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Original Research Article

Effect of intratrial mean 25(OH)D concentration on diabetes risk, by race and weight: an ancillary analysis in the D2d study

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A B S T R A C T

Background: Higher serum 25-hydroxyvitamin D [25(OH)D] is associated with lower type 2 diabetes risk. 25(OH)D varies due to skin pigmentation and weight.

Objectives: This analysis aims to determine whether the effect of vitamin D differs among people of color and those with overweight/obesity (who have higher diabetes risk) compared with individuals who are White or have normal weight.

Methods: The D2d study is a randomized clinical trial in people with prediabetes that tested the effects of daily vitamin D_3 4000 IU vs. placebo on diabetes risk (median followup 2.5 y). We compared baseline and intratrial mean 25(OH)D concentrations, defined as the mean of all available annual 25(OH)D values, among groups defined by self-reported race and body mass index (BMI). We used Cox proportional hazards models to assess the associations between intratrial mean 25(OH)D and diabetes risk by race- and BMI-based groups.

Results: Asian (n=130), Black (n=616), and White (n=1616) participants were included. Both baseline and intratrial mean 25(OH)D concentrations differed significantly by race groups (both $P < 0.001$) and were lower in Asian and Black vs. White participants, and in those with higher vs. lower BMI adjusted for race (both $P < 0.001$). Compared with those with lower concentrations, Black and White participants with intratrial mean 25(OH)D $\geq$ 40 ng/mL had significantly reduced diabetes risk [HR (95% CI): Black: 0.51 (0.29, 0.92); White: 0.42 (0.30, 0.60)] and with a similar reduction in diabetes risk among Asian participants: 0.39 (0.14, 1.11). Compared with those with lower concentrations, participants with baseline BMI < 40 kg/m^2 who achieved intratrial mean 25(OH)D concentrations $\geq$ 40 ng/mL had a significantly reduced diabetes risk. There was no statistically significant interaction between intratrial 25(OH)D and race or between intratrial 25(OH)D and BMI on diabetes risk.

Conclusions: Among people with prediabetes, particularly for Black and White race groups and those with BMI < 40 kg/m^2, the optimal 25(OH)D concentration may be $\geq$ 40 ng/mL to optimize diabetes-prevention efforts.

This trial was registered at clinicaltrials.gov as NCT01942694.

Keywords: blood 25(OH)D, race, body mass index (BMI), diabetes prevention, diabetes risk, vitamin D supplementation

Introduction

Over one-third of the US population has prediabetes, which is a condition associated with an increased risk of diabetes. Prediabetes and diabetes disproportionately affect people of color in the United States, including Black and South Asian populations, and people with obesity [1–5]. Vitamin D deficiency has been shown to be a risk factor for diabetes, including in people of color [6–11]. In the Vitamin D and Type 2 Diabetes (D2d) study, which comprises participants at high-risk for

Abbreviations: 25(OH)D, serum 25-hydroxyvitamin D; 2hPG, 2-h plasma glucose after 75g glucose load; ADA, American Diabetes Association; D2d, The Vitamin D and Type 2 Diabetes study; FPG, fasting plasma glucose; HR, hazard ratio; IU, international units; NAM, National Academy of Medicine.

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diabetes, participants who achieved an intratrial mean 25-hydroxyvitamin D [25(OH)D] ≥ 40 ng/mL had a significantly reduced risk of incident diabetes [7]. Vitamin D status varies in different populations, with a higher prevalence of vitamin D deficiency in people of color and people with obesity [12–16]. It is not known whether vitamin D status impacts diabetes risk disparately by individual characteristics, including race and weight.

The most commonly accepted marker of vitamin D status is serum 25(OH)D, which is determined by 2 main components: *1*) synthesis of vitamin D_3 in the skin, requiring sun exposure, and *2*) vitamin D intake in the diet (foods or supplements). The synthesis of vitamin D in the skin is affected by the concentration of melanin, which is reflected by one's skin color or pigmentation, as well as by the intensity of UV light on the skin, which can differ by season and geography [17,18]. Skin color can differ by race, because individuals have historically been racialized based on skin pigmentation/melanin content. Additionally, people with overweight/obesity are known to have lower 25(OH)D concentrations than people of normal weight through different potential mechanisms [19–23]. Studies have found that with a given dose of vitamin D supplement, serum 25(OH)D concentrations increase less in people with obesity compared with leaner people [24].

The National Academy of Medicine (NAM) recommended daily allowances of vitamin D for all adults of 600–800 IU daily, depending on age [20]. Concentrations of serum 25(OH)D that are considered "sufficient" vary by guidelines and range from ≥20 ng/mL (≥50 nmol/L) to ≥30 ng/mL (≥75 nmol/L) and do not vary by individual characteristics [20,25]. However, "optimal" doses or concentrations may differ by characteristics including skin pigmentation and weight. It is possible that specific populations may require different amounts of vitamin D to achieve different "optimal" 25(OH)D concentrations to reduce the risk of diabetes, a chronic disease that disproportionately affects people of color and people who are overweight/obese.

The D2d study is a randomized clinical trial of participants with prediabetes who were randomized to 4000 IU daily of vitamin D_3 vs. placebo over a median of 2.5 y to determine the impact on diabetes risk [6,26]. Although the primary intent-to-treat analysis did not find a statistically significant reduction in diabetes risk with vitamin D supplementation secondary analyses found that among participants randomized to vitamin D, the risk of diabetes was lower among those who achieved an intratrial mean 25(OH)D concentration ≥ 40 ng/mL (≥ 100 nmol/L) compared with those with lower intratrial mean 25(OH)D concentrations [7]. Given differences in vitamin D status by individual characteristics, including skin pigmentation and weight, we hypothesize that the impact of vitamin D on 25(OH)D concentrations and on diabetes risk may also differ by these characteristics. Therefore, using data from the D2d study, we compare, by race group and BMI: *1*) mean serum 25(OH)D concentrations at baseline; *2*) effects of vitamin D_3 4000 IU daily on intratrial mean serum 25(OH)D; and *3*) the associations of intratrial mean serum 25(OH)D concentrations with diabetes risk. The overall goal of these analyses is to provide insight into whether concentrations of 25(OH)D needed to reduce diabetes risk vary for different race and BMI groups.

Subjects and Methods

The D2d study is a randomized, double-blind, placebo-controlled, multisite clinical trial designed to evaluate the safety and efficacy of vitamin D for diabetes prevention in adults with prediabetes (clinicaltrials.gov NCT01942694). The methods of D2d and the results of the primary outcome have been reported [6,26]. The study was approved by the institutional review board of each collaborating site and monitored by an independent Data and Safety Monitoring Board; all participants provided written informed consent.

Study population

From October 2013 to February 2017, people who met ≥2 of 3 glycemic criteria for prediabetes as defined by the 2010 American Diabetes Association (ADA) guidelines, fasting plasma glucose (FPG) 100–125 mg/dL (5.6–6.9 mmol/L); plasma glucose 2 h after a 75-g oral glucose load (2hPG) 140–199 mg/dL (7.8–11.0 mmol/L); hemoglobin A1c (HbA1c) 5.7%–6.4% (39–47 mmol/mol), were recruited [27]. Other inclusion criteria were age ≥30 y (25 y for participants of American Indian, Alaska Native, Native Hawaiian, or other Pacific Islander race) and BMI of 24–42 kg/m^2 (22.5–42 kg/m^2 for participants with self-reported Asian race). We did not include 25(OH)D concentration as part of the eligibility criteria, and values for participants' baseline serum 25(OH)D concentrations were not available at the time of recruitment [26]. Participants were recruited from 22 clinical sites around the United States (see d2dstudy.org/sites). The complete list of eligibility criteria and the recruitment and screening process have been described [28].

Intervention and procedures

Participants (2423) were randomized to take once daily a single soft-gel that contained either 4000 IU of vitamin D_3 (cholecalciferol) or a matching placebo assigned by a web-based program. Block randomization was stratified by site, BMI (<30 or ≥ 30 kg/m^2), and race (White or any of the following: American Indian, Alaska Native, Native Hawaiian, or other Pacific Island, Asian, Black, or other). The program provided the study pill bottle number assigned to each participant, which was dispensed to the participant based on individual site procedures. Participants and all study staff were blinded to the treatment assignment. Participants were asked to refrain from using diabetes-specific or weight-loss medications during the study and to limit the use of outside-of-study vitamin D to 1000 IU per day from all supplements, including multivitamins [6,26].

Follow up and measurements

At baseline and annually, a 75-g oral glucose tolerance test was performed after a 8-h overnight fast. The last study encounter took place in December 2018 when the number of prespecified diabetes events had occurred per protocol. Blood was obtained while fasting and at 30 and 120 min after ingestion of the glucose load. Plasma for glucose was processed locally and shipped to the central laboratory for immediate measurement. Specimens for c-peptide and insulin were processed locally and shipped to the central laboratory for long-term storage at −80°C until analyses. HbA1c was measured on refrigerated whole blood samples. Samples were analyzed for these measures in a central laboratory using standardized methods and equipment, and these methods have been described [7,29,30].

A new diagnosis of diabetes was based on glycemic testing. Glycemic status was assessed annually with FPG, HbA1c, and 2hPG and semiannually with FPG and HbA1c. If ≥2 of the glycemic measures met the ADA thresholds for diabetes (FPG ≥ 126 mg/dL [7.0 mmol/L], 2hPG ≥ 200 mg/dL [11.1 mmol/L], or HbA1c ≥ 6.5% [48 mmol/mol]) [10], the participant was considered to have met the diabetes outcome definition. When only 1 glycemic measure met the threshold, confirmatory testing was performed within 8 wk. If a diagnosis of diabetes was made outside of D2d visits, the diagnosis was validated by in-study

laboratory testing or adjudicated by an independent clinical outcomes committee [6].

Serum 25(OH)D concentrations were measured at baseline and annually; measures were run on stored, fasting samples by liquid chromatography–tandem mass spectrometry with calibrators that are traceable to the National Institute of Standards and Technology and validated by a quarterly proficiency testing program administered by the Vitamin D External Quality Assessment scheme (DEQAS) [7,31,32]. Intratrial mean 25(OH)D, considered to be the intratrial vitamin D exposure, was calculated as a cumulative average measure of 25(OH)D during followup. For each participant, intratrial vitamin D exposure was calculated as a mean of all available annual 25(OH)D values before the occurrence of the primary end point of new-onset diabetes, start of a diabetes or weight-loss medication (before the diagnosis of diabetes), or last followup [7]. Serum 25(OH)D was analyzed as a continuous variable and also in clinically relevant categories as follows: <20 ng/mL (<50 nmol/L), 20 to <30 ng/mL (50–74 nmol/L), which was considered the reference group for our analyses, 30 to <40 ng/mL (75–99 nmol/L), and ≥40 ng/mL (≥100 nmol/L).

Race and ethnicity were self-reported by participants and categorized by the National Institutes of Health guidelines [29]. Participants who self-identified as Asian, Black, and White were included in these analyses; participants that self-identified as races other than these were excluded due to small sample sizes. Participants self-identified their ethnicity as Hispanic or Latino. At the baseline visit, weight was measured on a digital scale, and height was measured with a stadiometer. BMI was calculated as weight/height^2 (kg/m^2). BMI was analyzed as both a continuous and categorical variable. Because people of the Asian race have different BMI cutoffs for classification of overweight and obesity, we examined different categories of BMI for different race groups [33] For participants of Black and White races, we examined categories of <30, 30 to <35, 35 to <40, and ≥40 kg/m^2; for participants of Asian race, we examined categories of <25, 25 to <30, 30 to <35, and ≥35 kg/m^2. For models assessing diabetes risk by BMI categories, we created BMI groups as follows: group 1: Black, White <30 kg/m^2, and Asian <25 kg/m^2; group 2: Black, White 30 to <35 kg/m^2, and Asian 25 to <30 kg/m^2; group 3: Black, White 35 to <40 kg/m^2, and Asian 30 to <35 kg/m^2; group 4: Black, White ≥40 kg/m^2, and Asian ≥35 kg/m^2. Waist circumference was measured in participants at the baseline examination using a Gulick tape following standardized procedures with directions to measure the waist at the concentration of the iliac crest. Waist circumference was analyzed continuously and was also categorized by gender as ≤88 cm or >88 cm in women and ≤102 cm or >102 cm in men.

Additional data points, including demographics, vital signs, medical history, and medication use, and physical activity, using the International Physical Activity Questionnaire, were collected by self-report or through in-person measurements at study visits, and these collection methods have been previously described [6,26,34].

Statistical analyses

We described baseline characteristics by race group and baseline 25(OH)D, with means and standard deviations or percentages. We further described baseline 25(OH)D concentrations by BMI categories within each race group. Similarly, we described intratrial mean 25(OH)D concentrations by race and BMI categories in the whole study population and, in supplementary materials, also stratified by the study treatment arm, i.e., vitamin D or placebo. We compared mean baseline and intratrial mean 25(OH)D concentrations between groups using ANOVA and ordinary least squares regression and race and BMI categories between groups using chi-squared tests. For analyses assessing the associations between intratrial mean 25(OH)D concentrations and diabetes risk by subgroups, we fit Cox proportional hazards models regressing the log hazard for diabetes on intratrial mean 25(OH)D concentration, categorized as described above. All models included site as a stratification variable of the baseline hazard. One minimally adjusted model included a race*vitamin D category interaction term and adjusted for treatment assignment. A second minimally adjusted model included a BMI*vitamin D category interaction term, with adjustment for treatment assignment. Additional models were fitted with further adjustment for either race or BMI, if not included in the minimally adjusted model, as well as gender, age, physical activity, and statin use. The interaction terms leverage having all observations in the model while allowing for similar inference to a stratified approach, which partitions the data and potentially reduces power.

Sensitivity analyses

We examined associations in a stratified approach, examining associations only among participants randomized to vitamin D. We examined baseline and intratrial mean 25(OH)D in all 3 groups when stratified by race and by waist circumference as an alternative measure of weight/adiposity (Supplemental Table 1). All statistical analyses were performed using SAS 9.4 software (SAS Institute).

Results

Of the 2423 D2d participants, 2362 were included in these analyses and self-identified their race: 130 as Asian, 616 as Black, and 1616 as White (Supplemental Figure S1). The mean (SD) age of all participants was 60.1 (9.9) y and differed somewhat by race, with White participants being slightly older. The mean (SD) BMI of all participants was 32.1 (4.5) kg/m^2, with Asian participants having a lower mean BMI compared with the others. Baseline characteristics by race group are described further in Table 1. The median follow up time was 2.5 y (interquartile 2.0–3.5 y).

Baseline 25(OH)D concentrations by race and BMI category are shown in Table 1 and Table 2. Mean baseline 25(OH)D concentrations differed among all 3 groups when stratified by race ($P < 0.001$), with mean (SD) concentrations of 25.9 (10.2), 24.2 (10.9), and 29.6 (9.5) ng/mL in Asian, Black, and White participants, respectively. Similarly, there were significant associations between race and 25(OH)D ($P < 0.01$), with fewer Asian and Black participants with higher concentrations of 25(OH)D compared with White participants, with 10% of Asian and 9% of Black, compared with 13% of White participants having 25(OH)D concentrations ≥ 40 ng/mL at baseline (Table 2).

Within each race group, baseline serum 25(OH)D concentrations were lower among the participants with higher BMI than those with a lower BMI. Among participants in the lowest BMI category, <30 kg/m^2, mean (SD) 25(OH)D concentrations for Asian, Black, and White participants were 26.5 (8.9), 26.3 (11.8), and 31.6 (9.9) ng/mL, respectively. Among participants in the highest BMI category, ≥40 kg/m^2, mean (SD) 25(OH)D concentrations for Asian, Black, and White participants were 22 (5.7), 22 (8.8), and 24.9 (8.4) ng/mL, all lower than their same race counterparts in the lower BMI categories, with a significant overall trend ($P < 0.001$ for BMI groups adjusted for race) (Table 2).

Intratrial mean 25(OH)D concentrations were higher than baseline 25(OH)D concentrations for all participant subgroups (Table 3). As expected, this was driven primarily by participants randomized to vitamin D (Supplementary Table S2A, B) [7]. Across all participants, intratrial mean 25(OH)D differed among the groups when stratified by race ($P < 0.001$) and remained lower in Asian and Black compared with White participants. Among participants who were in the lowest BMI category, <30 kg/m^2, intratrial mean (SD) 25(OH)D concentrations for Asian, Black, and White participants were 37.1 (13.7), 37.1 (17.8), and 42.1 (14.7) ng/mL, respectively. In contrast, intratrial mean (SD) 25(OH)D concentrations among Black and White participants in the highest BMI category, ≥40 kg/m^2, were lower at 29.4 (11.4) and 34.0 (14.1) ng/mL compared with the lowest BMI subgroups of the same race, again, with a significant overall trend ($P < 0.001$ for weight groups adjusted for race). There were too few Asian participants in the highest BMI category to be included in this comparison.

Among all of the subgroups analyzed, a higher percentage of participants of White race and a higher percentage of participants in the lower BMI categories achieved an intratrial mean 25(OH)D concentration ≥ 40 ng/mL. Overall, for participants with a BMI <30 kg/m^2, 40% of Asian participants, 40% of Black participants, and 50% of White participants achieved this 25(OH)D concentration, with lower percentages for Black and White participants achieving this concentration with higher BMIs (*n* for Asian participants with BMI ≥35 kg/m^2 was too small) (Table 3). Among the participants with a BMI < 30 kg/m^2 who were randomized to vitamin D, 69% of Asian participants, 67% of Black participants, and 82% of White participants achieved an intratrial mean 25(OH)D concentration ≥ 40 ng/mL, with lower percentages for Black and White participants (47% and 57%, respectively) achieving this concentration with higher BMIs (*n* was too small for Asian participants) (Supplementary Table 2A).

TABLE 1
Baseline characteristics

Characteristic	Race (*n*=2362)		
	Asian (*n*=130)	Black/African American (*n*=616)	White (*n*=1616)
Age, y	55.2 ± 11.1	56.8 ± 9.5	61.7 ± 9.5
Women, no. (%)	46 (35.4)	298 (48.4)	714 (44.2)
Body mass index, kg/m^2	28.2 ± 3.8	32.7 ± 4.5	32.1 ± 4.4
Body mass index, kg/m^2, no. (%)			
<25	22 (16.9)	17 (2.8)	42 (2.6)
25 to <30	69 (53.1)	165 (26.8)	526 (32.5)
30 to <35	31 (23.8)	243 (39.4)	614 (38.0)
35 to <40	6 (4.6)	149 (24.2)	348 (21.5)
≥40	2 (1.5)	42 (6.8)	86 (5.3)
Waist circumference, cm	96.0 ± 11.5	103.8 ± 10.9	106.4 ± 11.7
Women >88 cm, no (%)	33 (71.7)	272 (91.3)	657 (92.0)
Men >102 cm, no (%)	20 (23.8)	178 (56.0)	646 (71.6)
Serum 25(OH)D, ng/mL [mean (SD)][1]	25.9 ± 10.2	24.2 ± 10.9	29.6 ± 9.5
Fasting glucose, mg/dL	107.3 ± 7.1	105.8 ± 7.4	108.8 ± 7.3
2-h postload glucose, mg/dL	140.5 ± 33.7	135.7 ± 32.5	137.7 ± 35.0
HbA1c, %	5.9 ± 0.2	6.0 ± 0.2	5.9 ± 0.2

Plus or minus values are means ± SD. Percentages may not add up to 100 because of rounding off.

[1] To convert 25-hydroxyvitamin D from ng/mL to nmol/L, multiply by 2.496.

The hazard ratios (HRs) for diabetes by race and by intratrial mean 25(OH)D concentrations are shown in Table 4. In both minimally and fully adjusted models, compared with those with 25(OH)D concentrations of 20 to <30 ng/mL, Black and White participants with an intratrial mean 25(OH)D concentration ≥ 40 ng/mL had educed risk of diabetes, with HRs (95% CI) from the fully adjusted models of 0.51 (0.29, 0.92) and 0.42 (0.30, 0.60), respectively. A similar (though statistically nonsignificant) pattern was observed in Asian participants. There was no statistically significant interaction between race and intratrial mean 25(OH)D concentrations on the risk of diabetes.

The HRs for diabetes by BMI category and by intratrial mean 25(OH)D concentrations are shown in Table 5. An intratrial mean 25(OH)D concentration ≥ 40 ng/mL was associated with reduced diabetes risk, and the reduced risk was present in BMI groups <40 kg/m^2. In fully adjusted models, the HRs (95% CI) of diabetes for the lowest to higher BMI groups (groups 1, 2, and 3) who achieved an intratrial mean 25(OH)D concentration ≥ 40 ng/mL were 0.42 (0.26, 0.69), 0.39 (0.25, 0.59), and 0.40 (0.23, 0.69), respectively (Table 5). The HR for diabetes for the highest BMI group (group 4) who achieved an intratrial mean 25(OH)D concentration ≥ 40 ng/mL was not statistically significant. There was no statistically significant interaction between BMI and intratrial mean 25(OH)D concentrations on the risk of diabetes.

In sensitivity analyses, among D2d participants who were randomized to vitamin D, there was a lower risk of diabetes in all race groups for those who achieved an intratrial mean 25(OH)D concentration ≥ 40 ng/mL, but this was statistically significant only among the participants of White race, probably due to sample sizes for the other race groups in this stratified approach (Supplementary Table S3). Among D2d participants who were randomized to vitamin D, there continued to be a statistically significantly lower risk of diabetes among participants with a BMI < 40 kg/m^2 who achieved intratrial mean 25(OH)D concentrations ≥ 40 ng/mL in fully adjusted models (Supplementary Table S4). In sensitivity analyses that considered the waist circumference as a measure of abdominal adiposity, we found similar trends regarding baseline and intratrial mean 25(OH)D concentrations, with women and men with greater waist circumference measures having lower 25(OH)D concentrations (Supplementary Tables S1 and S2A, B). Given this similar pattern with BMI and 25(OH)D concentrations, we did not evaluate the associations between 25(OH)D groups and diabetes risk based on the waist circumference.

Discussion

In this analysis of a subset of the D2d study cohort, we evaluated baseline serum 25(OH)D and intratrial mean 25(OH)D concentrations by self-identified race and BMI, 2 characteristics that are known to influence serum 25(OH)D concentrations; additionally, we determined whether intratrial mean 25(OH)D concentrations impacted diabetes risk similarly in subgroups defined by race and BMI. As expected, we found that, compared with participants of the White race, baseline 25(OH)D concentrations were lower among the participants of Asian and Black races. Intratrial mean 25(OH)D concentrations increased in all 3 groups when stratified by race, but, compared to participants of the White race, remained lower in the participants of Asian and Black races. Similarly, as expected, compared with those with lower BMI, baseline 25(OH)D concentrations were lower among participants in all three groups when stratified by race with higher BMI; however, the differences in 25(OH)D concentrations (both baseline and intratrial mean) between the highest and lowest BMI categories were statistically

TABLE 2
Baseline serum 25(OH)D concentration by race and BMI

Race category	*n* (%)	Mean serum 25(OH)D, ng/mL ± SD[1]	Vitamin D categories, *n* (%)			
			< 20 ng/mL (<50 nmol/L)	20 to <30 ng/mL (50-74 nmol/L)	30 to <40 ng/mL (75-99 nmol/L)	≥ 40 ng/mL (≥100 nmol/L)
Asian	130	25.9 ± 10.2[3]	42 (32.3)	43 (33.1)	32 (24.6)	13 (10.0)[2]
			15.1 ± 3.4	24.7 ± 2.8	33.8 ± 3.0	45.2 ± 6.8
BMI[4], kg/m²						
<25	22 (16.9)	27.8 ± 7.2	5 (22.7)	7 (31.8)	9 (40.9)	1 (4.6)
25 to <30	69 (53.1)	26.1 ± 9.4	21 (30.4)	22 (31.9)	20 (29.0)	6 (4.6)
30 to <35	31 (23.9)	24.8 ± 14.1	14 (45.2)	9 (29.0)	2 (6.5)	6 (19.4)
≥35	8 (6.2)	23.8 ± 5.5	2 (25.0)	5 (62.5)	1 (12.5)	0 (0)
Black	616	24.2 ± 10.9[3]	239 (38.8)	206 (33.4)	116 (18.8)	55 (8.9)[2]
			14.1 ± 3.6	24.4 ± 2.8	34.0 ± 2.7	46.8 ± 7.9
BMI[4], kg/m²						
<30	182 (29.5)	26.3 ± 11.8	64 (35.2)	53 (29.1)	42 (23.1)	23 (12.6)
30 to <35	243 (39.4)	24.3 ± 10.6	87 (35.8)	90 (37.0)	45 (18.5)	21 (8.6)
35 to <40	149 (24.2)	22.1 ± 10.1	66 (44.3)	51 (34.2)	23 (15.4)	9 (6.0)
≥40	42 (6.8)	22.0 ± 8.8	22 (52.4)	12 (28.6)	6 (14.3)	2 (4.8)
White	1616	29.6 ± 9.5[3]	230 (14.2)	605 (37.5)	562 (34.8)	218 (13.5)[2]
			15.4 ± 3.1	25.1 ± 2.9	34.1 ± 2.9	45.7 ± 6.0
BMI[4], kg/m²						
<30	568 (35.2)	31.6 ± 9.9	63 (11.1)	185 (32.6)	214 (37.7)	106 (18.7)
30 to <35	614 (38.0)	29.4 ± 9.2	77 (12.6)	251 (41.0)	213 (34.8)	72 (11.8)
35 to <40	348 (21.5)	27.9 ± 8.9	62 (17.8)	137 (39.4)	114 (32.8)	35 (10.1)
≥40	86 (5.3)	24.9 ± 8.4	28 (32.6)	32 (37.2)	21 (24.4)	5 (5.8)

Plus or minus values are mean ± SD. Percentages may not add up to 100 because of rounding off.
Row percentages add up to 100.
[1] To convert 25-hydroxyvitamin D from ng/mL to nmol/L, multiply by 2.496.
[2] Chi-squared test comparing % of participants of each race group with baseline 25(OH)D ≥ 40 ng/L, $P < 0.01$.
[3] ANOVA test comparing baseline mean 25(OH)D concentrations between all 3 race groups, $P < 0.001$.
[4] Ordinary least square regression $P < 0.001$, significant overall trend pf 25(OH)D concentrations for weight groups adjusted for race.[1]

significant only for those of the White race. Intratrial mean 25(OH)D concentrations increased in participants of all races and BMI categories; generally, compared with lower BMI groups, lower intratrial mean 25(OH)D concentrations were achieved among those with higher BMI.

We found that participants of Black or White race achieving an intratrial mean 25(OH)D concentration of ≥40 ng/mL had similar and significantly reduced risks of diabetes; we found a similar trend among the participants of Asian race, but this did not reach statistical significance, probably due to the smaller sample size. We observed significant reductions in the risk of incident diabetes among participants with a BMI in groups 1, 2, and 3 who achieved an intratrial mean 25(OH)D concentration of ≥40 ng/mL, but we did not find risk reductions among the participants in the highest BMI group 4 achieving similar 25(OH)D concentrations.

Based on this analysis, among people at high risk for diabetes, we found that "optimal" 25(OH)D for reduced diabetes risk was similar for participants of Black or White race and that this "optimal" 25(OH)D was ≥40 ng/mL, which is higher than the 20 or 30 ng/mL target concentrations currently recommended by expert groups and guidelines for the general population. To achieve this "optimal" 25(OH)D concentration, ≥ 40 ng/mL, for diabetes risk, higher doses of vitamin D may be needed for populations that have lower 25(OH)D concentrations. People of color, including people of Asian or Black race, who often have higher melanin content, have lower 25(OH)D concentrations at least in part due to differences in skin production of vitamin D_3. Additionally, differences in lactose intolerance by racial groups can lead to differences in the intake of vitamin D-supplemented foods [35,36]. Studies assessing the effects of different doses of vitamin D on 25(OH)D in participants of Black or White race have demonstrated similar incremental responses [37–39].

People who are overweight and obese have lower 25(OH)D concentrations compared with normal weight individuals, matched for age and race, and have a higher prevalence of vitamin D insufficiency [40]. Although skin pigmentation impacts 25(OH)D concentrations by impacting the synthesis of cutaneous vitamin D, adiposity affects serum 25(OH)D concentrations by different mechanisms. People with overweight/obesity have lower 25(OH)D concentrations compared with people with leaner weight, in part due to a dilutional effect or greater circulating volume [23]. Small studies suggest that serum 25(OH)D may be stored in adipose tissue, resulting in lower circulating concentrations in people with greater adiposity [19]. Another cause of lower circulating 25(OH)D in people with obesity is related to enzymatic mechanisms that convert vitamin D to 25(OH)D, some of which are blunted in obesity, with studies demonstrating a decrease in the expression of the main hepatic vitamin D 25-hydroxylase enzyme in animal models and humans with obesity [21,41]. Studies have also demonstrated that overweight/obese individuals have lower incremental responses in serum 25(OH)D with vitamin D supplementation than people of normal weight [20,24,42,43]. Interestingly, weight loss is associated with small increases in 25(OH)D concentrations, possibly due to reduced circulating volumes, potentially due to a mobilizable adipose tissue pool of vitamin D and/or increased 25-hydroxylase activity in the liver [20,44]. We do not have a clear explanation why there was no significant decrease in diabetes risk among the participants in the highest BMI group (group 4), even with an intratrial mean 25(OH)D concentration over 40 ng/mL. This could be due to the small sample size of this subgroup, or this finding could suggest that the severity of

TABLE 3
Intratrial mean serum 25(OH)D concentration by race and BMI

Race category	*n* (%)	Mean intratrial serum 25(OH)D, ng/mL ± SD[1]	Vitamin D categories, *n* (%)			
			<20 ng/mL (<50 nmol/L)	20 to <30 ng/mL (50-74 nmol/L)	30 to <40 ng/mL (75-99 nmol/L)	≥40 ng/mL (≥100 nmol/L)
Asian	117	35.8 ± 13.8 [3]	16 (13.7)	21 (17.9)	35 (29.9)	45 (38.5)[2]
			14.3 ± 3.5	24.7 ± 2.9	34 ± 2.8	50 ± 7.2
BMI,[4] kg/m²						
<25	21 (17.9)	36.2 ± 12.4	3 (14.3)	3 (14.3)	8 (38.1)	7 (33.3)
25 to <30	64 (54.7)	37.4 ± 14.2	7 (10.9)	10 (15.6)	20 (31.3)	27 (42.2)
30 to <35	28 (23.9)	31.2 ± 13.8	6 (21.4)	8 (28.6)	5 (17.9)	9 (32.1)
≥35	4 (3.4)	40.1 ± 8.8	0 (0)	0 (0)	2 (50.0)	2 (50.0)
Black	530	33.7 ± 16.2[3]	125 (23.6)	121 (22.8)	111 (20.9)	173 (32.6)[2]
			15 ± 3.4	24.8 ± 2.8	34.8 ± 2.6	52.7 ± 10.6
BMI,[4] kg/m²						
<30	161 (30.4)	37.1 ± 17.8	32 (19.9)	33 (20.5)	31 (19.3)	65 (40.4)
30 to <35	208 (39.2)	32.8 ± 15.6	46 (22.1)	57 (27.4)	43 (20.7)	62 (29.8)
35 to <40	124 (23.4)	31.9 ± 15.5	36 (29.0)	22 (17.7)	29 (23.4)	37 (29.8)
≥40	37 (7.0)	29.4 ± 11.4	11 (29.7)	9 (24.3)	8 (21.6)	9 (24.3)
White	1455	39.2 ± 14.4[3]	100 (6.9)	302 (20.8)	424 (29.1)	629 (43.2)[2]
			16 ± 3	25.5 ± 2.9	34.6 ± 2.9	52.6 ± 10
BMI,[4] kg/m²						
<30	519 (35.7)	42.1 ± 14.7	19 (3.7)	89 (17.1)	153 (29.5)	258 (49.7)
30 to <35	546 (37.5)	39.2 ± 14.0	27 (4.9)	129 (23.6)	154 (28.2)	236 (43.2)
35 to <40	314 (21.6)	36.0 ± 13.7	37 (11.8)	71 (22.6)	95 (30.3)	111 (35.4)
≥40	76 (5.2)	34.0 ± 14.1	17 (22.4)	13 (17.1)	22 (28.9)	24 (31.6)

Plus or minus values are mean ± SD. Percentages may not add up to 100 because of rounding off.
Row percentages add up to 100.
[1] To convert 25-hydroxyvitamin D from ng/mL to nmol/L, multiply by 2.496.
[2] Chi-squared test comparing % of participants of each race group achieving an intratrial mean 25(OH)D ≥ 40 ng/L, $P < 0.01$.
[3] ANOVA test comparing intratrial mean 25(OH)D concentrations between all 3 race groups, $P < 0.001$.
[4] Ordinary least square regression $P < 0.001$, significant overall trend pf 25(OH)D concentrations for weight groups adjusted for race.

adiposity and associated pathophysiologic pathways (eg, insulin resistance, inflammation, or lipotoxicity) might override putative beneficial pathways conferred by optimal vitamin D concentrations. Further studies in a larger sample size are needed for populations with higher BMIs, eg, ≥40 kg/m², to determine whether a more aggressive supplementation that attains even higher concentrations of 25(OH)D would decrease diabetes risk without untoward effects.

This study has limitations. One limitation is that our study relies on the premise that people of self-reported Asian or Black race have more melanin in their skin compared with those of self-reported White race; however, we recognize that this is not always the case. Another limitation is the small sample sizes of participants of Asian race, as well as participants with a BMI in the highest weight categories. Additionally, given the overall sample size, we were not able to stratify groups further to determine if achieving a concentration of 25(OH)D higher than 40 ng/mL was more beneficial. Moreover, we do not have data on modulators of vitamin D metabolism, including parathyroid hormone concentrations that may exhibit individual variability and impact

TABLE 4
Hazard ratios for diabetes by race and intratrial mean 25(OH)D concentration

Race category	Intratrial mean 25(OH)D concentrations			
	<20 ng/mL (<50 nmol/L)	20 to <30 ng/mL (50-74 nmol/L)	30 to <40 ng/mL (75-99 nmol/L)	≥40 ng/mL (≥100 nmol/L)
Asian				
N	16	21	35	45
Minimally adj model[1]	1.17 (0.36, 3.77)	Reference	0.68 (0.24, 1.90)	0.41 (0.15, 1.12)
Fully adj model[2]	1.53 (0.47, 4.96)	Reference	0.70 (0.25, 1.98)	0.39 (0.14, 1.11)
Black				
N	125	121	111	173
Minimally adj model[1]	1.41 (0.81, 2.46)	Reference	1.04 (0.58, 1.87)	0.53 (0.30, 0.94)*
Fully adj model[2]	1.41 (0.80, 2.49)	Reference	0.94 (0.52, 1.72)	0.51 (0.29, 0.92)*
White				
n	100	302	424	629
Minimally adj model[1]	1.21 (0.79, 1.85)	Reference	0.98 (0.73, 1.30)	0.42 (0.30, 0.59)*
Fully adj model[2]	1.08 (0.70, 1.66)	Reference	0.96 (0.72, 1.28)	0.42 (0.30, 0.60)*

* Indicates significantly different as compared to reference range.
[1] Minimally adjusted model adjusted for randomization; interaction $P = 0.975$; continuous model interaction $P = 0.68$.
[2] Fully adjusted model adjusted for randomization, BMI (continuous), gender, age, physical activity, statin use; interaction $P = 0.927$.

TABLE 5
Hazard ratios for diabetes by BMI and intratrial mean 25(OH)D concentration

BMI category	Intratrial mean 25(OH)D concentrations			
	<20 ng/mL (<50 nmol/L)	20 to <30 ng/mL (50–74 nmol/L)	30 to <40 ng/mL (75–99 nmol/L)	≥40 ng/mL (≥100 nmol/L)
Group 1				
N	54	125	192	330
Minimally adj model[1]	0.93 (0.46, 1.87)	Reference	1.00 (0.62, 1.60)	0.50 (0.31, 0.81)*
Fully adj model[2]	0.94 (0.45, 1.96)	Reference	0.89 (0.55, 1.45)	0.42 (0.26, 0.69)*
Group 2				
N	80	196	217	325
Minimally adj model[1]	1.25 (0.76, 2.05)	Reference	0.97 (0.66, 1.42)	0.43 (0.28, 0.66)*
Fully adj model[2]	1.54 (0.92, 2.56)	Reference	0.89 (0.61, 1.30)	0.39 (0.25, 0.59)*
Group 3				
N	79	101	129	157
Minimally adj model[1]	1.05 (0.60, 1.82)	Reference	1.03 (0.64, 1.66)	0.46 (0.27, 0.79)*
Fully adj model[2]	1.13 (0.65, 1.98)	Reference	0.97 (0.60, 1.58)	0.40 (0.23, 0.69)*
Group 4				
n	28	22	32	35
Minimally adj model[1]	2.75 (0.68, 11.15)	Reference	2.33 (0.59, 9.18)	1.76 (0.46, 6.75)
Fully adj model[2]	2.39 (0.59, 9.74)	Reference	1.85 (0.47, 7.28)	1.42 (0.37, 5.45)

Group 1: Black, White <30 kg/m^2, Asian <25 kg/m^2; Group 2: Black, White 30 to <35 kg/m^2, Asian 25 to <30 kg/m^2; Group 3: Black, White 35 to <40 kg/m^2, Asian 30 to <35 kg/m^2; Group 4: Black, White ≥ 40 kg/m^2, Asian ≥ 35 kg/m^2.

* Indicates significantly different as compared to reference range.

[1] Minimally adjusted model adjusted for randomization; interaction $P = 0.832$; continuous model interaction $P = 0.80$.

[2] Fully adjusted models adjusted for randomization, race, gender, age, physical activity, statin use; interaction $P = 0.754$.

diabetes risk. Finally, our study does not provide explanatory mechanisms related specifically to beta-cell function or insulin sensitivity for the observed association of higher intratrial mean 25(OH)D and lower diabetes risk.

The strengths of this study include the study population, which was diverse by race and weight status; as well as the dose of vitamin D_3, 4000 IU daily, which was higher than other large vitamin D trials and resulted in large differences in 25(OH)D concentrations, with a significant proportion of the study population achieving a 25(OH)D concentration that was found to be beneficial for diabetes risk. Additional strengths include the use of the gold standard assay for 25(OH)D, standardized to the National Institute of Standards and Technology, use of the latest ADA glycemic criteria to define prediabetes and diabetes, and ascertainment for diabetes at regular intervals by blood glucose testing using a central laboratory, with the majority of cases of diabetes diagnosed by these laboratory-based criteria [6].

In conclusion, we found that participants of the Asian or Black race and participants with higher BMI have lower baseline and intratrial mean 25(OH)D concentrations compared with participants of White race and participants with lower BMI. We found that, among people with prediabetes, a lower percentage of participants of Asian or Black race and in the higher BMI categories, compared with participants of White race and participants in the lower BMI categories, were able to achieve an intratrial mean 25(OH)D concentration of ≥40 ng/mL. These findings are consistent with our knowledge regarding vitamin D synthesis, storage, and metabolism, which differ by race and weight. Additionally, we found that participants of Black or White race with a BMI < 40 kg/m^2 who did achieve an intratrial mean 25(OH)D concentration ≥ 40 ng/mL experienced a significantly lower risk of diabetes. Taken together, our findings suggest that the optimal 25(OH)D concentration for diabetes prevention may be higher than currently accepted "sufficient" concentrations for the general healthy population; that the "optimal" dose of vitamin D may need to be tailored to achieve this optimal 25(OH)D concentration; and that the "optimal" dose of vitamin D supplementation may be higher than the conventionally recommended daily allowances, particularly for some higher-risk populations, if the goal is diabetes prevention.

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Author contributions

The author responsibilities were as follows—RC, SDJ, CAD, EMV, KCJ, SRK, ESL, JN, AGP, and BDH: designed research; JN and EMV: analyzed data and performed statistical analyses; RC: wrote the first draft of the manuscript and has primary responsibility for the final content; and all authors: read and approved the final manuscript.

Conflict of interest

The authors report no potential conflicts of interest.

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Data availability

Data described in the manuscript, code book, and analytic code are not publicly available but will be made available from the D2d Coordinating Center at Tufts Medical Center on reasonable request. Protocol synopsis, contact details, publications, and the process for collaboration and data requests can be found on the website (d2dstudy.org).

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ajcnut.2023.03.021.

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