Vitamin D, Parathyroid Hormone Levels, and the Prevalence of Metabolic Syndrome in Community-Dwelling Older Adults

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OBJECTIVE — Accumulating research suggests low-circulating vitamin D concentrations, i.e., 25-hydroxyvitamin-D [25(OH)D], may be associated with an increased prevalence of metabolic syndrome; however, previous studies have not accounted for parathyroid hormone (PTH) levels. We examined the association of 25(OH)D and PTH with the prevalence of metabolic syndrome in a community-based cohort of older adults.

RESEARCH DESIGN AND METHODS — Participants included 410 men and 660 women, 44–96 years old, who completed a follow-up clinic visit in 1997–1999 as part of the Rancho Bernardo Study. Sex-specific logistic regression models were fit to estimate the odds of ATP III (Adult Treatment Panel III)-defined metabolic syndrome across quintiles of 25(OH)D and PTH, adjusting for age, season, and major lifestyle factors.

RESULTS — In men, there was a significant trend ($P = 0.03$) of increasing adjusted odds for metabolic syndrome with increasing PTH concentrations, primarily due to an odds ratio of 2.02 (95% CI 0.96–4.24) in men in the top quintile (≥63 ng/l) of PTH concentration. This association remained unchanged after taking into account 25(OH)D levels and excluding men with diabetes or impaired renal function; it was attenuated after adjustment for the homeostasis model assessment of insulin resistance. Neither PTH in women nor 25(OH)D levels in either sex was related to the metabolic syndrome.

CONCLUSIONS — These findings suggest an increased risk of metabolic syndrome with elevated PTH levels in older men and no effect of 25(OH)D concentrations in either sex. The reason for the sex difference in the PTH–metabolic syndrome association is unknown. Prospective studies are necessary to better determine the roles of 25(OH)D and PTH in the etiology of metabolic syndrome.

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Decreased vitamin D and elevated parathyroid hormone (PTH) levels may play a role in the etiology of metabolic syndrome, either through an association with individual components of metabolic syndrome or via insulin resistance (1,2). Vitamin D levels have been shown to be inversely related both with fasting glucose concentrations (3–5) and adiposity (6–10) and have been suspected to be involved in the regulation of blood pressure, based on blood pressure reduction with vitamin D_3 supplementation in patients with essential hypertension (11,12). Other evidence suggests a role for vitamin D in maintaining normal insulin synthesis and secretion (13,14). Deficient 25-hydroxyvitamin D [25(OH)D] may also be a risk factor for diabetes (5,15,16), although previous studies have been inconsistent (17). In addition, evidence from a small clinical sample (1) and a national population-based cohort participating in the Third National Health and Nutrition Examination Survey (18) has implicated low 25(OH)D with an increased prevalence of metabolic syndrome.

Vitamin D and PTH are both responsible for maintaining extracellular calcium homeostasis (19). Vitamin D increases the efficiency of intestinal calcium absorption, and PTH is secreted in response to low-circulating calcium concentrations. Elevated PTH secondary to low vitamin D increases calcium resorption from the skeleton at the expense of an increased risk of fracture (20). Secondary hyperparathyroidism may also increase the risk of developing components of metabolic syndrome, including hypertension (21–26), obesity (6,9,10,27–29), and diabetes (30–32). However, we are unaware of previous research investigating whether PTH levels are also associated with the metabolic syndrome.

Previous studies linking low 25(OH)D with an increased prevalence of metabolic syndrome (1,18) were limited by their inability to simultaneously account for PTH, since both vitamin D and PTH operate within a tightly controlled feedback system to maintain extracellular calcium concentrations (19). The purpose of the present study was to examine the cross-sectional association of both 25(OH)D and PTH concentrations with the prevalence of metabolic syndrome in a community-based cohort of older adults.

RESEARCH DESIGN AND METHODS

Study participants were members of the Rancho Bernardo Study cohort, elsewhere described in detail (33). Briefly, between 1972 and 1974, 82% of all adults living in the southern California community of Rancho Bernardo were enrolled in a study of heart disease risk factors as part of the Lipid Research Clinics Prevalence Study. Nearly all subjects were Caucasian and of middle to upper-middle class, as assessed by the Hollingshead's index (34). Between 1997 and 1999, 89% (420 men

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Abbreviations: 25(OH)D, 25-hydroxyvitamin-D; CBP, competitive binding protein; HOMA-IR, homeostasis model assessment of insulin resistance; PTH, parathyroid hormone.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

and 676 women) of the local surviving community-dwelling members aged 44–96 years attended a follow-up visit, at which a medical evaluation was performed and a blood sample obtained. After excluding participants who did not have adequate blood samples for measurement of 25(OH)D and PTH levels ($n = 18$) and those who were missing values for one or more of the components of metabolic syndrome ($n = 8$), there remained 410 men and 660 women for these analyses. The University of California, San Diego Human Subjects Protections Program approved this study, and all participants provided written informed consent before participation.

Clinical evaluation

During the clinic visit, standardized questionnaires were used to obtain medical history and lifestyle behavior information. Data on the frequency of alcoholic beverage consumption (daily or almost daily, three or four times per week, once or twice per week, once or twice per month, or less often then once per month), cigarette smoking (current, former, or never), and participation in strenuous exercise 3 or more days per week (yes/no) were obtained. Women were also asked about their current or former use of hormone replacement therapy. Current use of estrogen with or without progestin, diabetes and blood pressure medications, and vitamin D and calcium supplement use were validated by the examination of pills and prescriptions brought to the clinic for that purpose.

Blood pressure was measured twice in seated subjects after a 5-min rest using a mercury sphygmomanometer according to the Hypertension Detection and Follow-up Program protocol (35). The average of the two measurements was used in analyses. Body weight and height were measured with a standard physician's scale and stadiometer while participants were wearing light clothing and no shoes. Waist circumference was measured at the bending point (the natural indentation when bending sideward) and at the narrowest circumference. The correlation between these two measures was 98%, and the measure at the bending point was used in these analyses.

Laboratory methods

Blood was obtained by venipuncture after an overnight fast and placed into tubes that were protected from sunlight. Serum was separated and stored at −70°C within 30 min of collection. Serum 25(OH)D [$25(OH)D_2 + 25(OH)D_3$] was measured in the research laboratory of M. Holick, using vitamin D competitive binding protein (CBP) recognition and chemiluminescence detection (Nichols Institute Diagnostics, San Clemente, CA) as described by Chen et al. (36). The rat serum vitamin D binding protein has high affinity for 25(OH)D. The intra- and interassay coefficients of variation (CVs) were 8 and 10%, respectively. The limit of detection was 12.5 nmol/l, and the reference range was 25–130 nmol/l. The PTH assay was performed in the same laboratory using a chemiluminescence assay (Nichols Institute Diagnostics) for the measurement of intact PTH; intra- and interassay CVs were both 6% with a reference range of 10–65 ng/l.

Plasma triglycerides and HDL were measured in a Centers for Disease Control and Prevention–certified lipid research clinic laboratory. Triglycerides were measured by enzymatic techniques using an ABA-200 biochromatic analyzer (Abbott Laboratories, Irving, TX). HDL was measured after precipitation of the other lipoproteins with heparin and manganese chloride according to standardized procedures of the Lipid Research Clinics manual (37). Fasting plasma glucose was measured by the glucose oxidase method. Fasting insulin was determined by a double antibody in a research laboratory (38). Serum creatinine levels were measured by SmithKline Beecham clinical laboratories. Creatinine clearance, calculated with the Cockcroft-Gault formula, {[140 − age (years)] × weight (kg)}/[72 × creatinine (mg/dl)] (multiplied by 0.85 for women), was used as a measure of renal function (39). Insulin resistance was estimated by the homeostasis model assessment of insulin resistance (HOMA-IR) index, calculated as [fasting glucose (mmol/l) × fasting insulin (μU/ml)]/22.5, as described by Levy et al. (40)

Statistical analysis

The metabolic syndrome was defined according to the NCEP/ATP III (National Cholesterol Education Program/Adult Treatment Panel III) (41). Participants were classified as having prevalent metabolic syndrome if they had three or more of the following five components: *1*) waist circumference >102 cm in men, > 88 cm in women; *2*) triglycerides ≥1.69 mmol/l (150 mg/dl); *3*) HDL <1.04 mmol/l (40 mg/dl) in men, < 1.3 mmol/l (50 mg/dl) in women; *4*) systolic blood pressure ≥130 mmHg, diastolic blood pressure ≥85 mmHg, or use of antihypertensive medication; or *5*) fasting glucose ≥6.1 mmol/l (110 mg/dl). BMI was calculated as weight in kilograms divided by the square of height in meters. Diabetes was defined by history (type 1 or type 2 diabetes), use of diabetes medications, or a fasting plasma glucose level ≥7.0 mmol/l (126 mg/dl). Impaired renal function was defined as a creatinine clearance <30.0 ml/min based on the Cockcroft-Gault formula (39).

Because the prevalence of metabolic syndrome and some of its components differed significantly between men and women, sex-specific analyses were performed. Age-adjusted rates were calculated by the direct method using the total population as the standard; differences by sex and presence of metabolic syndrome were tested with the stratified Mantel-Haenszel test. Age-adjusted means of continuous characteristics were compared by sex and metabolic syndrome status using ANOVA. PTH was positively skewed and was therefore log transformed or categorized depending on the type of analysis conducted; untransformed means are reported for ease of interpretation. Sex-specific logistic regression models were fit to estimate the odds of metabolic syndrome and its components across quintiles of 25(OH)D and PTH after adjusting for age (years), current smoking, alcohol use (≥3 times per week), exercise, season of study participation, and, for women, hormone therapy. Models of metabolic syndrome components were additionally adjusted for the other components. Men and women in the lowest quintile of either 25(OH)D or PTH served as the referent groups unless otherwise noted. Tests for a linear trend were conducted by entering the categorical 25(OH)D and PTH variables into the regression models as an ordinal term. Because diabetes is frequently associated with vitamin D insufficiency and mild renal impairment may affect 25(OH)D-PTH homeostasis, analyses were repeated after exclusion of those with diabetes or impaired renal function. Effect modification by current hormone use in women was investigated in stratified models. SAS (version 9.1; SAS Institute, Cary, NC) was used to perform all analyses, with statistical significance at $P < 0.05$ using two-sided tests.

RESULTS — Men and women were of similar age (men 74.5 ± 9.5 years;

Table 1—*Age-adjusted characteristics of the study sample: Rancho Bernardo, CA, 1997–1999*

Variables	Men	Women	*P*
n	410	660	
Clinical			
Age (years)*	74.5 ± 9.5	74.6 ± 10.7	0.1
BMI (kg/m^2)	26.5 ± 0.2	24.9 ± 0.2	<0.0001
Waist (cm)	95.0 ± 0.5	79.9 ± 0.4	<0.0001
SBP (mmHg)	135.4 ± 1.0	136.7 ± 0.8	0.3
DBP (mmHg)	75.2 ± 0.5	72.9 ± 0.4	<0.0001
Diabetes (%)	13.2	7.1	0.001
Biochemical measures†			
Triglycerides (mmol/l)	1.4 ± 0.04	1.4 ± 0.03	0.7
Glucose (mmol/l)	5.9 ± 0.02	5.4 ± 0.02	<0.0001
HDL (mmol/l)	1.3 ± 0.05	1.7 ± 0.04	<0.0001
ATP III–defined MetSyn (%)	23.5	18.0	0.03
MetSyn criteria (%)‡			
Abdominal obesity	20.3	22.0	0.5
High blood pressure	72.5	68.2	0.1
High triglycerides	23.2	26.9	0.2
Hyperglycemia	30.8	12.0	<0.0001
Low HDL	20.9	17.2	0.1
Number of MetSyn criteria (%)‡			0.004
0	13.5	19.3	
1	40.0	41.3	
2	22.9	21.3	
3	14.3	11.2	
4	7.0	5.3	
5	2.2	1.5	
Serum 25(OH)D (nmol/l)	108.9 ± 0.3	101.6 ± 0.2	0.002
PTH (ng/l)§	51.3 ± 1.2	50.1 ± 1.0	0.3

Data are means ± SE or percentages unless otherwise indicated. *Unadjusted means ± SD. †To convert to conventional units (mg/dl), multiply triglycerides by 89, glucose by 39, and HDL by 18. ‡Criteria as defined by the NCEP/ATP III (41). §Untransformed means ±SE; *P* based on log-transformed data. DBP, diastolic blood pressure; MetSyn, metabolic syndrome; SBP, systolic blood pressure.

women 74.6 ± 10.7 years). The age of >92% (n = 379) of men and >89% (n = 587) of women was ≥60 years. The age-adjusted prevalence of metabolic syndrome was higher in men than women (23.5 vs. 18.0%, respectively, P = 0.03) (Table 1). The prevalence of metabolic syndrome components defined according to the sex-specific cut-points of NCEP/ATP III did not vary significantly by sex, except for fasting hyperglycemia, which was more common in men than women (30.8 vs. 12.0%, respectively, P < 0.0001). Women had significantly lower mean 25(OH)D concentrations (P = 0.002) than men, but PTH levels did not vary by sex (P = 0.30).

Hormone therapy and alcohol consumption were significantly lower among women with the metabolic syndrome compared with women without the metabolic syndrome (Table 2). Both men and women with the metabolic syndrome reported lower rates of exercise than those without. Mean PTH levels were significantly higher among men with the metabolic syndrome compared with men without the metabolic syndrome (P = 0.004) but were similar by metabolic syndrome status in women (P = 0.9). Neither diastolic blood pressure nor mean 25(OH)D concentrations varied by presence of metabolic syndrome in either sex.

The sex-specific associations of 25(OH)D and PTH with the metabolic syndrome and its components are displayed in Table 3. In men, a significant positive trend (P = 0.03) in the adjusted odds of metabolic syndrome across increasing quintiles of PTH was found; this association was largely explained by odds ratio (OR) 2.02 (95% CI 0.96–4.24) among men in the top quintile of PTH (≥63 ng/l). A modest J- or U-shaped association was found (*P* value for quadratic PTH = 0.08). Results were not materially changed after including 25(OH)D levels as a covariate in the multivariate model (OR 1.90 [95% CI 0.90–4.02], comparing the highest PTH quintile with the lowest; P_{trend} = 0.04) nor after excluding men with diabetes or impaired renal function (2.17 [0.80–5.89] comparing the highest PTH quintile with the lowest; P_{trend} = 0.08). Adjustment for HOMA-IR, however, appeared to at least partly explain the elevated risk of increased PTH on the metabolic syndrome (1.68 [0.64–4.40], comparing the highest PTH quintile with the lowest; P_{trend} = 0.2). Partial correlations comparing 25(OH)D and PTH with HOMA-IR were r = −0.13 and 0.12 (P < 0.05 for both), respectively, in men and r = −0.07 and 0.01 (P > 0.05 for both), respectively, in women. When adjusted for BMI, the OR for the metabolic syndrome comparing men in the highest quintile of PTH with men in the lowest did not change (2.03 [0.84–4.89], P_{trend} = 0.04). No significant associations of 25(OH)D or PTH with the metabolic syndrome in women nor 25(OH)D with the metabolic syndrome in men were found (Table 3). Further evaluation of the 25(OH)D–PTH–metabolic syndrome associations among women who were current users of hormone therapy versus never/former users revealed similar nonsignificant findings (data not shown).

To more fully examine the potential effect of 25(OH)D on the increased odds of metabolic syndrome observed in men in the top quintile of PTH, we jointly classified men into groups defined by quintile of PTH and median 25(OH)D levels (105.0 nmol/l) [i.e., high vs. low 25(OH)D]. Results of this analysis revealed similar increases but nonsignificant adjusted odds of metabolic syndrome among men in the highest quintile of PTH with high and low 25(OH)D (OR 1.89 [95% CI 0.73–4.91] and 2.11 [0.74–6.02], respectively) compared with men in the lowest quintile of PTH and high 25(OH)D.

Among the components, a significant inverse multivariate association of 25(OH)D with fasting hyperglycemia in men and a positive association with high triglycerides in women were present (P_{trend} = 0.01 for both) (Table 3). The adjusted odds of high blood pressure, hyperglycemia, and low HDL were significantly elevated among men in the highest quintile of PTH compared with men in the lowest quintile. A positive association of PTH with abdominal obesity in women was noted (P_{trend} = 0.03).

CONCLUSIONS — In the current study, we found no evidence of an association of 25(OH)D with the metabolic

Table 2—*Age-adjusted metabolic syndrome* components, health-related behaviors, 25(OH)D, and PTH levels in men and women with and without metabolic syndrome: Rancho Bernardo, CA, 1997–1999*

	Men			Women		
	MetSyn present	MetSyn absent	*P*	MetSyn present	MetSyn absent	*P*
n	97	313		120	540	
Age (years)†	72.9 ± 8.9	75.0 ± 9.7	0.07	75.8 ± 9.7	74.3 ± 11.0	0.2
MetSyn components						
Waist circumference (cm)	103.6 ± 0.9	92.2 ± 0.5	<0.0001	92.0 ± 0.9	77.2 ± 0.4	<0.0001
SBP (mmHg)	140.5 ± 2.0	133.7 ± 1.1	0.003	141.4 ± 1.8	135.7 ± 0.9	0.005
DBP (mmHg)	75.0 ± 0.9	75.2 ± 0.5	0.8	73.5 ± 0.9	72.7 ± 0.4	0.5
Triglycerides (mmol/l)‡§	2.3 ± 0.1	1.1 ± 0.1	<0.0001	2.1 ± 0.1	1.3 ± 0.03	<0.0001
Fasting glucose (mmol/l)‡	6.9 ± 0.1	5.6 ± 0.05	<0.0001	6.4 ± 0.1	5.3 ± 0.04	<0.0001
HDL (mmol/l)‡	1.1 ± 0.03	1.4 ± 0.02	<0.0001	1.3 ± 0.04	1.8 ± 0.02	<0.0001
Health-related behaviors (%)						
Vitamin D supplement use	10.2	9.3	0.7	26.8	28.9	0.7
Calcium supplement use	14.9	23.8	0.08	55.6	58.3	0.6
Thyroid hormone use	6.7	8.9	0.4	22.8	20.7	0.8
Current hormone therapy	—	—	—	36.9	50.6	0.005
Current smoker	2.5	4.8	0.4	3.4	5.0	0.5
Alcohol use (≥3 times per week)	57.8	57.7	0.9	28.4	45.0	0.001
Exercise (≥3 times per week)	68.6	80.4	0.01	51.7	73.1	<0.0001
Serum 25(OH)D (nmol/l)	104.0 ± 3.4	110.4 ± 1.9	0.1	97.9 ± 3.2	102.5 ± 1.5	0.2
PTH‡ (ng/l)	57.3 ± 2.7	49.4 ± 1.5	0.004	51.2 ± 2.2	49.8 ± 1.1	0.9

Data are means ± SE or percentages unless otherwise indicated. *Criteria as defined by the NCEP/ATP III (41), see text for full description. †Unadjusted means ± SD. ‡To convert to conventional units (mg/dl), multiply triglycerides by 89, fasting glucose by 39, and HDL by 18. §Untransformed means ± SE; *P* based on log-transformed data. DBP, diastolic blood pressure; MetSyn, metabolic syndrome; SBP, systolic blood pressure.

syndrome in either sex, but there was a significant trend for increasing odds of metabolic syndrome with increasing PTH levels in older men. This association was independent of the potential confounding effects of age, season, major lifestyle factors, diabetes, renal function, and 25(OH)D levels and was not observed in women with or without current hormone use. To our knowledge, this is the first population-based study to investigate the association of both 25(OH)D and PTH with the metabolic syndrome.

Vitamin D and PTH are together responsible for maintaining extracellular calcium homeostasis. Vitamin D facilitates intestinal calcium absorption, while low serum calcium concentrations stimulate the secretion of PTH to increase calcium resorption from the skeleton and increase the renal reabsorption of calcium. This resultant secondary hyperparathyroidism has been shown to increase the risk of fracture (20), hypertension (21,22,24–26), obesity (6,9,10,27–29), and diabetes (30–32). Results of the present study suggest that hyperparathyroidism may contribute to the development of metabolic syndrome, an association that is biologically plausible based on epidemiologic studies showing a significant association of higher dietary calcium and dairy intake with a reduced risk of metabolic syndrome in young and middle-aged adults (42,43). Thus, a dietary pattern characterized by a high intake of calcium may downregulate PTH release, resulting in a reduced risk of metabolic syndrome. In the present study, the use of calcium supplements was not significantly associated with the metabolic syndrome (see Table 2). Further studies are needed to confirm the observed association of PTH with the metabolic syndrome and to uncover the potential role of PTH in studies of calcium intake in association with the metabolic syndrome.

In the present study, HOMA-IR partly explained the association of elevated PTH with the metabolic syndrome in men, suggesting that insulin resistance may at least partly mediate the association of high PTH levels with increased odds of metabolic syndrome. Primary and secondary hyperparathyroidism have been previously suspected to be involved in glucose metabolism and diabetes (44). Clinical investigations consistently show a two- to fourfold elevated risk of diabetes among individuals with hyperparathyroidism (30–32). In addition, elevated PTH has been associated with impaired glucose tolerance (45) and decreased insulin sensitivity in normotensive, glucose-tolerant adults (2). Insulin resistance is widely proposed as the mechanism underlying the metabolic syndrome (46). Alternatively, the association of increased PTH with the metabolic syndrome may be explained through relations with individual components, especially high blood pressure, hyperglycemia, and low HDL, which were all significantly elevated in men with the highest PTH levels (see Table 3).

The results of this study suggest that the association of increased PTH with the metabolic syndrome may be limited to men, especially those with the highest PTH levels. We are unsure as to why this association was not observed in women, although these findings may be at least partly attributable to sex differences in the prevalence of metabolic syndrome or calcium absorption. It has been previously demonstrated that increases in estrogen levels result in concomitant increases in the intestinal absorption of calcium (47). In addition, in the current study, 57.8% of women reported the use of calcium supplements, compared with 21.8% of men. Thus, the greater bioavailability of

Table 3—*Age-adjusted prevalence, adjusted ORs, and 95% CIs of metabolic syndrome and its components by quintiles of 25(OH)D and PTH among men and women: Rancho Bernardo, CA, 1997–1999*

	Metabolic syndrome*		Abdominal obesity		High blood pressure		High triglycerides		Hyperglycemia		Low HDL	
Quintiles	Prevalence†	OR (95% CI)‡	Prevalence†	OR (95% CI)§	Prevalence†	OR (95% CI)§	Prevalence†	OR (95% CI)§	Prevalence†	OR (95% CI)§	Prevalence†	OR (95% CI)§
25 (OH)D (nmol/l)												
Men												
I (<087.5)	29.6	1.0 (ref.)	29.8	1.0 (ref.)	75.8	1.0 (ref.)	32.0	1.0 (ref.)	42.9	1.0 (ref.)	23.2	1.0 (ref.)
II (8.75–97.4)	26.7	0.83 (0.39–1.73)	17.3	0.51 (0.22–1.20)	72.4	0.92 (0.41–2.07)	19.3	0.52 (0.22–1.19)	37.5	0.93 (0.45–1.93)	21.7	1.03 (0.44–2.42)
III (97.5–110.0)	22.7	0.68 (0.32–1.43)	22.3	0.82 (0.38–1.79)	73.1	0.90 (0.41–1.96)	23.4	0.69 (0.32–1.50)	25.7	0.46 (0.22–0.96)	21.7	1.39 (0.61–3.18)
IV (110.1–126.2)	21.4	0.65 (0.32–1.34)	18.0	0.61 (0.28–1.32)	69.7	0.88 (0.42–1.84)	23.2	0.78 (0.37–1.63)	28.1	0.53 (0.26–1.08)	19.5	1.11 (0.49–2.52)
V (≥126.3)	21.8	0.57 (0.26–1.25)	17.9	0.47 (0.20–1.13)	72.2	1.28 (0.58–2.81)	21.9	0.62 (0.28–1.41)	24.7	0.43 (0.20–0.95)	23.0	1.51 (0.63–3.62)
P_{trend}	0.08	0.1	0.04	0.2	0.6	0.6	0.1	0.5	0.004	0.001	0.6	0.4
Women												
I (<77.5)	24.4	1.0 (ref.)	32.9	1.0 (ref.)	74.7	1.0 (ref.)	27.1	1.0 (ref.)	18.8	1.0 (ref.)	24.0	1.0 (ref.)
II (77.5–92.4)	15.5	0.96 (0.48–1.90)	22.2	0.84 (0.44–1.61)	65.2	0.77 (0.40–1.46)	21.1	0.85 (0.44–1.62)	9.1	0.60 (0.26–1.39)	18.5	1.30 (0.64–2.65)
III (92.5–103.7)	17.2	0.96 (0.51–1.79)	21.7	0.82 (0.45–1.50)	66.3	0.80 (0.44–1.47)	22.5	0.93 (0.51–1.69)	12.1	0.84 (0.40–1.76)	17.8	1.15 (0.58–2.26)
IV (103.8–119.9)	20.9	1.33 (0.69–2.57)	22.5	0.82 (0.43–1.56)	66.5	0.81 (0.43–1.53)	33.5	1.68 (0.92–3.08)	13.2	0.94 (0.44–2.04)	14.1	0.78 (0.37–1.63)
V (≥120.0)	12.6	0.88 (0.43–1.80)	15.0	0.51 (0.26–1.02)	71.5	1.01 (0.53–1.93)	29.6	1.68 (0.91–3.10)	8.2	0.62 (0.26–1.46)	11.0	0.77 (0.35–1.69)
P_{trend}	0.1	0.9	0.01	0.09	0.8	0.8	0.2	0.01	0.1	0.6	0.02	0.3
PTH (ng/l)												
Men												
I (<35.0)	19.7	1.0 (ref.)	19.5	1.0 (ref.)	63.8	1.0 (ref.)	26.6	1.0 (ref.)	22.3	1.0 (ref.)	17.0	1.0 (ref.)
II (35.0–42.9)	16.6	0.62 (0.27–1.44)	17.3	0.74 (0.31–1.78)	73.6	2.15 (1.03–4.47)	16.9	0.53 (0.23–1.23)	23.5	0.94 (0.42–2.10)	19.1	1.37 (0.56–3.35)
III (43.0–49.9)	23.0	0.93 (0.42–2.05)	22.6	1.17 (0.51–2.70)	70.2	1.43 (0.70–2.92)	22.6	0.89 (0.40–1.97)	24.9	0.76 (0.34–1.70)	17.0	1.03 (0.42–2.56)
IV (50.0–62.9)	21.9	0.88 (0.40–1.94)	18.7	0.76 (0.33–1.78)	75.9	1.80 (0.87–3.74)	20.8	0.73 (0.33–1.63)	33.4	1.41 (0.66–3.03)	18.7	1.23 (0.51–2.98)
V (≥63.0)	36.0	2.02 (0.96–4.24)	21.8	0.65 (0.28–1.53)	80.1	2.41 (1.10–5.26)	30.9	0.96 (0.44–2.12)	46.4	2.16 (1.01–4.59)	33.6	2.33 (1.02–5.35)
P_{trend}	0.009	0.03	0.6	0.4	0.4	0.08	0.2	0.8	<0.001	0.02	0.02	0.07
Women												
I (<33.0)	16.6	1.0 (ref.)	16.0	1.0 (ref.)	61.4	1.0 (ref.)	32.4	1.0 (ref.)	10.3	1.0 (ref.)	16.0	1.0 (ref.)
II (33.0–40.9)	19.9	1.38 (0.70–2.71)	20.7	1.31 (0.65–2.63)	67.7	1.25 (0.70–2.22)	24.1	0.62 (0.34–1.11)	13.2	1.12 (0.50–2.51)	21.0	1.52 (0.74–3.14)
III (41.0–48.9)	15.7	0.85 (0.41–1.75)	18.7	1.22 (0.60–2.51)	70.0	1.51 (0.84–2.72)	26.0	0.79 (0.44–1.41)	7.9	0.60 (0.24–1.50)	14.5	0.84 (0.39–1.84)
IV (49.9–63.9)	18.5	1.02 (0.51–2.06)	30.6	2.53 (1.28–5.00)	72.0	1.50 (0.81–2.78)	26.8	0.70 (0.38–1.27)	11.9	0.77 (0.33–1.81)	18.6	0.82 (0.38–1.75)
V (≥64.0)	21.2	1.13 (0.57–2.26)	26.0	1.70 (0.85–3.40)	68.1	1.27 (0.70–2.31)	28.4	0.86 (0.48–1.54)	17.6	1.31 (0.59–2.92)	16.4	0.69 (0.31–1.50)
P_{trend}	0.6	0.9	0.02	0.03	0.3	0.3	0.9	0.8	0.3	0.7	0.9	0.1

*Criteria as defined by the NCEP/ATP III (41). †Adjusted for age (years). ‡Adjusted for age (years), current smoking, alcohol use (≥3 times per week), exercise (≥3 times per week), season of study participation, and, in women, hormone therapy. §Adjusted for variables listed above in addition to other components of metabolic syndrome.

calcium and the increased use of dietary supplements may result in significant metabolic differences regarding circulating calcium homeostasis. In fact, in the present study, mean 25(OH)D concentrations were significantly lower in women compared with men. To compensate for low bioavailable vitamin D, it would be expected that PTH levels would be higher in women. However, no significant sex differences in mean PTH concentrations were observed. Future studies are required to confirm these sex-specific findings.

Results of this study differ from two recent reports showing a significant inverse association between 25(OH)D levels and the prevalence of metabolic syndrome (1,18). Using cross-sectional data from the Third National Health and Nutrition Examination Survey, Ford et al. (18) showed that the odds of metabolic syndrome were 54% lower (OR 0.46 [95% CI 0.32–0.67]) among U.S. adults in the highest quintile of 25(OH)D compared with those in the lowest quintile, with a significant trend of decreasing ORs across increasing quintiles ($P_{trend} < 0.001$). These results were independent of numerous confounding factors. In another study of 126 healthy, glucose-tolerant adults, the crude prevalence of metabolic syndrome was nearly three times higher among those with vitamin D insufficiency [25(OH)D <50 nmol/l] compared with those with higher 25(OH)D levels (30 versus 11%, $P = 0.0076$) (1). The nonsignificant findings in the present cohort may reflect their residence in a southern California community, which has a sunny and temperate year-round climate, reducing the variability observed in 25(OH)D. Skin exposure to sunlight (UVB radiation) is the predominant source of vitamin D, and UVB exposure varies greatly by latitude of residence (48). Thus, an effect of vitamin D in the pathogenesis of the metabolic abnormalities underlying the metabolic syndrome should not be completely ruled out.

This study is limited by the cross-sectional nature of these data, which impedes the ability to infer causality due to the absence of a temporal relation, and by the possibility that unmeasured or residual confounding may explain our findings. The fairly high 25(OH)D levels observed here likely reflect latitude and year-round sun exposure. However, these elevated 25(OH)D levels may also be due to the CBP assay used to assess 25(OH)D levels. At the time the blood samples were measured, a radioimmunoassay was not available, and high-performance liquid chromatography was more costly and labor intensive. Recently, laboratory comparisons have shown that CBP assays may produce higher 25(OH)D levels compared with radioimmunoassay or high-performance liquid chromatography methods (49,50). Nevertheless, routine assays accurately rank individuals across the range of 25(OH)D levels (50), and therefore the use of the CBP assay should not have affected the associations or lack of associations between 25(OH)D and the metabolic syndrome reported here. We acknowledge that the external validity of our findings may be limited to middle- to upper-middle class Caucasians and may not be generalizable to other groups or to individuals residing outside a climate similar to that of southern California.

In conclusion, we found that elevated PTH levels were associated with an increased prevalence of metabolic syndrome in men, but not women, and this association was not explained by age, season, major lifestyle factors, diabetes, renal function, or 25(OH)D concentrations. We also found evidence that this association may be at least partly mediated through insulin resistance. The reason for the sex difference in the PTH–metabolic syndrome association is unknown. No association of 25(OH)D with the metabolic syndrome was found in either sex. Prospective studies are needed to further investigate the putative etiologic roles for 25(OH)D and PTH in the development of metabolic syndrome in older adults.

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