MIND Diet Adherence Might be Associated with a Reduced Odds of Multiple Sclerosis: Results from a Case–Control Study

Morvarid Noormohammadi · Zeinab Ghorbani · Abdorreza Naser Moghadasi ·

Zahra Saeedirad · Sahar Shahemi · Milad Ghanaatgar ·

Nasim Rezaeimanesh · Azita Hekmatdoost · Amir Ghaemi ·

Soodeh Razeghi Jahromi

ABSTRACT

Introduction: The Mediterranean Dietary Approaches to the Stop Hypertension (DASH) Intervention for Neurodegenerative Delay (MIND) diet has been shown to have beneficial neuroprotective effects. The purpose of this research was to evaluate the link between the MIND diet adherence and multiple sclerosis (MS), a degenerative neurological illness.
Methods: In a hospital-based case–control setting, 77 patients with relapsing–remitting multiple sclerosis (RRMS) and 148 healthy individuals were recruited. A validated 168-item semi-quantitative food frequency questionnaire was used to assess participants' dietary intakes and the MIND diet score. A logistic regression model was used to evaluate the association between MIND diet adherence and MS.
Results: There was significant difference between RRMS and control groups in the med-

M. Noormohammadi
Student Research Committee, Department of Nutrition, School of Public Health, Iran University of Medical Sciences, Tehran, Iran

Z. Ghorbani
Cardiovascular Diseases Research Center, Department of Cardiology, Heshmat Hospital, School of Medicine,, Guilan University of Medical Sciences, Rasht, Iran

Z. Ghorbani
Department of Clinical Nutrition, School of Medicine, Guilan University of Medical Sciences, Rasht, Iran

A. Naser Moghadasi · N. Rezaeimanesh ·
S. Razeghi Jahromi (✉)
Multiple Sclerosis Research Center, Neuroscience Institute, Tehran University of Medical Sciences, Tehran, Iran
e-mail: razeghi@sina.tums.ac.ir;
soodehrazeghi@gmail.com

Z. Saeedirad · S. Shahemi · M. Ghanaatgar ·
N. Rezaeimanesh · A. Hekmatdoost ·
S. Razeghi Jahromi
Department of Clinical Nutrition and Dietetics, Faculty of Nutrition and Food Technology, Shahid Beheshti University of Medical Sciences, Tehran, Iran

S. Shahemi
Nutrition and Endocrine Research Center, Research Institute for Endocrine Sciences, Shahid Beheshti University of Medical Sciences, Tehran, Iran

A. Ghaemi
Department of Virology, Pasteur Institute of Iran, Tehran, Iran

ian (Q1-Q3) of age (years, P value < 0.001), body mass index (BMI) (kg/m^2, P value < 0.001), and total intake of calories (kcal, P value $= 0.032$), carbohydrates (g, P value $= 0.003$), animal-based protein (g, P value $= 0.009$), and fiber (g, P value $= 0.001$). Adherence to the MIND diet was associated with a reduced odds of MS [adjusted odds ratio (aOR) $= 0.10$, 95 percent confidence interval (95% CI) $= 0.01$–0.88, P for trend $= 0.001$]. MS odds was significantly lower in the last tertile of green leafy vegetables (aOR $= 0.02$, 95% CI $= 0.00$–0.21, P value < 0.001), other vegetables (aOR $= 0.17$, 95% CI $= 0.04$–0.73, P value $= 0.001$), butter and stick margarine (aOR $= 0.20$, 95% CI $= 0.06$–0.65, P value $= 0.008$), and beans (aOR $= 0.05$, 95% CI $= 0.01$–0.28, P value < 0.001) consumption. While it was significantly higher in the last tertile of cheese (aOR $= 4.45$, 95% CI $= 1.70$–11.6, P value $= 0.003$), poultry (aOR $= 3.95$, 95% CI $= 1.01$–15.5, P value $= 0.039$), pastries and sweets (aOR $= 13.9$, 95% CI $= 3.04$–64.18, P value < 0.001), and fried/fast foods (aOR $= 32.8$, 95% CI $= 5.39$–199.3, P value < 0.001).

Conclusion: The MIND diet and its components, including green leafy vegetables, other vegetables, and beans, seem to decrease the odds of MS; besides butter and stick margarine, the MIND diet's unhealthy components seem to have the same protective effects, while pastries and sweets, cheese, poultry, and fried/fast foods have an inverse effect.

Keywords: Case–control study; Diet; MIND diet; Multiple sclerosis

Key Summary Points

Why carry out this study?

An estimated 50–300 people per 100,000 are diagnosed with multiple sclerosis (MS), an autoimmune degenerative and inflammatory neurological condition without any known cure.

Studies have shown a link between specific dietary patterns like the Mediterranean diet and reduced risk of multiple sclerosis.

The newly introduced Mediterranean Dietary Approaches to the Stop Hypertension (DASH) Intervention for Neurodegenerative Delay (MIND) diet is a combination of Mediterranean and DASH dietary patterns. This study aimed to investigate the association between the MIND diet and MS.

What was learned from the study?

The odds of MS are negatively associated with the MIND diet score and its components, including green leafy vegetables, other vegetables, and beans.

It was learned from the study that encouraging individuals to follow a dietary pattern high in plant-based foods and low in animal-based/high in saturated fat foods, like the MIND diet, may be helpful in preventing multiple sclerosis.

INTRODUCTION

Multiple sclerosis (MS) is an autoimmune, degenerative, inflammatory neurological disorder of the central nervous system, resulting in myelin and axon destruction [1, 2]. MS is expected to affect about 2.3 million individuals globally, with a prevalence of 50–300 per 100,000 individuals [2]. Among the Middle East countries, the prevalence of MS in the Iranian population is high [3]. A recent meta-analysis in

Iran reported the pooled prevalence of MS to be 100 in 100,000 [4]. MS patients usually appear between the ages of 20 to 40 years, with women outnumbering males at a 2:1 ratio [5]. MS is categorized into four subtypes: relapsing–remitting (RRMS), primary-progressive, secondary-progressive, and clinically isolated syndrome. Only some patients with the clinically isolated syndrome will develop into MS [6]. In most patients, MS initiates with a relapsing–remitting phase, and, subsequently, a secondary progressive phase starts between 5 and 35 years after that [5, 7]. The cause is not yet apparent, but genetic, environmental, and behavioral aspects are thought to be associated. Albeit MS does not have a definite treatment, certain disease-adaptive medications and dietary and lifestyle adjustments have been shown to be effective [8].

The Mediterranean diet is among the four dominant dietary patterns reported in a sample of the Iranian population [9]. The Mediterranean diet is a well-studied dietary pattern that has been linked to a decreased MS risk and improved MS course and disability in previous studies [10–14]. The Dietary Approaches to Stop Hypertension (DASH) is a less well-studied dietary strategy concerning MS [15]. Considering that particular dietary ingredients promoting brain function have not been incorporated in DASH and Mediterranean diets, Morris et al. have recently proposed a combination of these two dietary patterns specifically demonstrating neuroprotective effects [16]. This new nutritional pattern called the Mediterranean–DASH Intervention for Neurodegenerative Delay (MIND) diet encourages natural plant-based meals and limits animal-based/high in saturated fat foods. It especially emphasizes berries and green leafy vegetables [16], rich in anti-inflammatory, anti-oxidant, and neuroprotective components [17]. Better adherence to the MIND diet has been linked to a decreased risk of cognitive deterioration [18]. However, to our knowledge, the association between the MIND diet and MS is not yet apparent. Hence, this study hypothesized that MIND diet adherence is associated with a reduced odds of MS.

METHODS

Ethical Considerations

The research protocol of the present study was confirmed by the Institutional Review Board of National Institute for Medical Research Development (NIMAD) (Research number = 962667). Also, the research ethics committee of NIMAD and the research ethics boards of the Sina MS research center, Tehran University of Medical Sciences, authorized the study (Ethics code: IR.NIMAD.REC.1396.320). The Helsinki Declaration of 1964 and its subsequent revisions were followed in the conduct of the research. All individuals have given written permission to participate in the study.

Study Participants

This research was a hospital-based case–control study conducted in Tehran, Iran, between January 2018 and January 2021. A sample of 80 newly-diagnosed participants with RRMS was chosen from the patients referred to a referral University hospital MS clinic using the convenience-sampling approach. RRMS was diagnosed by a neurologist and MS specialist according to physical examination, patient history, and magnetic resonance imaging (MRI) using revised McDonald's diagnostic criteria [19]. On overage, the patients were included in the current study with 1 week to maximum 1 month after definite diagnosis of MS. The most common drugs received by MS patients were Rituximab, followed by Glatiramer acetate, Interferon beta-1a, Interferon beta-1b, Dimethyl fumarate, while Fingolimod, Teriflunomide, Natalizumab, Ocrelizumab, and Azathioprine were also reported in smaller percentages. Furthermore, a set of 150 hospital-based healthy controls was selected from those referred to the emergency department. Patients with confirmed RRMS diagnosis in the past 12 months, age 18–50 years, and expanded disability status less than 5 were included. Exclusion criteria included adhering to a particular diet in the preceding year and taking dietary supplements, pregnancy and lactation, other

types of MS, having had corticosteroid injection (pulse therapy) or RRMS relapse throughout the past month prior to participating in the research, having neurological diseases other than RRMS, and suffering from chronic illness or metabolic disorders that affected their dietary intake (e.g., diabetes and chronic kidney disease). Participants were eliminated from the research if they left more than 70 items blank on the food frequency questionnaire (FFQ). The research protocol of the present study was confirmed by the Institutional Review Board of NIMAD (Research number = 962667). Also, the research ethics committee of NIMAD authorized the study (Ethics code: IR.NIMAD.REC.1396.320). Additionally, all subjects provided written informed permission.

Demographic and Anthropometric Data

A certified nutritionist interviewed each participant face-to-face to collect demographic and anthropometric information. Age, adherence to a specific diet, and drug use history were all considered. A Seca digital body weight scale was used to measure weight with an accuracy of 100 g while standing in light clothing. Height was measured with a tape measure while standing without shoes with a precision of 1 cm. Body mass index (BMI) was calculated using weight and height measurements by dividing the weight in kilograms by the height in square meters.

Dietary Assessments

In a face-to-face interview with participants, a certified nutritionist gathered the participants' typical diet over the previous year using a Willet format semi-quantitative FFQ with 168 food items, for which its validity and reliability have been approved for the Iranian population [20–23]. Individuals reported the frequency of each food item's intake daily, weekly, monthly, or yearly. Then, using the household scale guide, the stated weight of each food item was converted to grams [24], and the United States Department of Agriculture food composition data were used to estimate each participant's macronutrient intake. The overall amount of energy consumed by each person was calculated by determining the energy content of each food item [25].

MIND Diet Score

The MIND diet score was created using 15 dietary parameters, 10 of which were referred to as brain-healthy food categories (green leafy vegetables, other vegetables, nuts, berries, beans, whole grains, fish, poultry, olive oil, and wine), with the other 5 being referred to as the brain unhealthy food category (red meats, butter and stick margarine, cheese, pastries and sweets, and fried/fast foods) [17]. Wine consumption was not included in the present study's score computation due to a lack of data in our dataset. The remaining 14 food categories were included in the MIND structure. The recommended portions from the original MIND diet rating were used. For example, persons who consumed 6 servings/week and more of green leafy vegetables were assigned a score of 1, those who consumed > 2–6 servings/week were assigned a score of 0.5, and those who consumed 2 and less than 2 servings/week were assigned a score of 0. More details are given in Table 1. The total MIND diet score was then computed by adding the scores for all the dietary factors [17]. As a result, each participant receives a score ranging from 0 to 14.

Statistical Analysis

Considering case:control 2:1, the study power of 80%, type I error of 0.05, and desired confidence interval (CI) of 0.95, the minimum required sample size was estimated to be 68 MS patients and 136 sex-matched healthy individuals. The data in this study were analyzed using the (SPSS) software (v.21; SPSS, Chicago, IL, USA). The Kolmogorov–Smirnov test was used to analyze the data's normal distribution. To compare normally distributed data across cases and control groups, an independent two-sample t test was used. The Mann–Whitney U test was used to analyze data that were not normally distributed. A Chi-square test was used to assess

qualitative confounding variables between the cases and the controls. According to the study controls intakes, all variables were divided into tertiles to investigate the relationship between MS and the MIND diet. Logistic regression models were used to generate the odds ratio (OR) with a 95% CI for each tertile, with the first tertile serving as the reference group. Age, gender, smoking, and energy intake were included in the basic binary logistic regression models. BMI (kg/m^2), carbohydrate consumption (g/day), animal-based protein intake (g/day), and fiber intake (g/day) were all included in binary logistic regression models to account for potential confounding factors. To be considered statistically significant, the P value had to be less than 0.05.

RESULTS

After removing ineligible individuals, the research comprised 77 cases and 148 controls. The median (Q1–Q3) of age in the control individuals was significantly greater than in the case group [35.5 (29.0–42.8) and 31.0 (28.5–37.0) years, respectively; P value < 0.001]. There was also a significant difference between the case and control groups in BMI (kg/m^2, P value < 0.001), total calories (kcal, P value = 0.032), total carbohydrates (g, P value = 0.003), total animal-based protein (g, P value = 0.009), and total fiber consumption (g, P value = 0.001) (Table 2).

In both the basic and adjusted models, the higher MIND diet score was shown to be statistically significantly associated with a reduced odds of MS (Table 3). In the basic model, those in the top tertile of MIND diet scores had a 95% reduced risk of developing MS than those in the lowest tertile (OR = 0.05, 95% CI 0.01–0.36, P for trend < 0.001). In the latter regression model adjusted additionally for BMI (kg/m^2), and carbohydrate (g/day), animal-based protein (g/day), and fiber intake (g/day), compared to those in the first tertile of MIND diet scores, those in the top tertile had 90% lower risk of developing MS [adjusted OR (aOR) = 0.10, 95% CI = 0.01–0.88, P for trend = 0.001]. In both basic and adjusted models, MS odds was lower in the last tertile of green leafy vegetables (aOR = 0.02, 95% CI = 0.00–0.21, P for trend < 0.001), other vegetables (aOR = 0.17, 95% CI = 0.04–0.73, P for trend = 0.001), and beans (aOR = 0.05, 95% CI = 0.01–0.28, P for trend < 0.001) consumption. In the adjusted model, MS odds was lower in last tertile of the butter and stick margarine (aOR = 0.20, 95% CI = 0.06–0.65, P for trend = 0.008). On the other hand, odds of MS was much greater in the last tertile of cheese (aOR = 4.45, 95% CI = 1.70–11.6, P for trend = 0.003), poultry (aOR = 3.95, 95% CI = 1.01–15.5, P for trend = 0.039), pastries and sweets (aOR = 13.9, 95% CI = 3.04–64.18, P for trend < 0.001) and fried/fast foods (aOR = 32.8, 95% CI = 5.39–199.3, P for trend < 0.001) consumption. Although the odds of MS was significantly lower in the third tertile of berries consumption (OR = 0.43, 95% CI = 0.20–0.90, P for trend = 0.024), this significant reduction was not observed after adjusting for confounders (Table 3) The association between MIND diet score and MS odds is also modeled as continuous variables (Supplementary Table 1).

DISCUSSION

Studying the MIND diet score in this retrospective research shows that higher adherence to the overall MIND dietary pattern may protect against MS. To put it another way, individuals in the third tertile of MIND scores had an estimated 90% lower odds of developing MS, whereas individuals in the middle tertile had an estimated 84% lower odds than those in the first tertile. The evaluated outcomes were unaffected by other dietary factors and BMI.

According to these findings, even a moderate level of MIND diet adherence may significantly impact the prevention of MS. Our findings were consistent with the only research on the MIND diet impacts on MS, which was conducted on 180 newly diagnosed MS patients from the RADIEMS cohort. The thalamic volumes of patients in the last quartile of MIND diet scores were greater than for patients in the first quartile [26].

Table 1 MIND diet factors, food items and scoring

Factors	Food items	Scores for each factor		
		0	0.5	1
Whole grains[a]	Whole grains	< 1/day	1–2/day	≥ 3/day
Green leafy vegetables [a]	Lettuce, spinach, veggies	≤ 2/week	> 2 to < 6/week	≥ 6/week
Other vegetables[a]	Celery, squash, cucumber, tomato, raw carrot, cooked carrot, green beans, garlic, onion, peppers, peas, turnip, zucchini, eggplant, cabbage	< 5/week	5 to < 7/week	≥ 1/day
Berries[a]	Strawberries, blackberries	< 1/week	1/week	≥ 2/week
Nuts[a]	Walnuts, pistachios, hazelnuts, almonds, peanuts	< 1/month	1/month to < 5/week	≥ 5/week
Beans[b]	Lentils, beans, split peas, mung bean, other beans	< 1/week	1–3/week	> 3/week
Fish (not fried)[b]	Fish	Rarely	1–3/month	≥ 1/week
Poultry (not fried)[b]	Chicken, turkey, duck, goose	< 1/week	1/week	≥ 2/week
Olive oil[c]	Olive oil	Not primary oil		Primary oil used
Cheese[a]	Cheese	≥ 7/week	1–6/week	< 1/week
Pastries and sweets[a]	All kinds of confections, ice cream, biscuit, cake, chocolate	≥ 7/week	5–6/week	< 5/week
Butter and stick margarine [a]	Butter, margarine	> 2/day	1–2/day	< 1/day
Red meats[b]	Mutton, beef, lamb, goat, ground meat, heart, liver, tongue, brain	≥ 7/week	4–6/week	< 4/week

Table 1 continued

Factors	Food items	Scores for each factor		
		0	0.5	1
Fried/fast foods	Hamburger, sausage, French fries, pizza, donates	$\geq$ 4 times/ week	1–3/week	< 1 time/ week

Food items adapted from Nouri-Majd et al.'s study [72]

MIND Mediterranean–DASH diet intervention for neurodegenerative delay (MIND); range: 0–14 points

[a]Factors expressed as servings number per day, week, or month

[b]Factors expressed as number of meals per week or month

[c]Considered as the primary oil used if it is consumed at least once a day

Table 2 General characteristics of participants with RRMS and controls

Characteristic[a]	RRMS (n = 77)	Control (n = 148)	P value[b]
Age, year	31.0 (28.5–37.0)	35.5 (29.0–42.8)	< 0.001
Gender, male, no (%)	18 (23.4)	40 (27)	0.553
Smoking, yes, no (%)	13 (16.9)	25 (16.9)	0.999
Alcohol, yes, no (%)	9 (11.7)	21 (14.2)	0.601
BMI, kg/m^2	24.8 (21.9–27.5)	27.3 (24.0–30.5)	< 0.001
Total calories, kcal	2507.7 (1963.4–3031.1)	2328.2 (1955.2–2778.8)	0.032
Total carbohydrates, g	318.0 (258.3–409.1)	294.4 (242.5–350.7)	0.003
Total fat, g	99.2 (80.2–125.5)	92.2 (75.8–114.9)	0.132
Total animal-based fat, g	30.6 (22.6–40.4	27.8 (19.9–37.9)	0.212
Total plant-based fat, g	67.4 (52.1–85.6)	61.9 (49.3–78.7)	0.265
Total protein, g	85.5 (62.8–103.0)	93.6 (73.3–115.0)	0.102
Total animal-based protein, g	36.2 (27.9–45.0)	42.5 (28.1–56.0)	0.009
Total plant-based protein, g	47.4 (33.0–63.0)	47.5 (37.0–59.5)	0.762
Total fiber, g	29.3 (23.2–39.1)	38.8 (30.3–44.3)	0.001
Total MIND diet score	6.5 (6–7.5)	7.5 (8.5–9.5)	< 0.001

[a]Values are median (Q_1–Q_3) unless otherwise noted

[b]Using Mann–Whitney U or χ^2 test, as appropriate

BMI body mass index

As previously indicated, the MIND diet combines the Mediterranean and DASH diets and focuses on brain health. The results of the studies on the Mediterranean diet and MS were

Table 3 Odds ratio (OR) estimates and 95% confidence intervals (CIs) for the association between MIND diet and MS in a sample of RRMS patients compared to healthy individuals based on the tertiles of MIND diet[a]

MIND diet	Tertiles of MIND diet score			P for trend
	1st	2nd	3rd	
MIND				
No. cases/no. controls	10/49	6/50	61/49	
Base model[b]	1.00 (Ref.)	0.07 (0.02–0.18)	0.05 (0.01–0.36)	< 0.001
Full model[c]	1.00 (Ref.)	0.16 (0.05–0.49)	0.10 (0.01–0.88)	0.001
Green leafy vegetables	Less than 57 g/day	57–100 g/day	More than 100 g/day	
No. cases/no. controls	73/49	4/50	0/49	
Base model[b]	1.00 (Ref.)	0.04 (0.01–0.13)	0.01 (0.00–0.10)	< 0.001
Full model[c]	1.00 (Ref.)	0.04 (0.01–0.17)	0.02 (0.00–0.21)	< 0.001
Other vegetables	Less than 165 g/day	165–280 g/day	More than 280 g/day	
No. cases/no. controls	60/49	14/50	3/49	
Base model[b]	1.00 (Ref.)	0.19 (0.09–0.41)	0.05 (0.01–0.16)	< 0.001
Full model[c]	1.00 (Ref.)	0.27 (0.11–0.67)	0.17 (0.04–0.73)	0.001
Nuts	Less than 5 g/day	5–10 g/day	More than 10 g/day	
No. cases/no. controls	40/49	16/50	21/49	
Base model[b]	1.00 (Ref.)	0.63 (0.30–1.30)	0.59 (0.28–1.25)	0.770
Full model[c]	1.00 (Ref.)	0.94 (0.38–2.33)	1.75 (0.65–4.70)	0.280
Berries	Less than 5 g/day	5–11 g/day	More than 11 g/day	
No. cases/no. controls	44/49	22/50	11/49	
Base model[b]	1.00 (Ref.)	0.64 (0.32–1.27)	0.43 (0.20–0.90)	0.024
Full model[c]	1.00 (Ref.)	0.86 (0.37–2.01)	1.02 (0.39–2.64)	0.981
Beans	Less than 36 g/day	36–66 g/day	More than 66 g/day	
No. cases/no. controls	64/49	9/50	4/49	
Base model[b]	1.00 (Ref.)	0.10 (0.04–0.24)	0.03 (0.01–0.11)	< 0.001
Full model[c]	1.00 (Ref.)	0.13 (0.05–0.37)	0.05 (0.01–0.28)	< 0.001
Whole grains	Less than 47 g/day	47–93 g/day	More than 93 g/day	
No. cases/no. controls	35/49	25/50	17/49	
Base model[b]	1.00 (Ref.)	0.87 (0.44–1.73)	0.54 (0.25–1.16)	0.123
Full model[c]	1.00 (Ref.)	0.99 (0.43–2.29)	0.43 (0.16–1.18)	0.131
Fish	Less than 5 g/day	5–12 g/day	More than 12 g/day	
No. cases/no. controls	26/49	23/50	28/49	
Base model[b]	1.00 (Ref.)	0.81 (0.39–1.69)	0.94 (0.45–1.96)	0.888

Table 3 continued

MIND diet	Tertiles of MIND diet score			P for trend
	1st	**2nd**	**3rd**	
Full model[c]	1.00 (Ref.)	1.53 (0.61–3.82)	1.95 (0.74–5.16)	0.177
Poultry	Less than 26 g/day	26–45 g/day	More than 45 g/day	
No. cases/no. controls	42/49	19/50	16/49	
Base model[b]	1.00 (Ref.)	0.93 (0.47–1.83)	0.73 (0.32–1.69)	0.491
Full model[c]	1.00 (Ref.)	2.10 (0.83–5.36)	3.95 (1.01–15.5)	0.039
Olive oil	Less than 0.5 g/day	0.5–2.6 g/day	More than 2.6 g/day	
No. cases/no. controls	36/49	23/50	18/49	
Base model[b]	1.00 (Ref.)	0.80 (0.40–1.58)	0.52 (0.25–1.09)	0.085
Full model[c]	1.00 (Ref.)	0.92 (0.36–2.34)	0.81 (0.31–2.08)	0.897
Red meats	Less than 34 g/day	34–52 g/day	More than 52 g/day	
No. cases/no. controls	24/49	18/50	35/49	
Base model[b]	1.00 (Ref.)	0.80 (0.36–1.80)	1.84 (0.85–3.98)	0.088
Full model[c]	1.00 (Ref.)	1.13 (0.42–3.04)	1.39 (0.52–3.70)	0.508
Butter and stick margarine	Less than 4 g/day	4–8 g/day	More than 8 g/day	
No. cases/no. controls	24/49	22/50	31/49	
Base model[b]	1.00 (Ref.)	0.62 (0.29–1.30)	0.62 (0.28–1.39)	0.250
Full model[c]	1.00 (Ref.)	0.36 (0.13–1.00)	0.20 (0.06–0.65)	0.008
Cheese	Less than 16 g/day	16–30 g/day	More than 30 g/day	
No. cases/no. controls	27/49	27/50	23/49	
Base model[b]	1.00 (Ref.)	0.52 (0.24–1.13)	1.93 (0.96–3.86)	0.056
Full model[c]	1.00 (Ref.)	0.89 (0.34–2.34)	4.45 (1.70–11.6)	0.003
Pastries and sweets	Less than 42 g/day	42–91 g/day	More than 91 g/day	
No. cases/no. controls	3/49	4/50	70/49	
Base model[b]	1.00 (Ref.)	1.87 (0.43–8.22)	26.05 (7.00–96.9)	< 0.001
Full model[c]	1.00 (Ref.)	1.64 (0.32–8.46)	13.9 (3.04–64.18)	< 0.001
Fried/fast foods	Less than 21 g/day	21–30 g/day	More than 30 g/day	
No. cases/no. controls	10/49	6/50	61/49	
Base MODEL[b]	1.00 (Ref.)	6.41 (1.37–29.9)	26.63 (5.93–119.5)	< 0.001

Table 3 continued

MIND diet	Tertiles of MIND diet score			*P* for trend
	1st	2nd	3rd	
Full model[c]	1.00 (Ref.)	7.12 (1.19–42.7)	32.8 (5.39–199.3)	< 0.001

[a]Logistic regression model

[b]Adjusted for age (years), gender (male/female), smoking (yes/no), total calories (kcal)

[c]Additionally adjusted for BMI (kg/m^2), carbohydrate intake (g/day), animal-based protein intake (g/day), fiber intake (g/day)

controversial. The Alternate Mediterranean Diet index was used to assess the dietary patterns of 480 MS patients in the Nurses Health Studies. After accounting for factors such as age, BMI, smoking status, and vitamin D consumption, the researchers found no link between MS risk and Mediterranean Diet adherence [15]. On the other hand, in a study on newly diagnosed MS patients in Croatia ($n = 219$ over the whole country), in the continental area with low adherence to the Mediterranean Diet, the mean annual incidence of MS was nearly two times greater compared to a coastal area with high adherence to the Mediterranean Diet [11]. According to two Iranian case–control studies, those who eat a diet rich in fresh fruits and vegetables typical of the Mediterranean diet were significantly less likely to develop MS [27, 28]. Observed differences may be attributed to differences in concordance to the Mediterranean diet. Only the greatest Mediterranean diet concordance was linked to disease protection in Alzheimer's disease [16]. Interestingly, according to the findings of the present study, even modest MIND diet adherence may be helpful in preventing MS.

The present results additionally demonstrated that greater vegetable consumption could decrease MS risk. The predicted effect was a 96% and 98% reduction in the odds of MS for persons who consume 57–100 g/day and > 100 g/day green leafy vegetables, respectively. Also, moderate (165–280 g/day) and high (> 280 g/day) intake of other vegetables reduced the odds of MS by 73 and 83%, respectively.

These results are in line with those of the previous studies [29–31]. Two extensive cohort studies on MS patients reported significantly better physical and mental health with greater fruit and vegetable intake. Both studies used the Diet Habits Questionnaire (DHQ) to assess dietary intakes. The DHQ was first designed for the cardiac rehabilitation population and has since been modified for people with MS. According to the DHQ, patients were grouped into three fruit and vegetable categories: poor (score 1 < 3.5), moderate (score 3.5 < 4.5), and healthy (score 4.5–5) based on their answers to 5 questions [30]. The Australian MS Longitudinal Study results showed an indirect association between physical and mental health and fruit and vegetable consumption, with the strongest associations observed for high intake (score 4.5–5) [31]. According to the results of the HOLISM study, those in the healthy and moderate fruit and vegetable groups had considerably reduced odds of having a greater disability level and a 12-month relapse. The results were similar for moderate and high fruit and vegetable consumption [30]. The DHQ does not define daily fruit and vegetable servings, and does not differentiate between the type of fruit and vegetables [32]. However, the MIND diet has a separate score for green leafy vegetables and recommends the number of servings. The highest score of vegetable consumption is achieved by ≥ 7 servings/week of green leafy vegetables and ≥ 1 serving/day of other vegetables. Moderate intake of vegetables is defined by 2–6 servings/week green leafy and 5–7 servings/

week other vegetables [17]. Likewise, in a cross-sectional study on 113 women with MS and 113 healthy controls, there was a significant association between vegetable consumption more than five times a week and a lower risk of MS [29].

Vitamin K, found primarily in green leafy vegetables, may be beneficial for MS, since it is required for sphingolipid metabolism, cell membranes, remyelination, and the formation of oligodendrocyte precursor cells [8, 33–36]. The fermentation process of gut microbiota on vegetables leads to short-chain fatty acids (SCFAs) synthesis. SCFAs may have immunomodulatory functions, such as gut epithelial cell integrity, inducing the regulatory T cell differentiation [37–39], decreasing pro-inflammatory cytokines and chemokines production through stimulation of G-protein-coupled receptors and histone deacetylase inhibition [40], and elevating the anti-inflammatory cytokine interleukin-10 [41, 42]. Cruciferous vegetables are an excellent source of the amino acid tryptophan. The tryptophan metabolites activate the aryl hydrocarbon receptor (AhR), leading to various effects on the peripheral immune system [43]. Numerous of these metabolites can pass through the blood–brain barrier and activate AhR on astrocytes. This process leads to nuclear factor kappa-light-chain-enhancer of activated B cells (NF-Kb) suppression, thus reducing monocyte enrolment, microglial activation, and neurotoxicity in the immediate environment [38, 44, 45]. Vegetable flavonoids also act as AhR agonists [46]. They also exert immunomodulatory and neurodegenerative effects through several additional pathways [47, 48]. Numerous studies have shown the efficacy of various flavonoid compounds in MS animal models, including neuroprotection [49, 50] and even remyelination promotion [51, 52]. Vegetables are also a good source of antioxidants and prebiotics, which can inactivate NF-kB and enhance intestinal microbial balance [42, 53]. Polyphenols in vegetables may also lead to downregulation of the synthesis of the pro-inflammatory molecule [42].

The current study showed a significant relationship between bean consumption and MS risk. In contrast, a pilot study on 20 RRMS patients showed that, except for potatoes and legumes, increasing vegetable consumption by one cup equivalent reduced the risk of relapse by 50% [54]. In this study, consumption of beans was also in negative correlation with MS odds. Like vegetables, beans are a great source of polyphenols that have anti-inflammatory effects [55].

Based on the current study outcomes, fast food and fried food consumption, rich in fat, especially saturated fat, is significantly associated with a greater odds of MS. According to the present outcomes, fast fried food consumption more than once per week increased the odds of MS by 32.8 times compared to eating this type of food less than once a week. The high prevalence of MS in Western nations might possibly be attributed to diets rich in sodium, animal fat, red meat, and fried foods [42]. According to the available evidence, a diet rich in animal or saturated fats may be associated with a higher risk of MS [56, 57]. The consumption of saturated fats is positively associated with increased inflammation and low-density lipoprotein cholesterol (LDL-C) [58]. According to Tettey et al., increased adiposity, non-high-density lipoprotein cholesterol (HDL-C), and the total cholesterol to HDL ratio are all linked with a greater disability progression rate in the long term. Increased adiposity and triglycerides are linked with relapse but not conversion to MS [59]. Weinstock-Guttman et al. showed a connection between lipid profile parameters, especially LDL-C and total cholesterol (TC) levels, with inflammatory MRI activity measurements in early MS [60]. According to Weinstock-Guttman et al. in another study, increased LDL, TC, and triglyceride levels are linked with worsening disability in MS patients [61]. Saturated fats affect the innate immune system by activating pro-inflammatory toll-like receptors, resulting in an enhanced NF-Kb inflammatory pathway [38, 62]. Saturated fats may also increase endotoxin, leading to an enhanced NF-kB pathway [38, 63]. The adaptive immune system is similarly significantly impacted by a high-fat diet. In a mouse model of MS that had been given a Western high fat diet, spinal cord production of pro-inflammatory cytokines IL-1B, IL-6, and

interferon, and T cell and macrophage infiltration, increased [38, 64]. Long-chain fatty acids found in processed foods may support the differentiation of naive T cells into pro-inflammatory TH1 (T helper) and TH17 cells [38, 41]. MIND can add more detail about the amount of recommended fast fried food intake (e.g., French fries and chicken nuggets) for MS prevention.

This research observed a strong significant negative relationship between sweets and pastry intake and the odds of MS, with MS odds being about ten times greater in individuals consuming more than seven servings of sweets per week in adjusted models. Western-style diets typified by sugar-sweetened beverages exacerbate inflammation. This kind of diet stimulates human cell metabolism toward biosynthetic pathways, including the synthesis of arachidonic acid and its pro-inflammatory byproducts that result in gut microbiota imbalance, altered gut immunity, and low-grade systemic inflammation [42]. A diet containing high-sugar and refined carbohydrates is linked with postprandial inflammation [42, 65–67].

In the adjusted model, cheese consumption was significantly associated with higher odds of MS. In this study, all kinds of cheese, including low-fat and high-fat, are included in cheese. According to the HOLISM study, dairy consumption was positively associated with relapse rate [30]. However, a case–control study in Iran compared the consumption of low-fat dairy, including cheese, between healthy individuals and patients with MS and reported higher consumption of low-fat dairy products in patients with MS [29]. Although calcium level may be a protective factor in neurological diseases [68], saturated fats promote the NF-kB pathway and the innate immune system [38, 62, 63].

Butter and stick margarine, which are included as unhealthy components in the MIND diet [16], were associated with a lower odds of MS in this study. According to previous research, dietary fat may negatively affect the risk of MS [69]. This result would be due to the different lipogenic characteristics of hard and soft margarine. In the dietary questionnaire used in this study, all the kinds of margarine consumed by individuals were just called 'margarine', which may have affected the result [70].

Poultry as a healthy MIND diet component [16] was associated with a higher odds of MS. In a previous study, no significant association was seen between poultry (including chicken with and without skin) and MS risk [71]. The method of cooking (boiled, steamed, or fried in oil) may have affected the result observed.

Strengths and Limitations

To the best of our knowledge, there has been no prior research on the MIND diet and the odds of MS. We considered just newly diagnosed cases to minimize recall bias. The person who completed the FFQ was unaware of the individual's presence in the case or the control group. The study had an acceptable sample size, and the control group individuals were similar to the cases in terms of demographic variables. The clinically isolated syndrome affects the dietary pattern of patients; therefore, these patients were not included in the study, and only those with RRMS were recruited.

However, we had some limitations. Participants were not age-matched and were selected from the hospital. Patients with MS from the hospital do not represent those in the community, which affects the issue of generalizability. The study lacked data on education levels, socioeconomic status, physical activity, and previous infection or vaccination history. It would also be better to consider information about other factors, such as the serum level of vitamin D.

CONCLUSIONS

Taken together, the current findings indicated that adherence to the MIND diet and its factors, including green leafy vegetables, other vegetables, and beans, is associated with reduced odds of MS. Butter and stick margarine, which assumes an unhealthy MIND component, were associated with lower odds, but this result may be due to the misclassification of soft and hard margarine as a whole group. In addition, high consumption of cheese, pastries and sweets, and

fried/fast foods leads to elevated odds of MS. Poultry as a healthy component was also associated with higher odds. Therefore, it seems that following the MIND diet may be a beneficial approach for preventing MS. However, further well-designed randomized clinical trials are needed to make a recommendation for routine adherence to the MIND diet in patients with MS or to prevent MS.

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