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Baseline Characteristics of the Vitamin D and Type 2 Diabetes (D2d) Study: A Contemporary Prediabetes Cohort That Will Inform Diabetes Prevention Efforts

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OBJECTIVE

To describe baseline characteristics of the Vitamin D and Type 2 Diabetes (D2d) study, the first large U.S. diabetes prevention clinical trial to apply current American Diabetes Association (ADA) criteria for prediabetes.

RESEARCH DESIGN AND METHODS

This is a multicenter (*n* = 22 sites), randomized, double-blind, placebo-controlled, primary prevention clinical trial testing effects of oral daily 4,000 IU cholecalciferol (D_3) compared with placebo on incident diabetes in U.S. adults at risk for diabetes. Eligible participants were at risk for diabetes, defined as not meeting criteria for diabetes but meeting at least two 2010 ADA glycemic criteria for prediabetes: fasting plasma glucose (FPG) 100–125 mg/dL, 2-h postload glucose (2hPG) after a 75-g oral glucose load 140–199 mg/dL, and/or a hemoglobin A_{1c} (HbA_{1c}) 5.7–6.4% (39–46 mmol/mol).

RESULTS

A total of 2,423 participants (45% of whom were women and 33% nonwhite) were randomized to cholecalciferol or placebo. Mean (SD) age was 59 (9.9) years and BMI 32 (4.5) kg/m^2. Thirty-five percent met all three prediabetes criteria, 49% met the FPG/HbA_{1c} criteria only, 9.5% met the 2hPG/FPG criteria only, and 6.3% met the 2hPG/HbA_{1c} criteria only. Black participants had the highest mean HbA_{1c} and lowest FPG concentration compared with white, Asian, and other races ($P < 0.01$); 2hPG concentration did not differ among racial groups. When compared with previous prediabetes cohorts, the D2d cohort had lower mean 2hPG concentration but similar HbA_{1c} and FPG concentrations.

CONCLUSIONS

D2d will establish whether vitamin D supplementation lowers risk of diabetes and will inform about the natural history of prediabetes per contemporary ADA criteria.

Prediabetes, typically defined as blood glucose concentrations above normal but below the threshold for diabetes, is a disease risk state that predicts an increased probability of developing diabetes and may itself be associated with health risks and complications (1). Although lifestyle changes can reduce the rate of progression to diabetes, achieving as well as maintaining sufficient lifestyle change is challenging (2). Therefore, simple, sustainable, and complementary prevention approaches are needed. The Vitamin D and Type 2 Diabetes (D2d) study is the largest clinical trial to examine the causal relationship between vitamin D supplementation and the development of diabetes in people at risk for diabetes (3). D2d is also the largest U.S.-based study to have assembled and followed a contemporary cohort of people at risk for diabetes, defined as meeting at least two prediabetes criteria by the American Diabetes Association (ADA) (4).

In 2003, the ADA revised the criteria for prediabetes to lower the threshold for fasting plasma glucose (FPG) from 110 to 100 mg/dL (5.6 mmol/L), and in 2010, hemoglobin A_{1c} (HbA_{1c}) of 5.7–6.4% (39–46 mmol/mol) was added as a criterion based on evidence of increased diabetes complications at these glycemic ranges (4). The 2-h postload glucose (2hPG) after a 75-g oral glucose load criterion was unchanged. The expanded criteria have been controversial (5,6). First, the natural history of prediabetes, based on the ADA's current definition, has not been established in the modern era. Second, most data on the natural history of prediabetes are >20 years old (7–10) or were not conducted in populations generalizable to the current U.S. population (8–12). Third, some have argued that lowering the FPG threshold and adding the HbA_{1c} criterion increase the prevalence of prediabetes without a clear association with clinically important outcomes and may lead to an unnecessary medicalization of prediabetes (13,14). Finally, there is evidence of interindividual variation in HbA_{1c} relative to underlying glucose levels, with a tendency for black individuals to have higher HbA_{1c} compared with whites with similar glucose levels (15).

In the current report, we describe the baseline characteristics of the D2d prediabetes cohort and compare them with prior diabetes prevention studies that used different enrollment criteria. As the largest clinical trial to enroll a contemporary cohort of American adults with prediabetes, D2d will fill important gaps in knowledge related to the current definition of prediabetes.

RESEARCH DESIGN AND METHODS

Overview of Study Design

D2d is a U.S.-based, multicenter, randomized (1:1), double-blind, placebo-controlled, parallel-group, primary prevention clinical trial comparing oral administration of 4,000 IU/day of cholecalciferol (vitamin D_3) versus placebo in people with prediabetes who are followed for incident diabetes for ~3 years after randomization. Cancer and cardiovascular disease are key secondary outcomes. The design of D2d has been published (3). The study is approved and monitored by an independent data- and safety-monitoring board and the institutional review board of each collaborating clinical research site.

Study Population and Setting

Target participants were adults at risk for diabetes. At the baseline visit, eligible participants met at least two of three glycemic criteria for prediabetes established by the ADA in 2010 (4): FPG 100–125 mg/dL (5.6–6.9 mmol/L), or impaired fasting glucose (IFG); 2hPG after a 75-g glucose load 140–199 mg/dL (7.8–11.0 mmol/L), or impaired glucose tolerance (IGT); HbA_{1c} 5.7–6.4% (39–46 mmol/mol), or—our designation—impaired A1c (*i*A1c). Other entry criteria included age ≥30 years (≥25 years for American Indians, Alaska Natives, Native Hawaiians, or other Pacific Islanders) and BMI 24–42 kg/m^2 (22.5–42 kg/m^2 for Asians). Key exclusion criteria included FPG, 2hPG, or HbA_{1c} in the diabetes range; conditions affecting HbA_{1c}, such as hemoglobinopathies; treatment with medications approved for treatment of diabetes; hyperparathyroidism; nephrolithiasis; bariatric surgery; use of supplements with vitamin D or calcium above study limitations (1,000 IU/day and 600 mg/day, respectively); regular use of tanning beds; medications or conditions that could interfere with absorption or metabolism of vitamin D; hypercalcemia; hypercalciuria; or chronic kidney disease (estimated glomerular filtration rate [eGFR] <50 mL/min per 1.73 m^2).

D2d is being conducted at 22 U.S. collaborating clinical sites (www.d2dstudy.org/sites). Several sites serve populations with substantial racial diversity, while 12 sites are located at high latitudes (above 37° N) to include participants with lower ultraviolet B exposure. D2d is an event-driven trial that will continue until the required number of diabetes outcome events is reached. Results are expected in 2019.

Screening and Baseline Assessment

Prescreening procedures were site specific and included telephone prescreenings, medical chart reviews, and—at some sites—targeted laboratory testing with FPG and HbA_{1c}. If potential participants met prescreening criteria, they were invited for in-person screening, which occurred in two steps. At screening visit 1, nonglycemic eligibility criteria (e.g., medical history, laboratory criteria for safety) were confirmed and glycemic criteria for prediabetes were preliminarily evaluated by measuring FPG and HbA_{1c}. Algorithms using the screening visit 1 FPG and HbA_{1c} results guided sites as to which participants should proceed to the next screening visit. At screening visit 2, a 75-g oral glucose tolerance test was performed after an 8-h overnight fast, and FPG, 2hPG, and HbA_{1c} were analyzed by the D2d central laboratory to determine final eligibility. Screening visit 2 served as the baseline visit for participants who were randomized.

At screening visit 1, participants self-reported demographics such as age, race, ethnicity, employment, education, and household income. Racial and ethnic categorization followed National Institutes

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**A complete list of the members of the D2d Research Group can be found in the Supplementary Data.*

of Health (NIH) guidelines. Personal health history, including smoking history, family history of diabetes, medication use, and use of dietary supplements, were captured by targeted questionnaires. Height and weight were measured with a stadiometer and calibrated balance beam or electrical digital scale, respectively, following standardized procedures.

Laboratory Methods

Specimens were processed locally. Plasma for glucose measurement was shipped frozen to the D2d central laboratory at the University of Vermont's Laboratory for Clinical Biochemistry Research (Colchester, VT). Whole blood for HbA_{1c} measurement was shipped refrigerated. HbA_{1c} was measured using an ion-exchange high-performance liquid chromatography method (Tosoh G8; Tosoh Bioscience, South San Francisco, CA). This method is certified by NGSP (formerly the National Glycohemoglobin Standardization Program), and the D2d central laboratory is certified by NGSP as a Level I Laboratory with documented traceability to the Diabetes Control and Complications Trial (DCCT) reference method (16). Plasma glucose was measured using a hexokinase method (Roche Glucose HK Gen.3 on the Cobas Integra 400 or Cobas c311 analyzer; Roche Diagnostics, Indianapolis, IN) and standardized against isotope dilution mass spectrometry. Creatinine was measured at each clinical site, and eGFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration equation (17). Serum 25-hydroxyvitamin D from the baseline and yearly visits will be analyzed at the end of the study. Serum insulin will also be analyzed at the end of the study and oral glucose tolerance test–based indices of insulin secretion and sensitivity will be derived (3).

Statistical Analysis

Baseline characteristics are reported as mean (SD) unless otherwise specified. Characteristics by sex, race, and ethnicity were compared using ANOVA tests and χ^2 tests as appropriate. Two-sided P values <0.05 were considered statistically significant. SAS (version 9.4; SAS Institute, Cary, NC) was used for all analyses.

RESULTS

Recruitment

Recruitment occurred from October 2013 through December 2016. At baseline, 3,288 people met at least one of the three ADA glycemic criteria for prediabetes and all other nonglycemic criteria. After exclusion of 865 people who met only one of the three criteria, 2,423 participants were randomized (Supplementary Fig. 1). Median enrollment at each site was 88 participants (range 29–318).

Demographics Overall

Baseline characteristics are shown in Table 1. At baseline, mean age was 59.4 years and BMI 32.0 kg/m^2. Waist circumference was 107.1 cm in men and 102.5 cm in women. A family history of diabetes was reported by 62.5% of participants, and 7.4% of women reported a history of gestational diabetes mellitus. D2d enrolled a diverse cohort: 33.3% of participants identified as nonwhite and 9.3% identified as Hispanic or Latino. The majority were employed at least part-time (58.6%), approximately half (50.8%) completed postsecondary education (i.e., bachelor's degree or higher), and more than half (53.3%) had an annual income over $75,000. Few (6.5%) reported current smoking. The most prevalent comorbidities were hypercholesterolemia (reported by 54.5% of the cohort) and hypertension (52.7%). In terms of supplement use, 42.6% of participants were taking vitamin D supplements (mean 730 IU/day) and 33.0% were taking calcium supplements (mean 311 mg/day). Across all participants (including those who did not take supplements), mean intakes were 311 IU/day for vitamin D and 103 mg/day for calcium.

Demographics by Sex

Women comprised 44.8% of the cohort (Table 1). Compared with men, women were younger and had higher BMI and lower waist circumference. Women and men also differed in racial and ethnic categories, employment status, education, and annual household income. Compared with men, women were less likely to report a history of hypercholesterolemia, cardiovascular disease, hypertension, sleep apnea, and medication use for these conditions. Women were also less likely to report a history of smoking. Women were more likely than men to report a family history of diabetes (68.1 vs. 57.9%; $P < 0.01$) or personal history of asthma, osteoarthritis, or osteoporosis/osteopenia. At baseline, compared with men, a higher proportion of women reported taking vitamin D (48.5% for women vs. 37.9% for men; $P < 0.01$) and calcium (37.5% for women vs. 29.4% for men; $P < 0.01$) supplements. Women had lower baseline blood pressure and higher eGFR, serum, and urine calcium concentration.

Glycemic Profile Overall

Mean baseline HbA_{1c} was 5.9% (41 mmol/mol), FPG 107.9 mg/dL, and 2hPG 137.2 mg/dL (Table 1). The baseline glycemic profile of the D2d cohort covers a wide spectrum of the prediabetes criteria (Table 1 and Supplementary Fig. 2). Overall, 35.3% of participants met all three prediabetes criteria (FPG, 2hPG, and HbA_{1c}), 48.9% met the FPG/HbA_{1c} criteria only, 9.5% met the 2hPG/FPG criteria only, and 6.3% met the 2hPG/HbA_{1c} criteria only. Overall, 84% of participants met both FPG and HbA_{1c} criteria, while 51.1% met the 2hPG criterion, which has been used as an inclusion criterion in many previous diabetes prevention trials.

Glycemic Profile by Sex

At baseline, mean FPG was lower among women than men (106.9 vs. 108.8 mg/dL respectively; $P < 0.01$; Table 1), while mean 2hPG was higher in women than men (139.7 vs. 135.3 mg/dL respectively; $P < 0.01$); HbA_{1c} concentrations did not differ (5.9 vs. 5.9% [41 vs. 41 mmol/mol]; $P = 0.23$). The proportions of women who met the four different combinations of prediabetes (*i*A1c/IFG, IFG/IGT, IGT/*i*A1c or *i*A1c/IFG/IGT) differed compared with men.

Glycemic Profile by Race and Ethnicity

Diabetes risk factors and glycemic profile differed by races and ethnicity (Table 2). White participants were older than participants of other races, while participants of Hispanic ethnicity were younger than non-Hispanic participants. Asian participants had lower BMI than other racial groups, while blacks had higher baseline BMI than whites. Waist circumference was generally lower in Asian participants. BMI did not differ by ethnicity, but Hispanic men had a lower waist circumference than non-Hispanics. White participants were less likely to report a family history of diabetes than black participants (59.5 vs. 68.1%, respectively; $P < 0.05$). Fewer non-Hispanic participants reported a family history of diabetes compared with Hispanics

Table 1—Demographics and clinical characteristics by sex in D2d

	Overall (*n* = 2,423)	Men (*n* = 1,337)	Women (*n* = 1,086)	*P* for men vs. women
Diabetes risk factors				
Age, years, mean (SD)	59.4 (9.9)	59.9 (10.3)	58.9 (9.4)	0.01
Age range, years, *n* (%)				<0.01
25–44	208 (8.6)	122 (9.1)	86 (7.9)	
45–59	910 (37.6)	459 (34.3)	451 (41.5)	
≥60	1,305 (53.9)	756 (56.5)	549 (50.6)	
BMI, kg/m^2, mean (SD)	32.0 (4.5)	31.5 (4.3)	32.7 (4.6)	<0.01
Waist circumference, cm, mean (SD)	105.0 (11.7)	107.1 (11.6)	102.5 (11.4)	<0.01
Self-reported family history of diabetes, *n* (%)	1,514 (62.5)	774 (57.9)	740 (68.1)	<0.01
Self-reported gestational diabetes mellitus, *n* (%) women	NA	NA	81 (7.4)	NA
Demographics, *n* (%)				
Race				0.04
Asian	130 (5.4)	84 (6.3)	46 (4.2)	
Black or African American	616 (25.4)	318 (23.8)	298 (27.4)	
White	1,616 (66.7)	902 (67.5)	714 (65.7)	
Other[1]	61 (2.5)	33 (2.5)	28 (2.6)	
Hispanic or Latino ethnicity	225 (9.3)	89 (6.7)	136 (12.5)	<0.01
Residence above 37° N latitude	1,791 (73.9)	1,022 (76.4)	769 (70.8)	<0.01
Socioeconomic, *n* (%)				
Current employment				<0.01
Homemaker	81 (3.3)	5 (0.4)	76 (7.0)	
Employed at least part-time	1,421 (58.6)	779 (58.3)	642 (59.1)	
Retired	781 (32.2)	479 (35.8)	302 (27.8)	
Not employed	63 (2.6)	29 (2.2)	34 (3.1)	
Other	63 (2.6)	40 (3.0)	23 (2.1)	
Unknown or not reported	14 (0.6)	5 (0.4)	9 (0.8)	
Education				<0.01
No schooling or less than high school (no diploma or GED)	126 (5.2)	48 (3.6)	78 (7.2)	
Completed high school	268 (11.1)	145 (10.8)	123 (11.3)	
Some post–high school education, no certificate or degree	420 (17.3)	236 (17.7)	184 (16.9)	
Some post–high school education, Associate's degree	379 (15.6)	201 (15.0)	178 (16.4)	
Bachelor's degree	644 (26.6)	377 (28.2)	267 (24.6)	
Graduate or professional degree	574 (23.7)	324 (24.2)	250 (23.0)	
Unknown or not reported	12 (0.5)	6 (0.4)	6 (0.6)	
Annual household income ($)				<0.01
<35,000	374 (15.4)	184 (13.8)	190 (17.5)	
36,000–50,000	352 (14.5)	175 (13.1)	177 (16.3)	
51,000–75,000	405 (16.7)	199 (14.9)	206 (19.0)	
75,000 or more	909 (37.5)	586 (43.8)	323 (29.7)	
Unknown or not reported	383 (15.8)	193 (14.4)	190 (17.5)	
Health history, *n* (%)				
Smoking				<0.01
Never	1,410 (58.7)	711 (53.6)	699 (64.9)	
Former	838 (34.9)	513 (38.7)	325 (30.2)	
Current	155 (6.5)	102 (7.7)	53 (4.9)	
Unknown or not reported	20 (0.8)	11 (0.8)	9 (0.8)	
Medical conditions, *n* (%)				
Hypercholesterolemia	1,321 (54.5)	807 (60.4)	514 (47.3)	<0.01
Cancer[2]	258 (10.6)	142 (10.6)	116 (10.7)	0.96
Cardiovascular disease[3]	1,360 (56.1)	802 (60.0)	558 (51.4)	<0.01
Hypertension	1,276 (52.7)	744 (55.6)	532 (49.0)	<0.01
Asthma	202 (8.3)	71 (5.3)	131 (12.1)	<0.01
Chronic obstructive pulmonary disease	34 (1.4)	18 (1.3)	16 (1.5)	0.79
Sleep apnea	299 (12.3)	203 (15.2)	96 (8.8)	<0.01
Osteoarthritis or degenerative joint disease	529 (21.8)	241 (18.0)	288 (26.5)	<0.01
Osteoporosis or osteopenia	76 (3.1)	7 (0.5)	69 (6.4)	<0.01
Medication use, *n* (%)				
Hypercholesterolemia	1,035 (42.7)	665 (49.7)	370 (34.1)	<0.01
Hypertension	1,192 (49.2)	693 (51.8)	499 (45.9)	<0.01
Osteoporosis	13 (0.5)	1 (0.1)	12 (1.1)	<0.01

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Table 1—Continued

	Overall (*n* = 2,423)	Men (*n* = 1,337)	Women (*n* = 1,086)	*P* for men vs. women
Dietary supplements[4]				
Vitamin D				
Participants taking vitamin D, *n* (%)	1,033 (42.6)	506 (37.9)	527 (48.5)	<0.01
Vitamin D intake among all participants, IU/day, mean (SD)	311 (397)	264 (369)	369 (422)	<0.01
Vitamin D intake among participants using supplements, IU/day, mean (SD)	730 (253)	699 (238)	761 (263)	<0.01
Calcium				
Participants taking calcium, *n* (%)	800 (33.0)	393 (29.4)	407 (37.5)	<0.01
Calcium intake among all participants, mg/day, mean (SD)	103 (175)	70 (126)	143 (214)	<0.01
Calcium intake among participants using supplements, mg/day, mean (SD)	311 (166)	238 (117)	381 (177)	<0.01
Clinical testing, mean (SD)				
Systolic blood pressure, mmHg	128.4 (13.4)	129.9 (12.8)	126.5 (13.9)	<0.01
Diastolic blood pressure, mmHg	77.0 (9.3)	78.7 (8.9)	74.9 (9.3)	<0.01
Serum creatinine, mg/dL	0.89 (0.19)	0.99 (0.17)	0.77 (0.14)	<0.01
eGFR[5], mL/min/1.73 m^2	87.1 (15.7)	85.8 (15.2)	88.6 (16.2)	<0.01
Serum calcium, mg/dL	9.41 (0.37)	9.38 (0.36)	9.44 (0.38)	<0.01
Urine calcium-to-creatinine ratio	0.09 (0.06)	0.08 (0.05)	0.09 (0.06)	<0.01
Glycemic testing, mean (SD)				
FPG, mg/dL	107.9 (7.4)	108.8 (7.4)	106.9 (7.3)	<0.01
2hPG, mg/dL	137.2 (34.3)	135.3 (35.9)	139.7 (32.1)	<0.01
HbA_{1c}, %	5.9 (0.2)	5.9 (0.2)	5.9 (0.2)	0.23
Prediabetes categories, *n* (%)				<0.01
*i*A1c + IFG	1,184 (48.9)	687 (51.4)	497 (45.8)	
IFG + IGT	152 (6.3)	83 (6.2)	69 (6.4)	
IGT + *i*A1c	231 (9.5)	103 (7.7)	128 (11.8)	
*i*A1c + IFG + IGT	856 (35.3)	464 (34.7)	392 (36.1)	

Health history and medication use were assessed by self-report. Self-reported gestational diabetes mellitus is among all women participants whether they were pregnant or not. Racial and ethnic categories follow NIH guidelines. "Hispanic" refers to ethnicity and includes any race. IFG defined as FPG 100–125 mg/dL (5.6–6.9 mmol/L). IGT defined as 2hPG glucose after a 75-g glucose load 140–199 mg/dL (7.8–11.0 mmol/L). *i*A1c defined as HbA_{1c} 5.7–6.4% (39–47 mmol/mol). [1]"Other" includes American Indian or Alaska Native, Native Hawaiian or other Pacific Islander, or other race. [2]Cancer (except for basal cell skin cancer) within 5 years of randomization was an exclusion criterion. Prostate cancer or well-differentiated thyroid cancer not expected to require treatment over the next 4 years were not exclusions. Volunteers with history of squamous cell cancer of the skin, which was completely excised and with no evidence of metastases, were eligible. [3]Cardiovascular disease included arrhythmias, chest pain, congestive heart failure, aortic or coronary artery disease, coronary artery bypass graft/percutaneous coronary intervention, hypertension, myocardial infarction, palpitations, peripheral vascular disease. [4]Data are derived from a direct question about medications and supplements—not from a food-frequency questionnaire. [5]eGFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration equation.

(61.8 vs. 68.9%, respectively; $P < 0.05$). Gestational diabetes mellitus was reported more commonly among white than black women (9.2 vs. 2.0%, respectively; $P < 0.05$) and among Hispanic than non-Hispanic women (16.2 vs. 6.2%, respectively; $P < 0.05$). Other racial differences were not statistically significant. D2d does not have data on the number of pregnancies per woman.

Black participants had a higher mean HbA_{1c} concentration than other races (6.0 vs. 5.9% [42 vs. 41 mmol/mol]; $P < 0.05$) despite having a lower mean FPG (105.8 vs. 108.8 mg/dL; $P < 0.05$) and a similar mean 2hPG concentration (135.7 vs. 137.7 mg/dL; $P = 0.19$). Glycemic concentrations did not differ between Hispanics vs. non-Hispanics. Compared with white participants, a higher percentage of black participants met both FPG and HbA_{1c} criteria (52.4 for blacks vs. 47.5% for whites; $P < 0.05$) and 2hPG and HbA_{1c} criteria (14.8 vs. 7.4%; $P < 0.05$), but a lower percentage met FPG and 2hPG criteria (2.8 vs. 7.8%; $P < 0.05$) or all three criteria (30.3 vs. 37.3%; $P < 0.05$).

Comparison With Other Prediabetes Trials

Glycemic eligibility criteria and the baseline characteristics of D2d are compared with other large diabetes prevention trials in Table 3 (7–12). The trials differ in several baseline characteristics (e.g., age, BMI) because they targeted different populations. D2d and the recently completed SCALE Obesity and Prediabetes trial (SCALE), which tested liraglutide versus placebo for diabetes prevention (11), are the only two large trials that used the 2010 ADA glycemic criteria to define a prediabetes cohort. SCALE required that participants meet at least one of the three ADA glycemic criteria (compared with D2d, which required at least two of the three criteria). The mean baseline 2hPG concentrations in D2d and SCALE were lower than in the older trials, which included the 2hPG as an inclusion criterion. Mean HbA_{1c} and FPG concentrations were comparable among all prediabetes trials.

Comparison With Other Trials of Vitamin D Supplementation

There are two other large trials specifically designed to test the hypothesis that vitamin D supplementation reduces the risk of diabetes among patients at risk for diabetes (Table 4) (18,19). D2d is significantly larger (2,423 participants vs. 511 and 750) and uses a different

vitamin D dosing regimen (daily D_3 vs. weekly D_3 vs. active vitamin D). The Tromsø Study (Norway) randomized 511 white adults with prediabetes to 20,000 IU/week (~2,900 IU/day) of vitamin D_3 or placebo and followed them for incident diabetes for an average of 3.3 years (19). Risk of developing diabetes was lower in the vitamin D versus placebo group throughout the study, but the difference was not statistically significant (hazard ratio 0.90 [95% CI 0.69–1.18]). The Diabetes Prevention with active Vitamin D (DPVD) trial has not reported findings despite concluding in 2013 (18). Three ongoing trials will explore the effect of vitamin D supplementation on diabetes risk or fasting glucose and insulin concentrations as secondary outcomes (Table 4). Two are very large (>20,000 participants) community-based trials with primary outcomes of cancer, cardiovascular disease, and mortality (20,21); the third is an efficacy trial with primary outcomes of nonvertebral fracture, functional and cognitive decline, blood pressure, and infection (22). In secondary analyses, D2d will assess the effect of vitamin D supplementation on indices of insulin secretion and insulin sensitivity after a 75-g oral glucose tolerance test.

CONCLUSIONS

D2d is a large randomized clinical trial testing the hypothesis that oral daily vitamin D_3 lowers risk of diabetes in U.S. adults with prediabetes. The study's large size, with recruitment from 22 sites across the U.S., ensures that the D2d cohort includes people with a wide spectrum of diabetes risk, appropriate for testing the underlying hypothesis, while the placebo group will provide information on the natural history of prediabetes in the current era.

When designing D2d, we used contemporary definitions to assemble a prediabetes cohort that follows the latest guidelines, reflects current diagnosis patterns, and identifies those at the highest risk of progression to diabetes. As such, D2d has assembled the largest cohort of U.S. adults with prediabetes based on the revised ADA criteria, which include HbA_{1c} and lower FPG thresholds. The contemporary ADA criteria have been controversial, as they increase the prevalence of prediabetes by identifying people at lower

Table 2—Glycemic profile by race and ethnicity in D2d

	Race					Ethnicity		
	White (N = 1,616)	Black (N = 616)	Asian (N = 130)	Other (N = 61)	P for race	Hispanic (N = 225)	Non-Hispanic (N = 2,198)	P for ethnicity
Diabetes risk factors								
Age, years, mean (SD)	61.2 (9.5)[1,2,3]	56.3 (9.5)[1]	54.7 (11.1)[2]	54.2 (10.0)[3]	<0.01	54.1 (9.8)	60 (9.8)	<0.01
BMI, kg/m^2, mean (SD)	32.1 (4.4)[1,2]	32.7 (4.5)[1,4]	28.2 (3.8)[2,4,6]	31.4 (4.3)[6]	<0.01	32.3 (4.5)	32.0 (4.5)	0.47
Waist circumference, cm, mean (SD)								
Men	108.8 (11.5)[1,2,3]	105.3 (10.6)[1,4]	97.3 (11.8)[2,4]	102.4 (9.1)[3]	<0.01	104.3 (11.1)	107.3 (11.6)	0.02
Women	103.3 (11.2)[1]	102.1 (10.9)[1,4]	93.7 (10.6)[4]	100.4 (14.0)	<0.01	101.1 (11.6)	102.7 (11.3)	0.14
Self-reported family history of diabetes, n (%)	962 (59.5)[1]	420 (68.1)[1]	86 (66.2)	46 (75.4)	<0.01	155 (68.9)	1,359 (61.8)	0.04
Self-reported gestational diabetes mellitus, n (%) women	66 (9.2)[1]	6 (2.0)[1]	5 (10.9)	4 (14.3)	<0.01	22 (16.2)	59 (6.2)	<0.01
Glycemic testing, mean (SD)								
FPG, mg/dL	108.8 (7.3)[1]	105.8 (7.4)[1]	107.3 (7.1)	107.3 (6.7)	<0.01	107.4 (7.3)	108 (7.4)	0.24
2hPG, mg/dL	137.7 (35.0)	135.7 (32.5)	140.5 (33.7)	135.3 (35.4)	0.41	135.2 (32.5)	137.5 (34.5)	0.36
HbA_{1c}, %	5.9 (0.2)[1]	6.0 (0.2)[1,4,5]	5.9 (0.2)[4]	5.9 (0.2)[5]	<0.01	5.9 (0.2)	5.9 (0.2)	0.56
Prediabetes categories, n (%)					<0.01			0.92
*i*A1c + IFG	768 (47.5)[1]	323 (52.4)[1]	64 (49.2)	29 (47.5)		112 (49.8)	1,072 (48.8)	
IFG + IGT	126 (7.8)[1]	17 (2.8)[1]	6 (4.6)	3 (4.9)		16 (7.1)	136 (6.2)	
IGT + *i*A1c	119 (7.4)[1]	91 (14.8)[1]	14 (10.8)	7 (11.5)		20 (8.9)	211 (9.6)	
*i*A1c + IFG + IGT	603 (37.3)[1]	185 (30.3)[1]	46 (35.4)	22 (36.1)		77 (34.2)	779 (35.4)	

The Tukey-Kramer test was used for post hoc pairwise comparisons between racial groups. Self-reported gestational diabetes mellitus is among all women participants whether they were pregnant or not. Racial and ethnic categories follow NIH guidelines. Hispanic refers to ethnicity and includes any race. IFG defined as FPG 100–125 mg/dL (5.6–6.9 mmol/L). IGT defined as 2hPG after a 75-g glucose load 140–199 mg/dL (7.8–11.0 mmol/L). *i*A1c defined as HbA_{1c} 5.7–6.4% (39–47 mmol/mol). [1]Difference between white and black significant at $P < 0.05$. [2]Difference between white and Asian significant at $P < 0.05$. [3]Difference between white and other significant at $P < 0.05$. [4]Difference between black and Asian significant at $P < 0.05$. [5]Difference between black and other significant at $P < 0.05$. [6]Difference between Asian and other significant at $P < 0.05$.

Table 3—Key baseline characteristics of D2d versus other large prediabetes trials

	D2d	SCALE	NAVIGATOR	DREAM	DPP	STOP-NIDDM	ACE
N	2,423	2,254	9,518	5,269	3,234	1,429	6,522
Years conducted (country)	2013–2018 (estimated) (U.S.)	2011–2015 (multiple countries worldwide)[1]	2002–2007 (multiple countries worldwide)[1]	2001–2006 (multiple countries worldwide)	1996–2001 (U.S.)[1]	1995–2000 (multiple countries worldwide)[1]	2009–2015 (China)
Study design and intervention	Two arms: vitamin D_3 vs. placebo	Two arms: liraglutide vs. placebo (2:1 ratio)	2 × 2 factorial design: nateglinide and/or valsartan vs. placebos	2 × 2 factorial design: ramipril and/or rosiglitazone vs. placebos	Three arms: metformin vs. intensive lifestyle vs. placebo	Two arms: acarbose vs. placebo	Two arms: acarbose vs. placebo
Glycemic criteria	At least two of three 2010 ADA criteria for prediabetes: 2hPG 140–199 mg/dL, FPG 100–125 mg/dL, HbA_{1c} 5.7–6.4%	At least one of three 2010 ADA criteria for prediabetes: 2hPG 140–199 mg/dL, FPG 100–125 mg/dL, HbA_{1c} 5.7–6.4%	2hPG 140–199 mg/dL and FPG 95–125 mg/dL	2hPG 140–199 mg/dL or FPG 110–125 mg/dL	2hPG 140–199 mg/dL and FPG 95–125 mg/dL	2hPG 140–199 mg/dL and FPG 101–139 mg/dL	2hPG 140–199 mg/dL
Age, years, mean	59.4	47.4	63.8	54.7	50.6	54.5	64.3
Women, %	45	76	51	59	68	51	27
BMI, kg/m^2, mean	32.0	38.9	30.5	30.9	34.0	31	25.4
Waist circumference, cm, mean	105.0	116.6	101	Not reported	105.1	101	91.2
White race, %	66.7	83	83.1	Not reported	55[2]	98	0
Family history of diabetes, %	62.5	Not reported	38	Not reported	69	Not reported	Not reported
FPG, mg/dL, mean	107.9	99.0	109.6	104.4	106.5	112.0	99.0
2hPG, mg/dL, mean	137.25	133.2	164.9	156.6	164.6	166.7	167.4
HbA_{1c}, %, mean	5.9	5.8	5.8	Not reported	5.9	Not reported	5.9
Duration of follow-up, years, mean	3 (estimated)	3.0	5.0	3.0	2.8	3.3	5.0
Cumulative incidence of diabetes in placebo group during mean follow-up, %	Not available	11	34	19	29	42	15

Trials selected for having >1,000 participants and at least 1 year of follow-up. DREAM, Diabetes Reduction Assessment with Ramipril and Rosiglitazone Medication; NAVIGATOR, Nateglinide and Valsartan in Impaired Glucose Tolerance Outcomes Research; STOP-NIDDM, Study to Prevent Non-Insulin-Dependent Diabetes Mellitus. [1]Study duration was estimated based on published information about the end of recruitment and follow-up time. [2]Non-Hispanic white.

risk for diabetes and cardiovascular complications, who may be less likely to benefit from interventions compared with people meeting earlier criteria (13,14). D2d's inclusion criteria resulted in a cohort with lower mean 2hPG concentrations but similar HbA_{1c} and FPG concentrations compared with previous cohorts. However, this hyperglycemia pattern likely matches more closely that of contemporary patients with prediabetes, since 8 of 10 D2d participants met both FPG and HbA_{1c} criteria, which are the tests most commonly used in clinical practice to diagnose prediabetes. The 2hPG criterion is used less often in the clinical setting, likely because of its patient and provider burden as well as low reproducibility (23).

We currently have little knowledge of how the 2010 ADA criteria are related to future diabetes risk in the general U.S. population (24,25). The control arm of other large trials, such as the Diabetes Prevention Program (DPP) or Acarbose Cardiovascular Evaluation (ACE) (7,12), cannot answer this question because they required the 2hPG criterion, which is rarely available in clinical practice. Reanalyses of data from older cohorts applying the new HbA_{1c} and FPG criteria retrospectively are limited because these criteria were not used to build the cohorts (26). In addition, many trials were conducted decades ago and changes in the background milieu (e.g., lifestyle changes, increased use of mobile technology, slowing in the growth of overweight and obesity) (27,28) make previous cohorts less representative of the current U.S. population at risk for diabetes. Because D2d used the current ADA criteria to identify people at risk for diabetes and will take into consideration all contemporary factors and influences, the study will help establish the natural history of prediabetes among U.S. adults followed in a clinical trial in the contemporary era; such information is important to make informed decisions about diabetes risk at both the personal and public health level. Although SCALE (liraglutide vs. placebo), conducted in 27 countries worldwide, also identified people with prediabetes using the 2010 ADA criteria, it only required that participants meet one of three glycemic criteria for prediabetes and had 50% loss to follow-up (11), limiting the ability to interpret the natural history of this lower-risk prediabetes cohort.

Table 4—Ongoing and completed randomized, placebo-controlled trials of vitamin D supplementation and diabetes risk

	D2d	Tromsø study	DPVD	VITAL	D-Health	DO-HEALTH
N	2,423	511	750 (target)	25,874	21,315	2,157
Years conducted (country)	2013–2018 (estimated) (U.S.)	2008–2015 (Norway)	2013–unknown (estimated) (Japan)	2010–2018 (estimated) (U.S.)	2014–2025 (estimated) (Australia)	2012–2017 (estimated) (Europe)
Diabetes outcome	Primary	Primary	Primary	Secondary[1]	Secondary[2]	Secondary (fasting glucose, insulin)[3]
Glycemic inclusion criteria	At least two of three ADA criteria for prediabetes: 2hPG 140–199 mg/dL, FPG 100–125 mg/dL, HbA_{1c} 5.7–6.4%	2hPG 140–198 mg/dL and/or FPG 108–124 mg/dL[4]	2hPG 140–199 mg/dL and fasting glucose <126 mg/dL and HbA_{1c} <6.5%	None	None	None
Active intervention	Two arms: 4,000 IU vitamin D_3 daily vs. placebo	Two arms: 20,000 IU vitamin D_3 weekly (~2,900 daily) vs. placebo	Two arms: 0.75 μg eldecalcitol ($1,25[OH]_2D_3$) daily vs. placebo	2 × 2 factorial design: 2,000 IU D_3 daily, 1 g daily marine n-3 fatty acid vs. placebos	Two arms: 60,000 IU D_3 monthly vs. placebo	2 × 2 × 2 factorial design: 2,000 IU D_3 daily, 1 g marine n-3 fatty acid daily, exercise program
Personal use of vitamin D from supplements, % of participants (maximum amount allowed)	43 (1,000 IU/day)	35 (<400 IU/day)	Not available	Not available (800 IU/day)	Not available (500 IU/day [2,000 IU/day if prescribed])	Not available (800 IU/day)
Treatment duration, years	~3 (estimated)	5	2.8	5	5	3

DO-HEALTH, Vitamin D3 – Omega3 – Home Exercise – HeALTHy Ageing and Longevity Trial; VITAL, VITamin D and OmegA-3. [1]Primary outcomes: cancer, major adverse cardiovascular events. [2]Primary outcome: all-cause mortality. [3]Primary outcomes: nonvertebral fracture, functional decline, blood pressure, cognitive decline, infection. [4]HbA_{1c} added as inclusion requirement midway through recruitment; all participants had HbA_{1c} between 5.8 and 6.9%.

The D2d cohort is well balanced by sex, which makes possible the evaluation of vitamin D's effect by sex given several sex-based differences in characteristics. Women participants are younger, use more vitamin D and calcium supplements, and have different health histories and baseline clinical testing results than men. Women also have lower FPG concentrations and higher 2hPG concentrations than men. This pattern has previously been noted (29,30), and it is not clear whether this is due to the same glucose load (75 g) being given to smaller individuals or to actual sex differences in glucose metabolism (31).

The D2d cohort is racially diverse, which allows testing for effect modification by race, especially among black individuals who have both higher diabetes risk and different vitamin D homeostasis (32,33). In the D2d cohort, key diabetes risk factors including age, BMI, waist circumference, family history of diabetes, history of gestational diabetes mellitus, and glycemic concentrations vary between racial and ethnic groups. Notably, black participants have a higher baseline mean HbA_{1c} concentration than other races, despite having lower FPG and similar 2hPG concentrations. This finding, which is increasingly recognized, suggests that HbA_{1c} overestimates mean glycemia in black compared with white individuals (16). Indeed, the Department of Veterans Affairs and Department of Defense 2017 guidelines recommend that HbA_{1c} 6.5–6.9% (48–52 mmol/mol) alone not be used to diagnose diabetes in the absence of a confirmatory FPG measurement (34). D2d will provide valuable data in this controversial area.

Given the wide range of glycemic phenotypes within the current ADA definition of prediabetes (e.g., *i*A1c, IFG, or IGT alone or *i*A1c, IFG, and IGT), it is likely that the definition of prediabetes will continue to evolve. Beyond glycemic criteria, there are several distinct clinical phenotypes that may be important to consider when classifying future risk of diabetes and diabetes-specific complications (35). Given the large size of the well-characterized D2d cohort and long-term follow-up with frequent (twice yearly) evaluations of glycemic status and other clinical outcomes (e.g., cancer, cardiovascular disease), D2d is well positioned to examine how different phenotypes influence future risk, including how glycemia (assessed by FPG and 2hPG) and HbA_{1c} are associated with future diabetes and cardiovascular risk and how risk varies by age, sex, race, and ethnicity.

Serum 25-hydroxyvitamin D values are not currently available. Per the study's protocol and analytical plan, 25-hydroxyvitamin D will be analyzed at the conclusion of the study in pairs (before/after intervention) and in the same analytical run to reduce systematic error and interassay variability. We expect baseline levels to be similar between the two groups, as factors that impact vitamin D status (e.g., geographical location, racial/ethnicity [36,37]) are balanced between groups. Nevertheless, in prespecified subgroup analyses, heterogeneity of treatment effects by baseline 25-hydroxyvitamin D levels will be assessed (3).

In conclusion, in a contemporary cohort of U.S. adults at risk for diabetes, D2d is expected to address two important knowledge gaps: *1*) whether vitamin D supplementation prevents diabetes and *2*) how the 2010 expanded ADA criteria for prediabetes impact the natural history of prediabetes. The answers to these questions will have extensive implications for the many U.S. adults at risk for diabetes.

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The sponsor did not have the right or ability to veto submission for publication. Study pills were purchased from an independent nutritional supplement manufacturing company that has no association with any members of the D2d Research Group.

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