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# Effect of dietary advice and n-3 supplementation in newly diagnosed MS patients

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*Objective* – To investigate whether supplementation with fish oil given together with dietary advice and vitamin supplementation influenced the clinical outcome in newly diagnosed multiple sclerosis (MS) patients. *Material and methods* – Sixteen consecutive, newly diagnosed patients with multiple sclerosis were recruited to an open intervention study. They were given dietary advice and supplemented with 0.9 g/day of long-chain marine fatty acids and vitamins. The patients were followed for 2 years with respect to dietary habits, blood parameters and neurological assessment including exacerbation rate. *Results* – There was a significant reduction in the mean annual exacerbation rate and the mean Expanded Disability Status Scale (EDSS) as compared to pre-study values. The plasma total phospholipid n-3 fatty acids increased and n-6 fatty acids decreased significantly. *Conclusions* – The results suggest that fish oil supplementation given together with vitamins and dietary advice can improve clinical outcome in patients with newly diagnosed MS.

**I. Nordvik[1], K.-M. Myhr[1], H. Nyland[1], K. S. Bjerve[2]**

[1]Department of Neurology, Haukeland University Hospital, 5016 Bergen and [2]Department of Clinical Chemistry, Trondheim University Hospital, N-7006 Trondheim, Norway

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Inger Nordvik, Department of Neurology, Haukeland University Hospital, N-5016 Haukeland, Norway

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Multiple sclerosis (MS) is an immunologically mediated disease in genetically susceptible individuals in response to environmental factors. Based on epidemiological dietary studies, saturated fat was suggested as a risk factor in MS already in the early 1950s (1). This was later supported by a Norwegian study, which showed that inland farming communities with high consumption of animal fat and dairy products had higher MS incidence rates than the coastal communities where the consumption of fish was high (2).

Subsequent epidemiological studies showed that total fat consumption, animal fat and dairy products were associated with MS (3–6), while fish, fruits and vegetables have shown a negative correlation (7, 8). Dietary intake of saturated and unsaturated fat is often inversely correlated, and therefore it was suggested in 1956 that a shortage of the essential fatty acids might be a risk factor in MS (9). Since n-3 fatty acids were not considered essential at that time, subsequent studies focused on the possible role of n-6 fatty acids. Reduced levels of linoleic (18:2n-6) and arachidonic acid (20:4n-6) were found in brain, serum, platelets and red cell lipids in MS patients (10–13), but the results have been conflicting (14, 15). More recent analysis of adipose tissue biopsies showed no difference in the concentration of linoleic acid between MS patients and controls. In contrast, the concentration of docosahexaenoic acid (22:6n-3, DHA) was highly significantly reduced in the patients (16).

Results from three randomized controlled double blind trials (17–19) using linoleic acid versus oleic acid supplementation have been inconclusive. However, a reanalysis (20) combining data from these three intervention trials, including only those pat-

ients with acute remitting disease, showed a reduction in both frequency and severity of relapses as well as a significant decrease in disability amongst this subgroup of early cases. The effect of dietary supplementation with γ-linolenic acid (18:3n-6, evening primrose oil) was also investigated, but no benefit was revealed (21).

Finally, intervention trials emphasizing low saturated fat intake and increased intake of essential fatty acids have tended to show better results in patients with a high intake of n-3 fatty acids (22–26).

In a pilot study we found that newly diagnosed MS patients had lower plasma total lipid concentrations of eicosapentaenoic acid (20:5n-3, EPA) and DHA, and lower ratio of total n-3/n-6 fatty acids compared to controls (27). The intake of vitamin C was also significantly reduced. It is well known that DHA and other long chain n-3 fatty acids are found in the highest concentrations in retinal cells and in synaptosomes and synaptic vesicles of brain cells (28). On this background, we have evaluated the effect of dietary advice supplemented with fish oil and vitamins on the relapse rate and disease progression in newly diagnosed MS patients.

## Patients and methods

### Study design

This study was an open, uncontrolled intervention trial of fish oil and vitamin supplementation in combination with dietary advice in relapsing–remitting multiple sclerosis (RRMS).

The patients were supplemented once daily at breakfast with 1 spoon (5 ml) of fish oil (Møllers Tran®, Peter Møller AS, Oslo, Norway) containing 0.4 g EPA, 0.5 g DHA, 1.0 mg of vitamin A, 10 μg of vitamin D and 5.5 mg vitamin E. In addition they received a vitamin B-complex (containing 2.25 mg of thiamin, 2.6 mg of riboflavin, 30 mg of niacin, 7 mg of pantothenic acid, 3 mg of pyridoxine, 150 μg of biotin, 100 μg of folic acid, 6 μg of cobalamin) and 200 mg of vitamin C (acid neutral).

The patients were advised to reduce the intake of saturated fat from meat and dairy products, eat fish for dinner 3–4 times weekly, increase the intake of vegetables, eat 1–2 fresh fruits daily, use whole grain bread products, reduce the intake of sugar and sugar containing food and beverages, and reduce the intake of coffee or tea to a couple of cups daily. They were also advised to avoid food items, to which they were allergic or intolerant, and to stop smoking and minimize alcohol consumption. The patients were given the opportunity to contact the nutritionist whenever they had questions regarding the diet.

The objectives of the study were to evaluate the efficacy of the intervention on clinical disease activity as measured by annual exacerbation rate and progression of disease as measured by the Extended Disability Status Scale (EDSS) (29). We also evaluated compliance using a dietary frequency questionnaire and blood analysis.

### Patients

The patients selected for the study were diagnosed within the 12 last months at the Department of Neurology, Haukeland University Hospital, Bergen, Norway, and had a disease duration ≤3 years. Patients should have clinical or laboratory supported definite relapsing–remitting multiple sclerosis (RRMS). The patients should have had stable neurological status the month before inclusion and should not have taken cod liver oil or other fish oil supplements or high doses of vitamin C (>100 mg/day) during the last 3 months before inclusion. Other exclusion criteria were previous or ongoing interferon treatment, immunosuppressive treatment during the previous year or steroid treatment the month before inclusion. Patients were also excluded if they had changed their dietary habits after onset of the disease. When clinically necessary, exacerbations were to be treated with corticosteroids according to standard protocols.

### Dietary assessments

The patients were seen by the nutritionist at inclusion and again after 1 and 2 years. A dietary frequency form was filled in by the patients prior to each visit. This form was used to calculate daily or weekly intakes of nutrients of particular interest for this study. To evaluate whether their diet was in accordance with dietary advises, a self-reporting 4-day weighed dietary record was performed at the end of each year. In addition smoking habits were recorded.

### Clinical assessments

Clinical assessment including EDSS (29) was performed at screening, baseline, every 12 months and at any exacerbations. An exacerbation was defined as the appearance of new symptoms from the nervous system or worsening of pre-existing ones lasting for at least 24 h in the absence of fever in a patient who had been neurologically stable or improving for the previous 30 days. The symptoms should be accompanied by objective change on neurological examination, worsening of 0.5 points on the EDSS or worsening by 1.0 point in two of the Functional Systems (FS) or 2.0 point in one of the FS. Annual exacerbation rates were

Table 1. Annual exacerbation rate and disability measured by EDSS in patients with relapsing–remitting multiple sclerosis treated with diet intervention

| | |
|---|---|
| Annual exacerbation rate | |
| Pre-study | 1.39 (0.17) |
| During year 1 | 0.06[a] (0.06) |
| During year 2 | 0.06[a] (0.06) |
| Expanded Disability Status Scale (EDSS) | |
| Pre-study | 2.16 (0.19) |
| After 2 years | 1.63[b] (0.20) |

Figures are given as mean (SEM).
[a] Compared to pre-study exacerbation rate: $P=0.001$ (Wilcoxon rank test);
[b] compared to EDSS at baseline: $P=0.005$ (Paired $t$-test).

based on the number of exacerbations during year 1 and 2. The pre-study exacerbation rate was defined as the total number of exacerbations (onset episode included) divided by duration of the disease before inclusion.

### Blood samples

Fasting venous blood samples were taken prior to start of the trial, and after 1 and 2 years. Routine blood analyses were performed at the Department of Clinical Biochemistry, Haukeland University Hospital, using standard methods. The concentration of total plasma phospholipid fatty acids was measured according to the method described by Bønaa et al. (30). Serum retinol, tocopherols and carotenes were measured by HPLC as described by Nierenberg et al. (31). Plasma ascorbic acid was analyzed by HPLC using electrochemical detection (32).

### Statistical analysis

The data are expressed as means and standard error of mean. A $t$-test was used to test for differences in plasma phospholipids, serum lipids, vitamins and minerals. The dietary intake of different food items and beverages showed a skewed distribution and the Wilcoxon rank-sum test was employed. $P$-values below 0.05 were considered to be statistically significant.

## Results

Sixteen of 35 screened patients (4 men and 12 women) fulfilled the inclusion criteria. The mean age at inclusion was 32.0 years (range 22–37 years), and the mean duration of disease was 1.6 years (range 1–3 years). The mean pre-study annual exacerbation rate was 1.39 ($\pm$0.17) and the mean EDSS score at inclusion was 2.16 ($\pm$0.19). (Table 1).

The dietary intervention significantly increased the intake of fish (Table 2), including both fat and lean fish. At the same time, there was a reduced intake of food items containing saturated fat and sugar. The number of smokers decreased from 7 to 2 during the study.

Table 2. Dietary intake of selected food items and beverages in patients with relapsing–remitting multiple sclerosis treated with diet intervention

| Food | At baseline | | After 1 year | | After 2 years | |
|---|---|---|---|---|---|---|
| | Mean | SEM | Mean | SEM | Mean | SEM |
| Breakfast and lunch | | | | | | |
| Bread (s/d) | 5.5 | 0.8 | 4.6 | 0.5 | 4.9 | 0.4 |
| Butter on bread (g/d) | 23.9 | 5.6 | 15.6 | 3.1 | 19.1 | 3.4 |
| Weekly number of open-faced sandwiches with: | | | | | | |
| Fish | 2.8 | 1.0 | 4.8 | 1.4 | 5.8[a] | 1.4 |
| Ham | 7.8 | 1.5 | 4.1 | 0.8 | 6.1 | 1.0 |
| Liver paté | 4.8 | 1.1 | 2.8 | 0.8 | 2.2 | 0.7 |
| Cheese (whole fat) | 5.9 | 2.9 | 3.2 | 1.1 | 3.0 | 1.3 |
| Salads with mayonnaise | 3.8 | 1.4 | 0.6[a] | 0.2 | 0.9[a] | 0.4 |
| Egg/week | 1.5 | 0.3 | 1.3 | 0.3 | 1.5 | 0.2 |
| Yogurt (whole fat)/day | 1.0 | 0.5 | 0.2 | 0.1 | 0.2[a] | 0.2 |
| Dinner | | | | | | |
| Fish dinner/week | 1.8 | 0.3 | 2.9[b] | 0.3 | 3.1[b] | 0.3 |
| Meat dinner/week | 3.8 | 0.3 | 3.2 | 0.3 | 2.8[b] | 0.3 |
| Potatoes with dinner/week | 4.1 | 0.5 | 4.6 | 0.5 | 4.8 | 0.5 |
| Vegetables with dinner/week | 4.1 | 0.5 | 5.0[a] | 0.5 | 5.8[b] | 0.3 |
| Beverages | | | | | | |
| Milk (whole fat) (gl/d) | 0.03 | 0.03 | 0.03 | 0.03 | 0.03 | 0.03 |
| Milk (medium fat) (gl/d) | 1.2 | 0.3 | 1.3 | 0.4 | 1.3 | 0.4 |
| Milk (low fat) (gl/d) | 0.7 | 0.4 | 0.8 | 0.3 | 0.7 | 0.3 |
| Juice (gl/w) | 2.6 | 0.9 | 4.1 | 0.8 | 2.4 | 0.7 |
| Coffee (c/d) | 2.8 | 0.7 | 2.3 | 0.5 | 1.8 | 0.4 |
| Soft drinks (gl/w) | 1.9 | 0.6 | 0.3[a] | 0.3 | 0.5 | 0.3 |

s/d = slices per day; g/d = grams per day; gl/d = glasses per day; gl/w = glasses per week; c/d = cups of 1.5 deciliters per day.
[a] $P<0.05$; [b] $P<0.01$.

Table 3. Concentration of plasma total phospholipid fatty acids in patients with relapsing–remitting multiple sclerosis treated with diet intervention

| | At baseline | | After 1 year | | After 2 years | |
|---|---|---|---|---|---|---|
| | Mean | SEM | Mean | SEM | Mean | SEM |
| Relative concentrations (weight percent) | | | | | | |
| 14:0 | 0.36 | 0.03 | 0.41 | 0.04 | 0.23[a] | 0.02 |
| 16:0 | 25.50 | 0.35 | 25.50 | 0.34 | 26.88[a] | 0.21 |
| 18:0 | 13.43 | 0.25 | 12.92[b] | 0.31 | 13.47 | 0.18 |
| 20:0 | 0.71 | 0.02 | 0.35[a] | 0.03 | 0.14[a] | 0.02 |
| 22:0 | 2.55 | 0.12 | 1.05[a] | 0.09 | 0.46[a] | 0.09 |
| 24:0 | 1.31 | 0.08 | 0.69[a] | 0.05 | 0.23[a] | 0.06 |
| 16:1 | 0.34 | 0.04 | 0.36 | 0.02 | 0.30 | 0.03 |
| 18:1 | 9.24 | 0.39 | 8.00 | 0.22 | 7.44[b] | 0.20 |
| 20:1 | 0.16 | 0.02 | 0.49[a] | 0.06 | 0.47[b] | 0.07 |
| 22:1 | 0.05 | 0.02 | 0.13[b] | 0.02 | 0.04 | 0.02 |
| 24:1 | 2.54 | 0.16 | 1.70[a] | 0.12 | 0.66[a] | 0.12 |
| 20:3n-9 | 0.08 | 0.02 | 0.05 | 0.01 | 0.05 | 0.03 |
| 18:2n-6 | 23.39 | 0.84 | 20.27[c] | 0.70 | 21.28 | 0.94 |
| 20:2n-6 | 0.55 | 0.04 | 0.34[a] | 0.02 | 0.27[a] | 0.02 |
| 20:3n-6 | 2.73 | 0.18 | 2.09[c] | 0.17 | 1.81[a] | 0.14 |
| 20:4n-6 | 8.55 | 0.39 | 7.92 | 0.32 | 7.96 | 0.42 |
| 22:4n-6 | 0.44 | 0.08 | 0.17[c] | 0.02 | 0.11[a] | 0.02 |
| 22:5n-6 | 0.12 | 0.02 | 0.07[b] | 0.01 | 0.00[a] | 0.04 |
| 18:3n-3 | 0.20 | 0.01 | 0.16 | 0.01 | 0.14[b] | 0.02 |
| 20:5n-3 | 1.43 | 0.19 | 5.34[a] | 0.66 | 5.41[a] | 0.67 |
| 22:5n-3 | 1.38 | 0.05 | 1.49 | 0.06 | 1.44 | 0.05 |
| 22:6n-3 | 5.94 | 0.38 | 10.45[a] | 0.44 | 11.19[a] | 0.69 |
| Total MUFA | 11.32 | 0.39 | 10.68 | 0.24 | 8.91[a] | 0.19 |
| Total SAT | 43.87 | 0.30 | 40.91[a] | 0.25 | 41.42[a] | 0.28 |
| Total n-3 | 8.95 | 0.53 | 17.49[a] | 0.99 | 18.19[a] | 1.28 |
| Total n-6 | 35.77 | 0.61 | 30.86[a] | 0.81 | 31.43[c] | 1.16 |
| Absolute concentrations (mg/l) | | | | | | |
| Total MUFA | 136.2 | 9.2 | 121.0 | 6.7 | 95.4[a] | 6.4 |
| Total SAT | 525.0 | 28.0 | 463.5[b] | 22.4 | 441.8[c] | 26.2 |
| Total (n-3) | 107.8 | 8.3 | 199.0[a] | 14.8 | 197.2[a] | 19.6 |
| Total (n-6) | 426.1 | 21.3 | 348.5[c] | 17.9 | 332.5[c] | 19.1 |

MUFA = monounsaturated fatty acids (includes the sum of 16:1, 18:1, 20:1, 22:1, 24:1). SAT = saturated acids (includes the sum of 14:0, 16:0, 18:0, 20:0, 22:0, 24:0).
[a] $P<0.001$; [b] $P<0.05$; [c] $P<0.01$.

The plasma phospholipids concentration of 20:5n-3, 22:6n-3 as well as total n-3 fatty acids increased significantly ($P<0.001$) during the first and second year. At the same time all n-6 fatty acids, with the exception of arachidonic acid, were significantly reduced (Table 3). These changes were apparently irrespective of analyzing the phospholipid fatty acid concentrations in relative terms (weight percent) or in absolute terms (mg/l, Table 3). The changes are typical for an increased intake of fish and of cod liver oil, and confirm that the dietary advice to increase fish intake as well taking cod liver oil was followed throughout the study period.

The serum concentration of retinol decreased after the first and second year compared to baseline, while β-carotene and α-tocopherols were unchanged (Table 4). Vitamin $B_{12}$ was significantly increased after 2 years. Both $Zn^{2+}$ and $Mg^{2+}$ showed a statistically significant, but clinically insignificant decrease during the study period.

Only 2 patients experienced exacerbations (1 each), giving a mean annual exacerbation rate of 0.06 ($P<0.001$ compared to pre-study rate). The mean EDSS score declined to 1.62 after the second year ($P<0.01$ as compared to pre-study score). Eleven patients improved, 4 patients were unchanged and 1 patient worsened during the study.

## Discussion

The dietary habits were changed towards a reduction in food items contributing to saturated fat, n-6 fatty acids and sugar, and an increase in food items containing long-chain n-3 fatty acids as well as vegetables. The change in fatty acid intake was reflected in a significant increase in n-3 fatty acids and a reduction in n-6 fatty acids and total saturated fatty acids in the plasma phospholipids.

We observed a significant reduction in the exacerbation rate during the study period. This

Table 4. Concentration of selected blood parameters in patients with relapsing–remitting multiple sclerosis treated with diet intervention

| | At baseline | | After 1 year | | After 2 years | |
|---|---|---|---|---|---|---|
| | Mean | SEM | Mean | SEM | Mean | SEM |
| P-Retinol (μmol/l) | 2.0 | 0.1 | 1.7[a] | 0.1 | 1.9[b] | 0.0 |
| P-β-Carotene (μmol/l) | 0.3 | 0.0 | 0.4 | 0.0 | 0.4 | 0.1 |
| S-Vitamin $B_{12}$ (pmol/l) | 360.0 | 35.4 | 447.7 | 49.9 | 423.4 | 42.0[a] |
| E-Folate (mmol/l) | 478.9 | 30.0 | 497.1 | 24.7 | 512.9 | 34.7 |
| P-Vitamin C (μg/ml) | 10.4 | 0.9 | 11.3 | 0.8 | 12.5[a] | 0.6 |
| P-α-Tocopherol (μmol/l) | 19.3 | 1.4 | 20.3 | 1.4 | 16.7 | 1.5 |
| B-Hemoglobin (g/dl) | 14.1 | 0.3 | 13.7[b] | 0.3 | 13.7[a] | 0.4 |
| S-Ferritin (μg/l) | 49.5 | 10.8 | 56.4 | 9.8 | 54.1 | 13.6 |
| S-Glucose (mmol/l) | 5.0 | 0.2 | 4.8 | 0.2 | 4.8 | 0.2 |
| S-Triglycerides (mmol/l) | 1.1 | 0.1 | 1.1 | 0.2 | 0.9 | 0.1 |
| S-Cholesterol (mmol/l) | 5.5 | 0.4 | 5.5 | 0.3 | 5.2 | 0.3 |
| S-HDL (mmol/l) | 1.4 | 0.1 | 1.4 | 0.1 | 1.4 | 0.1 |
| S-LDL (mmol/l) | 3.6 | 0.3 | 3.6 | 0.2 | 3.4 | 0.3 |
| $Cu^{2+}$ (μmol/l) | 15.7 | 0.5 | 20.8[c] | 2.4 | 18.9 | 1.6 |
| $Mg^{2+}$ (μmol/l) | 0.9 | 0.0 | 0.8[c] | 0.0 | 0.8[b] | 0.0 |
| $Zn^{2+}$ (μmol/l) | 14.5 | 0.4 | 13.9 | 0.5 | 13.0[a] | 0.5 |

[a] $P<0.05$; [b] $P<0.01$; [c] $P=0.001$. Table 4. Annual exacerbation rate and disability measured by EDSS in patients with relapsing–remitting multiple sclerosis.

reduction was still significant after exclusion of the onset-attack from the pre-study exacerbation rate (data not shown). Further, the magnitude of the reduction was higher than expected from natural history studies (33–35). We also observed a significant reduction in EDSS. Although all patients were neurologically stable during the month before inclusion, it is still possible that some patients were in a plateau phase of a remission at inclusion and therefore experienced a spontaneous improvement. However, this is probably not true for the whole group. As many as 11 patients (69%) improved in EDSS scores during the observation period which is higher than found in a recent immunoglobulin treatment study where 31% of the patients in the treatment group showed improved EDSS scores (36). Some of this difference may be related to a lower EDSS score (2.2 versus 3.3) and a shorter pre-study disease duration (1.6 versus 6.8 years) at inclusion time in the present study. There is also some limitation related to the design of the present study, since it is open and uncontrolled. However, we still think the results indicate a beneficial effect of the intervention.

Dietary studies with increased n-3 fatty acid intake in the form of cod liver oil, fish oil and/or increased fish intake (22–26), have all shown a trend towards reduced rate and severity of exacerbations, but EDSS scores however, were not improved in these studies. In contrast to our study, these previous intervention trials advised the patients also to increase their intake of n-6 fatty acids, which may reduce the effect of n-3 therapy. The western diet tends to supply an abundance of n-6 fatty acids. Based on this knowledge, combined with the results from our previous pilot study (27), we did not encourage increased intake of n-6 fatty acids, and the patients were recommended to substitute vegetable oils for olive oil.

The n-3 fatty acids may be beneficial in MS through immune modulation. Due to the competition between n-3 and n-6 fatty acids, an increased intake of n-3 fatty acid will reduce the synthesis of pro-inflammatory leukotriene $B_4$ and prostaglandin $E_2$ (37, 38) and concomitantly increase the synthesis of the less inflammatory leukotriene $B_5$ and prostaglandin $E_3$ (39). This will also effect the synthesis of cytokines (40–46). Recently, n-3 supplementation in MS patients have been shown to reduce the levels of several pro-inflammatory cytokines as well as the production of the pro-inflammatory eicosanoids, prostaglandin $E_2$ and leukotriene $B_4$ (47).

Children with Zellweger Syndrome have extremely low values of DHA because of deficient synthesis of DHA from EPA due to congenital peroxisomal disorders. Dietary supplementation with pure DHA in these patients normalized DHA concentrations in plasma and erythrocyte lipids, improved CNS function, and MRI showed clear evidence of re-myelination in the brain (48). Since myelin lipids are not particularly rich in DHA, this effect on myelin might be reached via the myelin-producing cell, the oligodendrocyte, which contains phospholipids rich in DHA (49, 50). MS patients have a normal capability of converting EPA into DHA, and supplementing with fish oil containing both EPA and DHA could result in

improved re-myelination, thereby contributing to the improved EDSS score in our trial.

The high content of polyunsaturated fatty acids in the CNS makes it susceptible to attack from free radicals. During inflammation the free radical formation and antioxidant protection may be imbalanced. Vitamin C is a water soluble free radical scavenger and therefore important in protecting against free radicals (51). To enhance antioxidant protection, we therefore supplemented the patients with 200 mg vitamin C daily. Plasma vitamin values were at baseline below reference values but showed a significant increase at the end of the trial. Optimal antioxidant protection combined with increased intake of n-3 fatty acids may be important for the clinical improvement observed in our patients. However, finding the optimal balance between oxidizable long-chain n-3 fatty acids and antioxidant vitamins is difficult, especially since vitamin C at higher daily doses, has been reported to act as a pro-oxidant under special conditions (52).

Only 2 of the 16 patients experienced a relapse each during the 2-year study period. These patients were the only regular smokers (~20 cigarettes/day), and during the study it was revealed that one of them also had hemochromatosis. Smoking results in increased production of free radicals (51), and ferrous iron is a potent catalyst for free radical production and lipid peroxidation. Our observation of relapses in smokers might be a coincidence, but could also reflect a connection between oxidative stress and disease activity.

The results from this study suggest that dietary advice and supplementation of n-3 fatty acids and vitamins can reduce the exacerbation rate and improve function in newly diagnosed MS patients. Further controlled studies are needed to determine more definitively the role of diet in the treatment of MS.


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