Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

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Vitamin D Supplementation and Prevention of Type 2 diabetes

SUPPLEMENTARY APPENDIX

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- Patricia Sheehan, RN MPH MS, (Spaulding Rehabilitation Network, Charlestown, MA)

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- William Knowler, MD DrPH (National Institute of Diabetes and Digestive and Kidney Diseases, Phoenix, AZ)

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- Bess Dawson-Hughes, MD
- Saul Malozowski, MD PhD, *NIDDK Program Officer*
- David M. Reboussin, PhD, *Statistical Consultant*
- David Robbins, MD
- Clifford Rosen, MD
- Myrlene Staten, MD, *NIDDK Project Scientist*

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- Ronald Ackermann, MD MPH FACP
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- Jim Neaton, PhD
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Complete Eligibility Criteria for the D2d Study

Inclusion Criteria

1. Pre-diabetes ("at increased risk for diabetes") defined by meeting 2-out-of-3 of the following glycemic criteria, established by the ADA in the 2010 clinical practice guidelines, at the baseline visit:
    a. FPG 100-125 mg/dL, inclusive
    b. 2hPG 140-199 mg/dL, inclusive
    c. HbA1c 5.7-6.4%, inclusive
2. Age ≥ 30 years (≥25 years for people of the following races: American-Indian, Alaska Native, Native Hawaiian or Other Pacific Islander).
3. BMI ≥ 24.0 (22.5 for Asians) and ≤ 42.0 kg/m.2
4. Provision of signed and dated written informed consent prior to any study procedures.

Exclusion Criteria

Exclusion Criteria were selected to: (1) ensure participants' safety; (2) avoid conditions that would affect the outcomes (i.e. minimize competing risk); (3) make recruitment targets realistic; (4) amplify generalizability of study results; (5) maximize participants' adherence with study procedures.

5. Diabetes based on either of the following criteria:
    a. History (past 1 year) of hypoglycemic pharmacotherapy (oral or injectable medication approved by the FDA for type 2 diabetes) used for any condition (e.g. pre-diabetes, diabetes, polycystic ovarian syndrome).
    b. Meeting a glycemic criterion for diabetes, as defined by the ADA guidelines (FPG ≥ 126 mg/dL, 2hPG ≥ 200 mg/dL or HbA1c ≥ 6.5%) at the baseline visit.
6. History (past 3 years) of hyperparathyroidism, symptomatic or asymptomatic (i.e., radiographic) nephrolithiasis or hypercalcemia. [Safety]
7. Any medical condition (past 3 years) that in the opinion of the site investigator may increase risk for nephrolithiasis or hypercalcemia during the trial (e.g. sarcoidosis). [Safety]
8. Use of tanning devices within 12 weeks of the baseline visit and unwilling to stop using tanning devices for the duration of the study [interference with intervention]

Medications and Supplements

9. Use of supplements containing vitamin D at total doses higher than 1000 IU/day within 8-12 weeks (depending on dose, as described in Manual of Operations) of the baseline visit initiating the protocol and unwillingness to limit vitamin D supplementation dosage to no higher than 1000 IU/day for the duration of the study. [Safety]
10. Use of supplements containing calcium at total doses higher than 600 mg/day within 1 week of the baseline visit initiating the protocol and unwillingness to limit calcium supplementation dosage to no more than 600 mg/day for the duration of the study. [Safety]
11. Current use of medications or conditions (e.g. untreated celiac disease) that would interfere with absorption or metabolism of vitamin D.
12. Current use of medications approved by the FDA for weight management.
13. Use of thiazide diuretics at a total dose greater than 37.5 mg/day.
14. Use of anticonvulsant drug started within 6 months of screening. Stable regimen of anticonvulsants is allowed.

15. History of intolerance to vitamin D supplements. [Safety]

Other Medical History

16. Severe symptomatic cardiovascular disease based on history and physical examination (unstable angina, dyspnea on exertion, paroxysmal nocturnal dyspnea, arrhythmia, congestive heart failure NYHA class II or higher, claudication).
17. History (past 1 year) of myocardial infarction, percutaneous coronary intervention or coronary artery bypass graft. [Safety]
18. History (past 1 year) of cerebrovascular disease (stroke, transient ischemic attack). [Safety]
19. Any type of cancer (past 5 years) except for basal cell skin cancer. [Safety] Participants with prostate cancer (for men over age 55) or well-differentiated thyroid cancer that are not expected to require treatment (except for suppression with thyroid hormone) over the next 4 years are not excluded. Volunteers with history of squamous cell cancer of the skin, which was completely excised and with no evidence of metastases, are eligible.
20. History (past 6 months) of treatment with oral (for > 7 days) or intravenous glucocorticoids or disease likely to require oral or intravenous glucocorticoid therapy during the study). [Interference with outcome assessment] Inhaled glucocorticoid use in not an exclusion. Epidural or intraarticular glucocorticoid injections are not exclusions but study visits need to be conducted at least a week after the injection. Persons with adrenal insufficiency treated with physiologic doses of glucocorticoids who are otherwise stable are not excluded.
21. History (past 1 year) of substance abuse or unstable psychiatric disorder that in the opinion of the site investigator would impede competence or adherence with study procedures or hinder completion of the study or increase risk. [Safety, adherence] Use of marijuana with a medical prescription is permitted.
22. History of bariatric surgery (e.g., Roux-en-Y gastric bypass, gastric sleeve) or planned bariatric surgery in the next 4 years. Participants with gastric banding more than 2 years ago with self-reported weight stability (defined as weight change no greater than 3 kg during the prior 6 months) are not excluded. [Interfere with vitamin D absorption]
23. A life-threatening event within 30 days of screening or currently planned major surgery.
24. Any other unstable active medical condition (including but not limited to liver disease, wasting illness, AIDS, tuberculosis, oxygen-dependent chronic obstructive pulmonary disease, organ transplant, Cushing's syndrome) that in the opinion of the site investigators would impede competence or adherence with study procedures or increase risk. [Safety, adherence, plasma 25OHD may decrease as an acute-phase response] Such conditions will be assessed based on self-report and/or review of medical records (if available).
25. Uncontrolled hypertension (systolic blood pressure > 160 mm Hg or diastolic blood pressure > 100 mm Hg). [Safety]
26. Poor venous access. [Safety]

Laboratory Evaluation

27. Serum liver transaminase (ALT or AST) higher than 3 times the normal range for the clinical site's laboratory [Safety]
28. Anemia (hematocrit < 32 for women, < 36 for men), whole blood transfusion (within 6 months of screening) or chronic requirement, whole blood donation (within 3 months of screening) or other condition (hemolysis, hemoglobinopathy) rendering HbA1c results unreliable as indicator of chronic glycemia. [Interference with outcome assessment] Participants who donate platelets are not

excluded. Whole blood transfusion or donation does not exclude participant, but screening and study visits need to be timed appropriately.

29. Low platelet count (< 50,000). [Safety for blood draws]
30. Chronic kidney disease, defined as estimated glomerular filtration rate [GFR] < 50 mL/min, from creatinine measured at the clinical site's laboratory and GFR calculated centrally. [Vitamin D homeostasis changes as GFR declines. These changes start when GFR falls around 40-60 mL/min per 1.73 m2. The planning committee selected 50 mL/min as the exclusion cutoff to ensure that participants maintain GFR > 40 mL/min during the study] Please note: to prevent potential confusion, GFR units will be denoted as mL/min throughout the protocol and associated documents.
31. Hypercalcemia, defined as serum calcium concentration greater than or equal to the upper limit of normal, measured at the clinical site's laboratory. [Safety]
32. Hypercalciuria, defined as spot urine (morning void) calcium-creatinine ratio > 0.275.258 [Safety]

Other

33. Participation (within 30 days of screening) in another interventional research study. [Conflict, "contamination"]
34. Previous randomization in the D2d study. Participants who did not qualify after screening may be screened again if the prior reason for exclusion has been addressed (e.g. high blood pressure is treated).
35. Any other reason that in the opinion of the site investigator would impede adherence with study procedures or hinder completion of the study or increase risk (e.g. use of non-approved or experimental drugs, inability to follow instructions or understand the informed consent, dementia, unable to remain in the program for the duration of the study, inability to comply with the study protocol for any reason). [Safety, adherence]

Women only

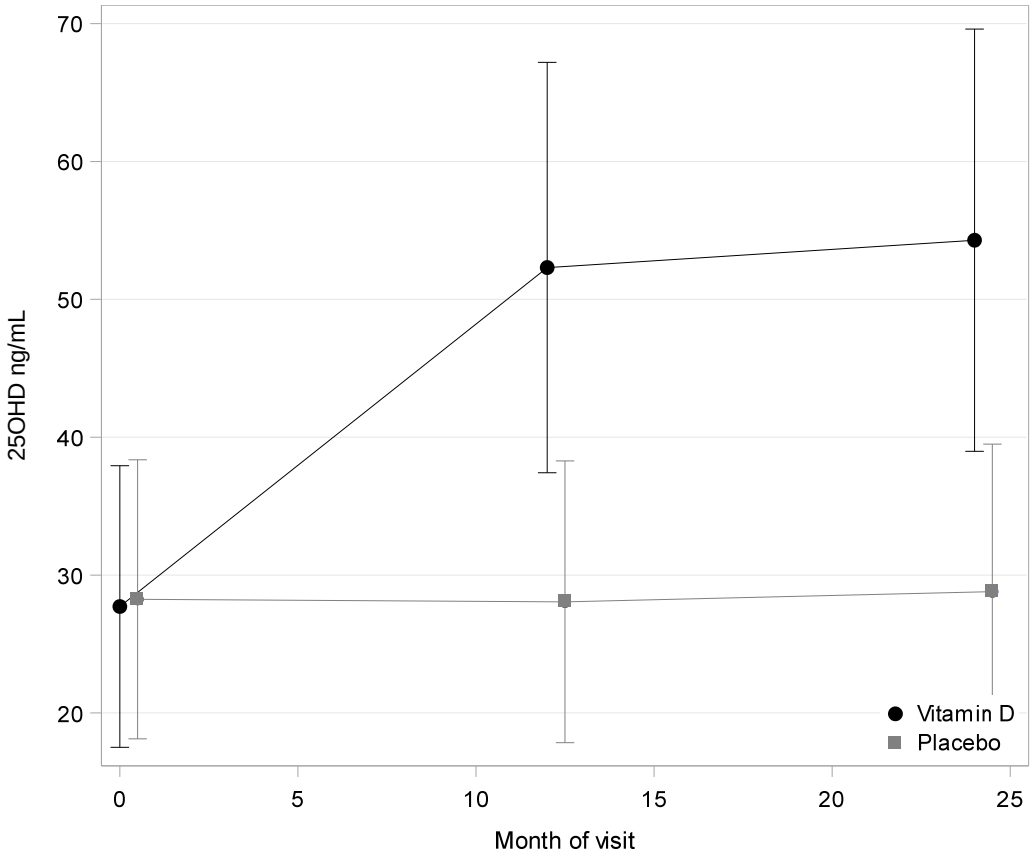
36. Pregnancy (past 1 year by report or positive pregnancy test at screening), intent to become pregnant in the next 4 years or unprotected intercourse. [Safety] History of gestational diabetes is not an exclusion criterion.
37. Currently breastfeeding. [Safety]
38. Use of oral contraceptives or menopausal hormone therapy started within 3 months of baseline. Stable regimen of oral contraceptives or any other hormonal method of contraception (e.g. implantable) is allowed. [Safety, interference with intervention]

Sensitivity Analysis for Non-Informative Censoring

We conducted a sensitivity analysis for non-informative censoring to assess the robustness of the primary outcome model under the assumption that all participants with incomplete data (died, withdrew or did not return for the last encounter) met the primary outcome of diabetes at the time of study exit. The result of the sensitivity analysis showed a hazard ratio for vitamin D of 0.90 (95%CI 0.78 to 1.03), which is essentially the same as the main analysis.

Supplementary Figures and Table

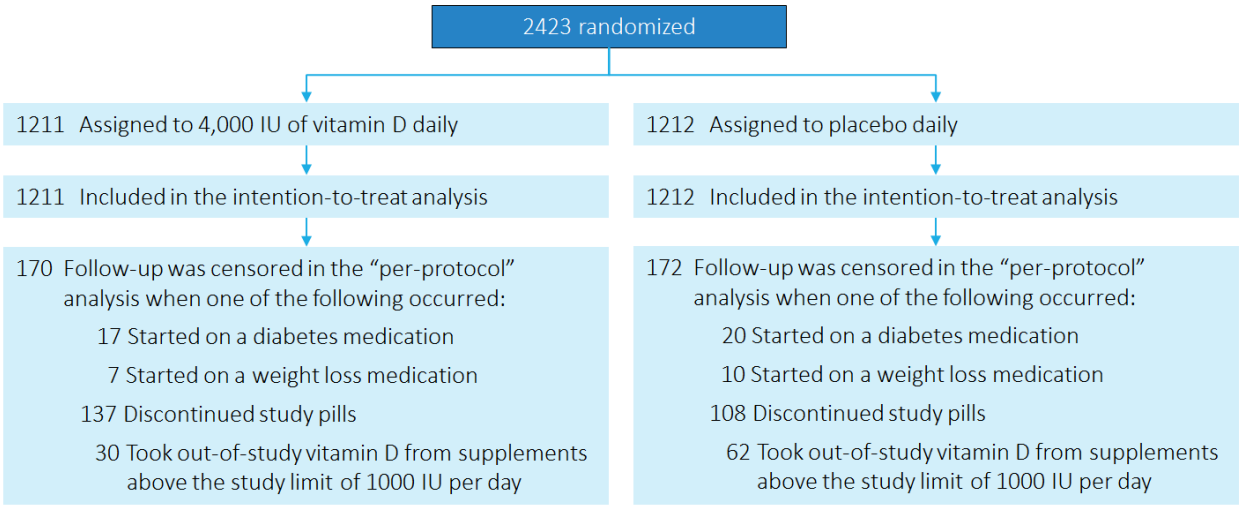
Supplementary Figure S1. Serum 25-hydroxyvitamin D concentration during the D2d study.



	Baseline	Month 12	Month 24
Vitamin D group	27.7 ± 10.2	52.3 ± 14.9	54.3 ± 15.3
Placebo group	28.2 ± 10.1	28.1 ± 10.2	28.8 ± 10.7

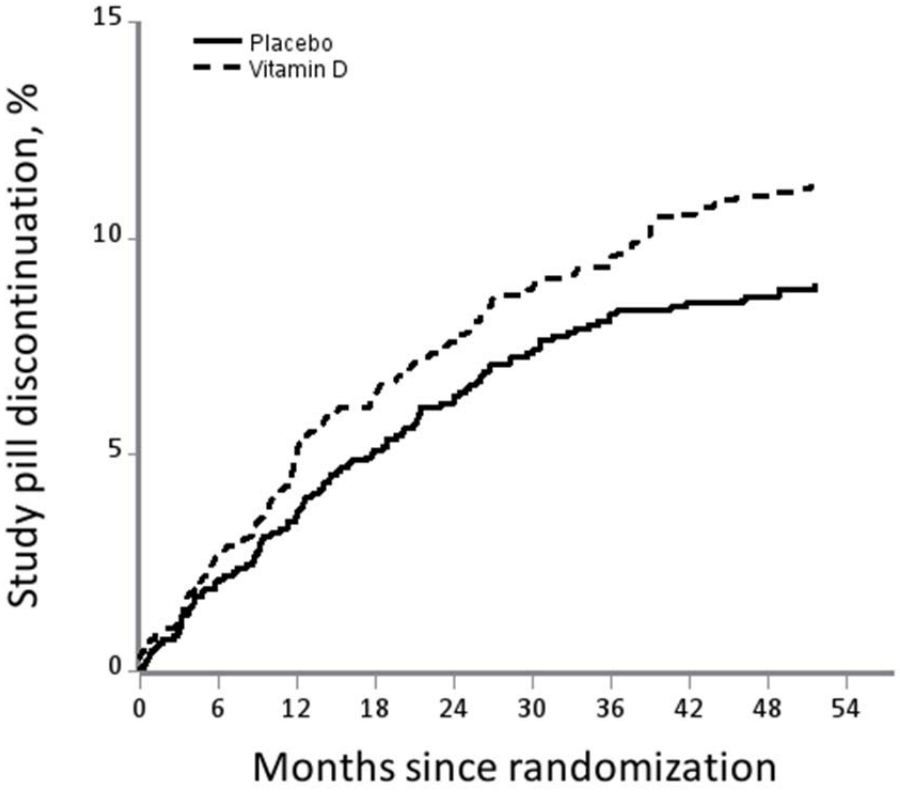
Plus-minus values are means±SD. Bars represent standard deviation around mean. Serum 25-hydroxyvitamin D was measured at baseline, month 12 and month 24 visits only.

Supplementary Figure S2. Flow of participants in per-protocol analysis.



The total number of participants (170 in the vitamin D group and 172 in the placebo group) is less than the sum of the events (191 events in the vitamin D group and 200 events in the placebo group) because a participant may have had more than one censoring event. In the "per-protocol" analysis, follow-up was censored at the first event.

Supplementary Figure S3. Cumulative percent of participants who stopped study pills for reasons other than death or withdrawal in the D2d study.



Supplementary Table S1. Detailed baseline characteristics of D2d participants [1]

Characteristic	Overall (n=2,423)	Vitamin D (N=1,211)	Placebo (N=1,212)
Age, years	60.0 ± 9.9	59.6 ± 9.9	60.4 ± 10.0
Women, no. (%)	1086 (44.8)	541 (44.7)	545 (45.0)
Race, no. (%) [2]			
Asian	130 (5.4)	66 (5.5)	64 (5.3)
Black or African-American	616 (25.4)	301 (24.9)	315 (26.0)
White	1616 (66.7)	810 (66.9)	806 (66.5)
Other	61 (2.5)	34 (2.8)	27 (2.3)
Hispanic or Latino Ethnicity, no. (%) [2]	225 (9.3)	120 (9.9)	105 (8.7)
Family history of diabetes (1st degree relative), no. (%)	1514 (62.5)	759 (62.7)	755 (62.3)
Smoking, no. (%)			
Never	1410 (58.2)	710 (58.6)	700 (57.8)
Former	838 (34.6)	416 (34.4)	422 (34.8)
Current	155 (6.4)	75 (6.2)	80 (6.6)
Unknown or Not reported	20 (0.8)	10 (0.8)	10 (0.8)
Dietary supplement use [3]			
Vitamin D			
Participants taking vitamin D supplements, no. (%)	1037 (42.8)	508 (41.9)	529 (43.6)
Vitamin D intake among all participants, IU/day [4]	313 ± 398	310 ± 401	316 ± 397
Vitamin D intake among participants using supplements, IU/day [3]	732 ± 254	739 ± 256	725 ± 253
Calcium			
Participants taking calcium supplements, no. (%)	804 (33.2)	385 (31.8)	419 (34.6)
Calcium intake among all participants, mg/day [4]	103 ± 176	100 ± 175	107 ± 176
Calcium intake among participants using supplements, mg/day [3]	312 ± 167	316 ± 168	308 ± 166
Physical activity, total MET hour/week	109.8 ± 158.7	110.7 ± 158.8	109.0 ± 158.6
Body-mass index, kg/m^2	32.1 ± 4.5	32.0 ± 4.5	32.1 ± 4.4
Body-mass index ≥ 30 kg/m^2, no. (%)	1559 (64.3)	776 (64.1)	783 (64.6)
Laboratory			
Fasting plasma glucose (FPG), mg/dL	107.9 ± 7.4	108.0 ± 7.4	107.8 ± 7.4
2-hour post-load plasma glucose (2hPG), mg/dL	137.2 ± 34.3	136.9 ± 34.3	137.6 ± 34.3
Hemoglobin A1c, %	5.91 ± 0.21	5.92 ± 0.21	5.91 ± 0.21
Pre-diabetes categories, no. (%)			
Met all 3 glycemic criteria (IGT + *i*A1c + IFG) [5]	856 (35.3)	427 (35.3)	429 (35.4)
Met two glycemic criteria only			
IGT + IFG	152 (6.3)	74 (6.1)	78 (6.4)
IGT + *i*A1c	231 (9.5)	103 (8.5)	128 (10.6)
IFG + *i*A1c	1184 (48.9)	607 (50.1)	577 (47.6)
Serum 25-hydroxyvitamin D, ng/mL	28.0 ± 10.2	27.7 ± 10.2	28.2 ± 10.1
Serum 25-hydroxyvitamin D categories, no. (%) [6]			
< 12 ng/mL	103 (4.3)	60 (5.0)	43 (3.6)
12-19 ng/mL	422 (17.4)	216 (17.8)	206 (17.0)
20-29 ng/mL	876 (36.2)	453 (37.4)	423 (34.9)
≥ 30 ng/mL	1021 (42.2)	482 (39.8)	539 (44.5)
Serum calcium, mg/dL	9.41 ± 0.37	9.40 ± 0.37	9.41 ± 0.38
Estimated glomerular filtration rate, mL/min/1.73m^2 [7]	87.1 ± 15.7	87.5 ± 15.6	86.7 ± 15.9
Fasting urine calcium-creatinine ratio	0.09 ± 0.06	0.09 ± 0.06	0.08 ± 0.06

[1]Plus-minus values are means±SD. Percentages may not add up to 100 because of rounding. To convert 25-hydroxyvitamin D from ng/mL to nmol/L, multiply by 2.456; To convert glucose from mg/dL to mmol/L, multiply by 0.055; to convert vitamin D intake from IU to mcg, divide by 40.

[2]Race and ethnicity were reported by the participant. The category "other" includes American Indian or Alaska Native; Native Hawaiian or other Pacific Islander; or other race. Ethnicity includes any race.

[3]Data on vitamin D and calcium intake are derived from a question about supplements, including multivitamins and high-dose prescribed doses. Participants were allowed to take from supplements up to 1000 IU/day of vitamin D and 600 mg/day of calcium. Dietary intake of vitamin D and calcium was not limited.

[4]Value shown is among all participants regardless of whether they reported use of supplements or not.

[5]IFG, impaired fasting glucose defined as fasting plasma glucose 100–125 mg per deciliter (5.6–6.9 mmol/L); IGT, impaired glucose tolerance defined as 2-hour post-load plasma glucose after a 75-gram glucose load 140–199 mg/dL (7.8–11.0 mmol/L) or; *i*A1c, impaired A1c defined as HbA1c 5.7–6.4% (39–47 mmol/mol)

[6]Based on 2010 Dietary Reference Intakes for Calcium and Vitamin D.

[7]Based on the Chronic Kidney Disease Epidemiology Collaboration equation.