Original Article

# Mediterranean diet adherence and risk of multiple sclerosis: a case-control study

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**Background and Objectives:** We conducted a hospital-based, case–control study to examine the association between Mediterranean diet (MD) and the risk of multiple sclerosis (MS) in Iran. **Methods and Study Design:** A total of 70 patients with MS and 142 controls underwent face-to-face interviews in the major neurological clinics of Tehran, Iran. Adherence to a MD was assessed using the 9-unit dietary score, to evaluate the level of conformity of the individual's diet to the Mediterranean dietary pattern. Multivariate logistic regression was used to estimate odds ratios (OR) and 95% confidence intervals (CI). **Results:** Higher consumption of fruits (OR=0.28, 95% CI: 0.12-0.63, *p*-value: 0.002) and vegetables (OR=0.23, 95% CI: 0.10-0.53, *p*-value: 0.001) were significantly associated with reduced MS risk. In both age adjusted and multivariate adjusted model, the OR of MS decreased significantly in the third as compared to the first tertile of MD score (age adjusted OR: 0.21, 95% CI: 0.06-0.67; *p*-trend: 0.01, Multivariate adjusted OR: 0.23, 95% CI: 0.06-0.89, *p*-trend: 0.04). **Conclusions:** Our study suggests that a high quality diet assessed by MD may decrease the risk of MS.

**Key Words: multiple sclerosis, Mediterranean diet, case control study**

## INTRODUCTION

Multiple sclerosis (MS) is a chronic demyelinating disorder with an unclear etiology.[1] In 2013, 2 million people were affected globally (prevalence: 29/100000) with rates differing widely in different parts of the world and among different populations.[2] Iran is a country which has previously been regarded a low-risk MS country.[3] However, Iran has recently experienced an 8.3-fold increase in the incidence of MS between 1989-2006.[3] Since genetic changes are unlikely to be responsible for this substantial rise in MS over the last few decades, environmental factors (and especially dietary factors) are dubious.[3]

Regarding dietary habits, mounting evidence in nutritional epidemiology suggest that pattern analysis is the most realistic approach to assess associations between overall diet and health or disease, instead of focusing on single dietary components.[4] The most recent pooled analyses of epidemiological studies supported strongly the hypothesis that the Mediterranean diet (MD) may play a role in preventing chronic diseases.[5] The geographic distribution of MS expressed by incidence was significantly correlated with some types of cancer which suggests the possibility of shared exposure.[6] Moreover a recent study has shown that the more closely people followed a MD, the less MRI evidence they showed of damage to small vessels in the brain.[7] So, the aim of the present study was to evaluate the association between the adherence to MD and risk of MS disease through a hospital-based case-control study. To our knowledge, this is the first study that assesses the association between MD and MS disease.

## MATERIALS AND METHODS

### *Subject*

This hospital-based case-control study was conducted from March 2011 through January 2012 in Tehran city, Iran. In this matched case-control study, 70 cases aged from 20 to 60 years, who were admitted to the major neurological clinics within referral hospitals in different regions of Tehran (11 millions inhabitants) were included -

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(participation rate=85.0%). The cases were newly registered patients that had not made changes in their dietary habits because of their disease. Cases were diagnosed with incident, neurologically confirmed MS (based on McDonald criteria[8]) within the past six months.

Private face-to-face interviews were conducted by specifically trained professional interviewers. Controls ($n$=142) were admitted to the same hospital as the cases did, for various medical conditions (for trauma and injuries, skin diseases, osteoarticular disorders, and for acute surgical conditions e.g., appendicitis and for other illnesses). Controls were frequency-matched with cases by sex and age (5-yr age groups). Two controls were excluded due to poor response to dietary questions. Furthermore, we excluded one patients from the analysis because their log scales of total energy intake was >3 from the mean, reflecting careless completion of the dietary questionnaire. Finally, the data were available for 69 cases with MS and 140 controls. All protocols and procedures of this study were approved by the Shahid Beheshti Ethics Committee.

***Dietary assessment***

Dietary habits of controls one year before the interview and cases one year before the diagnosis were obtained by trained dietitians using a valid and reproducible 147-item semi-quantitative food frequency questionnaire (FFQ).[9,10] The consumption frequency of each food items was gathered on a daily, weekly, or monthly basis; the portion sizes were then converted to grams using household measures.[11]

Adherence to a MD was assessed using the 9-Unit dietary score proposed by Trichopoulou et al,[12] to evaluate the level of conformity of the individual's diet to the Mediterranean dietary patterns. It included nine components: vegetables, legumes, fruits and nuts, cereals, fish, meat, dairy products, alcohol, and the ratio of monounsaturated fatty acid (MUFA) to saturated fatty acid (SFA). In the current study, the components of MDS were modified as follows: the fruits and nuts component was divided into two groups, the alcohol component was removed due to religious practices, the ratio of red to white meat was considered as a negative point, whole grains and refined grains were separated, and the ratio of unsaturated (the sum of monounsaturated and polyunsaturated lipids) to saturated lipids were included to allow for the low consumption of olive oil-derived monounsaturated lipids in non-Mediterranean countries. The final components of the modified MDS were: (1) vegetables, (2) fruits, (3) legumes, (4) nuts, (5) ratio of unsaturated to saturated lipids, (6) fish, (7) refined grains, (8) dairy products, (9) and ratio of red and processed meats to white meat. Sex specific median intakes of food groups were calculated. A value of 0 or 1 was assigned to each component of this score as follows: for components that are more consumed in Mediterranean countries (vegetables, legumes, fruits, nuts, fish, and a high ratio of unsaturated to saturated lipids), individuals whose consumption was below or equal to the sex-specific median were assigned a value of 0, otherwise 1 was assigned. For components traditionally less consumed in Mediterranean countries (dairy, meat and meat products, refined grains), individuals whose consumption was below the sex-specific median were assigned a value of 1, otherwise a 0 was assigned to them. High scores correspond to high adherence to the Mediterranean dietary pattern (score's range: 0-9).

Diet history of vitamin D supplement intake (before being diagnosed with MS) was asked. Since our participants did not answer the alcohol and opium consumption question due to cultural barriers, it was not included in the final analysis.

***Other measures***

Weight was measured with participants standing without shoes on digital scales (Soehnle, Germany) and was recorded to the nearest 100 g. Height was calculated while patients were in a standing position without shoes, using a non-stretch tape meter fixed to a wall and was recorded to the nearest 0.5 cm. Body mass index (BMI) was then computed by dividing weight in kilograms by square of height in meters. Moreover, smoking (yes/no), leisure-time physical activities (yes/no), parents age at the time of patient birth (years), season (spring, summer, autumn and winter) and place of the patient birth, past medical history of rubella and measles (yes/no) and MS family history (yes/no) were collected.

***Statistical analysis***

Descriptive analyses of the demographic variables and MD score are presented using median for quantitative variables due to lack of normality, and percentages for qualitative variables. To compare differences between cases and controls, Mann Whitney U test, chi-square test (Fisher's exact test) were applied for continuous and categorical variables, respectively. Logistic regression was used to assess the relationship between MD score (MDS) and MS, with individuals in the lowest tertile of MD as the reference category. $p$ for trend was calculated using logistic regression and median of MD in each tertile as the independent variable. Age, total energy intake, family history of MS and season of birth were considered as potential confounders and were included in the models. Statistical analyses were performed using Statistical Package for Social Sciences (SPSS v. 14, Chicago, IL). All reported $p$-values are two-sided.

**RESULTS**

Table 1 shows the characteristics of 69 cases with MS and 140 controls. By design, distribution of age and sex was similar in cases and controls. Fifty seven women and 12 men with MS attended in this study (with a female-to-male ratio of 4.7). The average age for MS cases was 29 years. More cases (24%) with MS than controls (13%) were born in autumn. Compared to the controls, prevalence of cases who reported MS family history was higher ($p$<0.05).

Table 2 shows the characteristics of participants across the MDS tertile categories. In cases, compared to the participants in the lowest tertile of MDS those in the highest tertile of MDS were more likely to be older (32 years vs 26 years, $p$=0.02), and less likely to be female (3.5% vs 47.4% in cases, $p$=0.01) and from Tehran (5.4% vs 56.8%, $p$=0.03). In controls, energy intake was higher in the highest tertile category of MDS compared to the lowest (2383 kcal vs 2987 kcal, $p$=0.01). In contrast, vitamin D

intake was higher in the first compared to the third tertiles of MDS ($p$=0.03).

Table 3 shows the Univariate and Multivariate adjusted Odds Ratios (ORs) and 95% Confidence Intervals (CIs) for MS risk by components of the Mediterranean dietary pattern (mutual adjustment). In multivariate model, Higher consumption of fruits (OR=0.23, 95% CI: 0.09-0.57, $p$-value: 0.01) and vegetables (OR=0.41, 95% CI: 0.17-0.99, $p$-value: 0.04) was significantly associated with reduced MS risk. In addition, this association between fruits and vegetables and MS risk was also significant in univariate model. In contrast, the risk of MS increased for high consumption of refined grain (OR=1.83, 95% CI: 1.09-3.33, $p$-value: 0.015) in univariate model.

In Table 4, OR of MS and the corresponding 95% CI across the tertiles of MDS are presented. In both age adjusted and multivariate adjusted model, the OR of MS decreased significantly in the third as compared to the first tertile of MDS (age adjusted OR: 0.21, 95% CI: 0.06-0.67; $p$-trend: 0.01, Multivariate adjusted OR: 0.23, 95% CI: 0.06-0.89, $p$-trend: 0.04).

**Table 1.** Socio-demographic characteristics of the multiple sclerosis patients and controls (n=209)*

| | Controls (n=140) n (%) | Multiple sclerosis patients (n=69) n (%) | $p$-value |
|---|---|---|---|
| Sex | | | |
| Men | 26 (18.6) | 12 (17.4) | >0.05 |
| Women | 114 (81.4) | 57 (82.6) | |
| Age (years) | | | |
| 20-29 | 71 (50.7) | 35 (50.7) | >0.05 |
| 30-39 | 53 (37.9) | 22 (31.9) | |
| ≥40 | 16 (11.4) | 12 (17.4) | |
| BMI (kg/m$^2$) | | | |
| <24.9 | 93 (66.9) | 35 (50.7) | >0.05 |
| 25-29.9 | 28 (20.1) | 26 (37.7) | |
| ≥30 | 18 (12.9) | 8 (11.6) | |
| Age of mother at birth (years) | | | |
| ≤18 | 14 (10.0) | 11 (15.9) | >0.05 |
| 18-29.9 | 76 (54.3) | 34 (49.3) | |
| 30-39.9 | 40 (28.6) | 21 (30.4) | |
| ≥40 | 10 ( 7.1) | 3 ( 4.3) | |
| Age of father at birth (years) | | | |
| 29-29.9 | 41 (29.3) | 23 (33.3) | >0.05 |
| 30-39.9 | 64 (45.7) | 31 (44.9) | |
| ≥40 | 35 (25.0) | 15 (21.7) | |
| Vitamin D supplementation before diagnosis† | | | |
| No | 110 (78.6) | 56 (81.2) | >0.05 |
| Yes | 30 (21.4) | 13 (18.8) | |
| Smoking‡ | | | |
| No | 130 (92.2) | 65 (94.2) | >0.05 |
| Physical activity§ | | | |
| No | 78 (55.7) | 43 (62.3) | >0.05 |
| Yes | 62(44.3) | 26 (37.7) | |
| Hometown | | | |
| Tehran (capital) | 69 (49.3) | 36 (52.2) | >0.05 |
| Other | 71 (50.7) | 33 (47.8) | |
| Season of birth | | | |
| Spring | 41 (30.4) | 27 (39.1) | <0.05 |
| Summer | 50 (37.0) | 12 (17.4) | |
| Autumn | 18 (13.3) | 17 (24.6) | |
| Winter | 26 (19.3) | 13 (18.8) | |
| History of Rubella | | | |
| No | 77 (55.0) | 38 (55.1) | >0.05 |
| Yes | 63 (45.0) | 31 (44.9) | |
| Family history of multiple sclerosis¶ | | | |
| No | 140 (100) | 59 (85.5) | <0.001 |
| Yes | 0 ( 0.0) | 10 (14.5) | |
| Type of fat used | | | |
| Vegetable oil | 75 (53.6) | 13 (18.8) | <0.001 |
| Fat (Ghee) | 14 (10.0) | 25 (36.2) | |
| Mixed | 51 (36.4) | 31 (44.9) | |

*$p$-values are derived using chi-squared analysis.
†Current vitamin D supplementation or former vitamin D consumption.
‡Yes means current smokers, No means never or former smokers.
§Physical activity means leisure time physical activity.
¶Family history refers to both first and second relatives.

**Table 2.** Characteristics of participants across the Mediterranean Dietary Pattern Score (MDS) tertile categories in a case-control study of multiple sclerosis in Iran[†]

| | Cases MDS tertiles | | | *p* trend[**] | controls MDS tertiles | | | *p* trend[**] |
|---|---|---|---|---|---|---|---|---|
| | 1 | 2 | 3 | | 1 | 2 | 3 | |
| n (%) | 31 (44.9) | 34 (49.3) | 4 (5.8) | | 49 (35.0) | 62 (44.3) | 29 (20.7) | |
| Women, n (%) | 27 (47.4) | 28 (49.1) | 2 (3.5) | 0.01 | 38 (33.3) | 50 (43.9) | 26 (22.8) | 0.17 |
| Age, yr | 26.0 (9.0) | 32.0 (17.0) | 32.0 (12.5) | 0.02 | 28.0 (11.0) | 27.5 (12.0) | 34 (14.5) | 0.12 |
| BMI, kg/m$^2$ | 23.5 (5.4) | 25.2 (4.2) | 21.8 (7.1) | 0.49 | 22.8 (4.5) | 23.8 (5.0) | 23.4 (7.8) | 0.28 |
| Energy, kcal | 2214 (841) | 2349 (672) | 2550 (5937) | 0.91 | 2087 (706) | 2352 (1155) | 2383.0 (1482.5) | 0.01 |
| Smoking (yes), n (%) | 2 (50) | 1 (25) | 1 (25) | 0.44 | 7 (70) | 1 (10) | 2 (20) | 0.12 |
| Vitamin D supplement (yes), n (%) | 3 (23.1) | 9 (69.2) | 1 (7.7) | 0.08 | 8 (26.7) | 17 (56.7) | 5 (16.7) | 0.93 |
| Place of birth | | | | | | | | |
| Tehran | 21 (56.8) | 14 (37.8) | 2 (5.4) | 0.03 | 25 (36.2) | 30 (43.5) | 14 (20.3) | 0.79 |
| Physical activity (yes), n (%) | 12 (46.2) | 12 (46.2) | 2 (7.7) | 0.75 | 21 (33.9) | 22 (35.5) | 19 (30.6) | 0.07 |
| Season of birth | | | | | | | | |
| Winter | 9 (64.3) | 4 (28.6) | 1 (7.1) | 0.24 | 9 (34.6) | 11 (42.3) | 6 (23.1) | 0.83 |
| Vitamin D intake (μg) | 1.1 (2.1) | 0.9 (2.1) | 0.9 (0.7) | 0.50 | 1.1 (2.1) | 0.9 (2.1) | 0.7 (2.2) | 0.02 |

[†]Data are presented as n (%) or median (IQ)
[**]The *p* value for trend was determined using the linear regression coefficient for MDS scores for continuous variables and the logistic regression coefficient for the dichotomous variables.

**Table 3**. Univariate and multivariate adjusted odds ratios (ORs) and 95% confidence intervals (CIs) for multiple sclerosis risk by components of the Mediterranean Dietary Pattern in a case-control study in Iran[†]

| | Univariate MS risk | | | Multivariate adjusted MS risk[‡] | | |
|---|---|---|---|---|---|---|
| | OR | 95% CI | *p* value | OR | 95% CI | *p* value |
| Vegetables | 0.25 | 0.13-0.50 | 0.01 | 0.41 | 0.17-0.99 | 0.04 |
| Fruits | 0.28 | 0.14-0.54 | 0.01 | 0.23 | 0.09-0.57 | 0.01 |
| Nuts | 0.70 | 0.39-1.25 | 0.23 | 0.92 | 0.42-2.01 | 0.84 |
| Legumes | 0.74 | 0.41-1.33 | 0.32 | 1.02 | 0.45-2.32 | 0.95 |
| Fish | 0.86 | 0.48-1.52 | 0.61 | 0.85 | 0.41-1.77 | 0.67 |
| Unsaturated/saturated lipids | 1.54 | 0.84-2.73 | 0.16 | 1.74 | 0.78-3.90 | 0.17 |
| High fat dairy product | 0.65 | 0.36-1.18 | 0.16 | 1.33 | 0.58-3.07 | 0.49 |
| Red meat/white meat | 0.95 | 0.45-1.73 | 0.65 | 1.10 | 0.85-3.70 | 0.85 |
| Refined grain | 1.83 | 1.09-3.33 | 0.04 | 2.07 | 0.83-5.14 | 0.11 |

[†]Reference (median)
[‡]Values are mutually adjusted for age, multiple sclerosis family history, season birth and energy intake and other variables in the table.

**Table 4.** Multivariate adjusted odds ratios for multiple sclerosis risk across the Mediterranean Dietary Score (MDS) tertile categories in a case-control study of multiple sclerosis in Iran

| MDS | Controls (n) | Cases (n) | Age adjusted OR | 95% CI | *p*-trend | Multivariate adjusted OR* | 95% CI | *p*-trend |
|---|---|---|---|---|---|---|---|---|
| Tertile1 | 49 | 31 | 1 | | 0.017 | 1 | | 0.04 |
| Tertile2 | 62 | 34 | 0.85 | 0.46-1.5 | | 1.07 | 0.53-2.17 | |
| Tertile3 | 29 | 4 | 0.21 | 0.06-0.67 | | 0.23 | 0.06-0.89 | |

*Age, multiple sclerosis family history, season birth and energy intake were also included in the regression models as covariates.

## DISUSSION

We assessed the association between MD and MS in a hospital-based case-control study. Finding of current study revealed that adherence to MD was associated with reduced risk of MS. Besides, the inverse relationship between vegetables and fruits consumption and MS risk and the positive association between refined grains and risk of MS were also observed in this study.

To our knowledge, this was the first study to assess MD score in relation to risk of MS. This research provided further evidence that the MD presents a healthy eating pattern associated with a reduced risk of MS. The association of MS risk with dietary patterns in Iran was reported in a recent study by Jahromi SR et al,[13] which showed inverse relationship between traditional (high in low-fat dairy products, red meat, vegetable oil, onion, whole grain, soy, refined grains, organ meats, coffee, and legumes), lacto vegetarian (high in nuts, fruits, French fries, coffee, sweets and desserts, vegetables, and high-fat dairy products) and vegetarian dietary patterns and MS risk. Furthermore participant with high animal fat dietary pattern scores had higher risk of MS,[13] which could explain the inverse relationship of MD with MS risk. Studies on the association of fruit and vegetable with MS risk are contradicting. Zhang SM et al reported that after adjustments for age, latitude of birthplace, smoking, and total energy intake, no significant association between fruits and vegetables and risk of MS was found.[14] However in another study in Serbia, the protective effect of fruits and vegetables consumption was suggested.[15] In a Canadian case-control study, significant negative associations were observed among women for intakes of fruit juices and risk of MS.[16] A study in the town of Čabar, Croatia (a high risk area for MS) has shown that the prevalence of daily consumption of fresh fruits and vegetables was lower among MS cases (*p*-value=0.009).[17] White matter has a low concentration of antioxidant enzymatic activities and is therefore highly sensitive to damage from exposure to reactive oxygen species.[14] Fruits and vegetables provide important compounds such as protease inhibitors, plant sterols phenols, dithioltion, indoles, and isoflavones that their beneficial effects in preventing diseases such as cancer has been proven.[18,19] Vitamin E and vitamin C, for their antioxidant properties, can defeat free radicals and prevent lipid peroxidation in brain white matter.[20]

Diet with high animal fat or saturated fat and low in polyunsaturated fat or fish omega-3 fatty acids might increase the risk of MS.[21] In a Canadian study, 33 g/day of animal fat caused twofold increase in risk of MS.[16] The mechanisms include increased consequent ischemic damage with platelet aggregation in the blood-brain barrier,[22] increased susceptibility to demyelinization to causes effects in the fatty acid composition of the myelin sheath,[23] and change formation of prostanoids, that affected alteration of immune responses.[23]

High vitamin D levels have been related with a decreased risk of MS.[3] Auto-reactive T cells may be developed in the absence of vitamin D.[13] The most important source of dietary vitamin D is fatty fish. Recent Swedish study (1879 incident cases of MS and 4135 controls) has detected this association between vitamin D and MS (adjusted OR 0.82; 95% CI 0.68-0.98).[24] This is in contradiction to our results. Fish intake is strongly related to a Nordic dietary tradition[24] but in Iran the fish consumption is still far below that recommended by food and nutrition authorities.[25] Thus when the variation in diet is insufficient the null association could be interpretable.[26]

We could not find any association between nuts and MS. However in a recent study,[13] an inverse relationship was noted between MS risk and lacto-vegetarian pattern that was loaded heavily on nuts consumption. Resveratrol is an anti-fungal compound found in nuts. Studies suggest that resveratrol might be an effective therapeutic agent in neurodegenerative diseases initiated or maintained by inflammatory processes.[27]

In the current study, fruits, vegetables and whole grains content of MD were good sources of fiber. The fiber role in preventing chronic diseases such as MS is based on their bioactive substances with antioxidant and anti-carcinogenic properties, especially those in the bran and germ (vitamins, minerals, trace elements, carotenoids, polyphones and alkylresorcinols). Whole-grain wheat is also a rich source of methyl donors and lipotropes (folates, methionine, betaine, choline and inositol) that may be involved in cardiovascular and hepatic protection, and lipid metabolism in brain white material.[28]

This study has several limitations. Firstly, like other case-control studies, recall bias and selection bias were inevitable. In case-control studies, there is the possibility that cases may recall their diets differently after MS diagnosis. However, our participants had little knowledge about the role of diet and nutrients in the MS risk, which should have reduced the possibility of recall bias. Furthermore, using hospital controls and administering validated FFQs by trained interviewers in a hospital setting might have further reduced the possibility of recall bias and improved comparability of information of cases and controls.[29] Regarding the selection bias, high response rate (85.0%) in this study reduced the risk for selective participation according to the lifestyle practices (such as diet). Secondly, because dietary intake was assessed

through a self-administered food-frequency questionnaire, measurement errors were inevitable. This might led to underestimation of associations.[30] In the present study, a validated FFQ was used which provided subjects with the option of answering in terms of day, week or month. In theory, an open-ended frequency response format might maintain further precision in reporting as the frequency of use is truly a continuous rather than a categorical variable.[26] Moreover, we asked incident MS patients diagnosed within 6 month of the interview to recall their diets from 1 year before diagnosis to take into account seasonal variations so that responses should not be dependent on the time of the year and be representative of habitual long-term intake. Furthermore cases, whose disease diagnosis was less than six months (incident case), were included in this study; therefore, the chance of diet modification was not high.

In conclusion, our results from this case-control study support the hypothesis that Mediterranean dietary pattern is associated with a reduced risk of MS. Future studies, including dietary intervention studies, will be needed to prove the effects of the Mediterranean dietary pattern on pathology of disease and on the prevention of new cases of disease.

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**AUTHOR DISCLOSURES**

None of the authors had any personal or financial conflicts of interest.

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Original Article

# Mediterranean diet adherence and risk of multiple sclerosis: a case-control study

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# 地中海式饮食依从性和多发性硬化症的风险：一项病例-对照研究

**背景与目的：**我们开展了以医院为基础的病例-对照研究，检查伊朗地区地中海式饮食（MD）和多发性硬化症（MS）之间的关系。**方法与研究设计：**对来自伊朗德黑兰主要神经科诊所的 70 例多发性硬化症患者和 142 例对照进行了面对面访谈，采用 9 级评分评估 MD 依从性，分析个人饮食水平与地中海式饮食模式间的遵从性程度。使用多变量 logistic 回归模型计算 OR 及 95%置信区间(CI)。**结果：**较高的水果和（OR 0.28，95% CI：0.12-0.63，*p*：0.002）和蔬菜消费量（OR 0.23，95% CI：0.10-0.53，*p*：0.001）与低 MS 风险显著相关。在校正年龄和校正多变量两个模型中，与 MD 得分第一分位数组相比，第三分位数 MS 的 OR 显著降低（年龄调整的 OR：0.21，95% CI：0.06-0.67，趋势 *p*：0.01；多变量调整的 OR：0.23，95% CI：0.06-0.89，趋势 *p*：0.04）。**结论：**该研究表明高质量 MD 饮食能降低 MS 的风险。

**关键词：多发性硬化症、地中海式饮食、病例对照研究**