Elmer Press

Original Article

J Neurol Res. 2014;4(2-3):72-80

Nutrient Patterns and Risk of Multiple Sclerosis: A Case-Control Study

Mahdieh Akhoondan[a], Maryam Behrooz[a], Farah Naja[b], Mahsa Jessri[c], Zohreh Hoseini[a], Bahram Rashidkhani[a, d]

Abstract

Background: The prevalence of multiple sclerosis (MS) in Iran is increasing. Although diet is an important modifiable risk factor for MS, the cumulative impact of micronutrients on MS is not yet fully understood. The objective was to evaluate the association between nutrient pattern and the risk of MS.

Methods: A validated food frequency questionnaire was used in the hospital-based case-control study. Sixty-eight patients with newly diagnosed MS and 140 controls were included.

Results: Cases and controls were selected from the Sinai Hospital in Tehran. Conducting principal component on 20 nutrients, four main nutrient patterns were revealed. Factor 1 included thiamin, selenium, niacin, copper and magnesium. Factor 2 was characterized by high riboflavin, calcium, vitamin D, zinc, linolenic acid and caffeine. Factor 3 was high in polyunsaturated fatty acids, monounsaturated fatty acids, alpha tocopherol, vitamin E and saturated fatty acids, and factor 4 was characterized by high loadings of vitamin C, β carotene and vitamin A. Using unconditional logistic regression, factors 2 and 4 were inversely associated to MS risk (OR = 0.25 (0.11 - 0.58) and OR = 0.43(0.21 - 0.87) respectively). Factors 1 and 3 showed no significant association with MS.

Conclusion: Findings suggested that nutrient patterns may be important in etiopathogenesis of MS and may offer new approaches to prevent MS.

Keywords: Multiple sclerosis; Nutrient; Case-control study

Introduction

Multiple sclerosis (MS) is the most common inflammatory demyelinating disease of the central nervous system (CNS). MS is identified as the main cause of neurological disability in young adults, with a distinct higher prevalence between the ages of 20 and 40 and among females [1, 2]. The neurodegenerative disease disables patients with a wide range of chronic symptoms including fatigue, tremors, spasticity, pain, numbness of limbs, bowel and bladder dysfunction and cognitive problems [1]. According to Kurtzke's geographical classification, Asia and Africa were considered as regions with low risk of MS (< 5/100,000) [3]. However, recent studies provided evidence of growing prevalence even in tropical and sub-tropical regions such as Iran, indicating that the distribution of MS is not exactly following the latitude gradient [4]. In Iran, incidence of MS has been dramatically increased over recent years; Isfahan and Tehran provinces were placed in high risk area for MS [5, 6].

The etiology of MS is complex and multi-factorial and involves genetics well as environmental factors. In susceptible individuals, exposing to environmental factors induces neurodegenerative autoimmune response against CNS, leading to inflammation, demyelination and neuronal injury [7]. Given the critical increase in the rate of the disease over the past two decades and considering the point that rearrangement of genetic materials cannot be responsible for such fast growth, it becomes plausible that changes in environmental factors such as nutrition and life style could have contributed to the rise in disease rates [6]. Several studies have examined the association between dietary intake and food groups and MS [8-13]. Other studies have also surveyed the role of a variety of singular vitamins and minerals [5, 9]. But the relationship between nutrient patterns and risk of MS has not been investigated.

Manuscript accepted for publication June 23, 2014

[a]Faculty of Nutrition Sciences and Food Technology, National Nutrition and Food Technology Research Institute (WHO Collaborating Center), Shahid Beheshti University of Medical Sciences, Tehran, Iran
[b]Department of Nutrition and Food Sciences, Faculty of Agriculture and Food Sciences, American University of Beirut, PO Box 11-0236, Riad El Solh, 11072020 Beirut, Lebanon
[c]Department of Nutritional Sciences, Faculty of Medicine, University of Toronto, Toronto, ON M5S 3E2, Canada
[d]Corresponding Author: Bahram Rashidkhani, Community Nutrition Department, Faculty of Nutrition Sciences and Food Technology, National Nutrition and Food Technology Research Institute, Shahid Beheshti University of Medical Sciences, Tehran, Iran.
Email: b_rashidkhani@sbmu.ac.ir

doi: http://dx.doi.org/10.14740/jnr277w

Combining nutrients in a pattern by using factor analysis, provides the opportunity of considering interactions, synergic and cumulative effects of nutrients, which may be neglected in analyzing nutrients in isolation [14]. In addition, using factor analysis to form nutrients patterns may expose the effect of nutrients which, in single nutrient analysis, may be too small to reveal or miss the association with disease by trying to separate the effects [14].

Therefore the present study was designed to analyze the relation of nutrient patterns and MS in order to achieve a more comprehensive understanding of the role of diet in the etiology of the MS.

Methods and Materials

This study was a hospital-based case-control study, conducted in Tehran, the capital of Iran. Seventy cases were selected by sequential sampling from patients referred by Tehran MS Society to Sinai Hospital Neurology Clinics. Patients with clinical definite MS according to the McDonald criteria [15] who were diagnosed less than a year ago were included in the study. Other inclusion criteria were: 1) age between 20 and 60 years; 2) did not introduce changes to one's diet since diagnosis.

As for controls, 142 patients were recruited from the same hospital. Exclusion criteria for controls were previous diagnosis of or history of cancer, inflammatory diseases of the peripheral nervous system, gastrointestinal and liver diseases, endocrine and metabolic disorders, immune system disorders as well as following special diets such as weight loss or vegetarian diets. Controls were matched to cases on age (5 years) and sex. Data for two controls and two cases were excluded from the analysis because their log scales of total energy intake were either > 3 or < 3 SD from the mean or poor responses with regard to dietary questions. The final study sample included 68 cases and 140 controls. Protocols and procedures of this study were approved by the Ethics Board of the National Nutrition and Food Technology Research Institute (No. 114), Iran, and all participants provided written consents after being informed of the purpose of this research, indicating their willingness to participate.

Data collection

General information and anthropometric measurements

In a one-to-one interview with trained field workers, cases and controls completed a brief socio-demographic and lifestyle questionnaire. Collected information included demographic variables, birth season and location of patient, parental age at birth, feeding of cow's milk in infancy, history of rubella and measles infection, family history of MS, vitamin D supplement intake before disease diagnosis, history on smoking and leisure time physical activity. Questions on alcohol intake and opium use were not answered by our participants because of their religious and cultural beliefs; therefore they were excluded from the analyses. Weight (without shoes) was measured with a digital scale with a precision of 100 g and height was measured using a non-stretch tape meter fixed to a wall with subjects standing without shoes and was recorded to the nearest 0.5 cm. Body max index (BMI) was calculated by dividing weight (kg) by square of height (m).

Dietary assessment

Dietary intake of subjects was assessed by a 125-item semi-quantitative food frequency questionnaire designed by Willet method. Reproducibility and validity of FFQ used in this study was previously tested using a group of 132 participants and was based on responses to the questionnaire twice with 1-year interval. Results indicated that the administered questionnaire was of reasonable relative validity and reproducibility for assessment of dietary intake in Tehranian adults [16, 17]. This questionnaire has been used before by Hajizadeh et al to study dietary patterns in relation to general obesity and central adiposity among Iranian women [18].

The FFQ collected information regarding food intake 1 year prior to diagnosis of MS for cases, and controls were asked to provide information about their dietary habits during 1 year prior to assessment.

The questionnaire assessed the intake of commonly consumed food items, with a reference portion, representing one standard serving expressed in household measures was defined for each food item. Participants were asked how often, on average, they consumed the specified portion size of every food item per day, per week, per month and per year. Common household measures, measuring cups, spoons and palm of hand were used for better estimation of the real portion consumed by the subject [19]. Portion sizes consumed from each food item, were then converted to daily gram intake using the household scales [19]. In addition to the daily energy, macronutrient and micronutrients consumption for participants was computed. Since Iranian food composition table (FCT) is incomplete and provides data only on a few nutrients, analyses of energy and nutrients were carried out using the USDA FCT. However, for some dairy products such as Kashk, wild plum, mint, sweet canned cherry and sour cherry that are not listed in the USDA FCT, Iranian FCT was used alternatively [19].

The field workers who conducted the interviews and obtained the anthropometric indices had no knowledge of the objectives of the study.

Statistical analysis

To explain the total variation in intake of 20 nutrients in

Table 1. Characteristics of Subjects in a Case-Control Study of MS, Iran

Characteristics	MS patients	Controls	Pearson Chi-square	P value
Number	68	140		
Age (years)	30.4 (9)	30.6 (8)		0.87
Gender				
Male	11.(16.2)	26 (18.6)	0.21	0.64
Female	57 (83.8)	114 (81.4)		
BMI	25.1 (5)	24.2 (4.4)		0.2
Energy intake	2,390 (587)	2,480.2 (821.5)		0.93
Smoking				
Yes	4 (5.8)	10 (7)	0.13	0.71
No	64 (94.2)	130 (93)		
Vitamin D supplement				
Yes	12 (17.6)	30 (21)	0.18	0.66
No	56 (82.3)	110 (78)		
Place of birth				
Tehran	36 (52.9)	69 (49.3)	0.34	0.55
Others	32 (47.1)	71 (50.7)		
Season of birth				
Spring	26 (38.2)	41 (30.4)		
Summer	11 (16.2)	50 (37.0)	11.00	0.01
Autumn	17 (25)	18 (13.3)		
Winter	14 (20.6)	26 (19.3)		
Cow milk consumption (within 2 first years of life)				
Yes	2 (2.9)	18 (12.9)	5.17	0.02
No	66 (97.1)	122 (87.1)		

terms of a few linear functions, principal component analysis was conducted in this study. Factor scores were rotated by using varimax rotation to provide uncorrelated factors. The number of factors was determined by considering eigenvalues and scree plot. We derived four factors with eigenvalues > 2 based on the scree plot and the interpretability of the factors. The factor score for each pattern was calculated by summing intakes of food groups weighted by their factor loadings and each patient received a factor score for each identified pattern. Scores were used to assess the associations of each nutrient pattern with the risk of MS. Four pattern scores were divided into two categories based on the medians. To evaluate the differences in distribution of categorical variables Chi-square test was preformed. To check the differences in distribution of continuous variables across the nutrient pattern score categories analysis of variance test or Mann-Whitney tests were used. We performed unconditional logistic regression to calculate odds ratio (OR) with 95% confidence interval (CI). Regression models were adjusted season of birth, feeding of cow's milk in infancy (yes/no) and total energy intake (kcal/day) as potential confounders. All analyses were performed using the Statistical Package for Social Sciences software version 16 (SPSS Inc., Chicago, IL, USA), and a two-sided P value < 0.05 was considered significant.

Results

Table 1 portrays general characteristics of cases (68) and controls (140) and distribution of selected risk factors. Match design of the study leads to age and sex similarity in case and control groups. In case group, female sex was more prevalent as compared to male sex (83.8% women vs. 16.2%

Table 2. Factor Loading Matrix for the Nutrients Representing the Four Major Nutrient Patterns in Case-Control Study of MS, Iran*

Nutrient	Factor 1	Factor 2	Factor 3	Factor 4
Thiamin (vitamin B1)	0.944	-	-	-
Selenium	0.908	-	-	-
Niacin (vitamin B3)	0.847	-	0.256	-
Cupper	0.822	0.265	0.218	0.301
Magnesium	0.665	0.552	0.214	0.345
Riboflavin (vitamin b2)	0.259	0.865	0.204	0.235
Calcium	0.308	0.830	-	0.274
Vitamin D	-	0.761	-	-
Zinc	0.585	0.657	0.293	
Linolenic acid	-	0.597	0.429	-
Caffeine	-	0.360	-	-
Docosa hexaenoic acid (DHA)	-	-	-	-
Polyunsaturated fatty acid (PUFA)	-	-	0.952	-
Mono nu saturated fatty acid (MUFA)	-	0.260	0.916	-
Alpha tocopherol	0.230	-	0.822	0.230
Saturated fatty acid (SFA)	-	0.580	0.669	-
Vitamin E	0.296	-	0.468	0.251
Beta carotene	-	-	-	0.925
Vitamin A	-	0.248	-	0.900
Vitamin C	0.281	-	-	0.545

*Absolute values of < 0.2 are not shown in the table for simplicity.

men). Compared to controls, more cases were fed of cow's milk in infancy. A higher percentage of cases (25%) were born in autumn compared to controls (13%).

Factor analysis retained four major nutrient patterns explaining about 64.2% of the total variance in the original nutrients. Factor-loading matrix of factors retained from the factor analysis is shown in Table 2.

Four major nutrient patterns were revealed in our study. Factor 1 presented high positive loadings of thiamin, selenium, niacin, copper and magnesium. Factor 2 was characterized by high intake of riboflavin, calcium, vitamin D, zinc, linolenic acid and caffeine. Factor 3 showed high loadings of polyunsaturated fatty acids (PUFA), monounsaturated fatty acids (MUFA), alpha tocopherol, vitamin E and saturated fatty acids (SFA) and factor 4 was characterized by high loadings of vitamin C, β carotene and vitamin A.

Distribution of BMI, feeding of cow's milk in infancy, vitamin D supplement intake before disease diagnosis and season of birth suggested no significant difference in four nutrient patterns. Total calorie intake in higher categories of all four nutrient patterns, was significantly higher compared to lower categories ($P < 0.05$, Table 3).

After adjusting for confounding factors, both factors 2 and 4 were inversely associated with the risk of MS (OR for

Table 3. Selected Participants' Characteristics According to Nutrient Pattern Scores in Case-Control Study of MS, Iran

	BMI (kg/m^2)		Total energy intake (kcal/day)		Season of birth %				Cow milk consumption within 2 first years of life		Vitamin D supplement	
	Mean	SEM	Mean	SEM	Spring %	Summer %	Autumn %	Winter %	No %	Yes %	No %	Yes %
Factor 1												
Low	24.8	0.48	2069	53.81	31.4	31.4	22.9	14.3	90.6	9.4	79.2	20.8
High	24.2	0.41	2910	95.44	35.4	28.3	11.1	25.3	90.3	9.7	79.6	20.4
P value	0.68		< 0.001		0.05				0.94		0.94	
Factor 2												
Low	24.1	0.42	2254	92.51	36.2	25.7	18.1	20	88.7	11.3	83	17
High	24.9	0.48	2719	74.52	30.3	34.3	16.2	19.2	92.2	7.8	75.7	24.3
P value	0.12		< 0.001		0.58				0.38		0.19	
Factor 3												
Low	24.6	0.35	2187	74.98	33.3	30.1	17.9	18.7	92.8	7.2	82.4	17.6
High	24.4	0.60	2925	85.00	33.3	29.6	16	21	86.9	13.1	75	25
P value	0.29		< 0.001		0.97				0.15		0.19	
Factor 4												
Low	24.2	0.42	2374	96.2	33	23.3	19.4	24.3	94.3	5.7	82.9	17.1
High	24.8	0.48	2594	75.5	33.7	36.9	14.9	14.9	86.5	13.5	76	24
P value	0.52		0.007		0.11				0.057		0.21	

Table 4. MS Risk Associated With Nutrient Pattern Scores in a Case-Control Study of MS, Iran

	Controls (n)	Cases (n)	Crude OR (CI)	P value	Adjusted OR (CI)*	P value
Factor 1						
Low	69	37	1.00 (ref)		1.00 (ref)	
High	71	31	0.84 (0.47 - 1.49)	0.55	0.63 (0.26 - 1.53)	0.31
Factor 2						
Low	61	44	1.00 (ref)		1.00 (ref)	
High	79	24	041 (0.22 - 0.74)	0.004	0.25 (0.11 - 0.58)	0.001
Factor 3						
Low	83	41	1.00 (ref)		1.00	
High	57	27	0.93 (0.51 - 1.68)	0.82	0.80 (0.35 - 1.81)	0.60
Factor 4						
Low	61	43	1.00 (ref)		1.00 (ref)	
High	79	25	0.43 (0.24 - 0.79)	0.007	0.43 (0.21 - 0.87)	0.02

*Total energy intake, season of birth, consumption of cow milk in childhood, were included in the regression models as covariates.

higher versus lower score was 0.25, 95% CI: 0.11 - 0.58, P = 0.001 for factor 2, and OR = 0.43, 95% CI: 0.21 - 0.87, P = 0.02 for factor 4). Meanwhile, factors 1 and 3 showed no significant associations with MS risk (OR = 0.63, 95% CI: 0.26 - 1.53, P = 0.31) and (OR = 0.80, 95% CI: 0.35 - 1.81, P = 0.6), respectively (Table 4).

Discussion

The aim of this study was to evaluate the association between nutrient patterns and MS in Tehran. Our findings revealed four main nutrient patterns: pattern1 (consisting of thiamin, selenium, niacin, copper and magnesium), pattern 2 (including high intake of riboflavin, calcium, vitamin D, zinc, linolenic acid and caffeine), pattern 3 (characterized by PUFA, MUFA, alpha tocopherol, vitamin E and SFA) and pattern 4 (characterized by vitamin C, β carotene and vitamin A). Out of these identified patterns, only patterns 2 and 4 were inversely associated with the risk of MS.

With the recent increase in MS prevalence in Iran and specifically in Tehran, there was a dire need to search for mitigating factors [5, 6]. Diet is an important modifiable risk factor for the disease and hence presents an opportunity to limit the burden of the disease [20]. In line with the results of our study, vitamin D has been consistently associated with a reduced risk of MS [21, 22]. Since epidemiological studies revealed the relationship between the MS prevalence and latitude, several studies have associated sunlight exposure [23], serum levels of vitamin D [24] and dietary vitamin D [25, 26] with MS. Munger et al [26] in Nurses' Health Study (NHS) and the NHS II reported a 40% reduced risk of MS among women in the highest quintile of vitamin D intake compared with the lowest quintile [26]. In addition, vitamin D supplementation was associated with remarkable reduction in the incidence of MS [26]. The protective effect of vitamin D in MS could be due to either role of vitamin D in nervous system by regulating myelin production or its beneficial effects on immune system regulation [27].

In addition to vitamin D, a variety of nutrients were examined in several studies. Ghadirian et al [9] in a case-control study found inverse association between vegetable protein, dietary fiber, vitamin C (high loaded in factor 4), thiamin, riboflavin (loaded in factor 2), calcium (high loaded in factor 2) and potassium and MS. These factors may prevent MS by antioxidant activity and radical scavenging or regulating process of nervous system [9, 28]. Unlike the suggested roles, no associations between carotenoids (loaded in factor 4), vitamin C (loaded in factor 4), and vitamin E and MS were found in NHS and NHS II cohorts studies [29].

In contrast to epidemiological studies indicating the association between prevalence of MS and the consumption of milk and dairy products [8, 30], proposed inverse effect of calcium on MS in our study, may be due to positive effect of vitamin D which can be increased by high calcium intake [31].

Our findings indicated an inverse association between linolenic acid (loaded in factor 2) and MS, which was consistent with previous studies [12]. NHS and NHS II studies [10] together with a Canadian case-control study [9] had non-significantly associated linoleic acid with lower risk of MS. Immunosuppressive activity of linolenic acid can be responsible for the protective effect [9]. Results from NHS and NHS II studies showed no relations between intakes of total fat, animal fat, vegetable fat, saturated fat, monounsaturated fat, n-6 polyunsaturated fat, trans-unsaturated fat and cholesterol [10].

Preventive effect of zinc on MS (loaded in factor 2), was consistent with the results of epidemiological studies that showed low prevalence of MS with high zinc intake [25]. Zinc as a part of copper zinc superoxide dismutase (CuZn-SOD) which is considered a powerful free radical scavenger, is postulate to prevent the myelin damage caused by peroxinitrite [32].

Caffeine, part of nutrient pattern 2, was inversely associated with MS risk.

Tsutsui et al [33] suggested a role for caffeine in the modulation of neuroinflammation, by upregulating A1 adenosine receptor (A1AR) on microglia in a mice study.

A1AR activation inhibits demyelination and associated axonal loss by suppressing pro-inflammatory and augmenting anti-inflammatory responses.

There are several considerable strong points in our study. The total participation rate for the both case and control groups was above 85%. Further strength of our study was to conduct the study in a province with a high-point prevalence of MS. To minimize selection bias, individuals in control group were only selected from patients with conditions not related to diet or other major risk factors of MS. In order to reduce the possibility of recall bias, only new cases were enrolled in the study.

A major criticism of factor analysis approach is that the dietary patterns extracted in one population are sample specific and cannot be extended to other populations [34]. Whereas, employment of factor analysis on nutrients regardless of the food sources, leads to nutrient patterns which can introduce prevention strategies and complementary treatments based on food habits of various populations. The fact that in factor analysis results can be affected by subjective analytic decisions is another limitation of this procedure [34]. However, taking into account the combination of nutrients as nutrient patterns, factor analysis reflects the complexity of dietary intake and allows the examination of nutrients derived from foods, their synergy, collinearity and interactions mechanisms by which diet may influence on risk of MS [14]. Therefore, it can expand our knowledge and offer new prospective on the etiology of MS.

Increasing prevalence of MS, points out the necessity of

finding preventive strategies. The study of nutrition and dietary intake as modifiable risk factors will provide probable clues to etiology of MS. In present study, conducting principal component on 20 nutrients retained four nutrient patterns. Significant protective effect was observed with factor 2 high in riboflavin, calcium, vitamin D, zinc, linolenic acid and caffeine, and factor 4 included vitamin C, β carotene and vitamin A, among dietary patterns found in our study. In this view, nutrient patterns by taking into account the combination of various nutrients, their interaction and cumulative effect can be a strong predictor of risk of the disease. This may offer new opportunities for further prospective studies to identify underlying nutritional factor which may involve in triggering autoimmune responses to myelin components.

Acknowledgement

We are grateful to all filed investigators, staffs and participants of the present study. This study was supported by a grant from the "National Nutrition and Food Technology Research Institute", Shahid Beheshti University of Medical Sciences (WHO Collaborating Center), Tehran, Iran.

Conflict of Interest

Authors declare no conflicts of interest.

References

1. Compston A, Coles A. Multiple sclerosis. Lancet. 2008;372(9648):1502-1517.
2. Farinotti M, Simi S, Di Pietrantonj C, McDowell N, Brait L, Lupo D, Filippini G. Dietary interventions for multiple sclerosis. Cochrane Database Syst Rev. 2007;(1):CD004192.
3. Kurtzke JF. A reassessment of the distribution of multiple sclerosis. Part one. Acta Neurol Scand. 1975;51(2):110-136.
4. Alonso A, Hernan MA. Temporal trends in the incidence of multiple sclerosis: a systematic review. Neurology. 2008;71(2):129-135.
5. Etemadifar M, Maghzi AH. Sharp increase in the incidence and prevalence of multiple sclerosis in Isfahan, Iran. Mult Scler. 2011;17(8):1022-1027.
6. Elhami SR, Mohammad K, Sahraian MA, Eftekhar H. A 20-year incidence trend (1989-2008) and point prevalence (March 20, 2009) of multiple sclerosis in Tehran, Iran: a population-based study. Neuroepidemiology. 2011;36(3):141-147.
7. Luessi F, Siffrin V, Zipp F. Neurodegeneration in multiple sclerosis: novel treatment strategies. Expert Rev Neurother. 2012;12(9):1061-1076; quiz 1077.
8. Malosse D, Perron H, Sasco A, Seigneurin JM. Correlation between milk and dairy product consumption and multiple sclerosis prevalence: a worldwide study. Neuroepidemiology. 1992;11(4-6):304-312.
9. Ghadirian P, Jain M, Ducic S, Shatenstein B, Morisset R. Nutritional factors in the aetiology of multiple sclerosis: a case-control study in Montreal, Canada. Int J Epidemiol. 1998;27(5):845-852.
10. Zhang SM, Willett WC, Hernan MA, Olek MJ, Ascherio A. Dietary fat in relation to risk of multiple sclerosis among two large cohorts of women. Am J Epidemiol. 2000;152(11):1056-1064.
11. Antonovsky A, Leibowitz U, Smith HA, Medalie JM, Balogh M, Kats R, Halpern L, et al. Epidemiologic Study of Multiple Sclerosis in Israel. I. An Overall Review of Methods and Findings. Arch Neurol. 1965;13:183-193.
12. Tola MR, Granieri E, Malagu S, Caniatti L, Casetta I, Govoni V, Paolino E, et al. Dietary habits and multiple sclerosis. A retrospective study in Ferrara, Italy. Acta Neurol (Napoli). 1994;16(4):189-197.
13. Sepcic J, Mesaros E, Materljan E, Sepic-Grahovac D. Nutritional factors and multiple sclerosis in Gorski Kotar, Croatia. Neuroepidemiology. 1993;12(4):234-240.
14. Newby PK, Tucker KL. Empirically derived eating patterns using factor or cluster analysis: a review. Nutr Rev. 2004;62(5):177-203.
15. McDonald WI, Compston A, Edan G, Goodkin D, Hartung HP, Lublin FD, McFarland HF, et al. Recommended diagnostic criteria for multiple sclerosis: guidelines from the International Panel on the diagnosis of multiple sclerosis. Ann Neurol. 2001;50(1):121-127.
16. Mirmiran P, Esfahani FH, Mehrabi Y, Hedayati M, Azizi F. Reliability and relative validity of an FFQ for nutrients in the Tehran lipid and glucose study. Public Health Nutr. 2010;13(5):654-662.
17. Esfahani FH, Asghari G, Mirmiran P, Azizi F. Reproducibility and relative validity of food group intake in a food frequency questionnaire developed for the Tehran Lipid and Glucose Study. J Epidemiol. 2010;20(2):150-158.
18. Hajizadeh B, Jessri M, Akhoondan M, Moasheri SM, Rashidkhani B. Nutrient patterns and risk of esophageal squamous cell carcinoma: a case-control study. Dis Esophagus. 2012;25(5):442-448.
19. Mouahedi A RR. Food Composition Table. National Nutrition and Food Technology Research Institute, Shahid Beheshti University of Medical Sciences. 1999.
20. Etemadifar M, Abtahi SH, Razmjoo H, Abtahi MA, Dehghani A, Salari M, Maghzi AH, et al. 25-hydroxyvitamin D Concentrations in Patients with Optic Neuritis as a Clinically Isolated Syndrome and Healthy Controls. Int J Prev Med. 2012;3(5):313-317.
21. Riccio P. The molecular basis of nutritional intervention in multiple sclerosis: a narrative review. Complement

Ther Med. 2011;19(4):228-237.
22. Habek M, Hojsak I, Brinar VV. Nutrition in multiple sclerosis. Clin Neurol Neurosurg. 2010;112(7):616-620.
23. Auer DP, Schumann EM, Kumpfel T, Gossl C, Trenkwalder C. Seasonal fluctuations of gadolinium-enhancing magnetic resonance imaging lesions in multiple sclerosis. Ann Neurol. 2000;47(2):276-277.
24. Munger KL, Levin LI, Hollis BW, Howard NS, Ascherio A. Serum 25-hydroxyvitamin D levels and risk of multiple sclerosis. JAMA. 2006;296(23):2832-2838.
25. Swank RL, Lerstad O, Strom A, Backer J. Multiple sclerosis in rural Norway its geographic and occupational incidence in relation to nutrition. N Engl J Med. 1952;246(19):722-728.
26. Munger KL, Zhang SM, O'Reilly E, Hernan MA, Olek MJ, Willett WC, Ascherio A. Vitamin D intake and incidence of multiple sclerosis. Neurology. 2004;62(1):60-65.
27. Cantorna MT. Vitamin D and multiple sclerosis: an update. Nutr Rev. 2008;66(10 Suppl 2):S135-138.
28. van Meeteren ME, Teunissen CE, Dijkstra CD, van Tol EA. Antioxidants and polyunsaturated fatty acids in multiple sclerosis. Eur J Clin Nutr. 2005;59(12):1347-1361.
29. Zhang SM, Hernan MA, Olek MJ, Spiegelman D, Willett WC, Ascherio A. Intakes of carotenoids, vitamin C, and vitamin E and MS risk among two large cohorts of women. Neurology. 2001;57(1):75-80.
30. Butcher PJ. Milk consumption and multiple sclerosis--an etiological hypothesis. Med Hypotheses. 1986;19(2):169-178.
31. Ramsaransing GS, Mellema SA, De Keyser J. Dietary patterns in clinical subtypes of multiple sclerosis: an exploratory study. Nutr J. 2009;8:36.
32. Johnson S. The possible role of gradual accumulation of copper, cadmium, lead and iron and gradual depletion of zinc, magnesium, selenium, vitamins B2, B6, D, and E and essential fatty acids in multiple sclerosis. Med Hypotheses. 2000;55(3):239-241.
33. Tsutsui S, Schnermann J, Noorbakhsh F, Henry S, Yong VW, Winston BW, Warren K, et al. A1 adenosine receptor upregulation and activation attenuates neuroinflammation and demyelination in a model of multiple sclerosis. J Neurosci. 2004;24(6):1521-1529.
34. Jacques PF, Tucker KL. Are dietary patterns useful for understanding the role of diet in chronic disease? Am J Clin Nutr. 2001;73(1):1-2.