

The Effectiveness of Modified Mediterranean and Traditional Persian Diets in Fatigue and Depressive Severity in People with Multiple Sclerosis: A Randomized Controlled Clinical Trial

Mohammad Hossein Sharifi^{1,2}, MD, PhD, MPH; Maryam Poursadeghfard³, MD; Maryam Afshari², MD; Zahra Alizadeh⁴, MSc; Mohammad Vatanpour⁵, MSc; Mitra Soltani^{4,6}, MSc; Hossein Molavi Vardanjani¹, PhD, MPH; Amir Mohammad Jaladat¹, MD, PhD, MPH; Majid Nimrouzi¹, MD, PhD, MPH

¹Research Center for Traditional Medicine and History of Medicine, Shiraz University of Medical Sciences, Shiraz, Iran;

²Non-Communicable Diseases Research Center, School of Medicine, Shiraz University of Medical Sciences, Shiraz, Iran;

³Clinical Neurology Research Center, Shiraz University of Medical Sciences, Shiraz, Iran;

⁴Imam Reza Specialized and Subspecialized Polyclinic, Shiraz University of Medical Sciences, Shiraz, Iran;

⁵Master Student of Nutrition Sciences, Department of Clinical Nutrition, School of Nutrition and Food Sciences, Shiraz University of Medical Sciences, Shiraz, Iran;

⁶Department of Clinical Nutrition, Tehran University of Medical Sciences, Tehran, Iran

Correspondence:

Majid Nimrouzi, MD, PhD, MPH;
Shiraz School of Medicine, Imam Hossein Sq., Zand Blvd., Postal code: 71348-45794, Shiraz, Iran

Tel: +98 71 32084028

Email: mnimrouzi@yahoo.com

Received: 10 March 2024

Revised: 16 May 2024

Accepted: 11 June 2024

What's Known

- There is a lack of scientific understanding of diet intervention's potential in managing multiple sclerosis (MS). As far as we know, few studies have been conducted to investigate the effect of traditional Persian food (hot, cold, or balanced food) and Mediterranean diet interventions on fatigue and depression in MS.

What's New

- Adhering to the Mediterranean diet can alleviate fatigue scores in MS patients while having no effect on the depression score. In contrast, adhering to the traditional Persian diet recommendation can reduce depression scores without affecting fatigue scores in MS patients.

Abstract

Background: Research into managing depression and fatigue, two typical symptoms of multiple sclerosis (MS), is constantly expanding. This study aimed to assess the efficacy of the modified Mediterranean (MED) diet or the Traditional Persian (TP) diet in terms of fatigue and depression severity in patients with MS.

Methods: In this single-center, single-blind, randomized clinical trial, 90 patients were enrolled. The patients were randomly assigned to either the MED or TP diet intervention and control groups for two months between July 2022 and February 2023, in Shiraz, Iran. The Krupp Questionnaire for Fatigue Severity Scale and the Beck Depression questionnaire were used. The Chi square test, Kruskal-Wallis test, One-way ANOVA, and backward elimination technique were employed. STATA statistical software (version 17) was utilized for data analysis. $P \leq 0.05$ was considered statistically significant.

Results: The mean age of 90 participants was 35.64 ± 9.12 , and 82.2% were women. The analysis revealed a negative correlation between fatigue severity and MED diet intervention ($-4.17 [-8.18-0.16]$; $P=0.04$). However, there was no association between fatigue severity and TP diet intervention ($-3.82 [-7.96, 0.32]$; $P=0.07$).

The analysis showed that there was a statistically significant relationship between lower depression scores and TP diet intervention ($-2.89 [-5.59, -0.19]$; $P=0.03$). However, there was no association between depression scores and MED diet intervention ($P=0.22$). Lower depression score was also associated with older age and higher socioeconomic status ($P=0.002$ and $P=0.006$). It was also shown that longer duration of disease ($P=0.05$) and higher fatigue severity ($P=0.001$) were associated with higher depression scores.

Conclusion: Adhering to the MED diet could reduce fatigue scores in MS patients while having no effect on the depression score. In contrast, adhering to the TP diet recommendation could reduce depression scores without affecting fatigue scores in MS patients.

Trial registration number: IRCT20181113041641N1.

Please cite this article as: Sharifi MH, Poursadeghfard M, Afshari M, Alizadeh Z, Vatanpour M, Soltani M, Molavi Vardanjani H, Jaladat AM, Nimrouzi M. The Effectiveness of Modified Mediterranean and Traditional Persian Diets in Fatigue and Depressive Severity in People with Multiple Sclerosis: A Randomized Controlled Clinical Trial. Iran J Med Sci. doi: 10.30476/ijms.2024.101961.3472.

Keywords • Fatigue • Depression • Mediterranean diet • Multiple sclerosis • Persian traditional medicine

Introduction

Multiple sclerosis (MS) is an autoimmune disease that afflicts the central nervous system (CNS) with an unknown etiology and a complex pathogenesis.¹ Approximately 2.5 million people worldwide suffer from MS. MS symptoms vary depending on the severity of CNS damage, while fatigue and depression are the most prevalent side effects.² MS symptom management might contribute to improved well-being and quality of life. The body of research seeking to identify the pathophysiological causes of fatigue or depression as two common MS symptoms is constantly expanding; however, the actual underlying cause remains unknown.³⁻⁵ Nutritional intervention, as a neutral approach, considers the potential of managing MS symptoms and promising beneficial outcomes regardless of MS activity and progression.⁶ While research on the relationship between diet intervention and the management of MS symptoms has been conducted, there is still lack of empirical proof of the potential of diet intervention, particularly the role of traditional diet intervention, in MS management.^{6, 7}

According to some studies, environmental risk factors, particularly unhealthy diet, are associated with an increased risk of MS.^{8, 9} However, it is still unknown how diet habits would affect patients with MS.⁷ Some evidence showed that diet could influence fatigue and depression. Besides, an unbalanced diet could exacerbate the condition.^{2, 10} Previous studies indicated that the Mediterranean (MED) diet, as an anti-inflammatory diet, could alleviate some MS symptoms and that high adherence to the MED diet could reduce the risk of MS.^{11, 12} This diet is characterized by a high intake of fish, fruits, vegetables, whole grains, legumes, olive oil, and a low to moderate intake of dairy, meat, and poultry. While an umbrella review of the meta-analyses found that a MED diet improved a variety of health outcomes, including a lower risk of mortality, cardiovascular disease, myocardial infarction, overall cancer incidence, neurodegenerative diseases, and diabetes, another umbrella review of the meta-analyses found a lack of strong consistent evidence for dietary interventions to improve disease progression and symptoms in individuals with MS.^{13, 14} Therefore, it appears that there was mixed results regarding the impact of food interventions based on the MED diet on MS fatigue and depression, and more research might be beneficial.

Traditional Persian Medicine (TPM) classifies foods as hot, cold, or balanced. Food nature is

a common concept in TPM as well as traditional medicine systems of the Roman, Greek, Indian, European, Arabic, and Chinese.¹⁵ Despite the fact that the concept of natural food is not intuitive to scientists, research in this field is expanding. Recent studies have examined foods using this notion and found that nutrients could be one of the key factors in determining their cold-hot properties.^{16, 17} Rezapour-Firouzi and others discovered that hot-natured foods improved the clinical score of individuals with MS through an immunomodulatory mechanism.¹⁸ A study by Sharifi and colleagues suggested that dietary patterns that are based on food and nature might raise the risk of MS.¹⁵ To the best of our knowledge, little research has been conducted on how Traditional Persian (TP) food interventions (hot, cold, or balanced nature of food) affect fatigue and depression in patients with MS. In a previously published study by the authors of the present study, for the first time in the world, a dietary pattern based on the cold and hot nature of food was established. This dietary pattern served as the basis of this clinical trial research.¹⁵

One of the major areas of research in MS clinical practice is the impact of diet interventions on health outcomes, MS progression, and symptom improvement. The purpose of this study was to determine the potential impact of the MED diet and TP diet on fatigue and the severity of depression in patients with MS. The second purpose of this study was to investigate the effectiveness of the modified MED diet versus the TP diet in terms of fatigue and depression severity in patients with MS.

Patients and Methods

Study Design and Sample Size Determination

This single-center, three parallel-arms, double-blind, randomized clinical trial was carried out from July 2022 to February 2023. The study protocol was approved by the Ethics committee of Shiraz University of Medical Sciences (code: IR.SUMS.REC.1401.525) and was registered in the Iranian Registry of Clinical Trials (code: IRCT20181113041641N1). The study protocol complied with the ethical guidelines of the 1975 Declaration of Helsinki.

Based on the estimated effect size by Opie and others, a mean difference of equal to or more than 50% of the baseline score of depressive symptoms was estimated.¹⁹ In this respect, a mean depression score (Beck depression questionnaire) of 25 ± 12 was expected to reduce to 12 ± 4 as a result of dietary interventions.¹⁹ Then, with a 5% type I error, a 20% type II error, and

a drop rate of 10% for two months, the minimum sample size in each group was calculated at 30 patients. A convenience sampling method was used. At first, the research population included 166 patients. According to the inclusion and exclusion criteria of the study, 90 patients were selected (figure 1). Prior to data collection, study objectives were explained, and all the participants provided voluntary written informed consent.

In the present study, primary outcomes were fatigue and depression severity scores, and secondary outcomes were MED and TP diet adherence.

Inclusion and Exclusion Criteria

Patients who were eligible for the study had a definite diagnosis of MS from MS specialists, a Kurtzke extended disability status score (EDSS) of less than 6, were between the ages of 20 and 60, and signed a consent form for the research survey. Pregnant women, patients on corticosteroid therapy, those with cardiovascular disease, taking anticoagulant or antiplatelet medications, and patients with psychiatric

disorders were all excluded. The EDSS was measured at baseline by a trained neuroscientist.

Recruitment and Randomization Methods

A randomized block design was developed using an online random sequence generator software (Create a blocked randomization list|Sealed Envelope). Blocked randomization with different block sizes of 3, 6, or 12 was used. To conceal the allocation, a fully sealed envelope covered in carbon paper was used. A statistician prepared the concealment envelopes, which remained hidden until the grouping training course was completed.

Interventions and Control Groups

All patients attended instructional sessions, where they were given a broad overview of the study groups, educational packages, and study objectives. The educational counseling structure was consistent for all patients. However, educational classes specific to the intervention group were added to the educational structure in the first, second, and third intervention groups.

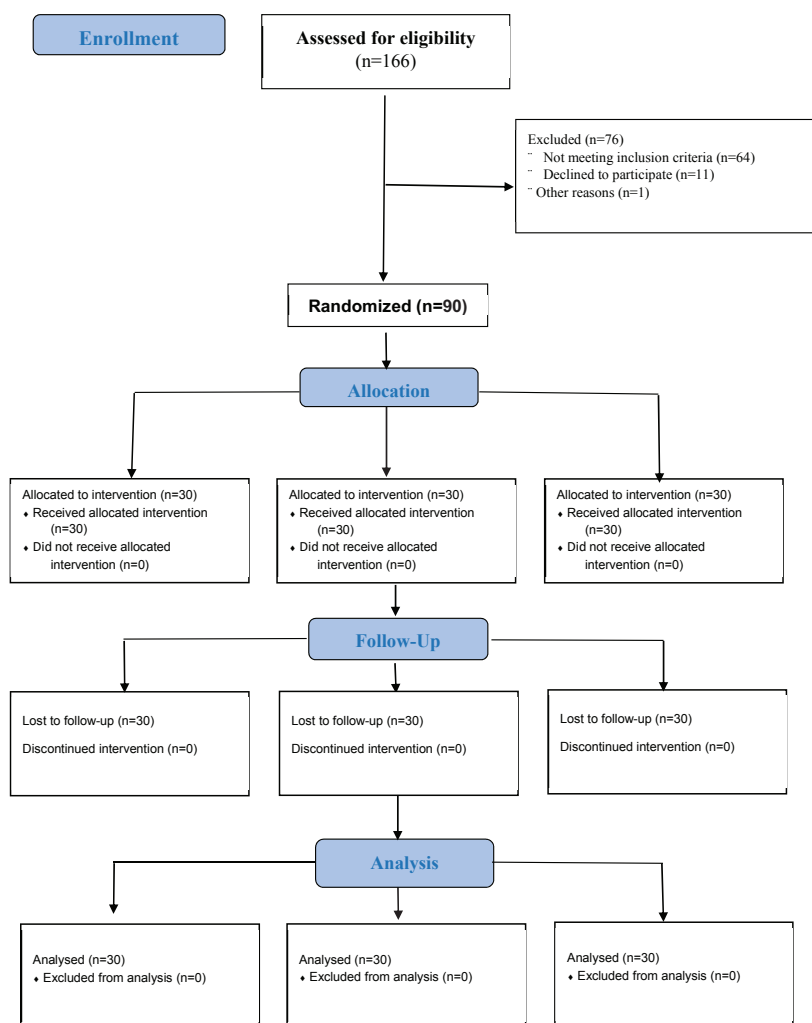


Figure 1: This figure represents the CONSORT flow diagram of the study.

After determining the patient's eligibility for the study, a neurologist introduced them to the research group. The neurologist was blinded to the group randomization procedure.

In the first intervention group (group A), a research team member assessed the patients' adherence to the MED diet using a questionnaire, and subsequently the patients received MED diet recommendations from a trainer to increase adherence to the MED diet.

The second intervention group (group B) received four dietary recommendations, based on the nature of food in the TP diet, the findings of Sharifi and others' study of the dietary pattern in people with MS in Shiraz, and Rezapour's study in Tehran.^{10, 15, 20} Dietary recommendations included consume two servings of nuts per day, consume only one serving of sweets and snacks per day, avoiding seasoning, and consume four servings of hot nature fruits per day but not consume cold nature fruits. Details of the recommendations were presented in the method section.

The third group (group C), which served as the control group, received dietary recommendations from the research team's healthcare practitioner, such as consuming less salt and lower-fat foods.

Blinding Procedure

In this trial, single blinding was used. Participants in this study were unaware of the study group allocation. Research assistants enrolled in one group intervention and consultation based on a specific protocol. Participants were recruited using advertisements in local media channels and clinicians' invitations. The participants were randomly assigned to the modified MED diet, the TP diet, and the control group using a computerized random sequence generator. The researcher who was involved in the randomization procedure was not involved in either the follow-up assessments or analysis.

Fatigue Severity Assessment

The Krupp questionnaire for fatigue severity scale (FSS) was utilized to measure the severity of MS fatigue before and 2 months after the intervention. The questionnaire included nine items on a seven-point Likert scale (1=strongly disagree to 7=strongly agree). The obtained scores ranged from 9 to 63, with higher scores indicating greater fatigue severity. The FSS questionnaire was validated by Azimian and others in the Iranian population with internal consistency (Cronbach's Alpha=0.96), convergent validity ($P<0.0001$), CVI=0.82-0.86, and CVR of at least 0.52 for each item.²¹

Depression Assessment

The depression score from the Beck depression questionnaire, short form (13 questions), was used to measure MS-related depression at baseline and two months after the intervention. Each scale item was scored on a four-point scale (0=least, 3=most), with a total summed score ranging from 0 to 39. The Beck depression questionnaire was validated by Dadfar and colleagues in the Iranian population. It had acceptable internal consistency (Cronbach's Alpha=0.85), convergent validity ($P=0.05$), CVI=0.82-0.86, and CVR of not less than 0.52 for each item.²²

The second researcher, who was unaware of the participant grouping, completed the fatigue and depression questionnaire for each patient at the end of the intervention.

Diet Adherences Assessment

The food intake of individuals in the modified MED diet group was assessed and validated using the 14-item MED diet adherence in the Iranian population.^{23, 24} The scale included 14 foods with standard serving sizes regularly consumed, with each question scoring 0 or 1. Med diet questionnaire was validated by Khalighi Sikaroudi and colleagues in the Iranian population, with a CVR \geq 0.714 and CVI=1. Moreover, a significant correlation was seen regarding the Pearson coefficient for test-retest reliability ($r=0.74$, $P<0.001$). The MED diet was maintained by administering a questionnaire both at registration and at the end of the intervention. The range of adherence scores was between 0 and 14.

To obtain TP diet adherence for the four recommendations listed in table 1, a standard three-day food record was used at registration and the end of the intervention.^{25, 26} Then, the researcher filled a four-point Likert scale form, based on each recommendation assessment scaled 0-3, as follows.²⁶ The total adherence scores for the four recommendations ranged from 0 to 12 (table 2).

Additionally, body weight was assessed by a digital scale (SECA scales 799, Seca, Germany) to the nearest 0.1 Kg; while wearing light clothing. Body mass index (BMI) was calculated by dividing weight (Kg) by the square of height (m).

Statistical Analysis

STATA statistical software version 17 (Stata Corporation, College Station, TX, USA) was utilized for data analysis. Quantitative and qualitative variables were described using mean \pm SD, frequencies, and percentages, respectively. To check the normality of variables, the Kolmogorov-Smirnov test was used.

Table 1: Four traditional Persian diet recommendations for people with multiple sclerosis (MS)

Nuts	Pistachio, almond, walnut, hazelnut, and peanut		Consume two servings daily
Sweets and snacks	Chips, cheese balls, sugar cubes, sugar, honey, jam, cola, traditional sweet snacks, chocolate, sugar plum, candy, Halva (traditional sweet), pepper, chili sauce, salty vegetables, pickles, salt, seasonings, cakes, sweets, biscuits, and crackers		Just 50 g of one type of sweets or snacks could be consumed per day.
Seasoning	Sour lemon, lemon juice, and vinegar		Should not be consumed
Fruits	Hot-natured	Pear, apple, fresh berries, cantaloupe, melon, fig, grape, kiwi, persimmon, banana, fruit juice, and fruit compote	Consume four servings daily
	Cold-natured	Watermelon, apricot, cherry, peach, nectarine, vegetables, grapefruit, orange, tangerine, pomegranate, plum, and strawberry.	Should not be consumed

Table 2: Diet adherence assessment scale

Four-point Likert scale for each recommendation	Three-day food record, before and after intervention			Scale
	Day 1	Day 2	Day 3	
Excellent adherence	Adhere	Adhere	Adhere	3
Good adherence		Adhere	Adhere	2
Poor adherence			Adhere	1
No adherence				0

For the bivariate analysis, the Chi square test, Kruskal-Wallis test, and One-way ANOVA were employed. To compare the mean response of final fatigue and depression scores between control and intervention groups, a generalized linear model was performed, which was adjusted for marital status, level of education, socioeconomic status, BMI, physical activity duration and intensity, the first symptom of MS, disease duration, family history of MS, comorbidity, tobacco smoking, drinking alcohol, and opium addiction. To do this, data was reshaped into a lengthy format and defined as a panel data format.

The probability distribution of the outcome variable was assumed to be Gaussian, and accordingly, GLM was done. Crude and adjusted mean differences and their 95% confidence intervals (95%CI) were estimated.

The final models were fitted using the backward elimination technique with an alpha-to-remove value of 0.10. The statistical significance was set at $P \leq 0.05$.

Results

Data from 90 participants, including 16 (17.8%) men and 74 (82.2%) women, were analyzed. The mean age of participants was 35.64 ± 9.12 , and more than half were married (54 [60%]). In group A, the baseline MED diet adherence score mean was 7 ± 3 , which increased to 11 ± 2 following intervention. In group B, the baseline TP diet adherence mean score was 3 ± 1 . After the intervention, the score was improved to 9 ± 3 . The details of the demographic characteristics of participants are presented in table 3.

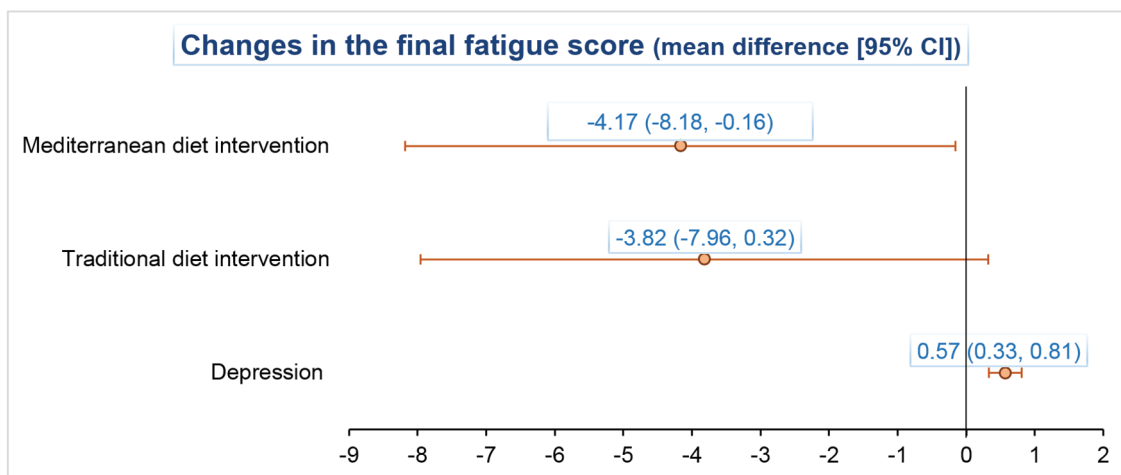


Figure 2: Associated factors of final fatigue score used the generalized linear model adjusted for marital status, educational level, socioeconomic status, BMI, physical activity, duration, and intensity, the first symptom of multiple sclerosis, disease duration, family history of multiple sclerosis, comorbidity, tobacco smoking, drinking alcohol, and opium addiction.

Table 3: The comparison of demographic characteristics of participants in the Mediterranean diet, Traditional diet, and control groups

Variables	Mediterranean diet (Group A)	Traditional Persian diet (Group B)	Control (Group C)	P value	
Age	36.63±8.88	35.37±10.76	34.90±7.76	0.70	
Sex, n (%)	Male	4 (25)	5 (31.3)	7 (43.8)	0.59
	Female	26 (35.1)	25 (33.8)	23 (31.1)	
Marital status, n (%)	Single	13 (36.1)	10 (27.8)	13 (36.1)	0.66
	Married	17 (31.5)	20 (37)	17 (31.5)	
Educational level, n (%)	Illiterate	0	0	0	0.32
	Elementary and high	15 (37.5)	15 (37.5)	10 (25)	
	Academic	15 (30)	15 (30)	20 (40)	
Socioeconomic status, n (%)	Low	18 (38.3)	14 (29.8)	15 (31.9)	0.85
	High	10 (27.8)	13 (36.1)	13 (36.1)	
	Moderate	2 (28.7)	3 (42.9)	2 (28.7)	
BMI	25.11±4.94	25.87±4.78	26.56±6.39	0.72	
Daily physical activity, n (%)	Less than 30 minute	11 (26.8)	15 (36.6)	15 (36.6)	0.68
	30 minutes	6 (31.6)	7 (36.8)	6 (31.6)	
	More than 30 minute	13 (43.3)	8 (26.7)	9 (30)	
Physical activity intensity, n (%)	Low	7 (58.3)	2 (16.7)	3 (25)	0.63
	Vigorous	11 (32.4)	12 (35.3)	11 (32.4)	
	Moderate	1 (33.3)	1 (33.3)	1 (33.3)	
The first symptom of multiple sclerosis, n (%)	Blurred vision	8 (29.6)	8 (29.6)	11 (40.7)	0.15
	Diplopia	2 (18.2)	6 (54.5)	3 (27.3)	
	Numbness	18 (48.6)	8 (21.6)	11 (29.7)	
	Weakness	2 (25)	4 (50)	2 (25)	
	Balance disorder	0	4 (57.1)	3 (42.9)	
Duration of disease	5.23±4.34	5.10±4.95	4.73±3.07	0.97	
Family history of multiple sclerosis, n (%)	Yes	9 (39.1)	7 (30.4)	7 (34.4)	0.91
	No	19 (30.6)	21 (33.9)	22 (35.5)	
Comorbidity, n (%)	Yes	12 (35.3)	6 (17.6)	16 (47.1)	0.08
	No	18 (32.1)	24 (42.9)	14 (25)	
Tobacco smoking, n (%)	Yes	2 (14.3)	6 (42.9)	6 (42.9)	0.26
	No	28 (36.8)	24 (31.6)	24 (31.6)	
Alcohol, n (%)	Yes	2 (14.3)	6 (42.9)	6 (42.9)	0.25
	No	28 (36.8)	24 (31.6)	24 (31.6)	
Opium addiction, n (%)	No	0	1 (100)	0	0.36
	Yes	30 (33.7)	29 (32.6)	30 (33.7)	
Fatigue score (baseline)	47.53±9.54	45.44±7.57	49.56±10.24	0.24	
Fatigue score (after intervention)	41.36±9.18	38.62±8.76	47.20±10.12	0.004	
Depression score (baseline)	10.46±6.71	6.07±4.23	8.96±6.71	0.06	
Depression score (after intervention)	9.26±6.45	3.86±4.04	9.56±7.57	0.005	

Data are presented as n (%) and mean±SD. P values were obtained from Chi Square, Kruskal-Wallis Test, and One-way ANOVA tests. P≤0.05 was considered statistically significant. BMI: Body mass index

Table 4 revealed that after the intervention, the mean fatigue score was significantly different in the control group (47.20±10.12), MED diet (41.36±9.18), and TP diet (38.62±8.76) intervention groups. There were also statistically significant differences between the mean depression score in the control group (9.56±7.57), MED diet (9.26±6.45), and TP diet (3.86±4.04) intervention groups.

Association between Diet Interventions and Fatigue and Depression Score

After adjustment, it was observed that the MED diet intervention, compared to the control

group as the reference group in the multivariable analysis, was associated with lower fatigue severity (-4.17 [-8.18, -0.16]) (table 5 and figure 2). However, there was no association between fatigue severity and TP diet intervention (-3.82 [-7.96, 0.32]). There was an association between fatigue severity and depression score in multivariable analysis (table 5).

Table 6 and figure 3 show a statistically significant association between lower depression scores and TP diet intervention (-2.89 [-5.59, -0.19]; P=0.03). However, after adjustment, there was no association between depression scores and MED diet intervention (1.50 [-1.12, 4.13]).

Table 4: The comparison fatigue and depression of participants in the Mediterranean diet, Traditional diet, and control groups

Variables	Mediterranean diet (Group A)	Traditional Persian diet (Group B)	Control (Group C)	P value
Fatigue score (baseline)	47.53±9.54	45.44±7.57	49.56±10.24	0.24
Fatigue score (after intervention)	41.36±9.18	38.62±8.76	47.20±10.12	0.004
Depression score (baseline)	10.46±6.71	6.07±4.23	8.96±6.71	0.06
Depression score (after intervention)	9.26±6.45	3.86±4.04	9.56±7.57	0.005

Data are presented as n (%) and mean±SD. P values were obtained from Chi square, Kruskal-Wallis Test, and One-way ANOVA tests. P≤0.05 was considered statistically significant.

Table 5: Associated factors of final fatigue score using a generalized linear model

Variables	Crude mean difference (95% CI)	P value ^a	Adjusted mean difference (95% CI)	P value ^b	
Age	0.05 (-0.15, 0.25)	0.63	0.14 (-0.05, 0.32)	0.14	
Sex	Male	Ref	Ref	0.12	
	Female	-4.96 (-9.75, -0.18)	0.04	-3.49 (-7.91, 0.92)	
Marital status	Married	Ref	-	-	
	Single	0.11 (-3.7, 3.93)	0.95	-	
Educational level	Elementary and high	Ref	-	-	
	Academic	3.49 (-.21, 7.18)			
Socioeconomic status	Low	Ref	-	-	
	Moderate	-0.82 (-4.74, 3.11)	0.68		
	High	0.61 (-6.57, 7.79)	0.86		
BMI	0.12 (-0.23, 0.47)	0.50	-	-	
Dietary intervention	Control	Ref	Ref	-	
	Mediterranean diet	-3.93 (-8.33, 0.46)	0.08	-4.17 (-8.18, -0.16)	0.04
	Traditional diet	-6.1 (-10.5, -1.69)	0.007	-3.82 (-7.96, 0.32)	0.07
Daily physical activity	Less than 30 minutes	Ref	-	-	
	30 minutes	-3.27 (-8.15, 1.6)	0.18		
	More than 30 minutes	-1.79 (-6.01, 2.42)	0.40		
Physical activity intensity	Low	Ref	-	-	
	Moderate	-3.68 (-7.73, 0.35)	0.07		
	Vigorous	-4.72 (-13.88, 4.43)	0.31		
The first symptom of multiple sclerosis	Blurred vision	Ref	-	-	
	Diplopia	0.11 (-4.33, 4.55)	0.96		
	Numbness	0.95 (-6.11, 8.02)	0.79		
	Weakness	-1.26 (-8.71, 6.17)	0.73		
	Balance disorder	-3.89 (-10.16, 2.38)	0.22		
Duration of disease	0.33 (-0.13, 0.77)	0.15	-	-	
Family history of multiple sclerosis	Yes	Ref	-	-	
	No	1.81 (-2.31, 5.93)	0.38		
Depression score	0.55 (0.31, 0.77)	≤0.001	0.57 (0.33, 0.81)	≤0.001	
Comorbidity	Yes	Ref	-	-	
	No	0.15 (-1.03, 1.35)	0.79		
Tobacco smoking	Yes	Ref	-	-	
	No	-3.12 (-8.24, 1.99)	0.23		
Alcohol	Yes	-	-	-	
	No	-0.33 (-5.49, 4.82)	0.89		
Opium addiction	Yes	Ref	-	-	
	No	-0.46 (-18.32, 17.39)	0.95		

Data are presented as crude and adjusted mean differences and 95% confidence intervals (95%CI). ^aP values are obtained from the generalized linear model. ^bP values are obtained from the generalized linear model, adjusted for marital status, educational level, socioeconomic status, BMI, physical activity duration and intensity, the first symptom of multiple sclerosis, disease duration, family history of multiple sclerosis, comorbidity, tobacco smoking, drinking alcohol, and opium addiction. P≤0.05 was considered statistically significant. BMI: Body mass index

In multivariable analysis, there was an association between depression score and age, high socioeconomic status, and duration of disease (table 6).

Other Associated Factors of Fatigue and Depression Score

As shown in table 3 and figure 2, there was a statistically significant relationship between fatigue

Table 6: Associated factors of final depression score using a generalized linear model

Variables		Crude mean difference (95% CI)	P value ^a	Adjusted mean difference (95% CI)	P value ^b
Age		-0.11 (-0.25, 0.02)	0.11	-0.21 (-0.33, -0.08)	0.002
Sex	Male	Ref	-	-	-
	Female	-0.51 (-3.83, 2.81)	0.76	-	-
Marital status	Single	Ref	-	-	-
	Married	-1.45 (-4.03, 1.12)	0.27	-	-
Educational level	Elementary and high	Ref	-	-	-
	Academic	0.08 (-2.48, 2.63)	0.95	-	-
Socioeconomic status	Low	Ref	-	Ref	-
	Moderate	-0.78 (-3.38, 1.81)	0.55	-0.87 (-3.14, 1.39)	0.44
	High	-5.32 (-10.1, -0.55)	0.02	-5.84 (-9.98, -1.71)	0.006
BMI		0.11 (-0.13, 0.35)	0.35	0.17 (-0.03, 0.38)	0.13
Dietary intervention	Control	Ref	-	Ref	-
	Mediterranean diet	0.6 (-2.31, 3.51)	0.68	1.50 (-1.12, 4.13)	0.22
	Traditional diet	-4.35 (-7.25, -1.44)	0.003	-2.89 (-5.59, -0.19)	0.03
Daily physical activity	Less than 30 minutes	Ref	-	-	-
	30 minutes	-0.07 (-3.40, 3.26)	0.96	-	-
	More than 30 minutes	-1.22 (-4.11, 1.66)	0.41	-	-
Physical activity intensity	Low	Ref	-	-	-
	Moderate	-1.77 (-4.51, 0.96)	0.20	-	-
	Vigorous	0.94 (-5.25, 7.14)	0.76	-	-
The first symptom of multiple sclerosis	Blurred vision	Ref	-	-	-
	Diplopia	-1.19 (-4.18, 1.79)	0.43	-	-
	Numbness	0.66 (-4.08, 5.42)	0.78	-	-
	Weakness	-4.30 (-9.31, -0.71)	0.09	-	-
	Balance disorder	-1.92 (-6.15, 2.29)	0.37	-	-
Duration of disease		0.12 (-0.18, 0.43)	0.43	0.27 (-0.02, 0.55)	0.05
Family history of multiple sclerosis	Yes	Ref	-	-	-
	No	0.48 (-0.32, 1.29)	0.23	-	-
Fatigue score		0.17 (0.09, 0.25)	≤0.001	0.16 (0.08, 0.23)	≤0.001
Comorbidity	Yes	Ref	-	-	-
	No	-0.85 (-3.74, 2.03)	0.56	-	-
Tobacco smoking	Yes	Ref	-	-	-
	No	0.06 (-3.44, 3.56)	0.97	-	-
Alcohol	Yes	Ref	-	-	-
	No	-0.74 (-4.24, 2.76)	0.67	-	-
Opium addiction	Yes	Ref	-	-	-
	No	2.54 (-9.57, 14.66)	0.68	-	-

Data are presented as crude and adjusted mean differences and 95% confidence intervals (95%CI). ^aP values are obtained from the generalized linear model. ^bP values are obtained from the generalized linear model, adjusted for sex, marital status, educational level, physical activity duration, and intensity, the first symptom of multiple sclerosis, family history of multiple sclerosis, comorbidity, tobacco smoking, drinking alcohol and opium addiction. P≤0.05 was considered statistically significant. BMI: Body mass index

severity and depression score (0.57 [0.33, 0.81]).

According to table 4 and figure 3, there was a statistically significant correlation between lower depression scores and older age (-0.21 [-0.33, -0.08]) and higher socioeconomic status (-5.84 [-9.98, -1.71]). It was also found that longer duration of disease (0.27 [-0.02, 0.55]) and higher fatigue severity (0.16 [0.08, 0.23]) were associated with higher depression scores.

Discussion

The current study found a negative relationship between fatigue severity and MED diet

intervention. Moreover, a statistically significant relationship was found between lower depression scores and traditional diet intervention.

The body of research on the relationship between diet intervention and MS progression and improvement symptoms such as fatigue score is conflicting.^{13, 14} While a meta-analysis found that a MED diet reduced the risk of noncommunicable diseases, such as cardiovascular disease, diabetes, and neurodegenerative diseases, another meta-analysis reported a lack of strong, consistent evidence for dietary interventions in individuals with MS disease progression and symptoms.^{13, 14}

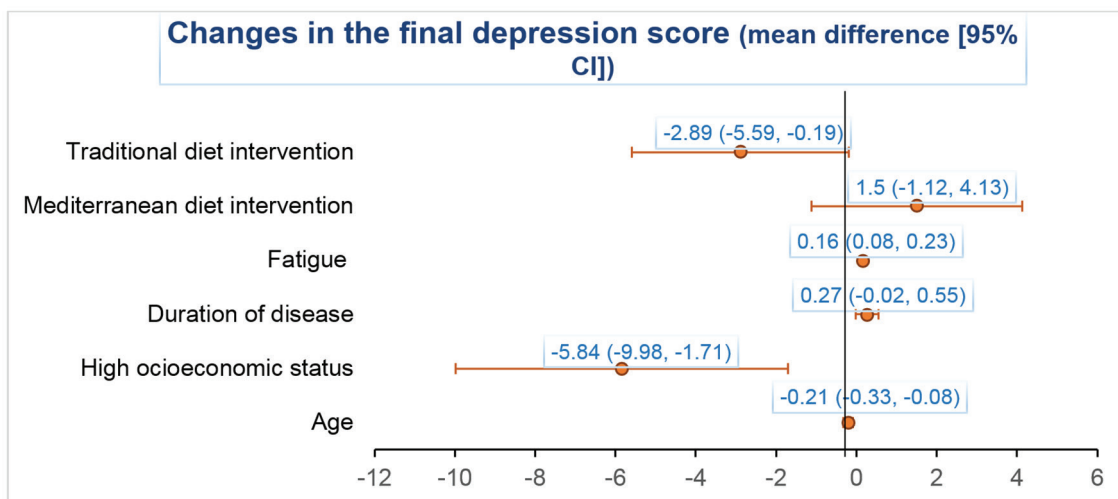


Figure 3: Associated factors of final depression score used generalized linear model adjusted for sex, marital status, educational level, physical activity duration, and intensity, the first symptom of multiple sclerosis, family history of multiple sclerosis, comorbidity, tobacco smoking, drinking alcohol, and opium addiction.

The participants with progressive MS were more likely to experience fatigue. More physical, cognitive, and psychological impairment was associated with higher levels of fatigue severity and impact.²⁷ People with MS frequently experience a lower quality of life due to fatigue, regardless of depression or disability. Fatigue is a significant socioeconomic consequence for patients with MS, with up to 75% reporting it, which can lead to lost work hours.³⁻⁵ Despite the continuous expansion of research efforts to identify the pathophysiological causes of fatigue in MS, the exact underlying cause remains unknown.³⁻⁵ Converging lines of evidence provide support to the theory of structural disconnection and dysfunctional thalamo-striato-cortical circuits as potential substrates.^{3,4} In the present study, MED diet intervention was associated with lower fatigue severity. However, there was no association between fatigue severity and TP diet intervention. These findings were similar to those reported by Yasemin Ertaş and others, who found that a MED diet could reduce fatigue severity. Thus, patients should be encouraged to increase their adherence to the MED diet.²⁸ The study by Moravejolahkami and others and Bohlouli and others found that adherence to MD for 6 months resulted in a reduction in fatigue score.^{10, 20} Certain MED diet components, such as consuming less red meat, saturated fats, sweets, and more fish, might show promise in reducing the severity of MS symptoms or fatigue.²⁸ After controlling for other variables, the present study found that there was no association between the fatigue severity score and the TP diet intervention after adjustment. Bohlouli and others reported similar results, indicating that the TP diet had

no positive impact effects on fatigue score.²⁰ This could be a productive area for additional work. Since the pathophysiological causes of fatigue in people with MS are unknown, a more comprehensive study of the relationship between diet intervention and MS progression and symptom improvement is recommended.

Researchers and clinicians are focusing more on diet intervention as a complementary medicine for reducing depression, which is significant due to the relationship between diet and mental health. Previous research found that a diet rich in fruits, vegetables, whole grains, fish, olive oil, low-fat dairy, and antioxidants, as well as low in animal foods was associated with a lower risk of depression.²⁹ Furthermore, high consumption of red and/or processed meat, refined grains, sugar, high-fat dairy products, butter, potatoes, and high-fat gravy, combined with low consumption of fruits and vegetables was associated with an increased risk of depression.²⁹ The present study found that there was no association between depression scores and MED diet intervention after adjustment, while there was a statistically significant relationship between lower depression scores and traditional diet intervention. According to a study conducted by Felice, a traditional diet consisting of vegetables, fruit, meat, fish, and whole grains was associated with a lower risk of major depression.³⁰ The explanation for the relationship between TP diet and depression severity score is difficult due to a lack of research in this area.³¹ A possible explanation is that a hot-natured food is high in carbohydrates and vitamin B6.¹⁷ According to a meta-analysis study, a high selenium diet could improve depression scores, and a higher vitamin B6 intake was associated with lower depression.³² Furthermore, previous

research indicated that hot-natured food could improve clinical scores of MS and depression by increasing cytokines such as interleukin 4.^{18, 33} These findings are somewhat astonishing, given that previous studies showed that foods high in vitamin B12 and folate can help with depression.^{34, 35} However, Xie conducted a study and found that cold-natured foods are high in vitamin B12 and folate.¹⁶ Thus, these findings should be interpreted with caution. Furthermore, a lack of association between depression scores and MED diet intervention was an unexpected finding. Previous research found an inverse significant association between adherence to the MED diet and depression in cross-sectional and intervention studies; while, no significant association was found in cohort studies.^{36, 37} This discrepancy could be attributed to the small sample size of the trials and the short intervention duration.

The present study found a statistically significant relationship between increasing fatigue severity and higher depression scores. This finding was consistent with that of a previous study which reported that fatigue and depression were highly correlated in people with MS.³⁸ Furthermore, Lee's study found that depression and fatigue were associated with increased immune system activation, which might be an important target for treatment.³⁹

To the best of our knowledge, this is the first clinical trial that aimed to determine the impact of a TP diet (hot and cold pattern of food) on fatigue and the severity of depression in patients with MS. As a result, this topic could direct researchers' attention toward specific research areas. Additionally, the findings of this study can help healthcare providers and specialists to guide the questions of MS patients regarding the relationship between TD and MD diet in relieving the symptoms of fatigue and depression. Although this study provided some preliminary insight into the potential role of TP dietary interventions in the management of depression and fatigue in patients with MS, it had several limitations. The energy and macro/micronutrient intakes, phase of MS, use of medications, and nature of the entire diet were some of the limitations of the present study. The primary focus of this study was on people with MS. Thus, more research is required to determine the long-term safety and the safety of TP diet intervention among patients with other autoimmune diseases.

Conclusion

The findings of the present study indicated that

adhering to the MED diet for 2 months could reduce fatigue scores in people with MS while having no effect on the depression score. In contrast, adhering to the TP diet recommendation could reduce depression scores without affecting fatigue scores in patients with MS. Since the underlying causes of fatigue and depression in MS patients are unknown, a more thorough investigation of the relationship between dietary intervention and MS progression and symptom improvement is recommended.

Acknowledgment

The authors would like to thank Shiraz University of Medical Sciences, Shiraz, Iran, and also the Center for Development of Clinical Research of Nemazee Hospital and Dr. Amir Yousef Farahmandi for editorial assistance.

Authors' Contribution

MH.Sh: Study concept, study design, data gathering, and drafting; M.P: Study concept, drafting, and reviewing; M.A: Data gathering and drafting; Z.A: Data gathering, and drafting; M.V: Data gathering, and drafting; M.S: Data gathering, and drafting; H.MV: Study design, data interpretation, and drafting; AM.J: Data gathering, and drafting; M.N: Data gathering and drafting; All authors read and approved the final manuscript and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work were appropriately investigated and resolved.

Conflict of Interest: None declared.

References

- 1 McGinley MP, Goldschmidt CH, Rae-Grant AD. Diagnosis and Treatment of Multiple Sclerosis: A Review. *JAMA*. 2021;325:765-79. doi: 10.1001/jama.2020.26858. PubMed PMID: 33620411.
- 2 Razeghi-Jahromi S, Doosti R, Ghorbani Z, Saeedi R, Abolhasani M, Akbari N, et al. A randomized controlled trial investigating the effects of a mediterranean-like diet in patients with multiple sclerosis-associated cognitive impairments and fatigue. *Curr J Neurol*. 2020;19:112-21. doi: 10.18502/cjn.v19i3.5424. PubMed PMID: 38011378; PubMed Central PMCID: PMC8185587.
- 3 Marchesi O, Vizzino C, Filippi M, Rocca MA. Current perspectives on the diagnosis and management of fatigue in multiple sclerosis.

- Expert Rev Neurother. 2022;22:681-93. doi: 10.1080/14737175.2022.2106854. PubMed PMID: 35881416.
- 4 Manjaly ZM, Harrison NA, Critchley HD, Do CT, Stefanics G, Wenderoth N, et al. Pathophysiological and cognitive mechanisms of fatigue in multiple sclerosis. *J Neurol Neurosurg Psychiatry*. 2019;90:642-51. doi: 10.1136/jnnp-2018-320050. PubMed PMID: 30683707; PubMed Central PMCID: PMC6581095.
 - 5 Capone F, Collorone S, Cortese R, Di Lazzaro V, Moccia M. Fatigue in multiple sclerosis: The role of thalamus. *Mult Scler*. 2020;26:6-16. doi: 10.1177/1352458519851247. PubMed PMID: 31138052.
 - 6 Stoiloudis P, Kesidou E, Bakirtzis C, Sintila SA, Konstantinidou N, Boziki M, et al. The Role of Diet and Interventions on Multiple Sclerosis: A Review. *Nutrients*. 2022;14. doi: 10.3390/nu14061150. PubMed PMID: 35334810; PubMed Central PMCID: PMC65895724.
 - 7 Rinaldo N, Pasini A, Straudi S, Piva G, Crepaldi A, Baroni A, et al. Effects of Exercise, Rehabilitation, and Nutritional Approaches on Body Composition and Bone Density in People with Multiple Sclerosis: A Systematic Review and Meta-Analysis. *J Funct Morphol Kinesiol*. 2023;8. doi: 10.3390/jfmk8030132. PubMed PMID: 37754965; PubMed Central PMCID: PMC65810532597.
 - 8 Keykhaei F, Norouzy S, Froughipour M, Nematy M, Saeidi M, Jarahi L, et al. Adherence to healthy dietary pattern is associated with lower risk of multiple sclerosis. *J Cent Nerv Syst Dis*. 2022;14:11795735221092516. doi: 10.1177/11795735221092516. PubMed PMID: 35558004; PubMed Central PMCID: PMC6589087291.
 - 9 Marck CH, Probst Y, Chen J, Taylor B, van der Mei I. Dietary patterns and associations with health outcomes in Australian people with multiple sclerosis. *Eur J Clin Nutr*. 2021;75:1506-14. doi: 10.1038/s41430-021-00864-y. PubMed PMID: 33531638.
 - 10 Moravejolahkami AR, Paknahad Z, Chitsaz A, Hojjati Kermani MA, Borzoo-Isfahani M. Potential of modified Mediterranean diet to improve quality of life and fatigue severity in multiple sclerosis patients: a single-center randomized controlled trial. *International Journal of Food Properties*. 2020;23:1993-2004. doi: 10.1080/10942912.2020.1840390.
 - 11 Alfredsson L, Olsson T, Hedstrom AK. Inverse association between Mediterranean diet and risk of multiple sclerosis. *Mult Scler*. 2023;29:1118-25. doi: 10.1177/13524585231181841. PubMed PMID: 37366345.
 - 12 Solsona EM, Tektonidis T, Reece JC, Simpson-Yap S, Black LJ, Rad EY, et al. Associations between diet and disease progression and symptomatology in multiple sclerosis: A systematic review of observational studies. *Mult Scler Relat Disord*. 2024;87:105636. doi: 10.1016/j.msard.2024.105636. PubMed PMID: 38678968.
 - 13 Dinu M, Pagliai G, Casini A, Sofi F. Mediterranean diet and multiple health outcomes: an umbrella review of meta-analyses of observational studies and randomised trials. *Eur J Clin Nutr*. 2018;72:30-43. doi: 10.1038/ejcn.2017.58. PubMed PMID: 28488692.
 - 14 Tredinnick AR, Probst YC. Evaluating the Effects of Dietary Interventions on Disease Progression and Symptoms of Adults with Multiple Sclerosis: An Umbrella Review. *Adv Nutr*. 2020;11:1603-15. doi: 10.1093/advances/nmaa063. PubMed PMID: 32504530; PubMed Central PMCID: PMC6587666914.
 - 15 Sharifi MH, Keshani P, Salehi A, Jaladat AM, Mirzaei Z, Nikseresht A. Association between multiple sclerosis and dietary patterns based on the traditional concept of food nature: a case-control study in Iran. *BMC Neurol*. 2021;21:453. doi: 10.1186/s12883-021-02483-3. PubMed PMID: 34794406; PubMed Central PMCID: PMC6588600729.
 - 16 Xie A, Huang H, Kong F. Relationship between food composition and its cold/hot properties: A statistical study. *Journal of Agriculture and Food Research*. 2020;2:100043. doi: 10.1016/j.jafr.2020.100043.
 - 17 Liu C, Sun Y, Li Y, Yang W, Zhang M, Xiong C, et al. The relationship between cold-hot nature and nutrient contents of foods. *Nutrition & Dietetics*. 2012;69:64-8. doi: 10.1111/j.1747-0080.2011.01565.x.
 - 18 Rezapour-Firouzi S, Arefhosseini SR, Mehdi F, Mehrangiz EM, Baradaran B, Sadeghihokmabad E, et al. Immunomodulatory and therapeutic effects of Hot-nature diet and co-supplemented hemp seed, evening primrose oils intervention in multiple sclerosis patients. *Complement Ther Med*. 2013;21:473-80. doi: 10.1016/j.ctim.2013.06.006. PubMed PMID: 24050582.
 - 19 Opie RS, O'Neil A, Itsiopoulos C, Jacka FN. The impact of whole-of-diet interventions on depression and anxiety: a systematic review of randomised controlled trials. *Public Health Nutr*. 2015;18:2074-93. doi: 10.1017/S1368980014002614. PubMed

- PMID: 25465596; PubMed Central PMCID: PMCPMC10271872.
- 20 Bohlouli J, Namjoo I, Borzoo-Isfahani M, Poorbaferani F, Moravejolahkami AR, Clark CCT, et al. Modified Mediterranean diet v. traditional Iranian diet: efficacy of dietary interventions on dietary inflammatory index score, fatigue severity and disability in multiple sclerosis patients. *Br J Nutr.* 2022;128:1274-84. doi: 10.1017/S000711452100307X. PubMed PMID: 34392854.
 - 21 Azimian M, Farahani AS, Dadkhah A, Fallahpour M, Karimlu M. Fatigue severity scale: the psychometric properties of the persian-version in patients with multiple sclerosis. *Res J Biol Sci.* 2009;4:974-7.
 - 22 Dadfar M, Kalibatseva Z. Psychometric Properties of the Persian Version of the Short Beck Depression Inventory with Iranian Psychiatric Outpatients. *Scientifica (Cairo).* 2016;2016:8196463. doi: 10.1155/2016/8196463. PubMed PMID: 27293979; PubMed Central PMCID: PMCPMC4886104.
 - 23 Mahdavi-Roshan M, Salari A, Soltanipour S. Reliability and Validity of the 14-point mediterranean diet adherence screener among the Iranian high risk population. *Mediterranean Journal of Nutrition and Metabolism.* 2018;11:323-9. doi: 10.3233/MNM-18205.
 - 24 Sikaroudi MK, Aghdam AK, Ebrahimi Z, Ramim T, Talebi A, Tabaeian SP, et al. Reliability and validity of the 14-item Mediterranean diet adherence screener among the healthy Iranian population. *Govaresh.* 2022;27:39-44.
 - 25 Smith MS, Teufel-Shone N. Editorial: Indigenous knowledge and chronic disease prevention among the first people of North America. *Front Public Health.* 2023;11:1150221. doi: 10.3389/fpubh.2023.1150221. PubMed PMID: 37293612; PubMed Central PMCID: PMCPMC10246768.
 - 26 Soria-Contreras DC, Chan CB. Monitoring adherence to the Canadian diabetes association nutrition therapy guidelines using the perceived dietary adherence questionnaire and a 3-day food record. *Canadian Journal of Diabetes.* 2012;36:S66. doi: 10.1016/j.jcjd.2012.07.432.
 - 27 Rooney S, Wood L, Moffat F, Paul L. Prevalence of fatigue and its association with clinical features in progressive and non-progressive forms of Multiple Sclerosis. *Mult Scler Relat Disord.* 2019;28:276-82. doi: 10.1016/j.msard.2019.01.011. PubMed PMID: 30639830.
 - 28 Ertas Ozturk Y, Helvacı EM, Sokulmez Kaya P, Terzi M. Is Mediterranean diet associated with multiple sclerosis related symptoms and fatigue severity? *Nutr Neurosci.* 2023;26:228-34. doi: 10.1080/1028415X.2022.2034241. PubMed PMID: 35143375.
 - 29 Li Y, Lv MR, Wei YJ, Sun L, Zhang JX, Zhang HG, et al. Dietary patterns and depression risk: A meta-analysis. *Psychiatry Res.* 2017;253:373-82. doi: 10.1016/j.psychres.2017.04.020. PubMed PMID: 28431261.
 - 30 Jacka FN, Pasco JA, Mykletun A, Williams LJ, Hodge AM, O'Reilly SL, et al. Association of Western and traditional diets with depression and anxiety in women. *Am J Psychiatry.* 2010;167:305-11. doi: 10.1176/appi.ajp.2009.09060881. PubMed PMID: 20048020.
 - 31 Nouri Saeidlou S, Kiani A, Ayremlou P. Association between Dietary Patterns and Major Depression in Adult Females: A Case-Control Study. *J Res Health Sci.* 2021;21:e00506. doi: 10.34172/jrhs.2021.37. PubMed PMID: 34024764; PubMed Central PMCID: PMCPMC8957692.
 - 32 Sajjadi SS, Foshati S, Haddadian-Khouzani S, Rouhani MH. The role of selenium in depression: a systematic review and meta-analysis of human observational and interventional studies. *Sci Rep.* 2022;12:1045. doi: 10.1038/s41598-022-05078-1. PubMed PMID: 35058530; PubMed Central PMCID: PMCPMC8776795.
 - 33 Wachholz S, Knorr A, Mengert L, Plumper J, Sommer R, Juckel G, et al. Interleukin-4 is a participant in the regulation of depressive-like behavior. *Behav Brain Res.* 2017;326:165-72. doi: 10.1016/j.bbr.2017.03.020. PubMed PMID: 28315756.
 - 34 Sangle P, Sandhu O, Aftab Z, Anthony AT, Khan S. Vitamin B12 Supplementation: Preventing Onset and Improving Prognosis of Depression. *Cureus.* 2020;12:e11169. doi: 10.7759/cureus.11169. PubMed PMID: 33251075; PubMed Central PMCID: PMCPMC7688056.
 - 35 Bender A, Hagan KE, Kingston N. The association of folate and depression: A meta-analysis. *J Psychiatr Res.* 2017;95:9-18. doi: 10.1016/j.jpsychires.2017.07.019. PubMed PMID: 28759846.
 - 36 Shafiei F, Salari-Moghaddam A, Larijani B, Esmailzadeh A. Adherence to the Mediterranean diet and risk of depression: a systematic review and updated meta-analysis of observational studies. *Nutr Rev.* 2019;77:230-9.

- doi: 10.1093/nutrit/nuy070. PubMed PMID: 30726966.
- 37 Altun A, Brown H, Szoek C, Goodwill AM. The Mediterranean dietary pattern and depression risk: A systematic review. *Neurology, Psychiatry and Brain Research*. 2019;33:1-10. doi: 10.1016/j.npbr.2019.05.007.
- 38 Schmidt S, Jostingmeyer P. Depression, fatigue and disability are independently associated with quality of life in patients with multiple Sclerosis: Results of a cross-sectional study. *Mult Scler Relat Disord*. 2019;35:262-9. doi: 10.1016/j.msard.2019.07.029. PubMed PMID: 31437741.
- 39 Lee CH, Giuliani F. The Role of Inflammation in Depression and Fatigue. *Front Immunol*. 2019;10:1696. doi: 10.3389/fimmu.2019.01696. PubMed PMID: 31379879; PubMed Central PMCID: PMC6658985.