Rationale and Design of the Vitamin D and Type 2 Diabetes (D2d) Study: A Diabetes Prevention Trial

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OBJECTIVE

Observational studies suggest that vitamin D may lower the risk of type 2 diabetes. However, data from long-term trials are lacking. The Vitamin D and Type 2 Diabetes (D2d) study is a randomized clinical trial designed to examine whether a causal relationship exists between vitamin D supplementation and the development of diabetes in people at high risk for type 2 diabetes.

RESEARCH DESIGN AND METHODS

D2d was designed with support from a U34 planning grant from the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK). The final protocol was approved by the D2d Research Group, the data and safety monitoring board, and NIDDK. Key eligibility criteria are age ≥30 years, BMI of 24 (22.5 for Asian Americans) to 42 kg/m², increased risk for diabetes (defined as meeting two of three glycemic criteria for prediabetes established by the American Diabetes Association [fasting glucose 100–125 mg/dL (5.5–6.9 mmol/L), 2-h postload glucose after 75-g glucose load 140–199 mg/dL (7.7–11.0 mmol/L), hemoglobin A_{1c} 5.7–6.4% (39–46 mmol/mol)]), and no hyperparathyroidism, nephrolithiasis, or hypercalcemia. D2d participants are randomized to once-daily vitamin D_3 (cholecalciferol 4,000 IU) or placebo and followed for an average of 3 years. The primary end point is time to incident diabetes as assessed by laboratory criteria during the study or by adjudication if diagnosed outside of D2d. Recruitment was initiated at the end of 2013.

CONCLUSIONS

D2d will test whether vitamin D supplementation is safe and effective at lowering the risk of progression to diabetes in people at high risk for type 2 diabetes.

The prevalence of diabetes and related costs are expected to more than double in the next quarter century (1), with >79 million Americans already at high risk for developing diabetes (2). In clinical trials, weight loss reduces the risk of diabetes in people with prediabetes (3); however, long-term weight maintenance has proven elusive. Even after successful weight loss, substantial residual risk (~50%) remains. Several medications approved to treat type 2 diabetes have been studied for prevention, and some have been shown to delay incident diabetes (3–5), but additional approaches for preventing diabetes are needed.

Based on recent evidence (6–8), vitamin D insufficiency has emerged as a potential key contributor to the pathophysiology of type 2 diabetes. The hypothesis that inadequate vitamin D may be a modifier of diabetes risk is biologically plausible

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because both impaired pancreatic β-cell function and insulin resistance have been reported with vitamin D insufficiency in human studies (6). Prospective observational studies consistently reported an inverse association between blood 25-hydroxyvitamin D (25OHD) concentration and incident diabetes. In a meta-analysis of 21 cohort studies with a total of 76,000 participants, a 38% lower risk of developing diabetes was found in adults at the highest tertile of blood 25OHD concentration compared with the lowest tertile (7). In another meta-analysis of 16 cohort studies with a total of 72,000 participants, those in the bottom quartile of blood 25OHD concentration had a 50% higher risk of developing diabetes compared with those in the top quartile (8). Despite the consistency of the results, the observational nature of these cohort studies precludes an assessment of cause and effect because reverse causality or residual confounding cannot be excluded. Confounding is of particular concern for vitamin D because blood 25OHD concentration is an excellent indicator of overall health, and therefore, low vitamin D concentration may be a consequence rather than a cause of poor health (9).

The effect of vitamin D supplementation on glycemia or incident type 2 diabetes has been studied in several trials with mixed results (10–13). In trials that included participants with normal glucose tolerance or established type 2 diabetes at baseline, vitamin D supplementation appears to have little or no effect on measures of glycemia or incident type 2 diabetes. The potential effect of vitamin D supplementation appears to be more promising among people at high risk for diabetes. In a post hoc analysis of data on fractures from a completed trial, combined vitamin D_3 (700 IU/day) and calcium carbonate (500 mg/day) supplementation prevented increases in insulin resistance and fasting glycemia in participants with impaired fasting glucose but not in those with normal fasting glucose at baseline (10). In this study, the reduction in glycemia over 3 years was similar to the reduction in fasting glucose achieved with metformin or lifestyle intervention in the Diabetes Prevention Program (3). In the Calcium and Vitamin D for Type 2 Diabetes Mellitus study, vitamin D supplementation

(4,000 IU/day) in adults at risk for type 2 diabetes ($n = 92$) improved β-cell function, as assessed by a frequently sampled intravenous glucose tolerance test, and achieved a nearly statistically significant reduction in hemoglobin A_{1c} (11). In contrast, other studies reported no effect of vitamin D supplementation on glucose homeostasis in populations with prediabetes (13,14).

Although the data from published studies have suggested a link between vitamin D and diabetes risk, the evidence to support general supplementation with vitamin D for diabetes prevention does not currently exist because such intervention would be based almost exclusively on observational studies, and interpretation of results from the available trials is hindered by several limitations, including the following: analyses on vitamin D and glycemic outcomes were post hoc, all but two trials were underpowered for glycemic outcomes, most trials reported poor adherence to the vitamin D supplementation, and the effect of concurrent diabetes pharmacotherapy on outcomes was rarely reported in studies of participants with established diabetes. Therefore, a trial designed and powered to test the effect of vitamin D supplementation on the risk of progression from prediabetes to diabetes is needed. The Vitamin D and Type 2 Diabetes (D2d) study is such a trial. Funded by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) of the National Institutes of Health (NIH), D2d is a randomized controlled clinical trial designed to examine the causal relationship between vitamin D supplementation and development of diabetes in people at high risk for diabetes.

RESEARCH DESIGN AND METHODS

The concept of a clinical trial to examine the safety and efficacy of vitamin D supplementation for the prevention of type 2 diabetes in people at high risk for diabetes was first presented to NIDDK by A.G.P. in December 2009. With provisional enthusiasm expressed by NIDDK, A.G.P., B.D.-H., C.J.R., and W.C.K. developed a preliminary proposal in early 2010. A U34 multicenter clinical study implementation planning grant (principal investigator A.G.P.) was awarded to Tufts Medical Center in July 2011. During the next

2 years, the authors of this article developed a complete study protocol and associated documents, including a manual of operations and template informed consent forms; solicited and selected study sites; and built the infrastructure necessary for the conduct of the trial.

D2d was reviewed favorably by an independent external evaluation committee (convened by NIDDK) in March 2012, recommended for funding by an NIDDK special emphasis review panel in August 2012, and approved by the NIDDK Advisory Council in February 2013. Funding for the study became available in June 2013 through a U01 cooperative agreement (principal investigator A.G.P.) to Tufts Medical Center where the D2d Coordinating Center is based (www.d2dstudy.org/coordinatingcenter).

The D2d data and safety monitoring board (DSMB), an independent review group appointed by NIDDK, reviewed the study in May 2013. The DSMB and the steering committee, which is comprised of the principal investigators of the collaborating clinical sites, selected members of the D2d Research Group, and representatives of NIDDK, approved the final study protocol in July 2013. After approval by the study site institutional review boards, recruitment began in October 2013.

Major Specific Aims
The primary aim of D2d is to assess whether oral daily vitamin D_3 (cholecalciferol) supplementation in participants with prediabetes reduces the rate of progression from prediabetes to diabetes. Secondary specific aims are to assess safety and tolerability of vitamin D supplementation; variation of response to vitamin D supplementation among subgroups defined by key baseline characteristics; variation by level of adherence; effect of vitamin D supplementation on glycemic measures, insulin resistance and secretion, blood pressure, and blood 25OHD concentration; and phenotypic characteristics associated with variation in achieved blood 25OHD concentration.

Other outcomes are being studied in parallel as part of distinct ancillary studies. Blood (serum, plasma, whole blood for DNA) and urine samples are saved for use in the ancillary studies.

Table 1—Summary of eligibility criteria for D2d

Inclusion criteria
1. Prediabetes (at increased risk for diabetes) defined at the baseline visit by meeting two of the following three glycemic criteria established by the American Diabetes Association in the 2010 clinical practice guidelines:
   a. FPG 100–125 mg/dL (5.5–6.9 mmol/L), inclusive
   b. 2hPG after 75-g glucose load 140–199 mg/dL (7.7–11.0 mmol/L), inclusive
   c. Hemoglobin A_{1c} 5.7–6.4% (39–46 mmol/mol), inclusive
2. Men or women age ≥30 years (≥25 years for people of the following groups: American Indian, Alaska Native, Native Hawaiian, or other Pacific Islander)
3. BMI ≥24 kg/m^2 (22.5 kg/m^2 for Asian Americans) and ≤42 kg/m^2
4. Provision of signed and dated written informed consent before any study procedures

Major exclusion criteria
1. Diabetes based on either of the following criteria:
   a. History (past 1 year) of hypoglycemic pharmacotherapy (oral or injectable medication approved by the Food and Drug Administration for type 2 diabetes) used for any condition (e.g., prediabetes, diabetes, polycystic ovary syndrome)
   b. Meeting glycemic criteria for diabetes, as defined by the American Diabetes Association clinical practice guidelines (FPG ≥126 mg/dL [7.0 mmol/L], 2hPG ≥200 mg/dL [11.1 mmol/L], or hemoglobin A_{1c} ≥6.5% [48 mmol/mol])
2. History (past 3 years) of hyperparathyroidism, nephrolithiasis, or hypercalcemia
3. 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)
4. Use of tanning devices within 12 weeks of the baseline visit and unwilling to stop the use of tanning devices for the duration of the study
5. Use of supplements containing vitamin D at total doses >1,000 IU/day within 12 weeks of the baseline visit and unwillingness to limit vitamin D supplementation dosage to no more than 1,000 IU/day for the duration of the study
6. Use of supplements containing calcium at total doses >600 mg/day within 1 week of the baseline visit and unwillingness to limit calcium supplementation dosage to no more than 600 mg/day for the duration of the study
7. Current use of medications or conditions (e.g., untreated celiac disease) that would interfere with absorption or metabolism of vitamin D
8. 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 >2 years ago with self-reported weight stability (defined as weight change no more than 3 kg during the prior 6 months) are not excluded
9. Chronic kidney disease defined as estimated glomerular filtration rate <50 mL/min/1.73 m^2 from creatinine level measured at the clinical site's laboratory and glomerular filtration rate calculated centrally
10. Hypercalcemia defined as serum calcium concentration greater than or equal to the upper limit of normal as measured at the clinical site's laboratory
11. Hypercalciuria defined as spot urine (morning void) calcium-creatinine ratio >0.275

Overall Study Design

D2d is a multicenter, randomized (1:1), double-masked, placebo-controlled, parallel-group, primary prevention clinical trial with two arms (oral daily vitamin D vs. placebo) in participants at high risk for diabetes (i.e., prediabetes) who will be followed for incident diabetes for 2–4 years after randomization. D2d was designed entirely by the planning group (the authors) with input from an NIDDK-appointed external evaluation committee and investigators at each collaborating site. No pharmaceutical manufacturers contributed to the planning or design or will participate in the conduct of D2d. Study pills were purchased from an independent nutritional supplement manufacturing company that has no association with any members of the D2d Research Group.

Study Population and Recruitment

Adults at increased risk for type 2 diabetes (prediabetes), defined as meeting two of three glycemic criteria for prediabetes established in 2010 by the American Diabetes Association (fasting plasma glucose [FPG] 100–125 mg/dL [5.5–6.9 mmol/L]; 2-h postload glucose [2hPG] after 75-g glucose load 140–199 mg/dL [7.7–11.0 mmol/L]; hemoglobin A_{1c} 5.7–6.4% [39–46 mmol/mol]), are eligible for enrollment in D2d. Because of the requirement to meet at least two of these criteria to be considered at risk for diabetes, it is expected that D2d

participants will be at relatively high risk for progression to diabetes. Other inclusion criteria and major exclusion criteria are shown in Table 1. The screening process is staged in two visits. At the first screening visit, all nonglycemic eligibility criteria are assessed, and FPG and hemoglobin A_{1c} are measured at the local laboratory to assess preliminary eligibility. If FPG and hemoglobin A_{1c} results are within range based on a site-specific algorithm, the volunteer proceeds to the second screening visit. At that visit, which also serves as the baseline visit for participants who qualify, a 75-g oral glucose tolerance test (OGTT) is performed for FPG, 2hPG, and hemoglobin A_{1c}, which are analyzed by the central laboratory.

Vitamin D status, defined by blood 25OHD concentration at baseline, is not an inclusion criterion because 1) in small trials, vitamin D appeared to benefit those with prediabetes irrespective of baseline 25OHD concentration (10,11); 2) the definition of optimal vitamin D status is controversial, and no consensus exists on optimal blood 25OHD level (15–19); 3) 25OHD concentration varies by season and race (15,20); 4) low 25OHD concentration is common in the U.S. adult population, especially among overweight and obese people (15,21); 5) the study is designed to be as inclusive as possible to ensure that results are generalizable to clinical practice; 6) baseline 25OHD is a potential effect modifier that will be tested in subgroup analyses; and 7) screening with blood 25OHD would be cumbersome and expensive. Blood for 25OHD concentration is collected at yearly intervals and will be measured after the study is completed to assess the efficacy of the supplementation at raising 25OHD concentration and to evaluate for heterogeneity of treatment effect.

Recruitment, which is expected to last for ~2 years, will be continuous to ensure balanced enrollment in the four seasons. Clinical sites will use a variety of methods to recruit participants, with emphasis placed on identifying potential participants by searches of electronic medical records and research volunteer databases.

D2d is being conducted at 21 U.S. collaborating clinical sites (www.d2dstudy.org/sites) selected by the coordinating center and the funding agency partly

because of their ability to recruit and retain a diverse population of research participants at risk for diabetes. Several sites are located at high latitude (to capture low ultraviolet B exposure), whereas other sites serve populations with substantial racial diversity. Each clinical site will enroll ~100–150 participants to reach the study-wide target enrollment of 2,382 participants.

Intervention
Study Intervention
Participants are randomized in a stratified (by site, BMI, and race) and blocked fashion and in a one-to-one ratio to receive once daily either a single softgel of vitamin D_3 (cholecalciferol 4,000 IU) or matching placebo for the duration of the study. Assignment is double masked. The vitamin D_3 and placebo pills are prepared by Tishcon Corp. in accordance with U.S. Pharmacopeia standards and Good Manufacturing Practices and shipped to the drug distribution center (Veterans Affairs Cooperative Studies Program, Albuquerque, NM) in bulk where they are packaged into bottles with enough pills for an 8-month period and then shipped to each site for storage before distribution to participants. Both the manufacturer and the drug distribution center perform quality control analyses on each lot, including assaying for the amount of the active ingredient (vitamin D_3). In addition, the drug distribution center performs periodic potency testing to ensure that the amount of active ingredient is within specified limits throughout its use.

In addition to receiving the study medication, all participants are encouraged to meet the Institute of Medicine–recommended amounts of supplemental vitamin D for their age (600 or 800 IU/day) (15). The planning committee recognized that for practical reasons, participants might take up to 1,000 IU/day vitamin D from supplemental sources outside of D2d because that is the dose of vitamin D contained in many commercially available supplements and the most commonly recommended by health-care providers.

At the randomization visit, D2d provides participants with written information on the current recommendations for the prevention of type 2 diabetes, emphasizing dietary and physical activity interventions aimed at weight loss.

Enrolled participants are invited to participate in the support and education program, which is expected to comprise group meetings convened twice yearly at each site to discuss specific topics on nutrition, exercise, and diabetes. These meetings provide an opportunity to meet other participants and potentially enhance retention. Participants also receive a newsletter at regular intervals, which includes a section on promoting physical activity and healthy nutrition.

Rationale
Cholecalciferol (D_3) was chosen over ergocalciferol (D_2) because supplementation with D_3 may result in a greater and more sustained increase in blood 25OHD concentration, D_2 may be less effective than D_3, and vitamin D_3 is the most commonly consumed vitamin D formulation. The dose being tested in this study (4,000 IU/day) provides an appropriate balance of safety and efficacy in terms of obtaining a substantial difference in blood 25OHD concentration between the active and placebo groups. Based on observational and short-term intervention studies (6,10,22–26), a blood 25OHD concentration of ~30–50 ng/mL is likely to be required to achieve a detectable reduction in risk of progression to type 2 diabetes. Study participants, who are overweight/obese and of whom approximately one-half are non-Caucasian race or Hispanic ethnicity, are expected to have a mean 25OHD concentration of ~20 ng/mL at study entry (10,11,21,22). A dose of 4,000 IU/day vitamin D is adequate to increase participants' mean 25OHD concentration to 35–40 ng/mL, especially during the winter (8,11,27,28).

Outcomes
The primary outcome of D2d is time to incident diabetes as assessed by laboratory criteria derived from glycemic testing done every 6 months, when symptoms consistent with hyperglycemia are reported, and at the end of the study. Glycemic measures are assessed, without interrupting the assigned treatment, at yearly visits by conducting a 75-g OGTT (FPG, hemoglobin A_{1c}, and 2hPG) and at semiannual visits by fasting blood tests (FPG and hemoglobin A_{1c}). The algorithms shown in Figs. 1 and 2 are followed to confirm incident diabetes. When only one glycemic test is positive for diabetes at the

initial visit, confirmatory testing is required. Diabetes diagnosis outside of D2d is validated by laboratory testing as part of D2d or, if the participants started diabetes-specific medication, by review of medical records by the clinical outcomes committee, whose members are independent of the D2d Research Group (Fig. 3).

Results of the screening and baseline glycemic measures are provided to participants and their health-care providers. After randomization, numeric results of glycemic tests are not provided to sites, participants, or health-care providers until a participant meets the primary end point of diabetes. At that point, glycemic results are shared with the site, participant, and health-care providers, and the participant is referred to his or her physician for further care in relation to diabetes; however, the participant continues in the study, taking the study pills without unmasking and returning for all scheduled visits (for assessment of other outcomes). Secondary outcomes include safety and tolerability of vitamin D supplementation; variation of response to vitamin D supplementation among subgroups defined by key baseline characteristics; variability of response to vitamin D supplementation by adherence based on pill counts and by achieved 25OHD concentration; effect of vitamin D supplementation on hemoglobin A_{1c}, FPG, and 2hPG as continuous variables, insulin resistance and secretion (indices derived from the OGTT), systolic and diastolic blood pressure and blood 25OHD concentration; and identification of phenotypic, including seasonal and geographic, characteristics associated with variation in achieved blood 25OHD concentration.

Statistical Analyses and Sample Size Calculations
In accordance with the intention-to-treat principle, the primary analysis will compare treatment groups defined by the randomization procedure and will include all events observed during the study irrespective of adherence to assigned treatment. When participants withdraw (i.e., go off study), follow-up will be censored at the date of the last visit. Exploratory per-protocol analyses and analyses in subgroups defined by level of adherence to study treatment will be undertaken as well but are not
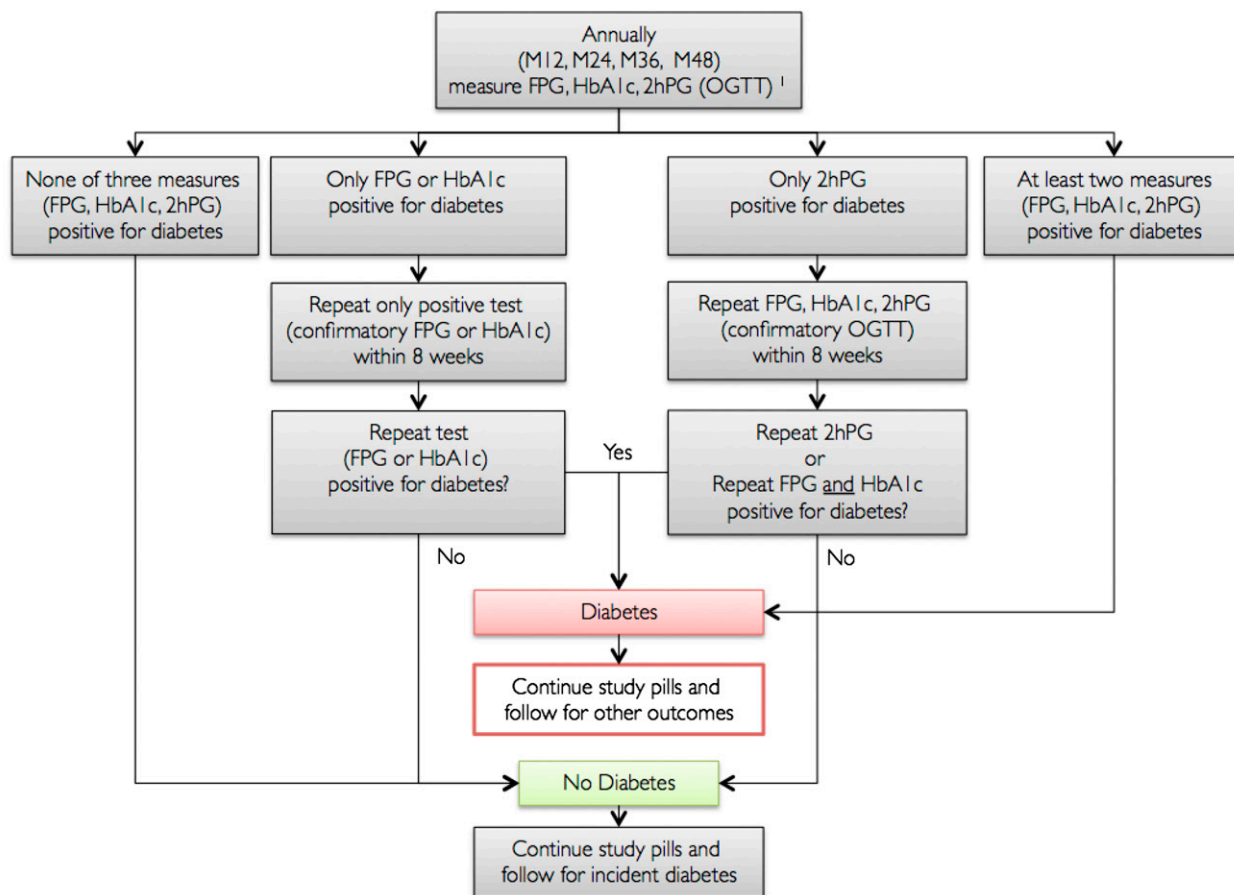
Figure 1—Flow diagram of laboratory diagnosis of diabetes at the annual D2d visit. M, month.

considered part of the confirmatory analysis plan.

Primary Outcome

The primary end point is time to incident diabetes. For most participants who develop diabetes during the study, incident diabetes will be diagnosed at one of the regularly scheduled study visits. When participants have been placed on a diabetes medication and the diagnosis cannot be confirmed or adjudicated by the clinical outcomes committee (Fig. 3), the participant will be considered to have not reached the primary study outcome, and follow-up will be censored at the date of initiation of diabetes treatment. Sensitivity analyses will be performed that include these occurrences as instances of incident diabetes. Kaplan-Meier estimates of time-to-confirmed diabetes distributions will be calculated for each treatment group. The log-rank test will then be used to perform an unadjusted comparison of

the time-to-event distributions in the two treatment groups. Follow-up of participants who withdraw or are lost to follow-up will be censored on the date of their last follow-up visit. All P values examined for statistical significance will be two-tailed, and $P < 0.05$ will be considered statistically significant. Cox proportional hazards models (29) will be used to calculate an estimate of the adjusted hazard ratio. To construct the model for the adjusted analysis, we will first construct a regression model that does not include the indicator for treatment group. Age, race, ethnicity, BMI, and other variables (FPG, 2hPG, hemoglobin A_{1c}, and 25OHD) to be specified a priori will be added to the proportional hazards regression model in a step-up fashion. Covariates making a statistically significant contribution to the model will be included in the final multivariate model. When the step-up procedure has been completed,

the covariate for treatment group will be added to the model. The regression coefficient for treatment group in this multiple regression model will be the adjusted estimate of the log hazard ratio.

Subgroup Analyses

Variability of response to vitamin D supplementation will be assessed by analyses of prespecified participant subgroups defined by baseline variables (e.g., race, ethnicity, BMI, waist circumference, age, geographic location, calcium intake, 25OHD concentration). Subgroups defined by clinically applicable cutoffs will also be compared (e.g., BMI as normal weight, overweight, or obese; 25OHD concentration by Institute of Medicine cutoffs). Each analysis of participant subgroups will include a test for interaction. Effect modification will be claimed only if the test for interaction reaches statistical significance. Although the primary outcome analysis
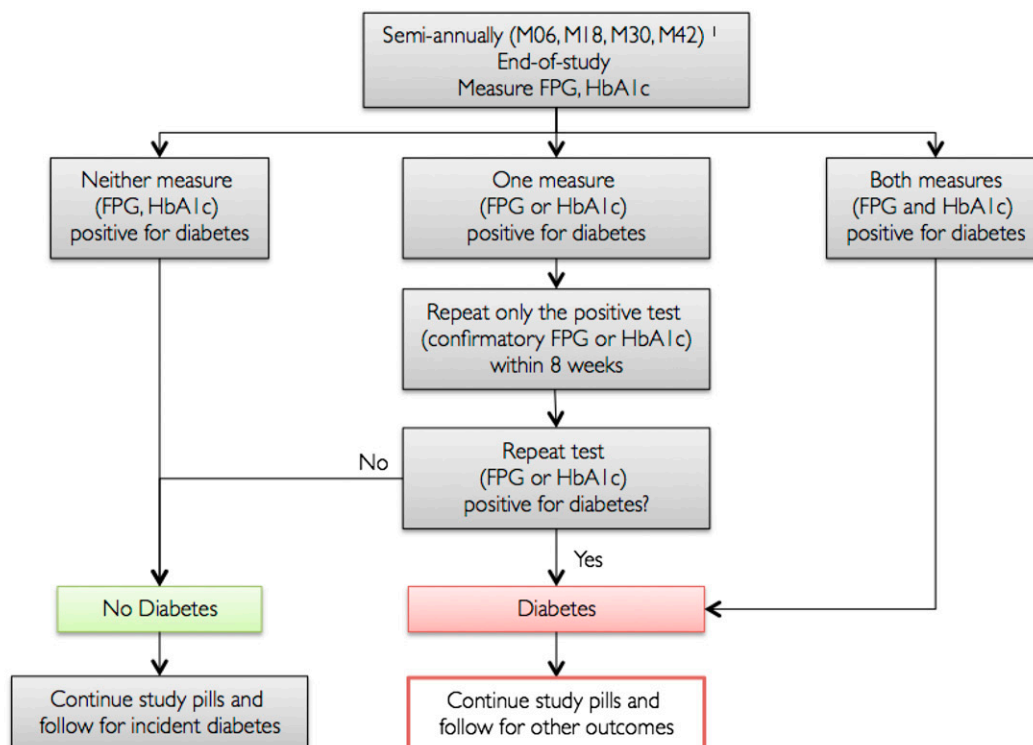
Figure 2—Flow diagram of laboratory diagnosis of diabetes at the semiannual D2d visits. M, month.

will be by randomization group (intention to treat, discussed previously), we will also assess variability of response to vitamin D supplementation (on-treatment analyses), where treatment is defined by adherence based on pill count or achieved 25OHD concentration. These analyses, although prespecified, are considered exploratory because the study is not powered for such analyses, and false results due to multiple comparisons must be considered when interpreting findings that are nominally statistically significant. Furthermore, on-treatment analyses lose the protection from confounding by unmeasured variables that is afforded by randomization.

Sample Size Calculations
The D2d study is designed as an event-driven trial to ensure that the intended power to detect the hypothesized treatment effect is achieved irrespective of the event rate in the placebo arm. The following considerations were used to determine the required number of events and sample size: *1*) hazard ratio of 0.75 in the vitamin D arm compared with the placebo arm, *2*) incidence rate of confirmed diabetes of 10% per year in

the placebo arm, *3*) two-sided type I error rate (α) of 0.05, *4*) power of 90%, *5*) recruitment period (accrual period) of 2 years, *6*) expected study duration of ~4 years, and *7*) loss-to-follow-up (i.e., going off study) rate of 5% per year of follow-up. Based on these assumptions, the required number of events is 508 (30), and the required sample size is 2,382 randomized participants.

The planning committee relied on observational longitudinal data and relevant intervention studies to estimate a plausible hazard ratio. In two meta-analyses that combined data from cohort studies, the pooled relative risk of type 2 diabetes comparing the highest with the lowest quartile of 25OHD concentration was 0.59 (95% CI 0.52–0.67) (31) and 0.62 (95% CI 0.54–0.70) (7), with little heterogeneity between studies. In a short-term trial, the 2,000 IU/day vitamin D_3 supplementation, which raised blood 25OHD concentration to 31 ng/mL, improved measures of β-cell function (disposition index) by ~40% and glycemia (hemoglobin A_{1c}) by ~50% after 4 months (11). After taking into consideration all published data and

short-term mechanistic studies on vitamin D and diabetes, a hazard ratio of 0.75 (i.e., 25% reduction in risk in the intervention arm) was used as the assumed treatment effect in sample size calculations.

Data Monitoring Plan
The D2d DSMB will regularly review accumulating safety and efficacy data. A single formal interim analysis of the accumulating primary end point data will take place when 70% of the expected events have accrued. The stopping boundary for the interim analysis will be based on the Haybittle-Peto approach (32,33). With this stopping boundary, the nominal *P* value representing statistical significance at the interim analysis will be 0.001, corresponding to a *Z* score of 3.89.

CONCLUSIONS
Approximately one in three U.S. adults age ≥20 years has prediabetes, a condition that progresses to diabetes at a rate of ~10% per year. Therefore, there is a continued need for the identification of interventions to lower progression to diabetes in populations at high risk.
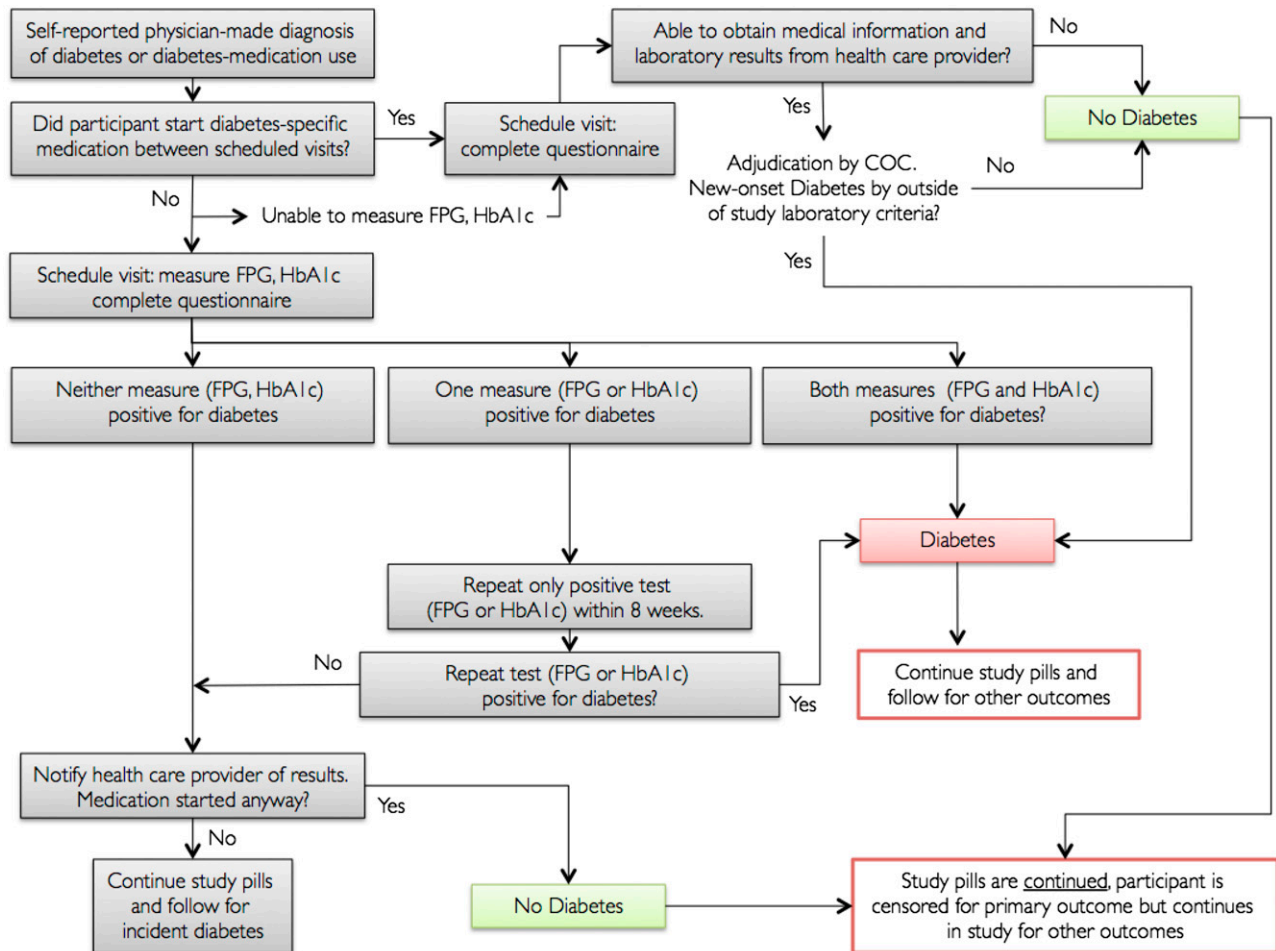
Figure 3—Flow diagram for evaluating self-reported physician diagnosis of diabetes or initiation of diabetes-specific pharmacotherapy between scheduled visits in D2d. COC, clinical outcomes committee.

Based on a large body of evidence over the past decade, vitamin D may play an important role in reducing the risk for type 2 diabetes. Although the evidence in favor of vitamin D supplementation appears promising, there is a crucial need for a definitive trial to determine the effects of vitamin D supplementation (23,34–40). D2d will address causality and rigorously assess the efficacy and safety of vitamin D supplementation in a target population most likely to benefit, people at high risk for diabetes. Study results are expected in 2018.

Given its anticipated diverse population (~40% nonwhites with a wide age and BMI range) selected without regard to baseline 25OHD concentration, its long-term follow-up, and its careful assessment of safety, D2d is expected to contribute important insights into the heterogeneity of treatment effect and safety profile of vitamin D

supplementation. Importantly, the study will serve as the backbone for ancillary analyses to meet additional vitamin D–related research needs and for various other studies to harness the considerable potential of the parent study for obtaining new knowledge beyond its primary goals (www.d2dstudy.org/ancillarystudies).

D2d addresses an important and timely question and could have a significant impact in the clinically important areas of vitamin D supplementation and type 2 diabetes prevention with extensive public health implications, especially given that the cost of supplementation is low compared with treating the chronic disease and its complications. If D2d confirms the hypothesis of a link between vitamin D and type 2 diabetes, then vitamin D supplementation will be integrated into conventional medical approaches to prevent type 2 diabetes

and ameliorate personal and societal disease burden.

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