

Lack of Association Between 25(OH)D Levels and Incident Type 2 Diabetes in Older Women

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OBJECTIVE—To examine whether lower serum levels of serum 25-hydroxyvitamin (OH) D [25(OH)D] are associated with increased risk of developing type 2 diabetes.

RESEARCH DESIGN AND METHODS—A post hoc analysis of three nested case-control studies of fractures, colon cancer, and breast cancer that measured serum 25(OH)D levels in women participating in the Women's Health Initiative (WHI) Clinical Trials and Observational Study who were free of prevalent diabetes at baseline. Diabetes was defined as self-report of physician diagnosis or receiving insulin or oral hypoglycemic medication. We used inverse probability weighting to make the study population representative of the WHI population as a whole. Weighted logistic regression models compared 25(OH)D levels (divided into quartiles, clinical cut points [<50 , 50 – <75 , ≥ 75 nmol/L], or as a continuous variable) using the distribution of control subjects and adjusted for multiple confounding factors.

RESULTS—Of 5,140 women (mean age 66 years) followed for an average of 7.3 years, 317 (6.2%) developed diabetes. Regardless of the cut points used or as a continuous variable, 25(OH)D levels were not associated with diabetes incidence in either age or fully adjusted models. Nor was any relationship found between 25(OH)D and incident diabetes when evaluated by strata of BMI, race/ethnicity, or randomization status in the Calcium Vitamin D trial.

CONCLUSIONS—Lower serum 25(OH)D levels were not associated with increased risk of developing type 2 diabetes in this racially and ethnically diverse population of postmenopausal women.

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Vitamin D has been shown to have numerous nonskeletal effects, including an important role in pancreatic insulin secretion and insulin action (1). Although several studies have reported a protective relationship between

vitamin D and the risk of developing diabetes, the data are not consistent. A recent meta-analysis found that three of six observational studies (OS) found an association between low vitamin D status and increased risk of incident type 2 diabetes

or metabolic syndrome (2). In contrast, eight clinical trials found vitamin D supplementation had no effect on glycemia or incident diabetes (1). It may be that higher doses of vitamin D than those tested in clinical trials may be required to affect diabetes risk. Alternatively, the associations of calcium and vitamin D intake with improved glucose metabolism reported in OS may be the result of confounding by other components of foods containing these nutrients (3), outdoor exercise associated with solar radiation, or other factors (4,5).

We undertook this analysis to further evaluate the relationship between 25-hydroxyvitamin D [25(OH)D] levels and diabetes risk in a large cohort of postmenopausal women participating in the Women's Health Initiative (WHI). Several nested case-control studies within the WHI measured 25(OH)D levels in over 5,000 women, providing a unique opportunity to evaluate an older, multiethnic population at high risk for both vitamin D insufficiency and diabetes (6,7). Our objectives were to examine whether decreased serum levels of 25(OH)D were associated with increased risk of incident type 2 diabetes and whether ethnicity or BMI modified the relationship.

RESEARCH DESIGN AND METHODS

This was a post hoc analysis of data collected from three nested case-control studies that measured 25(OH)D levels among women participating in the WHI clinical trials (CT) and OS who did not have prevalent diabetes at baseline (Supplementary Data).

Between 1993 and 1998, the 40 WHI clinical centers throughout the United States recruited postmenopausal women aged 50–79 years for participation in trials of postmenopausal hormone therapy (HT), dietary modification (DM), and calcium and vitamin D (CaD) supplementation (8). Women who were not eligible for or chose not to participate in the clinical trials were enrolled in the WHI OS. At 1–2 years after joining the hormone or diet intervention trials, 36,282 women were enrolled in the CaD supplementation trial to be randomly assigned to either

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placebo or calcium carbonate 1,000 mg combined with 25(OH) vitamin D₃ 400 IU daily. Women were allowed to continue their personal use of calcium and vitamin D as long as vitamin D intake did not exceed 600 IU (and later 1,000 IU) daily. Within the CaD trial, three nested case-control studies were conducted to analyze associations between serum concentrations of 25(OH)D and incidence of colorectal cancer, breast cancer, or hip, spine, or lower wrist fracture; control subjects were matched on age, race/ethnicity, blood draw date, and clinic center at CaD randomization. The CaD breast cancer nested case-control study was also matched on HT and DM trial arm. In the WHI OS, incident hip fracture cases were identified through August 2004; control subjects were matched to case subjects on age, race/ethnicity, and blood draw date.

We analyzed baseline and semiannual visits and annual questionnaires as of the termination dates for the clinical trials (9–12). Diabetes was defined as self-report of physician diagnosis of “sugar diabetes” treated with insulin or oral medications, or use of an oral hypoglycemic agent or insulin on a medication inventory (13). Physical activity was measured in MET-hrs/wk spent on recreational physical activity. Cardiovascular disease (CVD) was defined as myocardial infarction (MI), coronary revascularization, stroke, and peripheral arterial disease other than abdominal aortic aneurysm.

Serum 25(OH)D concentrations, which reflect total body stores of vitamin D (14), were obtained from fasting serum samples drawn at the baseline (OS) or year 1 (CT) visit that was processed and stored at -80°C . Serum 25(OH)D concentrations (nmol/L) were determined using the DiaSorin LIAISON chemiluminescence method (DiaSorin, Stillwater, MN), and the coefficient of variation (CV) determined using blinded controls was 11.8%, which was similar the CV found in other cohort studies (15). Serum 25(OH)D concentrations varied by month of blood draw, thus month of blood draw was adjusted for in the statistical analyses.

Statistical analysis

We combined three separate nested case-control studies that included measurement of 25(OH)D concentrations and disease outcomes (CaD/fracture, colorectal cancer; CaD/breast cancer; OS/hip fracture) into one population (Supplementary Data) to evaluate the association between

serum 25(OH)D on incident diabetes. The CaD case-control studies supplied 86% of participants in this analysis. Because fractures and breast and colon cancer are not considered along the causal pathway of diabetes, both case and control subjects were included in the analysis; indeed, diabetes incidence was similar across case-control status. Because individuals in these studies were matched for other conditions, we used inverse probability weighting so that our study population would be representative of the WHI population as a whole. The explanatory variables in the models used for weighting included age, ethnicity, latitude of clinical center, and month of blood draw. Previous case-control outcomes (hip fracture, spine fracture, lower arm/wrist fracture, breast cancer, and colorectal cancer) were included in the models as well. For example, because fracture case and control subjects were a large part of our sample, we have a significantly older population in our sample (mean age at blood draw was 66.3 years) than in the full CaD/OS cohort (mean age 63.6 years). Therefore, the highest weights were assigned to those participants least likely to be sampled (for example, younger participants with no fractures). Overall, the weights increased the influence of the control subjects in the analysis while still preserving information from the case subjects. This method better represents the whole population than unrestricted analysis of case and control subjects or a control subjects-only analysis. Nonetheless, we conducted sensitivity analyses to evaluate control subject-only specimens from the above case-control subject pairs (i.e., those serving as control subjects for the fracture cases, colorectal cancer cases, and breast cancer cases), as well as using unweighted data.

We used weighted logistic regression models to compare exposure levels (divided into quartiles or clinical cut points <50 , $50-<75$, ≥ 75 nmol/L), using the distribution of the controls (and simultaneously adjusting for multiple confounding factors and effect modifiers), or used as a continuous variable. Models were adjusted for known diabetes risk factors as well as sun exposure (based on latitude of clinical center), which may be a potential effect modifier of vitamin D level that may also influence diabetes risk. To examine the independent relationship of 25(OH)D to risk of diabetes, we evaluated 25(OH)D as a predictor of diabetes after progressively adjusting for potential confounders;

model 1: age and ethnicity; model 2: model 1 covariates + latitude of clinical center, month of blood draw, and WHI study indicators (clinical trial, randomization assignment, and case-control status); and model 3: model 2 covariates + BMI, hypertension, fiber intake, magnesium intake, and physical activity. The variables in model 3 were selected by taking an initial full model using the covariates in model 3, along with Langley units, smoking, history of CVD, intake of protein, fruits and vegetables, calcium, fat, alcohol, total glycemic load, multivitamin use, hormone use, waist circumference, education level, and skin cancer, then applying backward selection techniques (P value criteria for removal from model = 0.10) to get a reduced model with BMI ($P < 0.0001$), hypertension ($P = 0.003$), fiber ($P = 0.010$), and magnesium ($P = 0.024$) (Supplementary Data). In addition to these four variables, all of the adjustments from model 2 and total physical activity (which may reflect sun exposure and is a risk factor for diabetes) were forced into the model. Logistic regression models using model 3 were used to evaluate associations between 25(OH)D and diabetes in women stratified by BMI (normal or underweight <25 kg/m², overweight $25-<30$, and obese ≥ 30), CaD trial enrollment (active, placebo), or race/ethnicity. Because logistic regression is a complete case subject analysis and we wanted to avoid excluding additional participants as a result of missing physical activity data ($\sim 10\%$ of the sample), an indicator variable for missing physical activity was included in all models. Sensitivity analyses were performed on unweighted data and without physical activity. At all levels of analysis, we tested the assumptions and examined the goodness-of-fit of logistic models. SAS 9.1 (SAS Institute, Cary, NC) was used.

RESULTS—Of 5,140 women, 1,263 (25%) had a 25(OH)D level <34.7 nmol/L, 2,741 (53%) had a 25(OH)D level <50 nmol/L, and 317 (6.2%) developed incident diabetes over a mean follow-up of 7.3 years. Mean age at blood draw was 66 years in women with and without diabetes, with a similar proportion ($\sim 38\%$) of those aged 70–79 years in both groups (Table 1). Nonwhite women were more likely to develop diabetes than white women. Women who developed diabetes had a higher prevalence of hypertension, obesity, and increased waist circumference, lower education and income

levels, lower levels of physical activity, a history of CVD, and were more likely to report a family history of diabetes or premature coronary heart disease. Women who developed diabetes were also more likely to be past or never alcohol users and to report consuming fewer servings of fruits and vegetables and more total, fat, and protein servings. Total vitamin D and calcium intakes were similar in women with and without diabetes, as were U.S. region of residence, sun exposure, season of blood draw, and history of skin cancer. Participants with a hysterectomy were more likely to develop diabetes than those without. Women who developed diabetes were no more likely to be in the CaD intervention group than the placebo group.

Increasing quartiles of serum 25(OH)D levels were associated with a suggestion of a possible trend toward lower diabetes incidence in the model adjusted for only age and ethnicity and in the model adjusted for age, ethnicity, latitude, month of blood draw, and trial enrollment (*P* for trend = 0.20; Table 2). However, after more complete adjustment for risk factors for BMI, hypertension, fiber, magnesium intake, and physical activity there was no association between 25(OH)D quartile and incident diabetes (odds ratio 1.01, *P* for trend = 0.94), nor was there evidence of a linear association between 25(OH)D level and diabetes risk using clinical cut points or a continuous variable (in 5 nmol/L increments). Although there was a suggestion of a U-shaped relationship between 25(OH)D level and diabetes risk, with the 50–<75 nmol/L group having the lowest odds ratio, the 95% CIs were broad and included an odds ratio of 1.

In the fully adjusted model, the *P* value for interaction between 25(OH)D quartile and BMI was of borderline significance (*P* = 0.045) (Table 3). All BMI–25(OH)D combinations had 95% CIs that included 1, although different patterns of diabetes risk were suggested for each BMI category: normal weight women in the highest 25(OH)D quartile (>64 nmol/L) had the lowest risk of diabetes whereas obese women had no difference in diabetes risk across 25(OH)D quartiles. No consistent pattern was observed for overweight women. On the other hand, there was no evidence of a BMI interaction with 25(OH)D clinical cut points on diabetes risk (*P* = 0.48). Nor was there evidence of increased diabetes risk by race/ethnicity or randomization status in the CaD trial for any 25(OH)D categorization (quartiles, clinical cut points, or as a continuous

Table 1—Baseline characteristics of study participants (CaD and OS) by incident diabetes status

	No diabetes	Diabetes	<i>P</i>
Age at blood draw (years), mean (SD)	66.26 (7.30)	66.29 (7.18)	0.597
50–59	1,044 (21.6)	61 (19.2)	
60–69	1,949 (40.4)	133 (42.0)	
70–79	1,830 (37.9)	123 (38.8)	
Ethnicity			<0.001
White	4,400 (91.2)	261 (82.3)	
Black	207 (4.3)	21 (6.6)	
Hispanic	96 (2.0)	19 (6.0)	
Other/Unknown	120 (2.5)	16 (5.0)	
U.S. region			0.383
Northeast	1,208 (25.0)	72 (22.7)	
South	1,009 (20.9)	79 (24.9)	
Midwest	1,199 (24.9)	76 (24.0)	
West	1,407 (29.2)	90 (28.4)	
Season of blood draw			0.227
Winter	1,064 (22.1)	57 (18.0)	
Spring	1,317 (27.3)	82 (25.9)	
Summer	1,238 (25.7)	92 (29.0)	
Fall	1,204 (25.0)	86 (27.1)	
Region by solar irradiance in Langley categories			0.237
475–500	975 (20.2)	68 (21.5)	
400–430	777 (16.1)	46 (14.5)	
375–380	464 (9.6)	40 (12.6)	
350	1,099 (22.8)	80 (25.2)	
300–325	1,506 (31.2)	83 (26.2)	
Smoking status			0.324
Never	2,541 (52.7)	176 (55.5)	
Past	1,895 (39.3)	114 (36.0)	
Current	337 (7.0)	26 (8.2)	
Hypertension at blood draw			<0.001
No	2,569 (53.3)	116 (36.6)	
Yes	2,254 (46.7)	201 (63.4)	
BMI at blood draw (kg/m ²), mean (SD)	27.86 (5.45)	31.27 (5.86)	<0.001
≤25	1,628 (33.8)	46 (14.5)	
25–<30	1,725 (35.8)	95 (30.0)	
≥30	1,470 (30.5)	176 (55.5)	
Waist ≥88 cm at blood draw			<0.001
No	2,755 (57.1)	97 (30.6)	
Yes	2,067 (42.9)	219 (69.1)	
Physical activity at blood draw (MET h/week), mean (SD)	11.63 (13.28)	8.98 (10.79)	0.003
<2	1,075 (22.3)	92 (29.0)	
2–<7.5	1,011 (21.0)	76 (24.0)	
7.5–17	1,218 (25.3)	60 (18.9)	
≥17	1,051 (21.8)	53 (16.7)	
Hysterectomy	3,017 (62.6)	165 (52.1)	<0.001
No	1,806 (37.4)	152 (47.9)	
Yes	1,011 (21.0)	76 (24.0)	
CaD arm			0.706
Not randomized	658 (13.6)	38 (12.0)	
Intervention	2,108 (43.7)	141 (44.5)	
Comparison	2,057 (42.6)	138 (43.5)	
HT arm			0.066
Not randomized	2,979 (61.8)	175 (55.2)	
Placebo	949 (19.7)	72 (22.7)	
Active	895 (18.6)	70 (22.1)	

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Table 1—Continued

	No diabetes	Diabetes	P
DM arm			0.953
Not randomized	1,906 (39.5)	123 (38.8)	
Intervention	1,808 (37.5)	119 (37.5)	
Comparison	1,109 (23.0)	75 (23.7)	
OS flag			0.404
No	4,165 (86.4)	279 (88.0)	
Yes	658 (13.6)	38 (12.0)	
HT use at blood draw			0.054
Never used	1,924 (39.9)	114 (36.0)	
Past user	803 (16.6)	69 (21.8)	
Current user	2,096 (43.5)	134 (42.3)	
Education			0.001
≤High school diploma/GED	1,131 (23.5)	86 (27.1)	
School after high school	1,843 (38.2)	143 (45.1)	
College degree or higher	1,823 (37.8)	85 (26.8)	
Family income			<0.001
<\$20,000	820 (17.0)	83 (26.2)	
\$20,000–\$49,999	2,262 (46.9)	135 (42.6)	
\$50,000–\$74,999	861 (17.9)	44 (13.9)	
\$75,000 +	627 (13.0)	34 (10.7)	
Alcohol use			0.007
Never drinker	512 (10.6)	45 (14.2)	
Past drinker	756 (15.7)	66 (20.8)	
Current drinker	3,522 (73.0)	203 (64.0)	
Cancer ever at blood draw			0.455
No	4,223 (87.6)	285 (89.9)	
Yes	534 (11.1)	28 (8.8)	
Skin cancer ever at blood draw			0.159
No	4,363 (90.5)	297 (93.7)	
Yes	396 (8.2)	17 (5.4)	
CVD ever at blood draw			0.014
No	4,497 (93.2)	282 (89.0)	
Yes	254 (5.3)	28 (8.8)	
Family history of adult diabetes			<0.001
No	3,248 (67.3)	168 (53.0)	
Yes	1,349 (28.0)	132 (41.6)	
Family hx premature MI (<55 male, <65 female)			0.055
No	3,521 (73.0)	213 (67.2)	
Yes	800 (16.6)	68 (21.5)	
Multivitamin use at blood draw			0.879
No	2,946 (61.1)	195 (61.5)	
Yes	1,877 (38.9)	122 (38.5)	
Total vitamin D intake at blood draw (IU), mean (SD)	374.09 (276.51)	374.57 (263.06)	0.332
<200	1,781 (36.9)	122 (38.5)	
200–<400	928 (19.2)	51 (16.1)	
400–<600	1,150 (23.8)	78 (24.6)	
≥600	955 (19.8)	64 (20.2)	
Total calcium intake (mg), mean (SD)	828.63 (438.66)	858.84 (458.64)	0.247
<513	1,212 (25.1)	71 (22.4)	
513–<740	1,214 (25.2)	71 (22.4)	
740–<1053	1,195 (24.8)	92 (29.0)	
≥1053	1,202 (24.9)	83 (26.2)	
Total magnesium intake (mg), mean (SD)	255.21 (95.32)	253.36 (98.01)	0.858
<187	1,209 (25.1)	80 (25.2)	
187–< 242	1,193 (24.7)	78 (24.6)	
242–< 311	1,208 (25.0)	85 (26.8)	

variable; Table 3). Similar relationships between 25(OH)D levels and diabetes risk were observed in fully adjusted analyses of controls only, unweighted participants, and without physical activity in model 3 (data not shown; Supplementary Data).

CONCLUSIONS—After adjustment for BMI and other risk factors, we found no relationship between serum 25(OH)D concentration and diabetes incidence over 7 years in this multiethnic cohort of over 5,000 older women. Nor was a relationship between 25(OH)D status and diabetes risk found upon further evaluation by race/ethnicity or CVD status. In the analysis stratified by BMI, there was a suggestion that normal weight women with the highest level of serum 25(OH)D (>64 nmol/L) may have had a lower risk of diabetes, but this relationship was not present using the clinical cut point of ≥75 nmol/L. Although this finding may merit further investigation in other prospective cohorts, the lack of a trend for a protective relationship for the similarly-sized group of overweight women suggests it may have been a spurious finding. No evidence of a relationship between 25(OH)D and diabetes was found in obese women—the group at greatest risk of developing diabetes.

Our observational findings are consistent with those of the WHI CaD intervention trial, which found that supplementation with elemental calcium 1,000 mg plus vitamin D₃ 400 IU did not reduce the risk of developing diabetes over 7 years of follow-up (12). The hazard ratio for incident diabetes associated with CaD treatment was 1.01 (95% CI 0.94–1.10) with no association found in subgroup analyses, or efficacy analyses accounting for nonadherence. A higher dose of 2,000 IU/d of vitamin D supplementation is undergoing evaluation in the VITamin D and Omega-3 Trial (VITAL) of 20,000 women aged ≥65 years and men aged ≥60 years who will be followed for 5 years (16). The primary end points are cancer, coronary heart disease, and stroke, with diabetes as one of the secondary end points.

The few small studies that have evaluated the association between circulating 25(OH)D and diabetes incidence have been conflicting, as have the larger epidemiologic cohort studies of dietary vitamin D intake (1). The Women's Health Study found an inverse relationship between vitamin D intake and incident diabetes risk when adjusted for age (17). In contrast, the even larger Nurses' Health

Table 1—Continued

	No diabetes	Diabetes	P
≥311	1,213 (25.2)	74 (23.3)	
Total fat intake (g), mean (SD)	55.54 (29.74)	59.97 (32.37)	0.177
<34.6	1,220 (25.3)	66 (20.8)	
34.6–< 49.5	1,201 (24.9)	79 (24.9)	
49.5–< 69.2	1,210 (25.1)	79 (24.9)	
≥69.2	1,192 (24.7)	93 (29.3)	
Total protein intake (g), mean (SD)	66.82 (26.73)	70.24 (29.83)	0.503
<47.6	1,218 (25.3)	69 (21.8)	
47.6–<63.2	1,203 (24.9)	78 (24.6)	
63.2–<81.8	1,202 (24.9)	86 (27.1)	
≥81.8	1,200 (24.9)	84 (26.5)	
Total glycemic load (total carbohydrates), mean (SD)	104.96 (41.74)	109.33 (52.32)	0.480
<75.1	1,201 (24.9)	82 (25.9)	
75.1–< 98.8	1,218 (25.3)	68 (21.5)	
98.8–<127.2	1,204 (25.0)	81 (25.6)	
≥127.2	1,200 (24.9)	86 (27.1)	
Total fiber intake (g) at blood draw, mean (SD)	16.26 (6.95)	15.71 (7.22)	0.423
<11.2	1,200 (24.9)	92 (29.0)	
11.2–<15.2	1,206 (25.0)	77 (24.3)	
15.2–<20.1	1,214 (25.2)	75 (23.7)	
≥20.1	1,203 (24.9)	73 (23.0)	
Fruit/vegetable servings at blood draw, mean (SD)	4.32 (2.12)	4.12 (2.35)	0.016
<2.7	1,192 (24.7)	98 (30.9)	
2.7–<4.0	1,156 (24.0)	82 (25.9)	
4.0–<5.6	1,262 (26.2)	62 (19.6)	
≥5.6	1,213 (25.2)	75 (23.7)	

Data are n (%) unless otherwise indicated.

Study found no relationship between vitamin D intake from supplements and incident type 2 diabetes after further adjustment for confounders—similar to the findings of our study (18). The Nurses' Health Study investigators did find one group with an inverse association

between vitamin D and diabetes: those with a combined intake of >1,200 mg calcium and >800 IU vitamin D (1.3% of the cohort) had a significantly lower risk of diabetes when compared with intakes <600 mg calcium and <400 IU vitamin D.

It is possible that in men or other racial or ethnic groups, more severe vitamin D deficiency, or vitamin D deficiency earlier in life could contribute to diabetes risk (19,20). Two small Finnish nested case-control studies evaluating serum 25(OH)D concentrations, rather than dietary intake, found no association between mean 25(OH)D level and diabetes in women, but did find an inverse association in men (21). On the other hand, an analysis of the Framingham Offspring study found an association between a higher prediction score for vitamin D status and diabetes risk in both men and women (22).

Vitamin D may influence the development of diabetes via a number of potential mechanisms (1). Vitamin D receptors for the biologically active form of vitamin D are present on the pancreatic β-cells, and severe vitamin D deficiency can inhibit insulin secretion in some animal models. Administration of 1,25(OH)₂D or its metabolites has improved insulin sensitivity and insulin secretion in some human in vitro and in vivo studies. Insulin sensitivity, β-cell function, and oral glucose tolerance have been shown to be inversely related to 25(OH)D concentrations in healthy normoglycemic individuals, elderly men, and east Asians. On the other hand, some studies have found that in the absence of vitamin D deficiency, vitamin D supplementation does not improve insulin sensitivity or glucose tolerance. Treatment with 100,000 IU vitamin D by intramuscular injection has been shown to improve C-peptide and insulin levels, although abnormal glucose tolerance by oral glucose tolerance test was unchanged (23).

The WHI was a well-characterized, large, ethnically diverse cohort of women.

Table 2—Relationship of serum 25(OH)D levels to incident type 2 diabetes among postmenopausal women in the Women's Health Initiative (N = 5,262)

	25(OH)D quartiles (nmol/L)				P*	Continuous†	25(OH)D levels			P*
	<34.7	34.7–47.8	47.9–64.2	>64.2			<50 nmol/L	50–< 75 nmol/L	≥75 nmol/L	
N	1,263	1,295	1,295	1,287		5,140	2,741	1,668	731	
Model 1‡	Reference	1.15 (0.73–1.79)	0.85 (0.55–1.32)	0.78 (0.48–1.26)	0.195	0.98 (0.95–1.02)	Reference	0.79 (0.55–1.13)	0.86 (0.53–1.40)	0.355
Model 2§	Reference	1.15 (0.73–1.80)	0.87 (0.56–1.35)	0.78 (0.47–1.29)	0.195	0.98 (0.95–1.02)	Reference	0.80 (0.56–1.15)	0.86 (0.52–1.42)	0.355
Model 3	Reference	1.25 (0.78–1.99)	1.00 (0.64–1.57)	1.05 (0.62–1.76)	0.935	1.01 (0.97–1.05)	Reference	0.89 (0.61–1.30)	1.14 (0.68–1.90)	0.873

Data are odds ratio (95% CI) unless otherwise indicated. *P for linear trend across quartiles. †5 nmol/L increase. ‡Adjusted for age and ethnicity. §Adjusted for age, ethnicity, latitude of clinical center, month of blood draw, and WHI study indicators. ||Adjusted for age, ethnicity, latitude of clinical center, month of blood draw, WHI study indicators, BMI, hypertension, fiber intake, magnesium intake, and physical activity.

Table 3—Relationship of serum 25(OH)D levels (categorical) to type 2 diabetes incidence by subgroups

	25(OH)D quartiles (nmol/L)				25(OH)D levels (nmol/L)			P*	25(OH)D (nmol/L) 5-unit increases	P*
	<34.7	34.7–47.8	47.9–64.2	≥64.2	<50	50–75	≥75			
BMI										
< 25	Ref.	0.70 (0.22–2.20)	1.26 (0.46–3.49)	0.37 (0.10–1.33)	0.04	1.21 (0.52–2.82)	0.70 (0.20–2.50)	0.48	0.96 (0.89–1.03)	0.29
25–< 30	Ref.	2.10 (0.91–4.85)	0.60 (0.22–1.65)	1.72 (0.74–4.03)		0.61 (0.29–1.29)	1.15 (0.51–2.60)		1.02 (0.96–1.08)	
≥30	Ref.	1.05 (0.59–1.89)	1.12 (0.63–1.99)	1.04 (0.54–2.03)		0.99 (0.60–1.61)	1.37 (0.67–2.82)		1.02 (0.97–1.07)	
Ethnicity										
White	Ref.	1.05 (0.65–1.69)	0.99 (0.62–1.60)	0.83 (0.49–1.41)	0.22	0.90 (0.61–1.34)	0.99 (0.58–1.70)	0.20	0.99 (0.95–1.03)	0.43
Black	Ref.	4.31 (1.12–16.54)	0.05 (0.01–0.49)	0.27 (0.02–3.09)		0.03 (0.00–0.24)	0.33 (0.03–4.08)		0.99 (0.87–1.13)	
Hispanic	Ref.	1.86 (0.25–13.85)	1.02 (0.25–4.28)	1.21 (0.12–12.65)		0.75 (0.20–2.86)	2.18 (0.23–20.33)		1.04 (0.91–1.18)	
Other†	Ref.	0.34 (0.04–2.74)	0.19 (0.03–1.24)	3.21 (0.58–17.83)		1.90 (0.35–10.42)	8.65 (1.54–48.44)		1.18 (1.00–1.40)	
CaD										
Placebo	Ref.	1.08 (0.56–2.08)	0.71 (0.36–1.41)	1.10 (0.53–2.26)	0.77	0.78 (0.43–1.41)	1.23 (0.59–2.56)	0.82	1.01 (0.96–1.07)	0.99
Active	Ref.	1.25 (0.64–2.42)	1.16 (0.60–2.24)	1.16 (0.57–2.33)		0.99 (0.57–1.73)	1.19 (0.55–2.56)		1.01 (0.96–1.06)	

Data are odds ratio (95% CI) unless otherwise indicated. Model adjusted for age, ethnicity, latitude of clinical center, month of blood draw, WHI study indicators, BMI, hypertension, fiber intake, magnesium intake, and physical activity. *P value for interaction. †Combined black, Hispanic, and other race/ethnicity because some cells contained zero.

Although we used women from several case-control studies, it does not appear that case-control status influenced our findings. Limitations of the study include reliance on a self-report of treated diabetes. Although we evaluated numerous potential confounders, residual confounding cannot be excluded. Because lipid levels were not measured in >85% of case and control subjects, we were unable to adjust for other fat soluble vitamins, such as vitamin E. We also had low power to detect race/ethnicity specific associations.

In conclusion, serum concentrations of 25(OH)D were not associated with the incidence of type 2 diabetes in this cohort of postmenopausal women after adjusting for BMI and other risk factors for diabetes. A number of plausible mechanisms have been proposed for a protective effect of 25(OH)D on insulin and glucose metabolism, and it may be that evaluation of other at-risk population groups or cohorts with higher serum levels of 25(OH)D may reveal a protective association between vitamin D and diabetes. The results of ongoing trials of higher doses of vitamin D supplementation are needed before recommendations for vitamin D supplementation for the prevention of type 2 diabetes or other nonskeletal chronic diseases could be justified.

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J.G.R. conceived of, designed, oversaw statistical analysis, and wrote the manuscript in addition to collecting data for WHI. J.E.M., S.L., B.V.H., Y.S., J.D.C., J.M.S., M.A., K.C.J., L.P., and N.W. contributed to the statistical analysis and critical revisions to the manuscript in addition to collecting data for WHI. J.L. performed the statistical analysis and contributed critical revisions to the manuscript.

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References

1. Song Y, Manson JE. Vitamin D, insulin resistance, and type 2 diabetes. *Curr Cardio Risk Rep* 2010;4:40–47
2. Pittas AG, Chung M, Trikalinos T, et al. Systematic review: Vitamin D and cardiometabolic outcomes. *Ann Intern Med* 2010;152:307–314
3. van Dam RM, Hu FB, Rosenberg L, Krishnan S, Palmer JR. Dietary calcium and magnesium, major food sources, and risk of type 2 diabetes in U.S. black women. *Diabetes Care* 2006;29:2238–2243
4. Birrell F, Francis RM. Invited commentary: physical activity and vitamin D. *Am J Epidemiol* 2008;168:587–589
5. Liu S, Choi HK, Ford E, et al. A prospective study of dairy intake and the risk of type 2 diabetes in women. *Diabetes Care* 2006;29:1579–1584
6. Ginde AA, Liu MC, Camargo CA Jr. Demographic differences and trends of vitamin D insufficiency in the US population, 1988–2004. *Arch Intern Med* 2009;169:626–632
7. Cheung BMY, Ong KL, Cherny SS, Sham P-C, Tso AWK, Lam KSL. Diabetes prevalence and therapeutic target achievement in the United States, 1999 to 2006. *Am J Med* 2009;122:443–453
8. The Women’s Health Initiative Study Group. Design of the Women’s Health Initiative clinical trial and observational study. *Control Clin Trials* 1998;19:61–109
9. Hsia J, Langer RD, Manson JE, et al.; Women’s Health Initiative Investigators. Conjugated equine estrogens and coronary heart disease: the Women’s Health Initiative. *Arch Intern Med* 2006;166:357–365
10. Rossouw JE, Anderson GL, Prentice RL, et al.; Writing Group for the Women’s Health Initiative Investigators. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the Women’s Health Initiative randomized controlled trial. *JAMA* 2002;288:321–333
11. Howard BV, Van Horn L, Hsia J, et al. Low-fat dietary pattern and risk of cardiovascular disease: The Women’s Health Initiative randomized controlled dietary modification trial. *JAMA* 2006;295:655–666
12. de Boer IH, Tinker LF, Connelly S, et al.; Women’s Health Initiative Investigators. Calcium plus vitamin D supplementation and the risk of incident diabetes in the Women’s Health Initiative. *Diabetes Care* 2008;31:701–707
13. Margolis KL, Lihong Qi, Brzyski R, et al.; Women Health Initiative Investigators. Validity of diabetes self-reports in the Women’s Health Initiative: comparison with medication inventories and fasting glucose measurements. *Clin Trials* 2008;5:240–247
14. Prentice A, Goldberg GR, Schoenmakers I. Vitamin D across the lifecycle: physiology and biomarkers. *Am J Clin Nutr* 2008;88:500S–506S
15. Liu E, Meigs JB, Pittas AG, et al. Plasma 25-hydroxyvitamin D is associated with markers of the insulin resistant phenotype in nondiabetic adults. *J Nutr* 2009;139:329–334
16. Harvard Medical School and the Brigham and Women’s Hospital. Vitamin D and Omega-3 Trial (VITAL). Boston, MA
17. Liu S, Song Y, Ford ES, Manson JE, Buring JE, Ridker PM. Dietary calcium, vitamin D, and the prevalence of metabolic syndrome in middle-aged and older U.S. women. *Diabetes Care* 2005;28:2926–2932
18. Pittas AG, Dawson-Hughes B, Li T, et al. Vitamin D and calcium intake in relation to type 2 diabetes in women. *Diabetes Care* 2006;29:650–656
19. Lu L, Yu Z, Pan A, et al. Plasma 25-hydroxyvitamin D concentration and metabolic syndrome among middle-aged and elderly Chinese individuals. *Diabetes Care* 2009;32:1278–1283
20. Delvin EE, Lambert M, Levy E, et al. Vitamin D status is modestly associated with glycemia and indicators of lipid metabolism in French-Canadian children and adolescents. *J Nutr* 2010;140:987–991
21. Knekt P, Laaksonen M, Mattila C, et al. Serum vitamin D and subsequent occurrence of type 2 diabetes. *Epidemiol* 2008;19:666–671
22. Liu E, Meigs JB, Pittas AG, et al. Predicted 25-hydroxyvitamin D score and incident type 2 diabetes in the Framingham Offspring Study. *Am J Clin Nutr* 2010;91:1627–1633
23. Boucher BJ, Mannan N, Noonan K, Hales CN, Evans SJW. Glucose intolerance and impairment of insulin secretion in relation to vitamin D deficiency in east London Asians. *Diabetologia* 1995;38:1239–1245

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