Nutrition and Food Sciences Research Vol 1, No 2, Oct-Dec 2014, pages: 27-33

Original Article

Association of Macro- and Micro-nutrients Intake with the Risk of Multiple Sclerosis: A Case Control Study

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Received: July 2014 **Accepted:** September 2014

A B S T R A C T

Background and Objectives: Multiple Sclerosis (MS) is the most prevalent autoimmune disease of the central nervous system, and it has been suggested that nutrition might play a role in the etiology of MS. This study was aimed to evaluate the relationship between MS risk and intake of some macro- and micro-nutrients in Tehran (Iran).

Materials and Methods: In this hospital based, case-control study, a total of 60 newly diagnosed patients with MS and 140 controls underwent face-to-face interviews. Information regarding the usual dietary intake of each individual in the past year was collected by using a valid and reliable 168-item semi-quantitative food frequency questionnaire. Multivariate logistic regression was used to estimate the odds ratios and 95% confidence intervals.

Results: Inverse significant associations were observed ($P< 0.05$) between the intake of protein (OR=0.19; 95% CI: 0.04-0.76) and micro-nutrients such as vitamin B1 (OR=0.10; 95% CI: 0.02-0.53) , vitamin B2 (OR=0.15; 95% CI: 0.04-0.50), cobalamin (OR=0.13; 95% CI: 0.04-0.38), vitamin C (OR=0.20; 95% CI: 0.07-0.58), vitamin A (OR=0.23; 95% CI: 0.09-0.59), vitamin D (OR=0.28; 95% CI: 0.11-0.72), vitamin E (OR=0.15; 95% CI: 0.05-0.41), β-carotene (OR=0.38; 95% CI: 0.15-0.97), zinc (OR=0.05; 95% CI: 0.01-0.27), magnesium (OR=0.12; 95% CI: 0.03-0.47) and calcium (OR=0.23; 95% CI: 0.08-0.67) and the risk of MS.

Conclusions: The results suggest that intake of some macro- and micro-nutrients might be associated with reduced risk of MS. It seems promising that intake of nutrients at least in the dietary reference levels may decrease the risk of MS.

Keywords: Multiple Sclerosis (MS); Micronutrients; Case-control study

Introduction

Multiple sclerosis (MS) is a progressive degeneration of the myelin sheath of nerve cells in the central nervous system (CNS) (1). The prevalence of MS varies in the world, depending on the country or specific population from 2 to 150 persons per 100,000 people (2). According to a recent systematic review, the incidence and prevalence of MS in Iran has been increasing rapidly, especially in females (3). However, recent studies, examining the prevalence of this disease in different parts of Iran such as Tehran, Tabriz, Isfahan, Shiraz, Qom, and Southeastern provinces of Iran, indicate that these regions are among the areas with moderate to high prevalence of MS (4). According to the newest studies, Tehran, Qom and Isfahan have the highest prevalence of MS (51 cases per 100,000 people) in Iran (4-6).

Environmental risk factors for MS have been widely assessed (7); however, studies on nutrition as a main environmental factor are sparse and unpersuasive. Research on the association of nutrient intakes or their plasma concentrations with MS risk is particularly limited and conflicting regarding the results. Vitamin D is among the nutrients, which has been investigated the most in Iran and other parts of the world, and reported to be a protective nutrient in the pathogenesis of MS (8-12); however, a recent study in Iran did show a protective association for serum vitamin D levels against disability in MS patients (13). Regarding other fat soluble vitamins, a systematic review demonstrated that vitamin E and vitamin A are relevant to MS pathogenesis (14); this finding was confirmed by another recent review, which discussed that

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vitamin A might have beneficial effects for controlling MS (15). Adequate intakes of B2 and B6 could prevent MS (16); in addition, folate and vitamin B12 were proposed as protective factors (17, 18). However, in a recent randomized clinical trial, vitamin B2 supplementation did not improve disability status (19). All these reports have been somehow conflicting in different populations, and need more confirmatory studies. Also most of them assessed the plasma concentrations of nutrients, and did not investigate their dietary intakes to suggest daily intakes for prevention and control of MS.

Given that there is little evidence in the literature about the relationship between micronutrient intakes and MS disease in the Middle East and North Africa region, the aim of the current study was to investigate the relation of some macro- and micro-nutrients intake with the risk of MS in a hospital-based case-control study conducted in Tehran.

Materials and Methods

In the present study, 70 patients with MS (aged 20 to 60 years) referring to the neurology clinics of hospitals in Tehran with pathologic data diagnosis in their medical history (with no more than one year of diagnosis) were selected; and 142 non-MS subjects as control group were selected from patients referred to the same hospitals due to orthopedic problems, ear, throat, nose, appendix, general surgery, dental care, eye diseases, and obstetrics. None of the study groups had special diet. The controls were matched to the cases based on age (5-year interval) and sex. In each age and sex group, the number of controls was twice of the cases. After obtaining informed consent, data including age, sex, history of feeding with cow milk in infancy, use of vitamin D supplements before diagnosis of disease, smoking, physical activity, parental age at birth of the patient, season and place of the patient's birth, history of rubella or measles, stress levels throughout the day and the family history of MS were collected by face-to-face interviews.

The Ethics Committee of the National Nutrition and Food Technology Research Institute affiliated with Shahid Beheshti University of Medical Sciences (Tehran/Iran) approved this study.

Dietary assessment: A valid and reliable 168-item semi-quantitative food frequency questionnaire (FFQ) was used by trained dietitians in face-to face interviews to evaluate the usual dietary intakes of the participants (20). They were asked to report their consumption frequency of food items during the previous year on a daily, weekly or monthly basis. The collected data were then converted into mean daily intakes. Portion sizes of the consumed foods, which were reported in household measures, were specified according to the US Department of Agriculture (USDA) standard portion sizes (e.g. apple, 1 medium; bread, 1 slice; and dairy, 1 cup) and were then converted into grams. When using the USDA portion sizes was impossible, household measures (e.g. beans, 1 tablespoon; chicken meat, 1 leg or wing; and rice, 1 large or small plate) were used alternatively (21).

Using the modified *Nutritionist 4* software, the daily intakes of total energy, protein, carbohydrate, fiber, total fat, MUFA, cholesterol, vitamin D, thiamine, riboflavin, vitamin A, selenium, magnesium, cobalamin, vitamin C, vitamin E, calcium, zinc, beta-carotene, Alpha-Tocopherol, linoleic acid, eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA) were determined.

Measurements: Stress level of the subjects during the day was collected by telephone interviews using DASS-21 questionnaire that is valid for the Iranian population (22). People were categorized into four groups in terms of their stress during the day (on the basis of information gained from the questionnaires): Normal (score 0 to 14), Mild (score 15-18), Moderate (score 19-25), Severe (score 26, 33), and Very severe (score of 34 and above).

Weight was measured while the subjects were minimally clothed without shoes using a digital scale (Seca, Hamburg, Germany), and recorded to the nearest 100 g. Height was measured in a standing position, without shoes, using a tape measure while the shoulders were in a normal position, and recorded to the nearest 0.5 cm. Body mass index (BMI) was calculated as weight in kilograms, divided by height in meters squared.

Statistical Analysis: To have a clinically significant association between dietary intakes and risk of MS (23), we based our sample calculation on dietary fat with an odds ratio ~ 3 with 95% CI and 80% power. Therefore, we found that a sample size of 70 for the cases and 140 for the controls was sufficient in each group.

To compare the cases and controls regarding the categorical variables, Chi-square test or Fisher's exact test and for continuous variables t-test or Mann–Whitney's test were used. Characteristics of the subjects were expressed as mean and SD for continuous variables, and as percentages for categorical variables.

Nutrient intakes were divided into tertiles. Multiple logistic regression models were used to examine the association between MS and each tertile of the macro- and micro-nutrients. The odds ratios (OR) and 95% CIs were calculated. The initial model was unadjusted; we further adjusted it for total energy intake, daily imposed stress (normal, low, medium, severe, and very severe), cow milk intake under age 2 (yes, no), and birth season (spring, summer, autumn, and winter). Tests of linear trend were conducted by assigning the medians of intakes in tertiles treated as a continuous variable. Statistical analysis was performed using the SPSS software (version 15.0; SPSS Inc, Chicago IL).

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Results

Overall, 70 patients with MS based on specialist physician's opinion and according to the inclusion criteria were enrolled, and 142 subjects were selected as controls. Two control subjects because of the incomplete dietary response (>60 missing items), and two case subjects because of over- or under-report of dietary intakes (3 SD > energy > 3 SD of the mean total energy) were excluded from the final analysis. Finally, the analyses were restricted to 68 cases, matched to 140 controls (response rate: 85%).

Table 1 presents the characteristics of cases and matched controls. The cases were predominantly female (83.8%) with the mean age of 30.4 years. Known risk factors significantly associated with MS were history of cow milk consumption in ages < 2 years, season of birth, and imposed daily stress. More cases (64.9%) compared to the controls (21.5%) experienced severe and very severe stress.

Macro- and micro-nutrients were associated with MS risk in the case-control study (Tables 2 and 3). The fully adjusted odds ratio comparing the highest to the lowest tertiles was 0.13 (95% CI: 0.04-0.38) for vitamin B12, 0.20 (95% CI: 0.07-0.58) for vitamin C, 0.15 (95% CI: 0.05-0.41) for vitamin E, 0.28 (95% CI: 0.11-0.72) for vitamin D, 0.10 (95% CI: 0.02-0.53) for thiamine, 0.15 (95% CI: 0.04-0.50) for riboflavin, 0.19 (95% CI: 0.04-0.76) for protein, 0.23 (95% CI: 0.08-0.67) for calcium, 0.38 (95% CI: 0.15-0.97) for beta-carotene, 0.05 (95% CI: 0.01-0.27) for zinc, 0.12 (95% CI: 0.03-0.47) for magnesium, and 0.23 (95% CI: 0.09-0.59) for vitamin A. No significant association was observed for carbohydrate, total fat, different kinds of fat, and selenium.

Table 1: General characteristics of the subjects in cases and control groups

Characteristics	Cases (n = 68)	Controls (n = 140)	P value*
Age (year)	29 (23-33)	29 (24-35)	0.87
Body mass index (kg/m^2)	29 (23-33)	29 (24-35)	0.18
Energy intake (kcal)	2316 (2013-2745)	2260 (1839-2990)	0.96
Female (%)	57 (83.8)	114 (81.4)	0.64
Smoking status (%)			
Yes	4 (5.8)	10 (7)	0.71
No	64 (94.2)	130 (93)	
Vitamin D supplement (%)			
Yes	12 (17.6)	30 (21)	0.66
No	56 (82.3)	110 (78)	
Place of birth (%)			
Tehran	36 (52.9)	69 (49.3)	0.55
Others	32 (47.1)	71 (50.7)	
Season of birth (%)			
Spring	26 (38.2)	41 (30.4)	0.01
Summer	26 (38.2)	50 (37.0)	
Autumn	11 (16.2)	18 (13.3)	
Winter	17 (25.0)	26 (19.3)	
Imposed stress (%)			
Normal	3 (4.8)	26 (20.2)	<0.001
Mild	6 (9.5)	30 (23.3)	
Moderate	15 (23.8)	46 (35.70)	
Severe	29 (46)	21 (16.3)	
Very severe	10 (15.9)	6 (4.7)	
Cow milk consumption within the first two years of life (%)	2 (2.9)	18 (12.9)	0.02
Routine exercise (%)	26 (38)	62 (44)	0.45

Data are median (IQ 25-75) or frequency (percentage).
*P values are for comparison between the two groups using Mann Withney's test or χ^2 test.

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Table 2. Multivariate-adjusted odds ratios for MS across the tertiles of macro-nutrients and cholesterol intakes among an Iranian population

	Intake			*P* for trend*
	T1	T2	T3	
Carbohydrate (g)	<273.6	273.6-360.5	>360.5	
Cases/Controls, n	20/50	27/43	21/47	
Model 1	1.00	1.57(0.77-3.18)	1.09(0.34-3.49)	
Model 2	1.00	1.1(0.53-2.31)	0.62(0.81-3.33)	0.62
Protein (g)	<68.2	68.2-87.8	>87.8	
Cases/Controls, n	26/44	24/46	18/50	
Model 1	1.00	0.88 (0.44-1.76)	0.60 (0.29-1.25)	
Model 2	1.00	0.41 (0.14-1.16)	0.19 (0.04-0.76)	0.01
Total fat (g)	<72.42	72.42-97.05	>72.42	
Cases/Controls, n	22/48	25/45	21/47	
Model 1	1.00	1.21(0.61-2.44)	0.75(0.28-1.98)	
Model 2	1.00	0.98(0.47-2.00)	0.6(0.18-1.97)	0.40
MUFA (g)	<21.6	21.6-29.33	>29.6	
Cases/Controls, n	20/50	27/43	21/47	
Model 1	1.00	1.57(0.77-3.18)	0.21(0.53-2.30)	
Model 2	1.00	1.46(0.57-3.68)	0.62(0.21-1.86)	0.40
PUFA (g)	<15.33	15.33-21.30	21.30	
Cases/Controls, n	18/51	27/43	23/46	
Model 1	1.00	1.77(0.86-3.60)	1.41(0.68-2.95)	
Model 2	1.00	2.89(1.02-8.21)	2.58(0.83-8.00)	0.12
EPA (mg)	<8	8-20	>20	
Cases/Controls, n	26/60	26/29	16/51	
Model 1	1.00	2.06 (1.02-3.11)	0.72 (0.35-1.49)	
Model 2	1.00	4.42 (1.72-2.43)	1.12 (0.45-2.76)	0.53
DHA (mg)	<10	10-30	>30	
Cases/Controls, n	21/52	31/35	16/53	
Model 1	1.00	2.19 (1.08-4.41)	0.74 (0.35-1.59)	
Model 2	1.00	2.96 (1.60-9.8)	1.12 (0.45-2.81)	0.58
Linoleic acid (g)	<12.35	12.35-17.43	>17.43	
Cases/Controls, n	18/52	26/44	24/44	
Model 1	1.00	1.70(0.82-3.51)	1.57(0.75-3.21)	
Model 2	1.00	1.59(0.65-3.18)	1.50(0.57-3.91)	0.40
Cholesterol (mg)	<186.6	186.6-267.6	>267.6	
Cases/Controls, n	20/50	27/43	21/47	
Model 1	1.00	1.57 (0.77-3.18)	1.09 (0.34-3.49)	
Model 2	1.00	1.11 (0.53-2.31)	0.62 (0.81-3.30)	0.62

MUFA: monounsaturated fatty acid; PUFA: polyunsaturated fatty acid; EPA: eicosapentaenoic acid; DHA: docosahexaenoic acid
Model 1: Unadjusted
Model 2: Adjusted for total energy intake, daily imposed stress (normal, low, medium, severe, and very severe), cow milk intake under age 2 (yes, no), and birth season (spring, summer, autumn, and winter)
* *P* for trend was reported for Model 2.

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Table 3. Multivariate-adjusted odds ratios for MS across the tertiles of selected micro-nutrients intake among an Iranian population

	Intake			*P* for trend*
	T1	T2	T3	
Vitamin B12 (mcg)	<3.8	3.8-5.4	>5.4	
Cases/Controls, n	29/39	27/41	12/60	
Model 1	1.00	0.88 (0.44-1.75)	0.26 (0.12-0.58)	
Model 2	1.00	0.60 (0.25-1.44)	0.13 (0.04-0.38)	<0.001
Vitamin C (mg)	<134	134-209.2	>209.2	
Cases/Controls, n	31/38	23/46	14/56	
Model 1	1.00	0.61 (0.30-1.22)	0.3 (0.14-0.65)	
Model 2	1.00	0.54 (0.23-1.38)	0.2 (0.07-0.58)	0.003
Vitamin E (mg)	<8.17	8.1-12.8	>12.8	
Cases/Controls, n	38/31	19/52	11/57	
Model 1	1.00	0.29 (0.14-0.60)	0.15 (0.07-0.35)	
Model 2	1.00	0.28 (0.11-0.67)	0.15 (0.05-0.41)	<0.001
Vitamin D (mcg)	<0.81	0.81-2.5	2.5	
Cases/Controls, n	29/40	19/49	20/51	
Model 1	1.00	0.53 (0.26-1.09)	0.54 (0.26-1.09)	
Model 2	1.00	0.29 (0.11-0.75)	0.28 (0.11-0.72)	0.009
Vitamin B1 (mg)	<1.7	1.7-2.2	>2.2	
Cases/Controls, n	23/45	26/44	19/51	
Model 1	1.00	1.15 (0.57-2.32)	0.72 (0.35-1.50)	
Model 2	1.00	0.37 (0.11-1.24)	0.10 (0.02-0.53)	0.007
Vitamin B2 (mg)	<1.7	1.7-2.2	>2.2	
Cases/Controls, n	28/41	25/45	15/54	
Model 1	1.00	0.81 (0.41-1.64)	0.40 (0.19-0.85)	
Model 2	1.00	0.37 (0.14-0.96)	0.15 (0.04-0.50)	0.002
Calcium (mg)	<834.9	834.9-1121.3	1121.3	
Cases/Controls, n	29/41	25/45	14/54	
Model 1	1.00	0.78 (0.39-1.55)	0.36 (0.17-0.78)	
Model 2	1.00	0.43 (0.17-1.07)	0.23 (0.08-0.67)	0.007
β-Carotene (mcg)	<482.3	482.3-960.1	>960.1	
Cases/Controls, n	28/41	25/44	15/55	
Model 1	1.00	0.83 (0.41-1.65)	0.39(0.18-0.84)	
Model 2	1.00	1.15 (0.49-2. 70)	0.38(0.15-0.97)	0.05
Zinc (mg)	<7.05	7.05-8.97	>8.97	
Cases/Controls, n	25/44	26/44	17/52	
Model 1	1.00	0.56 (0.18-1.12)	0.26 (0.12-0.57)	
Model 2	1.00	0.20 (0.07-0.57)	0.05 (0.01-0.27)	<0.001
Magnesium (mg)	<246.1	246.1-317.3	>317.3	
Cases/Controls, n	15/54	32/38	21/48	
Model 1	1.00	1.06 (0.54-2.01)	0.47 (0.22-1.01)	
Model 2	1.00	0.49 (0.17-1.37)	0.12 (0.03-0.47)	0.003
Vitamin A (RE)	<916.73	916.73-1477.3	>1477.3	
Cases/Controls, n	40/66	7/22	21/52	
Model 1	1.00	0.65 (0.32-1.32)	0.32 (0.15-0.66)	
Model 2	1.00	0.59 (0.26-1.35)	0.23 (0.09-0.59)	0.007
Selenium (mg)	<0.05	0.05-0.07	>0.07	
Cases/Controls, n	23/48	26/44	19/48	
Model 1	1.00	1.23 (0.61-2.46)	0.82 (0.39-1.71)	
Model 2	1.00	1.52 (0.63-3.68)	0.63 (0.23-1.74)	0.43

Model 1: Unadjusted

Model 2: Adjusted for total energy intake, daily imposed stress (normal, low, medium, severe, and very severe), cow milk intake under age 2 (yes, no), and birth season (spring, summer, autumn, and winter)

* *P* for trend was reported for Model 2.

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Discussion

In the present study, several micro-nutrients and protein predicted MS risk, independent of total energy intake, daily imposed stress, cow milk intake under age 2, and season of birth.

The association between each micronutrient and risk of MS has been investigated in several studies. An inverse relation of calcium, riboflavin, cobalamin, vitamin C, and plant protein intake with reduced risk of MS was observed (23-26). The role of micronutrients in immune function, nervous system, and formation of myelin configure has been explained (23, 26, 27).

Findings indicate that patients with MS have lower level of cobalamin in serum and cerebrospinal fluid than normal subjects (28). Cobalamin deficiency has been reported as a cause of demyelination in the CNS, and the role of this vitamin as a cofactor in myelin formation and proper function of the nervous and immune systems has been pointed out (18, 28). Furthermore, elevated level of plasma homocysteine caused by cobalamin deficiency has been explained as a risk factor for MS (29). In the present study, cobalamin intake two fold greater than dietary reference intake (DRI) was accompanied by reduced risk of MS.

Several studies suggest that the risk of MS is inversely associated with high intake of vitamin D through regulatory role on inflammation in MS (7, 14, 25). Calcium and vitamin D are both participating in regulation of the immune system. Also calcium deficiency has significant effects on lipid synthesis in the myelin sheath (24). However, further studies are needed to prove the relationship between calcium intake and MS. It is worth mentioning that intake of vitamin D in the current study was still far from the amounts of DRI, which needs attention to ameliorate vitamin D deficiency in the population.

Ascherio *et al.* have noted the possible relationship of low intake of vitamin C and beta-carotene with increased risk of MS (7). Furthermore, the role of antioxidants in prevention of lipid peroxidation and induction of materials leading to the destruction of the myelin sheath in the CNS has been explained (30). Among the studied antioxidant compounds, vitamin C had more important and proven role in prevention of MS (7). In contrast, Zhang *et al.* did not find significant relation between the intakes of vitamin C, vitamin E, and carotenoids, and risk of MS in a prospective study (31). In the current study, there were significant inverse relations between increased intakes of zinc, vitamin E and magnesium, and the risk of MS, which is in agreement with findings of Johnson *et al.* who found that the gradual depletion of reserves of zinc, riboflavin, vitamin D and vitamin E was involved in the pathogenesis of MS. Reduced risk of MS was observed in the amounts nearly equal to DRI for zinc and vitamin E. In the present study, the prevalence of MS in females was more than in males, which may be due to accumulation of copper and decrement of zinc absorption in the age of menarche reducing copper and zinc superoxide dismutase enzyme activity, and ultimately, increasing the levels of superoxide, and myelin damage. Females of reproductive age have lower levels of magnesium and pyridoxine as well.

It is worthy to mention that micro-nutrient deficiency leads to retention of nitric oxide in the cells; therefore, free radicals are produced due to combination of nitric oxide with superoxide and causing severe injuries to myelin (16). The role of vitamin A in the etiology of MS has been investigated previously, and found that low consumption of vitamin A may be associated with an increased risk of MS (14, 32, 33).

The present study had several strengths. First, all probable confounders were identified and adjusted using comprehensive literature review. Therefore, residual confounders were low. Second, a valid and reliable FFQ was used to assess dietary intakes of the subjects. Third, the number of controls was twice of the cases to increase the power of the study. Fourth, incident cases (within the first year of diagnosis) were enrolled, so it is less likely that they change their eating habits. Among the limitations of the study, selection bias may be present due to the nature of the case-control study; however, because of the high participation rate (85%), it seems that selection bias is not an effective factor in changing the results of study. Finally, the case control study design could not show the causality between dietary intakes and MS incident; however, recruiting the new cases may reduce this limitation.

In summary, the current case-control study suggests that a diet high in protein, vitamin D, thiamine, riboflavin, cobalamin, vitamin C, vitamin E, calcium, beta-carotene, zinc, magnesium, and vitamin A tends to reduce the risk of MS. Additional cohort studies of dietary intakes in our as well as in other populations are needed to further clarify the protective effects of these nutrients on MS risk.

Acknowledgements

We are grateful to all field investigators, staffs and participants of the present study.

Financial disclosure

We have no financial relationships relevant to this article, nor do we have conflicts of interest to disclose.

Funding/Support

National Nutrition and Food Technology Research Institute

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