.6

*Reference Number:

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† Values were calculated based on average usual intakes of the participants in Traditional Iranian Diet.

‡ modified Mediterranean Diet; adopted from 1999 Greek Dietary Guidelines (1999): Ministry of health and welfare, supreme scientific health council: Dietary guidelines for adults in Greece. *Arch. Hell. Med.* 1999, 16, 516–524. Serving sizes specified as: 25 g bread, 100 g potato, 50–60 g cooked pasta, 100 g vegetables, 80 g apple, 60 g banana, 100 g orange, 200 g melon, 30 g grapes, 1 cup milk or yoghurt, 1 egg, 60 g meat, 100 g cooked dry beans.

Table 2. Characteristics of participants between diet study groups.

group		mMeD	Control	P-value[†]
continuous variables		(n=68)	(n=79)	
		M ± SD	M ± SD	
Age (y)		38.6 ± 8.6	40.0 ± 9.6	0.309
Body Weight (kg)		71.2 ± 10.1	68.5 ± 10.5	0.556
Height (cm)		165.4 ± 7.0	163.0 ± 6.8	0.473
BMI (kg/m ²)		26.1 ± 4.1	25.9 ± 4.5	0.757
Duration of the disease (y)		8.1 ± 5.7	9.3 ± 6.9	0.395
EDSS		1.7 ± 0.7	2.0 ± 0.9	0.059
DII [‡]		2.38 ± 0.21	2.38 ± 0.21	0.687
DII (plus supplements)		1.87 ± 1.25	2.01 ± 0.93	0.069
Categorical variables		mMeD	Control	P-value[§]
		(n=68)	(n=79)	
		n (%)	n (%)	
gender	Male (17%)	11 (16.2)	14 (17.7)	0.830
	Female (83%)	57 (83.8)	65 (82.3)	
Education	Illiterate	3 (4.4)	3 (3.8)	0.332
	Elementary	7 (10.3)	5 (6.3)	
	Junior school	7 (10.3)	9 (11.4)	
	Diploma	29 (42.6)	46 (58.2)	
	University	22 (32.4)	16 (20.3)	
Family history	Yes	10 (14.7)	12 (15.2)	0.999
	No	58 (85.3)	67 (84.8)	
BMI classification	Normal	28 (41.2)	34 (43.0)	0.948
	Underweight	2 (2.9)	3 (3.8)	
	Overweight	18 (26.5)	22 (27.8)	
	Obese	20 (29.4)	20 (25.3)	
Nutritional supplement	Vitamin D	60 (88.2)	62 (78.5)	0.764
	Omega-3	26 (38.2)	23 (29.1)	

intakes	Multivitamin & minerals	18 (26.5)	17 (21.5)	
	L-carnitine or caffeine	11 (16.1)	18 (22.8)	

Abbreviations: mMeD, modified Mediterranean Diet; BMI, Body Mass Index; yr, year; SD, Standard Deviation; EDSS, Extended Disability Status Scale; %, within group percent; DII, dietary inflammatory index; control, Traditional Iranian Diet.

†obtained from independent t-test, EXCEPT for Duration of the disease, BMI, and EDSS, that was analyzed by Man-Whitney U test; P<0.05 considered significant

‡determined with Chi Square, EXCEPT for gender, and Family history, that was analyzed by Fisher's Exact test, P<0.05 considered significant

§Negative number represents an anti-inflammatory score, while positive number reflects a proinflammatory score.

Table 3. Dietary inflammatory index (DII) parameters and scores in patients with relapsing-remitting multiple sclerosis that received either modified Mediterranean Diet (mMeD) or Traditional Iranian Diet (control).

Dietary group	DII food parameters	Group	Baseline	End of trial	P-val	Δ^2	P-value ³
energy	Energy (kcal/day)	mMeD	2670.6 ± 468.6	2193.6 ± 317.3	< 0.00	-477.0 ± 300.1	< 0.001*
		Control	2575.7 ± 437.0	2588.7 ± 419.5	0.828	13.0 ± 531.5	
Macro nutrients	Carbohydrate (g/day)	mMeD	405.2 ± 86.6	317.5 ± 57.7	< 0.00	-87.7 ± 54.2	< 0.001*
		Control	391.4 ± 78.3	394.8 ± 75.1	0.083	3.4 ± 97.3	
	Protein (g/day)	mMeD	92.0 ± 7.5	87.0 ± 8.4	< 0.00	-5.0 ± 8.8	0.327
		Control	90.5 ± 6.9	90.1 ± 7.1	0.642	-0.36 ± 10.0	
	Total fat (g/day)	mMeD	77.3 ± 13.1	66.9 ± 7.5	0.001	-10.4 ± 12.4	0.052
		Control	74.0 ± 13.0	74.0 ± 12.7	0.057	0.10 ± 15.8	
	Cholesterol (mg/day)	mMeD	307.1 ± 105.3	266.0 ± 37.2	0.055	-81.1 ± 103.2	0.134
		Control	283.8 ± 104.6	284.8 ± 105.2	0.072	1.0 ± 132.4	
	Saturated fat (g/day)	mMeD	26.5 ± 10.4	18.7 ± 5.2	0.002	-7.8 ± 9.7	0.061
		Control	24.3 ± 10.4	24.4 ± 10.5	0.044	0.07 ± 13.0	
	Trans fat (g/day)	mMeD	1.2 ± 0.98	0.6 ± 0.87	0.012	-0.6 ± 0.3	0.671
		Control	1.3 ± 0.85	1.2 ± 0.60	0.741	-0.1 ± 0.7	
	n-6 Fatty acids (g/day)	mMeD	11.3 ± 1.8	12.8 ± 0.8	0.002	1.5 ± 1.7	0.036
		Control	11.5 ± 2.0	11.6 ± 1.8	0.292	0.1 ± 2.5	
n-3 Fatty acids	mMeD	0.18 ± 0.07	0.2 ± 0.06	0.429	0.02 ± 0.09	0.711	

	(g/day)	Control	0.18 ± 0.07	0.18 ± 0.06	0.207	-0.00 ± 0.08	
	MUFA (g/day)	mMeD	22.9 ± 2.6	26.0 ± 4.0	0.013	3.1 ± 4.1	0.019
		Control	25.1 ± 3.7	25.1 ± 3.7	0.091	-0.01 ± 4.6	
	PUFA (g/day)	mMeD	15.2 ± 3.5	17.0 ± 1.5	0.022	1.9 ± 4.1	0.172
		Control	15.3 ± 3.4	15.3 ± 3.3	0.333	0.00 ± 4.5	
	Fiber (g/day)	mMeD	27.7 ± 8.0	32.0 ± 5.1	0.407	4.2 ± 9.0	0.431
Control		29.0 ± 8.0	28.9 ± 8.4	0.431	-0.1 ± 11.1		
minerals	Iron (mg/day)	mMeD	29.6 ± 6.5	24.6 ± 3.6	<0.00	-5.0 ± 5.34	0.029
		Control	28.5 ± 6.0	28.4 ± 6.0	0.139	-0.1 ± 7.8	
	Magnesium (mg/day)	mMeD	253.4 ± 50.5	292.7 ± 36.8	0.348	39.2 ± 58.9	0.038
		Control	259.0 ± 51.0	257.0 ± 52.2	0.611	-1.9 ± 70.9	
	Zinc (mg/day)	mMeD	9.0 ± 1.1	9.0 ± 0.9	0.650	0.0 ± 1.5	0.168
		Control	8.9 ± 1.0	8.9 ± 1.1	0.543	-0.05 ± 1.6	
	Selenium (µg/day)	mMeD	118.3 ± 25.2	93.0 ± 13.1	<0.00	-25.3 ± 20.5	0.004
		Control	112.2 ± 24.9	114.0 ± 24.4	0.091	1.8 ± 31.4	
Fat-soluble vitamins	Beta Carotene (µg/day)	mMeD	710.7 ± 895.8	1746.2 ± 973.6	0.006	1035.5 ± 1084.4	0.032
		Control	856.2 ± 962.3	801.8 ± 924.4	0.214	-54.3 ± 1236.6	
	Vitamin E (mg/day)	mMeD	3.6 ± 0.6	3.8 ± 0.6	0.001	0.2 ± 1.0	0.650
		Control	3.6 ± 0.6	3.5 ± 0.6	0.226	-0.1 ± 0.8	
	Vitamin D (µg/day)	mMeD	1.6 ± 1.2	2.3 ± 1.2	0.319	0.6 ± 1.8	0.061
		Control	1.6 ± 1.2	1.6 ± 1.2	0.657	0.0 ± 1.7	

	Vitamin A (RE/day)	mMeD	1139.9 ± 545.5	1663.2 ± 648.4	0.085	523.3 ± 754.3	0.152
		Control	1203.8 ± 600.0	1172.1 ± 569.1	0.757	31.6 ± 779.6	
Water-soluble vitamins	Vitamin C (mg/day)	mMeD	94.4 ± 53.2	141.5 ± 37.3	0.109	47.0 ± 58.7	0.069
		Control	104.4 ± 54.6	101.9 ± 54.3	0.215	-2.5 ± 71.4	
	Vitamin B12 (µg/day)	mMeD	5.1 ± 2.0	3.7 ± 0.8	0.289	-1.3 ± 2.2	0.401
		Control	4.6 ± 2.1	4.6 ± 2.1	0.298	0.06 ± 2.8	
	Vitamin B6 (mg/day)	mMeD	1.7 ± 0.3	1.6 ± 0.4	0.581	-0.08 ± 0.5	0.478
		Control	1.7 ± 0.4	1.7 ± 0.4	0.708	0.00 ± 0.5	
	Folic acid (µg/day)	mMeD	334.2 ± 138.8	395.7 ± 102.9	0.828	61.4 ± 170.5	0.374
		Control	357.6 ± 144.0	355.9 ± 148.0	0.310	-1.6 ± 194.2	
	Niacin (mg/day)	mMeD	29.8 ± 6.3	24.0 ± 3.6	<0.00	-5.7 ± 4.2	0.018
		Control	28.7 ± 5.5	28.7 ± 5.3	0.326	0.01 ± 7.2	
	Riboflavin (mg/day)	mMeD	2.1 ± 0.4	2.2 ± 0.4	0.006	0.02 ± 0.7	0.444
		Control	2.1 ± 0.4	2.1 ± 0.4	0.935	0.00 ± 0.6	
Thiamin (mg/day)	mMeD	2.9 ± 0.5	2.4 ± 0.4	<0.00	-0.5 ± 0.3	<0.001*	
	Control	2.8 ± 0.4	2.8 ± 0.4	0.200	0.01 ± 0.6		
Specific foods	Alcohol ⁵ (g/day)	mMeD	0	0	-	0	-
		Control	0	0	-	0	
	Garlic (g/day)	mMeD	0.68 ± 1.87	1.24 ± 3.47	<0.00	0.56 ± 1.22	<0.001*
		Control	0.70 ± 2.00	0.59 ± 1.55	0.803	-0.11 ± 2.52	
	Onion (g/day)	mMeD	8.9 ± 2.78	10.23 ± 5.74	0.142	1.23 ± 4.03	0.049

	Ginger (g/day)	Control	8.0 ± 1.89	7.4 ± 3.22	0.241	-0.6 ± 1.20	0.015	
		mMeD	0.32 ± 0.87	1.0 ± 0.9	0.023	0.7 ± 1.5		
	Saffron (g/day)	Control	0.26 ± 0.80	0.20 ± 0.91	0.441	-0.06 ± 0.51	0.314	
		mMeD	0.02 ± 0.11	0.03 ± 0.27	0.095	0.01 ± 0.47		
	Turmeric (mg/day)	Control	0.02 ± 0.28	0.02 ± 0.54	0.176	-0.00 ± 0.44	0.041	
		mMeD	8.4 ± 6.5	10.7 ± 3.8	0.047	2.3 ± 1.3		
	Green/black tea (g/day)	Control	7.9 ± 4.4	8.0 ± 4.5	0.341	0.1 ± 1.4	0.274	
		mMeD	4.5 ± 0.4	5.0 ± 1.1	0.057	0.5 ± 1.7		
	Pepper (g/day)	Control	4.1 ± 0.6	4.1 ± 0.6	0.748	0.00 ± 0.8	0.031	
		mMeD	0.7 ± 1.5	5.3 ± 2.3	<0.00	4.6 ± 3.1		
	Thyme/oregano (mg/day)	Control	0.8 ± 1.1	0.9 ± 1.8	0.188	0.1 ± 1.1	<0.001*	
		mMeD	0.04 ± 0.27	29.8 ± 8.1	<0.00	29.7 ± 9.9		
	Rosemary (mg/day)	Control	0.16 ± 0.44	0.13 ± 0.79	0.552	-0.03 ± 0.20	<0.001*	
		mMeD	0.00 ± 0.05	33.4 ± 6.6	<0.00	33.4 ± 8.2		
	Flavonoids ⁶	Flavan-3-ol (mg/day)	Control	0.00 ± 0.02	0.00 ± 0.06	0.656	0.00 ± 0.02	0.068
			mMeD	74.2 ± 24.2	160.3 ± 69.8	0.046	86.1 ± 12.4	
		Flavones (mg/day)	Control	68.9 ± 51.1	77.1 ± 44.4	0.121	8.2 ± 10.7	0.059
			mMeD	4.2 ± 1.6	5.5 ± 4.8	0.180	1.3 ± 0.9	
Flavonols (mg/day)		Control	3.3 ± 5.1	3.1 ± 2.2	0.470	-0.2 ± 0.5	0.214	
		mMeD	30.8 ± 8.4	44.5 ± 10.3	0.065	13.7 ± 4.8		
			Control	22.7 ± 4.5	20.3 ± 6.6	0.113	-2.4 ± 1.1	

	Flavonones (mg/day)	mMeD	11.6 ± 6.1	17.3 ± 9.9	0.080
		Control	11.0 ± 2.5	11.0 ± 1.9	0.914
	Anthocyanidins (mg/day)	mMeD	10.6 ± 5.5	59.3 ± 11.2	<0.00
		Control	10.2 ± 4.4	11.0 ± 3.8	0.252
	Isoflavones ⁷ (mg/day)	mMeD	4.2 ± 3.1	13.7 ± 0.9	0.044
		Control	4.1 ± 3.0	4.5 ± 2.8	0.230
miscellaneous	Eugenol ⁸ (mg/day)	mMeD	0.01 ± 0.2	0.2 ± 0.1	0.074
		Control	0.00 ± 0.1	0.00 ± 0.1	0.234
	Caffeine (g/day)	mMeD	0.004 ± 0.003	0.003 ± 0.001	<0.00
		Control	0.004 ± 0.003	0.004 ± 0.003	0.164
Overall DII score⁴	mMeD	2.38 ± 0.21	-1.87 ± 0.86	<0.00	
	Control	2.21 ± 0.44	2.14 ± 1.01	0.771	

DII, Dietary inflammatory index; mMeD, modified Mediterranean Diet; control, Traditional Iranian Diet; MUFA, monounsaturated fatty acids.

Data has been presented as mean ± SD.

¹obtained from paired t test; except for protein and Vitamin A, that were analyzed via nonparametric Wilcoxon test. P<0.05

²mean changes between end of trial and baseline values.

³obtained from MANCOVA test; adjusted for age, gender, body weight, body mass index, education level, supplement use. P<0.05 considered as significant.

Flavonoid intake was estimated based on “USDA Database for the Flavonoid Content of Selected Foods; Release 3.2”. It was calculated with N4 software.

⁴ obtained by dietary intakes only. Negative number indicates an anti-inflammatory score, while positive number reflects a pro-inflammatory score.

⁵ due to the cultural features of Iranian, the intake of alcohol-contained products was close to zero; thus, we modified the standard version of MeD by eliminating any alcohol beverages e.g. red wine.

⁶ calculated from USDA Database for the Flavonoid Content of Selected Foods Release 3.3 (March 2018)

⁷ calculated from USDA Database for the Isoflavone Content of Selected Foods Release 2.0 (September 2008)

⁸ Eugenol (mg) intake was measured based on Phenol-Explorer database (latest version 3.6; released on December 2016)

5.7 ± 3.3	0.247
0.00 ± 0.47	
48.7 ± 10.0	<0.001*
0.8 ± 1.8	
9.5 ± 1.6	0.049
0.4 ± 0.6	
0.19 ± 0.2	0.033
0.00 ± 0.1	
-0.001 ± 0.000	0.618
-0.000 ± 0.000	
-4.25 ± 1.54	<0.001*
-0.07 ± 0.62	

d fatty acids; PUFA,

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history and duration of MS, and

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version of MeD by eliminating any

Table 4. Comparison of fatigue & disability-related variables in patients with relapsing-remitting multiple sclerosis that received either modified Mediterranean Diet (mMeD) or Traditional Iranian Diet (control).

Variables	Subscale	Group	Baseline	End of trial	P-val
MFIS	Physical	mMeD	31.2 ± 10.4	28.5 ± 8.8	<0.00
		Control	32.9 ± 9.2	33.7 ± 10.2	0.124
	Cognitive	mMeD	35.8 ± 11.1	30.2 ± 8.5	<0.01
		Control	36.6 ± 9.9	36.1 ± 7.1	0.092
	Psychosocial	mMeD	5.4 ± 3.1	5.2 ± 2.6	0.244
		Control	6.0 ± 2.9	6.1 ± 3.4	0.157
	Total score	mMeD	72.4 ± 17.2	63.9 ± 14.2	<0.00
		Control	69.5 ± 13.2	75.9 ± 15.3	0.771
EDSS		mMeD	1.7 ± 0.7	1.7 ± 0.6	0.334
		Control	2.0 ± 0.9	2.1 ± 0.8	0.112

MFIS, Modified Fatigue Impact Scale; EDSS, Extended Disability Status Scale; mMeD, modified Mediterranean Diet; MUFA, monounsaturated fatty acids; PUFA, polyunsaturated fatty acids.

Data has been presented as mean ± SD.

¹obtained from paired t test. P<0.05 considered as significant.

²mean changes between end of trial and baseline values.

³obtained from MANCOVA test; adjusted for age, gender, body weight, body mass index, education level, sup use, family history and duration of MS, and P<0.05 considered as significant.

osis that received

Δ^2	P-value ³
-2.7 ± 0.7	<0.001*
0.8 ± 0.8	
-5.6 ± 1.8	0.027
-0.5 ± 0.1	
-0.2 ± 0.2	0.088
0.1 ± 0.4	
-8.5 ± 2.74	<0.001*
6.4 ± 1.62	
-0.02 ± 0.07	0.065
0.1 ± 0.02	

control, Traditional Iranian

use, family history and duration

Table 5. Predictors and covariates for MFIS total score and EDSS in mMeD group.

Dependent variables	Covariates	B	95% CI		P val	adjusted R
			Lower	Upper		
MFIS total score	Age	0.035	-0.006	0.068	0.122	.098
	Gender	-0.362	-0.388	-0.340	0.950	
	body weight	0.045	0.033	0.057	0.069	
	BMI	0.277	0.127	0.428	0.212	
	education level	0.022	0.018	0.026	0.199	
	supplement use	0.860	0.510	1.176	0.320	
	family history	0.232	0.047	0.417	0.478	
	duration of MS	1.007	0.946	1.069	0.321	
DII	1.701	1.329	2.073	0.041		
EDSS	Age	0.018	-0.024	0.060	0.625	.157
	Gender	0.112	-0.089	0.313	0.164	
	body weight	1.022	0.142	1.902	0.311	
	BMI	0.987	0.975	0.998	0.584	
	education level	-0.221	-0.381	-0.061	0.358	
	supplement use	0.675	0.504	0.846	0.166	
	family history	1.328	0.297	2.359	0.254	
	duration of MS	2.547	2.113	2.981	0.323	
DII	3.809	2.505	5.114	0.067		

B, unstandardized regression coefficient; 95% CI, 95% confidence interval of the unstandardized regress
MFIS, modified fatigue impact scale; DII, dietary inflammatory index; EDSS, extended disability status
mass index; MS, multiple sclerosis

fficient.
MI, body