Vitamin D and Calcium Intake in Relation to Type 2 Diabetes in Women

ANASTASSIOS G. PITTAS, MD[1]
BESS DAWSON-HUGHES, MD[1,2]
TRICIA LI, MD[3]
ROB M. VAN DAM, PHD[3]
WALTER C. WILLETT, MD, DRPH[3]
JOANN E. MANSON, MD, DRPH[3,4]
FRANK B. HU, MD, PHD[3]

OBJECTIVE — The purpose of this study was to prospectively examine the association between vitamin D and calcium intake and risk of type 2 diabetes.

RESEARCH DESIGN AND METHODS — In the Nurses' Health Study, we followed 83,779 women who had no history of diabetes, cardiovascular disease, or cancer at baseline for the development of type 2 diabetes. Vitamin D and calcium intake from diet and supplements was assessed every 2–4 years. During 20 years of follow-up, we documented 4,843 incident cases of type 2 diabetes.

RESULTS — After adjusting for multiple potential confounders, there was no association between total vitamin D intake and type 2 diabetes. However, the relative risk (RR) of type 2 diabetes was 0.87 (95% CI 0.75–1.00; *P* for trend = 0.04) comparing the highest with the lowest category of vitamin D intake from supplements. The multivariate RRs of type 2 diabetes were 0.79 (0.70–0.90; *P* for trend <0.001) comparing the highest with the lowest category of calcium intake from all sources and 0.82 (0.72–0.92; *P* for trend <0.001) comparing the highest with the lowest category of calcium intake from supplements. A combined daily intake of >1,200 mg calcium and >800 IU vitamin D was associated with a 33% lower risk of type 2 diabetes with RR of 0.67 (0.49–0.90) compared with an intake of <600 mg and 400 IU calcium and vitamin D, respectively.

CONCLUSIONS — The results of this large prospective study suggest a potential beneficial role for both vitamin D and calcium intake in reducing the risk of type 2 diabetes.

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There is evidence to suggest that altered vitamin D and calcium homeostasis may play a role in the development of type 2 diabetes. The role of vitamin D in type 2 diabetes is suggested by cross-sectional studies showing that low serum concentrations of 25-hydroxyvitamin D [25(OH)D] are associated with impaired glucose tolerance and diabetes (1–3). The role of calcium in the development of type 2 diabetes is suggested indirectly by cross-sectional studies in which high calcium intake has been found to be inversely associated with body weight and fatness (4–6). The results from small clinical trials have been inconsistent (7–11).

The purpose of the present study was to prospectively evaluate the association between vitamin D and calcium intake and the risk of type 2 diabetes in a large cohort of women followed for 20 years.

RESEARCH DESIGN AND METHODS

— The Nurses' Health Study cohort was established in 1976 when 121,700 female nurses, aged 30–55 years, living in 11 U.S. states, responded to an initial mailed questionnaire on medical history, lifestyle, and other risk factors (12). Of the women, ~98% are white, reflecting the ethnic distribution of registered nurses in the 1970s. Follow-up questionnaires have been mailed every 2 years to update information on health-related behavior and determine incident disease, including diabetes and other chronic diseases.

For the present analysis, follow-up began in 1980, when the first dietary questionnaires were mailed to women who were free of diabetes, coronary heart disease, stroke, or cancer. After excluding participants with incomplete data on variables required for the analysis, a total of 83,779 women contributed to the analysis with follow-up completed in June 2000.

Assessment of dietary intake

Dietary intake was assessed with the semiquantitative validated Food Frequency Questionnaire (13), first in 1980 and subsequently in 1984, 1986, 1990, 1994, and 1998. Dietary intake of vitamin D, calcium, and other nutrients was calculated by multiplying the frequency of consumption of each food item with the nutrient content of each food. Multivitamin intake was assessed at baseline and every 2 years thereafter. Specific vitamin D supplement use was assessed starting in 1984.

Total intakes of vitamin D and calcium were calculated by adding intake from different food sources to intake from multivitamins and vitamin D/calcium supplements. The validity of vitamin D intake as a surrogate of body vitamin D stores has been documented in this cohort (14). Energy-rich nutrients (e.g., saturated fat) are presented as a percentage of total daily energy. Intake of other nutrients that are correlated with total energy intake (including vitamin D and calcium) was adjusted for total energy intake with regression analysis (15).

Assessment of nondietary covariates

Data on body weight, physical activity, smoking status, alcohol use, family history of diabetes, and physician-diagnosed hypertension and high cholesterol were

From the [1]Division of Endocrinology, Diabetes and Metabolism, Tufts-New England Medical Center, Boston, Massachusetts; the [2]Bone Metabolism Laboratory, Jean Mayer U.S. Department of Agriculture Human Nutrition Research Center on Aging, Tufts University, Boston, Massachusetts; the [3]Harvard School of Public Health and Channing Laboratory, Boston, Massachusetts; and the [4]Division of Preventive Medicine, Brigham and Women's Hospital, Boston, Massachusetts.

Address correspondence and reprint requests to Anastassios G. Pittas, MD, Division of Endocrinology, Diabetes and Metabolism, Tufts-New England Medical Center, 750 Washington St., #268, Boston, MA 02111. E-mail: apittas@tufts-nemc.org.

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Abbreviations: 25(OH)D, 25-hydroxyvitamin D.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

self-reported on all biennial questionnaires. BMI (measured as weight in kilograms divided by the square of height in meters) was calculated by using height from the 1976 questionnaire.

Ascertainment of diabetes

At each 2-year questionnaire cycle, participants were asked whether they had a diagnosis of diabetes. For each self-reported diagnosis of diabetes, a supplemental questionnaire was sent, asking about diabetes symptoms, diagnostic tests, and treatments. A diagnosis of diabetes was made when any one of the following criteria were met: *1*) one or more classic symptoms of diabetes and elevated plasma glucose levels (fasting plasma glucose ≥7.8 mmol/l or randomly measured plasma glucose ≥11.1 mmol/l), *2*) elevated plasma glucose on at least two occasions in the absence of symptoms, or *3*) treatment with oral hypoglycemic medication or insulin. Our criteria for the diagnosis of diabetes are consistent with those proposed by the National Diabetes Data Group (16) because most cases were diagnosed before 1997. For diagnoses of diabetes established after 1998, the new American Diabetes Association criteria (fasting plasma glucose ≥7 mmol/l) were used. We excluded women with type 1 diabetes or gestational diabetes. The diagnosis of type 2 diabetes by the use of the supplemental questionnaire has been validated (17).

Statistical analysis

We divided vitamin D intake and calcium intake into clinically relevant categories based on the latest guidelines set by the Institute of Medicine (18) and expert opinion (19). Person-time of follow-up for each participant was calculated from the date of the return of the baseline questionnaire in 1980 to censoring (either date of type 2 diabetes diagnosis, death, or end of follow-up in June of 2000, whichever occurred first). For each category, we calculated incidence rates for type 2 diabetes as the number of new cases divided by person-years. Relative risks (RRs) were calculated as the rate of occurrence of type 2 diabetes in each category of vitamin D or calcium intake divided by the corresponding rate in the lowest category, and 95% CIs were calculated.

We used Cox proportional hazard models (20) to estimate RR and adjusted for several risk factors that have been previously associated with type 2 diabetes, including age in 5 categories, BMI in 10 categories, physical activity (hours of moderate or vigorous leisure time activity) in 5 categories, personal history of hypertension (yes or no), family history of diabetes (yes or no), smoking status (never, past, or current smokers in 4 categories), and alcohol consumption in 4 categories. We adjusted (in quintiles) for several dietary variables that have been associated with risk of type 2 diabetes, such as type of fat (saturated, polyunsaturated, or trans), fiber, glycemic load, magnesium, and caffeine intake. Finally, we adjusted for retinol because there is evidence to suggest that retinol antagonizes vitamin D action (21).

To represent long-term intake of the exposure variable (vitamin D or calcium) and to reduce measurement error, intake of vitamin D, calcium, and other nutrients was calculated as a cumulative daily mean intake of all reported intakes up to the time of censoring. For example, diabetes incidence over the period between 1980 and 1984 was related to total vitamin D (or calcium) intake from the 1980 questionnaire, and diabetes incidence between 1984 and 1986 was related to average total vitamin D (or calcium) intake from the 1980 and 1984 questionnaires. Tests for trend were conducted using the median value of each category of vitamin D or calcium intake as a continuous variable. We used median values to reduce the potential influence of outliers, as spline regression showed no evidence of departure from linearity.

We examined associations between total, dietary, or supplemental intakes of vitamin D or calcium and type 2 diabetes. To examine the combined effects of vitamin D intake and calcium on type 2 diabetes risk, we calculated multivariate RRs according to joint categories of vitamin D and calcium intake. *P* values are two-sided. Statistical analysis was performed using SAS version 8.2 (SAS, Cary, NC).

RESULTS

Participant characteristics, vitamin D and calcium intake

During 20 years of follow-up (1,580,957 person-years), we documented 4,843 incident cases of type 2 diabetes. At baseline, the average age of the cohort was 46.0 years, and their BMI was 24.2 kg/m^2. The mean daily cumulative intake of vitamin D over the entire follow-up period was 309 IU, whereas mean daily cumulative intake of calcium was 867 mg. With increasing vitamin D and calcium intake, we observed higher use of multivitamins and supplements, higher intake of milk and dairy products, less smoking and alcohol consumption, and an overall more favorable dietary profile (Table 1).

During the 20-year follow-up, the average intake of total vitamin D increased from 291 to 342 IU/day and calcium intake increased from 731 to 980 mg. The increase was accounted for by an increase in the percentage of the study population that used multivitamins (34–52%) and calcium supplements (10–48%). During follow-up, milk intake remained unchanged at 0.9 serving/day, whereas total dairy intake increased slightly from 1.8 to 2.0 servings/day. Based on the latest guidelines set by the Institute of Medicine (18), only 3% of women in our cohort had adequate vitamin D intake, and only 24% had adequate calcium intake at the final dietary assessment in 1998.

Vitamin D intake and risk of diabetes

After adjusting for age, BMI, and nondietary covariates, we observed a significant inverse association between total vitamin D intake and risk of type 2 diabetes (Table 2). Women who consumed 800 IU or more of total vitamin D per day had a 23% lower risk for development of incident diabetes compared with women who consumed <200 IU/day. The association, however, was attenuated after adjustment for dietary factors. The dietary variables solely responsible for attenuation of the results were magnesium and calcium, which share sources with vitamin D. After final adjustment, the highest category of total vitamin D intake still tended to be associated with a lower risk of type 2 diabetes, but the test for the linear trend was not statistically significant (RR 0.87 [95% CI 0.69–1.09]; *P* for trend 0.67).

We investigated the association between dietary vitamin D intake and risk of incident type 2 diabetes by excluding women who were specific vitamin D supplement users and adjusting for the use of multivitamins. After multivariate adjustment including magnesium, retinol, and calcium, no association was evident between dietary vitamin D intake and type 2 diabetes risk (Table 2).

To distinguish the effects of vitamin D from other nutrients that share common food sources, we examined the association between supplemental vitamin D intake (from multivitamins and specific vitamin D supplements) and incident

Table 1—*Age-adjusted characteristics of the Nurses Health Study cohort by total vitamin D and calcium intake at baseline (1980)*

	Total vitamin D intake (IU/day)					Total calcium intake (mg/day)				
Characteristic	≤200	201–400	401–600	601–800	>800	≤600	601–800	801–1,000	1,001–1,200	>1,200
Number of women	42,731	19,986	11,094	6,345	3,623	32,584	23,016	13,867	7,820	6,519
Vitamin D intake (IU/day)										
Total	108	283	498	687	1152	191	271	345	416	590
Dietary only	108	236	197	227	268	93	154	208	271	362
Calcium intake (mg/day)										
Total	584	881	823	899	1049	458	695	890	1091	1450
Dietary only	584	877	808	877	953	457	692	884	1078	1374
Age (years)	46.0	45.9	46.1	46.4	46.6	45.8	46.2	46.1	45.0	46.4
State of residence (% southern states)*	19	18	21	21	25	20	19	19	18	19
BMI (kg/m^2)	24.3	24.3	23.9	24.1	24.0	24.2	24.2	24.3	24.2	24.5
Family history of diabetes (%)	25	24	24	24	23	24	25	24	25	24
History of high cholesterol (%)	5	5	5	6	6	5	5	5	5	5
History of hypertension (%)	15	14	15	16	15	16	14	14	14	15
Current smoker (%)	31	26	27	24	25	32	27	26	26	26
Physical activity (h of moderate/vigorous activity per week)	3.8	3.9	4.2	4.2	4.1	3.7	4.0	4.1	4.2	4.1
Caffeine intake (mg/day)	422	381	375	363	364	381	419	413	394	393
Alcohol consumption (g/day)	7.2	5.3	6.9	5.2	4.2	7.8	6.3	5.6	4.8	4.0
Current use (%)										
Multivitamin	7	29	87	98	100	28	34	38	40	45
Specific vitamin D supplement	2	2	3	4	5	2	3	3	3	3
Calcium supplement	6	9	16	19	22	8	10	11	12	14
Magnesium intake (mg/day)	281	304	302	308	313	258	296	317	331	352
Retinol (IU/day)	2,524	4,201	8,152	10,663	16,961	3,906	4,718	5,546	5,987	7,965
Dairy foods (servings/day)	1.3	2.5	2.3	2.2	2.0	0.9	1.7	2.4	3.1	3.9
Milk (servings/day)	0.4	1.5	1.2	1.2	1.2	0.3	0.7	1.2	1.9	2.6
Diet										
Saturated fat (% daily energy intake)	15.9	15.4	15.6	14.9	14.4	15.9	15.6	15.3	15.3	15.2
Polyunsaturated fat (% daily energy intake)	5.3	5.3	5.1	5.1	5.1	5.6	5.3	5.0	4.8	4.5
Trans fatty acids (% daily energy intake)	2.3	2.3	2.2	2.1	2.0	2.4	2.2	2.1	2.0	1.9
Cereal fiber (g/day)	2.4	2.7	2.5	2.6	2.6	2.3	2.6	2.6	2.5	2.4
Glycemic load/100	86	86	85	86	86	87	86	85	84	82

Data are means unless otherwise indicated. Intakes of alcohol, caffeine, vitamin D, calcium, magnesium, retinol, cereal fiber, and glycemic load are adjusted for total daily energy intake. *Southern states are California, Florida, and Texas. Northern states are Connecticut, Maryland, Massachusetts, Michigan, New Jersey, New York, Ohio, and Pennsylvania. †Glycemic load is the sum of (glycemic index of individual food [white bread as reference = 1] × carbohydrate content of the food item) for each food.

type 2 diabetes. Women who consumed ≥400 IU/day vitamin D from supplements compared with women who consumed ≤100 IU/day had a 13% lower risk of diabetes (Table 2) in the multivariate adjustment model (including adjusting for multivitamin use, dietary vitamin D, and total calcium intake).

Calcium intake and risk of diabetes

Total calcium intake was inversely associated with incident type 2 diabetes after adjustment for age, BMI, and nondietary and dietary covariates including vitamin D intake (Table 3). Women who consumed ≥1,200 mg/day total calcium had a 21% lower risk for development of incident diabetes compared with women who consumed <600 mg/day.

Higher intake of calcium from food was not associated with a lower risk of type 2 diabetes after multivariate adjustment including dietary factors (Table 3). Magnesium and vitamin D intake were the dietary covariates primarily responsible for the attenuation of the association.

Although use of calcium supplements was infrequent in 1980 (10% of the cohort), it increased during follow-up (48% of the cohort in 1998). When we examined the association between calcium intake from supplements only and incident diabetes, we observed an inverse association even after adjusting for all covariates. In the multivariate adjustment model (including adjustment for multivitamin use, dietary calcium intake, and total vitamin D), women who consumed ≥500 mg/day calcium from supplements compared with women who consumed ≤250 mg/day had an 18% lower risk of diabetes (Table 3).

Table 2—*Intake of vitamin D and risk of type 2 diabetes in the Nurses Health Study*

	Total vitamin D intake (IU/day)					
	≤200	201–400	401–600	601–800	> 800	*P* for trend
No. of new cases of diabetes	1,780	1,812	832	313	106	
Follow-up person-years	603,041	553,325	271,764	107,174	45,653	
RR (95% CI)						
Age adjusted	1.00	0.94 (0.88–1.00)	0.87 (0.80–0.94)	0.86 (0.76–0.97)	0.74 (0.61–0.91)	<0.001
Multivariate without diet*	1.00	0.93 (0.87–0.99)	0.93 (0.86–1.01)	0.89 (0.79–1.01)	0.77 (0.63–0.94)	0.002
Multivariate with diet†	1.00	0.97 (0.89–1.05)	0.99 (0.88–1.10)	0.94 (0.81–1.10)	0.80 (0.64–1.00)	0.15
Multivariate with diet + calcium	1.00	1.00 (0.93–1.10)	1.05 (0.93–1.18)	1.01 (0.86–1.19)	0.87 (0.69–1.09)	0.67
	Dietary vitamin D intake (IU/day)‡					
	≤100	101–200	201–300	301–400	>400	*P* for trend
No. of new cases of diabetes	829	2031	1257	350	80	
Follow-up person-years	299,091	670,048	371,830	109,938	29,595	
RR (95%CI)						
Age adjusted	1.00	0.92 (0.85–1.00)	0.98 (0.89–1.07)	0.95 (0.84–1.08)	0.91 (0.72–1.14)	0.80
Multivariate without diet*	1.00	0.86 (0.80–0.94)	0.89 (0.81–0.97)	0.82 (0.73–0.94)	0.81 (0.64–1.01)	0.01
Multivariate with diet†	1.00	0.90 (0.83–0.98)	0.98 (0.89–1.08)	0.93 (0.81–1.01)	0.91 (0.72–1.16)	0.86
Multivariate with diet + calcium	1.00	0.94 (0.85–1.03)	1.06 (0.95–1.18)	1.02 (0.88–1.19)	1.00 (0.78–1.29)	0.25
	Supplemental vitamin D intake (IU/day)§					
	≤100	101–200	201–300	301–400	>400	*P* for trend
No. of new cases of diabetes	2,956	678	497	347	365	
Follow-up person-years	947,379	206,980	155,352	125,792	145,455	
RR (95% CI)						
Age adjusted	1.00	0.87 (0.80–0.95)	0.88 (0.80–0.97)	0.81 (0.72–0.90)	0.79 (0.71–0.88)	<0.001
Multivariate without diet*	1.00	0.92 (0.84–1.00)	0.97 (0.89–1.07)	0.90 (0.81–1.01)	0.88 (0.79–0.98)	0.007
Multivariate without diet†	1.00	0.91 (83–1.00)	0.96 (0.85–1.07)	0.88 (0.76–1.00)	0.84 (0.73–0.97)	0.01
Multivariate with diet + calcium	1.00	0.92 (0.84–1.01)	0.97 (0.87–1.09)	0.90 (0.78–1.03)	0.87 (0.75–1.00)	0.04

*RR adjusted for age, BMI, hypertension, family history of diabetes, smoking, physical activity, caffeine, alcohol, and state of residence (southern states [California, Florida, and Texas] or northern states [Connecticut, Maryland, Massachusetts, Michigan, New Jersey, New York, Ohio, and Pennsylvania]). †RR adjusted for everything in footnote * plus type of fat (saturated, polyunsaturated, or trans), cereal fiber, glycemic load, magnesium, and retinol. ‡Women who were specific vitamin D supplement users were excluded at baseline and during follow-up (2,058 at baseline, 8,745 during follow-up). The entire analysis for supplemental vitamin D was also adjusted for multivitamin use (yes or no). §The entire analysis was adjusted for multivitamin use (yes or no) and dietary vitamin D intake.

Combined vitamin D and calcium intake and risk of diabetes

We examined the combined effects of total vitamin D and calcium intake on type 2 diabetes risk by creating a nine-category variable with three vitamin D intakes and three calcium intakes (Table 4). Compared with the lowest total vitamin D/calcium intake (<400 IU vitamin D and <600 mg/day calcium), increasing calcium intake was associated with lower risk of diabetes at all levels of vitamin D intake. Total vitamin D intake >800 IU/day was associated with a lower risk of incident diabetes if the calcium intake was >1,200 mg/day. Women with the highest calcium (>1,200 mg/day) and vitamin D (>800 IU/day) intakes (1.3% of the cohort) had the lowest risk of diabetes (RR 0.67 [95% CI 0.49–0.90]) after multivariate adjustment.

Although menopause is not an established risk factor for type 2 diabetes (22), we repeated our analyses including menopause and use of postmenopausal hormones as covariates, and the results did not change. Also, because of concern that certain conditions may interfere with vitamin D absorption, we performed a sensitivity analysis by excluding women who reported ulcerative colitis/Crohn's disease (n = 1,316), and the results did not change.

Because the major dietary source of vitamin D and calcium is dairy foods, in a separate analysis we examined the risk of type 2 diabetes by dairy intake. Compared with women who consumed less than one serving per day of dairy food, women who consumed three or more servings per day had an 11% lower risk of type 2 diabetes (RR 0.89 [95% CI 0.81–0.99], *P* for trend 0.008). After adjustment for total vitamin D and calcium intake, this association was attenuated (0.94 [0.83–1.06], *P* for trend 0.12).

CONCLUSIONS — In this large cohort of middle-aged women, we found that both vitamin D and calcium intakes were inversely associated with development of type 2 diabetes, and the benefits of the two nutrients appear to be additive. For both vitamin D and calcium, intakes from supplements rather than from diet were significantly associated with a lower risk of type 2 diabetes. To our knowledge, this is the first prospective study to report an association between vitamin D and calcium intake and risk of incident type 2 diabetes and the first to examine the combined effects of both vitamin D and calcium intake on diabetes risk.

Table 3—*Intake of calcium and risk of type 2 diabetes in the Nurses Health Study*

	Total calcium intake (mg/day)					
	≤600	601–800	801–1,000	1,001–1,200	>1,200	*P* for trend
No. of new cases of diabetes	1,115	1,277	1,084	696	671	
Follow-up person-years	367,985	414,177	338,966	229,764	230,066	
RR (95% CI)						
Age adjusted	1.00	0.88 (0.81–0.96)	0.85 (0.78–0.92)	0.76 (0.69–0.84)	0.68 (0.62–0.75)	<0.001
Multivariate without diet*	1.00	0.88 (0.82–0.96)	0.86 (0.79–0.94)	0.80 (0.73–0.88)	0.74 (0.67–0.82)	<0.001
Multivariate with diet†	1.00	0.91 (0.84–0.99)	0.90 (0.82–0.99)	0.85 (0.76–0.95)	0.88 (0.71–0.89)	<0.001
Multivariate with diet + vitamin D	1.00	0.91 (0.83–1.00)	0.90 (0.81–1.00)	0.85 (0.76–0.96)	0.79 (0.70–0.90)	<0.001

	Dietary calcium intake (mg/day)‡				
	≤500	501–750	751–1,000	>1,000	*P* for trend
No. of new cases of diabetes	497	1056	621	291	
Follow-up person-years	172,838	357,642	205,813	113,274	
RR (95% CI)‡					
Age adjusted	1.00	0.92 (0.82–1.02)	0.94 (0.83–1.06)	0.86 (075–1.00)	0.09
Multivariate without diet*	1.00	0.93 (0.83–1.03)	0.88 (0.78–0.99)	0.81 (0.70–0.94)	0.003
Multivariate with diet†	1.00	0.96 (0.86–1.08)	0.93 (0.81–1.07)	0.85 (0.72–1.01)	0.06
Multivariate with diet + vitamin D	1.00	0.99 (0.88–1.13)	0.99 (0.85–1.15)	0.92 (0.76–1.12)	0.41

	Supplemental calcium intake (mg/day)§			
	≤250	251–500	>500	*P* for trend
No of new cases of diabetes	3854	657	332	
Follow-up person-years	1,246,189	212,495	122,274	
RR (95% CI)§				
Age adjusted	1.00	0.74 (0.68–0.81)	0.62 (0.56–0.70)	<0.001
Multivariate without diet*	1.00	0.90 (0.82–0.98)	0.79 (0.70–0.88)	<0.001
Multivariate with diet†	1.00	0.92 (0.84–1.00)	0.81 (0.72–0.92)	<0.001
Multivariate with diet + vitamin D	1.00	0.92 (0.84–1.00)	0.82 (0.72–0.92)	<0.001

*RR adjusted for age, BMI, hypertension, family history of diabetes, smoking, physical activity, caffeine, alcohol, and state of residence (southern states [California, Florida, and Texas] or northern states [Connecticut, Maryland, Massachusetts, Michigan, New Jersey, New York, Ohio, and Pennsylvania]). †RR adjusted for everything in footnote * plus type of fat (saturated, polyunsaturated, or trans), cereal fiber, glycemic load, magnesium, and retinol. ‡Women who were calcium supplement users were excluded at baseline and during follow-up (8,380 at baseline and 51,878 during follow-up). The entire analysis for dietary calcium intake was also adjusted for multivitamin use (yes or no). §The entire analysis for supplemental calcium was also adjusted for multivitamin use (yes or no) and dietary calcium intake.

The mechanisms by which vitamin D may affect the risk of type 2 diabetes are not clear. Both insulin resistance and impaired pancreatic β-cell function have been reported with vitamin D insufficiency (3,9,11,23–26). These observations together with the finding of vitamin D receptors in β-cells (27) and the finding of impaired insulin secretory capacity in mice lacking a functional vitamin D receptor (28) indicate an important role for vitamin D in regulating β-cell function. Short-term intervention studies with vitamin D supplementation in patients with type 2 diabetes have shown conflicting results (8–11). The mechanisms by which calcium intake may alter diabetes risk are speculative. Abnormal regulation of intracellular calcium affecting both insulin sensitivity and insulin release has been suggested as a potential mechanism to explain the putative association between calcium insufficiency and risk of diabetes (29,30).

The main function of vitamin D is facilitating intestinal calcium absorption. Therefore, insufficient calcium absorption may be the culprit mechanism for the observed associations in our study, either due to vitamin D insufficiency (from low intake) or low calcium intake. This hypothesis is further supported by data indicating that calcium is essential in normalizing glucose intolerance due to vitamin D deficiency in vivo (31). The additive effect of calcium and vitamin D intake that we observed in the joint analysis suggests that increased vitamin D intake may potentiate the effect of calcium intake, but it does not rule out a direct effect of vitamin D independent of its role in calcium homeostasis. Indeed, in vitro animal data suggests that the effect of vitamin D on β-cells appears to be direct and independent of prevailing plasma calcium concentration (26).

We observed a statistically significant inverse association between supplemental vitamin D and calcium and type 2 diabetes risk, but the association between dietary vitamin D and calcium and diabetes was not significant. Several explanations are possible. First, the range for both dietary vitamin D and calcium intake is limited, as very few participants consumed very high quantities of dietary vitamin D and very few consumed very low quantities of dietary calcium. Next, in our cohort (98% white), vitamin D levels from sun exposure may be the main de-

Table 4—*RR of type 2 diabetes according to joint categories of total intake of vitamin D and calcium in the Nurses Health Study*

Variable	Vitamin D intake (IU/day)		
	≤400	401–800	>800
Calcium ≤600 mg/day			
Number of new cases of diabetes	1,008	99	8
Follow-up person-years	326,293	37,515	4,177
RR (95% CI)*	1.00†	1.08 (0.86–1.34)	0.75 (0.37–1.52)
Calcium 601–1,200 mg/day			
No. of new cases of diabetes	2,334	676	47
Follow-up person-years	743,538	219,904	19,465
RR (95% CI)*	0.89 (0.83–0.98)	0.92 (0.82–1.04)	0.86 (0.63–1.17)
Calcium >1,200 mg/day			
No. of new cases of diabetes	250	370	51
Follow-up person-years	86,536	121,520	22,011
RR (95% CI)*	0.81 (0.70–0.95)	0.83 (0.72–0.97)	0.67 (0.49–0.90)

*RR adjusted for age, BMI, hypertension, family history of diabetes, smoking, physical activity, caffeine, alcohol, and state of residence (southern states [California, Florida, and Texas] or northern states [Connecticut, Maryland, Massachusetts, Michigan, New Jersey, New York, Ohio, and Pennsylvania], type of fat (saturated, polyunsaturated, or trans) cereal fiber, glycemic load, magnesium, and retinol. †Women with vitamin D intake <400 IU/day and total calcium intake <600 mg/day served as the reference group.

terminant of vitamin D status, and nutrient D intake may play a less significant role in determining body vitamin D levels. Therefore, the association of vitamin D intake and type 2 diabetes may be biased toward null in our cohort. Finally, the dietary and supplemental analyses may be confounded by other alterations in dietary and lifestyle patterns that cannot be measured (32).

The strengths of our study include its large size, long-term follow-up, and validated measurements of the exposure variable, the outcome, and various covariates. The major limitation of our study is its observational nature; therefore, residual confounding cannot be completely ruled out for unmeasured or unmeasurable variables. Moreover, although both intake of vitamin D and exposure to ultraviolet light determine body stores of vitamin D, cutaneous synthesis is a more significant determinant of vitamin D status as measured by the serum 25(OH)D level (18). Finally, our results may not be directly extrapolated to women of other racial or ethnic groups or to men.

In conclusion, we found that a high intake of vitamin D and calcium was associated with a lower risk of type 2 diabetes. If these results are confirmed in prospective studies examining the association between 25(OH)D and type 2 diabetes risk or in randomized trials of calcium and vitamin D, they will have important public health implications because both of these interventions can be implemented easily and inexpensively to prevent type 2 diabetes.

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