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Plasma 25-hydroxyvitamin D and risk of metabolic syndrome: an ancillary analysis in the Diabetes Prevention Program

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Abstract

Background/Objectives—Low blood levels of 25-hydroxyvitamin D (25OHD) have been associated with cardiometabolic disease but results are inconsistent. The objective of the study was to investigate the association of 25OHD with metabolic syndrome in a population at increased risk for diabetes.

Subjects/Methods—Using baseline data from the placebo and lifestyle intervention arms of the Diabetes Prevention Program (DPP) (N=2000), multivariable logistic regression models were used to estimate the odds of prevalent metabolic syndrome and each of its individual components across 25OHD tertiles. Multivariable linear regression was used to estimate the adjusted mean difference of insulin secretion and sensitivity across the same 25OHD tertiles. In participants free of metabolic syndrome at baseline (N=546), incident metabolic syndrome in the first two years of follow-up was assessed using discrete-time proportional hazards regression to test its association with 25OHD concentration.

Results—After multivariate adjustment, participants in the highest tertile of 25OHD had lower odds of prevalent metabolic syndrome (odds ratio 0.62; 95%CI 0.45-0.84), smaller waist circumference, higher high-density lipoprotein, and lower fasting plasma glucose compared to participants in the lowest tertile of 25OHD. Higher plasma 25OHD concentration was associated with greater insulin sensitivity and lower insulin secretion. After multivariate adjustment, there

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was a non-significant lower risk of metabolic syndrome in the highest tertile of 25OHD (hazard ratio 0.79; 95% CI, 0.48-1.32) compared to the lowest tertile.

Conclusion—In a population at increased risk for diabetes, higher plasma 25OHD concentration was inversely associated with prevalent metabolic syndrome and non-significantly with incident metabolic syndrome.

Keywords

metabolic syndrome; vitamin D

INTRODUCTION

A growing body of evidence suggests that low 25-hydroxyvitamin D (25OHD) concentration is associated with cardiometabolic disease.[1-3] The apparent link may be explained by vitamin D modifying cardiovascular disease risk factors, such as metabolic syndrome and each of its individual components.

Recent studies have reported on the association between vitamin D status and metabolic syndrome and its individual components. While some studies showed an inverse association between vitamin D and metabolic syndrome, other studies have failed to show this association. [4-13] The lack of concordance is likely secondary to lack of adjustment for important potential confounders such as adiposity, race/ethnicity, systemic inflammation and kidney function. It is well established that adiposity and insulin resistance play a pivotal role in the pathogenesis of metabolic syndrome. However, studies in overweight and obese populations have not consistently shown an inverse association between vitamin D concentration and metabolic syndrome.[10, 13-15] Furthermore, while there are well-recognized differences in vitamin D metabolism among different race/ethnic groups,[16] most of the literature on vitamin D and metabolic syndrome in non-white populations come from studies in Asians.[3] Prior studies have not examined the association between vitamin D status and metabolic syndrome in specific multiethnic populations identified as being at increased risk for diabetes and cardiovascular disease.

The purpose of the present study was to examine the association between plasma 25OHD concentration and prevalent metabolic syndrome and its traditional and non-traditional components, and risk of developing metabolic syndrome in the Diabetes Prevention Program (DPP), which represents a large multiethnic sample of U.S. adults with pre-diabetes.

MATERIAL AND METHODS

Study Participants

The DPP was a randomized controlled clinical trial conducted from 1996 to 2001 at 27 sites in the U.S. that compared the effects of intensive lifestyle intervention, metformin, or placebo on the development of diabetes in adults at high risk for the disease. The eligibility criteria, design, and methods of the DPP have been described in detail elsewhere.[17] Briefly, inclusion criteria included age ≥25 years, body mass index (body mass index) ≥24 kg/m^2

(≥22 kg/m^2 in Asian Americans), fasting plasma glucose 5.3 to 6.9 mmol/L (95 to 125 mg/dL) (≤6.9 mmol/L for American Indian sites) and a 2-hour plasma glucose 7.8 to 11 mmol/L (140 to 199 mg/dL) after a 75-gram oral glucose tolerance test. The Institutional Review Board at each site approved the protocol and all participants gave written informed consent. The present study was approved by the Tufts University Institutional Review Board.

The present observational study was conducted among participants randomized to two arms, the intensive lifestyle (n=1,079) and placebo (standard lifestyle, n=1,082). The metformin arm of the DPP was excluded to minimize the cost associated with measurement of plasma 25OHD. One hundred and twenty-two participants were also excluded because of lack of consent for ancillary studies (n=120) or no available specimen for measurement of 25OHD (n=2) or other covariates (n=9). After exclusions, 2,000 participants had data available for the unadjusted cross-sectional analyses and 1,959 had complete data for all covariates used in the multivariate analyses. For the prospective analysis of incident metabolic syndrome, 578 participants were free of the condition at baseline and 546 had available data on 25OHD and metabolic syndrome during the first two years of the study (32 developed diabetes or were lost to follow-up).

Measurement of plasma 25OHD concentration

Plasma 25OHD concentration was measured in baseline samples stored since collection at −70°C. Stability of vitamin D metabolites during transport and long-term freezing has been documented previously.[18] Plasma 25OHD was measured at the Metabolic Laboratory at Tufts Medical Center by liquid chromatography, tandem mass spectrometry (LC/MS/MS) (Waters Acquity UPLC with TQD triple quadrupole mass spectrometer), certified through the National Institute of Standards and Technology (NIST) vitamin D quality assurance program. In the most recent testing, correlation with the NIST external standard for total 25-hydroxyvitamin D was r^2=0.994.

Metabolic Syndrome, traditional components

Metabolic syndrome was defined according to the modified criteria from the National Cholesterol Education Program's Adult Treatment Panel III (NCEP ATP III)[19] based on the presence of three or more of the following five criteria: 1) central obesity: waist circumference ≥102 cm (men), ≥88 cm (women); 2) triglycerides ≥150 mg/dl, 3) high density lipoprotein (HDL) <40 mg/dL (men), <50 mg/dL (women); 4) systolic blood pressure ≥130 mm Hg and/or diastolic blood pressure ≥85 mm Hg or current antihypertensive drug treatment in a patient with a history of hypertension; and 5) fasting plasma glucose ≥100 mg/dL. We also repeated the analyses with the higher threshold of glucose (≥110 mg/dL) used in the original definition of metabolic syndrome.

Metabolic Syndrome, Non-traditional (non-ATP III) components

Two measures of insulin secretion[20] and two measures of insulin sensitivity[21] were calculated as previously described in the DPP cohort.[22] Glucose and insulin are expressed as mg/dL and μU/mL, respectively, unless otherwise specified. Insulin secretion was estimated as: insulinogenic index (IGI)), (insulin at 30 minutes – insulin at 0 minutes) ÷ (glucose at 30

minutes – glucose at 0 minutes); the corrected insulin response (CIR), calculated as follows: (100 × insulin at 30 minutes) ÷ (glucose at 30 minutes × [glucose at 30 minutes – 70 mg/dL]). Insulin sensitivity was estimated as: 1÷fasting insulin; the insulin-sensitivity index (ISI), which is the reciprocal of insulin resistance according to the homeostasis model assessment and is calculated by the following equation: 22.5 ÷ (fasting insulin × [fasting glucose ÷ 18.01]). Both measures of insulin secretion strongly correlate with each other, as do both measures of insulin sensitivity.[22] The oral disposition index (DI), was calculated by two methods: DI_1=IGI × (1/fasting insulin) and DI_2= CIR × ISI.[23]

Assessment of Potential Confounders and Laboratory Assessment

At baseline, self-reported level of leisure physical activity was assessed with the Modifiable Activity Questionnaire.[24] Usual daily nutrient intake was assessed with the use of a modified version of the Block food-frequency questionnaire.[25] Data on vitamin D intake were not available. Standardized interviewer-administered questionnaires were used to obtain self-reported data on personal medical history, smoking, medications, alcohol use, and family medical history. Self-reported race/ethnicity was classified according to the 1990 U.S. Census questionnaire. Weight and height were measured using standard calibrated scale and stadiometer, respectively and body mass index was calculated (Kg/m^2). Fasting blood was obtained and processed following standardized procedures. Measurement methods for glucose and C-reactive protein have been described previously.[17] A yearly ultraviolet index for each site based on the National Weather Service data on the monthly means of ultraviolet index for each geographic location in 1997 was constructed.

Statistical Analysis

Descriptive statistics for 25OHD, outcomes of interest and each of the covariates were conducted. Variable distributions were assessed for potential violations of statistical assumptions and residual analyses were performed to identify violations and influential observations. Data transformations and non-parametric methods were performed when necessary. Characteristics of the study sample are presented by metabolic syndrome status and compared using two sample t-tests or Wilcoxon rank-sum tests for continuous variables where appropriate and chi-square tests for categorical variables. Multivariable logistic regression models were used to estimate the odds and 95% confidence interval of prevalent metabolic syndrome and each of its individual components by tertiles of 25OHD, after adjusting for potential confounders. Multivariable linear regression models were used to estimate the adjusted average differences in non-traditional metabolic syndrome components (insulin secretion and sensitivity) between 25OHD tertiles. In multivariable logistic and linear regression models, we adjusted for DPP clinical site location, month of blood draw, age, gender, race, ultraviolet radiation index at participant's recruitment location, smoking status, alcohol consumption, C-reactive protein, self-reported physical activity, total energy intake and BMI. We assessed the association between 25OHD concentration with the number of metabolic syndrome components using the Spearman correlation coefficient.

For ease of interpretation, we define differences in 25OHD concentration between participants categorized into three groups using tertiles (33.3^{rd} and 66.7^{th} percentiles) of baseline 25OHD concentration. Tests of linear trend across increasing groups were

performed by modeling the median of each 25OHD tertile group as a continuous variable. The lowest tertile class is used as the referent group. The odds of metabolic syndrome and its individual components in each of the higher groups is compared with the referent by extrapolating the per unit change in estimated odds from the multivariate model. Similarly, the adjusted average difference of each continuous variable from the multivariate model is used to compare the highest two groups to the referent lowest group by extrapolating the per unit change from the multivariate model. Age, gender, race and month of blood draw were forced into all models. We accounted for clustering at sites using generalized estimating equation (GEE) models for correlated data.

For the prospective analysis, discrete-time proportional hazards models were used to assess the association between plasma 25OHD (by baseline defined tertile groups) and incident metabolic syndrome to account for interval-censored data. Participants who developed diabetes prior to an incident metabolic syndrome assessment were censored to account for competing risks. In multivariable models, we adjusted for similar potential confounders adjusted for in the cross-sectional. To account for additional unmeasured effects of intervention, we also adjusted for treatment assignment.

The predictor (25OHD) and other variables (physical activity and body weight) whose values were measured at multiple time points entered the prospective analyses as time-varying “lagged” covariates. At each successive annual visit when the outcome (metabolic syndrome) was assessed, the value of these variables was calculated as the mean of the current and previous non-missing value prior to that visit. For the time-varying variables, if either the current or most recent value was missing, we imputed values using the non-missing observation (current or most recent). If both current and most recent values were missing, then no value was imputed. Covariates measured only at baseline and year 1 visits (alcohol consumption, CRP, and total energy intake) were treated as time-invariant predictors by calculating the mean of the baseline and year 1 values. Tests of linear trend across increasing groups were performed by modeling the median of each 25OHD tertile group as a continuous variable and the risk of metabolic syndrome in each of the highest two groups was compared with the lowest group by extrapolating the per unit change in estimated hazard from the multivariable model.

We investigated the following possible effect modifiers on the associations of 25OHD with prevalent metabolic syndrome: baseline age, gender, race/ethnicity, and baseline body weight. We checked for the statistical significance of the interaction by using Wald chi-square tests. Tests for interactions were not conducted in the prospective analyses, due to the small number in each subgroup. All p-values are based on two-sided tests. Statistical analyses were performed using SAS version 9.2 (SAS, Cary, NC).

RESULTS

The mean age of the cohort was 51 years with 67% being women (table 1). The racial/ethnic distribution was diverse with 57% self-reported Whites and 20% self-reported African Americans. Participants with metabolic syndrome were younger, were more likely to be

smokers, reported lower alcohol consumption, were less likely to be physically active, had higher CRP and were more likely to live in areas with high ultraviolet index.

Association between plasma 25OHD concentration and prevalent metabolic syndrome

The overall prevalence of metabolic syndrome in the cohort was 71%. This number is higher compared to the previously reported prevalence of metabolic syndrome in the entire DPP cohort,[26] because the previous publication used the higher glucose criterion of 110 mg/dL. When participants were categorized into tertiles of 25OHD, the prevalence of metabolic syndrome was 76%, 72% and 66% in the lower, middle and higher vitamin D tertiles, respectively (Table 2). There was a 50% lower odds of metabolic syndrome (OR 0.50; 95% CI 0.38 to 0.65) in the highest tertile of 25OHD concentration (median [interquartile range] 25OHD 30.6 [27.5-34.9] ng/mL) compared to the lowest tertile (12.1 [9.7-14.3] ng/mL) after adjusting for location, month of blood draw, age, gender and race (Table 2). Further adjustments for average yearly ultraviolet radiation index at participant's study site, smoking status, alcohol consumption, C-reactive protein, self-reported physical activity, and total energy intake, did not change the association (OR 0.49; 95% CI 0.36 to 0.67). Further adjustment for BMI attenuated the association but it remained significant (OR 0.62; 95% CI 0.45 to 0.84). After repeating the analyses using the higher cutoff for glucose (110 mg/dL), results were unchanged (data not shown).

Association between plasma 25OHD concentration and individual metabolic syndrome components

There was a small but statistically significant inverse association between 25OHD concentration and the number of metabolic syndrome components (Spearman correlation coefficient, $r=-0.11$, $p<0.0001$) (Figure 1). There was a significant inverse linear trend in the multivariate adjusted odds of metabolic syndrome across increasing tertiles of 25OHD for three components of metabolic syndrome, larger waist circumference, higher fasting plasma glucose and lower HDL cholesterol (Table 2). There was no statistically significant difference in the prevalence of high triglyceride concentration or high blood pressure according to 25OHD tertiles; however the odds ratios were in the same direction as other components.

Association between plasma 25OHD concentration and insulin sensitivity and insulin secretion

Insulin sensitivity significantly increased across tertiles of 25OHD (adjusted average difference 0.143; 95% CI 0.081 to 0.212) (Table 4). Conversely, insulinogenic index decreased across 25OHD tertiles (adjusted average difference −0.098; 95%CI −0.158 to −0.025). The disposition indices increased across 25OHD tertiles, although only the DI_1 was statistically significantly different (adjusted average difference 0.348; 95% CI 0.089 to 0.607).

Subgroup Analyses

The inverse associations between 25OHD concentration and metabolic syndrome were generally consistent across all subgroups (Table 5) and did not differ by age, gender or race.

The association between 25OHD and metabolic syndrome appeared to be stronger among non-obese versus obese. However, the study was not powered to assess the significance of the association across subgroups and the tests for interaction were not statistically significant for any of these factors (Table 5, p for interactions >0.05).

Association between plasma 25OHD concentration and incident metabolic syndrome

In the prospective analysis, after multivariate adjustment including treatment arm, participants in the highest tertile of 25OHD (median 25OHD 31 ng/mL) had a non-significant lower risk for developing metabolic syndrome (HR 0.79; 95% CI, 0.48 to 1.32) compared to participants in the lowest tertile (median 25OHD 12.3 ng/mL) (Table 3). After adjusting further for change in body weight, the direction of the association remained the same (HR 0.83; 95%CI 0.50, 1.39).

DISCUSSION

In a large multiethnic population at increased risk for diabetes, plasma 25OHD concentration was inversely associated with prevalence of metabolic syndrome and risk of developing metabolic syndrome although the latter association lost statistical significance after multivariate adjustment. The prevalence of larger waist circumference, lower HDL-cholesterol and higher fasting plasma glucose was lower with increasing 25OHD levels. Although the difference in mean 25OHD between those with and those without metabolic syndrome did not appear to be large, increasing 25OHD concentration was associated with lower prevalence of metabolic syndrome, especially when comparing those in the highest tertile (mean 30.6 ng/mL) vs. the lowest quartile (12.1 ng/mL) of 25OHD concentration. Insulin sensitivity was greater and insulin secretion was lower with increasing levels of 25OHD.

The biological mechanisms by which vitamin D may influence cardiometabolic risk factors have not been completely elucidated. There is a growing body of evidence suggesting that vitamin D plays a role in insulin resistance, which is generally regarded as the central mechanism for metabolic syndrome.[27] On the other hand, insulin secretion is central to development of hyperglycemia. Vitamin D may enhance insulin sensitivity in several ways, including increasing the expression of insulin receptors,[28] activating transcription factors important in glucose homeostasis[29] or indirectly via regulating calcium, which is essential for insulin-mediated intracellular processes. *In vivo and in vitro* studies have also shown an effect of vitamin D on insulin secretion.[30-32] The effect on beta cell function is likely mediated by binding of the active form, $1,25(OH)_2D$, to vitamin D receptor, which is expressed in beta cells[33] or by the activation of vitamin D which may occur within the beta cell by the 25-OHD-1α-hydroxylase (CYP27B1), which is expressed in beta cells.[34] Vitamin D can also affect beta-cell function indirectly via calcium regulation, which in turn affects insulin secretion, a calcium-dependent process.[35]

Our results from the cross-sectional analysis are consistent with, and build on, the results of other studies.[3, 7, 9-11, 36-39] Based on data from the third National Health and Nutrition Examination Survey (NHANES III),[9] 25OHD concentration was inversely associated with metabolic syndrome but not after adjustment for BMI. In contrast, our results remained

significant after adjustment for BMI suggesting that the relationship between vitamin D and metabolic syndrome is independent of obesity. More recently, Reis et al showed an inverse association between vitamin D and metabolic syndrome in the NHANES; however, the study was limited by the inability to account for the season in which blood samples were obtained.[36] The same authors had previously failed to show this association between vitamin D and metabolic syndrome in the Rancho-Bernardo study, which included US residents from southern California, which may – at least in part – be attributed to generally higher vitamin D levels.[12] The mean level of vitamin D in the current study was 21.6 ng/mL, which is about 50% lower than the mean levels among participants from the Rancho Bernardo study. It is possible that there is a threshold or range for the association between vitamin D and metabolic syndrome.

Results from other prospective observational studies on 25OHD and incident metabolic syndrome are inconsistent. Forouhi et al. found that higher baseline 25OHD was associated with lower metabolic syndrome risk after 10 years of follow-up; however the association lost significant after multivariate adjustment, similarly to our results.[40] On the other hand, Gagnon et al. found an inverse association between vitamin D and metabolic syndrome, where the incidence of metabolic syndrome was higher in the lowest vitamin D quintile (25OHD < 18ng/mL) compared to the highest quintile (25OHD ≥ 34 ng/mL), (OR 1.41; 95%CI 1.02-1.95).[41] Our results showed an inverse association, which was non-statistically significant possibly due to inadequate statistical power and also the fact that the DPP study included an intervention known to improve many of the components of metabolic syndrome.

There are well-recognized differences in vitamin D metabolism among different race/ethnic groups; [16] In our study, the observed cross-sectional association did not differ by race, as a proxy for altered vitamin D homeostasis in persons with dark skin,[42] suggesting that in persons at high risk for diabetes, vitamin D may be important in modulating cardiometabolic risk independent of race/ethnicity. However, it is important to note that our study was not powered to test for differences in ethnic groups.

The complementary changes in insulin sensitivity and insulin secretion are in line with some observational studies that have reported an association between vitamin D status and insulin sensitivity.[40, 43-45] However, previous studies assessing the association between 25OHD and beta cell function have yielded inconsistent results.[38, 46] This is likely secondary to use of different measures of beta-cell function and lack of concurrent adjustment for insulin resistance. In the present study, disposition index, a measure of insulin secretion that accounts for the prevailing insulin sensitivity, and a validated predictor of diabetes risk, increased across 25OHD tertiles indicating improved beta cell function among participants with higher 25OHD concentration. These results are consistent with our previous findings in the DPP cohort, where higher 25OHD concentration was associated with a lower rate of progression to type 2 diabetes.[47]

Our study has a number of strengths. Primarily, we used data from a large multiethnic sample reflecting the diversity of the U.S. population with pre-diabetes. Our analyses took into account many potential covariates that might confound the observed association and we used validated measurements of the exposure and outcome variables and covariates;

nevertheless, residual confounding remains a potential limitation. Additionally, in the cross-sectional analysis, the potential of reverse causation cannot be ruled out. And since the study is observational, we refrain from making any from statements about optimal 25OHD concentration. In the prospective analysis, the lack of significant inverse association between 25OHD and metabolic syndrome could be attributed to the lack of power. Finally, the use of a single 25OHD measurement may not capture overall vitamin D status due to geographical and seasonal variation;[48] however, our analyses adjusted for recruitment location and month of blood collection and in addition we have used the mean of repeated measures of 25OHD for the prospective analysis.

In conclusion, higher plasma 25OHD concentration was associated with a lower prevalence of metabolic syndrome among persons at increased high risk of diabetes and a lower, but non-statistically significant, risk of incident metabolic syndrome. A causal relationship needs to be established in randomized trials of vitamin D supplementation in high-risk populations.

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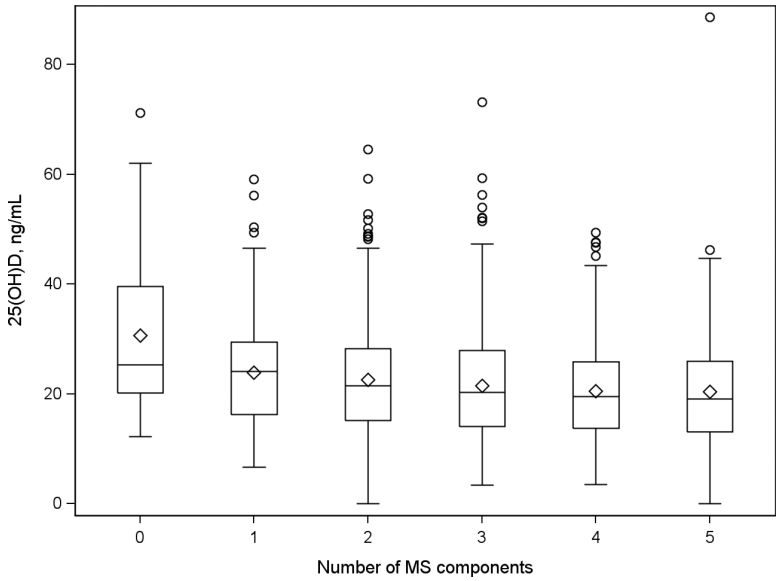

Figure 1.

Cross-sectional association between 25-hydroxyvitamin D (25OHD) and the number of metabolic syndrome components.

Table 1

Baseline characteristics of the Diabetes Prevention Program population by metabolic syndrome status

Characteristic	Overall cohort	Metabolic syndrome absent	Metabolic syndrome present	P-value[1]
Number of participants	2000	578	1422	
Age, mean (SD), years	51.0 (10.8)	51.8 (11.5)	50.7 (10.6)	0.0392
Gender, No. (%) women	1337 (66.9)	379 (65.6)	958 (67.4)	0.4385
Race, No. (%)				
White	1142 (57.1)	313 (54.2)	829 (58.3)	0.0091
African-American	405 (20.3)	142 (24.6)	263 (18.5)	
Other (Hispanic, Asian, American Indian)	453 (22.7)	123 (21.3)	330 (23.2)	
Weight, mean (SD), kg	94.5 (20.5)	86.2 (18.6)	97.9 (20.3)	<0.0001
Body mass index, mean (SD), kg/m^2	34.0 (6.7)	31.3 (6.1)	35.1 (6.7)	<0.0001
Waist circumference, mean (SD), cm	105.1 (14.7)	97.6 (13.3)	108.1 (14.1)	<0.0001
Annual UV index, mean (SD), 90J/m2/hour [2]	4.6 (1.4)	4.5 (1.3)	4.7 (1.4)	0.0135
Hypertension, No. (%) [3]	975 (48.8)	131 (22.7)	844 (59.4)	<0.0001
Physical Activity, mean (SD), MET-hours [4]	15.9 (25.6)	17.4 (22.2)	15.2 (26.9)	0.0004
Smoking status, No. (%)				
Never	1145 (57.3)	333 (57.6)	812 (57.1)	0.0085
Past	715 (35.8)	220 (38.1)	495 (34.8)	
Current	140 (7.0)	25 (4.3)	115 (8.1)	
Alcohol consumption, mean (SD), g/day	2.2 (5.6)	2.6 (6.1)	2.1 (5.4)	0.0050
Total energy intake, mean (SD), kcal/d	2091.0 (1027.8)	1978.7 (946.5)	2136.6 (1056.0)	0.0009
Calcium intake, mean (SD), mg/day	1102.2 (724.3)	1086.2 (681.4)	1108.7 (741.2)	0.7559
Systolic blood pressure, mean (SD), mmHg	124.0 (14.6)	118.5 (13.3)	126.3 (14.5)	<0.0001
Diastolic blood pressure, mean (SD), mmHg	78.4 (9.1)	75.2 (7.8)	79.7 (9.3)	<0.0001
Fasting plasma glucose, mean (SD), mg/dL	106.8 (8.1)	104.3 (8.4)	107.8 (7.7)	<0.0001
Fasting insulin, mean (SD), μU/mL	26.4 (15.1)	20.2 (10.7)	28.9 (15.9)	<0.0001
Insulin Sensitivity				
Insulin sensitivity, mean (SD), $(\mu U/mL)^{-1}$	0.05 (0.03)	0.06 (0.04)	0.05 (0.03)	<0.0001
Insulin sensitivity index (ISI), mean (SD), $[(\mu nU/mL)^{*}(mg/dL)]^{-1}$	0.20 (0.14)	0.25 (0.16)	0.18 (0.12)	<0.0001
Insulin Secretion				
Insulinogenic Index (IGI), mean (SD), (μU/mL)/(mg/dL)	1.22 (0.88)	1.12 (0.87)	1.26 (0.89)	<0.0001
Corrected insulin response (CIR), mean (SD), $[(\mu U/mL)/(mg/dL)^2]$	0.62 (0.40)	0.57 (0.41)	0.64 (0.40)	<0.0001
Disposition Indices (DI)				
DI 1: IGI * Insulin sensitivity, mean (SD)	0.05 (0.04)	0.06 (0.05)	0.05 (0.04)	<0.0001

Characteristic	Overall cohort	Metabolic syndrome absent	Metabolic syndrome present	P-value[1]
DI 2: CIR * ISI, mean (SD)	0.10 (0.07)	0.12 (0.08)	0.10 (0.07)	<0.0001
Total Cholesterol, mean (SD), mg/dL	204.5 (36.2)	204.5 (35.8)	204.5 (36.4)	0.9882
Triglycerides, mean (SD), mg/dL	165.6 (95.4)	113.0 (48.8)	186.8 (101.3)	<0.0001
HDL cholesterol, mean (SD), mg/dL	45.5 (12.1)	54.0 (12.2)	42.1 (10.2)	<0.0001
LDL cholesterol, mean (SD), mg/dL	125.6 (32.8)	127.4 (32.7)	124.9 (32.9)	0.1250
C-reactive protein, mean (SD), mg/L	5.8 (6.9)	5.0 (7.3)	6.1 (6.7)	<0.0001
25-hydroxyvitamin D, mean (SD), ng/mL	21.6 (9.7)	23.2 (10.3)	20.9 (9.4)	<0.0001

Values are means (standard deviation) for continuous variables or n (%) for categorical variables. To convert plasma 25OHD concentration from ng/mL to nmol/L multiply by 2.459; to convert triglycerides from mg/dL to mmol/L multiply by 0.0113; to convert glucose from mg/dL to mmol/L multiply by 0.0555; to convert cholesterol from mg/dL to mmol/L multiply by 0.0259.

[1] P values for differences between metabolic syndrome status (present vs. absent) for continuous variables are based on t-tests. For categorical variables, the p value is based on chi-square tests.

[2] Average ultraviolet index at participants' clinical site.

[3] Hypertension defined as blood pressure ≥ 130/85 mmHg or the use of antihypertensive medication.

[4] MET denotes metabolic equivalent. MET-hours represent the average amount of 588 time engaged in specified physical activities multiplied by the MET value of each activity.

Table 2

Adjusted odds ratios (OR) of prevalent metabolic syndrome and its components by tertiles of plasma 25-hydroxyvitamin D concentration in the lifestyle and placebo arms of the Diabetes Prevention Program population.

	Metabolic syndrome	Metabolic syndrome components				
		Large waist circumference	High blood pressure	High triglycerides	High fasting plasma glucose	Low HDL cholesterol
25OHD concentration*	**Prevalence (n/N)**	**Prevalence (n/N)**	**Prevalence (n/N)**	**Prevalence (n/N)**	**Prevalence (n/N)**	**Prevalence (n/N)**
1st tertile	75.7 (504/666)	86.8 (577/665)	48.8 (325/666)	40.2 (267/664)	85.6 (570/666)	62.8 (417/664)
2nd tertile	71.5 (477/667)	79.5 (530/667)	51.1 (341/667)	49.3 (328/666)	81.0 (540/667)	57.7 (384/666)
3rd tertile	66.1 (441/667)	72.7 (485/667)	46.3 (309/667)	49.3 (328/666)	77.4 (516/667)	50.2 (334/666)
	OR (95%CI)	***OR (95%CI)***	***OR (95%CI)***	***OR (95%CI)***	***OR (95%CI)***	***OR (95%CI)***
1st tertile	1.00 ref	1.00 ref	1.00 ref	1.00 ref	1.00 ref	1.00 ref
2nd tertile	0.82 (0.73, 0.91)	0.73 (0.65, 0.81)	0.90 (0.80, 1.01)	1.12 (1.00, 1.26)	0.76 (0.67, 0.86)	0.83 (0.75, 0.93)
3rd tertile	0.63 (0.49, 0.81)[2]	0.49 (0.38, 0.63)[2]	0.78 (0.60, 1.03)	1.30 (1.00, 1.68)	0.54 (0.40, 0.71)[2]	0.66 (0.52, 0.84)[2]
1st tertile	1.00 ref	1.00 ref	1.00 ref	1.00 ref	1.00 ref	1.00 ref
2nd tertile	0.73 (0.65, 0.83)	0.67 (0.58, 0.78)	0.95 (0.84, 1.07)	0.94 (0.85, 1.04)	0.76 (0.67, 0.87)	0.77 (0.69, 0.85)
3rd tertile	0.50 (0.38, 0.65)[2]	0.41 (0.29, 0.57)[2]	0.89 (0.68, 1.17)	0.87 (0.69, 1.10)	0.54 (0.40, 0.74)[2]	0.55 (0.43, 0.70)[2]
1st tertile	1.00 ref	1.00 ref	1.00 ref	1.00 ref	1.00 ref	1.00 ref
2nd tertile	0.73 (0.64, 0.84)	0.66 (0.57, 0.78)	0.95 (0.84, 1.08)	0.94 (0.85, 1.03)	0.76 (0.67, 0.88)	0.77 (0.69, 0.85)
3rd tertile	0.49 (0.36, 0.67)[2]	0.40 (0.27, 0.57)[2]	0.89 (0.67, 1.19)	0.86 (0.69, 1.07)	0.54 (0.40, 0.74)[2]	0.55 (0.44, 0.69)[2]
1st tertile	1.00 ref	1.00 ref	1.00 ref	1.00 ref	1.00 ref	1.00 ref
2nd tertile	0.81 (0.71, 0.93)	0.77 (0.64, 0.93)	1.01 (0.88, 1.16)	0.94 (0.85, 1.04)	0.80 (0.70, 0.93)	0.82 (0.74, 0.91)
3rd tertile	0.62 (0.45, 0.84)[2]	0.56 (0.36, 0.85)[2]	1.03 (0.76, 1.41)	0.86 (0.68, 1.08)	0.61 (0.44, 0.85)[2]	0.63 (0.50, 0.80)[2]

[Λ]Results are presented for tertiles of plasma 25-hydroxyvitamin D (median [interquartile range] concentration, ng/mL, 1st tertile 12.1 [9.7,14.3]; 2nd tertile 20.3 [18.3, 22.7]; 3rd tertile 30.6 [27.5, 34.9]; odds ratio and 95% confidence interval (CI) of metabolic syndrome and its components in each of the two highest tertiles of plasma 25-hydroxyvitamin D concentration was compared with the lowest tertile by extrapolating the per unit change in estimated odds from the multivariate model; large waist circumference is defined as waist circumference ≥ 102 cm (male) and ≥ 88 cm (female); high blood pressure is defined as systolic blood pressure ≥ 130 mm Hg and/or diastolic blood pressure > 85 mm Hg or current antihypertensive drug treatment in a patient with a history of hypertension; high triglycerides is defined as triglycerides ≥ 150 mg/dL; high fasting plasma glucose is defined as fasting plasma glucose ≥ 100 mg/dL; low HDL is defined as HDL < 40 mg/dL in men and < 50 mg/dL in women; to convert plasma 25OHD concentration from ng/mL to nmol/L multiply by 2.459; to convert triglycerides from mg/dL to mmol/L multiply by 0.0113; to convert glucose from mg/dL to mmol/L multiply by 0.0555; to convert HDL- cholesterol from mg/dL to mmol/L multiply by 0.0259.

*p-value for trend was less than 0.01.

Table 3

Risk of incident metabolic syndrome during the first 2 years of follow-up by tertiles of continuous plasma 25-hydroxyvitamin D concentration in the lifestyle and placebo arms of the Diabetes Prevention Program.

	No. of person years	No. of participants	Tertile of 25-hydroxyvitamin D concentration			P value
			1 (Lowest)	2	3 (Highest)	
Number of participants at baseline (events)			162 (53)	190 (68)	226 (60)	
Plasma 25-hydroxyvitamin D concentration at baseline, median (interquartile range), ng/mL	---	578	12.3 (10.0, 14.7)	20.4 (18.4, 23.1)	31.0 (27.4, 36.8)	---
Hazard ratio (95% confidence interval)						
Unadjusted Model	949	546	1.00 (reference)	0.82 (0.70, 0.98)	0.65 (0.44, 0.95)	0.0261
Model adjusted for age, gender	949	546	1.00 (reference)	0.85 (0.71, 1.00)	0.68 (0.46, 1.01)	0.0542
Multivariate model [1]	945	544	1.00 (reference)	0.81 (0.65, 1.01)	0.62 (0.38, 1.01)	0.0562
Multivariate model and baseline weight [2]	945	544	1.00 (reference)	0.87 (0.70, 1.09)	0.73 (0.44, 1.21)	0.2207
Multivariate model and treatment arm [3]	945	544	1.00 (reference)	0.90 (0.72, 1.13)	0.79 (0.48, 1.32)	0.3749
Multivariate model and change in weight [4]	945	544	1.00 (reference)	0.92 (0.73, 1.16)	0.83 (0.50, 1.39)	0.4831

Results are presented for baseline tertiles of plasma 25-hydroxyvitamin D concentration; hazard ratio of diabetes in each of the two highest tertiles was compared with the lowest tertile by extrapolating the per unit change in estimated hazard from the multivariate model; variables measured at multiple time points throughout the study (25-hydroxyvitamin D and physical activity) entered the analyses as time-varying “lagged” covariates, as the mean of the previous and current visit at which diabetes status was assessed; to convert plasma 25- hydroxyvitamin D concentration from ng/mL to nmol/L multiply by 2.459

[1] Adjusted for recruitment location, age (years), gender (male or female), month of blood draw, race (black, white, or other), smoking status at baseline (never, past, or currently smoking), alcohol consumption (average of values self-reported at baseline and 1-year follow-up visit, g/day), C-reactive protein (average of values at baseline, 1-year follow-up visits, mg/L), and self-reported physical activity (MET-hours per week) and total energy intake (average of values self-reported at baseline and 1-year follow-up visit, kcal/day) plus ultraviolet radiation index at participant's recruitment location (mean annual in 1997, 90J/m2/hour).

[2] Adjusted for everything in in footnote (1) plus baseline body weight (kg)

[3] Adjusted for everything in in footnote (2) plus treatment arm (intensive lifestyle or placebo)

[4] Adjusted for everything in in footnote (3) plus change in body weight from previous non-missing visit

Table 4

Adjusted average difference of non-traditional components of metabolic syndrome factors by tertiles of continuous plasma 25-hydroxyvitamin D concentration in the lifestyle and placebo arms of the Diabetes Prevention Program population.

	No. of participants	Tertile of 25- hydroxyvitamin D concentration			P value
		1 (Lowest)	2	3 (Highest)	
Number of participants	2000	N = 666	N = 667	N = 667	---
Number with MS	2000	N = 504	N = 477	N = 441	---
Plasma 25-hydroxyvitamin D concentration, median (interquartile range), ng/mL	2000	12.1 (9.7, 14.3)	20.3 (18.3, 22.7)	30.6 (27.5, 34.9)	---
Adjusted average difference (95% confidence interval)					
[1]Insulin sensitivity, μU/mL^{-1}	1957	0.00 (reference)	0.061 (0.035, 0.089)	0.143 (0.081, 0.212)	< 0.001
[1]Insulin sensitivity index, [(μU/mL)*(mg/dL)]-1	1957	0.00 (reference)	0.070 (0.041, 0.101)	0.164 (0.095, 0.241)	< 0.001
[1]Insulinogenic index, IGI (μU/mL)/(mg/dL)	1893	0.00 (reference)	−0.045 (−0.074, −0.011)	−0.098 (−0.158, −0.025)	0.0111
[1]Corrected insulin response, CIR (μU/mL)/(mg/dL)^2	1926	0.00 (reference)	−0.039 (−0.065, −0.009)	−0.086 (−0.141, −0.020)	0.013
Disposition Index 1 (LN(IGI) * LN(Insulin sensitivity))	1893	0.00 (reference)	0.154 (0.039, 0.268)	0.348 (0.089, 0.607)	0.0083
Disposition Index 2 (LN(CIR) * LN(Insulin sensitivity index))	1925	0.00 (reference)	0.016 (−0.042, 0.074)	0.037 (−0.095, 0.168)	0.5855

Results are presented for tertiles of plasma 25-hydroxyvitamin D concentration; differences in each of the two highest tertiles was compared with the lowest tertile by calculating the difference in predicted values from the multivariate model; all models are adjusted for recruitment site and month of blood draw, age (years), gender (male or female), race (black, white, or other), ultraviolet radiation index at participant's study site (mean annual in 1997, 90J/m2/hour), smoking status at baseline (never, past, or currently smoking), alcohol consumption (g/day), C-reactive protein (mg/L), self-reported physical activity (MET-hours per week), total energy intake (kcal/day), and body mass index; to convert plasma 25-hydroxyvitamin D concentration from ng/mL to nmol/L multiply by 2.459.

[†]Differences between tertiles for log transformed dependent variables are presented in the original scale.

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Table 5

Subgroup analyses for odds of metabolic syndrome by tertiles of continuous plasma 25-hydroxyvitamin D concentration in the lifestyle and placebo arms of the Diabetes Prevention Program cohort by subgroups

	No. of participants	**Tertile of 25-hydroxyvitamin D concentration**			**P value**	**P value for interaction**
		1 (Lowest)	2	3(Highest)		
Number of participants	2000	N = 666	N = 667	N = 667	---	---
Number with MS	2000	N = 504	N = 477	N = 441	---	---
Plasma 25-hydroxyvitamin D concentration, median (interquartile range), ng/mL	2000	12.1 (9.7, 14.3)	20.3 (18.3, 22.7)	30.6 (27.5, 34.9)	---	---
Odds ratio (95% confidence interval)						
Age (median, y)						0.1190
< 50	932	1.00 (reference)	0.83 (0.71, 0.96)	0.65 (0.46, 0.92)	0.0154	
Participants (number with Metabolic Syndrome)		359 (272)	280 (208)	293 (199)		
>= 50	1027	1.00 (reference)	0.79 (0.65, 0.96)	0.59 (0.38, 0.90)	0.0153	
Participants (number with Metabolic Syndrome)		289 (219)	375 (260)	363 (235)		
Gender						0.5047
Female	1308	1.00 (reference)	0.84 (0.71, 0.98)	0.67 (0.47, 0.97)	0.0317	
Participants (number with Metabolic Syndrome)		486 (369)	412 (295)	410 (274)		
Male	651	1.00 (reference)	0.75 (0.58, 0.99)	0.53 (0.29, 0.97)	0.0393	
Participants (number with Metabolic Syndrome)		162 (122)	243 (173)	246 (160)		
Race						0.7822
White	1128	1.00 (reference)	0.86 (0.72, 1.02)	0.71 (0.48, 1.05)	0.0841	
Participants (number with Metabolic Syndrome)		242 (194)	407 (305)	479 (318)		
Non-White	831	1.00 (reference)	0.80 (0.65, 0.99)	0.61 (0.38, 0.98)	0.0393	
Participants (number with Metabolic Syndrome)		406 (297)	248 (163)	177 (116)		
Body mass index (kg/m^2)						0.0648
< 30	637	1.00 (reference)	0.76 (0.58, 1.00)	0.54 (0.29, 1.00)	0.0503	
Participants (number with Metabolic Syndrome)		138 (79)	221 (119)	278 (136)		
>= 30	1322	1.00 (reference)	0.85 (0.71, 1.01)	0.69 (0.46, 1.02)	0.0596	
Participants (number with Metabolic Syndrome)		510 (412)	434 (349)	378 (298)		

Results are presented for tertiles of plasma 25-hydroxyvitamin D concentration at the baseline visit of the Diabetes Prevention Program cohort; odds ratio of metabolic syndrome in each of the two highest tertiles was compared with the lowest tertile by extrapolating the per unit change in estimated odds from the multivariate model; all models are adjusted for recruitment site and month of blood draw; to convert plasma 25-hydroxyvitamin D concentration from ng/mL to nmol/L multiply by 2.459. Subgroup models adjusted for recruitment location, month of blood draw, age (years), gender (male or female; except for analysis by gender), race (black, white, or other; except for analysis by race), ultraviolet radiation index at participant's study site (mean annual in 1997, 90J/m2/hour), smoking status at baseline (never, past, or currently smoking), alcohol consumption (g/day), C-reactive protein (mg/L), self-reported physical activity (MET-hours per week), total energy intake (kcal/day), and body mass index.