On behalf of the Incredible D2d TEAM

Study design

n=2423

22 U.S. sites

By site, BMI, race

n=1211

4000 IU/day vitamin D_3

n=1212

Placebo

All participants receive current recommendations for pre-diabetes, vitamin D and calcium intake

Central Lab

Every 6m: FPG, HbA1c

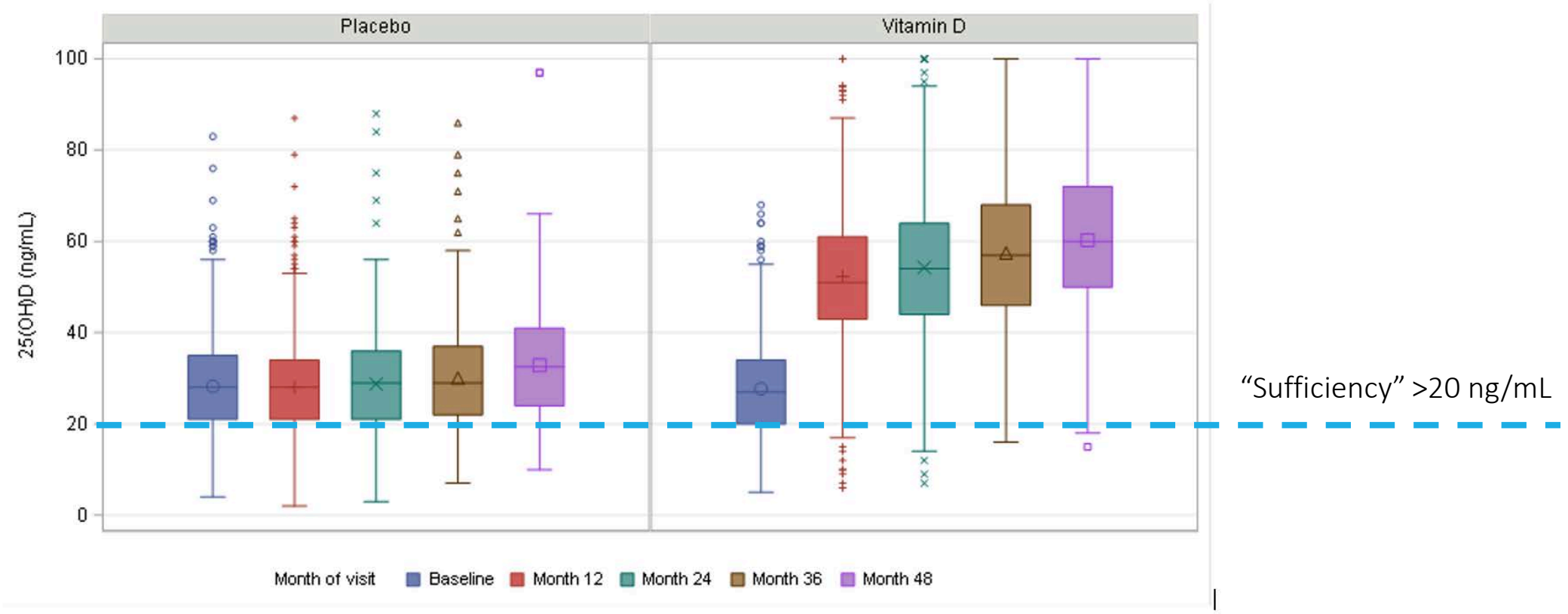
Every 12m: FPG, HbA1c, 2hPG

Diabetes outcome if

- ✓ Two (+) tests
- ✓ One (+) test confirmed on repeat testing

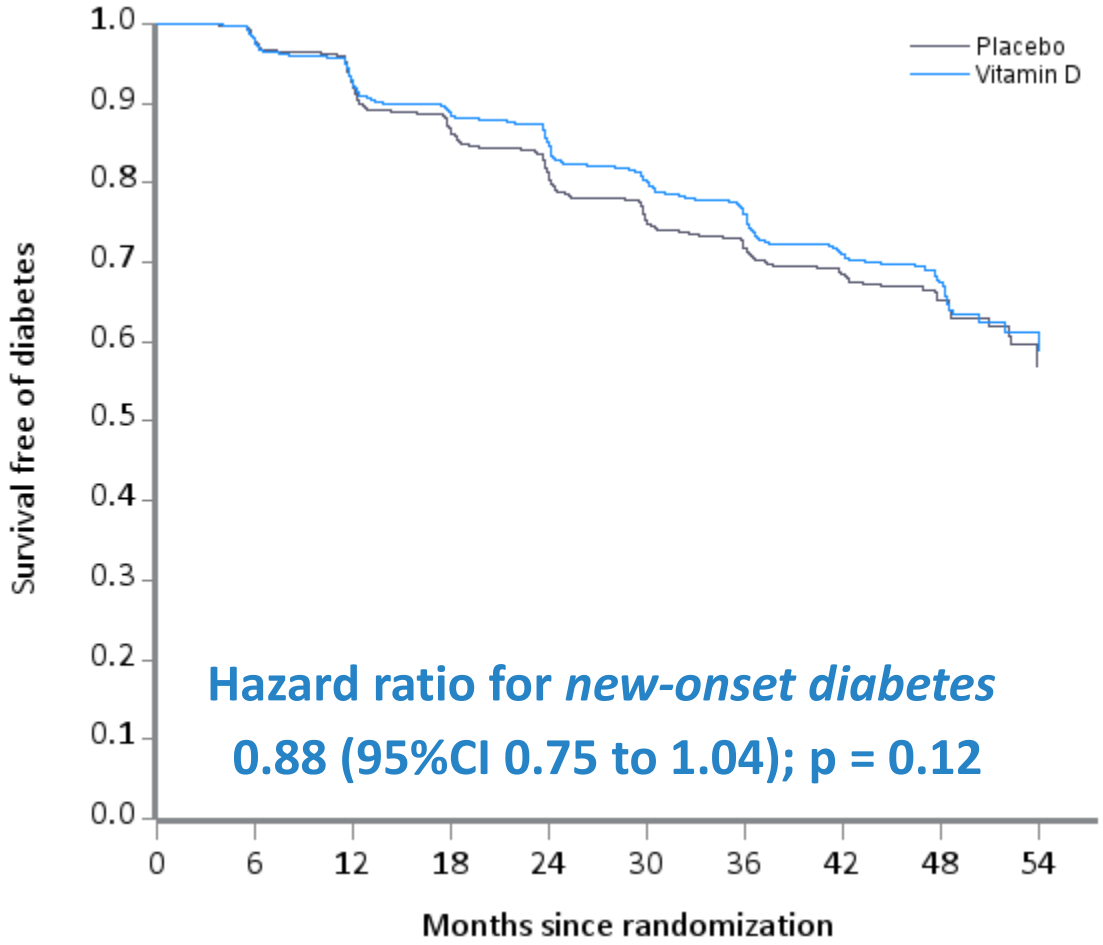
Pittas et al Diabetes Care 2014

Mean serum 25(OH)D level during D2d



"Sufficiency" >20 ng/mL

Cumulative survival rates *free of diabetes, Intention-to-treat*



No. at risk	0	6m	12m	18m	24m	30m	36m	42m	48m	54m
Vitamin D 4000 IU/d	1211	1171	1089	1001	812	625	466	283	141	21
Placebo	1212	1171	1091	975	779	577	419	258	121	13

The primary outcome does not achieve statistical significance

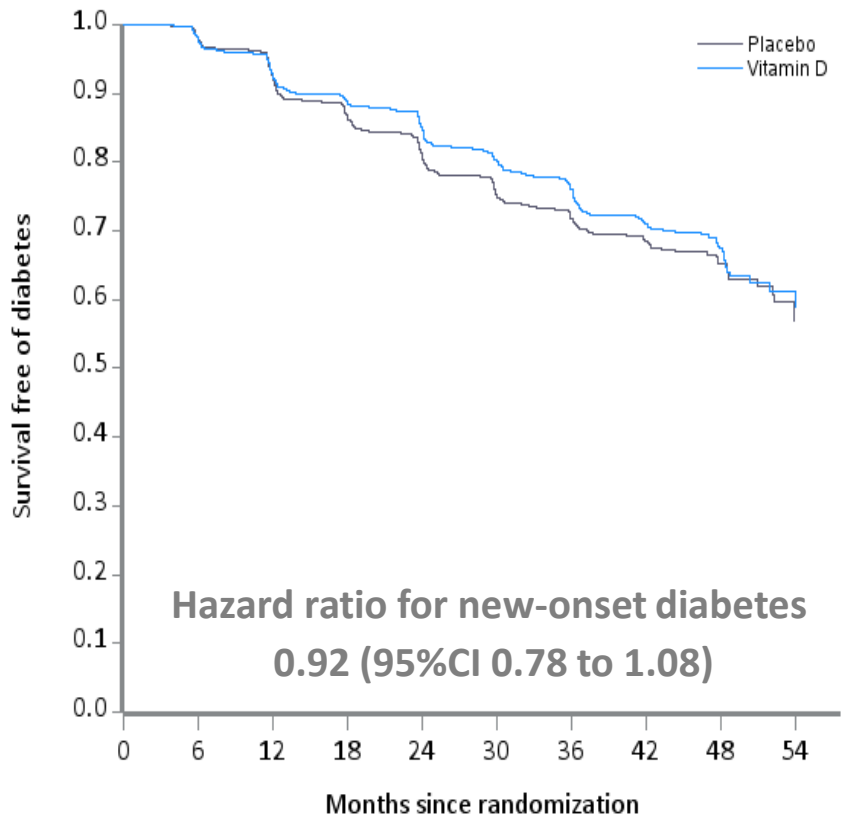
Now what?

- Is there some indication of potential benefit? – *YES*
- Was the trial underpowered? – *Not for the projected 25% reduction*
- Was the trial population appropriate? – *YES*
- Was the treatment regimen appropriate? – *YES*
- Was the primary outcome appropriate or accurately defined? – *YES*
- Was the duration of intervention and follow-up adequate – YES
- Were there deficiencies in trial conduct? – *No*
- Is a claim of non-inferiority of value? – *Not applicable*
- **Do subgroup findings elicit positive signals? – *YES***
- **Can alternative analyses help? – *YES***
- **Does additional external evidence exist? – *YES***
- Is there a strong biologic rationale that favors the treatment? – *YES*

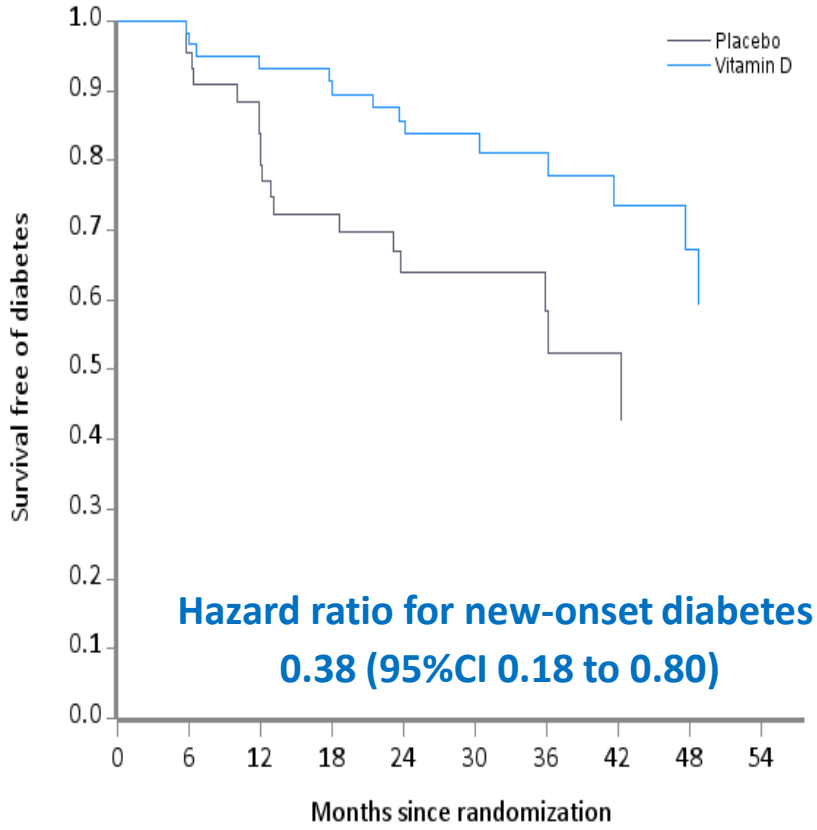
Pittas et al JCEM 2020; Pocock and Stone NEJM 2016

Effect of vitamin D supplementation on diabetes prevention according to **vitamin D deficiency** at baseline

25-hydroxyvitamin D ≥ 12 ng/mL; N=2319



25-hydroxyvitamin D < 12 ng/mL; N=103

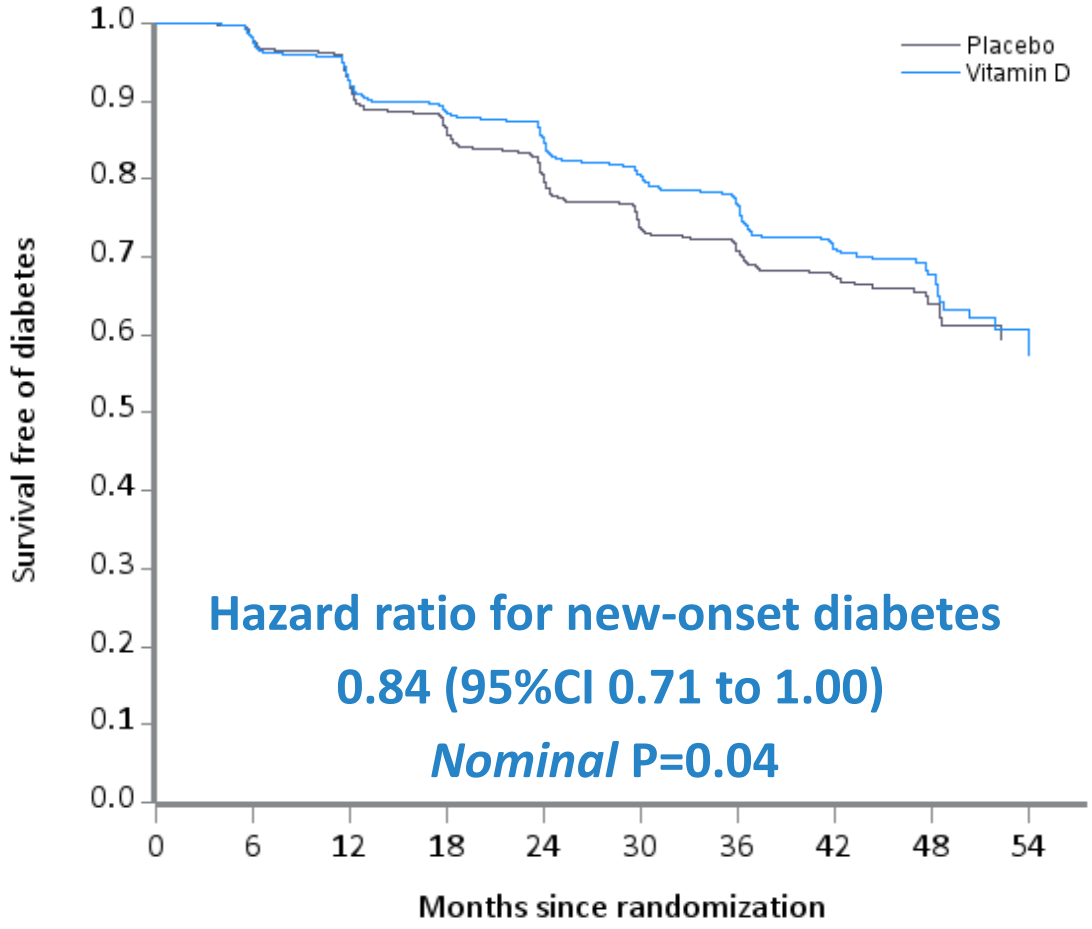


Post-hoc analysis; Nominal P-value for the interaction term = 0.023

Protocol-specified, exploratory, *per-protocol* analysis

FOLLOW-UP CENSORED WHEN PARTICIPANTS

- Stopped study pills
- Started diabetes or weight-loss medication
- Took out-of-study vitamin D above study limitation (1000 IU per day)



Intra-trial 25(OH)D and new-onset diabetes in D2d

	<50 nmol/L (<20 ng/mL)	50-74 nmol/L (20-29 ng/mL)	75-99 nmol/L (30-39 ng/mL)	100-124 nmol/L (40-49 ng/mL)	≥125 nmol/L (≥50 ng/mL)
	Randomized to placebo				
	n=225	n=378	n=265	n=94	n=22
Median level, nmol/L	43	66	90	111	146
	1.23 [0.86 to 1.75]	Reference	1.03 [0.76 to 1.38]	0.67 [0.40 to 1.12]	0.47 [0.15 to 1.52]
	Randomized to vitamin D				
	n=22	n=78	n=225	n=319	n=430
Median level, nmol/L	40	64	86	110	145
	1.03 [0.34 to 3.14]	Reference	0.86 [0.51 to 1.44]	0.48 [0.29 to 0.80]	0.29 [0.17 to 0.50]

Model adjusted for site, BMI (at baseline), race (white, Black, other), sex, age, physical activity, statin use.

Dawson-Hughes et al Diabetes Care 2020

Vitamin D and prevention of diabetes: Comparison of available trials

Large, long-term trials specifically designed and conducted to test the effect of vitamin D for diabetes prevention in people with prediabetes

Study	N	Pre-diabetes definition Baseline 25OHD	Baseline 25OHD, ng/mL	Intervention	Achieved 25OHD, ng/mL	Follow-up (yrs.)	**Hazard ratio**
Tromsø (Norway)	511	IFG, IGT, iA1c	24	D_3 at 20,000 IU weekly (~2,900 IU daily)	48	Up to 5	**0.90 (0.69 to 1.18)**
DPVD (Japan)	1,256	IGT	Not Avail.	Eldecalcitol (active vitamin D analog) daily	NA	Mean 2.6	**0.87 (0.68 to 1.09)**
D2d (US)	2,423	IFG, IGT, iA1c	28	D_3 at 4,000 IU daily	52	Mean 2.5	**0.88 (0.75 to 1.04)**

Jorde et al JCEM 2016; Kawahara et al Diabetes 2017 (**abstract;** manuscript in preparation)

Published Manuscripts

Vitamin D supplementation and kidney function

PI: Sun Kim, MD MS
EMAIL: sunhkim@stanford.edu

Vitamin D and cancer outcomes

PI: Ranee Chatterjee, MD
EMAIL: ranee.chatterjee@duke.edu

Intra-trial exposure to vitamin D and risk of diabetes

PI: Bess Dawson-Hughes, MD
EMAIL: bess.dawson-hughes@tufts.edu

Reproducibility of a prediabetes classification

PI: Chhavi Chadha, MD
EMAIL: chhavi.x.chadha@healthpartners.com

Vitamin D supplementation and insulin resistance sensitivity and secretion

PI: Neda Rasouli, MD
EMAIL: NEDA.RASOULI@CUANSCHUTZ.EDU

Hemoglobin glycation index on the diagnosis of prediabetes and diabetes

PI: Daniel Hsia, MD
EMAIL: Daniel.Hsia@pbrc.edu

Vitamin D supplementation and prevention of type 2 diabetes

PI: Anastassios Pittas, MD MS
EMAIL: apittas@tuftsmedicalcenter.org

EHR recruitment approach to trial recruitment

PI: Vanita Aroda, MD
EMAIL: varoda@bwh.harvard.edu

Baseline characteristics of the Vitamin D and Type 2 Diabetes (D2d) Study

PI: Erin LeBlanc, MD
EMAIL: Erin.S.LeBlanc@kpchr.org

Management of incidentally discovered hemoglobin variants

PI: Michael Lewis, MD
EMAIL: Michael.Lewis@uvm.edu

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Assessment of the NDEP toolkit

PI: Roshni Devchand, MPH
EMAIL: rdevchand@hagersharp.com

Financial management of large, multi-center trials

PI: Olivia Lovegreen
EMAIL: OLovegreen@tuftsmedicalcenter.org

Rational and design of D2d

PI: Anastassios Pittas
EMAIL: apittas@tuftsmedicalcenter.org

Manuscripts in Progress and Future Directions

Baseline insulin and cardiovascular risk

PI: Sangeeta Kashyap, MD
EMAIL: KASHYAS@ccf.org

Quality of life and mood assessment

PI: Rowena Dolor, MD
EMAIL: rowena.dolor@duke.edu

Participant retention

PI: Vanita Aroda, MD
EMAIL: varoda@bwh.harvard.edu

Effect of vitamin D supplementation on incident CVD

submitted

PI: Cyrus Desouza, MD
EMAIL: cdesouza@unmc.edu

Dietary patterns impacting risk of type 2 diabetes

PI: Emily Newbold, PhD
EMAIL: enewbold@kumc.edu

Safety and tolerability of vitamin D

submitted

PI: Karen Johnson, MD
EMAIL: kjohnson@uthsc.edu

Prevalence of NAFLD/NASH in D2d cohort and progression to diabetes

PI: Richard Pratley, MD
EMAIL: Richard.Pratley.MD@AdventHealth.com

Racial and ethnic differences of glycemia

PI: Erin LeBlanc, MD
EMAIL: Erin.S.LeBlanc@kpchr.org

Diabetes and statin use

PI: Jean Park, MD
EMAIL: Jean.Y.Park@medstar.net

Vitamin D impacts on glycemia

PI: Daniel Hsia, MD
EMAIL: Daniel.Hsia@pbrc.edu

Effect of vitamin D by race weight status

PI: Ranee Chatterjee, MD
EMAIL: ranee.chatterjee@duke.edu

Vitamin D supplementation and bone related outcomes

PI: Lisa Ceglia, MD
EMAIL: lceglia@tuftsmedicalcenter.org

Natural history of pre-diabetes

PI: Anastassios Pittas, MD MS
EMAIL: apittas@tuftsmedicalcenter.org

Meta-analysis of trials on the effect of vitamin D on diabetes

PI: Anastassios Pittas, MD MS
EMAIL: apittas@tuftsmedicalcenter.org

Data Sharing Overview

OVERVIEW

- Fully screened 3,969 people
- Randomized 2,423 people with prediabetes to either 4,000 IU vitamin D_3 or placebo
- Followed for a median of 2.6 years (diabetes) / 3.0 years (other outcomes)

STORED REPOSITORY SAMPLES *analyses require funding

- Urine (baseline and annually)
- Serum and plasma blood samples (baseline, month 6, and annually)
- Whole blood for DNA (baseline only)

SUPPORT

The D2d Coordinating Center can provide statistical support.

DATA POINTS (*available at baseline only)

- Demographics: DOB, sex, race, ethnicity
- Socioeconomic data: education, marital status, employment status, household income
- Medical history (structured data fields for menopausal status, history of gestational diabetes and cancer, smoking history)
- Family history of diabetes and cancer
- Sunlight-related lifestyle data
- Medications for hypertension, lipid- and glycemia-lowering, osteoporosis, weight loss, and aspirin
- Supplemental vitamin D and calcium intake
- Vital signs: blood pressure, height, weight, waist*
- Dietary intake (FFQ) and physical activity (IPAQ)
- Quality of life (at M24 only)
- Study pill adherence
- Adverse events (adjudicated nephrolithiasis, cancer, and serious cardiovascular events)
- Fasting blood measures: WBC*, Hgb*, HCT*, ALT*, AST*, platelets*, serum calcium, serum creatinine, calculated eGFR, HbA1c, glucose, insulin, CRP, urine calcium creatinine ratio, urine albumin creatinine ratio, 25-hydroxyvitamin D (total, D_2, and D_3), total cholesterol, HDL, LDL, triglycerides
- At 30 min and 120 min post 75-g glucose load: glucose, insulin, C-peptide
- C-Telopeptide, osteocalcin, and parathyroid hormone (on a subset of participants)

Have an idea? Contact the D2d Coordinating Center at

D2d@tuftsmedicalcenter.org