

Adiposity, Cardiometabolic Risk, and Vitamin D Status: The Framingham Heart Study

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OBJECTIVE—Because vitamin D deficiency is associated with a variety of chronic diseases, understanding the characteristics that promote vitamin D deficiency in otherwise healthy adults could have important clinical implications. Few studies relating vitamin D deficiency to obesity have included direct measures of adiposity. Furthermore, the degree to which vitamin D is associated with metabolic traits after adjusting for adiposity measures is unclear.

RESEARCH DESIGN AND METHODS—We investigated the relations of serum 25-hydroxyvitamin D (25[OH]D) concentrations with indexes of cardiometabolic risk in 3,890 nondiabetic individuals; 1,882 had subcutaneous adipose tissue (SAT) and visceral adipose tissue (VAT) volumes measured by multidetector computed tomography (CT).

RESULTS—In multivariable-adjusted regression models, 25(OH)D was inversely associated with winter season, waist circumference, and serum insulin ($P < 0.005$ for all). In models further adjusted for CT measures, 25(OH)D was inversely related to SAT (-1.1 ng/ml per SD increment in SAT, $P = 0.016$) and VAT (-2.3 ng/ml per SD, $P < 0.0001$). The association of 25(OH)D with insulin resistance measures became nonsignificant after adjustment for VAT. Higher adiposity volumes were correlated with lower 25(OH)D across different categories of BMI, including in lean individuals (BMI < 25 kg/m²). The prevalence of vitamin D deficiency (25[OH]D < 20 ng/ml) was threefold higher in those with high SAT and high VAT than in those with low SAT and low VAT ($P < 0.0001$).

CONCLUSIONS—Vitamin D status is strongly associated with variation in subcutaneous and especially visceral adiposity. The mechanisms by which adiposity promotes vitamin D deficiency warrant further study. *Diabetes* 59:242–248, 2010

Vitamin D deficiency, as reflected by circulating 25-hydroxyvitamin D (25[OH]D) levels less than 20 ng/ml, is prevalent in as many as one half of middle-aged to elderly adults in developed countries (1). In addition to its effects on musculoskeletal health, a growing body of evidence suggests that individuals with vitamin D deficiency are at increased risk of cardiovascular morbidity and mortality (2–4). Thus, understanding the characteristics that promote vitamin D deficiency in the general population has important clinical implications.

The major source of vitamin D is endogenous production in the skin as a result of sunlight exposure (1). Notably, one of the clinical characteristics most consistently associated with vitamin D deficiency in prior studies is obesity (5–9). It is possible that the association between obesity and vitamin D deficiency is indirect, arising from obese individuals having less outdoor activity than lean individuals and, in turn, less sunlight exposure. However, direct negative effects of obesity on vitamin D status have also been hypothesized (10–12). Because vitamin D is fat soluble, vitamin D may be sequestered and stored in fat tissues (10). Accordingly, experimental and human studies suggest that greater storage of vitamin D in body fat decreases the bioavailability of endogenously produced vitamin D in the circulation (11,12).

Vitamin D deficiency has also been linked to insulin resistance and the metabolic syndrome (13–15). Previous studies suggest that the association of vitamin D deficiency with insulin resistance is not attributable entirely to obesity, although those studies have relied predominantly on anthropometric measures such as BMI and waist circumference. Computed tomography (CT) imaging permits reliable characterization of the subcutaneous and visceral adipose tissue volumes (16), the latter being the fat compartment more closely tied to insulin resistance and metabolic risk (16). Using CT techniques, recent studies in selected populations suggest that vitamin D may be related to variation in regional adiposity (17,18).

Therefore, we investigated the cross-sectional relations of vitamin D status with anthropometric, biochemical, and imaging measures of adiposity and insulin resistance in a large, community-based sample. First, we sought to assess whether serum concentrations of 25(OH)D (the circulating form that best reflects vitamin D stores) were related to

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measures of adiposity after accounting for physical activity and dietary vitamin D intake. Second, we assessed whether 25(OH)D status correlated more closely with subcutaneous or visceral adipose tissue. Third, we examined whether serum 25(OH)D was associated with measures of insulin resistance after accounting for adiposity.

RESEARCH DESIGN AND METHODS

Study sample. The Framingham Heart Study was established in 1948, when 5,209 residents of Framingham, Massachusetts were enrolled in a longitudinal cohort study designed to prospectively identify risk factors for cardiovascular disease (19). In 1971, an additional 5,124 participants (offspring of the original cohort subjects and their spouses) were enrolled in the Framingham Offspring Study (20). Beginning in 2002, 4,095 Third Generation Study participants, who had at least one parent in the Offspring cohort, were also enrolled and underwent standardized clinic examinations at the Heart Study between 2002 and 2005 (21). A total of 3,890 Third Generation participants (96% of attendees) were free of known cardiovascular disease and diabetes, had a serum creatinine ≤ 1.2 mg/dl, and had measurements of serum 25(OH)D. This sample (99.5% white and of European ancestry) was used in analyses relating serum 25(OH)D concentrations with clinical, anthropometric, and biochemical measures of adiposity and insulin resistance.

Contemporaneous with serum 25(OH)D measurements, a subset of 2,111 Third Generation participants also underwent multidetector CT imaging between 2002 and 2005. As previously described (16), inclusion in this subset that underwent imaging was weighted toward participants who resided in the greater New England area. Participants were eligible if they weighed < 350 pounds and were men ≥ 35 years of age or women ≥ 40 years of age and not pregnant. Of the participants who underwent CT scans, 1,882 (90%) had abdominal subcutaneous adipose tissue (SAT) and visceral adipose tissue (VAT) volumes measured, were free of cardiovascular disease and diabetes, and had measurement of 25(OH)D. This sample was used for all analyses relating vitamin D status to regional (i.e., subcutaneous and visceral) adiposity. Individuals who underwent CT imaging were older (45 vs. 35 years), more likely to be male (57 vs. 43%), and had a slightly higher BMI (27 vs. 26 kg/m²) than those who did not undergo CT imaging.

The institutional review boards of the Boston University School of Medicine and Massachusetts General Hospital approved the study protocol. All subjects provided written informed consent.

Clinical assessment. Definitions for standard cardiovascular risk factors have been detailed previously (22). Physical activity was assessed using a physical activity index, calculated from the number of hours spent each day at various activity levels, weighted according to the estimated oxygen consumption required for each activity (23). Data regarding total vitamin D intake from supplements and diet were obtained using a detailed food-frequency questionnaire (24).

Laboratory assays. Serum samples were obtained in the morning after an overnight fast and frozen at -80°C . Serum 25(OH)D was determined by radioimmunoassay (DiaSorin, Stillwater, MN). The intraassay coefficient of variation was 12.5%. For the present analysis, vitamin D deficiency was defined as having a 25(OH)D concentration < 20 ng/ml (1). Plasma insulin and proinsulin were measured by separate ELISA procedures (Millipore Bioscience, Billerica, MA), each of which had negligible cross-reactivity with other insulin-like molecules. The intraassay coefficients of variation for these assays were 2.7 and 2.4%, respectively. The homeostasis model assessment of insulin resistance (HOMA-IR) was assessed from fasting insulin and glucose levels, (25) where individuals with values in the top quartile were considered to have elevated HOMA-IR.

Abdominal adipose tissue imaging and measurements. Imaging was performed with an 8-slice multidetector CT scanner (Lightspeed Ultra; General Electric, Milwaukee, WI) using a standard protocol that has been reported previously (26). Briefly, 25 contiguous 5-mm-thick slices were acquired above the level of S1. The abdominal muscular wall separating visceral from subcutaneous fat compartments was manually traced on acquired images and volumetric assessments were made. Intrareader and interreader reproducibility was high, with interclass correlations of 0.997 for SAT and 0.992 for VAT (18). High and low values for VAT and SAT measures were defined as being above or below 90th percentile sex-specific cutoffs for men and women from a healthy reference sample (27).

Statistical analyses. Continuous variables with skewed distributions were logarithmically transformed (triglycerides, vitamin D intake, insulin, and proinsulin). Multivariable linear regression was performed in the total sample to examine the association of 25(OH)D (dependent variable) with the following clinical, anthropometric, and metabolic variables (independent variables): age, sex, cigarette smoking, log triglycerides, HDL cholesterol, systolic blood

pressure, antihypertensive treatment, BMI, waist circumference, physical activity index, log dietary vitamin D intake, fasting glucose, log insulin, log proinsulin, HOMA-IR (≥ 75 th percentile), and the metabolic syndrome (presence of ≥ 3 of the following: waist circumference ≥ 40 inches in men or ≥ 35 inches in women; serum triglycerides ≥ 150 mg/dl or taking medication for hypertriglyceridemia [fibrates or niacin derivatives]; HDL cholesterol < 40 mg/dl in men or < 50 mg/dl in women or taking medication for reduced HDL cholesterol [fibrates or niacin derivatives]; systolic blood pressure ≥ 130 mmHg or diastolic blood pressure ≥ 85 mmHg or taking antihypertensive medication; and fasting glucose ≥ 100 mg/dl) (28). The association of each variable with 25(OH)D was initially examined with adjustment for age, sex, and winter season (January through April) (29,30). We then conducted multivariable regression analyses with stepwise forward selection to evaluate the independent association of 25(OH)D with each of the clinical, anthropometric, and metabolic variables listed above. A P value < 0.10 was the significance criterion for covariates to enter and remain in the regression model.

For the subset of individuals who underwent multidetector CT, clinical and metabolic covariates that were significant in the stepwise model were entered into a multivariable regression model along with SAT and VAT, incorporating the latter two separately and conjointly. To assess whether SAT or VAT was more strongly associated with 25(OH)D, we performed a bootstrap analysis to compare the standardized regression coefficients for SAT and VAT (31). Specifically, 10,000 random samples with replacement were taken from the original sample, and two multivariable linear regressions (one with SAT and one with VAT) were run on each sample. An overall estimate of the SAT and VAT regression coefficients, their variances, and their covariance were then estimated using the bootstrap approach on the 10,000 samples, and a Z test for the difference in regression coefficients was calculated. Anthropometric variables (BMI or waist circumference) were included in models with VAT but not in models with SAT, to avoid collinearity between SAT and anthropometric indexes (16). In all models that examined the relations of 25(OH)D with SAT or VAT, we included additional covariates known to correlate with CT measures of adiposity, that is, hormone replacement therapy (in women), menopausal state (in women), and alcohol use (32). To assess the relation of insulin resistance with 25(OH)D after accounting for different measures of adiposity, we entered each of four surrogate markers of insulin resistance (fasting glucose, log insulin, HOMA-IR, log proinsulin) as a separate additional covariate into multivariable models that adjusted for one of the following adiposity measures: BMI, waist circumference, SAT, or VAT.

In secondary analyses, we repeated the analyses using generalized estimating equations to account for correlations among related individuals (siblings) in the study sample (PROC GENMOD; SAS Institute, Cary, NC) (33). To examine adiposity and body size separately, we repeated multivariable analyses of adiposity measures within subgroups defined by BMI category (< 25 , 25 to < 30 , and ≥ 30 kg/m²).

All analyses were performed using SAS Version 9.1.3 (SAS Institute), and a two-tailed P value of < 0.05 was considered statistically significant.

RESULTS

The characteristics of the study sample are shown in Table 1. The mean age was 40 years, and 54% of participants were women. Overall, 22% of participants were obese (BMI ≥ 30 kg/m²) and 35% were overweight (BMI ≥ 25 kg/m² and < 30 kg/m²).

The age-, sex-, and season-adjusted associations of 25(OH)D with clinical and metabolic traits are shown in Table 2. 25(OH)D was positively related to dietary vitamin D intake ($P < 0.0001$) and physical activity ($P < 0.0001$). Significant inverse associations were noted between 25(OH)D and each of the remaining clinical and metabolic covariates, including measures of insulin resistance. After adjusting for age, sex, and season, the presence of metabolic syndrome was associated with lower 25(OH)D concentration (-4.5 ng/ml, $P < 0.0001$).

Multivariable analyses. Results of the stepwise multivariable regression model are shown in Table 3. Higher 25(OH)D was associated with nonwinter season, smaller waist circumference, increased physical activity, and greater vitamin D intake. After adjustment for these covariates, 25(OH)D was also inversely associated with serum insulin levels ($P = 0.004$).

TABLE 1
Study sample characteristics

	Whole sample (<i>n</i> = 3,890)
Clinical and anthropometric measures	
Age (years)	40.0 ± 8.7
Women	54
Winter season	30
BMI (kg/m ²)	26.7 ± 5.3
Waist circumference (cm)	99.5 ± 14.7
Systolic blood pressure (mmHg)	116 ± 14
Diastolic blood pressure (mmHg)	75 ± 10
Hypertension	17
Smoker	17
Physical activity index	37.5 ± 7.8
Postmenopausal	6
Hormone replacement therapy	3
Alcohol use*	15
Vitamin D intake (IU)	378 ± 290
Metabolic syndrome	19
Biochemical measures	
25(OH)D (ng/ml)	37.2 ± 14.5
HDL cholesterol (mg/dl)	54.7 ± 16.1
Triglycerides (mg/dl)	91.0 (64–135)
Fasting plasma glucose (mg/dl)	93.1 ± 8.5
Impaired fasting glucose†	5
Insulin (pmol/l)	25.2 (18.7–36.5)
HOMA-IR†	0.8 (0.6–1.2)
Proinsulin (pmol/l)	5.9 (4.1–9.3)
CT measures‡	
SAT (cm ³)	2,754.8 ± 1,397.0
VAT (cm ³)	1,568.5 ± 893.3

Data are means ± SD (for continuous variables that are normally distributed), median (interquartile range) (for continuous variables that are not normally distributed), or percent. *Defined as >14 drinks/week (men) or >7 drinks/week (women). †Fasting plasma glucose 100–125 mg/dl. ‡Data from the sample subset (*n* = 1,882) with CT-based adiposity measures available.

In the subgroup of individuals who had CT measures of regional adiposity, multivariable analyses were performed relating 25(OH)D to regional adiposity adjusting for the clinical and metabolic covariates derived from the aforementioned stepwise regression model. When SAT and VAT were entered separately into these models, 25(OH)D was inversely associated with each of these adiposity measures ($P < 0.0001$ for both VAT and SAT). These relations were significant when SAT and VAT were treated as either continuous or categorical measures (Table 4). When further adjustment for waist circumference was made, the association of 25(OH)D with VAT remained statistically significant. Notably, after inclusion of VAT in multivariable models, the association of 25(OH)D with both waist circumference ($P = 0.183$) and HOMA-IR ($P = 0.394$) became nonsignificant. In bootstrap analyses, the multivariable-adjusted regression coefficient for a standard deviation increment in VAT was significantly greater than that for the same increment in SAT ($P = 0.009$). When both SAT and VAT were entered into a single model, as shown in Table 4, each of these measures remained inversely associated with 25(OH)D ($P = 0.016$ for SAT, $P < 0.0001$ for VAT).

The multivariable-adjusted relations of 25(OH)D with several markers of insulin resistance, including fasting glucose, serum insulin, and HOMA-IR, remained significant in models adjusting for BMI or waist circumference.

TABLE 2
Age-, sex-, and season-adjusted relations of individual clinical and metabolic covariates and serum 25(OH)D (*n* = 3,890)

	Coefficient (SE)*	<i>P</i>
Age	−0.71 (0.22)	0.001
Female sex	2.50 (0.44)	<0.0001
Winter season	−9.53 (0.48)	<0.0001
Smoker	−1.22 (0.59)	0.037
Log triglycerides	−1.48 (0.23)	<0.0001
HDL cholesterol	1.51 (0.25)	<0.0001
Systolic blood pressure	−1.66 (0.24)	<0.0001
Antihypertensive treatment	−1.22 (0.79)	0.125
BMI	−2.81 (0.23)	<0.0001
Waist circumference	−3.11 (0.24)	<0.0001
Physical activity index	1.30 (0.22)	<0.0001
Log vitamin D intake	2.34 (0.23)	<0.0001
Fasting glucose	−3.63 (0.53)	<0.0001
Log insulin	−2.29 (0.24)	<0.0001
HOMA-IR	−4.31 (0.54)	<0.0001
Log proinsulin	−1.96 (0.25)	<0.0001
SAT†	−2.65 (0.31)	<0.0001
VAT†	−3.58 (0.36)	<0.0001

*Coefficients represent change in 25(OH)D (ng/ml) for an increase in the value of the predictor variables shown (1-SD increase for continuous predictor variables). The coefficient change for age, sex, and season are each adjusted for the other two covariates. †Data are from the sample subset (*n* = 1,882) with CT-based adiposity measures available.

These relations were moderately attenuated in models adjusting for SAT and nonsignificant in models adjusting for VAT (Table 5). 25(OH)D was not associated with serum proinsulin in multivariable models adjusting for any measure of obesity.

Results were similar when the analyses were repeated using generalized estimating equations. In analyses within BMI subgroups, the association of 25(OH)D with regional adiposity was more consistent for VAT than SAT (Table 6). The multivariable-adjusted association of 25(OH)D with SAT was significant in overweight and obese people, but not in lean people. On the other hand, the association of 25(OH)D with VAT was significant in all BMI subgroups.

TABLE 3
Stepwise multivariable-adjusted relations of clinical and metabolic covariates with 25(OH)D in the absence of SAT or VAT as potential covariates

	Coefficient (SE)*	<i>P</i>
Female sex	0.91 (0.53)	0.084
Winter season	−9.08 (0.52)	<0.0001
Systolic blood pressure	−0.48 (0.27)	0.080
Waist circumference	−2.42 (0.33)	<0.0001
Physical activity index	1.08 (0.25)	<0.0001
Log vitamin D intake	2.16 (0.24)	<0.0001
Log insulin	−0.87 (0.30)	0.004

*Coefficients represent change in 25(OH)D (ng/ml) for an increase in the value of the predictor variables shown (1-SD increase for continuous predictor variables). The stepwise multivariable model adjusted for the following variables: age, sex, season, smoker, log triglycerides, HDL cholesterol, systolic blood pressure, antihypertensive treatment, BMI, waist circumference, physical activity, log vitamin D intake, fasting glucose, log insulin, log proinsulin, and HOMA-IR. Variables that were entered into but did not remain significant in this stepwise forward regression model included age, smoker, log triglycerides, HDL cholesterol, antihypertensive treatment, BMI, fasting glucose, log proinsulin, and HOMA-IR.

TABLE 4
Multivariable-adjusted relations of adiposity measures with 25(OH)D

	Model 1*		Model 2		Model 3	
	Regression coefficient (SE)†	P	Regression coefficient (SE)	P	Regression coefficient (SE)	P
Continuous variables						
SAT	-2.02 (0.41)	<0.0001	—	—	-1.12 (0.47)	0.016
VAT	—	—	-3.00 (0.51)	<0.0001	-2.34 (0.58)	<0.0001
Categorical variables‡						
High SAT (vs. low SAT)	-2.94 (0.83)	0.0004	—	—	-2.22 (0.86)	0.010
High VAT (vs. low VAT)	—	—	-3.32 (0.86)	0.0001	-2.67 (0.90)	0.003

*In models 1 and 2, SAT and VAT are entered separately while adjusting for sex, season, systolic blood pressure, physical activity, log vitamin D intake, and log insulin. In model 3, both SAT and VAT are entered in the model while adjusting for the same aforementioned covariates. †Coefficients represent change in 25(OH)D (ng/ml) for an increase in the value of the predictor variables shown (1-SD increase for continuous predictor variables). ‡High SAT and VAT were defined as values >90th sex-specific percentile, as derived from a healthy reference sample.

Prevalence of vitamin D deficiency. Overall, vitamin D deficiency (<20 ng/ml) was more frequent among individuals with high SAT compared with those with low SAT (13.7 vs. 6.7%, $P < 0.0001$) and in individuals with high compared with low VAT (15.4 vs. 5.7%, $P < 0.0001$). The prevalence of vitamin D deficiency rose with increasing VAT tertile, even among lean individuals (Fig. 1). Individuals with both high SAT and high VAT had an approximately threefold prevalence of vitamin D deficiency compared with those with both low SAT and low VAT (15.8 vs. 5.1%, $P < 0.001$; Fig. 2).

TABLE 5
Multivariable-adjusted relations of 25(OH)D with insulin resistance measures

	Regression coefficient (SE)*	P
Model adjusting for standard covariates plus BMI		
Fasting glucose	-1.14 (0.57)	0.047
Log insulin	-0.90 (0.30)	0.003
HOMA-IR	-1.62 (0.62)	0.009
Log proinsulin	-0.24 (0.31)	0.445
Model adjusting for standard covariates plus waist circumference		
Fasting glucose	-0.95 (0.57)	0.099
Log insulin	-0.82 (0.30)	0.006
HOMA-IR	-1.54 (0.62)	0.014
Log proinsulin	-0.17 (0.31)	0.586
Model adjusting for standard covariates plus SAT		
Fasting glucose	-1.68 (0.80)	0.036
Log insulin	-0.93 (0.41)	0.024
HOMA-IR	-1.54 (0.84)	0.066
Log proinsulin	-0.58 (0.40)	0.152
Model adjusting for standard covariates plus VAT		
Fasting glucose	-1.13 (0.82)	0.166
Log insulin	-0.50 (0.43)	0.245
HOMA-IR	-0.75 (0.86)	0.383
Log proinsulin	-0.07 (0.43)	0.874

*Coefficients represent change in 25(OH)D (ng/ml) for an increase in the value of the predictor variables shown (1-SD increase for continuous predictor variables). All models include adjustment for the following standard covariates: sex, winter season, systolic blood pressure, physical activity index, and log vitamin D intake.

DISCUSSION

Principal findings. The principal findings of our study are threefold. First, we observed a relation of lower vitamin D concentrations with greater BMI that was not explained by variation in physical activity or vitamin D intake. Second, we found an inverse relation of 25(OH)D with subcutaneous and especially visceral adiposity, even among lean individuals, underscoring the specific importance of adipose tissue, above and beyond body size, as a correlate of vitamin D status. Third, associations between 25(OH)D and commonly used markers of insulin resistance were markedly attenuated when accounting for variations in regional and particularly visceral adiposity.

Vitamin D and obesity. Prior studies have described an association between vitamin D deficiency and obesity, but residual confounding could exist from factors such as limited physical activity (7,9) or low vitamin D intake (7–9,34). One of the advantages of our cohort was that participants were generally young to middle-aged, with few comorbidities, and very low rates of medication use. Furthermore, information on physical activity level and vitamin D intake from diet and supplements was routinely ascertained. We observed a robust association between 25(OH)D and anthropometric measures even after taking into account these potential confounders.

A limitation of anthropometric measures is that they do not distinguish fat from lean mass. A few studies have reported an inverse correlation between vitamin D and total body fat, assessed using skin-fold measures or dual-energy X-ray absorptiometry, (35–37) but these methods

TABLE 6
Multivariable-adjusted relations of adiposity measures with 25(OH)D by BMI

BMI category	SAT		VAT	
	Regression coefficient (SE)*	P	Regression coefficient (SE)	P
Lean: <25 kg/m ²	0.68 (1.53)	0.656	-3.30 (1.59)	0.038
Overweight: 25 to <30 kg/m ²	-2.39 (1.15)	0.039	-2.78 (0.89)	0.002
Obese: ≥30 kg/m ²	-1.64 (0.71)	0.023	-2.11 (0.90)	0.019

*Coefficients represent change in 25(OH)D (ng/ml) for an increase in the value of the predictor variables shown (1-SD increase for continuous predictor variables). Relations of adiposity measures with 25(OH)D are adjusted for sex, season, systolic blood pressure, physical activity, vitamin D intake, and log insulin.

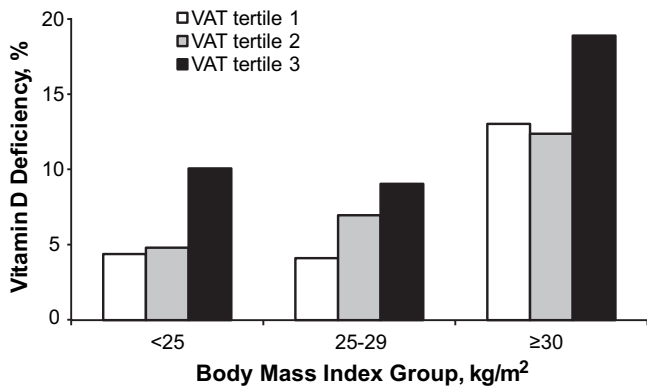


FIG. 1. Prevalence of vitamin D deficiency (defined as 25(OH)D <20 ng/ml) by VAT sex-specific tertiles across BMI groups.

are unable to characterize the type and distribution of fat deposits. On the other hand, CT imaging allows for a detailed, volumetric quantification of the subcutaneous and visceral abdominal adipose tissue compartments. Recent studies have reported an association of 25(OH)D with regional adiposity assessed by CT in nonwhite individuals (17) and in obese adolescents (18). Our data extend these findings to a larger, predominantly white cohort, unselected on the basis of BMI or vitamin D status. The size of the cohort enabled subgroup analyses within strata of BMI, as well as multivariable models incorporating a range of clinical and biochemical variables.

Although SAT and VAT are highly correlated with each other, (16) they appeared independently associated with 25(OH)D. This observation suggests that subcutaneous and visceral fat depots are each separately related to vitamin D status. Interestingly, the association of VAT with 25(OH)D was also present within categories of BMI, even among individuals with low BMI. In contrast, the association of SAT with 25(OH)D was attenuated in the lowest BMI subgroup. Because SAT and BMI are closely correlated, it is possible that most of the association between SAT and 25(OH)D is attributable to variation in body size that is also captured by BMI.

Vitamin D deficiency may be related to adiposity via several mechanisms. Some have theorized that obesity is associated with decreased sunlight exposure, from less outdoor activity or clothing habits that limit cutaneous vitamin D synthesis. As noted above, however, the associ-

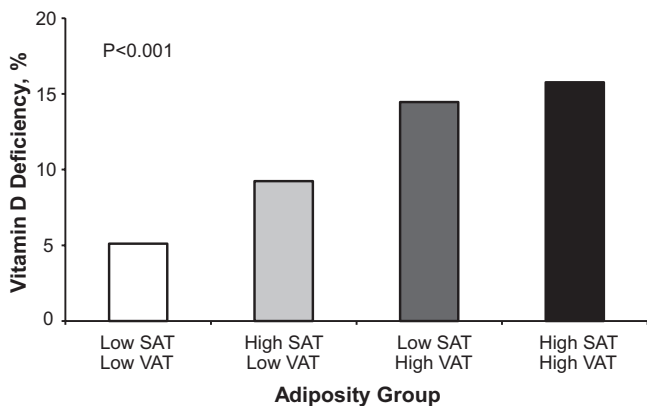


FIG. 2. Prevalence of vitamin D deficiency (defined as 25(OH)D <20 ng/ml) by adiposity group. High and low SAT and VAT levels are defined by values above and below 90th percentile sex-specific cut points, respectively.

ation between 25(OH)D and adipose tissue volumes was unchanged by adjustment for physical activity and was present even in analyses restricted to lean individuals. Furthermore, experimental studies indicate that differences in sunlight exposure are not enough to account for the differences in vitamin D concentrations seen between obese and nonobese volunteers (12). Thus, confounding by differences in sunlight exposure is highly unlikely as an explanation for poorer vitamin D status with greater adiposity.

Because vitamin D is fat soluble, many investigators have proposed that the sequestration of vitamin D metabolites in fat compartments decreases their bioavailability in obese compared with nonobese people (12). According to this hypothesis, variation in serum 25(OH)D, the storage form of vitamin D, should correlate closely with variation in measures of SAT, which is by far the body's largest volume depot of fat. Although SAT was indeed associated with 25(OH)D, we observed an even stronger relation of 25(OH)D with VAT.

There are some experimental data to suggest that vitamin D deficiency could promote greater adiposity. Moderate to severe vitamin D deficiency leads to elevated parathyroid hormone, which may promote calcium influx into adipocytes and thereby enhance lipogenesis (38). Moreover, accumulating evidence suggests that 1,25-hydroxyvitamin D modulates adipogenesis through vitamin D receptor-dependent inhibition of critical molecular components of adipogenesis such as peroxisome proliferator-activated receptor γ and C/EBP α (39). Therefore, depletion of vitamin D stores may lead to excess differentiation of preadipocytes to adipocytes.

Taken together, our findings suggest that multiple mechanisms could potentially contribute to the robust association of vitamin D with adiposity. Although 25(OH)D was more strongly related to VAT than SAT, having greater adiposity in both visceral and subcutaneous compartments appeared to have an additive relation to vitamin D status. Indeed, being in the highest compared with lowest category of total abdominal fat volume (SAT and VAT together) was associated with a threefold higher rate of vitamin D deficiency.

Vitamin D, visceral adiposity, and insulin resistance. As with prior studies, we observed that vitamin D deficiency was associated with insulin resistance and related traits (40–42). It has been proposed that vitamin D deficiency directly promotes insulin resistance, although prior data are conflicting (15). Experimental studies indicate that vitamin D has the ability to stimulate pancreatic insulin secretion (43–45). However, results of studies examining the effects of vitamin D administration on insulin secretion in humans have been mixed (46–48).

Interestingly, although the association between 25(OH)D and insulin resistance measures persisted with adjustment for BMI and waist circumference, it became attenuated after adjustment for SAT and nonsignificant after adjustment for VAT. This observation raises the possibility that the relation between vitamin D deficiency and metabolic traits (10,34,49) could be explained, in large part, by its association with adiposity, particularly in the visceral compartment. Although both subcutaneous and visceral fat depots are metabolically active (22), VAT is considered the more pathogenic compartment and is more often associated with secretion of adipokines, mediators of hemostasis and fibrinolysis, and growth factors (16). Furthermore, VAT is more strongly correlated than SAT with cardiovascular risk factors such as hypertension, hypertri-

glyceridemia, impaired fasting glucose, and the metabolic syndrome (16,27,50).

Limitations and strengths. Several limitations of this study merit consideration. We did not have specific information on sun exposure or time spent outdoors. Thus, both season and the physical activity index were used as surrogates for solar radiation, which directly influences cutaneous vitamin D production. The use of cross-sectional data precludes inference of a causal relation between regional adiposity and vitamin D deficiency. It remains possible that specific patterns of adiposity promote vitamin D deficiency, that depletion of vitamin D stores contributes to specific patterns of adiposity, or that both are the product of another primary process. Further research is needed to explore these potential relations.

The results of our study may not be generalizable to all racial/ethnic groups or age groups given that our sample was primarily white and young to middle-aged. Multivariable analyses were unable to adjust for parathyroid hormone because this was not measured in our sample. Furthermore, adiposity measures were performed on only a subset of the population. We did not subdivide subcutaneous fat into superficial and deep compartments, and so we cannot comment on the relative importance of these subcompartments with respect to variation in vitamin D concentrations. Also, we measured only abdominal and not truncal or limb SAT (35).

Notwithstanding the above limitations, the present study had several strengths, including the use of a community-based sample not selected on the basis of adiposity-related traits, cardiovascular disease risk factors, or vitamin D status. We used a highly reproducible volumetric method of assessing SAT and VAT, which accounts for heterogeneity of fat distribution throughout the abdomen. Lastly, our large sample size provided adequate power to perform multivariable analyses and compare strengths of association.

Clinical implications. We observed that lower 25(OH)D was associated with greater regional adiposity, a finding that was not attributable to differences in physical activity or vitamin D intake. The association between 25(OH)D and adiposity was stronger for visceral than subcutaneous abdominal adiposity, and significant across the spectrum of body size. In fact, the relation of 25(OH)D with adiposity was present even among healthy, lean individuals who might otherwise not be considered at risk for vitamin D deficiency. Furthermore, relations of 25(OH)D with insulin resistance markers were markedly attenuated by adjustment for visceral adiposity, suggesting that excess visceral adiposity could contribute to the observed relationship of vitamin D with insulin resistance and the metabolic syndrome.

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