Vitamin D intake and incidence of multiple sclerosis

K. L. Munger, S. M. Zhang, E. O'Reilly, et al.

Neurology 2004;62;60
DOI 10.1212/01.WNL.0000101723.79681.38

Vitamin D intake and incidence of multiple sclerosis

K.L. Munger, MSc; S.M. Zhang, MD, ScD; E. O'Reilly, MSc; M.A. Hernán, MD, DrPH; M.J. Olek, DO; W.C. Willett, MD, DrPH; and A. Ascherio, MD, DrPH

Abstract—*Background:* A protective effect of vitamin D on risk of multiple sclerosis (MS) has been proposed, but no prospective studies have addressed this hypothesis. *Methods:* Dietary vitamin D intake was examined directly in relation to risk of MS in two large cohorts of women: the Nurses' Health Study (NHS; 92,253 women followed from 1980 to 2000) and Nurses' Health Study II (NHS II; 95,310 women followed from 1991 to 2001). Diet was assessed at baseline and updated every 4 years thereafter. During the follow-up, 173 cases of MS with onset of symptoms after baseline were confirmed. *Results:* The pooled age-adjusted relative risk (RR) comparing women in the highest quintile of total vitamin D intake at baseline with those in the lowest was 0.67 (95% CI = 0.40 to 1.12; p for trend = 0.03). Intake of vitamin D from supplements was also inversely associated with risk of MS; the RR comparing women with intake of ≥400 IU/day with women with no supplemental vitamin D intake was 0.59 (95% CI = 0.38 to 0.91; p for trend = 0.006). No association was found between vitamin D from food and MS incidence. *Conclusion:* These results support a protective effect of vitamin D intake on risk of developing MS.

NEUROLOGY 2004;62:60–65

The incidence of multiple sclerosis (MS) is low in the tropics and increases with distance from the equator in both hemispheres.[1] One hypothesis is that sunlight exposure and the resulting increase in vitamin D may exert a protective effect.[2-5] During the winter at high latitudes, ultraviolet sunlight is too low to produce adequate amounts of vitamin D_3, and vitamin D insufficiency lasting 4 to 6 months of the year at latitudes of ≥42° is common in individuals with low vitamin D intake.[6,7] Vitamin D has strong immunoregulatory effects,[8-10] and vitamin D supplementation prevents experimental autoimmune encephalomyelitis (EAE), an autoimmune disease in animals that is used as a model of MS.[11] Studies on vitamin D and MS have found that individuals with MS tend to have insufficient vitamin D levels[12,13] and that periods of low vitamin D precede the occurrence of high lesion activity, whereas periods of high vitamin D precede low lesion activity, as detected by MRI.[14,15] There are, however, no prospective studies relating vitamin D to risk of developing MS. Therefore, we used the data from two large prospective cohorts to examine whether or not high vitamin D intake reduces the risk of MS.

Methods. *Study population.* The study population comprised women participating in two prospective studies of female registered nurses living in the USA: the Nurses' Health Study (NHS) and the Nurses' Health Study II (NHS II). The NHS was established in 1976 and recruited 121,700 nurses aged 30 to 55 years; the NHS II was established in 1989 and recruited 116,671 nurses aged 25 to 42 years. As the first dietary assessment was conducted in 1980 in the NHS and in 1991 in the NHS II, the dates of return of the 1980 and 1991 questionnaires were chosen as the baseline (beginning of the follow-up). Women with incomplete baseline food frequency questionnaires or implausible caloric intakes (<500 or >3,500 kcal/day in NHS, <800 or >4,200 kcal/day in NHS II) were excluded from the analyses. Further, as the occurrence of neurologic symptoms may have caused changes in diet or use of vitamin supplements, we excluded women whose symptoms of MS started before baseline. These exclusions left a total of 92,253 women for the analyses in the NHS and 95,310 in the NHS II.

Ascertainment of MS. Newly diagnosed cases of MS were identified by self-report on biennial questionnaires sent to all participants and confirmed by asking the treating neurologist to complete a questionnaire on the certainty of the diagnosis (definite, probable, possible, not MS), clinical history (including date of MS diagnosis and date of the first symptoms of MS), and laboratory tests. If a neurologist was not involved or did not respond, we sent the questionnaire to the patient's internist.[16] In 90% of women with MS, the treating physician was a neurologist, and the diagnosis was supported by positive MRI findings in 76% (NHS) and 89% (NHS II) of the cases. The higher percentage of MRI in the NHS II reflects the higher proportion of cases with recent onset, as in both cohorts 89% of the cases diagnosed after 1990 had an MRI-supported diagnosis. For purposes of the investigation, we confirmed as cases women with a diagnosis of definite or probable MS according to their neurologist or physician; the validity of this approach has been previously reported.[16] The sensitivity of the results to diagnostic errors was examined by restricting the analyses to definite MS cases. We documented 76 cases of MS (53 definite and 23 probable) in the NHS and 97 cases (76 definite and 21 probable) in the NHS II with onset of symptoms after baseline.

Assessment of vitamin D intake. Participants in the NHS completed comprehensive semiquantitative food frequency questionnaires in 1980, 1984, 1986, 1990, and 1994 and those in the NHS II cohort in 1991 and 1995. The baseline 1980 questionnaire

From the Departments of Nutrition (Drs. Willett and Ascherio, K.L. Munger and E. O'Reilly) and Epidemiology (Drs. Zhang, Hernán, Willett, and Ascherio), Harvard School of Public Health, and Division of Preventive Medicine (Dr. Zhang) and Channing Laboratory (Drs. Zhang, Willett, and Ascherio), Department of Medicine, Harvard Medical School and Brigham and Women's Hospital, Boston, MA; and Multiple Sclerosis Center (Dr. Olek), Department of Neurology, University of California at Irvine.

Supported by NIH grants CA87969, CA50385, and NS35624.

Received July 22, 2003. Accepted in final form September 17, 2003.

Address correspondence and reprint requests to Ms. K.L. Munger, Department of Nutrition, Harvard School of Public Health, 665 Huntington Ave., Boston, MA 02115; e-mail: kgorham@hsph.harvard.edu

Table 1 *Baseline age-adjusted characteristics of participants in NHS (1980) and NHS II (1991) according to quintiles of total vitamin D intake*

	NHS					NHS II				
	Quintile of total vitamin D intake					Quintile of total vitamin D intake				
Characteristics	1	2	3	4	5	1	2	3	4	5
Ever smoker, %	62	57	54	54	56	37	36	34	34	34
Born in north tier, %	40	41	44	44	42	30	34	37	38	38
Use of multivitamins, %	6	7	13	48	97	8	16	30	70	96
Mean daily food intake										
Skim/low-fat milk, servings/d	0.1	0.3	0.7	1.2	1.0	0.2	0.7	1.3	1.4	1.5
Whole milk, servings/d	0.1	0.2	0.4	0.4	0.3	0.0	0.1	0.1	0.1	0.1
Fish, servings/d	0.16	0.16	0.17	0.19	0.18	0.06	0.10	0.12	0.13	0.14
Mean daily nutrient intake (with supplements)										
Calcium, mg	484	613	763	904	899	687	847	1,028	1,162	1,374
Vitamin A, IU	10,289	10,515	11,034	13,476	19,669	9,397	10,540	11,565	13,830	18,584
Vitamin E, mg	35	34	37	64	163	22	24	30	52	98
Folate, μg	229	247	270	381	705	286	325	369	540	866
Vitamin C, mg	216	220	226	306	571	171	187	210	284	439
Vitamin B_1, mg	1.6	1.7	1.9	2.6	5.6	2.0	2.2	2.6	3.8	7.5
Vitamin B_2, mg	2.1	2.3	2.6	3.5	6.5	2.1	2.4	3.0	4.3	8.3
Vitamin B_6, mg	1.8	2.0	2.0	2.9	6.1	4.7	5.1	5.9	9.2	16.6
Vitamin B_{12}, μg	5.3	5.9	6.6	9.3	17.7	5.8	6.8	8.0	10.8	17.9
Zinc, mg	6.1	6.2	6.5	7.3	9.6	11	12	13	17	24

NHS = Nurses' Health Study.

in the NHS cohort included 61 items; subsequent questionnaires were expanded to approximately 130 items. These questionnaires have been described in detail, and the validity and reproducibility of food and nutrient intakes have been previously documented.[17,18] The food items that mostly contributed to vitamin D intake were skim/low-fat milk (38 to 40% of vitamin D from foods) and fish (10 to 12%). The correlations between intakes estimated from the food frequency questionnaire and those from four 1-week diet records were 0.81 for skim milk and 0.66 for fish.[17,18] The information on current use, brand, and dosage of multivitamin supplements was collected on each biennial questionnaire. Current use of individual vitamin D supplements was also collected biennially; the dose of vitamin D supplements was not specified in the questionnaire and was assumed to be 400 IU (10 μg). The validity of vitamin D intake was assessed by comparing it with the plasma concentrations of 25-hydroxyvitamin D (25[OH]D) among 323 healthy NHS women.[19] The mean 25(OH)D was 22.0 ng/mL among women in the bottom quintile of vitamin D intake and 30.1 ng/mL among women in the top quintile; for plasma collected between January and April, the corresponding values were 15.9 and 27.9 ng/mL. Validity of estimated vitamin D intake in the NHS is further supported by its inverse association with risk of hip fractures.[19]

Statistical analyses. Each participant contributed person-time of follow-up from the date of return of the first food frequency questionnaire (1980 in NHS and 1991 in NHS II) to the date at onset of the first symptoms of MS, death from any cause, or end of follow-up, whichever came first. The end of follow-up was May 31, 1998, in NHS and May 31, 1999, in NHS II. Separate analyses were conducted within each cohort. For the main analyses, women were categorized by quintiles of intake of total (from foods and supplements) energy-adjusted vitamin D at baseline; adjustment for total energy intake was achieved using the residuals of the regression of vitamin D intake on total caloric intake.[20] For each quintile of vitamin D intake, we estimated the incidence rate by dividing the number of MS cases by the number of person-years of follow-up. Relative risks (RR) were calculated by dividing the incidence rate in each quintile by the corresponding rate in the lowest quintile, which was used as the reference category. Similar analyses were conducted to examine the separate effects of vitamin D from foods or from supplements. In these analyses, intake of vitamin D from supplements (from either multivitamin or specific vitamin D supplements) was categorized in three groups: none, <400 IU/day, and ≥400 IU/day. In separate analyses that incorporated the repeated dietary measurements, the incidence of MS was related to the cumulative average of vitamin D intake from all the available dietary questionnaires up to the start of each 2-year follow-up interval.[21] Cox proportional hazards models were used to adjust the RR estimates simultaneously for risk factors for MS, including pack-years of smoking[22] and latitude at birth (north, middle, or south).[16] The two cohorts were combined, and pooled RR were estimated using Cox's proportional hazards models stratified by age (5-year age groups) and cohort. Tests for trend were conducted by using the median values of quintiles of vitamin D intake or of categories of vitamin D supplement intake as a continuous variable. Heterogeneity of RR estimates from the two cohorts was tested using a Wald test, where the squared difference between the log RR was divided by the sum of the variances of each of the log RR. All p values are two tailed.

Results. Women in the top quintile of total vitamin D intake at baseline were less likely to have ever smoked and more likely to be current users at baseline of multivitamin supplements than women in the bottom quintile (table 1). Almost all the women in the top quintile of total vitamin D intake at baseline were multivitamin users as compared with <10% of women in the bottom quintile. As a result,

Table 2 *Relative risk of MS according to baseline intake of vitamin D for NHS (1980–1998) and NHS II (1991–1999)*

	NHS*			NHS II*			Pooled*	Pooled†
Parameters	Median IU/d	Cases/ person-y	RR (95% CI)	Median IU/d	Cases/ person-y	RR (95% CI)	RR (95% CI)	RR (95% CI)
Total vitamin D								
Quintile 1	58	17/320,108	Ref.	128	20/149,878	Ref.	Ref.	Ref.
2	124	21/320,460	1.24 (0.65–2.35)	217	26/149,899	1.30 (0.72–2.34)	1.27 (0.83–1.96)	1.28 (0.83–1.98)
3	197	15/321,047	0.89 (0.44–1.77)	317	18/150,044	0.90 (0.47–1.70)	0.89 (0.56–1.43)	0.89 (0.56–1.43)
4	344	14/319,014	0.81 (0.40–1.65)	472	17/150,187	0.87 (0.46–1.64)	0.84 (0.52–1.35)	0.83 (0.52–1.35)
5	641	9/318,652	0.55 (0.25–1.22)	742	16/150,069	0.77 (0.40–1.50)	0.67 (0.40–1.12)	0.69 (0.42–1.15)
		76/1,599,281			97/750,075			
p trend			0.05			0.22	0.03	0.03
p heterogeneity								0.42
Vitamin D from food								
Quintile 1	49	14/319,365	Ref.	110	19/149,803	Ref.	Ref.	Ref.
2	100	17/320,496	1.21 (0.59–2.45)	177	15/149,968	0.79 (0.40–1.55)	0.97 (0.60–1.57)	0.97 (0.60–1.58)
3	147	18/320,059	1.29 (0.64–2.61)	234	30/149,933	1.58 (0.89–2.81)	1.46 (0.94–2.27)	1.47 (0.94–2.30)
4	204	14/320,201	1.01 (0.48–2.13)	302	18/150,130	0.95 (0.50–1.80)	0.97 (0.60–1.59)	0.97 (0.60–1.58)
5	311	13/319,159	0.93 (0.43–2.00)	414	15/150,243	0.78 (0.39–1.54)	0.84 (0.51–1.40)	0.84 (0.51–1.40)
		76/1,599,281			97/750,075			
p trend			0.61			0.56	0.44	0.42
p heterogeneity								1.0
Vitamin D from supplements, IU/d								
0	0	64/1,120,418	Ref.	0	63/436,790	Ref.	Ref.	Ref.
< 400	228	5/153,468	0.53 (0.21–1.33)	228	16/147,326	0.75 (0.43–1.29)	0.68 (0.42–1.08)	0.68 (0.43–1.08)
≥ 400	400	7/325,394	0.39 (0.18–0.85)	400	18/165,960	0.75 (0.44–1.26)	0.59 (0.38–0.91)	0.60 (0.39–0.92)
		76/1,599,281			97/750,075			
p trend			0.007			0.20	0.006	0.009
p heterogeneity								0.16

* Adjusted for age in 5-y groups.
† Further adjusted for smoking (never, <10 packs/y, 10–24 packs/y, 25+ packs/y) and latitude at birth.

MS = multiple sclerosis; NHS = Nurses' Health Study; RR = relative risk.

vitamin D intake was strongly associated with intakes of other components of multivitamins such as vitamins A, E, and folic acid. Consumption of skim/low-fat milk, the major contributor of dietary vitamin D in these cohorts, was also severalfold higher among women in the top quintile of total vitamin D than among those in the bottom quintile (see table 1).

Total vitamin D intake at baseline was inversely associated with risk of MS (table 2). The age-adjusted pooled RR comparing the highest with the lowest quintile of consumption was 0.67 (95% CI = 0.40 to 1.12; *p* for trend = 0.03). Intake of vitamin D from supplements only was also inversely associated with risk; the RR comparing women with intake of ≥400 IU/day with those with no supplemental vitamin D intake was 0.59 (95% CI = 0.38 to 0.91; *p* for trend = 0.006). Both associations were stronger in the NHS than in the NHS II cohort, but tests for heterogeneity were not significant (see table 2). These RR did not materially change after further adjustment for pack-years of smoking and latitude at birth (see table 2). In contrast, we found no associations between vitamin D intake from food only and risk of MS. The RR comparing women in the highest quintile of dietary vitamin D with those in the lowest were 0.93 (95% CI = 0.43 to 2.0) in the NHS and 0.78 (95% CI = 0.39 to 1.54) in the NHS II (see table 2). Similar nonsignificant results were obtained after excluding women with any intake of supplemental vitamin D; the corresponding RR were 1.13 (95% CI = 0.47 to 2.73) in the NHS and 1.13 (95% CI = 0.50 to 2.57) in the NHS II. Inverse associations between total vitamin D intake or vitamin D intake from supplements were also found in analyses using the cumulative average of intake. Overall, these associations were similar to those using vitamin D intake at baseline (table 3). Analyses restricted to cases of definite MS gave similar results. In these analyses, the age-adjusted RR comparing the highest with the lowest quintile were 0.62 for baseline total vitamin D intake (*p* for trend = 0.02) and 0.56 for cumulative total vitamin D intake (*p* for trend = 0.01); the RR for baseline and cumulative supplemental vitamin D intakes were 0.52 (*p* for

Table 3 *Relative risk of MS according to updated cumulative average intake of vitamin D for NHS (1980–1998) and NHS II (1991–1999)*

	NHS*			NHS II*			Pooled*	Pooled†
Parameters	Median IU/d	Cases/ person-y	RR (95% CI)	Median IU/d	Cases/ person-y	RR (95% CI)	RR (95% CI)	RR (95% CI)
Total vitamin D								
Quintile 1	87	19/316,294	Ref.	135	18/149,943	Ref.	Ref.	Ref.
2	167	15/322,409	0.78 (0.40–1.54)	226	30/149,309	1.68 (0.94–3.02)	1.22 (0.79–1.88)	1.23 (0.79–1.90)
3	250	13/320,897	0.70 (0.35–1.41)	326	18/150,515	1.01 (0.52–1.94)	0.85 (0.53–1.37)	0.84 (0.52–1.35)
4	373	22/321,275	1.20 (0.65–2.19)	468	16/150,578	0.92 (0.47–1.80)	1.06 (0.68–1.66)	1.03 (0.65–1.63)
5	599	7/318,406	0.41 (0.18–0.94)	714	15/149,730	0.83 (0.41–1.67)	0.61 (0.36–1.04)	0.63 (0.37–1.07)
		76/1,599,281			97/750,075			
p trend			0.16			0.13	0.04	0.05
p heterogeneity								0.92
Vitamin D from food								
Quintile 1	71	12/315,641	Ref.	112	19/149,785	Ref.	Ref.	Ref.
2	123	24/322,065	2.00 (1.00–3.99)	176	17/149,443	0.90 (0.47–1.73)	1.33 (0.83–2.11)	1.33 (0.83–2.12)
3	165	17/320,988	1.46 (0.70–3.05)	230	31/150,843	1.62 (0.92–2.87)	1.56 (0.99–2.45)	1.57 (1.00–2.47)
4	214	10/321,864	0.89 (0.39–2.03)	294	17/150,309	0.89 (0.46–1.72)	0.89 (0.53–1.49)	0.89 (0.53–1.49)
5	298	13/318,723	1.15 (0.52–2.53)	399	13/149,695	0.68 (0.33–1.39)	0.86 (0.51–1.45)	0.87 (0.52–1.47)
		76/1,599,281			97/750,075			
p trend			0.53			0.29	0.22	0.22
p heterogeneity								0.75
Vitamin D from supplements, IU/d								
0	0	43/784,669	Ref.	0	56/381,710	Ref.	Ref.	Ref.
< 400	152	29/600,089	1.12 (0.69–1.81)	200	27/232,136	0.81 (0.51–1.29)	0.94 (0.68–1.32)	0.99 (0.70–1.40)
≥ 400	400	4/214,532	0.35 (0.13–0.98)	400	14/136,229	0.70 (0.39–1.26)	0.57 (0.34–0.94)	0.58 (0.35–0.96)
		76/1,599,281			97/750,075			
p trend			0.10			0.18	0.04	0.06
p heterogeneity								0.47

* Adjusted for age in 5-y groups.
† Further adjusted for smoking (never, <10 packs/y, 10–24 packs/y, 25+ packs/y) and latitude at birth.

MS = multiple sclerosis; NHS = Nurses' Health Study; RR = relative risk.

trend = 0.004) and 0.53 (p for trend = 0.03). Some women reported use of calcium supplements but not vitamin D supplements. As calcium supplements often contain vitamin D, vitamin D intake of these women could have been underestimated; their exclusion from the analyses, however, did not materially change the results.

Vitamin D intake may be more important for women living in regions at high latitude where winter sunlight is insufficient. Therefore, we examined the interaction between quintiles of vitamin D intake and latitude at birth and at age 15. Neither interaction was significant (birth: $p = 0.71$; age 15: $p = 0.12$).

Supplemental vitamin D intake was mostly from multivitamins, as only a small percentage of women reported using vitamin D-specific supplements. As a result, vitamin D intake was correlated with intakes of other multivitamin components such as vitamins A, C, and E, folic acid, and the B vitamins (see table 1). A trend toward lower risk of MS with increasing total vitamin D intake or vitamin D intake from supplements and risk of MS remained after adjustment for quintile of vitamin A (p for trend = 0.02 for total vitamin D, $p = 0.003$ for vitamin D from supplements) or vitamin C ($p = 0.02$ and $p = 0.003$) but not after adjustment for vitamin E, folic acid, or vitamins B_1, B_2, B_6, or B_{12}. However, none of these vitamins was itself significantly associated with risk of MS after adjustment for total vitamin D or vitamin D from supplements. Duration of use of multivitamins was also inversely associated with risk of MS; the RR using women who never used multivitamins as a reference were 0.61 (95% CI = 0.34 to 1.07) for <5 years of use, 0.70 (95% CI = 0.46 to 1.06) for 5 to 9 years of use, and 0.41 (95% CI = 0.18 to 0.93) for ≥10 years of use (p for trend = 0.006). The use of multivitamin supplements without vitamin D was too infrequent to determine its association with MS risk.

Discussion. In this large prospective study, we found that women who used supplemental vitamin

D, largely from multivitamins, had a 40% lower risk of MS than women who did not use vitamin D supplements.

A protective role of vitamin D has been proposed to explain the well-known latitude gradient in MS incidence and prevalence.[2] A study among US veterans found that the average annual hours of sunshine and the average December daily solar radiation at place of birth were strongly and inversely correlated with MS: −0.73 and −0.80, respectively[3]; similar results were obtained in Australia[4] and among immigrants to Israel.[5] However, the correlation between latitude and sunlight exposure is so high that it prevents the assessment of their independent contributions in ecologic studies, and none of several climatic factors—including annual solar radiation—was independently correlated with the risk of MS after accounting for latitude.[23] In a small German study,[14] seasonal fluctuation of gadolinium-enhancing lesions was found, with a greater number of active lesions seen in spring (March to May) than in autumn (September to November).[15] This seasonal fluctuation was compared with median 25(OH)D levels from the German population, and high 25(OH)D levels in the summer (July to August) were strongly correlated with low lesion activity in autumn and low 25(OH)D levels in the winter (January to March) correlated with high lesion activity in spring.[15] More compelling is the experimental evidence that vitamin D supplementation can prevent or favorably affect the course of EAE, an induced autoimmune disease used as an animal model of MS. Onset of EAE occurs earlier in vitamin D-deficient mice[11,24] and is prevented by administration of $1,25(OH)_2D_3$ prior to injection of the inducing antigens.[11,24,25] Further, progression of the disease is considerably slowed when $1,25(OH)_2D_3$ is given at the first sign of clinical symptoms,[11,24-26] and progression recurs when $1,25(OH)_2D_3$ supplementation is interrupted.[11] The mechanisms of these favorable effects of vitamin D are not entirely known but could be related to the ability of $1,25(OH)_2D_3$ to inhibit the production of the Th1-associated cytokines interleukins-12 and 2, interferon-γ, and tumor necrosis factor-α, thus suppressing the development and proliferation of the inflammatory Th1 cells.[27-30] Consistent with these mechanisms is the recent report of a lower risk of type 1 diabetes among individuals supplemented with vitamin D in the first year of life.[31]

An important limitation of our study is that we could not assess the effects of vitamin D intake on risk of MS independently of use of multivitamins, which was also inversely associated with risk of MS. Plausible candidates for a protective effect include several components of multivitamins, such as vitamin E, folic acid, zinc, and vitamins B_1, B_2, B_6, and B_{12}. In a previous analysis in these cohorts, we found no associations between use of multivitamin supplements and risk of MS.[32] That analysis, however, was based on a shorter follow-up period, and because of the small number of cases, we included women who completed their first food frequency questionnaire after the onset of symptoms of MS. The previous null finding could thus be explained if some women with MS started taking multivitamins after experiencing neurologic symptoms, but before the diagnosis. As a statistical separation of the individual associations of multivitamin components with MS risk is not possible in our study, the interpretation should rely on the biologic plausibility of specific hypotheses. Protective effects of antioxidants,[33] zinc,[34] and vitamins B_2,[34] B_6,[34] and B_{12}[35] on the risk of developing MS have been proposed, but the experimental evidence is not as strong for any of these as it is for vitamin D. Therefore, a protective effect of vitamin D seems a more likely explanation of the observed associations. Finally, analyses were adjusted for known MS risk factors (age, smoking, and latitude of residence at birth) with no appreciable change in the RR; however, confounding by unknown factors cannot be excluded.

We found a 40% reduction in risk of MS among women who use supplemental vitamin D, primarily in the form of multivitamins, compared with women who do not use supplements. Whether or not this finding reflects a protective effect of vitamin D intake on risk of MS remains to be established. Because of the difficulty in separating the effects of different dietary components and of the contribution of sunlight to circulating levels of vitamin D, future prospective studies should measure directly circulating levels of 25(OH)D before the onset of MS. Further, it may be important to assess whether vitamin D supplementation may slow the progression of MS.

Acknowledgment

The authors thank the participants in the Nurses' Health Study and Nurses' Health Study II for their continuing cooperation. They also thank Karen Corsano, Laura Sampson, Gary Chase, Barbara Egan, Lori Ward, and Elsa Jiménez for technical assistance.

References

1. Kurtzke JF. Geography in multiple sclerosis. J Neurol 1977;215:1–26.
2. Goldberg P. Multiple sclerosis: vitamin D and calcium as environmental determinants of prevalence (a viewpoint). Part 1: sunlight, dietary factors and epidemiology. Int J Environ Studies 1974;6:19–27.
3. Acheson ED, Bachrach CA, Wright FM. Some comments on the relationship of the distribution of multiple sclerosis to latitude, solar radiation, and other variables. Acta Psychiatry Scand 1960;147(suppl):132–147.
4. Sutherland JM, Tyrer JH, Eadie MJ. The prevalence of multiple sclerosis in Australia. Brain 1962;85:146–164.
5. Leibowitz U, Sharon D, Alter M. Geographical considerations in multiple sclerosis. Brain 1967;90:871–886.
6. Webb AR, Kline L, Holick MF. Influence of season and latitude on the cutaneous synthesis of vitamin D3: exposure to winter sunlight in Boston and Edmonton will not promote vitamin D3 synthesis in human skin. J Clin Endocrinol Metab 1988;67:373–378.
7. Ladizesky M, Lu Z, Oliveri B, et al. Solar ultraviolet B radiation and photoproduction of vitamin D3 in central and southern areas of Argentina. J Bone Miner Res 1995;10:545–549.
8. Provvedini DM, Tsoukas CD, Deftos LJ, Manolagas SC. 1,25-Dihydroxyvitamin D3 receptors in human leukocytes. Science 1983;221:1181–1183.
9. Bhalla AK, Amento EP, Clemens TL, Holick MF, Krane SM. Specific high-affinity receptors for 1,25-dihydroxyvitamin D3 in human peripheral blood mononuclear cells: presence in monocytes and induction in T lymphocytes following activation. J Clin Endocrinol Metab 1983;57:1308–1310.

10. Deluca HF, Cantorna MT. Vitamin D: its role and uses in immunology. FASEB J 2001;15:2579–2585.
11. Cantorna MT, Hayes CE, DeLuca HF. 1,25-Dihydroxyvitamin D3 reversibly blocks the progression of relapsing encephalomyelitis, a model of multiple sclerosis. Proc Natl Acad Sci USA 1996;93:7861–7864.
12. Cosman F, Nieves J, Herbert J, Shen V, Lindsay R. High-dose glucocorticoids in multiple sclerosis patients exert direct effects on the kidney and skeleton. J Bone Miner Res 1994;9:1097–1105.
13. Nieves J, Cosman F, Herbert J, Shen V, Lindsay R. High prevalence of vitamin D deficiency and reduced bone mass in multiple sclerosis. Neurology 1994;44:1687–1692.
14. Auer DP, Schumann EM, Kumpfel T, Gossl C, Trenkwalder C. Seasonal fluctuations of gadolinium-enhancing magnetic resonance imaging lesions in multiple sclerosis. Ann Neurol 2000;47:276–277.
15. Embry AF, Snowdon LR, Vieth R. Vitamin D and seasonal fluctuations of gadolinium-enhancing magnetic resonance imaging lesions in multiple sclerosis. Ann Neurol 2000;48:271–272.
16. Hernán MA, Olek MJ, Ascherio A. Geographic variation of MS incidence in two prospective studies of US women. Neurology 1999;53: 1711–1718.
17. Willett WC, Sampson L, Browne ML, et al. The use of a self-administered questionnaire to assess diet four years in the past. Am J Epidemiol 1988;127:188–199.
18. Salvini S, Hunter D, Sampson L, Stampfer M, Colditz G, Willett W. Food-based validation of a dietary questionnaire: the effects of week-to-week variation in food consumption. Int J Epidemiol 1989;18:858–867.
19. Feskanich D, Willett WC, Colditz GA. Calcium, vitamin D, milk consumption, and hip fractures: a prospective study among postmenopausal women. Am J Clin Nutr 2003;77:504–511.
20. Willett WC, Howe GR, Kushi LH. Adjustment for total energy intake in epidemiologic studies. Am J Clin Nutr 1997;65(suppl 4):1220S–1231S.
21. Hu FB, Stampfer MJ, Rimm E, et al. Dietary fat and coronary heart disease: a comparison of approaches for adjusting for total energy intake and modeling repeated dietary measurements. Am J Epidemiol 1999;149:531–540.
22. Hernán MA, Olek MJ, Ascherio A. Cigarette smoking and incidence of multiple sclerosis. Am J Epidemiol 2001;154:69–74.
23. Norman JE, Kurtzke JF, Beebe GW. Epidemiology of multiple sclerosis in U.S. veterans: 2. Latitude, climate and the risk of multiple sclerosis. J Chron Dis 1983;36:551–559.
24. Branisteanu DD, Waer M, Sobis H, Marcelis S, Vandeputte M, Bouillon R. Prevention of murine experimental allergic encephalomyelitis: cooperative effects of cyclosporine and 1 alpha, 25-(OH)2D3. J Neuroimmunol 1995;61:151–160.
25. Lemire JM, Archer DC. 1,25-Dihydroxyvitamin D3 prevents the in vivo induction of murine experimental autoimmune encephalomyelitis. J Clin Invest 1991;87:1103–1107.
26. Nataf S, Garcion E, Darcy F, Chabannes D, Muller JY, Brachet P. 1, 25 Dihydroxyvitamin D3 exerts regional effects in the central nervous system during experimental allergic encephalomyelitis. J Neuropathol Exp Neurol 1996;55:904–914.
27. D'Ambrosio D, Cippitelli M, Cocciolo MG, et al. Inhibition of IL-12 production by 1,25-dihydroxyvitamin D3. Involvement of NF-kappaB downregulation in transcriptional repression of the p40 gene. J Clin Invest 1998;101:252–262.
28. Lemire JM, Archer DC, Beck L, Spiegelberg HL. Immunosuppressive actions of 1,25-dihydroxyvitamin D3: preferential inhibition of Th1 functions. J Nutr 1995;125(suppl 6):1704S–1708S.
29. Reichel H, Koeffler HP, Tobler A, Norman AW. 1 Alpha,25-dihydroxyvitamin D3 inhibits gamma-interferon synthesis by normal human peripheral blood lymphocytes. Proc Natl Acad Sci USA 1987;84: 3385–3389.
30. Rigby WF, Noelle RJ, Krause K, Fanger MW. The effects of 1,25-dihydroxyvitamin D3 on human T lymphocyte activation and proliferation: a cell cycle analysis. J Immunol 1985;135:2279–2286.
31. Hypponen E, Laara E, Reunanen A, Jarvelin MR, Virtanen SM. Intake of vitamin D and risk of type 1 diabetes: a birth-cohort study. Lancet 2001;358:1500–1503.
32. Zhang SM, Hernán MA, Olek MJ, Spiegelman D, Willett WC, Ascherio A. Intakes of carotenoids, vitamin C, and vitamin E and MS risk among two large cohorts of women. Neurology 2001;57:75–80.
33. Mickel HS. Multiple sclerosis: a new hypothesis. Perspect Biol Med 1975;18:363–374.
34. Johnson S. The possible role of gradual accumulation of copper, cadmium, lead and iron and gradual depletion of zinc, magnesium, selenium, vitamins B2, B6, D, and E and essential fatty acids in multiple sclerosis. Med Hypotheses 2000;55:239–241.
35. Reynolds EH, Linnell JC. Vitamin B12 deficiency, demyelination, and multiple sclerosis. Lancet 1987;2:920.