

Association of 25-Hydroxyvitamin D and Parathyroid Hormone With Incident Hypertension



MESA (Multi-Ethnic Study of Atherosclerosis)

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- Objectives** This study investigated whether lower 25-hydroxyvitamin D and higher parathyroid hormone concentrations are associated with incident hypertension.
- Background** Disturbances in vitamin D metabolism are plausibly related to hypertension.
- Methods** MESA (Multi-Ethnic Study of Atherosclerosis) is a community-based, prospective cohort with baseline measurements obtained between 2000 and 2002. We studied 3,002 men and women free of prevalent cardiovascular disease and hypertension, age 45 to 84 years at baseline. Serum 25-hydroxyvitamin D and intact parathyroid hormone were measured from previously frozen baseline samples using liquid chromatography–mass spectroscopy and a 2-site immunoassay, respectively. We used a complementary log–log model with interval censoring to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for 25-hydroxyvitamin D and parathyroid hormone concentrations with incident hypertension through 2010.
- Results** During a median follow-up of 9.0 years, 41% of the cohort (n = 1,229) developed hypertension. Mean serum 25-hydroxyvitamin D was 26.3 ± 11.2 ng/ml and mean parathyroid hormone was 41.2 ± 17.3 pg/ml. Compared with 25-hydroxyvitamin D ≥ 30 ng/ml, 25-hydroxyvitamin D < 20 ng/ml was associated with a greater hypertension risk (HR: 1.28 [95% CI: 1.09 to 1.50]), although the association was attenuated and not statistically significant after adjusting for potential confounders (HR: 1.13 [95% CI: 0.96 to 1.33]). Compared with parathyroid hormone < 33 pg/ml, parathyroid hormone ≥ 65 pg/ml was associated with a significantly greater risk of hypertension (HR: 1.27 [95% CI: 1.01 to 1.59]) after adjusting for potential confounders.
- Conclusions** Lower 25-hydroxyvitamin D concentrations were not associated with a greater risk of incident hypertension. Higher serum parathyroid hormone concentrations showed a significant, but statistically marginal, relationship to the development of hypertension. These findings will require further confirmation. (Multi-Ethnic Study of Atherosclerosis; [NCT00005487](https://doi.org/10.1016/j.jacc.2014.01.012)) (J Am Coll Cardiol 2014;63:1214–22) © 2014 by the American College of Cardiology Foundation

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Hypertension is a major risk factor for cardiovascular disease, with established complications of stroke, myocardial infarction, and heart failure (1). Despite the high worldwide prevalence of hypertension and known clinical consequences, the underlying causes of hypertension are not fully elucidated. Identifying novel risk factors for hypertension is important for understanding the etiology of and the suggestion of possible new treatment targets to reduce the high burden of morbidity and mortality.

Disturbances in vitamin D and parathyroid hormone (PTH) metabolism are plausibly related to hypertension through diverse mechanisms. Primary hyperparathyroidism

is long recognized for its association with prevalent hypertension, and more recent prospective studies demonstrate associations of greater serum PTH concentrations with higher blood pressure in men (2) and with incident hypertension in the general population (3,4). Vitamin D deficiency promotes secondary hyperparathyroidism, increases the secretion of aldosterone, and stimulates the renin-angiotensin system (5). Lower serum 25-hydroxyvitamin D (25[OH]D) concentrations are associated with higher blood pressure and hypertension risk (6,7). Furthermore, disturbances in both serum 25(OH)D and PTH are related to arterial stiffness and vascular dysfunction, which are strong determinants of future hypertension (8).

Despite intriguing potential physiologic connections of biomarkers of vitamin D and PTH metabolism with blood pressure, few studies have prospectively evaluated associations of serum 25(OH)D and PTH concentrations with the initial development of hypertension (3,4,6,7,9,10). Previous studies have assessed single biomarkers, used self-reported hypertension data, did not investigate both sexes, or were conducted among racially homogenous populations. Understanding prospective associations of vitamin D and PTH with the onset of hypertension would provide insight into disease mechanisms and may be important for developing future preventive strategies.

We measured serum 25(OH)D and PTH concentrations in 3,002 individuals from a community-based, middle-aged, multi ethnic cohort free of clinical hypertension and cardiovascular diseases. We hypothesized that lower serum 25(OH)D and higher serum PTH concentrations would be associated with incident hypertension during long-term follow-up.

Methods

Design and sample. The MESA (Multi-Ethnic Study of Atherosclerosis) is a prospective study of cardiovascular disease among 6,814 community-dwelling residents age 45 to 84 years who were free of cardiovascular disease at baseline. Between 2000 and 2002, participants were recruited from 6 centers across the United States with different self-reported ethnic backgrounds (11). Participants with any previous history of cardiovascular diseases were excluded at baseline as previously described (11). MESA included 4 follow-up examinations at approximately 18 months, 36 months, 4 years, and 10 years from the baseline examination between 2002 and 2010, along with periodic telephone contacts every 6 to 12 months.

We excluded MESA participants who had baseline hypertension, defined as a systolic blood pressure ≥ 140 mm Hg, diastolic blood pressure ≥ 90 mm Hg ($n = 3,058$), or use of any antihypertensive medication ($n = 279$). We further excluded for self-reported hypertension ($n = 171$), missing data for anti-hypertension medication use ($n = 2$), or inadequate sample volume for measuring 25(OH)D or PTH ($n = 153$). None of the remaining participants used lithium

medication or loop diuretics, which may alter calcium metabolism. Finally, we excluded participants who did not return for any follow-up MESA examinations ($n = 149$), leaving a final analytic sample of 3,002 participants, free of hypertension at baseline with complete serum 25(OH)D and PTH measurements (Fig. 1). Compared with participants excluded, included participants were younger (58.6 years vs. 64.9 years) and less likely to be black (19.6% vs. 34.2%). Study protocols were approved by the institutional review board at each participating institution, and all participants granted informed consent.

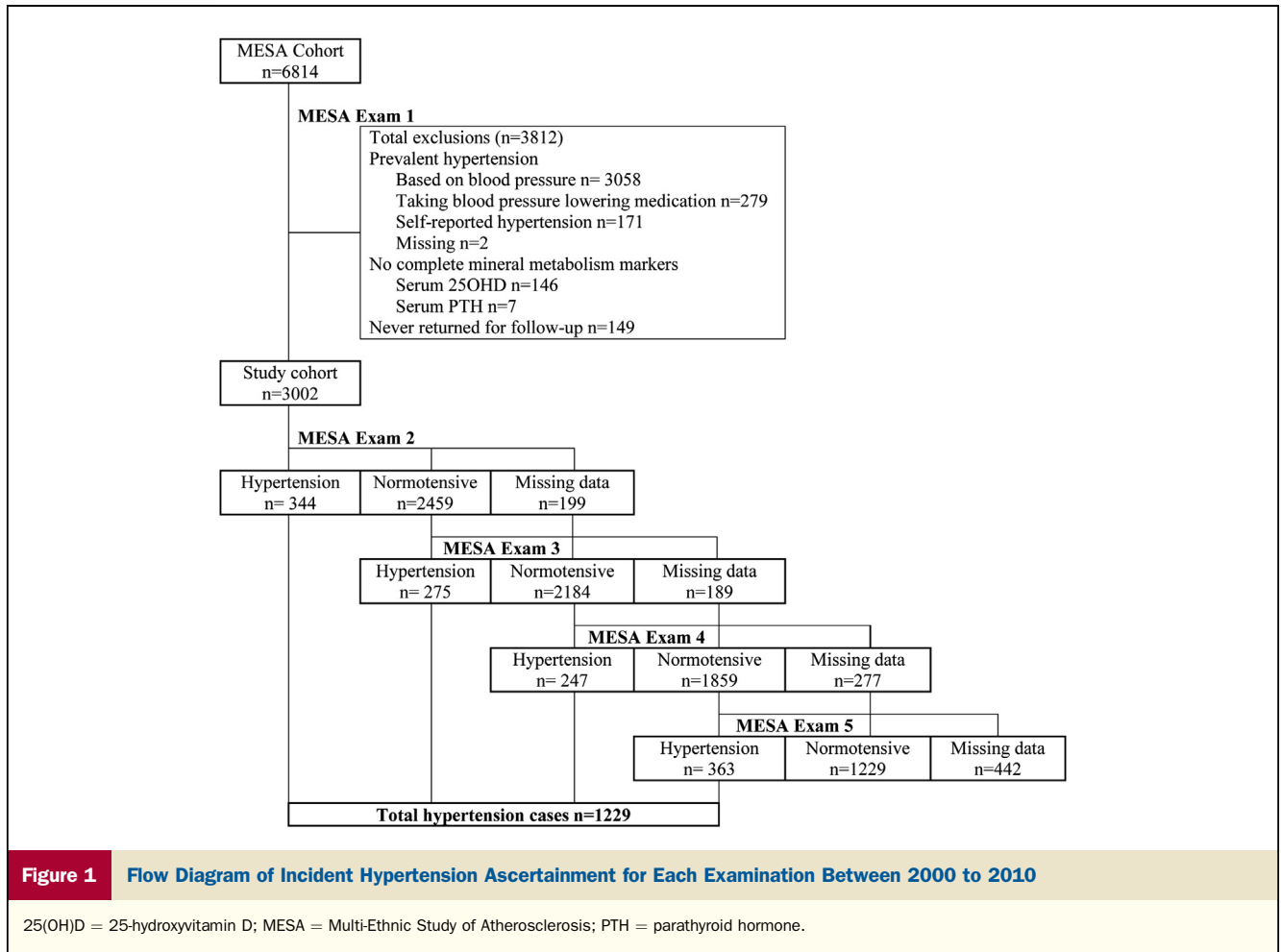
Measurements of vitamin D and PTH. We measured serum 25(OH)D and PTH concentrations in baseline serum samples that were collected in the morning after an 8- to 12-h overnight fast. Samples were stored at -80°C and thawed before analysis in 2011. We measured total serum 25(OH)D (25OHD₂ + 25OHD₃) using liquid chromatography–mass spectrometry on a Quattro Micro mass spectrometer (Waters, Milford, Connecticut) (inter assay CV $< 3.4\%$). We verified calibration of serum 25(OH)D concentrations using SRM 972 from the National Institutes of Standards and Technology. We measured intact serum PTH concentrations using an automated 2-site immunoassay (Beckman-Coulter, Inc., Brea, California) (interassay coefficient of variation between 3.4% and 6.1%) (12).

Determination of incident hypertension. MESA study personnel assessed blood pressure and antihypertensive medications at each examination. During each examination, study personnel obtained 3 blood pressure measurements at 5 min apart with the participant seated using an automated Dinamap sphygmomanometer (Critikon, General Electric, Madison, Wisconsin). We calculated the mean of the second 2 measurements for analysis. MESA study personnel instructed participants to bring all of their medications to each examination, and medication use was assessed by the inventory method. We defined incident hypertension as a systolic blood pressure ≥ 140 mm Hg, diastolic blood pressure ≥ 90 mm Hg, or the use of any antihypertensive medication during any of the follow-up examinations.

Covariates. Study personnel collected detailed data regarding demographics, comorbidities, and medication use at enrollment (11). We measured serum phosphate and calcium to incorporate other important factors of the mineral metabolism in our analyses. We measured serum phosphate using a timed-rate colorimetry reaction and serum calcium by indirect ion selective electrode (12). Participants completed questionnaires to determine race/ethnicity, smoking status, alcohol consumption, physical activity, income, and attained education (11). The highest level of attained education was categorized into 3 categories: some high school or less,

Abbreviations and Acronyms

25(OH)D	=	25-hydroxyvitamin D
BMI	=	body mass index
CKD	=	chronic kidney disease
CRP	=	C-reactive protein
eGFR	=	estimated glomerular filtration rate
HR	=	hazard ratio
PTH	=	parathyroid hormone



completed high school, or completed college or more. Body mass index (BMI, kg/m²) categories were based on measured height and weight, defined as normal weight (<25 kg/m²), overweight (25 to 30 kg/m²) and obese (>30 kg/m²). Type 2 diabetes was defined as a reported history of diabetes, use of any diabetes medication, or a blood glucose level ≥7 mmol/l (≥126 mg/dl). Impaired fasting glucose was defined by a glucose level of 5.6 to 7.0 mmol/l (100 to 125 mg/dl). Estimated glomerular filtration rate (eGFR) was calculated from serum calibrated creatinine and cystatin C concentrations using the Chronic Kidney Disease (CKD) Epidemiology Collaboration 2012 equation. We defined CKD as eGFR <60 ml/min/1.73 m². The Laboratory for Clinical Biochemistry Research measured high-sensitivity C-reactive protein (CRP) levels by using the BN II nephelometer (Siemens, Erlangen, Germany).

Statistical Analysis

We adjusted serum 25(OH)D concentrations for season using methods previously established in MESA (13). We examined Spearman's correlations between serum 25(OH)D and PTH concentrations to describe univariate associations.

We tabulated baseline participant characteristics by widely used categories of 25(OH)D (<20 ng/ml; >20 to 30 ng/ml; and >30 ng/ml) and by PTH categories that combined tertiles with a threshold value of 65 pg/ml (<33 pg/ml; >33 to 44.2 pg/ml; >44.2 to 65 pg/ml; >65 ng/ml). The PTH value of 65 pg/ml represents the upper limit of normal for this assay based on the central 95% of values from 43 normal laboratory personnel who had normal 25(OH)D concentrations in March 2005 (12). We defined primary hyperparathyroidism as a serum PTH concentration ≥65 pg/ml plus a serum calcium concentration >10.2 mg/dl (14).

We calculated risk time for incident hypertension as elapsed time from the baseline examination until the first examination at which incident hypertension was diagnosed, the last MESA examination, or the last examination before loss to follow-up, whichever came first. We calculated unadjusted hypertension rates as the number of events per 100 person-years.

We used a complementary log–log model to estimate hazard ratios (HRs) for 25(OH)D and PTH with incident hypertension (15). This model is very similar to a Cox proportional hazards model, but is able to account for the time between the discrete time points because the exact date

of the development of hypertension is unknown. To account for the time that hypertension could occur between the discrete time intervals, we used interval-censored analyses to estimate HRs, under the assumption that the hazard is constant within each interval, but can vary across intervals. This assumption of piecewise-constant hazards is preferred for discrete time intervals because risk estimates can change over time. We used a Wald test to calculate p values and 95% confidence intervals (CIs). Based on visual inspection of the hazard functions by Schoenfeld residuals, we found no evidence to contradict the proportionality assumption.

We adjusted serial nested models for demographic variables and known hypertension risk factors. In the first model, we adjusted for age, sex, race, and clinic site. In the second model, we added adjustment for smoking (yes/no), education (3 categories), total family income (5 categories), diabetes status (3 categories), BMI, low-density lipoprotein cholesterol, nonsteroidal anti-inflammatory medication and cyclooxygenase-2 inhibitor use, and physical activity. We further adjusted models of PTH for serum 25(OH)D (ng/ml) because vitamin D deficiency is a known risk factor for hyperparathyroidism. To separately study potential confounding by kidney function, we adjusted the final model for urinary albumin creatinine ratio and eGFR. We analyzed age, BMI, low-density lipoprotein cholesterol, physical activity, eGFR, and albumin creatinine ratio as continuous variables in the multivariate models. Finally, we assessed dose-response relations of 25(OH)D and PTH with incident hypertension using restricted cubic spline models adjusted for covariates specified in model 3.

We looked for potential effect modification by race, sex, BMI, CKD, and interaction by 25(OH)D with PTH using interaction terms, and present combined results for the total study sample if estimates were similar. To test the stability of the estimates, we conducted several sensitivity analyses: 1) excluding participants with incident hypertension diagnosed solely by incident use of antihypertensive medications because medication may be prescribed to participants with diabetes but without hypertension; and 2) excluding participants with borderline hypertension at baseline, defined as systolic blood pressure ≥ 130 mm Hg and diastolic blood pressure ≥ 85 mm Hg at baseline, for a meaningful change in blood pressure. We conducted analyses using IBM SPSS 20.0 for Windows 7 (SPSS Inc., Chicago, Illinois).

Results

Study sample. Among the 3,002 MESA participants, mean age was 59 ± 9.7 years and 53% were female. After completing the baseline examination, 2,258 MESA participants completed all 4 subsequent examinations, 487 participants completed 3, 151 participants completed 2, and 106 participants completed 1 follow-up examination. Approximately 15% of participants were current smokers, 6% had type 2 diabetes, 6% had CKD, and <1% ($n = 17$) had primary

hyperparathyroidism. Excluded participants who did not attend any follow-up visit ($n = 149$) were older (61 years vs. 59 years), more likely to be male (53% vs. 47%), had higher systolic blood pressure (116 mm Hg vs. 114 mm Hg), higher prevalence of diabetes (9% vs. 6%), less likely to be white (28% vs. 43%), and more likely to be Hispanic (40% vs. 23%).

Description of serum 25(OH)D and PTH concentrations.

The distribution of serum 25(OH)D and PTH concentrations were both unimodal and approximately symmetric, with mean values of 26.3 ± 11.2 ng/ml and 41.2 ± 17.3 pg/ml. Serum 25(OH)D concentrations were inversely correlated with serum PTH concentrations (correlation coefficient -0.34). Lower serum 25(OH)D concentrations were related to younger age, black and Hispanic race, lower attained education, higher prevalence of type 2 diabetes, current smoking, higher BMI, lower high-density lipoprotein cholesterol, and higher PTH, eGFR, and CRP concentrations (Table 1). Higher serum PTH concentrations were associated with older age; black and Hispanic race; higher BMI, systolic blood pressure, and CRP concentrations; and lower 25(OH)D and phosphate concentrations.

Incident hypertension. During a median follow-up of 9.0 years (range 1.2 to 11.1 years), 1,229 participants (41%) developed incident hypertension. The determination of incident hypertension was made by blood pressure measurements alone in 349 participants, antihypertensive medication use alone in 249 participants, and both blood pressure and medication use in 631 participants.

Associations of 25(OH)D with incident hypertension.

Lower serum 25(OH)D categories were associated with greater unadjusted incident hypertension rates during follow-up (Table 2). Associations of 25(OH)D with hypertension persisted after minimal adjustments; however, further adjustment for potential confounders, plus measures of kidney function, progressively attenuated these associations, which were no longer statistically significant (HR: 1.13 [95% CI: 0.96 to 1.33]). Fully adjusted spline models of continuous serum 25(OH)D concentrations showed a tendency toward greater hypertension risks with lower 25(OH)D concentrations, although not statistically significant (Fig. 2A).

Associations of 25(OH)D and hypertension were similar across subgroups defined by age, sex, race, CKD, and PTH (p for interaction > 0.10). We found evidence for an interaction between 25(OH)D categories and BMI categories in relation to incident hypertension (interaction $p < 0.001$) with greater and statistically significant risk among obese participants (BMI range ≥ 30 to 52 kg/m²) (Fig. 3A). However, when adjusting for BMI as a continuous variable because associations may be driven by the severity of BMI within the BMI categories, the results attenuated notably and were no longer significant within BMI strata (HR: 1.17 [95% CI: 0.92 to 1.42] for overweight and 1.32 [95% CI: 0.88 to 1.75] for obese participants).

Table 1 Characteristics of 3,002 Participants by Serum 25(OH)D and PTH Concentrations

	Serum 25(OH)D (ng/ml)*			Serum PTH (pg/ml)*			
	<20	>20–30	>30	<33	>33–44.2	>44.2–65	>65
Demographic data							
n	922	1,028	1,052	1,056	912	789	245
Age, yrs	57.0 ± 9.4	59.0 ± 9.7	60.0 ± 9.8	58.0 ± 9.4	58.0 ± 9.8	60.0 ± 9.7	60.0 ± 10.0
Females	497 (54)	511 (50)	572 (53)	566 (54)	463 (51)	410 (52)	141 (58)
Race							
White	204 (22)	441 (43)	661 (63)	540 (51)	407 (45)	287 (36)	72 (29)
Black	391 (43)	139 (14)	58 (5)	125 (12)	173 (19)	208 (26)	82 (34)
Chinese	94 (10)	187 (18)	135 (13)	193 (18)	131 (14)	83 (11)	9 (4)
Hispanic	233 (25)	261 (25)	198 (19)	198 (19)	201 (22)	211 (27)	82 (33)
Highest level of education							
Some high school or less	141 (15)	170 (17)	141 (13)	147 (14)	142 (16)	121 (15)	42 (17)
Completed high school	386 (42)	390 (38)	369 (35)	401 (38)	331 (36)	311 (40)	102 (42)
Completed college or more	393 (43)	466 (45)	541 (52)	506 (48)	437 (48)	357 (45)	100 (41)
Type 2 diabetes	75 (8)	67 (7)	40 (4)	62 (6)	54 (6)	53 (7)	13 (5)
IFG	131 (14)	112 (11)	77 (7)	91 (9)	98 (11)	95 (12)	36 (15)
CKD	38 (4)	58 (6)	95 (9)	61 (6)	55 (6)	55 (7)	20 (8)
Cigarette smokers	185 (20)	132 (13)	124 (12)	171 (16)	145 (16)	100 (13)	25 (10)
Physical activity (MET-min/week)	6,703 ± 6,455	5,692 ± 5,509	6,484 ± 6,052	6,254 ± 5,853	6,203 ± 5,859	6,326 ± 6,339	6,577 ± 6,321
BMI, kg/m ²	29.0 ± 5.9	27.0 ± 4.6	26.0 ± 4.2	25.9 ± 4.3	27.3 ± 5.0	28.1 ± 5.1	30.0 ± 6.3
SBP, mm Hg	115.0 ± 12.3	114.0 ± 12.9	114.0 ± 13.3	112.0 ± 12.9	114.0 ± 13.0	116.0 ± 12.7	117.0 ± 12.1
DBP, mm Hg	70.0 ± 8.3	69.0 ± 8.6	68.0 ± 8.8	68.0 ± 8.6	69.0 ± 8.8	69.0 ± 8.5	69.0 ± 8.7
Metabolic variables							
25(OH)D, ng/ml	14.0 ± 3.8	25.0 ± 2.8	38.0 ± 8.4	30.0 ± 11.3	27.0 ± 10.3	23.0 ± 10.3	19.0 ± 10.1
PTH, pg/ml	49.0 ± 20.8	40.0 ± 15.0	35.0 ± 12.9	26.0 ± 4.8	38.0 ± 3.2	52.0 ± 5.6	81.0 ± 21.6
Calcium, mg/dl	9.6 ± 0.4	9.6 ± 0.4	9.7 ± 0.4	9.7 ± 0.4	9.6 ± 0.4	9.6 ± 0.4	9.6 ± 0.5
Phosphate, mg/dl	3.7 ± 0.5	3.7 ± 0.5	3.7 ± 0.5	3.8 ± 0.5	3.7 ± 0.5	3.6 ± 0.5	3.5 ± 0.5
LDL cholesterol, mg/dl	120.0 ± 34.1	119.0 ± 29.7	118.0 ± 30.1	119.0 ± 29.3	119.0 ± 32.0	121.0 ± 31.5	118.0 ± 34.0
eGFR, ml/min/1.73 m ²	93.0 ± 15.4	90.0 ± 15.1	87.0 ± 15.0	90.0 ± 14.6	90.0 ± 15.2	90.0 ± 16.0	89.0 ± 16.4
Triglycerides, mg/dl	125.0 ± 91.0	132.0 ± 104	123.0 ± 73.7	127.0 ± 75.8	131.0 ± 118	123.0 ± 75.7	119.0 ± 66.7
CRP, mg/l	3.9 ± 5.6	2.9 ± 4.7	2.9 ± 4.8	2.9 ± 5.3	3.1 ± 4.6	3.5 ± 4.7	3.9 ± 6.2
Urinary ACR, mg/g [†]	5.2 ± 2.4	5.0 ± 2.3	4.8 ± 2.2	4.6 ± 2.1	5.0 ± 2.4	5.4 ± 2.4	6.0 ± 2.5
Medication use							
Thyroid agents	46 (5)	56 (6)	68 (7)	70 (7)	41 (5)	46 (6)	13 (5)
NSAID	139 (15)	170 (17)	205 (20)	207 (20)	148 (16)	122 (16)	37 (15)
COX-2 inhibitor	42 (5)	37 (4)	51 (5)	43 (4)	32 (4)	43 (6)	12 (5)

Values are mean ± SD or n (%). *To convert 25(OH)D values into mmol/l multiply by 2.5; to convert PTH values into pmol/l divide by 9.4. †Geometric mean.

25(OH)D = 25-hydroxyvitamin D; ACR = albumin creatinine ratio; BMI = body mass index; CKD = chronic kidney disease; COX-2 inhibitor = cyclooxygenase-2 inhibitor use; CRP = C-reactive protein; DPB = diastolic blood pressure; eGFR = estimated glomerular filtration rate; IFG = impaired fasting glucose; LDL = low-density lipoprotein; MET = metabolic equivalent of task; NSAID = nonsteroidal anti-inflammatory drug; PTH = parathyroid hormone; SBP = systolic blood pressure.

Associations of PTH with incident hypertension. In unadjusted and demographic-adjusted models, higher serum PTH concentrations were associated with greater rates of incident hypertension (Table 2). Further adjustment for potential confounders, including 25(OH)D and different measures of kidney function attenuated this trend across PTH categories. However, serum PTH concentrations ≥65 pg/ml remained associated with incident hypertension in fully adjusted models (HR: 1.27 [95% CI: 1.01 to 1.59]). The adjusted spline models were consistent with this observation, demonstrating greater hypertension risks for serum PTH concentrations approximately >70 pg/ml (Fig. 2B).

For PTH, we also found significant interaction with BMI categories in relation to hypertension (p for interaction <0.001), with a greater risk for obese participants (Fig. 3B). After adjusting for BMI as a continuous variable, the associations were no longer statistically significant: HR: 1.23 (95% CI: 0.83 to 1.63) for overweight and 1.38 (95% CI: 0.92 to 1.74) for obese participants. Associations of PTH with incident hypertension were similar across subgroups of age, sex, race, CKD, and 25(OH)D. Adjustment for mineral metabolism markers including calcium and phosphate did not appreciably change the observed associations.

Table 2 Associations of Serum 25(OH)D and PTH With Incident Hypertension Among 3,002 Participants

Mineral Metabolism Markers	n	Cases	Incidence Rates per 100 Person-Years	Model 1	Model 2	Model 3
25(OH)D <20 ng/ml	922	414 (44.9)	6.7	1.28 (1.09-1.50)	1.17 (0.99-1.38)	1.13 (0.96-1.33)
25(OH)D ≥20-30 ng/ml	1,028	428 (41.6)	6.2	1.23 (1.06-1.41)	1.14 (0.98-1.32)	1.14 (0.98-1.31)
25(OH)D >30 ng/ml	1,052	387 (36.8)	5.2	Ref	Ref	Ref
p for trend			<0.001	0.003	0.140	0.199
PTH <33 pg/ml	1,056	384 (36.4)	5.1	Ref	Ref	Ref
PTH ≥33-44.2 pg/ml	912	361 (39.6)	5.7	1.03 (0.90-1.19)	1.02 (0.87-1.19)	1.00 (0.86-1.17)
PTH ≥44.2-65 pg/ml	789	359 (45.5)	6.9	1.16 (1.00-1.35)	1.11 (0.95-1.30)	1.09 (0.94-1.28)
PTH ≥65 pg/ml	245	125 (51.0)	8.1	1.36 (1.10-1.68)	1.30 (1.03-1.64)	1.27 (1.01-1.59)
p for trend			<0.001	0.016	0.124	0.150

Values are n (%) or adjusted hazard ratio (95% confidence interval) unless otherwise indicated. Model 1 is adjusted for age, sex, race, and clinic site. Model 2 is model 1 + smoking, education, income, diabetes status, body mass index, low-density lipoprotein, nonsteroidal anti-inflammatory drug use, cyclooxygenase-2 inhibitor use, physical activity (in case of PTH, adjusted for 25(OH)D). Model 3 is model 2 + albumin creatinine ratio and estimated glomerular filtration rate.

25(OH)D = 25-hydroxyvitamin D; PTH = parathyroid hormone; Ref = reference category.

Sensitivity analyses. After excluding 248 participants who had incident hypertension diagnosed solely by use of antihypertensive medications, the adjusted associations of 25(OH)D and PTH with hypertension were numerically similar. Similarly, excluding the 444 participants who had borderline hypertension at baseline or the 17 participants who had evidence of primary hyperparathyroidism did not appreciably change these associations.

Discussion

In this study, we report associations of serum 25(OH)D and PTH with incident hypertension in a large, multi-ethnic cohort during 9 years of follow-up. Lower 25(OH)D was associated with greater hypertension risk, although the association became nonsignificant after adjusting for potential confounders. In contrast, higher serum PTH remained significantly associated with a greater risk of incident hypertension after adjustments. These findings suggest that

higher PTH concentrations might play a role in the pathogenesis of developing hypertension. These associations may underlie the increased risk for cardiovascular disease among participants with high PTH (16).

Previous studies that investigated circulating 25(OH)D concentrations and hypertension risk are sparse and showed inconsistent results. In a case-control study among young women, lower plasma 25(OH)D was significantly associated with self-reported hypertension risk (6), although the sample excluded obese women and almost two-thirds of the women were vitamin D deficient. Another study showed that plasma 25(OH)D was inversely associated with self-reported incident hypertension in a subsample of older men and women, and the risk estimates for predicted 25(OH)D concentrations showed stronger estimates in the larger sample (7). It should be noted that most participants had only predicted 25(OH)D values, the study did not include measured blood pressure, and confidence intervals were wide. Differences in study design, ascertainment of hypertension, and

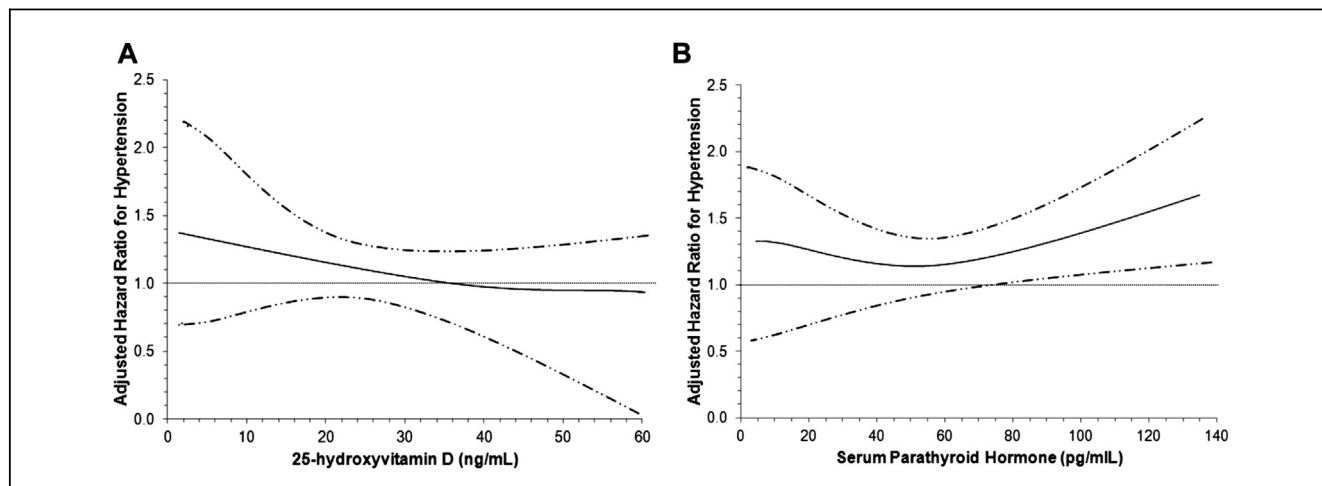
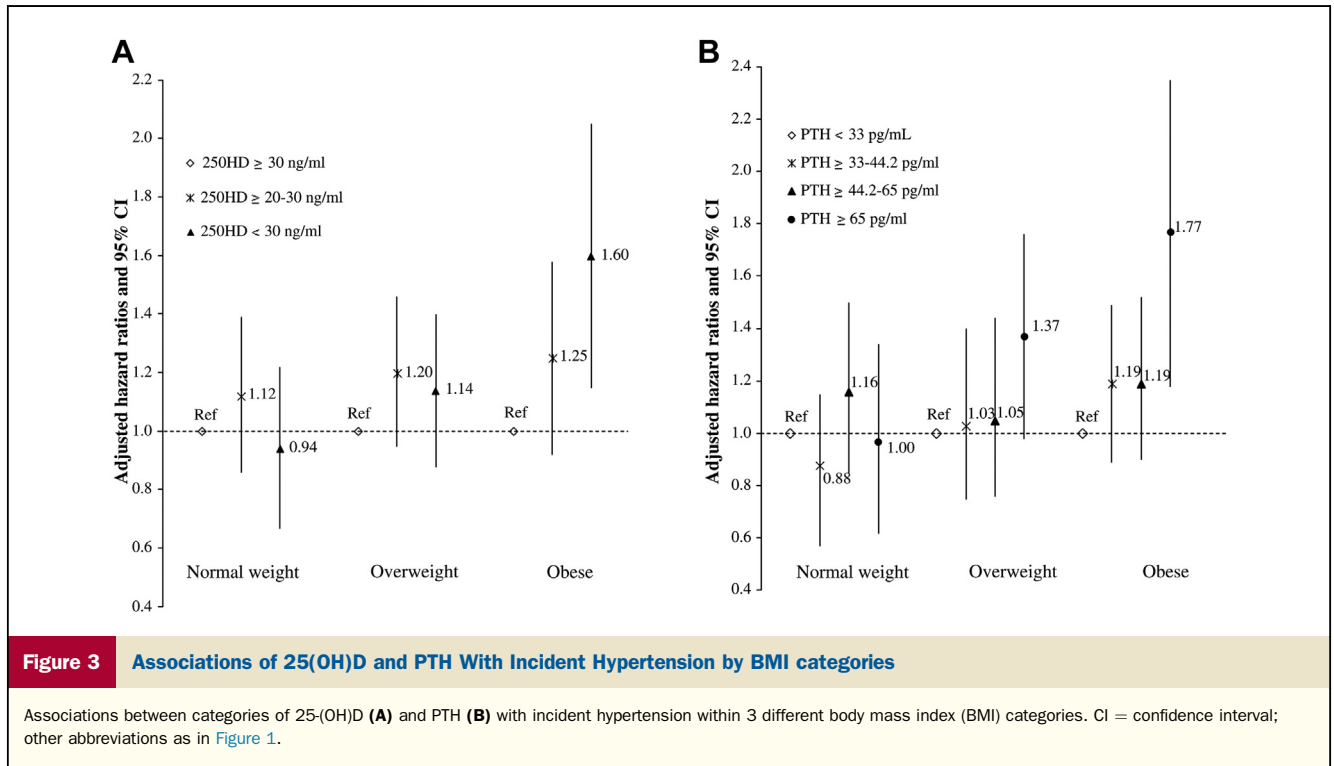


Figure 2 Continuous Associations of 25(OH)D and PTH Concentrations With Incident Hypertension

Adjusted dose-response relations of serum 25(OH)D (A) and PTH (B) concentrations with incident hypertension. Abbreviations as in Figure 1.



sex differences may explain the observed differences compared with our study.

Our study confirms previous work that showed weak inverse relationships between circulating 25(OH)D concentrations and measured incident hypertension risk among a Norwegian sample that included a broad age spectrum of men and women (17), a large cohort of post-menopausal women (9), and Finnish middle-aged male smokers (10). The inconsistent results for 25(OH)D and incident hypertension indicate that the relationship between 25(OH)D and hypertension risk is less clear. Intervention trials that investigated vitamin D supplementation and blood pressure are scarce. A study among post-menopausal women reported that daily supplementation of calcium (1,200 mg) and calcium and vitamin D (800 IU) for 8 weeks reduced systolic blood pressure by 8 mm Hg (18). In a dose-response study in black patients, 3 months of vitamin D supplementation (1,000/2,000/4,000 IU) significantly lowered systolic blood pressure in a dose-dependent manner (19). Other studies did not observe effects of vitamin D on blood pressure among different populations (20–22). These clinical trials of vitamin D supplementation have been limited by inadequate vitamin D dosage, insufficient duration of therapy, and the use of *bolus therapy* to replete vitamin D. Moreover, our results should be interpreted in the growing recognition of heterogeneity of response to vitamin D deficiency, according to variation in vitamin D metabolism genes (23,24).

Previous studies that investigated PTH and hypertension risk showed similar risk estimates as ours (3,4). Among older men, plasma PTH concentrations were positively

associated with hypertension risk (3). Anderson et al. (4) reported that higher PTH was borderline associated with incident hypertension in an older population (HR: 1.50 [95% CI: 0.99 to 2.24]) (4).

Taken together, our study provides further evidence for an association between higher PTH concentrations and future hypertension risk in different ethnic groups. Hypertension contributes to the development of vascular aging and is a major risk factor for cardiovascular diseases. Moreover, in the MESA study, serum PTH was cross-sectionally associated with endothelial dysfunction and arterial stiffness, and may partially explain associations of elevated serum PTH with hypertension risk (12).

Although we can only speculate on potential mechanisms, several important observations regarding the biologic actions of PTH warrant discussion. The fact that serum PTH was associated with greater hypertension risk after adjustment for 25(OH)D suggests that PTH, independent of 25(OH)D, contributes to the development of hypertension. Multiple mechanisms may explain how PTH might influence the vasculature. Recent evidence suggests that there is an interaction between aldosterone and PTH by modulating angiotensin signaling (5). Furthermore, circulating PTH may affect intracellular signaling, causing intracellular calcium overload and leading to severe cell injury and death (25,26). Also, PTH stimulates the renin-angiotensin system (27). Among 123 ambulatory older adults undergoing 24-h blood pressure monitoring, higher PTH levels were independently related with higher blood pressure (28). Among 85 women selected from a population-based study, higher

PTH levels were related with both higher systolic and diastolic blood pressure (29). One potential mechanism is that PTH excess, by precipitating increases in blood pressure, may predispose individuals to a higher risk of hypertension and eventually cardiovascular disease (30). The complexity of the mineral metabolism makes it hard to fully disentangle the individual contribution of these factors to the vasculature and warrants further investigation.

In our study, we found a significant interaction of 25(OH)D and PTH with BMI categories. In obese participants, but not in overweight and normal-weight persons, lower 25(OH)D and higher PTH concentrations were associated with incident hypertension (Fig. 3). However, after adjustment for BMI as a continuous variable within each BMI stratum, the association in obese persons attenuated and was no longer significant, suggesting residual confounding due to BMI in this group. Intervention studies have shown a lower impact of vitamin D supplementation on serum 25(OH)D concentrations in obese versus normal-weight individuals among different age and ethnic groups (31,32) and increased concentrations after weight loss (33). These trials indicate that vitamin D concentrations are likely to be dependent on adiposity and could explain the observed associations with higher BMI categories due to a greater fat mass. This could be due to changes in serum leptin, FGF-23, or bone alkaline phosphatase concentrations (34). Adjusting for BMI led to significant attenuation of the associations, suggesting that BMI is a very important factor, even within BMI strata, that should be taken into account when studying these relationships.

Strengths of our study are the use of a large, community-based cohort without pre-existing cardiovascular or prevalent hypertension at baseline and a considerable length of follow-up. To our knowledge, this is the first study that simultaneously assessed the relationship of serum 25(OH)D and PTH with incident hypertension. These findings add new knowledge to underlying subclinical cardiovascular disease mechanisms and strengthen the case for disturbances in high PTH as a cardiovascular risk factor. We studied a multi-ethnic cohort that allows generalization to other ethnicities, although generalization to younger age groups should be done with caution because the pathophysiology may differ between age groups. Additionally, we used standardized methods to assess serum 25(OH)D and PTH, hypertension risk factors, several measures of kidney function, and comorbid conditions, therein minimizing the possibility of residual confounding.

Study limitations. Important limitations include possible misclassification of hypertension, ascertainment of hypertension at discrete time points, and the potential for confounding by measurement error in available characteristics. These concerns are to some extent mitigated by sensitivity analyses demonstrating robust associations with only minor changes in the magnitude between serum 25(OH)D and PTH in relation to incident hypertension. The observational

design does not confirm causal relationships with incident hypertension and residual confounding by unmeasured characteristics that cannot be excluded. Exposure markers—serum 25(OH)D and PTH—were assessed at baseline (2000 to 2002), and changes in exposure over time can lead to misclassification; however, the prospective design favors nondifferential misclassification, which would most likely dilute the observed associations. Future studies should confirm whether the observed associations are similar for younger individuals.

Conclusions

We report associations of higher PTH concentrations with greater incident hypertension in a community-based, middle-aged, multi-ethnic cohort. Vitamin D-deficiency and PTH excess are common findings among the general population, and a better understanding of the clinical implications of the pathogenesis of hypertension may help to promote cardiovascular health.

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- Key Words:** incident hypertension ■ parathyroid hormone ■ prospective study ■ vitamin D.