Published in final edited form as:
J Neurol. 2011 March ; 258(3): 479–485. doi:10.1007/s00415-010-5783-1.

Dietary intake of vitamin D during adolescence and risk of multiple sclerosis

Kassandra L. Munger,
Department of Nutrition, Harvard School of Public Health, 665 Huntington Ave, Bldg. 2, 3rd Fl., Boston, MA 02115, USA

Tanuja Chitnis,
Partners Multiple Sclerosis Center, Department of Neurology, Brigham and Women's Hospital, Harvard Medical School, Boston, MA 02115, USA

A. Lindsay Frazier,
Department of Pediatric Oncology, Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA 02115, USA

Channing Laboratory, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA 02115, USA

Edward Giovannucci,
Department of Nutrition, Harvard School of Public Health, 665 Huntington Ave, Bldg. 2, 3rd Fl., Boston, MA 02115, USA

Channing Laboratory, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA 02115, USA

Department of Epidemiology, Harvard School of Public Health, Boston, MA 02115, USA

Donna Spiegelman, and
Department of Epidemiology, Harvard School of Public Health, Boston, MA 02115, USA

Department of Biostatistics, Harvard School of Public Health, Boston, MA 02115, USA

Alberto Ascherio
Department of Nutrition, Harvard School of Public Health, 665 Huntington Ave, Bldg. 2, 3rd Fl., Boston, MA 02115, USA

Channing Laboratory, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA 02115, USA

Department of Epidemiology, Harvard School of Public Health, Boston, MA 02115, USA

Kassandra L. Munger: kgorham@hsph.harvard.edu

Abstract

Adolescence may be an important etiological period in the development of multiple sclerosis (MS), and studies suggest that adequate vitamin D nutrition is protective. Here, the authors examined whether dietary intake of vitamin D during adolescence decreases the risk of MS in adulthood. In 1986 in the Nurses' Health Study and in 1998 in the Nurses' Health Study II

Correspondence to: Kassandra L. Munger, kgorham@hsph.harvard.edu.

The authors have no financial conflicts of interest to disclose.

(NHSII), women completed a food frequency questionnaire regarding their dietary intake during adolescence. From this, daily intake of vitamin D was calculated. Adolescent diet was available for 379 incident MS cases confirmed over the combined 44 years of follow-up in both cohorts, and for 67 prevalent cases in the NHSII who had MS at baseline (1989). Cox proportional hazards models were used to calculate relative risk estimates and 95% confidence intervals. Total vitamin D intake during adolescence was not associated with MS risk. Intake of ≥400 IU/day of vitamin D from multivitamins was associated with a non-statistically significant reduced risk (RR compared to no intake = 0.73, 95% CI: 0.50–1.07, $P = 0.11$), whereas intake of whole milk, an important source of dietary vitamin D, was associated with an increased risk. The possibility of opposite effects of vitamin D and milk intake on MS risk should be considered in future studies.

Keywords

Multiple sclerosis; Vitamin D; Cohort study; Epidemiology

Introduction

Current evidence suggests that multiple sclerosis (MS) is caused by an environmental factor(s) in genetically susceptible individuals [1,2], and that adolescence may be an important etiologic period for the development of MS [3,4]. Insufficient vitamin D nutrition has been proposed as a possible risk factor for MS and studies showing an inverse association between MS and sun exposure during childhood [5], dietary vitamin D intake in adulthood [6], and high serum levels of vitamin D [7] provide evidence which supports the hypothesis. Using two large cohorts of US women, we examined whether dietary intake of vitamin D during adolescence was associated with the risk of MS in adulthood.

Materials and methods

Study population

The Nurses' Health Study (NHS) is a cohort of 121,700 female registered nurses, who were 30–55 years old when the cohort began in 1976. The Nurses' Health Study II (NHSII) cohort is comprised of 116,671 female registered nurses, who were 25–45 years old when the cohort began in 1989. Women in both cohorts complete detailed questionnaires every two years regarding their lifestyle practices and medical conditions. This study was approved by the institutional review board of Brigham and Women's Hospital.

Case ascertainment

Women who report an MS diagnosis are sent a request to allow study investigators to contact their treating neurologists. Neurologists are sent a questionnaire asking if the MS diagnosis is definite, probable, or possible, and whether laboratory test results, such as MRI and oligoclonal banding, support the diagnosis. In a previous validation study, there was 93% agreement between the treating neurologists' diagnosis and the diagnosis made by a study neurologist after medical record review [8]. Therefore, we considered the diagnosis definite or probable if made by the treating neurologist or after medical record review by our study neurologist. We have confirmed 248 incident definite/probable cases in the NHS between 1976 and 2004, and 413 in the NHSII between 1989 and 2005. In the NHSII, we have also confirmed 140 women, who had prevalent definite/probable MS when the cohort began in 1989 following the same confirmation procedures as described above.

Adolescent diet assessment

Typical diet during adolescence (approximately aged 13–18) was assessed in the NHS cohort in 1986 with a 24-item high school food frequency questionnaire (HS-FFQ) included in the biennial questionnaire, and in a subset of women in the NHSII (n = 47,355) in 1998 with a supplemental 131-item HS-FFQ. Women were asked to report their average consumption frequency of a variety of foods, including dairy foods, during the years they were in high school using one of nine categories ranging from never or less than once/month to six or more/day. Portion size was specified for each food item as appropriate (e.g. one 8-oz glass of milk). Women were also asked about their multivitamin use (yes/no), and frequency of use (in the NHS using the same nine categories as for food items; in the NHSII: ≤2 pills/week, 3–5, 6–9, or ≥10). Both the NHS and NHSII HS-FFQ included milk, fish, and multivitamins, the main sources of dietary vitamin D. Intake of vitamin D (total, dairy, non-dairy, from multivitamins) for each participant was calculated as the frequency of food/multivitamin item intake multiplied by the nutrient composition of the specified portion size of each food, with frequencies weighted in proportion to one per day being equal to one. For example, women who reported intake of a food once/day would have a daily intake of vitamin D from that food equal to the amount of vitamin D in the specified portion multiplied by one. Likewise, intake of food 2–3 times/day is weighted as 2.5 (average frequency) so that daily vitamin D intake from food is the amount in the specified portion ×2.5. For food items consumed less than daily, the average frequency was divided by seven to estimate a “daily” intake. Total daily vitamin D intake was the sum of all daily vitamin D intake from each food/multivitamin item. Similarly, dairy vitamin D was from dairy sources only and non-dairy vitamin D from non-dairy sources only.

Reproducibility of the HS-FFQ has been assessed in both cohorts, and for total vitamin D intake the correlation between the two assessments was 0.51 (NHS) [9] and 0.71 (NHSII) [10]. The reproducibility correlation for milk intake was 0.76 in the NHSII, but was not available in the NHS. The validity of the 131-item HS-FFQ was indirectly assessed by asking mothers of NHSII participants to recall their daughters’ high school diet using the HS-FFQ. The correlation between the daughters’ and mothers’ recall for vitamin D intake was 0.48 and was 0.43 for milk intake [10]. Further, reported adolescent diet was not highly correlated with current dietary intake in either cohort [9,10]. Overall, these studies suggest that remote recall of diet during adolescence has good reproducibility in these cohorts and may be used to assess associations between diet in early life and adult-onset disease.

Statistical analysis

Women with unrealistic caloric intakes per day [<500 or >4,500 (NHS n = 1,230)/<600 or >5,000 (NHSII n = 1,243)] were excluded from the analyses. Complete information on dietary intake during adolescence was available for 73,938 women in the NHS and 45,848 women in the NHSII, including 177 (71%, NHS) and 202 (49%, NHSII) incident MS cases, and 67 (48%) prevalent cases (NHSII). Cox proportional hazards models, stratified by age in months and 2-year time periods, were used to estimate the rate ratios and 95% confidence intervals. In multivariate analyses, we adjusted for caloric intake, ethnicity, latitude of residence at age 15, and pack-years of cigarette smoking [8]. We created quintiles of vitamin D intake (total, dairy only, non-dairy only) based on the distribution of intake for each cohort. Supplemental vitamin D was categorized in IU/day as 0, <400, ≥400 (400 IU being the typical amount in a multivitamin). Because previous ecologic studies have suggested an increased prevalence of MS in areas with higher milk consumption [11,12], and individuals with MS have elevated antibodies to some milk proteins which may cross-react with myelin [13,14], we hypothesized that an inverse association with vitamin D may be masked by a positive association with dairy intake; therefore, we also conducted analyses adjusting for dairy intake and for the association between specific dairy foods and MS. Tests for linear

trends were conducted by modeling the median nutrient intake for each quintile/category or the number of servings of total dairy or milk per day as continuous variables. All analyses were conducted separately among the NHS incident, NHSII incident, and NHSII prevalent cases, and were pooled using the inverse variance of the effect estimates as the weight. A Q-statistic was used to assess heterogeneity of the rate ratios across the three groups [15]. Analyses were also conducted restricted to the prospective subgroup, for instance, cases diagnosed and person-time accrued after return of the HS-FFQ in 1986 (NHS, $n = 108$ cases) or 1998 (NHSII, $n = 68$ cases) and to definite cases only (NHS, $n = 116$; NHSII, $n = 149$). Finally, we conducted an exploratory analysis restricted to women who were living in the northern tier of the US at age 15 (NHS, $n = 88$; NHSII, $n = 73$), as diet becomes a more significant source of vitamin D at higher latitudes during the winter months when vitamin D production by sun exposure is markedly reduced or absent. Analyses were conducted using SAS version 9. A P value <0.05 was considered statistically significant.

Results

Women with greater vitamin D or whole milk intake were more likely to live in the northern tier of the US at age 15, have a Scandinavian ancestry, and were less likely to be ever have been smokers at baseline (Table 1).

Although neither total vitamin D intake nor intake of vitamin D from supplements during adolescence were significantly associated with MS risk, there was a suggestion of a 27% reduction in MS risk with intake of at least 400 IU of vitamin D from supplements (Table 2). In analyses restricted to women living in the northern tier at age 15, while there was still no relation between total vitamin D intake and MS risk, the inverse association between vitamin D from supplements and MS risk was stronger [Pooled relative risk (RR) comparing intake of at least 400 IU/day to no intake = 0.51; 95% CI: 0.21, 1.24] and approached significance (P for trend = 0.05). The interaction between latitude of residence and supplemental vitamin D intake was not significant ($P = 0.63$).

Total vitamin D intake from dairy sources only was not associated with MS risk (Table 2), while there was a non-statistically significant 22% reduction in risk with vitamin D from non-dairy sources (top vs. bottom quintile, $P = 0.14$) (Table 2). In analyses based on servings per day of dairy products, total dairy intake was not related to MS risk, but women who consumed whole milk three or more times per day had a 47% increased risk of MS ($P = 0.04$) (Table 2). Among other dairy foods, only cream cheese (Pooled RR ≥2 servings/week vs. <1/month = 1.57; 95% CI: 1.01, 2.44; $P = 0.04$), was associated with MS risk (data not shown).

The above analyses were also prospectively conducted (i.e., restricted to person–time and cases occurring after return of the HS-FFQs—1986 in the NHS and 1998 in the NHSII). While there was still no association with total vitamin D intake (Pooled RR top vs. bottom quintile = 1.03; 95% CI: 0.49, 2.15; P for trend = 0.58), the suggestion of an inverse association with ≥400 IU/day of supplemental vitamin D intake versus none (Pooled RR = 0.79; 95% CI: 0.46,1.36) and a positive association with ≥3 servings/day versus <1/month of whole milk remained (Pooled RR = 1.43; 95% CI: 0.75, 2.74), though neither was statistically significant in trend tests. Results were also similar when analyses were restricted to definite cases and those with relapsing–remitting MS (data not shown).

In a previous study in these cohorts, we found that intake of vitamin D from supplements during adulthood was inversely associated with MS [6]. Therefore, we also examined the effect of “lifetime” high vitamin D intake from supplements (i.e., during both adolescence and adulthood) on MS risk. Compared to women with no intake, the relative risk of MS

among women with intake ≥400 IU/day of vitamin D during both periods was 0.71 (95% CI: 0.36, 1.39; $P = 0.32$).

Discussion

In these two large cohorts of US women, total vitamin D intake during adolescence was not associated with risk of MS in adulthood. There was a non-statistically significant lower risk of MS among women with high intake of vitamin D from supplements during adolescence, particularly those living at higher latitude, whereas intake of three or more servings per day of whole milk during adolescence was associated with an increased MS risk.

The results of previous investigations are consistent overall with the hypothesis that MS risk is related to vitamin D status at different ages [16], possibly starting in utero [17–20] and extending through early childhood [21], adolescence [5,22,23], and adult life [6,7], although a lack of association between use of vitamin D supplements in adolescence (age 10–15) and MS risk has also been reported [5]. Several factors may explain why vitamin D intake during adolescence was not associated with MS risk in our study. First and foremost, vitamin D status is largely dependent on sun exposure [24], and therefore, even if high vitamin D concentrations reduced the risk of MS, only a modest association would be expected with vitamin D intake. Even a relatively large study has therefore only sub-optimal power. This limitation is compounded by the difficulty in obtaining an accurate measure of vitamin D intake during adolescence. While previous reproducibility [9,10] and validation studies [10] in these cohorts suggest recall of diet during high school using an FFQ is adequate for purposes of studying adolescent diet–adult disease associations, and previous studies using the HS-FFQs in these cohorts found associations between adolescent diet and risk of breast cancer [25–27], non-differential error in reporting of food item intake is likely and would likely bias associations between vitamin D intake and MS risk towards the null. Additionally, women in the NHS cohorts were recruited past the peak age of MS incidence (late 20s to early 30s) and therefore have an average age of MS onset which is older than in the general population (NHS = 42 years; NHSII = 38 years); migration studies suggest that exposures during childhood or adolescence are important in the etiology of MS, and vitamin D intake during adolescence may be more important for MS onset at younger rather than older ages. On the other hand, due to the high collinearity between vitamins from supplemental sources, we cannot exclude the possibility of confounding from other vitamins found in the supplements. Finally, the moderate inverse association that we found is consistent with recent evidence suggesting that the effects of vitamin D on MS risk may depend on genetic susceptibility—in a recent study in the Nurses' Health Study cohorts, dietary intake of vitamin D during adulthood was only associated with a reduced risk of MS among women who had the vitamin D receptor 'ff' genotype [28].

Observations of high correlations between prevalence of MS and milk consumption in ecologic studies [11,12], and increased antibodies to some milk proteins that may cross-react with myelin proteins in MS patients [13,14] led us to examine milk and other dairy as possible confounders of the vitamin D association, essentially masking a protective effect of vitamin D. While the associations we observed with vitamin D intake and MS risk did not change, we did observe an increased risk of MS with whole milk intake of at least three servings/day during adolescence; this association persisted in analysis adjusted for latitude of residence at age 15, and is thus unlikely to simply reflect an increased milk consumption in northern states. In a prospective study of dietary intake in adulthood and risk of MS in the NHS and NHSII [29], there was no association with dairy food consumption. Therefore, the association with whole milk seen here should be interpreted cautiously and needs confirmation in other populations.

In summary, in this large investigation, we observed no association between total vitamin D intake during adolescence and risk of MS in adulthood. However, there was a non-statistically significant 27% reduction of MS with ≥400 IU/day of vitamin D from supplements and a slight increased risk associated with consumption of ≥3 servings of whole milk per day during adolescence. These results are relevant for the planning of further investigations, which should consider the possibility of opposing effects of vitamin D and other milk components on MS risk.

Acknowledgments

This work was supported by the National Institute of Neurological Disorders and Stroke at the National Institutes of Health (grant NS047467). We thank K. Claire Simon, ScD, and Leslie Unger for technical support.

References

1. Ascherio A, Munger KL. Environmental risk factors for multiple sclerosis. Part I: the role of infection. Ann Neurol. 2007; 61:288–299. [PubMed: 17444504]
2. Ascherio A, Munger KL. Environmental risk factors for multiple sclerosis. Part II: noninfectious factors. Ann Neurol. 2007; 61:504–513. [PubMed: 17492755]
3. Cabre P. Migration and multiple sclerosis: the French West Indies experience. J Neurol Sci. 2007; 262:117–121. [PubMed: 17651756]
4. Gale CR, Martyn CN. Migrant studies in multiple sclerosis. Prog Neurobiol. 1995; 47:425–448. [PubMed: 8966212]
5. van der Mei IA, Ponsonby AL, Dwyer T, Blizzard L, Simmons R, Taylor BV, Butzkueven H, Kilpatrick T. Past exposure to sun, skin phenotype, and risk of multiple sclerosis: case-control study. BMJ. 2003; 327:316–321. [PubMed: 12907484]
6. Munger KL, Zhang SM, O'Reilly E, Hernan MA, Olek MJ, Willett WC, Ascherio A. Vitamin D intake and incidence of multiple sclerosis. Neurology. 2004; 62:60–65. [PubMed: 14718698]
7. Munger KL, Levin LI, Hollis BW, Howard NS, Ascherio A. Serum 25-hydroxyvitamin D levels and risk of multiple sclerosis. JAMA. 2006; 296:2832–2838. [PubMed: 17179460]
8. Hernan MA, Olek MJ, Ascherio A. Geographic variation of MS incidence in two prospective studies of US women. Neurology. 1999; 53:1711–1718. [PubMed: 10563617]
9. Frazier AL, Willett WC, Colditz GA. Reproducibility of recall of adolescent diet: Nurses' Health Study (United States). Cancer Causes Control. 1995; 6:499–506. [PubMed: 8580297]
10. Maruti SS, Feskanich D, Colditz GA, Frazier AL, Sampson LA, Michels KB, Hunter DJ, Spiegelman D, Willett WC. Adult recall of adolescent diet: reproducibility and comparison with maternal reporting. Am J Epidemiol. 2005; 161:89–97. [PubMed: 15615919]
11. Butcher J. The distribution of multiple sclerosis in relation to the dairy industry and milk consumption. NZ Med J. 1976; 83:427–430.
12. Malosse D, Perron H, Sasco A, Seigneurin JM. Correlation between milk and dairy product consumption and multiple sclerosis prevalence: a worldwide study. Neuroepidemiology. 1992; 11:304–312. [PubMed: 1291895]
13. Banwell B, Bar-Or A, Cheung R, Kennedy J, Krupp LB, Becker DJ, Dosch HM. Abnormal T-cell reactivities in childhood inflammatory demyelinating disease and type 1 diabetes. Ann Neurol. 2008; 63:98–111. [PubMed: 17932975]
14. Guggenmos J, Schubart AS, Ogg S, Andersson M, Olsson T, Mather IH, Linington C. Antibody cross-reactivity between myelin oligodendrocyte glycoprotein and the milk protein butyrophilin in multiple sclerosis. J Immunol. 2004; 172:661–668. [PubMed: 14688379]
15. DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials. 1986; 7:177–188. [PubMed: 3802833]
16. Handel AE, Giovannoni G, Ebers GC, Ramagopalan SV. Environmental factors and their timing in adult–onset multiple sclerosis. Nat Rev Neurol. 2010; 6:156–166. [PubMed: 20157307]

17. Gardener H, Munger KL, Chitnis T, Michels KB, Spiegelman D, Ascherio A. Prenatal and perinatal factors and risk of multiple sclerosis. Epidemiology. 2009; 20:611–618. [PubMed: 19333127]

18. Ramagopalan SV, Dyment DA, Ebers GC, Sadovnick AD. Gestational diabetes and multiple sclerosis. Epidemiology. 2009; 20:783–784. [PubMed: 19680044]

19. Staples J, Ponsonby AL, Lim L. Low maternal exposure to ultraviolet radiation in pregnancy, month of birth, and risk of multiple sclerosis in offspring: longitudinal analysis. BMJ 340. 2010

20. Willer CJ, Dyment DA, Sadovnick AD, Rothwell PM, Murray TJ, Ebers GC. Timing of birth and risk of multiple sclerosis: population based study. BMJ. 2005; 330:120. [PubMed: 15585537]

21. Islam T, Gauderman WJ, Cozen W, Mack TM. Childhood sun exposure influences risk of multiple sclerosis in monozygotic twins. Neurology. 2007; 69:381–388. [PubMed: 17646631]

22. Kampman MT, Wilsgaard T, Mellgren SI. Outdoor activities and diet in childhood and adolescence relate to MS risk above the Arctic Circle. J Neurol. 2007; 254:471–477. [PubMed: 17377831]

23. Munger KL, Chitnis T, Ascherio A. Body size and risk of MS in two cohorts of US women. Neurology. 2009; 73:1543–1550. [PubMed: 19901245]

24. Holick MF. Environmental factors that influence the cutaneous production of vitamin D. Am J Clin Nutr. 1995; 61:638S–645S. [PubMed: 7879731]

25. Frazier AL, Li L, Cho E, Willett WC, Colditz GA. Adolescent diet and risk of breast cancer. Cancer Causes Control. 2004; 15:73–82. [PubMed: 14970737]

26. Frazier AL, Ryan CT, Rockett H, Willett WC, Colditz GA. Adolescent diet and risk of breast cancer. Breast Cancer Res. 2003; 5:R59–R64.

27. Linos E, Willett WC, Cho E, Colditz G, Frazier LA. Red meat consumption during adolescence among premenopausal women and risk of breast cancer. Cancer Epidemiol Biomarkers Prev. 2008; 17:2146–2151. [PubMed: 18669582]

28. Simon KC, Munger KL, Xing Y, Ascherio A. Polymorphisms in vitamin D metabolism related genes and risk of multiple sclerosis. Mult Scler. 2010; 16:133–138. [PubMed: 20007432]

29. Zhang SM, Willett WC, Hernan MA, Olek MJ, Ascherio A. Dietary fat in relation to risk of multiple sclerosis among two large cohorts of women. Am J Epidemiol. 2000; 152:1056–1064. [PubMed: 11117615]

Table 1

Selected characteristics of women in NHS and NHSII by total vitamin D and whole milk intake during adolescence

	Quintile of vitamin D intake					Whole milk intake (servings/day)		
	1	**2**	**3**	**4**	**5**	**≤1**	**1 to <2**	**2 to <3**
NHS								
No. of women	15,038	15,029	15,064	15,010	15,029	30,338	13,321	27,049
Age baseline, mean	43.7	43.4	43.3	43.1	42.1	42.9	43.5	43.2
Residence in North tier at age 15 (%)	28	34	39	41	39	30	34	42
Scandinavian ancestry (%)	2.7	3.6	4.1	4.5	4.5	3.3	3.9	4.5
History of smoking at baseline (%)	55	55	55	53	52	55	54	54
NHSII								
No. of women	9,173	9,184	9,157	9,172	9,168	26,232	6,712	9,937
Age baseline, mean	34.4	34.4	34.6	34.7	34.6	33.8	35.2	35.8
Residence in North tier at age 15 (%)	28	31	34	35	35	29	33	38
Scandinavian ancestry (%)	3.6	4.1	4.5	5.2	5.8	4.6	3.9	4.9
History of smoking at baseline (%)	37	35	33	32	29	33	36	32

Each category is directly standardized to the baseline age distribution of the corresponding cohort

NHS Nurses' Health Study; *NHSII* Nurses' Health Study II

Table 2

RRs and 95% CI for vitamin D and dairy intake during adolescence and MS, NHS (1976–2004) and NHSII (1989–2005)

	NHS		NHSII			Multivariate[b] Pooled	
	Median (IU/day)	Incident[a] cases/py	Median (IU/day)	Incident[a] cases/py	Prevalent[a] cases/py	Incident RR (95% CI)	Incident and prevalent RR (95% CI)
Total vitamin D							
Quintile 1	143	28/396,481	148	41/142,419	15/70,091	1	1
Quintile 2	230	36/399,926	227	32/142,750	20/70,046	0.97 (0.60, 1.57)	1.04 (0.73, 1.48)
Quintile 3	304	35/402,704	316	43/142,190	12/70,542	1.08 (0.78, 1.50)	1.03 (0.76, 1.39)
Quintile 4	386	43/400,735	404	47/142,520	10/70,545	1.22 (0.89, 1.68)	1.12 (0.80, 1.56)
Quintile 5	695	35/397,520	586	39/142,381	10/69,328	0.99 (0.71, 1.38)	0.94 (0.69, 1.28)
Total		177/1,997,367		202/712,260	67/350,552		
P trend[c]						0.93	0.66
P het[d]						0.71	0.31
Vitamin D supplements only							
0	0	144/1,649,117	0	174/598,924	58/296,409	1	1
<400	70	11/105,999	228	22/71,727	7/33,974	1.03 (0.72, 1.48)	1.04 (0.75, 1.44)
≥400	500	22/242,250	400	6/41,609	2/20,169	0.72 (0.43, 1.21)	0.73 (0.50, 1.07)
Total		177/1,997,367		202/712,260	67/350,552		
P trend						0.23	0.18
P het						0.51	0.78
Non-dairy vitamin D							
Quintile 1	39	30/395,878	34	48/142,205	11/74,971	1	1
Quintile 2	67	35/403,269	45	33/142,463	21/74,322	0.83 (0.58,1.18)	1.03 (0.62, 1.72)
Quintile 3	97	44/402,256	58	48/142,458	11/67,653	1.15 (0.84, 1.56)	1.14 (0.85, 1.52)
Quintile 4	146	32/396,419	110	42/142,514	16/64,913	0.91 (0.66, 1.27)	1.00 (0.74, 1.36)
Quintile 5	541	36/399,546	236	31/142,619	8/68,693	0.78 (0.55, 1.08)	0.78 (0.57, 1.07)
Total		177/1,997,367		202/712,260	67/350,552		
P trend						0.27	0.16
P het						0.27	0.37
Dairy vitamin D							

	NHS		NHSII			Multivariate[b] Pooled	
	Median (IU/day)	Incident[a] cases/py	Median (IU/day)	Incident[a] cases/py	Prevalent[a] cases/py	Incident RR (95% CI)	Incident and prevalent RR (95% CI)
Quintile 1	52	28/396,904	57	45/142,595	13/68,490	1	1
Quintile 2	128	41/398,965	117	26/142,571	19/69,073	0.88 (0.37, 2.08)	1.01 (0.54, 1.88)
Quintile 3	190	39/402,127	176	38/142,347	15/70,548	1.02 (0.64, 1.63)	1.02 (0.75, 1.39)
Quintile 4	255	37/404,259	256	45/142,468	9/70,964	1.06 (0.77, 1.46)	1.00 (0.74, 1.34)
Quintile 5	359	32/395,112	362	48/142,278	11/71,477	1.07 (0.77, 1.48)	1.03 (0.76, 1.39)
Total		177/1,997,367		202/712,260	67/350,552		
P trend						0.35	0.90
P het						0.47	0.23
Total dairy[e]							
<1 servings/day		15/205,228		12/45,437	2/23,701	1	1
1 to <2		39/407,293		35/137,041	14/67,045	1.10 (0.70, 1.71)	1.16 (0.76, 1.78)
2 to <3		29/354,834		27/140,772	20/67,925	0.85 (0.53, 1.36)	0.99 (0.56, 1.76)
3 to <4		31/404,657		49/154,106	14/76,097	1.02 (0.64, 1.62)	1.07 (0.68, 1.66)
4 to <5		23/184,227		30/107,698	8/52,852	1.24 (0.75, 2.05)	1.25 (0.78, 2.02)
5 to <6		20/228,900		23/58,667	2/29,012	1.26 (0.75, 2.14)	1.21 (0.73, 2.01)
≥6		20/212,227		26/68,540	7/34,514	1.25 (0.72, 2.18)	1.29 (0.76, 2.18)
Total		177/1,997,367		202/712,260	67/350,552		
P trend						0.10	0.29
P het						0.43	0.31
Total milk							
<1 servings/day		57/692,596		68/250,359	25/123,016	1	1
1 to <2		39/380,460		34/156,801	20/76,301	0.97 (0.63, 1.49)	1.03 (0.76, 1.39)
2 to <3		62/785,972		75/237,315	15/118,111	1.00 (0.76, 1.32)	0.90 (0.66, 1.25)
≥3		19/138,339		25/67,785	7/33,124	1.38 (0.94, 2.02)	1.30 (0.92, 1.84)
Total		177/1,997,367		202/712,260	67/350,552		
P trend						0.29	0.84
P het						0.46	0.16
Total whole milk							
<1 servings/day		67/789,381		110/407,655	37/191,340	1	1

	NHS		NHSII			Multivariate[b] Pooled	
	Median (IU/day)	Incident[a] cases/py	Median (IU/day)	Incident[a] cases/py	Prevalent[a] cases/py	Incident RR (95% CI)	Incident and prevalent RR (95% CI)
1 to <2		34/358,314		21/104,276	16/53,694	0.90 (0.57, 1.42)	1.03 (0.69, 1.53)
2 to <3		61/730,412		51/154,238	7/81,826	1.05 (0.81, 1.36)	0.88 (0.57, 1.35)
≥3		15/119,260		20/46,091	7/23,692	1.49 (1.00, 2.22)	1.47 (1.03, 2.11)
Total		177/1,997,367		202/712,260	67/350,552		
P trend						0.17	0.45
P het						0.46	0.32

NHS Nurses' Health Study; *NHSII* Nurses' Health Study II; *RR* relative risk; *CI* confidence interval; *MS* multiple sclerosis; *IU* International Units; *py* person–years

[a] Incident cases diagnosed between 1976–June 2004 (NHS) and between 1989–June 2005 (NHSII); prevalent cases diagnosed before 1989 (NHSII)

[b] Adjusted for age (months), 2-year time periods, total caloric intake (kcal/day) (except supplemental vitamin D), latitude of residence age 15 (north, middle, south), ethnicity (Scandinavian, Southern European, other Caucasian, other), pack-years smoking (never,<10, 10–24, >24)

[c] *P* value for linear trend calculated from Cox proportional hazards models

[d] *P* value for heterogeneity of the pooled effect estimate from Chi-squared test

[e] Total dairy: non/low-fat milk, whole milk, milkshake/frappe, ice cream, cheese, butter; NHSII only also included: chocolate milk, sherbet, yogurt, cottage/ricotta cheese, instant breakfast drink, cream cheese, pudding