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Vitamin D Intake and Risks of Systemic Lupus Erythematosus and Rheumatoid Arthritis in Women

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Abstract

Objectives—Vitamin D has immune-modulating effects and may protect against the development of Systemic Lupus Erythematosus (SLE) and Rheumatoid Arthritis (RA).

Methods—We identified incident cases of SLE and RA among 186,389 women followed from 1980-2002 in the Nurses' Health Study and Nurses' Health Study II cohorts. We excluded subjects with non-confirmed SLE or RA by medical record review, and those who failed to return questionnaires. Semi-quantitative food frequency questionnaires assessed vitamin D intake from food and supplements. We used cumulative-updated total energy-adjusted dietary exposures for each two year cycle.

Relationships between vitamin D intake and incident SLE and RA were examined in age-adjusted and Cox proportional hazards models, adjusted for confounders. Results were pooled using meta-analysis random effects models.

Results—We confirmed 190 incident cases of SLE and 722 of RA with dietary information. Increasing levels of vitamin D intake had no relationship to the relative risk of developing either SLE or RA.

Conclusions—Vitamin D intake was not associated with risk of SLE or RA in these large prospective cohorts of women.

Keywords

systemic lupus erythematosus; rheumatoid arthritis; risk factors; epidemiology; vitamin D

Vitamin D status may be important in autoimmune disease pathogenesis[1,2], as active 1,25-dihydroxyvitamin D has multiple immunomodulating effects. [1,3,4] Systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA) are related autoimmune diseases of

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unknown etiology. Both primarily affect women and are characterized by autoantibody production, inflammatory polyarthritis, and systemic inflammation.

The hypothesis that vitamin D intake could be related to risk of SLE or RA is attractive for several reasons. The vitamin D receptor is expressed constitutively by macrophages and dendritic cells and is induced with lymphocyte activation.[5] 1,25-dihydroxyvitamin D is produced by activated macrophages in response to interferonγ and toll-like receptor signaling. [6] *In vivo*, 1, 25hydroxyvitamin D supplementation forestalls development of arthritis in experimental models.[7] Increased vitamin D intake is associated with decreased risk of other autoimmune diseases, including type I diabetes mellitus[8] and multiple sclerosis.[9] Vitamin D deficiency is prevalent in SLE [10-12] and RA [13-15], but this may be due to disease.

In the Iowa Women's Health Study, higher baseline vitamin D intake was associated with decreased risk of RA[16], but serum 25-hydroxyvitamin D was not related to future RA in a Dutch case-control study using blood bank samples.[17] Potential associations of vitamin D intake or serum level with risk of SLE have never been investigated prospectively.

Our aim was to investigate associations between, vitamin D intake and two outcomes, incident SLE and RA, among women in the Nurses' Health Study (NHS) and Nurses' Health Study II (NHSII), the largest cohorts of women followed prospectively for rheumatic disease.

Methods

Study Population

NHS is a prospective cohort of 121,700 female nurses, aged 30-55 years in 1976 at study inception. The first semi-quantitative food frequency questionnaire (FFQ) [18] was mailed to NHS participants in 1980. NHSII was established in 1989, when 116,608 female nurses aged 25-42 completed a baseline questionnaire about lifestyle and medical history. The first semi-quantitative FFQ was mailed to NHSII participants in 1991. Ninety-four percent of the NHS participants from 1976-2002 and 95% of NHSII participants from 1989-2003 remain in active follow-up (5-6% no longer respond to questionnaires and have not been confirmed as dead). Information is prospectively collected in both cohorts via biennial questionnaires. The Brigham and Women's Hospital Institutional Review Board approved this study.

Identification of SLE and RA

As previously described [19-22], we employed a two-stage procedure in which nurses who reported connective tissue disease received a connective tissue disease screening questionnaire (CSQ) [23], and, if positive, a medical record review. Two rheumatologists trained in chart abstraction independently conducted a medical record review examining the charts for the American College of Rheumatology (ACR) diagnostic criteria for SLE [24,25] and RA. [26] SLE and RA cases were confirmed if they met ACR criteria. Case validation rates for both SLE and RA were 7% of the total self-reports.

Population for Analysis

We excluded prevalent cases of SLE and RA, and all women who reported any connective tissue disease that was not subsequently confirmed as SLE or RA as above. We included only nurses who had completed the FFQ at baseline, 1980 in the NHS and 1991 in NHSII. Women were censored at last response to questionnaires, as incident cases could not be identified. The final group included 91,739 women followed from 1980-2002 in the NHS and 94,650 women followed from 1991-2001 in the NHSII. In a sensitivity analysis, we excluded women who reported any cancer (except non-melanoma skin cancer) at any time, as cancer and its treatment may affect vitamin intake and health behaviors.

Nutritional factors

The semi-quantitative FFQ on which participants reported the frequency of consumption for specified foods over the past year was used to assess nutritional factors. NHS participants completed the FFQ in 1980, 1984, 1986, 1990 and 1994, and 1998, and NHSII participants returned FFQs in 1991, 1995 and 2001. Dietary nutrients (i.e., vitamin D, calcium, protein, vitamin A), alcohol and caffeine were calculated according to the nutrient content of foods, derived from the U.S. Department of Agriculture, food manufacturers, and other published sources. The accuracy and reproducibility of the FFQ for nutrients and foods have been documented in validation studies.[18,27,28] In a study comparing the FFQ to weekly complete diet diaries in NHS, the correlation was 0.81 for skim milk and 0.66 for fish, the two largest contributors to dietary vitamin D.[27] The correlation between serum 25-hydroxy vitamin D level and vitamin D intake as assessed by the semi-quantitative FFQ in NHS participants was 0.25 ($p<0.001$).[29]

In NHS, multivitamin use was first assessed in 1980 and use of calcium or vitamin D supplements was added in 1982. In NHSII, all three supplements were assessed in 1991, and, in both cohorts, they were included on every questionnaire after the initial measurement. Participants were asked for the name brand of multivitamins, as well as number of tablets taken per week. For calcium supplements, participants specified dose per day. Vitamin D supplement use was coded as 400 IU/day. The sensitivity and specificity of the FFQ regarding any supplement use were 78 and 93% respectively.[30]

Total nutrient intakes included amounts from multivitamins, specific supplements, and foods. Nutrient intakes correlated with total energy intake (all except caffeine and alcohol) were adjusted for total energy intake with linear regression analyses.[31] All nutrient intake values were cumulatively updated in each two-year follow-up cycle, i.e. each nutrient was calculated as the mean of intakes to that time. Vitamin D from food and from supplements were examined separately and together in quintiles, quartiles, as continuous values, in categories of international units (IU) per day: (0, < 200, 200-399, and ≥ 400), and defined dichotomously as < 400 or ≥ 400 IU per day.

Covariate Information

Age was updated each cycle. Based on past findings, risk factors for RA and SLE in these cohorts [20,22,32], including smoking, age at menarche, menstrual regularity, and menopausal status were included as potential confounders. We included parity and total duration of breastfeeding in RA analyses. Postmenopausal hormone use was included as a covariate in NHS cohort analyses, but not in NHSII cohort analyses as few women were postmenopausal during these years.

Body mass index (BMI) was computed for each two-year time interval using most recent weight in kilograms divided by height in meters squared. Hours per week spent in physical activities were assessed seven times in NHS and four times in NHSII. A validation study found a correlation of 0.79 between one week exercise recall and exercise reported on the NHS questionnaire.[33] Husband's educational level was assessed in 1992 in NHS and 1999 in NHSII.

In 1992 (NHS) and 1991 (NHSII), participants reported state of birth and state of residence at ages 15 and 30 (82% response rate in NHS and 85% in NHSII), and current address was verified for each biennial questionnaire mailing. To examine latitude of residence at each time period, we divided the continental U.S. into Northern (above 41 degrees latitude), middle (between 37 and 41 degrees latitude) and Southern (below 37 degrees latitude) tiers, categories used in analyses of risk of multiple sclerosis in these cohorts.[34]

As 80% of the body's 25-hydroxy vitamin D stores are derived from ultraviolet (UV) light exposure[2], we employed the mean UV index, a measure of mean ultraviolet radiation level on a 1-11 scale developed by the National Weather Service and the Environmental Protection Agency, [35-37], of state of residence at birth, and at ages 15 and 30 for the month of August. This measurement accounts for time of day, cloud cover, haze, ozone concentration, latitude and altitude by estimating incident UV radiation on the earth's surface, and is associated with increased risk of squamous and basal cell carcinomas in women in NHS.[38]

In 1992 and 1991, NHS and NHSII participants reported their racial and ethnic ancestry as African, Asian, Hispanic, Caucasian, or other. Most women (98% in NHS and 97% in NHSII) reported Caucasian ancestry, reflecting the racial background of nurses in the U.S. during the cohort enrollment years. Natural hair color at age 18 was asked in 1982 (NHS) and 1991 (NHSII), and skin type (likelihood to sunburn) was assessed in 1982 (NHS) and 1989 (NHSII).

Statistical analysis

All analyses were initially conducted separately in the two cohorts. Person-years of follow-up accrued from return of the baseline questionnaire until diagnosis of SLE or RA, report of connective tissue disease not confirmed as SLE or RA, death, or loss-to-follow-up. Age-adjusted relative risks were calculated stratifying participants into 5-year age categories. Cox proportional hazards regression models were employed to study the association between vitamin D intake and SLE and RA (developing from ages 29-78), while adjusting for covariates. The primary analyses were performed for cumulatively updated average intake of vitamin D. Secondary analyses employed baseline vitamin D intake and most recent vitamin D intake. We used time-varying information for covariates from each two-year questionnaire to analyze risk of SLE and RA in the next two-year cycle. All tests for linear trend across quintiles were performed in Cox models employing the midpoint of each category (in age-adjusted and multivariable models). To increase precision of risk estimates and to obtain a single summary from NHS and NHSII cohorts, relative risk results from the two cohorts were meta-analytically pooled using a random effects model.[39] Data were combined only when there was no significant evidence of heterogeneity between results from the two cohorts.

In a sensitivity analysis, we excluded all women who reported any cancer at baseline or during follow-up from both cohorts, as cancer may affect vitamin intake. In a subanalysis, we examined the relationship between vitamin D intake and risk of rheumatoid factor positive RA in both cohorts. SAS version 9 was employed for all analyses.[40]

Results

The characteristics of the women participating in the NHS and NHS2 in 1990 and 1991 respectively are shown in Table 1 according to quintiles of Vitamin D intake. Women with higher vitamin D intake had other markers of a healthy lifestyle. Fewer were current smokers and more were past smokers, they had more physical activity, lower intake of caffeine, higher intake of calcium, protein and vitamin A, and a higher proportion had breastfeed their infants for a year or more. Only 3-4% of participants were postmenopausal in NHSII in 1991. In NHS, more postmenopausal women, and more taking postmenopausal hormones, had high vitamin D intake. There were no differences in race, susceptibility to sunburn, natural hair color, BMI, husband's educational status, geographic area at age 15, age at menarche, or parity according to vitamin D intake. There were also no important differences in the characteristics (listed in Table 2) of women who responded to our additional mailings compared to those who did not respond (data not shown).

Characteristics at diagnosis of the SLE and RA cases included in these analyses in each of the cohorts are shown in Tables 2a and 2b. Almost all cases of SLE had antinuclear antibodies at

diagnosis and 57% of RA cases were rheumatoid factor positive at diagnosis. Most cases in both cohorts were diagnosed by a physician who was an ACR member.

Results of age-adjusted and multivariable Cox proportional hazards models investigating the relative risks of developing SLE or RA according to quintile of cumulative intake of vitamin D from food and supplements combined, and supplements alone, are shown in Tables 3 and 4. The final multivariable models for SLE included age at menarche, oral contraceptive use, menopausal status, postmenopausal hormone use, cigarette smoking, latitude of residence at age 15 (North, Middle or South U.S.), physical activity in metabolic equivalent hours per week, BMI in kg/m^2, and race. Final multivariable models for RA included the same covariates plus parity and total duration of breastfeeding as we have found these to be related to risk of RA in our prior analyses.[22] Additional adjustments for BMI at age 18, alcohol intake, husband's educational level, menstrual regularity, skin type, hair color, UV index in state of residence at birth, and ages 15 and 30, did not affect the relative risks in any of the multivariable models in either cohort and so these variables were not included in the final models. There was no evidence of statistical heterogeneity between the cohorts (p heterogeneity > 0.05) for all analyses.

We observed no associations between cumulative average vitamin D intake, defined in different models as vitamin D from food sources only, from food and supplements, and divided into quintiles, into quartiles, in multiple or dichotomous categories of daily intake, or as a continuous measure, and the risks of SLE or RA. The only significant association we observed was for > 400 IU/day of supplemental vitamin D with increased risk of RA among women in the NHSII younger cohort (p trend =0.04). (Table 4) This association was not seen in the NHS cohort or in the combined analyses. The point estimates for the relative risk of RA among women in the higher categories of supplemental vitamin D intake in the NHSII cohort did increase after adjustment in our multivariable models. We did not find that any single covariate in the multivariable models was responsible for confounding however. The pooled relative risk for incident SLE in the highest category of vitamin D intake was 1.4 (95%CI 0.8, 2.3) and the pooled relative risk for RA was 1.0 (95%CI 0.8, 1.3). In a sensitivity analysis excluding women who reported cancer at baseline or during follow-up, results in both cohorts and for both outcomes were unchanged. No relationship between vitamin D intake and the risk of rheumatoid factor-positive RA was observed in either cohort. Analyses of vitamin D from the baseline questionnaire only or updated vitamin D intake reflecting more recent intake were similarly null for both diseases.

Discussion

In our prospective analyses involving over 180,000 women followed for up to 22 years, we have found no strong evidence of association between vitamin D intake and the risks of SLE or RA. No clear trends of increasing risk of either of these autoimmune diseases were found in relation to vitamin D intake.

In the Iowa Women's Health Study a fairly strong protective effect of high vitamin D intake at baseline on RA risk over the ensuing 11 years was observed (RR 0.67, 95%CI 0.44, 1.00, p trend 0.05).[16] In that prospective cohort study of 29,368 postmenopausal women with 152 incident cases of RA, inverse associations were seen for the risk of RA according to a single measurement of vitamin D intake at study baseline, which we did not observe. It is unclear whether differences in the study populations, such as age and relative vitamin D status, or other factors such as chance, bias or confounding explain the discrepant results. In a recent study in the Netherlands that took advantage of serial banked blood samples from 79 individuals who subsequently developed RA, 25-hydroxy vitamin D deficiency was equally prevalent among cases and controls.[17]

Our study includes a large number of incident cases, as well as detailed, repeated assessment of exposures allowing for assessment of average and more recent diet, time-varying covariates, prospective assessment of most exposures, and long follow-up. The accuracy and validity of the semi-quantitative FFQ have been well-studied and, in past analyses in NHS and NHSII, associations between vitamin D intake and risks of hip fractures[29], type II diabetes mellitus [41], multiple sclerosis[9] and pancreatic cancer[42] have been observed. Our two stage validation process includes careful medical record reviews, and all women who self-reported any connective tissue disease not confirmed as definite SLE or RA were excluded to reduce misclassification. Results were similar excluding women with malignancy, and for seropositive RA only.

Limitations include use of self-reported exposure data, observational study design, and applicability of results to Caucasian female populations only. With 190 validated cases of SLE and 722 cases of RA developing during the years studied, we have limited power to detect a small effect of vitamin D intake and the confidence intervals were relatively wide, in particular in the SLE analyses. Most of vitamin D stores are derived from UV exposure stimulating dermal synthesis.[2] We controlled for latitude and UV index, natural hair color, skin type, and physical activity, and none were related to SLE or RA risk, nor did they confound observed relationships. We do not have measures of recent UV exposure, accurate measures of sunscreen use or time outdoors, although these questions recently have been added.

The current prospective study does not lend evidence to the hypothesis that increasing vitamin D intake can protect against SLE or RA, important autoimmune diseases in women.

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Table 1

Age-adjusted characteristics of the cohort participants

	NHS subjects in 1990 (ages 44-69)					NHSII subjects in 1991 (ages 27-44)				
	Quintiles of Vitamin D Intake*					Quintiles of Vitamin D Intake**				
	1	2	3	4	5	1	2	3	4	5
Age in years, mean	56	56	57	57	58	37	37	37	36	36
White race, %	98	98	98	98	98	96	97	98	98	97
Smoking status										
Past smoker, %	34	37	37	38	39	20	22	23	23	24
Current smoker, %	21	17	16	15	14	17	13	11	11	10
Age at menarche ≤ 10 years, %	6	6	6	6	7	8	8	8	8	8
Oral contraceptive ever use, %	48	47	49	50	51	85	85	85	84	84
Parous, %	91	92	92	92	91	74	75	75	74	69
Lifetime breastfeeding ≥ 12 months, among parous women, %	15	18	20	21	20	33	39	44	45	45
Postmenopausal, %	68	69	69	70	69	4	3	3	3	4
Current use PMH, among postmenopausal, %	17	19	21	24	25	82	83	81	85	83
Physical exercise, >3 hours/ week	22	27	30	31	32	66	71	74	75	76
Body mass index, (kg/m2)	23	23	24	24	23	25	25	25	24	24
Lived in South† at age 15 (%)	28	32	34	34	31	25	29	32	32	32
Ultraviolet index ≥ 7γ in state age 15 (%)	10	10	10	11	11	22	21	19	20	21
Natural dark brown/black haircolor (%)	42	42	42	41	40	43	43	41	41	41
Usually no sunburn (%)	56	57	58	56	56	54	53	52	52	51
Husband >college education (%)	15	17	18	18	17	21	23	25	25	26
Daily multivitamin use (%)	4	11	24	45	62	8	16	30	70	96
Mean daily intake:										
Alcohol (gm)	4	4	4	4	4	4	3	3	3	3
Caffeine (mg)	301	279	260	248	228	268	259	243	227	196
Calcium (mg)	698	839	967	1095	1301	687	846	1028	1162	1373

	NHS subjects in 1990 (ages 44-69)					NHSII subjects in 1991 (ages 27-44)				
	Quintiles of Vitamin D Intake*					Quintiles of Vitamin D Intake**				
	1	2	3	4	5	1	2	3	4	5
Protein‡ (gm)	71	75	77	78	79	80	85	88	89	90
Vitamin A‡ (mcg)	956	1179	1435	1956	2989	810	1011	1245	1874	3192

*NHS quintile cutoffs: 1= 2-160.25; 2=>160.25-234.4; 3=>234.4-333.6; 4=>333.6-489.1; 5= > 489.1-3964.8

**NHSII quintile cutoffs: 1= 3-187.9; 2=> 187.9-280.9; 3=>280.9-392.0; 4=> 392.0-558.7; 5= > 558.7-5203.0

†Southern states and territories: Alabama, Arizona, Arkansas, Southern California, Florida, Georgia, Hawaii, Louisiana, Mississippi, New Mexico, North Carolina, Oklahoma, Puerto Rico, South Carolina, Tennessee, Texas.

γUltraviolet index based on the mean for the month of August for state of residence

≠Nutrients include intakes from food plus supplements, adjusted for total energy intake.

Table 2

Table 2a. Characteristics of the SLE cases at diagnosis

	NHS N=118	NHSII N=72
Mean age at diagnosis, years	53.6 (± 8.2)	42.1 (± 5.3)
Anti-nuclear antibody positive[≠], N (%)	112 (96%)	72 (100%)
Anti-dsDNA antibody positive[*], N (%)	18 (15%)	39 (54%)
Arthritis, N (%)	23 (19%)	48 (67%)
Hematologic involvement, N (%)	23(19%)	40 (56%)
Renal involvement, N (%)	3 (3%)	4 (6%)
Mean number of ACR criteria[**]	4.6 (±1.0)	4.7(±1.1)
Diagnosed by ACR member	87 (74%)	65 (90%)

Table 2b. Characteristics of the RA cases at diagnosis

	NHS N=559	NHSII N=163
Mean age at diagnosis, years	58.0 (± 8.6)	44.1(± 5.4)
Rheumatoid factor positive, N (%)	318(57%)	95 (58%)
Rheumatoid nodules, N (%)	69(12%)	18 (9%)
Radiographic changes, N (%)	156(28%)	42 (26%)
Mean number of ACR criteria[**]	4.6 (± 0.8)	4.5 (± 0.7)
Diagnosed by ACR member	461(84%)	155 (95%)

[≠] Anti-nuclear antibody ≥ 1:40 by medical record review

[*] Anti-double stranded DNA antibody positive by medical record review

[**] 4/11 criteria required for diagnosis of SLE by American College of Rheumatology criteria [24,25]

[**] 4/7 criteria required for diagnosis of RA by American College of Rheumatology criteria [26]

Table 3

Vitamin D intake and risk of SLE among women in the Nurses' Health Study 1980-2002 and the Nurses' Health Study II 1991-2003

	NHS Cases	Person-Years	Age-adjusted RR (95% CI)	Multivariable RR (95% CI) *	NHSII Cases	Person-Years	Age-adjusted RR (95% CI)	Multivariable RR (95% CI) *	NHS & NHSII Pooled MV RR††
Total Vitamin D intake (IU/day)†									
Quintile 1	20	362228	1.0 (Ref.)	1.0 (Ref.)	13	221374	1.0 (Ref.)	1.0 (Ref.)	1.0 (Ref.)
Quintile 2	25	364092	1.3 (0.7, 2.3)	1.4 (0.8, 2.6)	19	221363	1.5 (0.7, 3.0)	1.6 (0.8, 3.4)	1.5 (0.9, 2.5)
Quintile 3	23	362938	1.2 (0.7, 2.1)	1.3 (0.7, 2.5)	12	222826	0.9 (0.4, 2.0)	1.0 (0.4, 2.2)	1.2 (0.7, 2.1)
Quintile 4	23	360426	1.2 (0.7, 2.2)	1.3 (0.7, 2.4)	14	222518	1.0 (0.5, 2.2)	1.2 (0.5, 2.6)	1.3 (0.8, 2.2)
Quintile 5	27	353521	1.4 (0.8, 2.6)	1.7 (0.9, 3.0)	14	220616	1.4 (0.6, 3.2)	1.2 (0.6, 2.7)	1.4 (0.8, 2.3)
p for trend∂			0.2	0.2			0.9	0.9	0.3
Vitamin D intake from supplements only (IU/day)**									
0	64	865504	1.0 (Ref.)	1.0 (Ref.)	29	491299	1.0 (Ref.)	1.0 (Ref.)	1.0 (Ref.)
1-199	21	422110	0.8 (0.5, 1.3)	0.8 (0.5, 1.4)	18	225856	1.4 (0.8, 2.6)	1.5 (0.8, 2.8)	1.1 (0.6, 2.0)
200-399	18	318718	0.9 (0.5, 1.5)	0.9 (0.5, 1.6)	13	218875	1.0 (0.6, 2.0)	1.0 (0.5, 2.0)	1.0 (0.6, 1.5)
>400	15	196287	1.1 (0.6, 1.9)	1.1 (0.6, 1.9)	12	172667	1.2 (0.6, 2.3)	1.4 (0.7, 2.7)	1.2 (0.8, 1.8)
p for trend∂			0.9	1.0			0.7	0.6	0.7

† Cumulative average of vitamin D intake from food and supplements

NHS quintile cutoffs: 1= 2-160.3; 2=>160.25-234.4; 3=>234.4-333.6; 4=>333.6-489.1; 5= > 489.1-3964.8

NHSII quintile cutoffs: 1= 3-187.9; 2=> 187.9-280.9; 3=>280.9-392.0; 4=> 392.0-558.7; 5= > 558.7-5203.0

* Multivariable model adjusted for: age at menarche, oral contraceptive use, menopausal status, postmenopausal hormone use, cigarette smoking, latitude of residence at age 15 (North, Middle or South U.S.), physical activity in metabolic equivalent hours per week, BMI in kg/m^2, and race.

†† Risk estimates pooled using Dersimonian and Laird random effects model. p heterogeneity for all models <0.05

** Also adjusted for vitamin D intake from food in multivariable models.

∂ p for trend is from the midpoint of the categories in both age-adjusted and MV models.

Table 4

Vitamin D intake and risk of RA among women in the Nurses' Health Study 1980-2002 and the Nurses' Health Study II 1991-2003

	NHS Cases	Person-Years	Age-adjusted RR (95% CI)	Multivariable RR (95% CI) *	NHSII Cases	Person-Years	Age-adjusted RR (95% CI)	Multivariable RR (95% CI) *	NHS & NHSII Pooled MV RR ††
Total Vitamin D intake (IU/day) †									
Quintile 1	96	367312	1.0 (Ref.)	1.0 (Ref.)	42	221349	1.0 (Ref.)	1.0 (Ref.)	1.0 (Ref.)
Quintile 2	109	369718	1.1 (0.9, 1.5)	1.1 (0.8, 1.4)	38	221355	0.9 (0.6, 1.4)	0.9 (0.6, 1.4)	1.0 (0.8, 1.3)
Quintile 3	118	368993	1.2 (0.9, 1.6)	1.1 (0.9, 1.5)	27	222806	0.7 (0.4, 1.1)	0.7 (0.4, 1.1)	0.9 (0.6, 1.5)
Quintile 4	123	366770	**1.3 (1.0, 1.7)**	1.2 (0.9, 1.5)	25	222500	**0.6 (0.4, 1.0)**	0.6 (0.4, 1.1)	0.9 (0.5, 1.6)
Quintile 5	113	360501	1.2 (0.9, 1.6)	1.1 (0.8, 1.5)	31	220604	0.7 (0.5, 1.2)	0.8 (0.5, 1.3)	1.0 (0.8, 1.3)
p for trend ∂			0.3	0.4			0.1	0.3	0.9
Vitamin D intake from supplements only (IU/day) **									
0	275	873548	1.0 (Ref.)	1.0 (Ref.)	73	491260	1.0 (Ref.)	1.0 (Ref.)	1.0 (Ref.)
1-199	115	433721	**0.8 (0.6, 1.0)**	**0.6 (0.5, 0.8)**	34	225836	0.9 (0.6, 1.3)	1.1 (0.7, 1.8)	0.8 (0.5, 1.5)
200-399	98	326721	0.9 (0.7, 1.1)	**0.7 (0.5, 1.0)**	28	218858	0.8 (0.5, 1.3)	1.5 (0.8, 2.8)	1.0 (0.5, 2.0)
>400	71	326541	1.0 (0.9, 1.5)	1.0 (0.6, 1.5)	28	172659	1.1 (0.7, 1.8)	**2.3 (1.1, 5.1)**	1.4 (0.6, 3.3)
p for trend ∂			0.7	0.5			0.8	0.04 *	0.6

† Cumulative average of vitamin D intake from food and supplements, in quintiles.

NHS quintile cutoffs: 1= 2-160.3; 2=>160.25-234.4; 3=>234.4-333.6; 4=>333.6-489.1; 5= > 489.1-3964.8

NHSII quintile cutoffs: 1= 3-187.9; 2=> 187.9-280.9; 3=>280.9-392.0; 4=> 392.0-558.7; 5= > 558.7-5203.0

* Multivariable model adjusted for: age at menarche, oral contraceptive use, parity, duration of breastfeeding, menopausal status, postmenopausal hormone use, cigarette smoking, latitude of residence at age 15 (North, Middle or South U.S.), physical activity, BMI, and race.

†† Risk estimates pooled using Dersimonian and Laird random effects model. p heterogeneity for all models <0.05

** Also adjusted for vitamin D intake from food in multivariable models.

∂ p for trend is from the midpoint of the categories in both age-adjusted and MV models.