Modified Mediterranean diet *v.* traditional Iranian diet: efficacy of dietary interventions on dietary inflammatory index score, fatigue severity and disability in multiple sclerosis patients

Jalal Bohlouli[1], Iman Namjoo[2], Mohammad Borzoo-Isfahani[2], Fariborz Poorbaferani[3], Amir Reza Moravejolahkami[4]*, Cain C. T. Clark[5] and Mohammad Ali Hojjati Kermani[6]

[1]*Department of Nutrition, Nutrition and Food Security Research Centre, School of Public Health, Shahid Sadoughi University of Medical Sciences, Yazd, Iran*
[2]*Department of Community Nutrition, School of Nutrition & Food Science, Isfahan University of Medical Sciences, Isfahan, Iran*
[3]*Food Security Research Center, Department of clinical Nutrition, School of Nutrition & Food Science, Isfahan University of Medical Sciences, Isfahan, Iran*
[4]*Department of Clinical Nutrition, School of Nutrition & Food Science, Isfahan University of Medical Sciences, Isfahan, Iran*
[5]*Centre for Intelligent Healthcare, Coventry University, Coventry, CV1 5FB, UK*
[6]*Clinical Tuberculosis and Epidemiology Research Center, National Research Institute of Tuberculosis and Lung Diseases (NRITLD), Shahid Beheshti University of Medical Sciences, Tehran, Iran*

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 with traditional Iranian diet (TID), in RRMS patients.

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 ($\sim$81 %). Dietary intakes of forty-five food parameters were assessed through the FFQ. The mMeD significantly reduced DII scores after 6 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, Modified Fatigue Impact Scale (MFIS) total score decreased significantly (72.4 ± 17.2 to 63.9 ± 14.2, $P < 0.001$), whereas there was no considerable improvement for Expanded Disability Status Scale (EDSS) in the mMeD group.

Methods: After initial screening (*n* 261), 180 RRMS patients were randomised to receive mMeD or TID (as control) for 6 months. DII score, EDSS and twenty-one-item MFIS were evaluated at baseline and trial cessation. Multivariate ANCOVA was conducted and adjusted for age, gender, body weight, BMI, education level, supplement use, family history and duration of MS.

Conclusion: Adherence to mMeD, for 6 months, improved dietary inflammatory status and fatigue severity in RRMS patients; however, the TID did not positively impact dietary inflammation and MFIS score.

Key words: Dietary inflammatory index: Mediterranean diet: Fatigue: Multiple sclerosis: randomised controlled trial

Multiple sclerosis (MS) is an autoimmune disease of the central nervous system, with unknown etiology, characterised 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 characterised 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 sweats 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 *v.* TID, on DII, disease disability and fatigue severity in RRMS patients. We hypothesised 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).

Materials & methods

Study design and sample size determination

In this single-centre, two parallel arms, single-blind, randomised 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].

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

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; $\overline{x}_1 - \overline{x}_2$, 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.

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 and 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 1 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 FFQ at baseline or were prescribed high dose corticosteroid therapy (>30 mg/d methylprednisolone).

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, MUFA, fish and low to moderate consumption of dairy products, meat and poultry. In practice, the prescribed mMeD was individualised 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 utilised to calculate the Basal Energy Expenditure 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 individualised 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.

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
$\omega6/\omega3$ 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

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

† Reference Number:

1. Bédard A, Riverin M, Dodin S, *et al.* (2012) Sex differences in the impact of the Mediterranean diet on cardiovascular risk profile. *Br J Nutr* 108, 1428–1434.
2. Cordain L, Eaton SB, Sebastian A, *et al.* (2005) Origins and evolution of the Western diet: health implications for the 21st century. *Am J Clin Nutr* 81, 341–354.
3. Kafatos A, Verhagen H, Moschandreas J, *et al.* (2000) Mediterranean diet of Crete: foods and nutrient content. *J Am Dietetic Assoc* 100, 1487–1493.

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.

Recruitment and randomisation 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 TID (control) group, with a computerised random sequence generator. Randomisation was performed by a research assistant who did not participate in either the follow-up assessments or analysis.

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.

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 Modified Fatigue Impact Scale (MFIS)). Socio-demographic and clinical characteristics were collected through a self-report survey completed at baseline, which included details on participants' age, body weight and height, 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.

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) was used to analyse 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.

Dietary Inflammatory Index calculation.

Shivappa *et al.*[36], after evaluation of 1943 articles (were published between 1950 and 2010), examined the association between inflammation and forty-five 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 eleven 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 was then summed to obtain an overall DII score.

Fatigue severity assessment.

The MFIS was used to determine the MS-related fatigue[37] at baseline and 6 months after the intervention. This standard twenty-one item questionnaire has three subscales (physical, ranges from 0 to 36; Cognitive, 0–40 and Psychosocial, 0–8). The total score is computed by summing scores from the three subscales and ranges from 0 to 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 utilised.

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).

Statistical analysis

Data were presented as means ± 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 nonparametric 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. 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.

Results

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 (Fig. 1). In total, 180 patients were dichotomised 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 analysed (based on per-protocol analysis). No side effects (diarrhoea, abdomen pain, constipation and appetite changes) were reported during the study period.

Baseline characteristics

Socio-demographic and medical characteristics, between the groups at baseline, are reported in Table 2. Overall, the participants were middle-aged adults (with mean age $39\cdot3 \pm 9\cdot2$ 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 n-3 (~33%) were the most common. Additionally, ~20 % of subjects had consumed L-carnitine or caffeine-containing supplements during the past 6 months. A small number of male participants (13 %) were irregular smokers (average 1–2 cigarettes in a week).
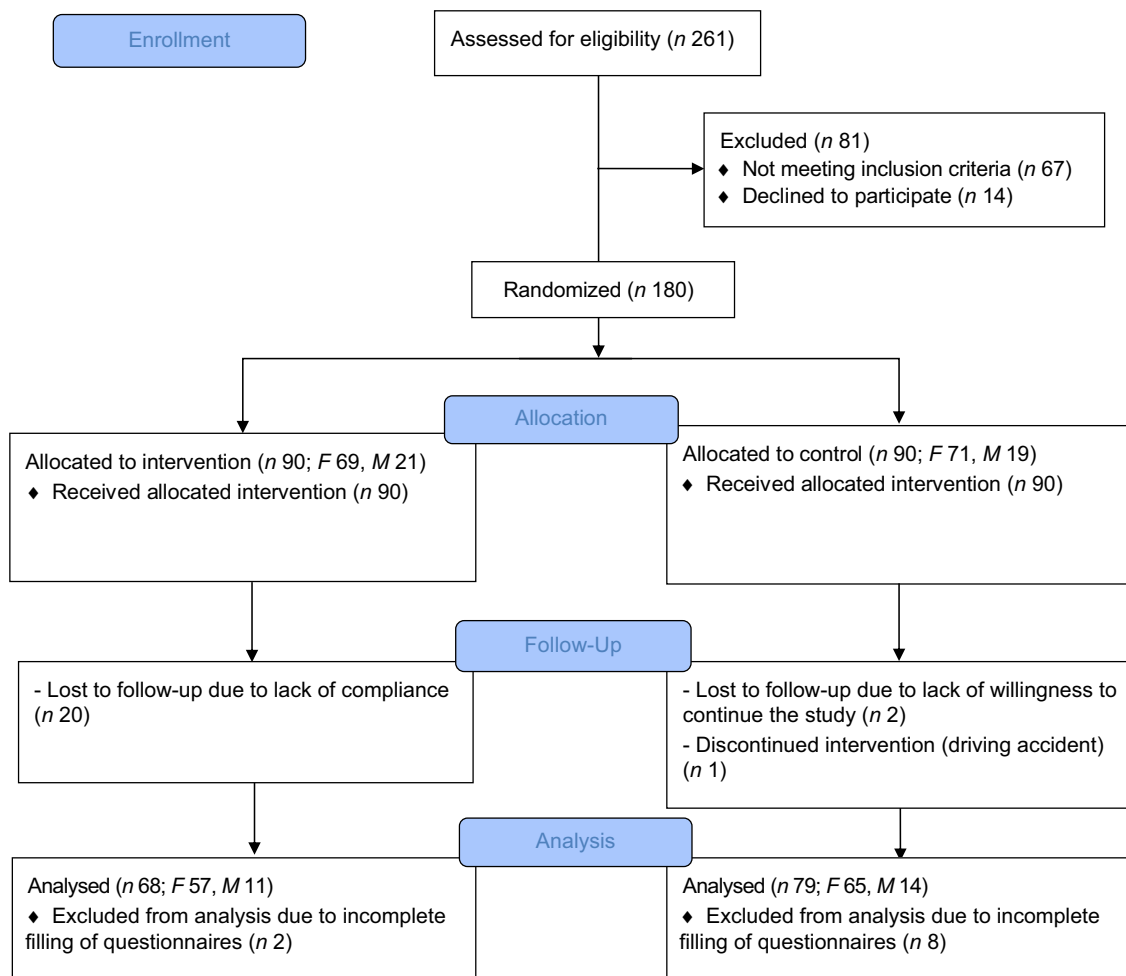

Fig. 1. Flow diagram representing study plan.

Table 2. Characteristics of participants between diet study groups
(Mean values and standard deviations; numbers and percentages)

Group	mMeD (*n* 68)		Control (*n* 79)		
Continuous variables	Mean	SD	Mean	SD	*P*-value*
Age (yr)	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 (yr)	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

		mMeD (*n* 68)		Control (*n* 79)		
Categorical variables		*n*	%	*n*	%	*P*-value‡
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 intakes	Vitamin D	60	88·2	62	78·5	0·764
	n-3	26	38·2	23	29·1	
	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.

Mean EDSS score was slightly higher in the control group (2·0 *v.* 1·7), although there were no significant differences between the study groups for EDSS and DII scores.

Clinical outcomes

Impact of diet interventions on Dietary Inflammatory Index. 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 *v.* −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, MUFA, PUFA, Se, beta carotene, vitamin E, riboflavin, garlic, onion, ginger, turmeric, pepper, thyme/oregano, rosemary, flavan-3-ol, anthocyanidins and isoflavones, in addition to lower intake of energy, carbohydrate, total fat, saturated fat, trans fat, Fe and caffeine in the mMeD group compared with TID group ($P < 0.05$).

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 *v.* 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 6 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.

Impact of diet interventions on disability. There was a nonsignificant reduction in EDSS at the end of the study period in the mMeD group (Δ = −0·02 ± 0·07, $P = 0.334$). Contrastingly, a nonsignificant 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 *v.* TID ($P = 0.065$) (Table 4).

Relationship between DII and the fatigue severity/disease disability. Significant predictors and covariates for MFIS total

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)
(Mean values and standard deviations)

Dietary group	DII food parameters	Group	Baseline Mean	SD	End of trial Mean	SD	P-value†	Δ‡		P-value§
Energy	Energy (kcal/d)	mMeD	2670·6	468·6	2193·6	317·3	<0·001	−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/d)	mMeD	405·2	86·6	317·5	57·7	<0·001	−87·7	54·2	<0·001
		Control	391·4	78·3	394·8	75·1	0·083	3·4	97·3	
	Protein (g/d)	mMeD	92·0	7·5	87·0	8·4	<0·001	−5·0	8·8	0·327
		Control	90·5	6·9	90·1	7·1	0·642	−0·36	10·0	
	Total fat (g/d)	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/d)	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/d)	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/d)	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/d)	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 (g/d)	mMeD	0·18	0·07	0·2	0·06	0·429	0·02	0·09	0·711
		Control	0·18	0·07	0·18	0·06	0·207	−0·00	0·08	
	MUFA (g/d)	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/d)	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/d)	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/d)	mMeD	29·6	6·5	24·6	3·6	<0·001	−5·0	5·34	0·029
		Control	28·5	6·0	28·4	6·0	0·139	−0·1	7·8	
	Magnesium (mg/d)	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/d)	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/d)	mMeD	118·3	25·2	93·0	13·1	<0·001	−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/d)	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/d)	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/d)	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/d)	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/d)	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 B_{12} (µg/d)	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 B_6 (mg/d)	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/d)	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/d)	mMeD	29·8	6·3	24·0	3·6	<0·001	−5·7	4·2	0·018
		Control	28·7	5·5	28·7	5·3	0·326	0·01	7·2	
	Riboflavin (mg/d)	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/d)	mMeD	2·9	0·5	2·4	0·4	<0·001	−0·5	0·3	<0·001
		Control	2·8	0·4	2·8	0·4	0·200	0·01	0·6	
Specific foods	Alcohol‖ (g/d)	mMeD	0		0		−	0		−
		Control	0		0		−	0		
	Garlic (g/d)	mMeD	0·68	1·87	1·24	3·47	<0·001	0·56	1·22	<0·001
		Control	0·70	2·00	0·59	1·55	0·803	−0·11	2·52	
	Onion (g/d)	mMeD	8·9	2·78	10·23	5·74	0·142	1·23	4·03	0·049
		Control	8·0	1·89	7·4	3·22	0·241	−0·6	1·20	
	Ginger (g/d)	mMeD	0·32	0·87	1·0	0·9	0·023	0·7	1·5	0·015
		Control	0·26	0·80	0·20	0·91	0·441	−0·06	0·51	
	Saffron (g/d)	mMeD	0·02	0·11	0·03	0·27	0·095	0·01	0·47	0·314
		Control	0·02	0·28	0·02	0·54	0·176	−0·00	0·44	
	Turmeric (mg/d)	mMeD	8·4	6·5	10·7	3·8	0·047	2·3	1·3	0·041
		Control	7·9	4·4	8·0	4·5	0·341	0·1	1·4	

Table 3. (*Continued*)

Dietary group	DII food parameters	Group	Baseline Mean	SD	End of trial Mean	SD	P-value†	Δ‡		P-value§
	Green/black tea (g/d)	mMeD	4·5	0·4	5·0	1·1	0·057	0·5	1·7	0·274
		Control	4·1	0·6	4·1	0·6	0·748	0·00	0·8	
	Pepper (g/d)	mMeD	0·7	1·5	5·3	2·3	<0·001	4·6	3·1	0·031
		Control	0·8	1·1	0·9	1·8	0·188	0·1	1·1	
	Thyme/oregano (mg/d)	mMeD	0·04	0·27	29·8	8·1	<0·001	29·7	9·9	<0·001
		Control	0·16	0·44	0·13	0·79	0·552	−0·03	0·20	
	Rosemary (mg/d)	mMeD	0·00	0·05	33·4	6·6	<0·001	33·4	8·2	<0·001
		Control	0·00	0·02	0·00	0·06	0·656	0·00	0·02	
Flavonoids¶	Flavan-3-ol (mg/d)	mMeD	74·2	24·2	160·3	69·8	0·046	86·1	12·4	0·068
		Control	68·9	51·1	77·1	44·4	0·121	8·2	10·7	
	Flavones (mg/d)	mMeD	4·2	1·6	5·5	4·8	0·180	1·3	0·9	0·059
		Control	3·3	5·1	3·1	2·2	0·470	−0·2	0·5	
	Flavonols (mg/d)	mMeD	30·8	8·4	44·5	10·3	0·065	13·7	4·8	0·214
		Control	22·7	4·5	20·3	6·6	0·113	−2·4	1·1	
	Flavonones (mg/d)	mMeD	11·6	6·1	17·3	9·9	0·080	5·7	3·3	0·247
		Control	11·0	2·5	11·0	1·9	0·914	0·00	0·47	
	Anthocyanidins (mg/d)	mMeD	10·6	5·5	59·3	11·2	<0·001	48·7	10·0	<0·001
		Control	10·2	4·4	11·0	3·8	0·252	0·8	1·8	
	Isoflavones** (mg/d)	mMeD	4·2	3·1	13·7	0·9	0·044	9·5	1·6	0·049
		Control	4·1	3·0	4·5	2·8	0·230	0·4	0·6	
miscellaneous	Eugenol†† (mg/d)	mMeD	0·01	0·2	0·2	0·1	0·074	0·19	0·2	0·033
		Control	0·00	0·1	0·00	0·1	0·234	0·00	0·1	
	Caffeine (g/d)	mMeD	0·004	0·003	0·003	0·001	<0·001	−0·001	0·000	0·618
		Control	0·004	0·003	0·004	0·003	0·164	−0·000	0·000	
Overall DII score‡‡		mMeD	2·38	0·21	−1·87	0·86	<0·001	−4·25	1·54	<0·001
		Control	2·21	0·44	2·14	1·01	0·771	−0·07	0·62	

DII, Dietary inflammatory index; mMeD, modified Mediterranean Diet; control, Traditional Iranian Diet; MUFA, monounsaturated fatty acids; PUFA, polyunsaturated fatty acids.
Data has been presented as mean ± SD.
Flavonoid intake was estimated based on 'USDA Database for the Flavonoid Content of Selected Foods; Release 3·2'. Other micro &macronutrients were calculated with N4 software.
† Obtained from paired *t* test; except for protein and Vitamin A, that were analyzed via nonparametric Wilcoxon test. *P* < 0·05 considered as significant.
‡ Mean changes between end of trial and baseline values.
§ Obtained from MANCOVA test; adjusted for age, gender, body weight, body mass index, education level, supplement use, family history and duration of MS, and *P* < 0·05 considered as significant.
∥ 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.
¶ Calculated from USDA Database for the Flavonoid Content of Selected Foods Release 3·3 (March 2018)
** Calculated from USDA Database for the Isoflavone Content of Selected Foods Release 2·0 (September 2008)
†† Eugenol (mg) intake was measured based on Phenol-Explorer database (latest version 3·6; released on December 2016).
‡‡ Obtained by dietary intakes only. Negative number indicates an anti-inflammatory score, while positive number reflects a proinflammatory score.

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)
(Mean values and standard deviations)

Variables	Subscale	Group	Baseline Mean	SD	End of trial Mean	SD	P-value†	Δ‡ Mean	SD	P-value§
MFIS	Physical	mMeD	31·2	10·4	28·5	8·8	<0·001	−2·7	0·7	<0·001
		Control	32·9	9·2	33·7	10·2	0·124	0·8	0·8	
	Cognitive	mMeD	35·8	11·1	30·2	8·5	<0·01	−5·6	1·8	0·027
		Control	36·6	9·9	36·1	7·1	0·092	−0·5	0·1	
	Psychosocial	mMeD	5·4	3·1	5·2	2·6	0·244	−0·2	0·2	0·088
		Control	6·0	2·9	6·1	3·4	0·157	0·1	0·4	
	Total score	mMeD	72·4	17·2	63·9	14·2	<0·001	−8·5	2·74	<0·001
		Control	69·5	13·2	75·9	15·3	0·771	6·4	1·62	
EDSS		mMeD	1·7	0·7	1·7	0·6	0·334	−0·02	0·07	0·065
		Control	2·0	0·9	2·1	0·8	0·112	0·1	0·02	

MFIS, Modified Fatigue Impact Scale; EDSS, Extended Disability Status Scale; mMeD, modified Mediterranean Diet; control, Traditional Iranian Diet; MUFA, monounsaturated fatty acids; PUFA, polyunsaturated fatty acids.
Data has been presented as mean ± SD.
† Obtained from paired *t* test. *P* < 0·05 considered as significant.
‡ Mean changes between end of trial and baseline values.
§ Obtained from MANCOVA test; adjusted for age, gender, body weight, body mass index, education level, supplement use, family history and duration of MS, and *P* < 0·05 considered as significant.

Table 5. Predictors and covariates for MFIS total score and EDSS in mMeD group
(Coefficient values and 95 % confidence intervals)

Dependent variables	Covariates	B	95 % CI Lower, Upper	P value	Adjusted R
MFIS total score	Age	0·035	−0·006, 0·068	0·122	0·098
	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	0·157
	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, unstandardised regression coefficient; 95 % CI, 95 % confidence interval of the unstandardised regression coefficient.
MFIS, modified fatigue impact scale; DII, dietary inflammatory index; EDSS, extended disability status scale; BMI, body mass index; MS, multiple sclerosis'

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.

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 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 MD 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 MD 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. *n*-3 PUFAs inhibit NF-kB 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 randomised 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 hypothesised 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 utilised[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 *v.* 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 forty-five 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 RRMS are limited; therefore, the present study provides a novel and important addition to the literature.

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 in disability. Comparatively, adherence to the TID 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.

Acknowledgements

References

1. Vidmar L, Maver A, Drulović J, et al. (2019) Multiple Sclerosis patients carry an increased burden of exceedingly rare genetic variants in the inflammasome regulatory genes. Sci Rep 9, 1–10.
2. Sowmya K & Khader A (2020) Multiple sclerosis an ayurvedic approach-a critical view. J Ayurveda Integrated Med Sci 4, 200–204.
3. Jamebozorgi K, Rostami D, Pormasoumi H, et al. (2021) Epigenetic aspects of multiple sclerosis and future therapeutic options. Int J Neurosci 131, 56–64.
4. Dolati S, Babaloo Z, Jadidi-Niaragh F, et al. (2017) Multiple sclerosis: therapeutic applications of advancing drug delivery systems. Biomed Pharmacother 86, 343–353.
5. Wang Q, Wang J, Yang Z, et al. (2019) Therapeutic effect of oligomeric proanthocyanidin in cuprizone-induced demyelination. Exp Physiol 104, 876–886.
6. Sato F, Martinez NE, Shahid M, et al. (2013) Resveratrol exacerbates both autoimmune and viral models of multiple sclerosis. Am J Pathol 183, 1390–1396.
7. Von Geldern G & Mowry EM (2012) The influence of nutritional factors on the prognosis of multiple sclerosis. Nat Rev Neurol 8, 678.
8. Halawani AT, Zeidan ZA, Kareem AM, et al. (2018) Sociodemographic, environmental and lifestyle risk factors for multiple sclerosis development in the Western Region of Saudi Arabia: a matched case control study. Saudi Med J 39, 808.
9. Khosravi-Largani M, Pourvali-Talatappeh P, Rousta AM, et al. (2018) A review on potential roles of vitamins in incidence, progression, and improvement of multiple sclerosis. Eneurologicalsci 10, 37–44.
10. Guo Ye, Suo N, Cui X, et al. (2018) Vitamin C promotes oligodendrocytes generation and remyelination. Glia 66, 1302–1316.
11. Paknahad Z, Sheklabadi E, Moravejolahkami AR, et al. (2020) The effects of Mediterranean diet on severity of disease and serum Total Antioxidant Capacity (TAC) in patients with Parkinson's disease: a single center, randomized controlled trial. Nutr Neurosci 1, 1–8.
12. Moravejolahkami A & Chitsaz A (2019) Mediterranean-Style diet co-supplemented with synbiotics improved quality of life, fatigue and disease activity in five secondary progressive multiple sclerosis patients. Ann Med & Surg Case Rep: AMSCR 1, 1–3.
13. Mousavi-Shirazi-Fard Z, Mazloom Z, Izadi S, et al. (2020) The effects of modified anti-inflammatory diet on fatigue, quality of life, and inflammatory biomarkers in relapsing-remitting multiple sclerosis patients: a randomized clinical trial. Int J Neurosci 7, 1–9.
14. Moravejolahkami AR, Paknahad Z & Chitsaz A (2019) Association of dietary patterns with systemic inflammation, quality of life, disease severity, relapse rate, severity of fatigue and anthropometric measurements in MS patients. Nutr Neuroscience 12, 1–11.
15. van Duijnhoven FJ, Brouwer JG, van Woudenbergh GJ, et al. (2020) Comment on 'Perspective: the Dietary Inflammatory Index (DII) – Lessons Learned, Improvements Made, and Future Directions'. Adv Nutr 11, 177–178.
16. Mutthuraj D, Vinutha T, Gopenath T, et al. (2020) Inhibition of pro-inflammatory molecules by ginger (zingiber officinale roscoe) and its anti-inflammatory effects on arthritis patients. J Drug Delivery Ther 10, 125–139.
17. Simin N, Mitić-Ćulafić D, Pavić A, et al. (2020) An overview of the biological activities of less known wild onions (genus Allium sect. Codonoprasum). BiologiaSerbica 40, 6–12.
18. Mahabamunuge J, Simione M, Horan C, et al. (2019) Association of proinflammatory and proinsulinemic food groups with maternal postpartum weight retention (18B). Obstet Gynecol 133, 25S.
19. Mayr HL, Thomas CJ, Tierney AC, et al. (2018) Randomization to 6-month Mediterranean diet compared with a low-fat diet leads to improvement in Dietary Inflammatory Index scores in patients with coronary heart disease: the AUSMED Heart Trial. Nutr Res 55, 94–107.
20. Ruiz-Canela M, Zazpe I, Shivappa N, et al. (2015) Dietary inflammatory index and anthropometric measures of obesity in a population sample at high cardiovascular risk from the PREDIMED (PREvencion con DIeta MEDiterranea) trial. Br J Nutr 113, 984–995.
21. Hodge A, Bassett J, Shivappa N, et al. (2016) Dietary inflammatory index, Mediterranean diet score, and lung cancer: a prospective study. Cancer Causes Contr 27, 907–917.
22. Abdollahpour I, Jakimovski D, Shivappa N, et al. (2020) Dietary inflammatory index and risk of multiple sclerosis: findings from a large population-based incident case-control study. Clin Nutr 39, 3402–3407.
23. Kurtzke JF (1983) Rating neurologic impairment in multiple sclerosis an expanded disability status scale (EDSS). Neurology 33, 1444.
24. General Assembly of the World Medical Association (2014) World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. J Am Coll Dent 81, 14.
25. Riccio P, Rossano R, Larocca M, et al. (2016) Anti-inflammatory nutritional intervention in patients with relapsing-remitting, primary-progressive multiple sclerosis: a pilot study. Exp Biol Med 241, 620–635.
26. Bédard A, Riverin M, Dodin S, et al. (2012) Sex differences in the impact of the Mediterranean diet on cardiovascular risk profile. Br J Nutr 108, 1428–1434.
27. Souri E, Amin G, Farsam H, et al. (2004) The antioxidant activity of some commonly used vegetables in Iranian diet. Fitoterapia 75, 585–588.
28. Bendavid I, Lobo DN, Barazzoni R, et al. (2020) The centenary of the Harris-Benedict equation: how to assess energy requirements best? Recommendations from the ESPEN Expert Group. Clin Nutr 40, 690–701.
29. Willet W & Lenart E (1998) Reproducibility and validity of food-frequency questionnaires. Monogr Epidemiol Biostat 1, 101–147.
30. Esmaillzadeh A, Mirmiran P & Azizi F (2005) Whole-grain consumption and the metabolic syndrome: a favorable association in tehranian adults. Eur J Clin Nutr 59, 353–362.

31. Mirmiran P, Esfahani FH, Mehrabi Y, *et al.* (2010) Reliability and relative validity of an FFQ for nutrients in the Tehran Lipid and Glucose Study. *Public Health Nutr* **13**, 654–662.

32. Nematy M, Nouri M, Ghazizahedi S, *et al.* (2013) Validity and reproducibility of Iranian food frequency questionnaire. *Switz Res Park J* **102**, 2137–2146.

33. Haytowitz DB, Wu X & Bhagwat S (2018) *USDA Database for the Flavonoid Content of Selected. Foods Release*. US Department of Agriculture. Maryland.

34. Bhagwat S, Haytowitz DB & Holden JM (2008) *USDA Database for the Isoflavone Content of Selected Foods, Release 2.0*. Maryland: US Department of Agriculture.

35. Yordi EG, Matos M, Martínez AP, *et al.* (2017) In Silico genotoxicity of coumarins: application of the phenol-explorer food database to functional food science. *Food Funct* **8**, 2958–2966.

36. Shivappa N, Steck SE, Hurley TG, *et al.* (2014) A population-based dietary inflammatory index predicts levels of C-reactive protein in the Seasonal Variation of Blood Cholesterol Study (SEASONS). *Public Health Nutr* **17**, 1825–1833.

37. Fisk JD, Ritvo PG, Ross L, *et al.* (1994) Measuring the functional impact of fatigue: initial validation of the fatigue impact scale. *Clin Infect Diseases* **18**, S79–S83.

38. Harirchian MH, Nasergivechi S, Maddah M, *et al.* (2013) Evaluation of the Persian version of modified fatigue impact scale in Iranian patients with multiple sclerosis. *Iranian J Neurol* **12**, 32.

39. Rietberg M, Van Wegen E & Kwakkel G (2010) Measuring fatigue in patients with multiple sclerosis: reproducibility, responsiveness and concurrent validity of three Dutch self-report questionnaires. *Disabil Rehabil* **32**, 1870–1876.

40. Hohol M, Orav E & Weiner H (1999) Disease steps in multiple sclerosis: a longitudinal study comparing disease steps and EDSS to evaluate disease progression. *Multiple Sclerosis J* **5**, 349–354.

41. Goudarzi R, Sedaghat M, Hedayati M, *et al.* (2020) Low advanced Glycation end product diet improves the central obesity, insulin resistance and inflammatory profiles in Iranian patients with metabolic syndrome: a randomized clinical trial. *J Diabetes Metab Disord* **2**, 1–10.

42. Moravejolahkami AR, Paknahad Z, Chitsaz A, *et al.* (2020) Potential of modified Mediterranean diet to improve quality of life and fatigue severity in multiple sclerosis patients: a single-center randomized controlled trial. *Int J Food Prop* **23**, 1993–2004.

43. Floor W (2020) From Quasi-vegetarians to Quasi-carnivores: the changing diet of Iranians. *Iranian Stud* **1**, 1–16.

44. Jahromi SR, Toghae M, Jahromi MJR, *et al.* (2012) Dietary pattern and risk of multiple sclerosis. *Iranian J Neurol* **11**, 47.

45. Agrawal S, Berggren KL, Marks E, *et al.* (2017) Impact of high iron intake on cognition and neurodegeneration in humans and in animal models: a systematic review. *Nutr Rev* **75**, 456–470.

46. Ghassemi H, Harrison G & Mohammad K (2002) An accelerated nutrition transition in Iran. *Public Health Nutr* **5**, 149–155.

47. Zhu J, Ling Y, Mi S, *et al.* (2020) Association between dietary inflammatory index and upper aerodigestive tract cancer risk: a systematic review and dose-response meta-analysis. *Oral Oncol* **104**, 587.

48. Fowler ME & Akinyemiju TF (2017) Meta-analysis of the association between dietary inflammatory index (DII) and cancer outcomes. *Int J Cancer* **141**, 2215–2227.

49. Wirth MD, Hébert JR, Shivappa N, *et al.* (2016) Anti-inflammatory Dietary Inflammatory Index scores are associated with healthier scores on other dietary indices. *Nutr Res* **36**, 214–219.

50. da Costa Silva BY, de Carvalho Sampaio HA, Shivappa N, *et al.* (2019) Dietary Inflammatory Index and clinical course of multiple sclerosis. *Eur J Clin Nutr* **73**, 979–988.

51. Silva BYDC, Sampaio HADC, Shivappa N, *et al.* (2018) Interactions between dietary inflammatory index, nutritional state and multiple sclerosis clinical condition. *Clin Nutr ESPEN* **26**, 35–41.

52. Shivappa N, Hebert JR, Behrooz M, *et al.* (2016) Dietary inflammatory index and risk of multiple sclerosis in a case-control study from Iran. *Neuroepidemiology* **47**, 26–31.

53. Uccelli A & Gattorno M (2018) Neurological manifestations in autoinflammatory diseases. *Clin Exp Rheumatol* **36**, S61–S7.

54. Sanchez JMS, DePaula-Silva AB, Libbey JE, *et al.* (2020) Role of diet in regulating the gut microbiota and multiple sclerosis. *Clin Immunol* **108**, 379.

55. Celarain N & Tomas-Roig J (2020) Aberrant DNA methylation profile exacerbates inflammation and neurodegeneration in multiple sclerosis patients. *J Neuroinflamm* **17**, 21.

56. Schwingshackl L & Hoffmann G (2014) Mediterranean dietary pattern, inflammation and endothelial function: a systematic review and meta-analysis of intervention trials. *Nutr Metab Cardiovasc Dis* **24**, 929–939.

57. Khalili H, Håkansson N, Chan SS, *et al.* (2020) Adherence to a Mediterranean diet is associated with a lower risk of later-onset Crohn's disease: results from two large prospective cohort studies. *Gut* **69**, 1637–1644.

58. Inoue T, Tanaka M, Masuda S, *et al.* (2017) *n*-3 polyunsaturated fatty acids suppress the inflammatory responses of lipopolysaccharide-stimulated mouse microglia by activating SIRT1 pathways. *Biochimica et Biophysica Acta (BBA) – Mol Cell Biol Lipid* **1862**, 552–560.

59. von Glehn F, Dias-Carneiro RP, Moraes AS, *et al.* (2018) Dimethyl fumarate downregulates the immune response through the HCA2/GPR109A pathway: implications for the treatment of multiple sclerosis. *Multiple Sclerosis Relat Disord* **23**, 46–50.

60. Zhang S, Xue R & Hu R (2019) The neuroprotective effect and action mechanism of polyphenols in diabetes mellitus-related cognitive dysfunction. *Eur J Nutr* **4**, 1–17.

61. Farinotti M, Vacchi L, Simi S, *et al.* (2012) Dietary interventions for multiple sclerosis. *Cochrane Database Syst Rev* **12**, CD004192.

62. Parks NE, Jackson-Tarlton CS, Vacchi L, *et al.* (2020) Dietary interventions for multiple sclerosis-related outcomes. *Cochrane Database Syst Rev* **5**, CD004192.

63. Zini A, Rio DD, Stewart AJ, *et al.* (2006) Do flavan-3-ols from green tea reach the human brain? *Nutr Neurosci* **9**, 57–61.

64. Hou D-X, Yanagita T, Uto T, *et al.* (2005) Anthocyanidins inhibit cyclooxygenase-2 expression in LPS-evoked macrophages: structure–activity relationship and molecular mechanisms involved. *Biochemical Pharmacol* **70**, 417–425.

65. Freedman SN, Shahi SK, Zarei K, *et al.* (2020) Isoflavone Rich Diet Ameliorates Experimental Autoimmune Encephalomyelitis (EAE) through modulation of gut bacteria depleted in multiple sclerosis patients. *Am Assoc Immnol* **204**, 141.

66. Yadav V, Marracci G, Kim E, *et al.* (2016) Low-fat, plant-based diet in multiple sclerosis: a randomized controlled trial. *Multiple Sclerosis Relat Disord* **9**, 80–90.

67. Meyer-Moock S, Feng Y-S, Maeurer M, *et al.* (2014) Systematic literature review and validity evaluation of the Expanded Disability Status Scale (EDSS) and the Multiple Sclerosis Functional Composite (MSFC) in patients with multiple sclerosis. *BMC Neurol* **14**, 1–10.

68. Hohol M, Orav E & Weiner H (1995) Disease steps in multiple sclerosis: a simple approach to evaluate disease progression. *Neurology* **45**, 251–255.