



Analysis of specific nutritional factors in the development of MS

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I. Overview

Multiple sclerosis (MS) is a chronic demyelinating disease of the central nervous system (CNS) that tends to strike in early adulthood and is more common in women than men. It appears to vary in prevalence across geographic regions and ethnic groups; for instance, MS appears to be much more common in northern European Caucasians than in Asians living in China. Little is known about how MS develops and why it is more prevalent among some groups than others. However, it has been hypothesized that diet and nutrition, in conjunction with other factors such as genetics, may affect the risk of MS.

This document, part of the Nutrition track of the Accelerated Cure Project's Cure Map, analyzes several vitamins, minerals, fats, and other nutrients that have been investigated for a potential role in MS etiology. It does not provide an all-inclusive list of nutrients assessed for a role in MS, but does attempt to cover those nutrients that have been investigated in multiple studies using a variety of approaches. The research on each of these nutrients is organized into an analysis table that addresses the following questions:

- Is the presence of the actual nutritional factor different in MS subjects compared with non-MS subjects?
- Does the exposure to or intake of foods containing this nutritional factor differ between MS subjects and non-MS subjects?
- Have any therapies aimed at controlling, eliminating, or elevating the amount of the nutritional factor been found to alter the risk or clinical features of MS?
- If any significant differences appear to exist for any of the above, have confounding factors been investigated?
- If any significant differences appear to exist for any of the above, have cause-effect relationships been established to rule out other types of connections? Is there any evidence of the nutritional factor affecting the CNS or immune system?

At this time, it is not possible to conclusively state that any particular nutrient affects the risk of developing MS and describe how that nutrient is involved in the pathogenesis of the disease. Nor is it possible to exclude a role for any nutrient. While the evidence is stronger and/or more consistent for some nutrients than for others, many knowledge gaps still remain and many issues complicate the interpretation of results. For example, food intake studies do not always control for factors such as smoking or socioeconomic status, and supplementation studies often lack a control arm. Recall bias can affect the results of food frequency questionnaires. Also, studies that find meaningful differences (e.g., in serum levels of a nutrient) between cases and controls often cannot determine whether these differences have to do with the disease's causation or with the effects of the disease itself. Indeed, nutritional status and disease activity can be inter-related in complex ways, making it difficult to unravel the sequence of events occurring in the development of the disease. (For example, see Miller, et al. (2005) for a discussion of possible inter-relationships between vitamin B₁₂ and MS.)

Nevertheless, it is our hope that with careful thought and well-designed experiments, further research will be able to reveal whether and how nutritional factors interact with other factors to cause MS. The goal of this document is to provide an outline of current knowledge on this topic that will help guide continued work in this area.

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II. Vitamins

Nutritional factor: Vitamin A (retinol) and carotenoids (peripheral chemical)
<i>Description:</i>
Vitamin A, also known as retinol, is a fat-soluble vitamin that plays an important role in vision, reproduction, cell division and differentiation, immune system regulation, myelin formation, and glycoprotein formation. Provitamin A carotenoids can be converted into vitamin A and function as antioxidants. Sources of retinol include eggs, milk, eggs, liver, and fortified cereal, while sources of carotenoids include carrots, cantaloupes, spinach, and sweet potatoes. Vitamin A deficiency is associated with zinc deficiency, since zinc is needed to synthesize the retinol binding protein for transporting vitamin A, and is characterized by night blindness and susceptibility to infections. Adverse effects of vitamin A toxicity include birth defects, liver abnormalities, bone mineral density loss leading to osteoporosis, and disorders of the CNS. High intake of carotenoids may turn the skin yellow but is not harmful.
<i>Is presence of actual nutritional factor different in MS subjects compared with non-MS subjects?</i>
Studies provide mixed results: One analysis found that serum levels of retinol, betacarotene, and other antioxidant vitamins were lower in MS subjects compared with controls ¹ ; however, two others found no differences in serum levels of retinol or beta-carotene between MS and non-MS subjects ^{2, 3} .
<i>Does exposure to or intake of foods containing this nutritional factor differ between MS subjects and non-MS subjects?</i>
No protective effect was found for intake of vitamin A-rich foods in a case-control study ⁴ . Similarly, a prospective cohort study indicated that higher intake of foods containing dietary carotenoids (e.g., carrots and cantaloupe) was unrelated to reduced risk of MS ⁵ .
<i>Have any therapies aimed at controlling, eliminating, or elevating the amount of nutritional factor been found to alter the risk or clinical features of MS?</i>
Vitamin A (1.0 mg) was a component of the fish oil used in an uncontrolled supplementation study involving 16 MS subjects that demonstrated a reduced relapse rate and EDSS over two years. Because other vitamins were also included in the regimen, any individual effect of vitamin A cannot be determined ⁶ .
<i>If any significant differences appear to exist for any of the above, have confounding factors been investigated?</i>
Not assessed
<i>If any significant differences appear to exist for any of the above, have cause-effect relationships been established to rule out other types of connections? Is there any evidence of the nutritional factor affecting the CNS or immune system?</i>
As an antioxidant, retinol may help protect lipids against peroxidation ⁷ .
<i>Conclusion:</i>
At this point there is very little evidence to suggest a significant role for vitamin A in the etiology of MS.

Nutritional factor: Vitamin B₁₂
<i>Description:</i>
Vitamin B ₁₂ (also known as cobalamine, Cbl) is an essential cofactor for two enzymes in human cells that are important for nucleic acid metabolism: methionine synthase and methylmalonyl-CoA synthase. It plays a role in oxidation of fatty acids, myelin formation, and the prevention of pernicious anemia (a type of megaloblastic anemia). Vitamin B ₁₂ cannot be synthesized in the body and must be supplemented in the diet with animal products such as meat and dairy. Vitamin B ₁₂ deficiencies and MS are both marked by demyelination and neural degeneration, and share similar neurological symptoms such as weakness, paresthesias, and gait disturbances.
<i>Is presence of actual nutritional factor different in MS subjects compared with non-MS subjects?</i>
Evidence is inconclusive: <ul style="list-style-type: none"> • Case reports have described low B₁₂ levels in people diagnosed with MS^{8,9}, although whether a causal connection existed between these comorbidities was not determined. Another case study described a patient initially diagnosed with MS whose symptoms were later believed to be due to vitamin B₁₂ deficiency¹⁰. • Some studies have reported normal serum B₁₂ concentrations in MS subjects and controls^{11,12}, while others reported significantly lower serum B₁₂ levels¹³. One study found that although 32 of 156 MS cases evaluated had low Cbl levels, only seven of these also had elevated homocysteine (HCY) or methylmalonic acid (MMA) levels, metabolites that accumulate under conditions of B₁₂ deficiency¹⁴. A similar study of 72 MS subjects and 23 knee surgery controls reported that despite an increase in mean plasma HCY levels in the MS group, only seven of the MS subjects had low serum vitamin B₁₂ levels, and only one of these had high plasma HCY and none had high serum MMA¹⁵. • In studies of cerebrospinal fluid (CSF), results are conflicting, with some studies reporting similar B₁₂ concentrations in MS cases and controls and others observing lower levels in MS cases^{11,16}. CSF HCY and MMA levels were similar between MS cases and healthy controls in one study¹⁵. • One study detected elevated plasma levels of the B₁₂ carrier protein R-binder, along with decreased serum B₁₂ levels, in MS subjects compared with OND (other neurological disorders) and healthy controls¹⁷. However, another investigation found lower vitamin B₁₂ binding capacities, and no decrease in serum B₁₂ levels, in Japanese MS subjects compared with OND and healthy controls¹².
<i>Does exposure to or intake of foods containing this nutritional factor differ between MS subjects and non-MS subjects?</i>
Vitamin B ₁₂ is provided by animal products such as meat and dairy products. No studies have suggested that overall intake of these foods is decreased in people with MS.
<i>Have any therapies aimed at controlling, eliminating, or elevating the amount of nutritional factor been found to alter the risk or clinical features of MS?</i>
Evidence is inconclusive: <ul style="list-style-type: none"> • A small sample of chronic progressive MS cases treated with massive-dose methyl B₁₂ did not show improvement in terms of motor disability but did demonstrate some improvement in visual and auditory potentials¹². Results suggest that high-dosage methyl B₁₂ treatment may be useful in conjunction with immunosuppressive treatments. • Insignificant beneficial effects were reported from a trial of injected vitamin B₁₂ in combination with lofepramine and L-phenylalanine (the "Cari Loder regime")¹⁸.
<i>If any significant differences appear to exist for any of the above, have confounding factors been investigated?</i>
The findings summarized above that show altered B ₁₂ levels in MS subjects are difficult to interpret for a number of reasons: <ul style="list-style-type: none"> • Vitamin B₁₂ deficiency and MS can be difficult to differentiate because of similar clinical course of disease and MRI findings¹⁹; at least one longstanding case of diagnosed MS has been reconsidered in favor of B₁₂ deficiency¹⁰. • MS and B₁₂ deficiency, or signs such as macrocytosis, have been shown to coexist in some subjects^{9,10,20,21}. The basis of these comorbidities is not known; however, similar racial and

gender distributions exist between MS and pernicious anemia, while similar HLA associations suggest a common genetic susceptibility of the two disorders²⁰.

- MS disease processes (such as increased demand for B₁₂ by immune cells) may lead to decreased concentrations of the vitamin in the body.

If any significant differences appear to exist for any of the above, have cause-effect relationships been established to rule out other types of connections? Is there any evidence of the nutritional factor affecting the CNS or immune system?

Since vitamin B₁₂ is a co-factor for myelin synthesis and demyelination throughout the CNS is characteristic of MS, a relationship between low B₁₂ levels and incidence of MS has been proposed. Furthermore, B₁₂ deficiency also has important immunomodulatory effects. Therefore, vitamin B₁₂ deficiency may worsen inflammatory and demyelination of MS as well as slow remyelination and repair¹⁹. On the other hand, it is also possible that any vitamin B₁₂ deficiencies detected in MS reflect an increased demand for the vitamin resulting from the immunological activity and/or tissue damage and repair that occur in MS.

Conclusion:

The relationship between MS and vitamin B₁₂ is ambiguous. While many studies do show vitamin B₁₂ deficiencies in people with MS, others reveal no correlation, and no cause-effect relationship has been substantiated. Furthermore, therapy with vitamin B₁₂ has produced meager results. Larger controlled intervention, prospective, and nested case-control studies have been suggested for more conclusive results.

Nutritional factor: Vitamin C (ascorbic acid)
<i>Description:</i>
Vitamin C, also known as ascorbic acid, is a water-soluble vitamin and a protective antioxidant. Vitamin C is necessary for the synthesis of collagen, the neurotransmitter norepinephrine, and carnitine (essential for transport of fat to mitochondria) and plays a role in wound healing. Sources include citrus fruits and dark-green vegetables. Severe vitamin C deficiency is known as scurvy, a potentially fatal disease characterized by a tendency to bleed and bruise easily, hair and tooth loss, and joint pain and swelling. While adverse effects of high doses of vitamin C have not yet been confirmed, potential problems include “rebound scurvy,” increased oxidative stress, excess iron absorption, and vitamin B12 deficiency.
<i>Is presence of actual nutritional factor different in MS subjects compared with non-MS subjects?</i>
A trial of vitamin supplementation in MS subjects found that vitamin C plasma levels were below reference values at baseline but increased during the course of treatment ⁶ . Also, a case-control study reported that serum levels of ascorbic acid were significantly lower in MS subjects compared with controls ¹ .
<i>Does exposure to or intake of foods containing this nutritional factor differ between MS subjects and non-MS subjects?</i>
Evidence is sparse: <ul style="list-style-type: none"> • One case-control study reported that higher intake of foods containing vitamin C was negatively associated with risk of MS⁴. However, other case-control studies found no significant differences between MS and non-MS subjects in terms of intake of fruits and vegetables^{22, 23}. • A prospective study of two large cohorts of women reported that intake of vitamin C-rich foods (e.g., oranges and orange juice) was not associated with a reduced risk of MS⁵.
<i>Have any therapies aimed at controlling, eliminating, or elevating the amount of nutritional factor been found to alter the risk or clinical features of MS?</i>
Evidence is inconclusive: <ul style="list-style-type: none"> • One study found that taking vitamin C supplements, even for more than 10 years, was not protective against MS⁵. • In an intervention study, supplementation with fish oil, vitamin B complex, and vitamin C over two years reduced exacerbation rate and EDSS in MS subjects; however, this study was small (16 subjects) and uncontrolled⁶.
<i>If any significant differences appear to exist for any of the above, have confounding factors been investigated?</i>
Not assessed.
<i>If any significant differences appear to exist for any of the above, have cause-effect relationships been established to rule out other types of connections? Is there any evidence of the nutritional factor affecting the CNS or immune system?</i>
It has been suggested that vitamin C’s antioxidant properties may protect lipids in the CNS against free radical activity resulting from MS inflammation ⁶ ; however, this has not been specifically tested.
<i>Conclusion:</i>
Although reduced levels of vitamin C in people with MS suggest some type of relationship, there is no compelling evidence at this point to link vitamin C intake with risk of MS.

Nutritional factor: Vitamin D
<i>Description:</i>
Vitamin D is a fat-soluble vitamin that is stored in the fat tissues. Vitamin D regulates the amounts of calcium, magnesium, and phosphorus in the blood and plays an important role in bone growth and in immune function. It has been suggested that vitamin D may decrease the incidence and severity of autoimmune diseases by regulating Th1 and dendritic cell function ²⁴ . Deficiency in vitamin D can result from inadequate sun exposure and can lead to bone deformities such as is characteristic of rickets, while toxicity, though rare, can cause hypercalcemia. Vitamin D can be obtained from sun exposure and from diets rich in fish oil.
<i>Is presence of actual nutritional factor different in MS subjects compared with non-MS subjects?</i>
Reductions in vitamin D levels have been demonstrated in certain groups of MS subjects: <ul style="list-style-type: none"> • In one study of women with MS, bone density and mean hydroxyvitamin D (25(OH)D) levels were much lower compared with healthy controls²⁵. • One Finnish study of serum concentrations of 25(OH)D in early relapsing-remitting MS (RRMS) subjects indicated significantly lower serum levels of 25(OH)D in these subjects versus healthy and OND controls in samples obtained from June to September. In the winter months, however, there were no differences in serum levels²⁶.
<i>Does exposure to or intake of foods containing this nutritional factor differ between MS subjects and non-MS subjects?</i>
Lower vitamin D intake and lower sunlight exposure have been associated with higher risk of MS: <ul style="list-style-type: none"> • A prospective study on two large cohorts of women found that total vitamin D intake and supplemental vitamin D intake were inversely associated with risk of MS. However, no associations were found between vitamin D intake from food only and MS²⁷. • Epidemiological studies of MS distribution among US veterans found a significant negative correlation between MS prevalence and average annual hours of sunshine and average December daily solar radiation at the veterans' birthplaces, indicating a protective effect of sunshine^{28, 29}. An Australian study also found an inverse relationship between ultraviolet radiation levels and MS prevalence³⁰. • In a study of vitamin D metabolism and bone density, 40% of MS patients admitted to a hospital reported almost no exposure to sunlight, and 80% had a dietary intake of vitamin D below the recommended level²⁵. • An investigation of past sun exposure indicated that higher sun exposure during childhood or early adolescence, as well as greater actinic damage reflecting greater lifetime exposure, corresponded with a reduced risk of MS³¹. • One Israeli study found that MS subjects reported spending more time than controls outdoors in the summer prior to onset, while no occupational differences regarding sunlight exposure were found, both findings contradicting the hypothesis of the protective effect of sunlight in MS²². Another study, however, found a negative association between mortality from MS and residential and occupational exposure to sunlight³².
<i>Have any therapies aimed at controlling, eliminating, or elevating the amount of nutritional factor been found to alter the risk or clinical features of MS?</i>
A few trials of vitamin D supplementation have been performed, with inconclusive results: <ul style="list-style-type: none"> • A reduction of relapse rate was observed during therapy with calcium, magnesium, and vitamin D (in cod liver oil), but the study was small and uncontrolled³³. • Another pilot study showed simply that vitamin D supplementation (via calcitriol) was well tolerated and did not appear to aggravate the disease³⁴.
<i>If any significant differences appear to exist for any of the above, have confounding factors been investigated?</i>
Studies that measure concentrations of vitamin D in MS subjects vs. controls do not always control for factors such as the use of supplements; furthermore, factors resulting from MS may contribute to vitamin D deficiencies, such as heat intolerance leading to lower sunlight exposure in warmer months, or physical disability leading to more time spent indoors.
<i>If any significant differences appear to exist for any of the above, have cause-effect relationships been</i>

established to rule out other types of connections? Is there any evidence of the nutritional factor affecting the CNS or immune system?

A lack of vitamin D may increase the risk of MS disease activity as has been demonstrated by two studies. One study found that seasonal variations in MS disease activity correlate with seasonal changes in blood levels of vitamin D. High levels of MRI lesion activity coincided with low levels of 25(OH)D, and vice versa, when 25(OH)D data was lagged by two months³⁵. Another study also showed that 25(OH)D levels are lower in people with MS during relapses than during remissions²⁶. The nature of the relationship between lower 25(OH)D levels and MS activity is not known, but it may involve an immunomodulatory effect of vitamin D³⁶.

Conclusion:

In general, a link appears to exist between vitamin D deficiency and MS risk. For instance, seasonal variations in MS disease activity correspond with seasonal changes in blood levels of vitamin D, with increased MS lesion activities in wintertime when there is a lower level of sunlight. Benefits of vitamin D supplementation are unclear, however, since only small studies have investigated the effects of vitamin D therapy.

Nutritional factor: Vitamin E (alpha-tocopherol)
<i>Description:</i>
Vitamin E is a fat-soluble vitamin and one of the major “chain-breaker” antioxidants. It protects essential fatty acids (EFAs) and vitamin A by inhibiting free radical oxidation and destruction of lipids. Alpha-tocopherol is the form of vitamin E that is actively maintained in the body, and thus is the most nutritionally significant. Sources include fish-liver oil, vegetable oil, green leafy vegetables, nuts, whole grains, eggs, butter, and fortified milk and cereal. Vitamin E deficiency is rare but may occur in individuals with severe malnutrition, genetic defects in the alpha-tocopherol transfer protein, and lipid malabsorption. Severe vitamin E deficiency can cause neurological problems, including nerve degeneration impairing sensations and coordination, spinal cord degeneration, muscle weakness, and retinal damage. In general, vitamin E supplementation appears to have few adverse effects, although long-term studies are limited.
<i>Is presence of actual nutritional factor different in MS subjects compared with non-MS subjects?</i>
Evidence is mixed: <ul style="list-style-type: none"> • Four studies reported significantly lower levels of plasma or serum vitamin E in MS subjects compared to healthy controls^{1, 2, 37, 38}. Two of these also found a reduced vitamin E to lipid ratio^{2, 38}. On the other hand, similar serum vitamin E levels were found in MS subjects and controls by Wikstrom et al. (1976)³⁹. • One study reported that CSF vitamin E levels and CSF/serum vitamin E ratio did not differ significantly between MS subjects and controls³⁸.
<i>Does exposure to or intake of foods containing this nutritional factor differ between MS subjects and non-MS subjects?</i>
Vitamin E is found in a wide variety of foods and its specific intake has been studied only infrequently as an influence on MS risk. For instance, a case-control study performed in Montreal, Canada did not find any association between vitamin E intake and risk of MS ⁴ . Similarly, a prospective cohort study found no evidence that intake of foods containing vitamin E were associated with reduced risk of MS ⁵ .
<i>Have any therapies aimed at controlling, eliminating, or elevating the amount of nutritional factor been found to alter the risk or clinical features of MS?</i>
Evidence is lacking: <ul style="list-style-type: none"> • The cohort study mentioned above did not find a reduced risk of MS in women taking vitamin E supplements, even over an extended period of time (greater than 10 years)⁵. • No clinical trials of vitamin E supplementation in people with MS have been reported although increasing vitamin E and selenium intake has been suggested as a means of reducing oxidative stress³⁷.
<i>If any significant differences appear to exist for any of the above, have confounding factors been investigated?</i>
Not assessed
<i>If any significant differences appear to exist for any of the above, have cause-effect relationships been established to rule out other types of connections? Is there any evidence of the nutritional factor affecting the CNS or immune system?</i>
It has been suggested that free radicals can cause a lipid peroxidation disturbance and induce protein and myelin sheath damage ^{2, 38, 40} . Increased lipid peroxidation has been reported in the CSF, blood, demyelinating plaques, and muscles of MS subjects ^{2, 37, 38} , while decreased vitamin E levels were found in demyelinated plaques in MS brains ⁴¹ . Therefore, increased free radical production combined with decreased antioxidant defense may play a pathogenic role in MS ² .
<i>Conclusion:</i>
Overall, evidence is mixed. Although several studies have found that people with MS have lower vitamin E levels in comparison with non-MS controls, other have found no differences between the MS and control groups. Furthermore, intake of vitamin E through food or supplements has not been shown to affect risk of MS. No specific trials of vitamin E supplementation in MS subjects have been conducted to assess whether this would affect the clinical characteristics of the disease.

III. Minerals

Nutritional factor: Calcium
<i>Description:</i>
Calcium is a macromineral that is important for maintaining strong bones and teeth, blood clotting, and proper functioning of the muscles and nerves. Calcium is also a co-factor in protein folding as well as an important intracellular messenger, especially for neurotransmission. The presence of vitamin D is necessary for calcium absorption. Dairy products provide the richest source of calcium in Western diets, while seaweed, nuts, greens, and fish also contribute to calcium in the diet. Calcium deficiency may lead to bone loss and osteoporosis.
<i>Is presence of actual nutritional factor different in MS subjects compared with non-MS subjects?</i>
Only one study was identified in our search, an analysis of 20 trace elements that reported no difference in calcium concentrations in the scalp-hair of MS subjects compared with controls ⁴² .
<i>Does exposure to or intake of foods containing this nutritional factor differ between MS subjects and non-MS subjects?</i>
<ul style="list-style-type: none">• Higher intake of calcium-containing foods was shown to be protective against MS in a food frequency study⁴.• Several studies have evaluated intake of dairy products in people with MS; most do not show a protective effect:<ul style="list-style-type: none">• Several ecologic studies have reported that dairy consumption is positively correlated with MS⁴³⁻⁴⁷.• Case-control studies have reported either no significant differences in dairy consumption between MS cases and controls^{22, 23, 48, 49}, or have found that greater dairy intake is associated with MS⁵⁰.• However, in a survey conducted in New Zealand, a higher percentage of MS subjects compared with controls reported rarely or never drinking milk at age 15 (no differences were noted for consumption at age 11)⁵¹.
<i>Have any therapies aimed at controlling, eliminating, or elevating the amount of nutritional factor been found to alter the risk or clinical features of MS?</i>
Only one trial of calcium supplementation has been identified. A relapse rate reduction was observed during therapy with calcium, magnesium, and vitamin D (in cod liver oil), but the study was small and uncontrolled ³³ .
<i>If any significant differences appear to exist for any of the above, have confounding factors been investigated?</i>
Linking dairy intake with risk of MS is confounded by the multiple other nutrients found in these products, such as fats. Other factors that may confound observed associations between MS and dairy intake include socioeconomic status, urban/rural environment, and ecologic/climatic factors.
<i>If any significant differences appear to exist for any of the above, have cause-effect relationships been established to rule out other types of connections? Is there any evidence of the nutritional factor affecting the CNS or immune system?</i>
The results of Cantorna, et al. (1999) in mice with EAE suggest calcium and vitamin D can interact to suppress autoimmune activity ⁵² . The New Zealand study of milk consumption suggests that decreased milk intake during the adolescent growth spurt may harm myelin formation ⁵¹ .
<i>Conclusion:</i>
Studies specifically dealing with calcium are too limited in quantity and scope to enable any conclusions. More work has been done to assess the intake of dairy products in people with MS. For the most part, these studies have found either increased or equivalent consumption of dairy products in MS cases compared with controls, which argues against calcium deficiency playing a role in MS. However, a study that specifically dealt with adolescent dairy consumption did show lower intake in MS subjects. Overall, more study is needed before any conclusions can be drawn.

Nutritional factor: Copper (trace element)
<i>Description:</i>
Copper is an essential mineral that is found in many enzymes, including cytochrome oxidase and superoxide dismutase, and is central to the oxygen-carrying pigment hemocyanin. Copper is also important for myelin synthesis and stabilization, metabolic co-factor production, and maintenance of bones, blood vessels, and nerves. Sources of copper include crab meat, vegetables and fruits, whole grains, and nuts. Copper deficiency is uncommon, while copper compounds should always be considered toxic.
<i>Is presence of actual nutritional factor different in MS subjects compared with non-MS subjects?</i>
In general, evidence does not suggest a role for copper in MS, but differences between MS cases and controls have been observed: <ul style="list-style-type: none"> • Many studies found similar or insignificantly lower copper levels in the blood and CSF of MS subjects when compared to controls^{39, 53, 54}. However, one study did find significantly elevated copper levels in the CSF of MS cases⁵⁵, another study reported decreased serum copper levels in MS cases compared to controls⁵⁶, and another found lower copper serum levels in MS subjects under 45 compared with healthy controls⁵⁷. • Smith, et al. (1989) reported no difference in plasma ceruloplasmin (copper-dependent enzyme) but significantly lower red blood cell (RBC) copper levels in MS cases receiving steroid treatment compared with healthy controls⁵⁴. • No significant difference in daily urinary excretions of copper was observed in MS cases and controls⁵⁸. • One study found significantly lower copper concentrations in MS versus control scalp-hair⁴².
<i>Does exposure to or intake of foods containing this nutritional factor differ between MS subjects and non-MS subjects?</i>
Not specifically assessed.
<i>Have any therapies aimed at controlling, eliminating, or elevating the amount of nutritional factor been found to alter the risk or clinical features of MS?</i>
Not assessed
<i>If any significant differences appear to exist for any of the above, have confounding factors been investigated?</i>
Not assessed
<i>If any significant differences appear to exist for any of the above, have cause-effect relationships been established to rule out other types of connections? Is there any evidence of the nutritional factor affecting the CNS or immune system?</i>
The following speculations about the possible involvement of Cu in MS have been made: <ul style="list-style-type: none"> • Lower RBC-Cu levels in MS subjects receiving steroid treatment and a significantly higher RBC Zn-Cu ratio in MS subjects suggest that copper/zinc homeostasis may be altered in MS⁵⁴. • Elevated CSF copper levels found in MS cases may be related to release of the Cu-containing enzyme cytochrome oxidase through damage to the mitochondrial electron transport chain⁵⁵. • Lipid peroxidation, which may alter myelin structure⁵⁹ can be inhibited by copper-dependent enzyme ceruloplasmin⁵⁴.
<i>Conclusion:</i>
The association between copper and MS has not been well studied. Most studies report similar or insignificant differences in copper concentrations in MS subjects and controls, suggesting no correlation between MS susceptibility and copper level in the body. Supplementation with copper has not yet been tested.

Nutritional factor: Selenium
<i>Description:</i>
Selenium is a trace mineral and antioxidant that helps prevent cellular damage by free radicals. Selenium is involved in thyroid function and the immune system. Sources include plant foods grown in selenium-rich soil, meat, seafood, grains, and eggs. Selenium deficiency is rare but occurs where soil concentration of selenium is low and may contribute directly or indirectly to a weakened immune system. Selenium toxicity, also rare, can cause selenosis, which is characterized by gastrointestinal problems, hair loss, and mild nerve damage.
<i>Is presence of actual nutritional factor different in MS subjects compared with non-MS subjects?</i>
Evidence is mixed: <ul style="list-style-type: none"> • Wikstrom, et al. (1976) found lower whole blood levels of selenium in MS subjects living in a high-risk area of Finland, but no differences in serum levels compared with controls³⁹. Clausen, et al. (1988) found lower concentrations of selenium in the serum, erythrocytes, and whole blood of MS subjects compared with controls⁶⁰. However, other studies reported similar or greater selenium levels in people with MS versus controls^{54, 61, 62}. • Some studies have reported lower concentrations/activity of the Se-containing enzyme glutathione peroxidase (GSH-Px) in people with MS⁶⁰⁻⁶³. However, Mazzella, et al. (1983) found no correlation between plasma and blood selenium concentrations and GSH-Px activity, concluding that selenium intake is probably unrelated to the etiology of MS⁶². • A multi-trace element analysis of scalp-hair samples mentions significantly higher concentrations of selenium in scalp-hair samples of MS subjects⁴².
<i>Does exposure to or intake of foods containing this nutritional factor differ between MS subjects and non-MS subjects?</i>
Not assessed, although Jensen, et al. (1980) notes that Denmark has a higher mortality rate of MS than Finland despite having higher selenium soil levels ⁶¹ .
<i>Have any therapies aimed at controlling, eliminating, or elevating the amount of nutritional factor been found to alter the risk or clinical features of MS?</i>
An intervention study reported increased GSH-Px activity in MS subjects after supplementation with selenium, vitamin C and E, but the clinical effects were not evaluated ⁶³ .
<i>If any significant differences appear to exist for any of the above, have confounding factors been investigated?</i>
Not assessed
<i>If any significant differences appear to exist for any of the above, have cause-effect relationships been established to rule out other types of connections? Is there any evidence of the nutritional factor affecting the CNS or immune system?</i>
It has been hypothesized that selenium, and Se-containing GSH-Px, are protective against MS because of their role as anti-oxidants in inhibiting lipid peroxidation ³⁹ . Many previous studies have reported reduced GSH-Px activity in the erythrocytes and leukocytes of MS subjects when compared to normal controls ⁶² . However, as mentioned above, not all studies have found a correlation between selenium levels and GSH-Px activity, suggesting that factors other than Se intake such as genetic variants may be responsible for GSH-Px abnormalities.
<i>Conclusion:</i>
In general, evidence is mixed. Some studies show correlation between selenium level, glutathione peroxidase activity, and MS, while others report no correlation. The potential benefits of selenium treatment have not been adequately assessed.

Nutritional factor: Zinc (trace element)
<i>Description:</i>
Zinc is an essential mineral that structurally supports biomembranes, stimulates numerous enzymes, activates lymphocytes in the immune system, is necessary for myelin formation and stability, and regulates gene expression. Zinc can be found in oysters, red meat, poultry, nuts, beans, whole grains, and dairy products. Zinc deficiency can inhibit growth, reproduction, and wound healing.
<i>Is presence of actual nutritional factor different in MS subjects compared with non-MS subjects?</i>
Evidence is inconclusive but may indicate the possibility of abnormal zinc metabolism in people with MS: <ul style="list-style-type: none"> • Plasma zinc levels in MS cases were found in one study to be much lower than in normal controls⁶⁴; another study found lower serum zinc levels in MS subjects and no difference in serum albumin, which binds zinc in serum⁵⁷. Other studies did not observe any statistically significant difference in serum zinc level^{54, 56, 65, 66}. • In a study of whole blood, significantly higher zinc levels were reported in MS and OND cases versus controls⁵³. Similarly, elevated erythrocyte zinc levels were reported in MS subjects when compared to healthy and OND controls⁶⁶; this was confirmed in another study which found that zinc concentration dropped dramatically during MS exacerbation and increased gradually with recovery⁶⁷. However, Smith, et al. (1989) reported normal RBC zinc levels in MS subjects⁵⁴. • In other tissues, CSF zinc concentrations did not differ significantly between MS cases and subjects with other neurological diseases⁶⁷ or between MS cases and normal controls⁵⁵⁻⁵⁷. Likewise, no significant differences in daily urinary excretions⁵⁸ or scalp-hair levels of zinc⁴² was observed between MS cases and controls.
<i>Does exposure to or intake of foods containing this nutritional factor differ between MS subjects and non-MS subjects?</i>
Although zinc intake has not been assessed directly, different studies suggest that higher or lower intakes of zinc may be involved in MS: <ul style="list-style-type: none"> • Lower consumption of fish (which is high in zinc) has been associated with increased MS risk^{43, 47}; MS prevalence has also been found to be lower in coastal regions where fish intake is expected to be higher⁶⁸. However, not all regions with low MS prevalence are associated with high fish intake. • Based on his analysis of a work-based MS cluster in New York, Schiffer (1987) proposed that occupational exposure to elemental zinc could be a risk factor in MS⁶⁹.
<i>Have any therapies aimed at controlling, eliminating, or elevating the amount of nutritional factor been found to alter the risk or clinical features of MS?</i>
Not assessed.
<i>If any significant differences appear to exist for any of the above, have confounding factors been investigated?</i>
Various factors can influence zinc concentration measurements including analysis technique, age of the subject, medication status (e.g., corticosteroid use in MS subjects can affect zinc levels), and fasting/nonfasting status. It may be that some of these factors are responsible for discrepancies in study results as reported above ⁶⁶ . It is also possible that zinc abnormalities are a result of MS disease activity rather than a cause ^{53, 66} .
<i>If any significant differences appear to exist for any of the above, have cause-effect relationships been established to rule out other types of connections? Is there any evidence of the nutritional factor affecting the CNS or immune system?</i>
A few hypotheses have been put forth concerning the possible involvement of zinc in MS: <ul style="list-style-type: none"> • Zinc is an essential part of carbonic anhydrase, which is a part of the myelin sheath. Decreased carbonic anhydrase activity as a result of zinc deficiency could change myelin metabolism and increase MS susceptibility⁶⁴. • Since zinc inhibits lipid peroxidation, zinc deficiency could increase peroxidative damage in MS⁵⁷ that may cause changes in myelin structure⁵⁹.
<i>Conclusion:</i>
No conclusions can yet be drawn regarding the involvement of zinc in the etiology of MS. In the blood, zinc levels in MS subjects versus controls vary from low to high depending on the type of blood sample

assessed (plasma/serum, whole blood, erythrocyte) and other study design factors. CSF zinc concentrations do not appear to be altered in people with MS. It is not clear which, if any, of several proposed mechanisms (protein binding, malabsorption, disease activity, chronic inflammation, and lipid peroxidation) account for those differences seen between MS and normal controls in terms of zinc levels. Treatment with zinc has not yet been studied.

Nutritional factor: Miscellaneous minerals (iron, magnesium, manganese, potassium, etc)
<i>Description:</i>
Minerals are necessary for good nutrition. Macrominerals (such as magnesium and potassium) are important in large body systems, such as the skeletal and nervous systems, and are found at active sites of proteins or enzymes. Trace minerals (such as iron and manganese) can play a role in enzymes, hormone function, bone formation, and antioxidant action.
<i>Is presence of actual nutritional factor different in MS subjects compared with non-MS subjects?</i>
<p>1. <u>Iron</u> (Fe):</p> <ul style="list-style-type: none"> • A histochemical study reported iron deposits surrounding demyelinated plaques of cerebral tissue in MS subjects⁷⁰, while another study found no such deposits in or around demyelinated plaques⁷¹. • A larger study found no difference in whole blood Fe levels in MS subjects compared with healthy controls⁵³; normal levels of iron have also been reported in daily urinary excretions⁵⁸. <p>2. <u>Magnesium</u> (Mg):</p> <ul style="list-style-type: none"> • No statistically significant differences were found between MS and non-MS subjects in serum or CSF⁵⁶ or scalp-hair⁴². • A study of autopsy samples reported significantly lower average Mg content in CNS tissues and visceral organs (except spleen) in four MS subjects when compared to five controls. In particular, the most dramatic reduction in Mg content was observed in CNS white matter including demyelinated MS plaques⁷². <p>3. <u>Manganese</u> (Mn):</p> <ul style="list-style-type: none"> • A study reported significantly decreased CSF Mn levels in MS cases compared with subjects with no known neurological disease⁵⁵; the authors speculate that this may be the result of increased demand for Mn in the brain during glial proliferation. • Significantly lower Mn concentrations were found in scalp-hair samples of MS subjects⁴². These levels were also lower in men compared with women. <p>4. <u>Other elements</u>:</p> <ul style="list-style-type: none"> • An investigation of daily urinary excretion of trace elements in MS subjects revealed no significant difference in metals (Pb, Ni, Ag, Cu, Fe, Mb, Zn) between MS cases and controls⁵⁸. • Significantly lower concentrations of Cu, I, Mn, S, and V and a significantly higher Se level were found in scalp-hair samples of MS subjects compared with normal controls. No difference was observed for Ag, Al, As, Au, Ba, Br, Ca, Cl, K, Mg, Na, Sb, Sr, and Zn⁴².
<i>Does exposure to or intake of foods containing this nutritional factor differ between MS subjects and non-MS subjects?</i>
<ul style="list-style-type: none"> • In a food frequency questionnaire, a significant protective effect on MS was found for potassium⁴. • In a geographic cluster of high MS prevalence, an environment predisposing to MS was suggested^{73, 74}: <ul style="list-style-type: none"> ○ Soil low in copper, iron, vanadium and high in lead, nickel, zinc in the upper soil layer ○ Water high in chloride, chromium, molybdenum, nitrate plus nitrate, and zinc, low in selenium and sulfate
<i>Have any therapies aimed at controlling, eliminating, or elevating the amount of nutritional factor been found to alter the risk or clinical features of MS?</i>
<ul style="list-style-type: none"> • Supplementation with calcium, magnesium, and vitamin D in a small, uncontrolled study was shown to significantly decrease the relapse rate of MS³³.
<i>If any significant differences appear to exist for any of the above, have confounding factors been investigated?</i>
Not assessed.
<i>If any significant differences appear to exist for any of the above, have cause-effect relationships been established to rule out other types of connections? Is there any evidence of the nutritional factor affecting the CNS or immune system?</i>
<ul style="list-style-type: none"> • It has been suggested that altered concentration of magnesium⁷² and lead, nickel and zinc⁷³ may affect the immune response in MS subjects

- Lower levels in CSF manganese in MS subjects could be a result of MS disease processes stimulating demand for manganese in the brain, rather than a cause of MS⁵⁵.

Conclusion:

In general, multi-trace element analyses indicate normal levels of trace elements in MS samples when compared to controls. A few studies have noted differences in concentrations for various elements between MS and non-MS subjects, but these have been too few in number to be conclusive.

IV. Proteins

Nutritional factor: Gluten
<i>Description:</i>
Gluten is a mix of elastic proteins (gliadin and glutenin) that is found in wheat, rye, barley, and other cereal grains. Individuals with gluten allergies must avoid gluten because it provokes an immune response that damages the inner lining of the small intestine and prevents normal digestion. Because of its effects on the immune system, gluten may potentially play a role in any autoimmune disease, as it does in celiac disease.
<i>Is presence of actual nutritional factor different in MS subjects compared with non-MS subjects?</i>
Not assessed.
<i>Does exposure to or intake of foods containing this nutritional factor differ between MS subjects and non-MS subjects?</i>
Evidence is mixed on whether higher cereal/bread consumption is a risk factor for MS: <ul style="list-style-type: none"> • One study reported significantly higher intake of cereal-derived products by MS subjects when compared to controls, concluding that high consumption of bread and pasta correlated positively with MS⁷⁵. Sepcic <i>et al.</i> (1993) also reported more frequent wheat and rye bread consumption among MS cases in a high-risk area of Croatia, although this difference was not statistically significant⁵⁰. • However, one study found no significant difference in intake of gluten-containing products between MS subjects and controls²², and another small case-control study observed no difference in bread and cereal intakes between cases and controls²³. • Yet another case-control study found a protective effect of higher cereal and bread intake on risk of MS⁴.
<i>Have any therapies aimed at controlling, eliminating, or elevating the amount of nutritional factor been found to alter the risk or clinical features of MS?</i>
A pilot study of 42 MS subjects given a gluten-free diet resulted in no apparent beneficial effect ⁷⁶ . An analysis of the plasma of MS subjects found that only one of 36 subjects showed evidence of gluten antibodies ⁷⁷ ; the authors concluded that a gluten-free diet is not recommended as standard treatment in MS. Animal studies also fail to show any benefits from a gluten-free diet; in fact, such a diet has been shown to exacerbate the course of experimental autoimmune encephalomyelitis (EAE) ⁷⁸ .
<i>If any significant differences appear to exist for any of the above, have confounding factors been investigated?</i>
Not assessed
<i>If any significant differences appear to exist for any of the above, have cause-effect relationships been established to rule out other types of connections? Is there any evidence of the nutritional factor affecting the CNS or immune system?</i>
Although gluten antigens are known to trigger an immune response in some people, no cause-effect relationships nor any strong associations have been established between MS and gluten intake. Furthermore, no findings of molecular mimicry between gluten proteins and myelin antigens have been reported, although an autism study did detect antibodies cross-reactive for gliadin and cerebellar antigens.
<i>Conclusion:</i>
Although gluten grains have been implicated in other autoimmune diseases, little evidence at this time exists to connect it to the development of MS.

V. Lipids

Nutritional factor: Saturated fat
<i>Description:</i>
Saturated fats are fats or fatty acids composed of chains of carbon atoms joined by single bonds (meaning that all carbons are fully saturated with hydrogen atoms). In general, saturated fats are solid at room temperature and have high melting points. Sources include all animal fat (meat, poultry, dairy), palm oil, coconut oil, and butter. Excess saturated fat has been associated with atherosclerosis and cardiovascular disease. Diets high in saturated fats are associated with higher levels of LDL cholesterol, which is thought to increase the risk of heart disease.
<i>Is presence of actual nutritional factor different in MS subjects compared with non-MS subjects?</i>
Holman, <i>et al.</i> (1989) found an increase of saturated fatty acids in the plasma phospholipids of MS subjects compared with controls; this increase compensates for a decrease in the levels of certain unsaturated fatty acids ⁷⁹ . Compensatory increases in saturated fatty acids in plasma and red blood cells were also reported by Navarro and Segura (1988 and 1989) ^{80, 81} . However, a more recent study found no significant differences in levels of saturated or unsaturated fat in the erythrocyte membranes of healthy controls compared with subjects with different subtypes of MS ⁸² . Investigations into whether the saturated/unsaturated fatty acid balance in MS brain tissue is altered have produced mixed results ⁸³⁻⁸⁶ .
<i>Does exposure to or intake of foods containing this nutritional factor differ between MS subjects and non-MS subjects?</i>
Evidence is mixed: <ul style="list-style-type: none"> • Several ecological and case-control studies have suggested a positive association between MS and high saturated and animal fat (meat, milk, butter, eggs) consumption^{4, 43, 45, 47, 50, 68, 75, 87-89}. For example: <ul style="list-style-type: none"> ○ A study comparing the prevalence of MS in countries with different dietary patterns found a significant, positive correlation of 0.70 between MS and intake of fats and oils and calories of animal origin⁸⁷. A similar study also found positive, significant correlations between MS prevalence rates and per capita consumption of pork, total fat, and total meat⁸⁸. ○ A case-control study reported a significantly higher frequency of consumption of animal-derived fats (butter and lard) in MS cases when compared to controls⁷⁵. • However, several population-based case-control studies, including a large prospective cohort study, have found that MS subjects and controls did not differ significantly in fat intake, or that MS subjects consumed less fat than controls prior to onset, suggesting that fat consumption does not increase the risk of MS^{22, 90, 91}.
<i>Have any therapies aimed at controlling, eliminating, or elevating the amount of nutritional factor been found to alter the risk or clinical features of MS?</i>
<ul style="list-style-type: none"> • Swank reported beneficial results from a low-fat diet treatment followed by 150 MS patients from 1949 to 1984. In this diet, fat intake was restricted to less than 20 g/day, often accompanied by an increase in oil intake. Among his findings were: <ul style="list-style-type: none"> ○ The frequency and severity of relapses, rate of loss of ability to walk and work, and death rate were all reduced⁹² ○ The lowest degree of deterioration was seen in those who consumed the least fat and the most oil⁹² ○ The greatest benefit was seen in those MS subjects with minimal disability to start with⁹³ • Another trial of a high polyunsaturated fat/low saturated fat diet showed that after 34 months, good compliers had on average no change in EDSS score, while poor compliers had a significant mean increase of 0.3 points⁹⁴. • A 16-subject, uncontrolled study of fish oil and vitamin supplementation together with reduction in saturated fat intake reported a reduced exacerbation rate and a decrease in EDSS score after two years⁶.
<i>If any significant differences appear to exist for any of the above, have confounding factors been investigated?</i>

Some of the potential confounding factors identified in the above intake studies include latitude, which correlated with pork consumption and risk of MS⁸⁸, and socioeconomic status, although one study that found an association with animal fat intake did not find a corresponding association with total calories or total protein⁸⁷. The prospective analysis of the Nurses' Health Study data adjusted for age, latitude at birth, and smoking; in addition, the occupation of all subjects was nursing⁹¹.

It is possible that any relationship between increased saturated fat intake and increased risk of MS may be due to the resulting lower intake of polyunsaturated fatty acids which are protective against MS, rather than any direct role of saturated fats themselves. (See the sections concerning polyunsaturated fatty acids.)

If any significant differences appear to exist for any of the above, have cause-effect relationships been established to rule out other types of connections? Is there any evidence of the nutritional factor affecting the CNS or immune system?

Several theories have been produced to explain a possible relationship between saturated fat and MS risk:

- Swank (1970) suggests that the attraction of fats for red blood cells in the bloodstream leads to MS by promoting the clumping of blood elements, reducing oxygen availability to tissues, and increasing permeability of the microcirculation of the brain, thus allowing agents harmful to myelin to enter the brain⁹².
- It has also been suggested that diet imbalances could result in defective blood-brain barrier membranes through attacks on the membranes by short-chain fatty acids or alterations in membrane structure by incorporation of trans fatty acids⁴³.
- Since the myelin sheath of nerves is mostly composed of lipids, a lipid imbalance could affect cell fluidity and myelination. Nanji and Narod (1986), who found an association between pork consumption and MS, have suggested that positions of double bonds in the fatty acid chains of pork as compared with beef may alter myelin sheath lipids so as to make an individual who consumes pork more susceptible to MS⁸⁸.
- Not only do saturated fats contain low levels of antioxidants, they may also antagonize the functions of eicosapentaenoic (EPA) and docosahexaenoic acids (DHA), two omega-3 unsaturated fatty acids, which may allow greater production of certain inflammatory leukotrienes^{7, 95}. The presence of these leukotrienes could disrupt the blood-brain barrier.

Conclusion:

The evidence from epidemiological and case-control studies about the intake of saturated fat and MS is mixed. While many studies cite an association between MS incidence and intake of saturated fat, others do not, and therefore conclusive evidence that high animal-fat intake is a causal factor in MS remains elusive. Low-fat diet treatment have shown clinical benefits, although controlled studies are lacking and the rigorous guidelines of the Swank diet may not be feasible for many.

Nutritional factor: Essential fatty acids: Omega-6 fatty acids (linoleic acid, arachidonic acid)
<i>Description:</i>
Omega-6 fatty acids are essential fatty acids (EFAs) named for the double bond situated six carbons away from the end of the carbon chain. Omega-6 EFAs include linoleic and arachidonic acids. These acids can be converted into hormonelike molecules called leukotrienes and prostaglandins that regulate inflammation, blood pressure, and heart, gastrointestinal, and kidney functions. Sources of omega-6 include safflower oil, sunflower oil, vegetable oil, poultry, seeds, and nuts. For omega-6 fatty acids to be effective, an appropriate balance of omega-3 fatty acids is also necessary. Since the Western diet is relatively high in omega-6 fatty acids, omega-6 deficiencies are rare in Westerners.
<i>Is presence of actual nutritional factor different in MS subjects compared with non-MS subjects?</i>
Evidence suggests that decreased concentrations of omega-6 fatty acids, especially linoleic acid, in MS subjects when compared to both normal or neurological controls: <ul style="list-style-type: none"> • Linoleic acid levels have been found to be significantly lower in MS subjects than in healthy and OND controls in serum, plasma, erythrocytes and lymphocytes⁹⁶⁻¹⁰¹, although not all studies have found lower linoleate levels in MS subjects^{102, 103}. Holman, et al. (1989) found normal levels of linoleic acid and increased levels of 18:3n6, but subnormal levels of all further n6 acids in the plasma phospholipids of MS subjects compared with controls. These subnormal levels were compensated with increased levels of saturated fatty acids⁷⁹. A recent study found no differences in omega-6 fatty acids in the membranes of erythrocytes from MS subjects compared with controls⁸². • One study detected significantly lower proportions of both linoleic and arachidonic acid in CSF cholesterol esters of MS subjects compared with healthy and head trauma controls⁹⁹.
<i>Does exposure to or intake of foods containing this nutritional factor differ between MS subjects and non-MS subjects?</i>
No significant differences in the intake of linoleic acid between MS subjects and controls were found by Gharidian, et al. (1998) ⁴ . Similarly, Zhang, et al. (2000) found no significant effect on risk of MS for intake of n-6 polyunsaturated fat ⁹¹ . An ecologic study found a negative correlation between MS risk and ratio of polyunsaturated to saturated fatty acids in the diet ⁸⁹ .
<i>Have any therapies aimed at controlling, eliminating, or elevating the amount of nutritional factor been found to alter the risk or clinical features of MS?</i>
Linoleate supplementation has produced encouraging results, particularly for subjects treated early in the course of disease: <ul style="list-style-type: none"> • Many studies have reported increased linoleic acid levels following supplementation in both MS cases and controls^{94, 97, 104, 105}. • Three studies have evaluated the clinical effects of linoleic acid supplementation compared with placebo in MS subjects: <ul style="list-style-type: none"> ○ One double-blinded, placebo-controlled study reported decreased frequency, duration, and severity of relapses upon two years of linoleate supplementation¹⁰⁶. ○ Another study reported no difference in frequency of attacks between RRMS subjects given linoleic acid and those who were given oleic acid, but it did show decreased duration and severity of attacks for the higher-dose linoleic acid group¹⁰⁴. ○ The third study found no therapeutic effect of supplementation on progression of disease, relapse rate, or severity¹⁰⁵. • A combined analysis of the results from the above three studies revealed that MS subjects with minimal disability who were supplemented with linoleic acid had a significantly smaller increase in disability over the course of the trials compared with controls. However, this effect was not seen for subjects with higher baseline disability. Reduced relapse severity and duration with supplementation was reported at all disability levels. No effect on relapse rate was found¹⁰⁷.
<i>If any significant differences appear to exist for any of the above, have confounding factors been investigated?</i>
As mentioned above, the intake of polyunsaturated fat can be affected by the intake of saturated fats, and therefore pinpointing the influence of these two types of lipids on MS may be difficult.
<i>If any significant differences appear to exist for any of the above, have cause-effect relationships been</i>

established to rule out other types of connections? Is there any evidence of the nutritional factor affecting the CNS or immune system?

- It is unknown why linoleate levels may be decreased in people with MS and whether this decrease is a cause or result of MS disease activity. Possible explanations for this observation include: less frequent entry of linoleic acid into blood⁹⁶; increased rate of linoleic acid removal from blood⁹⁶; activities in the central nervous system leading to altered exchange of linoleic acid with the plasma⁹⁶; and a possible defect in the metabolic pathway used in the absence of large amounts of linoleate⁹⁷. However, studies of fat absorption in MS cases indicate that lowered fatty acid levels in CSF and serum of people with MS are not due to impaired intestinal absorption^{3, 97, 99}.
- If lower levels of linoleic acid present in the body contribute to MS disease activity, it may be through a depression in their immunosuppressive functions. Linoleic acid supplementation in clinical trials appeared to affect the duration and severity of acute exacerbations, an action which resembles that of the adrenocorticotrophic hormone^{104, 107}.

Conclusion:

In general, omega-6 fatty acid levels, particularly linoleic acid levels, in the blood and brain are significantly lower in MS subjects than controls. Linoleate supplementation has yielded mixed results. Several studies have found increased linoleic acid levels in both MS cases and controls after supplementation, but various double-blind, controlled trials have reported different effects of supplementation on the frequency, duration, and severity of MS relapses. Large clinical studies are needed to assess the effects of dietary intervention.

Nutritional factor: Essential fatty acids: Omega-3 fatty acids (linolenic acid, eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA); fish oil
<i>Description:</i>
Omega-3 fatty acids are polyunsaturated fatty acids with a double bond at the third carbon from the end of the carbon chain. The main n-3 fatty acid is alpha-linolenic acid, which can be converted into eicosapentaenoic acid (EPA) and then docosahexaenoic acid (DHA) in the body. EPA can, in turn, be converted into the hormone-like eicosanoids, which play a role in organ function and intracellular activity. Sources include fish oil, canola oil, flaxseed oil, some dark green vegetables, and walnuts. Omega-3 fatty acids are important for cell wall formation. Omega-3 deficiencies may lead to decreased mental capabilities, immune function, and membrane function. Some experts believe that an appropriate dietary balance of omega-6 to omega-3 EFAs is about 3:1, but in the typical Western diet, the ratio is closer to 20:1.
<i>Is presence of actual nutritional factor different in MS subjects compared with non-MS subjects?</i>
Evidence is limited: <ul style="list-style-type: none"> • A few studies have reported low levels of omega-3 acids in red blood cells, adipose tissue, and plasma of people with MS^{79, 101, 103}. However, a recent study found no differences in omega-3 fatty acids in the membranes of erythrocytes from MS subjects compared with healthy controls⁸².
<i>Does exposure to or intake of foods containing this nutritional factor differ between MS subjects and non-MS subjects?</i>
Reduced intake of fish and fish oil, which are high in n-3 fatty acids, is often associated with increased MS risk: <ul style="list-style-type: none"> • Lower MS prevalence rates have been measured along Norwegian coastal regions compared with inland areas; the coastal areas were associated with higher levels of fish intake than the inland areas⁶⁸. • Comparison of multi-national MS data with food intake data showed that fish fat consumption was correlated with a lower risk of MS⁴³. • Analysis of sociogeographic factors in conjunction with MS rates in US states identified low fish intake (along with colder climate and high dairy intake) as a potential MS risk factor; however this study noted that some populations have low MS prevalence despite the absence of fish in the diet⁴⁷. • An ecologic study by Esparza, et al. (1995) found a negative correlation between MS risk and ratio of polyunsaturated (such as fish fat) to saturated fatty acids⁸⁹. • However, analysis of data from the Nurses' Health Study and the Nurses' Health Study II found no association between MS risk and intake of fish or omega-3 fatty acids from fish⁹¹.
<i>Have any therapies aimed at controlling, eliminating, or elevating the amount of nutritional factor been found to alter the risk or clinical features of MS?</i>
Results from fish oil supplementation in low saturated fat diets are mixed: <ul style="list-style-type: none"> • A very small study of vitamin supplementation that used fish oil supplements to provide vitamin D reported a reduction in the relapse rate (compared with case history) in ten MS subjects³³. • An uncontrolled study of nutritional counseling (83 subjects) showed increases in the levels of plasma essential fatty acids, as well as stabilization of EDSS, in good compliers⁹⁴. • A two-year, 312-subject randomized trial of fish oil vs. olive oil supplementation showed only a trend toward lower progression in the fish oil group¹⁰⁸. • Reduced levels of proinflammatory eicosanoids and some immunoenhancing cytokines in the blood of both MS and control subjects were demonstrated in a six-month trial of fish oil capsules and dietary advice in 20 MS subjects and 15 healthy controls¹⁰⁹. • Comparison of a fish oil-supplemented 15% fat diet with an olive oil-supplemented 30% fat diet showed enhanced physical and mental quality of life for the fish oil group, reduced fatigue for the olive oil group, fewer relapses in both groups, and no significant changes in inflammatory cytokines, chemokines or adhesion molecules in either group (31 subjects total) over the course of a year¹¹⁰.
<i>If any significant differences appear to exist for any of the above, have confounding factors been investigated?</i>

As mentioned above, the intake of polyunsaturated fat can be affected by the intake of saturated fats, and therefore pinpointing the influence of these two types of lipids on MS may be difficult.

If any significant differences appear to exist for any of the above, have cause-effect relationships been established to rule out other types of connections? Is there any evidence of the nutritional factor affecting the CNS or immune system?

- It is not known why levels of omega-3 appear to be lower in various tissues in MS subjects compared with controls; diet may play a role as suggested by certain food intake studies, but other factors may also contribute to these findings. Omega-3 levels have also been found to be reduced in several other disease states so this reduction may be a result of rather than a trigger of MS¹¹¹.
- One consequence of lower levels of omega-3 in people with MS may be alteration of immune system function. For example, disruptions in the balance between omega-6 and omega-3 fatty acids may lead to higher production of proinflammatory prostaglandins and leukotrienes.

Conclusion:

People with MS appear to have lower levels of omega-3 fatty acids in blood and other tissues. Whether this phenomenon is related to increased risk of MS is unknown, but it may lead to a proinflammatory environment. Although some food intake studies indicate that higher fish consumption is associated with lower MS risk, and although trials of omega-3 supplementation suggest clinical benefits in MS, evidence relating n-3 fatty acids and MS is too sparse to recommend supplementation as a means of reducing MS risk.

VI. Conclusion

The information in these tables reveals a long-active scientific interest into finding nutritional risk factors for MS. The idea of identifying nutrients that influence the risk of MS is an attractive one, because diet is a component of health that can be modified fairly readily. At this time, although suggestive evidence exists for nutrients such as vitamin D and saturated/unsaturated fats, no solid evidence exists linking a particular nutrient with the development of MS, and therefore no specific nutritional guidance can be given to people who may be at risk of developing MS. As with many other aspects of research into complex diseases such as MS, there are numerous challenges associated with proving that an individual nutritional factor can affect someone's risk of MS. Nevertheless, we hope that with new research approaches and methodologies, these challenges can eventually be overcome.

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