Calcium Plus Vitamin D Supplementation and the Risk of Incident Diabetes in the Women's Health Initiative

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OBJECTIVE — Experimental and epidemiologic studies suggest that calcium and vitamin D may reduce the risk of developing diabetes. We examined the effect of calcium plus vitamin D supplementation on the incidence of drug-treated diabetes in postmenopausal women.

RESEARCH DESIGN AND METHODS — The Women's Health Initiative Calcium/Vitamin D Trial randomly assigned postmenopausal women to receive 1,000 mg elemental calcium plus 400 IU of vitamin D3 daily, or placebo, in a double-blind fashion. Among 33,951 participants without self-reported diabetes at baseline, we ascertained by treatment assignment new diagnoses of diabetes treated with oral hypoglycemic agents or insulin. Effects of the intervention on fasting measurements of glucose, insulin, and insulin resistance were examined among a subset of participants.

RESULTS — Over a median follow-up time of 7 years, 2,291 women were newly diagnosed with diabetes. The hazard ratio for incident diabetes associated with calcium/vitamin D treatment was 1.01 (95% CI 0.94–1.10) based on intention to treat. This null result was robust in subgroup analyses, efficacy analyses accounting for nonadherence, and analyses examining change in laboratory measurements.

CONCLUSIONS — Calcium plus vitamin D3 supplementation did not reduce the risk of developing diabetes over 7 years of follow-up in this randomized placebo-controlled trial. Higher doses of vitamin D may be required to affect diabetes risk, and/or associations of calcium and vitamin D intake with improved glucose metabolism observed in nonrandomized studies may be the result of confounding or of other components of foods containing these nutrients.

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Experimental and epidemiologic studies suggest that calcium and vitamin D may reduce the risk of developing diabetes (1). In animal-experimental studies, administration of calcium and vitamin D improved pancreatic β-cell function and peripheral insulin sensitivity (2–4). These effects may be mediated by modulation of intracellular calcium concentrations, stimulation of insulin gene transcription, and/or insulin receptor expression (4–7). Cross-sectional human studies correlating dietary calcium intake, dietary vitamin D intake, and serum vitamin D concentrations with β-cell function, peripheral insulin sensitivity, and reduced prevalence of the metabolic syndrome suggest that effects observed in animal-experimental studies may be clinically relevant (8–12). Moreover, cohort studies have documented associations of dietary calcium and vitamin D intake with reduced risk of subsequent diabetes (13–16).

However, intervention studies assessing the effect of calcium and vitamin D supplements on glucose metabolism have yielded mixed results (17–21), and data from controlled trials assessing the effect of long-term supplement use on the risk of diabetes are not available. Thus, we examined the effect of calcium plus vitamin D supplementation on the risk of incident diabetes over 7 years of follow-up in the Women's Health Initiative (WHI). The WHI offers a unique opportunity to address the effect of calcium plus vitamin D supplementation on the development of diabetes because of its large size, placebo control, and relatively long duration of treatment and observation (22).

RESEARCH DESIGN AND METHODS

The WHI enrolled generally healthy postmenopausal women ages 50–79 years in an observational study and in clinical trials (22). Participants enrolled in the Dietary Modification trial, Hormone Therapy trial, or both were invited to join the Calcium/Vitamin D (CaD) trial at their first (n = 33,070) or second (n = 3,212) annual follow-up visit (22). Study protocol was approved by the institutional review board at each participating institution, and written informed consent was granted by each participant. This study includes CaD trial participants who did not have prevalent diabetes at the time of CaD trial enrollment (n = 33,951). Prevalent diabetes was defined as a self-reported physician diagnosis of "sugar diabetes" or use of pills or insulin shots for diabetes.

Fasting glucose and insulin concentrations were measured in a 6% sample of WHI clinical trial participants (23). Random sampling was stratified by age, clinical site, hysterectomy status, and race/

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Abbreviations: CaD, Calcium/Vitamin D; HOMA-IR, homeostasis model assessment of insulin resistance; WHI, Women's Health Initiative.

ethnicity to oversample for minority populations. Glucose and insulin measurements were completed at years 1 (CaD baseline), 3, and 6. Serum 25-hydroxyvitamin D concentrations, which reflect total body stores of vitamin D (24), were measured at CaD baseline in a separate participant subset. These vitamin D concentrations were obtained for a nested case-control study examining fractures, and only results for participants selected as control subjects were included in this study (n = 1,699).

Calcium/vitamin D intervention

Participants were randomly assigned in a double-blind fashion to receive 1,000 mg elemental calcium plus 400 IU vitamin D3 daily, or placebo (22). Active tablets consisted of 500 mg calcium (as calcium carbonate) and 200 IU vitamin D3 (provided by GlaxoSmithKline). Participants were instructed to take two tablets daily, preferably in divided doses with meals. Women were allowed to continue their own personal use of calcium and vitamin D as long as personal use of vitamin D did not exceed 600 IU daily. The upper limit of personal vitamin D intake was raised to 1,000 IU after the Institute of Medicine released its report on the tolerable upper limits of vitamin D intake (24). At year 3, 16% of participants reported nonstudy use of calcium-only supplements, 4% vitamin D–only supplements, and 44% multivitamins, which may have contained some calcium and/or vitamin D. Adherence to study medication was assessed by weighing returned bottles and was <80% during at least one 6-month time interval among 20,109 participants (59%). Serum 25-hydroxyvitamin D concentrations were measured on treatment at year 3 among a subset of 448 participants selected without regard to nonstudy supplement use or adherence to study medication. This participant subset differed from those for glucose/insulin and baseline 25-hydroxyvitamin D measurements. Compared with participants assigned to placebo, mean 25-hydroxyvitamin D concentration at year 3 was 23 nmol/l higher among women assigned to active therapy.

Incident diabetes

Incident diabetes, the primary outcome of this study, was defined as a new physician diagnosis of diabetes treated with oral hypoglycemic agents or insulin, as in prior WHI publications (25,26). Diabetes was an outcome of interest, though not a designated primary outcome for WHI trials, and this study is performed as a post hoc analysis. Case identification was by participant self-report. At each semi-annual contact, participants were asked, "Since the date given on the front of this form, has a doctor prescribed any of the following pills or treatments?" A positive response for either "pills for diabetes" or "insulin shots for diabetes" was used to define incident diabetes. The accuracy of self-reported treated diabetes in the WHI trials has been assessed using medication and laboratory data (K.L.M., R. Brzyski, D.E. Bonds, B.V.H., S. Kempainen, S. Liu, L.S. Phillips, J.G. Robinson, M.M. Safford, L.F.T., unpublished data). At the baseline visit, 79% of women with prevalent self-reported treated diabetes brought an oral hypoglycemic agent or insulin to the baseline drug inventory, and 73% of women with self-reported diabetes whose fasting glucose was measured had a result ≥126 mg/dl. Seventy-eight percent with incident self-reported treated diabetes during the first year of the trial brought a diabetes medication to the year 1 drug inventory.

Laboratory outcomes

Blood samples for glucose and insulin were obtained in the fasting state (at least 12 h) and maintained at 4°C for up to 1 h. Centrifuged aliquots were put into −70°C freezers within 2 h of collection and sent on dry ice to the central repository for storage at −70°C. Fasting glucose was analyzed using the hexokinase method (Hitachi 747; Boehringer Mannheim Diagnostics, Indianapolis, IN), with interassay coefficients of variation <2%. Homeostasis model assessment of insulin resistance (HOMA-IR) was calculated from fasting glucose and insulin values (27).

Covariates

Demographic and health history data were self-reported at WHI baseline. Dietary data were collected using a validated food frequency questionnaire (28). Total calcium and vitamin D intakes included both dietary and supplement sources. Metabolic equivalent of the task (MET) scores were calculated from the frequency and duration of recreational physical activity (29). Solar irradiance was defined by recruitment site (30). BMI was calculated as weight in kilograms divided by the square of height in meters. Waist circumference was measured at the narrowest part of the torso at end-expiration. Fasting glucose was characterized as normal, impaired, or diabetic according to American Diabetes Association guidelines, (31), and the metabolic syndrome was defined according to National Cholesterol Education Program–Adult Treatment Panel III criteria (32). 25-Hydroxyvitamin D concentrations were measured using the DiaSorin Liaison chemiluminescent immunoassay system (Stillwater, MN).

Statistical methods

Unadjusted incidence rates, calculated as the number of incident diabetes cases divided by total follow-up time, were reported as an annualized percent. Cox proportional hazards models, stratified by age and randomization status for other WHI trials, were used to assess risk associated with CaD treatment assignment. Participants were considered at risk for incident diabetes from entry into the CaD trial until diagnosis of diabetes or until the last semi-annual visit for which outcome data were available. Twenty potential covariate-treatment interactions were selected based on risk factors for diabetes and nonstudy sources of calcium and vitamin D. Approximately one interaction was expected to be significant by chance alone at the $\alpha = 0.05$ level of significance. Primary analyses were by intention to treat. Secondary efficacy analyses assessed the impact of *1*) nonadherence to study medications ("dropout") by censoring time at risk 6 months after the first semiannual report indicating <80% use of study medication (as-treated analysis) and *2*) nonstudy supplement use ("drop-in") using models that included nonstudy use of calcium or vitamin D supplements as a time-dependent covariate.

Among participants with laboratory measurements, "incident treated plus untreated diabetes" was defined as "pills for diabetes," "insulin shots for diabetes," or a fasting glucose concentration ≥126 mg/dl (31). Absolute differences in fasting glucose, insulin, and HOMA-IR score from baseline were compared by CaD treatment assignment at the year 3 and 6 study visits using a t test, weighted for sampling design; use of unweighted or log-transformed data did not change interpretation of results. SAS version 9.1 (Cary, NC) was used for all analyses.

Table 1—*Incident diabetes by calcium/vitamin D treatment assignment, presented for all participants and within subgroups*

	Calcium/vitamin D		Placebo		Hazard ratio associated with calcium/vitamin D treatment (95% CI)	*P* (treatment-covariate interaction)
	Number of events/number at risk	Annualized %	Number of events/number at risk	Annualized %		
All participants	1,154/16,999	0.96	1,137/16,952	0.95	1.01 (0.94–1.10)	
Age at screening (years)						0.95
50–59	431/6,384	0.91	426/6,358	0.91	1.01 (0.88–1.15)	
60–69	535/7,696	1.01	518/7,674	0.98	1.03 (0.91–1.17)	
70–79	188/2,919	0.95	193/2,920	0.98	0.98 (0.80–1.20)	
Race/ethnicity						0.86
White	846/14,260	0.84	855/14,297	0.85	0.99 (0.90–1.09)	
Black	166/1,430	1.66	163/1,409	1.66	1.04 (0.84–1.30)	
Hispanic	89/714	1.81	71/659	1.57	1.15 (0.83–1.59)	
American Indian	4/65	0.87	5/67	1.05	0.20 (0.02–1.86)	
Asian-Pacific Islander	32/338	1.41	24/313	1.13	1.30 (0.75–2.27)	
Unknown	17/192	1.29	19/207	1.37	0.84 (0.43–1.64)	
Education						0.06
Less than high school diploma/GED	103/867	1.73	90/811	1.60	1.02 (0.76–1.36)	
High school diploma/GED	223/3,056	1.03	253/3,124	1.16	0.90 (0.75–1.08)	
School after high school	465/6,729	0.98	489/6,668	1.04	0.95 (0.83–1.08)	
College degree or higher	354/6,238	0.79	297/6,235	0.67	1.18 (1.01–1.38)	
Family history of diabetes						0.29
No	554/10,877	0.72	524/10,825	0.69	1.05 (0.93–1.19)	
Yes	527/5,281	1.41	547/5,267	1.47	0.96 (0.85–1.09)	
Total calcium intake (mg/day)						0.05
<800	445/5,656	1.11	399/5,543	1.01	1.10 (0.96–1.26)	
800 to <1,200	303/4,406	0.97	302/4,347	0.99	0.98 (0.84–1.15)	
≥1,200	375/6,610	0.81	409/6,730	0.87	0.93 (0.81–1.07)	
Total vitamin D intake (IU/day)						0.47
<200	463/6,369	1.02	428/6,207	0.97	1.07 (0.93–1.22)	
200 to <400	212/3,145	0.95	211/3,197	0.93	1.02 (0.84–1.24)	
≥400	448/7,158	0.90	471/7,216	0.94	0.95 (0.83–1.08)	
Dairy servings per day						0.02
<1	416/5,509	1.08	382/5,503	0.99	1.09 (0.95–1.26)	
1–2.5	578/9,124	0.89	581/9,031	0.91	0.99 (0.88–1.11)	
>2.5	160/2,361	0.96	174/2,417	1.01	0.92 (0.74–1.14)	
Multivitamin use						0.29
No	777/10,946	1.00	738/10,820	0.96	1.05 (0.94–1.16)	
Yes	377/6,132	0.89	399/6,052	0.93	0.95 (0.82–1.09)	
Alcohol intake						0.15
Nondrinker	140/1,698	1.19	140/1,677	1.17	1.04 (0.82–1.31)	
Past drinker	246/2,800	1.28	270/2,770	1.38	0.92 (0.78–1.10)	
<1 drink/week	468/5,909	1.10	415/6,018	1.00	1.12 (0.98–1.28)	
1 to <7 drinks/week	230/4,574	0.71	228/4,555	0.70	0.99 (0.83–1.20)	
≥7 drinks/week	61/1,858	0.46	81/1,860	0.62	0.67 (0.48–0.94)	
Smoking						0.91
Never smoked	595/8,824	0.96	601/8,734	0.96	1.00 (0.89–1.12)	
Past smoker	447/6,670	0.93	427/6,774	0.91	1.04 (0.91–1.19)	
Current smoker	100/1,284	1.09	100/1,326	1.12	0.93 (0.70–1.23)	
Region by solar irradiance (Langleys)						0.75
400–500	459/6,455	1.02	435/6,431	0.97	1.05 (0.92–1.20)	
350–380	414/5,475	1.08	423/5,467	1.10	0.97 (0.85–1.11)	
300–325	281/5,069	0.77	279/5,054	0.77	1.02 (0.86–1.20)	
Physical activity (MET hours/week)						0.18
≤3.00	404/5,061	1.16	453/5,017	1.32	0.89 (0.77–1.01)	
>3.00 to <11.75	347/5,088	0.99	308/5,132	0.87	1.14 (0.98–1.33)	
≥11.75	276/5,302	0.75	259/5,219	0.72	1.04 (0.87–1.23)	

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Table 1—*Continued*

	Calcium/vitamin D		Placebo		Hazard ratio associated with calcium/vitamin D treatment (95% CI)	*P* (treatment-covariate interaction)
	Number of events/number at risk	Annualized %	Number of events/number at risk	Annualized %		
BMI (kg/m^2)						0.38
≥25	126/4,628	0.38	119/4,720	0.36	1.08 (0.84–1.39)	
>25 to <30	317/6,166	0.72	319/6,183	0.73	0.99 (0.84–1.15)	
≥30	710/6,120	1.66	697/5,958	1.67	1.00 (0.90–1.11)	
Waist circumference (cm)						0.08
<88	279/8,924	0.44	264/8,988	0.41	1.05 (0.88–1.24)	
≥88	872/8,029	1.55	870/7,913	1.57	0.99 (0.90–1.09)	
Dietary modification trial assignment						0.36
Not randomized	346/5,189	0.97	355/5,092	1.01	0.95 (0.82–1.11)	
Intervention	318/4,467	1.00	297/4,593	0.91	1.11 (0.95–1.31)	
Comparison	490/7,343	0.93	485/7,267	0.94	1.00 (0.88–1.14)	
Hormone therapy use at CaD baseline						0.31
Never	414/5,360	.10	371/5,254	1.00	1.10 (0.95–1.26)	
Past	209/2,808	1.05	203/2,743	1.05	1.01 (0.83–1.23)	
Current‡	531/8,831	0.85	563/8,955	0.89	0.95 (0.85–1.07)	
Fasting glucose (mg/dl)*†						0.88
<100	28/767	0.53	30/777	0.55	1.05 (0.57–1.93)	
≥100	56/261	3.11	58/275	3.01	1.03 (0.63–1.68)	
Metabolic syndrome*†§						0.44
No	20/668	0.43	28/709	0.56	0.77 (0.40–1.48)	
Yes	64/359	2.59	60/333	2.59	1.06 (0.67–1.68)	
25-Hydroxyvitamin D concentration (nmol/l)*						0.59
<32.2	30/381	1.08	33/391	1.17	1.07 (0.62–1.82)	
32.2–43.6	17/371	0.64	30/394	1.05	0.66 (0.36–1.23)	
43.7–60.1	22/366	0.82	16/402	0.54	1.60 (0.80–3.18)	
≥60.2	20/395	0.70	24/397	0.83	0.62 (0.32–1.20)	

*Limited to participants with available measurements. †Proportional hazards model used to estimate hazard ratio additionally stratified by race/ethnicity to account for sampling scheme. ‡Includes both randomized and observational use of hormone therapy. §Metabolic syndrome defined according to NCEP-ATPIII criteria (32). MET, metabolic equivalent of the task.

RESULTS

Baseline characteristics

Mean age was 62 years. Of the participants, 84% described themselves as Caucasian, 8% Black, 4% Hispanic, <1% American Indian, and 2% Asian/Pacific Islander. Baseline 25-hydroxyvitamin D concentration was <80 nmol/l for 89% of participants, and <50 nmol/l for 61%. Participant characteristics, described in detail in Table 1, did not differ by calcium/vitamin D treatment assignment.

Incident diabetes

Over a median follow-up time of 7 years, 2,291 women developed incident diabetes. A total of 2,177 participants reported use of oral hypoglycemic agents (95% of case subjects), and 227 reported use of insulin (10% of case subjects), with some participants reporting use of both. The cumulative incidence of diabetes at 7 years was 6.5% and did not differ by calcium/vitamin D treatment assignment (Fig. 1*A*). Based on intention to treat, the hazard ratio for incident diabetes associated with calcium/vitamin D treatment was 1.01 (95% CI 0.94–1.10).

A number of participant characteristics, measured at baseline, were associated with increased risk for incident diabetes: non-Caucasian race/ethnicity, less formal education, family history of diabetes, lesser alcohol intake, greater BMI, greater waist circumference, lower intakes of calcium and vitamin D, less physical activity, lack of hormone therapy, elevated fasting glucose, and presence of the metabolic syndrome (Table 1, columns displaying annualized incidence rates). However, the effect of calcium/vitamin D treatment on risk of incident diabetes did not differ among subgroups defined by any baseline participant characteristic examined (Table 1, column displaying treatment-covariate interaction *P* values), with the possible exceptions of trends toward a protective effect of calcium/vitamin D therapy among women who consumed greater dietary calcium or dairy products (*P* for interaction = 0.05 and 0.02, respectively). Baseline intakes of dietary calcium and dairy products were moderately correlated (Pearson correlation coefficient, $r = 0.58$). When time at risk was censored for adherence <80% (Fig. 1*B*), the hazard ratio for incident diabetes associated with calcium/vitamin D treatment was 0.97 (95% CI 0.86–1.09). Nonstudy use of calcium supplements, including multivitamins, was reported at least once by 79% of participants, and nonstudy use of vitamin D supplements was reported by 75%. When adjustment was made for nonstudy use of calcium or vitamin D, the hazard ratio for incident diabetes associated with calcium/vitamin D treatment was 1.01 (95% CI 0.93–1.10) or 1.02 (0.94–1.10), respectively.

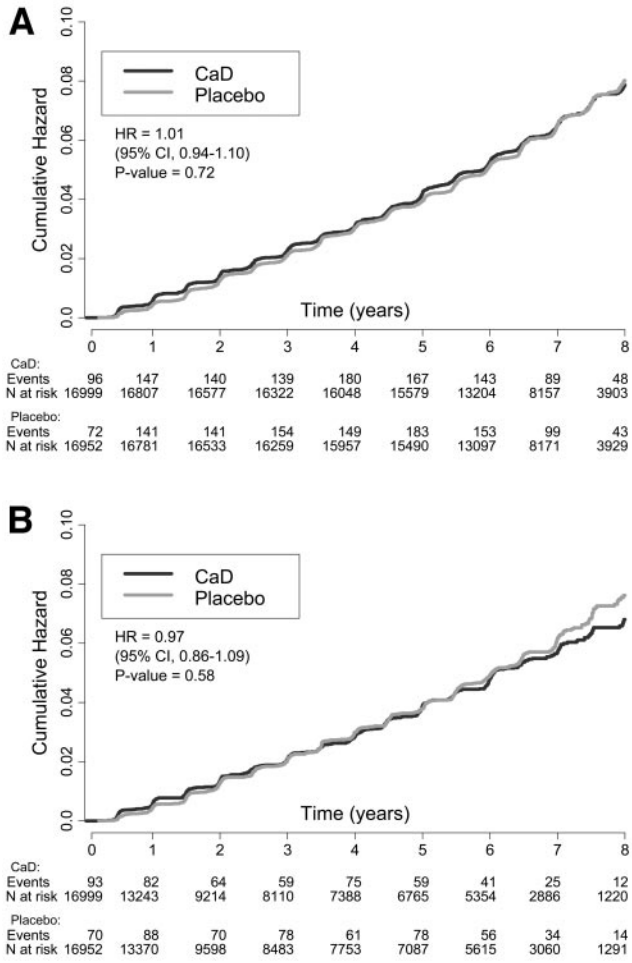

Figure 1—*Cumulative incidence of diabetes by calcium/vitamin D treatment assignment.* A*: Intention to treat.* B*: As treated (censoring time at risk for <80% adherence to study medications). CaD, active calcium/vitamin D treatment assignment.*

Laboratory outcomes

Baseline fasting glucose measurements were available for 2,080 participants (6.1%). Fasting glucose was ≥126 mg/dl in 60 participants (2.9%), who were excluded from further analyses of laboratory outcomes. Among the remaining group, the year 6 cumulative incidence of both treated diabetes and treated plus untreated diabetes did not differ by calcium/vitamin D treatment assignment: treated diabetes developed in 21 of 738 participants assigned to active treatment (2.8%) and 25 of 771 participants assigned to placebo (3.2%), whereas treated or untreated diabetes developed in 59 (8.0%) and 65 (8.4%), respectively. The relative risk of incident diabetes associated with calcium/vitamin D treatment assignment was very similar comparing the treated diabetes outcome (relative risk 0.88, 95% CI 0.50–1.55) to the treated plus untreated diabetes outcome (relative risk 0.95, 0.68–1.33).

Changes in fasting glucose concentrations, insulin concentrations, and HOMA-IR scores from CaD baseline to years 3 and 6 were assessed by calcium/vitamin D treatment assignment in the overall group with available blood samples and in a subgroup with impaired fasting glucose at baseline (Table 2). We found no significant effect of treatment on parameters of glucose metabolism in either group. Results did not differ when analyses were restricted to participants who maintained adherence to study medications ≥80% through the time of measurement.

CONCLUSIONS — Calcium plus vitamin D3 supplementation (1,000 mg plus 400 IU daily, respectively) did not reduce the risk of developing drug-treated diabetes over 7 years of follow-up in the WHI CaD randomized placebo-controlled trial. This null result was robust in subgroup analyses, efficacy (adherence-based) analyses, and analyses examining change in laboratory measurements of glucose, insulin, and insulin resistance as assessed by HOMA-IR scores. The hazard ratio for incident diabetes of 1.01 and tight surrounding 95% CI (0.94–1.10) suggest that a clinically significant benefit for this specific intervention with regard to diabetes prevention is unlikely among generally healthy postmenopausal women.

In prior observational studies, greater baseline intakes of calcium, vitamin D, and/or dairy products were associated with reduced risk for subsequent diabetes (13–16). In the current study, when we examined our data as an observational cohort study, greater baseline total calcium and vitamin D intakes were associated with modestly lower unadjusted incidence rates of diabetes. These observational results are consistent with prior observational studies, but carry similar potential limitations. In contrast, null results examining the randomly assigned calcium/vitamin D intervention conflict with observational studies.

What explains this discrepancy? First, it is possible that calcium and/or vitamin D do prevent diabetes, but that the doses used in the WHI CaD trial were insufficient to affect this outcome. This explanation appears unlikely for calcium, since the dose of calcium used is large compared with typical dietary intakes (24). For vitamin D, however, a relatively small dose was prescribed. Vitamin D3 400 IU daily would be expected to raise 25-hydroxyvitamin D concentrations from 43.7 nmol/l (the median baseline value in this study) to ~65.7 nmol/l (33), still less than the 80 nmol/l threshold currently recommend by many experts (34). Alternatively, it is possible that calcium and vitamin D have no causal effect on glucose metabolism and that observational studies, as well as the observational results presented here, were limited by confounding. Differences in dietary calcium, dietary vitamin D, and serum vitamin D concentrations may reflect differences in lifestyle (for example, dietary preferences or physical activity not easily ascertained) or unmeasured attributes of health status (such as body composition). It is also possible that nutrients commonly consumed with calcium and vitamin D may improve glucose metabolism, while calcium and vitamin D in themselves do not, or that foods rich in

Table 2—*Change in fasting glucose, insulin, and HOMA-IR measurements over time, by calcium/vitamin D treatment assignment and baseline fasting glucose concentration*

	Calcium/vitamin D		Placebo		Difference*	
	n	Mean ± SD	*n*	Mean ± SD	Mean ± SE	*P*
Baseline glucose ≤125 mg/dl						
Glucose						
Year 3–baseline	866	0.64 ± 12.08	890	0.62 ± 12.39	0.02 ± 0.65	0.979
Year 6–baseline	738	3.80 ± 14.16	771	4.61 ± 14.71	−0.82 ± 0.82	0.320
Insulin						
Year 3–baseline	795	1.12 ± 6.73	818	1.55 ± 7.24	−0.43 ± 0.39	0.271
Year 6–baseline	718	−0.97 ± 8.69	739	−0.82 ± 6.74	−0.15 ± 0.44	0.728
HOMA-IR score						
Year 3–baseline	795	0.32 ± 1.80	818	0.41 ± 1.96	−0.10 ± 0.10	0.352
Year 6–baseline	718	−0.02 ± 2.78	739	0.01 ± 2.16	−0.03 ± 0.14	0.809
Baseline glucose 100–125 mg/dl						
Glucose						
Year 3–baseline	197	−1.26 ± 18.02	211	−2.03 ± 19.29	0.77 ± 2.19	0.725
Year 6–baseline	172	3.93 ± 22.46	178	4.69 ± 22.94	−0.76 ± 2.88	0.791
Insulin						
Year 3–baseline	189	0.53 ± 8.08	195	−0.15 ± 8.62	0.68 ± 0.97	0.484
Year 6–baseline	171	−0.59 ± 10.11	173	−1.21 ± 9.83	0.62 ± 1.30	0.630
HOMA-IR score						
Year 3–baseline	189	0.17 ± 2.37	195	0.02 ± 2.70	0.15 ± 0.30	0.615
Year 6–baseline	171	0.25 ± 3.79	173	0.05 ± 3.50	−0.20 ± 0.47	0.672

*Difference calculated as change in calcium/vitamin D group minus change in placebo group.

calcium and/or vitamin D may displace other foods that cause diabetes.

Prior intervention studies assessing the effects of vitamin D supplementation on glucose metabolism have yielded mixed results (1,17–20). These studies were generally limited by small size, short duration, and/or lack of appropriate controls. Recently, a larger ($n = 314$) 3-year study of calcium plus vitamin D3 supplementation (500 mg plus 700 IU, respectively) reported improvement in fasting glucose concentrations and HOMA-IR scores, compared with placebo, among women with baseline impaired fasting glucose, but not among women with normal fasting glucose (21). Similar effect modification by baseline glucose concentration was not observed in the current study. Differences in dose and formulation of study medications, adherence and nonstudy supplement use, and/or sample size may contribute to differing results.

We observed a trend toward a protective effect of calcium/vitamin D supplementation among participants with greater baseline dietary intakes of calcium or dairy products. It is possible that greater nonstudy calcium intake allowed for a synergistic effect with study vitamin D; however, this seems unlikely, since all participants receiving active study medication also received relatively large doses of calcium. Alternatively, this may represent a chance finding from multiple testing of interactions, with two potentially significant interactions observed because of correlation between dietary calcium and dairy intake.

There are a number of potential limitations to this study. First, longitudinal fasting glucose measurements were available for only a subset of trial participants, limiting the primary study outcome to self-reported drug-treated diabetes. Although not strictly consistent with the American Diabetes Association definition of diabetes (31), it is important to note that drug-treated diabetes is a clinically relevant outcome. Moreover, two observations suggest that the outcome definition used in this study is valid: *1*) results were similar whether the outcome was defined as treated diabetes only or treated plus untreated diabetes (American Diabetes Association definition) among the subset of participants with laboratory measurements, and *2*) expected associations of covariates with incident diabetes were observed. Second, nonadherence and nonstudy use of supplements may have biased results toward the null. However, reasonable separation of 25-hydroxyvitamin D concentrations by treatment assignment was observed within the subgroup of participants for whom measurements were made, and sensitivity analyses accounting for nonadherence and nonstudy use of supplements suggested that the study result was robust. Finally, only one intervention dose was prescribed, which may have included insufficient vitamin D to influence diabetes risk.

This study also has important strengths. The large number of incident diabetes cases lends great power to this study and facilitates accurate subgroup analyses. For analyses of laboratory outcomes, the subset of participants with available measurements in itself was larger than prior intervention studies. More importantly, the randomly assigned intervention and long duration of follow-up allow a valid and unique assessment of the long-term risk of incident diabetes associated with calcium and vitamin D supplementation.

In conclusion, calcium plus vitamin D3 supplementation did not reduce the risk of developing diabetes over 7 years of follow-up in this randomized placebo-controlled trial of generally healthy postmenopausal women. Future research should seek explanations for differing results comparing observational studies to

randomized trials and/or examine higher doses of vitamin D.

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