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# Food and dietary patterns and multiple sclerosis: a case-control study in Belgrade (Serbia)

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## Abstract

**Background:** The aetiology of multiple sclerosis (MS) is unclear, but numerous studies suggest that different exogenous factors can lead to the development of the disease in genetically susceptible individuals. The objective of this case-control study was to determine the role of food and dietary patterns in patients with MS in the population of Belgrade (Serbia).

**Methods:** In this matched case-control study, we included 110 cases with definite MS according to McDonald's criteria, in whom the onset symptoms occurred up to 2 years prior to the interview, who were followed-up at the Institute of Neurology, Clinical Centre of Serbia, Belgrade. The identical number of controls from the same institution, individually matched by sex, age and area of residence, was recruited from patients with various non-autoimmune neurological disorders. Dietary information was obtained by using a frequency history approach.

**Results:** According to univariate conditional logistic regression analysis the following factors were significantly related to MS: body mass index (BMI) less than 25 (OR=2.2, p=0.009), frequent consumption of beef (OR=1.7, p=0.043), chicken (OR=2.0, p=0.045), meat of the lamb (OR=2.1, p=0.013), butter (OR=1.7, p=0.056) and ice-cream (OR=1.8, p=0.031), with dose-response relationship. Consumption of majority of various fruit was more frequently reported by controls. According to multivariate conditional logistic regression analysis, BMI less than 25 (OR=2.3, p=0.008), consumption (weekly) of beef (OR=2.0, p=0.017) and butter (OR=1.9, p=0.027) was significantly related to MS, while regular consumption of cherry (OR=0.4, p=0.024) had protective role.

**Conclusions:** This study might assist in potential defining of the dietary factors that could contribute to the risk of developing MS.

*Key words: multiple sclerosis, food habits, dietary pattern, risk factors, case-control study*

### Introduction

Multiple sclerosis (MS) is a T-cell mediated demyelinating disease of the central nervous system, typically begins in the early adult years. The aetiology of MS is unclear, but numerous studies suggest that different exogenous, environmental and behavioural factors can lead to the development of the disease in genetically susceptible individuals [1]. Various non-genetic risk factors associated with MS have been analyzed, among which most frequently infections [2, 3].

The majority of reports on MS and food patterns, based on ecological correlation studies, support an association between MS and increased intake of animal saturated fats, milk and dairy products [4,5]. Relation between nutritional factors and MS was studied through several case-control and cohort studies, but with very inconsistent results [6-9]. Recently, a growing volume of data suggests association of vitamin D intake and MS [1, 9 - 15].

The objective of our case-control study was to investigate the importance of exogenous factors for the occurrence of MS in the Belgrade population. In this report, we analyzed the possible relationship between dietary factors and MS.

## Methods

The investigation was performed in Belgrade (Serbia), during 2001 to 2006.The Belgrade region extends over an area of 3222 km2 and comprises population of 1,576,126 inhabitants (2002 census). The age-adjusted prevalence of MS in Belgrade on December 31, 1996 was 41.5/100,000 [16], although at the end of 2007 prevalence exceeded 60/100,000 (Belgrade MS Registry, unpublished data).

The study group included 110 consecutive MS cases with clinically and/or laboratory supported definite MS according to McDonald's criteria [17]. All patients were evaluated by neurologists (JD, SM, IDB and NS) at the Institute of Neurology, Clinical Centre of Serbia in Belgrade, which is primary referral national centre for MS in Serbia. Included in the study were MS patients in whom onset of symptoms occurred up to 2 years prior to the interview.

The identical number of controls was recruited from patients with various non-autoimmune neurological disorders who were also treated at the Institute of Neurology, Belgrade, during the same time period. The control group comprised of patients with: epilepsy (26; 23.6%), tension headache (23; 20.9%), root compression syndromes (23; 20.9%), non-inflammatory peripheral neuropathy and myopathy of various aetiology (20; 18.2%), and minor cerebrovascular disorders (18; 16.4%).

All patients signed informed consent. Neither any of MS patients nor any controls refused to participate in the study. This investigation is approved by the Institutional Review Committee for human subjects of School of Medicine in Belgrade.

MS cases and controls were individually matched by sex, age (±1 year) and area of residence (urban vs. rural). Urban and rural population represents population of localities established as such by corresponding legal act or agreement of competent socio-political communities valid at the time of census [18]. Our study was comprised of an ethnically homogenous population.

Both MS case and control subjects were interviewed by epidemiologists (TP, DKT), either during hospitalization or during regular control neurological examinations at the Institute of Neurology in Belgrade, using a standard questionnaire (previously validated). It included questions about different factors that are supposed to be possible risk or protective factors for MS. The questionnaire was comprised of several sections for the detection of: demographic and socioeconomic factors, occupational history, personal experience of past infections, non-infectious diseases and surgical history, allergies, vaccinations, reproductive history, exposure to solvents and radiation, contact with animals, physical trauma, habits (smoking, coffee and alcohol consumption, sport and recreation), stressful life events, family history, and diet. Dietary information was obtained using a frequency history approach. Subjects were asked how often (daily, weekly, monthly, rare, never) they consumed each one of the main food groups or food items before the onset of the disease.The analysis of consumption was based on median frequency of consumption (Tables 1-4).

Odds ratios (OR) and 95% confidence intervals (95%CI) according to Miettinen procedure were separately calculated for each variable using univariate conditional logistic regression analysis [19]. The variables that were related to MS at a significant level of $p < 0.05$, entered the final model of multivariate conditional logistic regression analysis to evaluate their independent contribution to the overall risk of MS. The statistical significance of dose response pattern was assessed by $\chi^2$ test for trend [20].

## Results

Thirty-three men and 77 women with MS, and the identical number of matched controls were included in this case-control study. Sex ratio was 1:2.3. At the time of the interview, the average age for MS cases and controls were 34.4±10.2 years and 35.0±10.0 years, respectively.

In this study, the mean body mass index (BMI) was 22.6±3.5 in MS cases and 23.8±3.4 in controls, with a statistically significant difference (OR=2.2, 95%CI 1.2-3.9, p=0.009). Overweight (BMI = 25.0-29.9) was present in 22 (20.0%) MS cases and 38 (34.5%) controls, and obesity (BMI ≥ 30) in 3 (2.7%) MS patients and 5 (4.5%) controls.

According to findings presented in Table 1, MS patients consumed all types of meat, meat products and fish, more frequently than controls. Among meat products, weekly consumption of beef (OR=1.7, p=0.043), chicken (OR=2.0, p=0.045) and lamb (OR=2.1, p=0.013) were reported significantly more frequently by MS cases than controls. For these three items, significant dose-response relationship was observed (beef- $\chi2$=5.063, p=0.024, chicken- $\chi2$=5.264, p=0.022, meat of the lamb- $\chi2$=5.423, p=0.019). Statistically significant increasing risk was also found for total meat consumption ($\chi2$=13.962, p=0.001).

Consumption (weekly vs. rarely) of butter (OR=1.7, p=0.056) and ice-cream (OR=1.8,

**Table 1. Consumption frequency* of different food groups and food items in MS patients and controls.**

| *Meat and meat products* | MS (No=110) | Control (No=110) | Odds ratio | 95%CI | p |
|---|---|---|---|---|---|
| Beef | 68 | 53 | 1.7 | (1.0-3.0) | 0.043 |
| Pork | 77 | 72 | 1.2 | (0.7-2.2) | ns |
| Chicken | 97 | 82 | 2.0 | (1.0-4.0) | 0.045 |
| Meat of the lamb | 41 | 24 | 2.1 | (1.2-3.9) | 0.013 |
| Fish | 33 | 29 | 1.2 | (0.7-2.2) | ns |
| Meat products** | 65 | 62 | 1.2 | (0.6-1.9) | ns |
| Bacon | 54 | 49 | 1.2 | (0.7-2.0) | ns |
| Nitrate treated meat | 15 | 10 | 1.6 | (0.7-3.7) | ns |
| Smoked meat | 75 | 64 | 1.5 | (0.9-2.7) | ns |
| Grill meat | 33 | 25 | 1.5 | (0.8-2.7) | ns |
| Roasted meat | 20 | 16 | 1.3 | (0.6-2.7) | ns |
| **ham, sausage, hot dog, meat paste | | | | | |
| *Milk, diary products and eggs* | | | | | |
| Milk | 80 | 78 | 1.1 | (0.6-2.0) | ns |
| Cheese | 83 | 82 | 1.0 | (0.6-1.9) | ns |
| Cream | 27 | 23 | 1.2 | (0.6-2.4) | ns |
| Yogurt | 90 | 85 | 1.1 | (0.5-2.3) | ns |
| Butter | 53 | 39 | 1.7 | (1.0-2.9) | 0.056 |
| Ice-cream | 59 | 43 | 1.8 | (1.1-3.1) | 0.031 |
| Eggs | 95 | 92 | 1.2 | (0.6-2.8) | ns |

*weekly vs. rarely
95%CI – 95% confidence interval

p=0.031) was more frequently reported by MS patients in comparison with controls. Additionally, a dose-response relationship was detected (butter- $\chi^2$=5.228, p=0.022, ice-cream- $\chi^2$=6.328, p=0.012).

All types of carbohydrates questioned, with the exception of sweets (OR=1.6, p=0.111), were noticeably more frequently consumed on a weekly basis by controls than by MS patients (Table 2).

Concerning the consumption of different kinds of vegetables (Table 3), MS cases more commonly than controls ate spinach (OR=2.1, p=0.010), beans (OR=1.7, p=0.076) and tomatoes (OR=2.0, p=0.046). The consumption of onion and garlic was also more frequently reported by MS patients. According to our results, cabbage, lettuce, pepper, potatoes, cauliflower, beet and cucumber seem to be vegetables which contribute to a lower risk of MS.

Consumption of almost all types of fruit, except for apricots, peaches and watermelon, was more frequently reported by controls (Table 4). The difference in consumption of cherries between MS cases and controls reached statistical significance (OR=0.4, 95% CI 0.2-0.9, p=0.024).

**Table 2. Consumption frequency* of different types of carbohydrates products in MS patients and controls.**

| Food items | MS (No=110) | Control (No=110) | Odds ratio | 95%CI | p |
|---|---|---|---|---|---|
| Rice | 57 | 67 | 0.7 | (0.4-1.2) | ns |
| Dough products | 73 | 75 | 0.9 | (0.5-1.6) | ns |
| Corn | 19 | 25 | 0.7 | (0.4-1.4) | ns |
| Flakes/muslli | 12 | 14 | 0.8 | (0.4-1.9) | ns |
| Bread | 104 | 106 | 0.6 | (0.2-2.4) | ns |
| Sweets | 81 | 70 | 1.6 | (0.9-2.8) | 0.100 |

*weekly vs. rarely

**Table 3. Consumption frequency of different types of vegetables in MS patients and controls.**

| Food items | MS (No=110) | Control (No=110) | Odds ratio | 95%CI | p |
|---|---|---|---|---|---|
| Cabbage* | 2 | 6 | 0.3 | (0.1-1.8) | ns |
| Spinach** | 71 | 51 | 2.1 | (1.2-3.6) | 0.010 |
| Lettuce* | 47 | 50 | 0.9 | (0.5-1.6) | ns |
| Leek** | 27 | 26 | 1.0 | (0.6-1.9) | ns |
| Pepper** | 21 | 22 | 0.9 | (0.5-1.9) | ns |
| String beans** | 74 | 71 | 1.1 | (0.6-2.0) | ns |
| Peas** | 72 | 70 | 1.1 | (0.6-1.9) | ns |
| Beans** | 84 | 72 | 1.7 | (0.9-3.1) | 0.076 |
| Potatoes* | 24 | 31 | 0.7 | (0.4-1.3) | ns |
| Tomato* | 93 | 81 | 2.0 | (1.0-4.0) | 0.046 |
| Cauliflower* | 1 | 5 | 0.2 | (0.1-1.7) | ns |
| Onion* | 21 | 27 | 1.3 | (0.6-2.8) | ns |
| Garlic* | 12 | 8 | 1.6 | (0.6-4.4) | ns |
| Beet* | 3 | 8 | 0.4 | (0.1-1.5) | ns |
| Cucumber** | 97 | 101 | 0.7 | (0.3-1.6) | ns |

*daily vs. rarely, **weekly vs. rarely, ***monthly vs. rarely

All variables that according to univariate logistic regression analysis were related to MS at a significant level of $p < 0.05$ were included into the model of multivariate logistic regression analysis. According to multivariate analysis the following factors were significantly related to MS: BMI less than 25 (OR=2.3, 95%CI 1.2-4.1, p=0.008), consumption (weekly) of beef (OR=2.0, 95%CI 1.1-3.4, p=0.017) and butter (OR=1.9, 95%CI 1.1-3.3, p=0.027), and regular consumption of cherries (OR=0.4, 95%CI 0.2-0.9, p=0.024).

## Discussion

It is well-known that investigation of the possible relationship between diet and MS is significantly burdened with difficulties related to collection of adequate dietary information. Additionally, recall bias and random misclassification, frequently present in retrospective data collection, may diminish the chances of detecting a true difference in dietary intake [4]. On the other hand, prospective studies of nutritional factors and MS are very rare [5].

Keeping in mind all limitations of retrospective approach, relation between MS and, diet and food patterns, in the population of Belgrade was investigated through case-control study, using a food frequency approach. We observed several statistically significant and possibly important associations between certain nutritional factors and MS.

In the present study, BMI less than 25 (OR=2.3, 95%CI 1.2-4.1, p=0.008), indicated significantly higher risk for developing MS, as already observed in case-control study carried out in Montreal [6]. There is no clear explanation for this association

**Table 4. Consumption frequency of different types of fruits in MS patients and controls.**

| Food items | MS (No=110) | Control (No=110) | Odds ratio | 95%CI | p |
|---|---|---|---|---|---|
| Lemon* | 8 | 12 | 0.6 | (0.2-1.8) | ns |
| Orange* | 8 | 15 | 0.5 | (0.5-1.3) | ns |
| Grapefruit* | 1 | 6 | 0.2 | (0.1-1.7) | 0.054 |
| Tangerine* | 7 | 12 | 0.6 | (0.2-1.6) | ns |
| Strawberry** | 72 | 71 | 1.0 | (0.6-1.9) | ns |
| Melon* | 12 | 17 | 0.7 | (0.3-1.6) | ns |
| Apricot* | 20 | 17 | 1.2 | (0.6-2.6) | ns |
| Peach* | 29 | 24 | 1.3 | (0.7-2.5) | ns |
| Plum** | 47 | 52 | 0.8 | (0.5-1.4) | ns |
| Raspberry** | 31 | 35 | 0.8 | (0.4-1.6) | ns |
| Blackberry*** | 57 | 59 | 0.9 | (0.5-1.6) | ns |
| Sour cherry*** | 48 | 65 | 0.8 | (0.4-1.3) | ns |
| Cherry* | 17 | 29 | 0.5 | (0.3-1.0) | 0.048 |
| Apple** | 84 | 90 | 0.7 | (0.4-1.4) | ns |
| Pear* | 15 | 17 | 0.9 | (0.4-1.9) | ns |
| Banana** | 42 | 51 | 0.7 | (0.4-1.2) | ns |
| Quince*** | 26 | 33 | 0.7 | (0.4-1.3) | ns |
| Watermelon** | 86 | 81 | 1.3 | (0.7-2.5) | ns |
| Fruit juice* | 27 | 35 | 0.7 | (0.4-1.3) | ns |

*daily vs. rarely, **weekly vs. rarely, ***monthly vs. rarely in the available literature.

MS cases significantly more frequently than controls consumed beef (OR=1.7, p=0.043), chicken (OR=2.0, p=0.045) and lamb (OR=2.1, p=0.013). Furthermore, statistically significant dose-response relationship was observed for these three items (beef-p=0.024, chicken-p=0.022, meat of the lamb-p=0.019), as well as for total meat consumption (p=0.001). Consumption of butter (OR=1.7, p=0.056) and ice-cream (OR=1.8, p=0.031) was more frequently reported by MS patients compared to controls, with a dose-response relationship (butter-p=0.022, ice-cream-p=0.012).

Relation between the increasing incidence of MS and the increasing consumption of saturated animal fats was first suggested by Swank [18]. Up to now, findings from case-control studies which examined the relationship between dietary fat and foods contributing to dietary fat and the risk of MS have been inconsistent [6, 22-25].According to the results reported by Gusev et al., a higher proportion of MS patients than controls reported a predominance of meat in their diet during childhood [25]. In a study in Gorski Kotar (Croatia), which is one of the highest risk zones for MS in Europe, the consumption of unskimmed milk, animal fat and smoked meat was more frequent in MS patients than in controls [24]. In Montreal study a higher energy intake (OR=2.0, 95%CI 1.1-3.7) and animal fat intake (OR=2.0, 95%CI 1.1-3.5) were significantly positively associated with the risk of the development of MS [6]. The results obtained from a retrospective study on dietary habits and MS in Ferrara suggested that an increased risk of MS was associated with higher consumption of butter, lard and horse meat before the age of 15 and with higher intake of eggs after the age of 15 [24]. On the contrary, in the case-control study in Western Poland, a significantly greater proportion of MS patients in comparison with controls consumed a low-fat diet below 50g of fats per week, while a proportionally smaller number of MS patients had a high-fat diet with 200-1000g of animal fats weekly [22]. In the same study, a lower number of MS patients than controls consumed cakes. Berr et al., reported that intake of meat, fat, milk, diary products and fish were unrelated to MS in a population case-control study in France [26].

In two large cohorts of women (the Nurses' Health Study and the Nurses' Health Study II), authors pointed out that intakes of dairy products, fish, red meats, poultry and processed meats were unrelated to risk of MS [7, 14, 15]. Contrary to expectations, authors found no evidence that higher intake of saturated fat or lower intake of polyunsaturated fat and fish omega-3 fatty acids was associated with increased risk of MS [7, 14, 15].

According to the findings obtained from experimental studies, there is some evidence that high exposure to milk protein butyrophilin can cause encephalitis in rats through antigenic mimicry with myelin oligodendrocyte glycoprotein [27]. The experimental data also suggest that an excess of saturated fatty acids, found mainly in animal products (meat, dairy products, processed foods etc.), could be responsible for modifying the stability of the myelin sheath, the target of the disease, and affect its' susceptibility to demyelinating agents [6, 28, 29]. Wallace et al. found the lowest ratio of production of proinflammatory (Th1) to anti-inflammatory cytokines (Th2) (as measured by the IFN-gama/IL-4 ratio) in mice fed with diets rich in n-3 or n-6 polyunsaturated fatty acids in comparison with those fed with low-fat or saturated fatty acids diets [30].

In our study, the usage of cabbage, lettuce, pepper, potatoes, cauliflower, beet and cucumber were frequently reported by subjects in control group than in MS group. The total consumption (daily vs. rarely) of green vegetables was associated with lower risk of the disease (OR=0.9, p=0.477). MS cases more commonly ate spinach (OR=2.1, p=0.010), beans (OR=1.7, p=0.076) and tomatoes (OR=2.0, p=0.046), in comparison to the controls. The consumption of almost all types of fruit, except for apricots, peaches and watermelon was more frequently reported by controls. A statistically significant difference between MS cases and controls was reached only for the consumption of cherries (OR=0.4, 95%CI 0.2-0.9, p=0.024).

The protective effect of fruit and vegetable consumption has been suggested for many chronic diseases, especially for cancer and cardiovascular diseases. In Canadian case-control study, a significant protective effect of vegetable protein, dietary and cereal fiber, vitamin C, thiamine, riboflavin, calcium and potassium in reducing risk for MS was observed, but the intake of carotene, vitamin E, fruits, and vegetables was unrelated to the risk of MS [6]. Ghadirian et al. suggested that factors such as vitamin C, vitamin E, thiamine, riboflavin, calcium and potassium, might be involved in the regulatory process of the nervous system [6]. Because of their antioxidant properties, dietary carotenoids, vitamin C and vitamin E can neutralize reactive oxygen species and therefore are suggested to have a possible role in reducing the risk of MS [31].

On the contrary, findings from a case-control study of MS conducted in France showed no associations between consumption of fruits and vegetables and the risk of MS [26]. Zhang et al. examined prospectively the association between intake of carotenoids, vitamin C and vitamin E with the risk of MS among US women [8]. Results from this study do not support the notion that a higher intake of dietary vitamins, as well as multivitamin supplements reduced the risk of MS in women [8].

In the present study, the absence of a statistically significant relationship between MS and a number of food items might be partly, explained by the fact that our study group was not large enough. Additionally, we used the frequency diet history method which had insufficiencies compared to the quantitative diet history method. In this case, the estimation of total caloric intake was impossible. Therefore, we assume that our findings necessitate further investigation of the association between MS and food patterns in other settings. These studies might assist in potentially defining the dietary factors that could contribute to the risk of developing MS.

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