Race-specific associations of 25-hydroxyvitamin D and parathyroid hormone with cardiometabolic biomarkers among US white and black postmenopausal women

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ABSTRACT

Background: Concentrations of 25-hydroxyvitamin D [25(OH)D] tend to be lower in African Americans than in non-Hispanic whites, but whether adding information on parathyroid hormone (PTH) can help explain the higher cardiometabolic risk among African Americans is unknown.

Objectives: This study examined race (black/white)-specific independent and joint associations of 25(OH)D and PTH with cardiometabolic biomarkers including high-sensitivity C-reactive protein (hs-CRP), estimated glomerular filtration rate (eGFR), and homeostasis model assessment of insulin resistance (HOMA-IR) and β-cell function (HOMA-B).

Methods: Among 1500 white and 1300 black postmenopausal women without cardiovascular disease from the Women's Health Initiative Observational Study, a weighted linear regression analysis and a novel penalized spline-based semiparametric model with contour plots, accounting for possible nonlinear relations and interactions simultaneously, were used to investigate the race-specific independent and joint associations of 25(OH)D and PTH with each biomarker.

Results: Black women had lower concentrations of 25(OH)D and higher PTH, HOMA-IR, HOMA-B, hs-CRP, and eGFR than white women (all P values < 0.0001). Lower 25(OH)D and higher PTH were each independently and jointly associated with higher HOMA-IR in both white and black women, whereas a similar joint relation with HOMA-B was observed in white women only. In contrast, PTH was nonlinearly associated with HOMA-B in black women and positively associated with hs-CRP in white women, independently of 25(OH)D. Whereas there was an inverse linear relation between PTH and eGFR in white women after accounting for 25(OH)D, PTH and 25(OH)D were jointly and nonlinearly associated with eGFR in black women.

Conclusions: We found that the joint association of 25(OH)D and PTH with β-cell function, systemic inflammation, and kidney function apparently differed between white and black women. Further studies are needed to determine whether differences in the vitamin D–PTH endocrine system contribute to racial disparities in cardiovascular health. *Am J Clin Nutr* 2020;112:257–267.

Keywords: racial differences, cardiometabolic biomarkers, 25-hydroxyvitamin D, parathyroid hormone, joint associations, postmenopausal women

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Supplemental Figures 1–3 are available from the "Supplementary data" link in the online posting of the article and from the same link in the online table of contents at https://academic.oup.com/ajcn/.

Data described in the article, code book, and analytic code will be made available upon request pending application and approval from the corresponding author.

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Abbreviations used: CKD, chronic kidney disease; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; FPG, fasting plasma glucose; FPI, fasting plasma insulin; HOMA-B, homeostasis model assessment of β-cell function; hs-CRP, high-sensitivity C-reactive protein; PTH, parathyroid hormone; RAAS, renin–angiotensin–aldosterone system; WHI-OS, Women's Health Initiative Observational Study; 25(OH)D, 25-hydroxyvitamin D.

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Introduction

Evidence from mechanistic studies indicates that the vitamin D and parathyroid hormone (PTH) endocrine system regulates diverse physiological functions, including insulin/glucose metabolism, the renin–angiotensin–aldosterone system (RAAS), vascular and cardiac cell function, inflammatory pathways, cell proliferation and differentiation, and immune response modulation (1–5). The hypothesized mechanisms underlying the relation between vitamin D and cardiometabolic health may operate through binding to the nuclear vitamin D receptor in a variety of tissues. Epidemiological studies suggest that vitamin D deficiency or PTH excess may be associated with intermediate cardiometabolic biomarkers, including HOMA-IR and homeostasis model assessment of β-cell function (HOMA-B), high-sensitivity C-reactive protein (hs-CRP), and estimated glomerular filtration rate (eGFR) (6–8), although the available evidence remains inconclusive (9–11). It has been consistently reported that, compared with whites, blacks have a higher prevalence of vitamin D deficiency, PTH excess, and the aforementioned cardiovascular disease (CVD) risk factors (12–15). There is also evidence for racial disparities in the associations of 25-hydroxyvitamin D [25(OH)D] or PTH with cardiometabolic biomarkers (16–18).

However, most previous studies have focused on independent associations of total 25(OH)D and PTH with CVD risk factors (6–11). Given the well-established interrelations between 25(OH)D and PTH, it remains unclear whether these patterns will extend to their joint associations with cardiometabolic biomarkers between whites and blacks.

By leveraging available core CVD biomarkers in the Women's Health Initiative Observational Study (WHI-OS), including HOMA-IR, HOMA-B, hs-CRP, and eGFR, we specifically evaluated the independent and joint associations of plasma total 25(OH)D and PTH with these 4 core cardiometabolic biomarkers among a random subcohort of US white and black postmenopausal women without CVD from the WHI-OS. Our aims were *1*) to examine both linear and nonlinear independent associations of total 25(OH)D and PTH with each cardiometabolic biomarker and *2*) to explore the joint association of 25(OH)D and PTH with each cardiometabolic biomarker, separately, for US white and black postmenopausal women.

Methods

Study population

We leveraged data from a case-cohort ancillary study conducted within the WHI-OS (19). The WHI-OS consisted of 93,676 ethnically diverse women aged 50–79 y recruited at 40 clinical centers across the United States between 1994 and 1998. With a 20% minority enrollment rate, the WHI-OS cohort roughly parallels the racial diversity of the US population (20). At baseline, all WHI participants self-reported their race and ethnicity, choosing from non-Hispanic white (referred to hereafter as white), non-Hispanic black (referred to hereafter as black), Hispanic, American Indian/Alaska Native, Asian (ancestry was Chinese, Indo-Chinese, Korean, Japanese, Pacific Islander, or Vietnamese), and other (21).

The ancillary case-cohort study included 2050 CVD cases and 2800 controls after excluding from the original WHI-OS cohort women with a history of stroke or myocardial infarction, or of receiving dialysis at baseline (19). We limited our study selection to blacks and whites in order to ensure adequate power for addressing black–white disparities in CVD risk and risk factors. All non-CVD controls, being representative samples of the entire WHI-OS cohort, were included in this study, yielding a final sample of 1500 white women and 1300 black women without baseline prevalent or incident CVD (**Supplemental Figure 1**). All participants provided written informed consent at study entry, and the study was approved by the institutional review boards of each participating center.

Biomarker assessment and outcomes

Blood samples were collected from all WHI-OS participants at baseline after ≥12 h of fasting and stored at −80°C before laboratory assays. All assays were performed in the laboratory of Nader Rifai (CERLab) at Boston Children's Hospital. Total 25(OH)D was measured by an enzyme immunoassay from Immunodiagnostic Systems Inc. PTH was determined by electrochemiluminescence immunoassay on the Roche E Modular system (Roche Diagnostics) with a lower limit of detection of 1.2 pg/mL. Plasma hs-CRP was measured using an immunoturbidimetric assay, creatinine by an enzymatic method, fasting glucose enzymatically, and fasting insulin by an electrochemiluminescence immunoassay; all assays were performed on the Roche E Modular system using Roche Diagnostic reagents (Roche Diagnostics). The mean intra-assay CVs for each assay were as follows: total 25(OH)D, 6.95%; PTH, 3.46%; hs-CRP, 3.34%; creatinine, 1.82%; fasting glucose, 3.26%; and fasting insulin, 2.49%. HOMA-IR was calculated by multiplying fasting plasma insulin (FPI) (μIU/mL) by fasting plasma glucose (FPG) (mmol/L), then dividing by the constant 22.5, i.e., HOMA-IR = (FPI × FPG)/22.5 (22). HOMA-B was computed using the following formula: HOMA-B = 20 × FPI (μIU/mL)/FPG (mmol/L) − 3.5 (22). We calculated eGFR using the well-validated Chronic Kidney Disease Epidemiology Collaboration equation, which has been shown to provide more accurate eGFR estimates than the Modification of Diet in Renal Disease equation (23):

$$\begin{aligned}\text{Estimated GFR (in mL} \cdot \text{min}^{-1} \cdot 1.73\ \text{m}^{-2}) \\ = 141 \times \min(\text{creatinine}/\kappa, 1)^{\alpha} \times \max(\text{creatinine}/\kappa, 1)^{-1.209} \\ \times 0.993^{\text{Age}} \times 1.018(\text{if female}) \times 1.159(\text{if black})\end{aligned}$$

where creatinine = standardized serum creatinine measures (mg/dL), $\kappa = 0.7$ for females or 0.9 for males, $\alpha = -0.329$ for females or −0.411 for males, min = the minimum of creatinine/κ or 1, max = the maximum of creatinine/κ or 1, and age = years.

HOMA-IR, HOMA-B, hs-CRP, and eGFR, as the well-established risk factors for cardiometabolic health, had been chosen as core CVD biomarkers and were widely measured in a large cohort of >25,000 participants in the WHI-OS. They were included in the present study as primary outcomes.

Covariates

Information on demographics, lifestyle behaviors, and medication history was collected from each woman at study entry (i.e., baseline) via self-administered questionnaires, including age (y), race (white compared with black), clinical center (Southern:

<35°N, Middle: 35–40°N, and Northern: >40°N), education (≤ high school graduate/General Educational Development, post–high school, and college graduate or higher), season of blood draw (spring, summer, autumn, and winter), cigarette smoking status (never, past, and current), alcohol consumption (never, past, and current), postmenopausal hormone therapy (never, past, and current), and physical activity levels (metabolic equivalent of task-h/wk). A physical examination was also performed, including height, weight, and other anthropometric measurements of each participant (20). BMI (in kg/m^2) was calculated.

Statistical analysis

We compared white and black women in terms of total 25(OH)D, PTH, and other baseline characteristics using Wilcoxon's rank-sum test for continuous variables and the chi-square test for categorical variables. Age-adjusted Spearman partial correlation coefficients were computed to examine the correlations of vitamin D biomarkers with each of the following cardiometabolic biomarkers: eGFR, hs-CRP, HOMA-IR, HOMA-B, fasting glucose, and fasting insulin.

As a random subsample of the WHI-OS cohort, our study population represents the entire cohort. Therefore, we performed a weighted linear regression analysis to assess the independent associations between vitamin D biomarkers and each cardiometabolic biomarker at baseline. To reflect the WHI-OS population characteristics, we used an inverse probability weighting method based on Barlow's approach (24). Each vitamin D biomarker was parameterized as a continuous variable by assuming that it had a linear relation with the cardiometabolic biomarkers. Results for direct comparison of effect sizes between 25(OH)D and PTH were reported per 1-SD increment in biomarker concentrations.

HOMA-IR, HOMA-B, and hs-CRP measures were log transformed owing to their skewed distributions. For ease of interpretation, regression coefficients (β) obtained from these models were back-transformed to a relative difference, which can be interpreted in terms of percentage change. Because of the potential nonlinear associations between vitamin D biomarkers and cardiometabolic biomarkers, we also divided all participants according to quartiles of 25(OH)D and PTH concentrations. For separate analyses with 25(OH)D and PTH as a continuous variable and as a categorical variable by quartiles, covariates adjusted in the main models included age, race, clinical center, education, season of blood draw, cigarette smoking status, alcohol consumption, postmenopausal hormone therapy, physical activity levels, and BMI. We tested for linear trends across quartiles of vitamin D biomarkers by using the median values of each category as a continuous variable in the models. In addition, we used quadratic and cubic terms of each vitamin D biomarker as a continuous variable to capture potential nonlinear trends. To investigate black–white differences in the associations between vitamin D biomarkers and cardiometabolic biomarkers, we repeated our multivariable analyses, stratifying by race. We also tested for interaction between race and vitamin D biomarkers by including an interaction term in our main models. Statistical analyses were performed using SAS version 9.4 (SAS Institute), unless otherwise specified.

We applied a novel penalized spline-based semiparametric regression model, developed by Tu and colleagues (25, 26), to explore the joint associations of total 25(OH)D and PTH with each cardiometabolic biomarker. By accommodating possible nonlinear relations and interactions between the 2 independent variables (i.e., vitamin D and PTH), a nonlinear bivariate surface function was used to depict the simultaneous influences of 25(OH)D and PTH on the cardiometabolic biomarkers, including HOMA-IR, HOMA-B, hs-CRP, and eGFR, in blacks and whites. The estimated surface functions were presented in the form of colored contour plots, where the height of the surface function at each combination of 25(OH)D and PTH represented the mean value of each cardiometabolic biomarker. By contrasting the shapes of the contour surfaces between black and white participants, one could make inferences about the potentially differential influences of 25(OH)D and PTH on CVD in the 2 racial groups. The quantile-quantile (Q-Q) plots of the empirical distributions of the cardiometabolic biomarkers were used to examine the normality assumption. We implemented the analysis using the *mgcv* package in R software, version 3.4.2 (R Foundation for Statistical Computing).

Results

Table 1 presents the baseline characteristics of our study population by ethnicity. Briefly, compared with white women, black women had significantly higher BMI, lower levels of physical activity, education, and current alcohol consumption, and less hormone therapy use, and were more likely to be current smokers and have a history of diabetes or hypertension, but less likely to have a family history of CVD. Plasma concentrations of total 25(OH)D were significantly lower, but PTH, HOMA-IR, HOMA-B, hs-CRP, and eGFR were significantly higher, in black women than in white women (all $P < 0.0001$).

We examined the correlations of vitamin D biomarkers with each cardiometabolic biomarker (**Table 2**). Among all participants, total 25(OH)D was inversely correlated with PTH and all cardiometabolic biomarkers, whereas PTH was positively correlated with HOMA-IR, HOMA-B, hs-CRP, fasting insulin, and fasting glucose. Whereas total 25(OH)D was significantly and inversely correlated with hs-CRP ($r = -0.08$; $P = 0.001$) and HOMA-B ($r = -0.19$; $P < 0.0001$) in white women only, PTH showed a significant inverse correlation with eGFR only in black women ($r = -0.07$; $P = 0.014$). Although the correlations of 25(OH)D with eGFR were similar between white ($r = -0.05$) and black women ($r = -0.06$), white women had a stronger correlation between 25(OH)D and HOMA-IR ($r = -0.23$) than black women ($r = -0.13$). In contrast, the correlations of PTH with HOMA-IR and HOMA-B appeared to be stronger in black women ($r = 0.13$ for HOMA-IR; $r = 0.15$ for HOMA-B) than in whites ($r = 0.11$ for HOMA-IR; $r = 0.08$ for HOMA-B).

We assessed the independent associations between total 25(OH)D concentrations and each cardiometabolic biomarker at baseline (**Table 3**). Higher total 25(OH)D concentrations were independently associated with lower HOMA-IR and eGFR in a dose-response manner among all participants, adjusting for age, race, clinical center, education, season of blood draw, cigarette smoking status, alcohol consumption, postmenopausal hormone therapy, physical activity, and BMI (model 3). The statistically

TABLE 1 Baseline characteristics by ethnicity in our subsample of participants from the Women's Health Initiative Observational Study[1]

Variables	Black women ($n = 1300$)	White women ($n = 1500$)	P value[2]
Age, y	62 ± 7.1	63 ± 7.1	<0.0001
BMI, kg/m^2	30.6 ± 6.5	26.7 ± 5.4	<0.0001
	29.5 [26–34]	25.6 [23–29.4]	
Family history of CVD	495 (42.2)	739 (52.2)	<0.0001
History of diabetes	115 (18.4)	81 (7.5)	<0.0001
History of hypertension	676 (52.8)	413 (28.2)	<0.0001
History of high cholesterol	193 (15.2)	206 (14.1)	0.437
Physical activity, MET-h/wk	6.5 [1.3–16]	10.5 [3.8–21]	<0.0001
Cigarette smoking status			<0.0001
Never	628 (49.3)	715 (48.5)	
Past	513 (40.2)	681 (46.2)	
Current	134 (10.5)	77 (5.2)	
Alcohol consumption status			<0.0001
Never	246 (19.2)	128 (8.7)	
Past	400 (31.2)	249 (16.9)	
Current	636 (49.6)	1099 (74.5)	
Hormone therapy use			<0.0001
Never	758 (58.6)	533 (35.8)	
Past	169 (13.1)	226 (15.2)	
Current	366 (28.3)	731 (49.1)	
Statin use	186 (14.4)	212 (14.2)	0.914
Educational levels			<0.0001
≤ High school graduate/GED	342 (26.4)	301 (20.2)	
Post–high school	484 (37.4)	512 (34.3)	
College graduate or higher	469 (36.2)	678 (45.5)	
Geographical latitudes (clinical center)			0.001
Southern: <35°N	442 (32.6)	444 (29.8)	
Middle: 35–40°N	428 (33.1)	434 (29.1)	
Northern: >40°N	445 (34.4)	613 (41.1)	
Season of blood draw			0.74
Spring	381 (29.8)	437 (29.4)	
Summer	348 (27.2)	431 (29.0)	
Autumn	279 (21.8)	318 (21.4)	
Winter	271 (21.2)	299 (20.1)	
Vitamin D biomarkers			
Total 25(OH)D, nmol/L	42.5 [33.4–54.7]	63.3 [51.1–76.7]	<0.0001
PTH, pg/mL	40.2 [31.4–51.7]	35.6 [28.4–44.2]	<0.0001
Cardiometabolic biomarkers			
Fasting glucose, mg/dL	94.0 [87.0–105.0]	93.0 [88.0–99.0]	0.0003
Fasting insulin, μIU/mL	9.1 [5.6–13.7]	6.6 [4.6–10.0]	<0.0001
HOMA-IR	2.2 [1.3–3.6]	1.5 [1.0–2.4]	<0.0001
HOMA-B	98.1 [62.9–145.9]	81.4 [57.3–116.4]	<0.0001
hs-CRP, mg/L	3.3 [1.4–7.2]	2.2 [0.9–4.9]	<0.0001
eGFR, mL · min^{-1} · 1.73 m^{-2}	94.1 ± 18	86.2 ± 13	<0.0001

[1] Values are means ± SDs, medians [IQRs], or n (%), unless otherwise indicated. CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; GED, General Educational Development; HOMA-B, homeostasis model assessment of β-cell function; hs-CRP, high-sensitivity C-reactive protein; MET, metabolic equivalent of task; PTH, parathyroid hormone; 25(OH)D, 25-hydroxyvitamin D.

[2] P values for differences between black and white women were obtained by Wilcoxon's rank-sum test for continuous variables and the chi-square test for categorical variables. Percentage calculations were based on completed data.

significant associations of 25(OH)D with HOMA-B and hs-CRP attenuated to nonsignificance after additional adjustment for BMI. The interaction term between race and 25(OH)D was significant for HOMA-B only (P for interaction = 0.029). When stratified by race, the observed associations of 25(OH)D with HOMA-IR (6.59% lower per 1-SD higher in 25(OH)D; P for linear trend = 0.0001) and HOMA-B (3.21% lower per 1-SD higher in 25(OH)D; P for linear trend = 0.03) persisted in white women only. In contrast, an inverse association between 25(OH)D and eGFR persisted in black women only ($\beta = -0.99$; $P = 0.028$).

We also assessed the independent associations between PTH concentrations and each cardiometabolic biomarker at baseline (**Table 4**). After adjusting for the same covariates as

TABLE 2 Age-adjusted Spearman correlation coefficients for vitamin D biomarkers and cardiometabolic biomarkers among postmenopausal women, stratified by race[1]

Biomarkers	Total 25(OH)D	Fasting glucose	Fasting insulin	PTH	eGFR	hs-CRP	HOMA-IR	HOMA-B
All participants ($n = 2800$)								
Total 25(OH)D	1	−0.13**	−0.26**	−0.37**	−0.16**	−0.14**	−0.26**	−0.17**
Fasting glucose		1	0.49**	0.07**	0.06**	0.18**	0.62**	−0.14**
Fasting insulin			1	0.17**	0.03	0.36**	0.98**	0.73**
PTH				1	0.01	0.08**	0.16**	0.14**
eGFR					1	0.04	0.04*	−0.04*
hs-CRP						1	0.36**	0.25**
HOMA-IR							1	0.61**
HOMA-B								1
American white women ($n = 1500$)								
Total 25(OH)D	1	−0.12**	−0.24**	−0.29**	−0.05*	−0.08**	−0.23**	−0.19**
Fasting glucose		1	0.47**	0.06*	0.04	0.1**	0.58**	−0.08**
Fasting insulin			1	0.11**	−0.01	0.31**	0.99**	0.81**
PTH				1	0.003	0.05	0.11**	0.08**
eGFR					1	0.02	−0.002	−0.04
hs-CRP						1	0.3**	0.28**
HOMA-IR							1	0.71**
HOMA-B								1
American black women ($n = 1300$)								
Total 25(OH)D	1	−0.07**	−0.12**	−0.36**	−0.06*	−0.05	−0.13**	−0.05
Fasting glucose		1	0.5**	0.05	0.06*	0.24**	0.67**	−0.24**
Fasting insulin			1	0.16	−0.03	0.35**	0.97**	0.64**
PTH				1	−0.07*	0.04	0.13**	0.15**
eGFR					1	−0.01	0.004	−0.11**
hs-CRP						1	0.37**	0.18**
HOMA-IR							1	0.46**
HOMA-B								1

[1]Age-adjusted Spearman partial correlation coefficients were calculated to examine the correlations of vitamin D biomarkers with each of the following cardiometabolic biomarkers. Among all participants, the SDs of vitamin D biomarkers and cardiometabolic biomarkers were 20.90 for 25(OH)D, 28.33 for fasting glucose, 8.11 for fasting insulin, 20.66 for PTH, 15.98 for eGFR, 6.76 for hs-CRP, 3.70 for HOMA-IR, and 62.19 for HOMA-B. *$P < 0.05$; **$P < 0.01$. eGFR, estimated glomerular filtration rate; HOMA-B, homeostasis model assessment of β-cell function; hs-CRP, high-sensitivity C-reactive protein; PTH, parathyroid hormone; 25(OH)D, 25-hydroxyvitamin D.

aforementioned, higher PTH concentrations were independently associated with lower eGFR among all participants. There was also a significant interaction between race and PTH on hs-CRP (P for interaction = 0.035). PTH was nonlinearly associated with eGFR across racial groups (P for nonlinearity = 0.005 for white women and 0.036 for black women). In a race-stratified analysis, higher PTH concentrations were significantly associated with higher HOMA-IR in white women only (3.29% increase per 1-SD increase in PTH) and higher HOMA-B in black women only (4.55% higher per 1-SD higher in PTH; P for nonlinearity = 0.003). Whereas there was a linear trend toward higher PTH associated with lower hs-CRP in black women (P for linear trend = 0.01), we found a nonlinear relation between PTH and hs-CRP among white women (P for nonlinearity = 0.039).

We further explored the joint associations of total 25(OH)D and PTH with each cardiometabolic biomarker (**Figure 1**A–H). In the color-filled contour plots, the mean concentrations of each cardiometabolic biomarker at all combinations of 25(OH)D and PTH concentrations were indicated by numbers on the contour lines after adjustment for confounding factors. On average, white women had lower HOMA-IR, HOMA-B, hs-CRP, and eGFR than black women. For example, in Figure 1A and B, contours with warmer color (yellow) indicate regions where the mean values of HOMA-IR were higher; contours with colder color (blue) indicate lower mean values. The parallel straight contour lines suggest linear relations of HOMA-IR with total 25(OH)D and PTH, simultaneously. In addition, closely spaced contour lines represent steeper slopes for the linear relation (Figure 1A) than those relatively spaced far apart (Figure 1B). Overall, the combination of lower total 25(OH)D and higher PTH was jointly associated with higher HOMA-IR in both white and black women with similar linear trends but varying slopes, suggesting a lack of racial differences. Specifically, in white women, when 25(OH)D $\geq$ 100 nmol/L and PTH $\leq$ 50 pg/mL, the mean levels of HOMA-IR on the logarithmic scale were ~0.4 or less; in contrast, its mean levels were ~0.7 or greater when 25(OH)D < 50 nmol/L and PTH $\geq$ 100 pg/mL (Figure 1A). Figure 1B shows a similar linear trend for the joint associations of 25(OH)D and PTH with HOMA-IR in black women. Conversely, black–white differences in the joint associations of 25(OH)D and PTH with HOMA-B, hs-CRP, and eGFR were evident (Figure 1C–H). Overall, the combination of lower 25(OH)D concentrations and higher PTH concentrations was jointly and linearly associated with higher HOMA-B in white women (Figure 1C), but there was a nonlinear association between PTH and HOMA-B in black women suggested by the curved contour lines mainly driven by PTH (Figure 1D). Whereas PTH alone was positively associated with hs-CRP in white women, there was a joint association of higher 25(OH)D and lower PTH with higher hs-CRP in black women (Figure 1E, F). To explore the unexpected results, we

TABLE 3 Multivariable weighted linear regression analysis between total 25(OH)D and cardiometabolic biomarkers among postmenopausal women[1]

Model		Least-squares mean[2] (95% CI) or ±SE				*P* for linear trend	*P* for nonlinearity	$\beta \pm$ SE	RD,[3] %	*P* for interaction[4]
		Quartile 1	Quartile 2	Quartile 3	Quartile 4					
HOMA-IR										
All participants ($n = 2800$)	Model 1[5]	2.23 (2.11, 2.35)	1.99 (1.89, 2.10)**	1.69 (1.60, 1.79)**	1.45 (1.37, 1.54)**	<0.0001	0.098	−0.27 ± 0.02**	−23.93	0.669
	Model 2[6]	2.17 (2.03, 2.31)	1.96 (1.84, 2.09)*	1.71 (1.60, 1.83)**	1.51 (1.40, 1.62)**	<0.0001	0.192	−0.24 ± 0.02**	−21.12	0.653
	Model 3[7]	2.01 (1.90, 2.13)	1.94 (1.83, 2.05)	1.82 (1.71, 1.94)**	1.72 (1.61, 1.83)**	<0.0001	0.221	−0.11 ± 0.02**	−10.65	0.340
American white women ($n = 1500$)	Model 1[5]	2.00 (1.87, 2.13)	1.72 (1.61, 1.84)**	1.54 (1.44, 1.64)**	1.31 (1.22, 1.40)**	<0.0001	0.521	−0.16 ± 0.02**	−14.77	—
	Model 2[6]	1.97 (1.80, 2.14)	1.71 (1.57, 1.86)**	1.58 (1.45, 1.72)**	1.36 (1.24, 1.49)**	<0.0001	0.643	−0.14 ± 0.02**	−13.29	—
	Model 3[7]	1.82 (1.69, 1.96)	1.73 (1.61, 1.86)	1.65 (1.53, 1.78)*	1.55 (1.43, 1.68)**	0.0001	0.583	−0.07 ± 0.02**	−6.59	—
American black women ($n = 1300$)	Model 1[5]	2.43 (2.22, 2.66)	2.29 (2.09, 2.50)	2.23 (2.04, 2.44)	1.85 (1.69, 2.02)**	<0.0001	0.783	−0.12 ± 0.02**	−10.91	—
	Model 2[6]	2.32 (2.10, 2.57)	2.21 (1.99, 2.44)	2.23 (2.01, 2.47)	1.88 (1.70, 2.09)**	0.002	0.826	−0.08 ± 0.02**	−8.14	—
	Model 3[7]	2.22 (2.02, 2.44)	2.13 (1.94, 2.35)	2.26 (2.06, 2.49)	2.03 (1.84, 2.23)	0.196	0.626	−0.04 ± 0.02	−3.45	—
HOMA-B										
All participants ($n = 2800$)	Model 1[5]	93.44 (89.67, 97.37)	93.44 (89.58, 97.55)	83.27 (79.62, 87.09)**	76.62 (73.14, 80.26)**	<0.0001	0.018	−0.15 ± 0.02**	−13.58	0.065
	Model 2[6]	92.26 (87.71, 97.03)	93.08 (88.35, 98.05)	84.48 (80.04, 89.17)**	78.95 (74.52, 83.64)**	<0.0001	0.0497	−0.12 ± 0.02**	−11.52	0.092
	Model 3[7]	88.18 (84.07, 92.49)	92.28 (87.83, 96.94)	87.41 (83.05, 92.01)	85.41 (80.82, 90.26)	0.103	0.037	−0.05 ± 0.02*	−4.64	0.029
American white women ($n = 1500$)	Model 1[5]	92.66 (87.95, 97.63)	86.30 (81.94, 90.88)	79.60 (75.59, 83.83)**	72.78 (69.13, 76.64)**	<0.0001	0.231	−0.09 ± 0.01**	−8.85	—
	Model 2[6]	91.87 (85.81, 98.36)	86.22 (80.66, 92.17)	81.33 (75.92, 87.12)**	75.16 (69.95, 80.76)**	<0.0001	0.317	−0.08 ± 0.01**	−7.66	—
	Model 3[7]	88.02 (82.68, 93.70)	87.06 (81.90, 92.55)	83.94 (78.81, 89.40)	81.93 (76.68, 87.54)*	0.03	0.249	−0.03 ± 0.01*	−3.21	—
American black women ($n = 1300$)	Model 1[5]	95.97 (89.46, 103.0)	92.32 (86.07, 99.03)	95.21 (88.76, 102.1)	90.65 (84.44, 97.31)	0.353	0.859	−0.03 ± 0.02	−3.28	—
	Model 2[6]	95.77 (88.14, 104.1)	91.44 (84.15, 99.35)	95.08 (87.38, 103.5)	92.20 (84.67, 100.4)	0.642	0.893	−0.02 ± 0.02	−2.42	—
	Model 3[7]	93.32 (86.11, 101.1)	89.88 (82.94, 97.39)	96.13 (88.58, 104.3)	96.32 (88.69, 104.6)	0.337	0.750	0.004 ± 0.02	0.35	—
hs-CRP										
All participants ($n = 2800$)	Model 1[5]	2.83 (2.59, 3.09)	2.81 (2.57, 3.08)	2.18 (1.98, 2.40)**	2.33 (2.11, 2.57)**	0.0002	0.457	−0.17 ± 0.04**	−15.97	0.650
	Model 2[6]	2.81 (2.53, 3.12)	2.92 (2.62, 3.26)	2.36 (2.11, 2.64)**	2.42 (2.15, 2.73)*	0.004	0.840	−0.16 ± 0.04**	−14.64	0.453
	Model 3[7]	2.58 (2.33, 2.85)	2.89 (2.61, 3.20)	2.55 (2.29, 2.83)	2.95 (2.63, 3.31)*	0.170	0.921	0.02 ± 0.04	1.85	0.381
American white women ($n = 1500$)	Model 1[5]	2.59 (2.30, 2.92)	2.09 (1.86, 2.35)*	1.92 (1.71, 2.17)**	2.03 (1.80, 2.29)**	0.004	0.357	−0.10 ± 0.03**	−9.83	—
	Model 2[6]	2.42 (2.08, 2.82)	2.09 (1.80, 2.43)	1.92 (1.65, 2.24)**	1.93 (1.64, 2.27)**	0.007	0.592	−0.10 ± 0.03**	−9.81	—
	Model 3[7]	2.21 (1.91, 2.54)	2.11 (1.83, 2.42)	2.05 (1.77, 2.37)	2.30 (1.97, 2.67)	0.650	0.980	0.001 ± 0.03	0.12	—
American black women ($n = 1300$)	Model 1[5]	3.33 (2.93, 3.79)	3.10 (2.73, 3.53)	3.01 (2.65, 3.43)	2.91 (2.56, 3.32)	0.163	0.492	−0.06 ± 0.03	−5.82	—
	Model 2[6]	3.48 (3.00, 4.04)	3.18 (2.74, 3.69)	3.42 (2.94, 3.98)	3.37 (2.89, 3.92)	0.958	0.282	−0.02 ± 0.03	−2.05	—
	Model 3[7]	3.28 (2.86, 3.76)	2.99 (2.61, 3.43)	3.50 (3.05, 4.02)	3.74 (3.26, 4.30)	0.042	0.303	0.05 ± 0.03	5.46	—
eGFR										
All participants ($n = 2800$)	Model 1[5]	91.30 ± 0.51	89.54 ± 0.52*	90.10 ± 0.55	88.98 ± 0.57**	0.010	0.131	−1.25 ± 0.46**	0.006	0.572
	Model 2[6]	92.04 ± 0.63	90.28 ± 0.65*	90.76 ± 0.67	89.71 ± 0.72**	0.016	0.139	−1.25 ± 0.48**	0.010	0.450
	Model 3[7]	92.07 ± 0.64	90.28 ± 0.66*	90.93 ± 0.69	89.80 ± 0.74**	0.018	0.384	−1.21 ± 0.51*	0.017	0.444
American white women ($n = 1500$)	Model 1[5]	87.38 ± 0.62	86.50 ± 0.61	85.51 ± 0.61*	85.80 ± 0.61	0.045	0.246	−0.63 ± 0.31*	0.040	—
	Model 2[6]	88.16 ± 0.83	87.16 ± 0.81	86.24 ± 0.83*	86.86 ± 0.87	0.125	0.227	−0.50 ± 0.33	0.125	—
	Model 3[7]	88.20 ± 0.83	87.34 ± 0.81	86.24 ± 0.84*	86.96 ± 0.88	0.137	0.505	−0.47 ± 0.34	0.172	—
American black women ($n = 1300$)	Model 1[5]	95.36 ± 0.92	93.97 ± 0.92	94.07 ± 0.91	93.06 ± 0.92	0.102	0.436	−0.70 ± 0.46	0.130	—
	Model 2[6]	96.14 ± 1.08	94.58 ± 1.08	95.00 ± 1.10	93.01 ± 1.10*	0.032	0.543	−0.97 ± 0.48*	0.045	—
	Model 3[7]	96.09 ± 1.09	94.63 ± 1.09	94.96 ± 1.11	92.88 ± 1.11*	0.028	0.507	−0.99 ± 0.50*	0.046	—

[1] Weighted linear regression models were performed to assess the independent associations between total 25(OH)D and each cardiometabolic biomarker. Least-squares mean was obtained when 25(OH)D was parameterized as quartiles; β coefficient was obtained when 25(OH)D was modeled as a continuous variable. *$P < 0.05$; **$P < 0.01$. eGFR, estimated glomerular filtration rate; hs-CRP, high-sensitivity C-reactive protein; HOMA-B, homeostasis model assessment of β-cell function; RD, relative difference; 25(OH)D, 25-hydroxyvitamin D.

[2] Values are least-squares means (95% CIs) for log-transformed HOMA-IR, HOMA-B, and hs-CRP, and least-squares means ± SEs for eGFR.

[3] RD was obtained from back-transformed β and is interpreted as percentage lower (negative value) or higher (positive value) concentrations of HOMA-IR, HOMA-B, or hs-CRP on the original scale for every 1-SD increase in total 25(OH)D.

[4] *P* for interaction was obtained by adding an interaction term between 25(OH)D and race into each model.

[5] Model 1 adjusted for age, clinical center, and race.

[6] Model 2 further adjusted for education, season of blood draw, cigarette smoking status, alcohol intake, postmenopausal hormone therapy use, and physical activity levels.

[7] Model 3 further adjusted for BMI.

TABLE 4 Multivariable weighted linear regression analysis between PTH and cardiometabolic biomarkers among postmenopausal women[1]

Model		Least-squares mean[2] (95% CI) or ±SE				*P* for linear trend	*P* for nonlinearity	$\beta \pm$ SE	RD,[3] %	*P* for interaction[4]
		Quartile 1	Quartile 2	Quartile 3	Quartile 4					
HOMA-IR										
All participants ($n = 2800$)	Model 1[5]	1.72 (1.63, 1.82)	1.78 (1.68, 1.88)	1.88 (1.78, 1.99)*	2.12 (2.01, 2.24)**	<0.0001	0.042	0.15 ± 0.02**	15.6	0.883
	Model 2[6]	1.77 (1.66, 1.89)	1.78 (1.67, 1.91)	1.91 (1.79, 2.04)*	2.09 (1.96, 2.22)**	<0.0001	0.693	0.13 ± 0.02**	14	0.699
	Model 3[7]	1.88 (1.77, 2.00)	1.83 (1.72, 1.94)	1.93 (1.82, 2.05)	1.95 (1.84, 2.07)	0.140	0.761	0.05 ± 0.02**	5.41	0.332
American white women ($n = 1500$)	Model 1[5]	1.49 (1.39. 1.59)	1.59 (1.48, 1.70)	1.60 (1.50, 1.72)	1.81 (1.69, 1.94)**	<0.0001	0.621	0.08 ± 0.02**	8.24	—
	Model 2[6]	1.57 (1.44, 1.72)	1.63 (1.49, 1.78)	1.66 (1.52, 1.81)	1.85 (1.69, 2.02)**	0.001	0.453	0.08 ± 0.02**	7.9	—
	Model 3[7]	1.70 (1.58, 1.83)	1.68 (1.55, 1.81)	1.68 (1.56, 1.81)	1.76 (1.63, 1.89)	0.352	0.370	0.03 ± 0.01*	3.29	—
American black women ($n = 1300$)	Model 1[5]	1.89 (1.73, 2.07)	2.07 (1.90, 2.27)	2.33 (2.13, 2.55)**	2.52 (2.30, 2.75)**	<0.0001	0.183	0.10 ± 0.02**	10.74	—
	Model 2[6]	1.93 (1.74, 2.14)	2.06 (1.86, 2.29)	2.28 (2.05, 2.52)*	2.36 (2.13, 2.61)**	0.001	0.644	0.08 ± 0.02**	8.16	—
	Model 3[7]	2.08 (1.89, 2.29)	2.09 (1.90, 2.30)	2.31 (2.10, 2.54)	2.16 (1.97, 2.37)	0.372	0.948	0.03 ± 0.02	2.65	—
HOMA-B										
All participants ($n = 2800$)	Model 1[5]	81.48 (78.00, 85.11)	85.38 (81.77, 89.15)	88.36 (84.67, 92.21)**	94.73 (90.89, 98.73)**	<0.0001	0.012	0.09 ± 0.02**	9.51	0.282
	Model 2[6]	83.74 (79.41, 88.30)	86.00 (81.57, 90.68)	88.89 (84.42, 93.60)*	94.18 (89.51, 99.09)**	<0.0001	0.606	0.08 ± 0.02**	8.43	0.484
	Model 3[7]	86.72 (82.48, 91.18)	86.92 (82.69, 91.37)	89.06 (84.83, 93.50)	90.97 (86.68, 95.46)	0.075	0.988	0.04 ± 0.02*	3.83	0.716
American white women ($n = 1500$)	Model 1[5]	77.77 (73.79, 81.96)	82.31 (78.12, 86.72)	82.41 (78.20, 86.84)	87.32 (82.86, 92.02)**	0.0003	0.323	0.04 ± 0.01**	4.37	—
	Model 2[6]	80.90 (75.51, 86.68)	83.93 (78.32, 89.95)	83.99 (78.45, 89.92)	88.56 (82.67, 94.87)*	0.019	0.219	0.04 ± 0.01**	4.14	—
	Model 3[7]	85.12 (79.93, 90.66)	85.45 (80.23, 91.02)	84.99 (79.88, 90.43)	86.50 (81.23, 92.10)	0.659	0.188	0.02 ± 0.01	1.51	—
American black women ($n = 1300$)	Model 1[5]	80.24 (74.81, 86.06)	91.43 (85.29, 98.01)**	99.50 (92.84, 106.6)**	105.0 (97.94, 112.6)**	<0.0001	<0.0001	0.08 ± 0.02**	8.33	—
	Model 2[6]	81.91 (75.32, 89.09)	90.72 (83.48, 98.58)*	98.80 (90.99, 107.3)	103.6 (95.50, 112.4)	<0.0001	<0.0001	0.07 ± 0.02**	7.34	—
	Model 3[7]	85.30 (78.60, 92.57)	91.32 (84.27, 98.97)	100.1 (92.32, 108.5)**	98.92 (91.36, 107.1)**	0.003	0.003	0.04 ± 0.02*	4.55	—
hs-CRP										
All participants ($n = 2800$)	Model 1[5]	2.49 (2.27, 2.73)	2.34 (2.14, 2.57)	2.61 (2.39, 2.86)	2.83 (2.59, 3.09)*	0.010	0.999	0.12 ± 0.04**	13.24	0.150
	Model 2[6]	2.69 (2.41, 3.00)	2.47 (2.21, 2.76)	2.64 (2.37, 2.94)	2.85 (2.56, 3.17)	0.162	0.970	0.09 ± 0.04*	9.83	0.133
	Model 3[7]	2.95 (2.66, 3.27)	2.57 (2.32, 2.85)*	2.72 (2.46, 3.01)	2.61 (2.36, 2.88)*	0.120	0.002	−0.01 ± 0.03	−1.24	0.035
American white women ($n = 1500$)	Model 1[5]	2.08 (1.84, 2.34)	2.00 (1.78, 2.25)	2.19 (1.94, 2.47)	2.34 (2.08, 2.64)	0.089	0.111	0.09 ± 0.03**	9.48	—
	Model 2[6]	2.08 (1.78, 2.43)	2.02 (1.74, 2.36)	2.07 (1.78, 2.41)	2.26 (1.94, 2.64)	0.249	0.200	0.07 ± 0.03*	7.31	—
	Model 3[7]	2.30 (1.99, 2.65)	2.09 (1.81, 2.41)	2.12 (1.84, 2.44)	2.13 (1.84, 2.45)	0.427	0.039	0.02 ± 0.03	1.6	—
American black women ($n = 1300$)	Model 1[5]	3.14 (2.77, 3.58)	2.58 (2.27, 2.94)*	3.53 (3.10, 4.01)	3.18 (2.80, 3.62)	0.271	0.482	0.03 ± 0.03	3.46	—
	Model 2[6]	3.61 (3.10, 4.20)	2.83 (2.43, 3.28)**	3.69 (3.18, 4.29)	3.39 (2.93, 3.93)	0.773	0.796	0.01 ± 0.03	0.64	—
	Model 3[7]	4.05 (3.53, 4.65)	2.90 (2.53, 3.32)**	3.75 (3.27, 4.30)	2.95 (2.58, 3.38)**	0.010	0.943	−0.08 ± 0.03*	−7.56	—
eGFR										
All participants ($n = 2800$)	Model 1[5]	90.37 ± 0.53	90.42 ± 0.53	90.86 ± 0.52	89.11 ± 0.51	0.077	0.034	−2.20 ± 0.42**	<0.0001	0.052
	Model 2[6]	91.20 ± 0.66	91.22 ± 0.66	91.66 ± 0.64	89.88 ± 0.63	0.066	0.032	−2.18 ± 0.43**	<0.0001	0.098
	Model 3[7]	91.23 ± 0.67	91.24 ± 0.67	91.84 ± 0.65	89.91 ± 0.65	0.040	0.043	−2.24 ± 0.43**	<0.0001	0.128
American white women ($n = 1500$)	Model 1[5]	85.88 ± 0.62	86.84 ± 0.61	86.90 ± 0.61	85.47 ± 0.62	0.504	0.002	−0.97 ± 0.31**	0.002	—
	Model 2[6]	86.80 ± 0.83	87.77 ± 0.83	87.74 ± 0.82	86.30 ± 0.83	0.425	0.003	−1.03 ± 0.31**	0.001	—
	Model 3[7]	86.96 ± 0.83	87.90 ± 0.83	87.84 ± 0.82	86.27 ± 0.83	0.310	0.005	−1.09 ± 0.31**	0.001	—
American black women ($n = 1300$)	Model 1[5]	95.80 ± 0.92	94.69 ± 0.91	94.50 ± 0.91	91.41 ± 0.91**	0.001	0.006	−2.14 ± 0.46**	<0.0001	—
	Model 2[6]	96.36 ± 1.10	95.18 ± 1.08	95.41 ± 1.08	92.13 ± 1.06**	0.001	0.025	−1.98 ± 0.47**	<0.0001	—
	Model 3[7]	96.31 ± 1.11	95.15 ± 1.09*	95.22 ± 1.10	92.20 ± 1.08**	0.002	0.036	−1.93 ± 0.48**	<0.0001	—

[1] Weighted linear regression models were performed to assess the independent associations between PTH and each cardiometabolic biomarker. Least-squares mean was obtained when 25-hydroxyvitamin D was parameterized as quartiles; β coefficient was obtained when PTH was modeled as a continuous variable. $^{*}P < 0.05$; $^{**}P < 0.01$. eGFR, estimated glomerular filtration rate; HOMA-B, homeostasis model assessment of β-cell function; hs-CRP, high-sensitivity C-reactive protein; PTH, parathyroid hormone; RD, relative difference.

[2] Values are least-squares means (95% CIs) for log-transformed HOMA-IR, HOMA-B, and hs-CRP, and least-squares means ± SEs for eGFR.

[3] RD was obtained from back-transformed β and is interpreted as percentage lower (negative value) or higher (positive value) concentrations of HOMA-IR, HOMA-B, or hs-CRP on the original scale for every 1-SD increase in PTH.

[4] *P* for interaction was obtained by adding an interaction term between PTH and race into each model.

[5] Model 1 adjusted for age, clinical center, and race.

[6] Model 2 further adjusted for education, season of blood draw, cigarette smoking status, alcohol intake, postmenopausal hormone therapy use, and physical activity levels.

[7] Model 3 further adjusted for BMI.

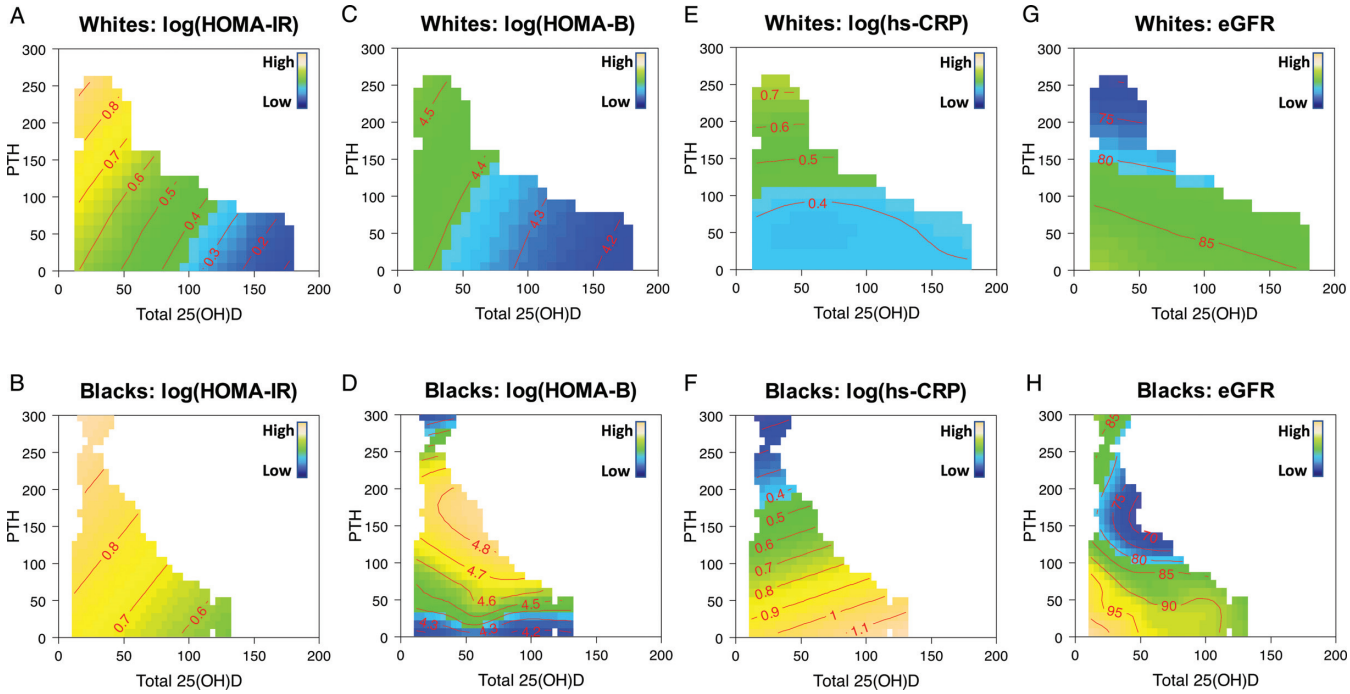

FIGURE 1 Estimated concurrent associations of 25(OH)D and PTH on HOMA-IR (A–B), HOMA-B (C–D), hs-CRP (E–F), and eGFR (G–H) by race (blacks compared with whites). A penalized spline-based semiparametric model with contour plots was performed for each cardiometabolic biomarker among white ($n = 1500$) and black women ($n = 1300$). In the color-filled contour plot, the mean concentrations of each cardiometabolic biomarker at all 25(OH)D–PTH combinations in blacks and whites are indicated by the numbers on the contour lines, adjusting for age, clinical center, education, season of blood draw, BMI, cigarette smoking status, alcohol consumption, postmenopausal hormone therapy, and physical activity levels. The SDs for each outcome were 0.67 for log(HOMA-IR), 0.52 for log(HOMA-B), 1.17 for log(hs-CRP), and 12.97 for eGFR in white women; and 0.82 for log(HOMA-IR), 0.64 for log(HOMA-B), 1.18 for log(hs-CRP), and 18.03 for eGFR in black women. eGFR, estimated glomerular filtration rate; HOMA-B, homeostasis model assessment of β-cell function; hs-CRP, high-sensitivity C-reactive protein; PTH, parathyroid hormone; 25(OH)D, 25-hydroxyvitamin D.

further performed a stratified analysis by BMI (<25 compared with ≥25) in black women. We found that 25(OH)D, jointly with PTH, was positively associated with hs-CRP in those with normal weight (**Supplemental Figure 2**). Among black women, the mean ± SD concentration of hs-CRP was lower in those with normal weight (2.91 ± 4.62 mg/L) than in those with overweight/obesity (6.29 ± 7.23 mg/L). We also observed some extreme values of hs-CRP in the scatterplot of PTH and hs-CRP in black women (**Supplemental Figure 3**). Although 25(OH)D and PTH were simultaneously associated with eGFR among both black and white women, there were notable racial differences in the shape of the associations (Figure 1G, H). Specifically, PTH appeared to be inversely and linearly associated with eGFR in white women, mainly confined to low 25(OH)D (Figure 1G); however, their joint association with eGFR took on a nonlinear and complex shape in black women and appeared to be predominantly driven by PTH concentrations (Figure 1H).

Discussion

In this large cohort of US postmenopausal women without CVD, total 25(OH)D was inversely correlated with PTH and all cardiometabolic biomarkers in both white and black participants but the joint association of 25(OH)D and PTH with β-cell function, systemic inflammation, and kidney function differed by race. However, higher PTH and lower 25(OH)D were independently and jointly associated with higher HOMA-IR in both white and black women, with similar linear patterns. Our findings suggest that the vitamin D–PTH endocrine system may play a role in explaining racial disparities in cardiometabolic health.

Our findings are consistent with most previous studies of the individual associations of 25(OH)D and PTH with either of these cardiometabolic biomarkers (27–34). Evidence from national surveys and recent observational studies suggested that 25(OH)D was inversely associated with HOMA-IR and HOMA-B and PTH was positively correlated with HOMA-IR and HOMA-B across different populations (27–31). No association between 25(OH)D and hs-CRP was observed in a cohort from the Framingham Offspring Study ($n = 1381$) (31). Several studies have demonstrated an inverse association of PTH and 25(OH)D with eGFR in patients with chronic kidney disease (CKD) and in general populations, respectively (32–34). However, inconsistent findings still exist (7, 34–37). Residual confounding due to different population characteristics, especially determinants of vitamin D status, may explain these null or contradictory findings. In addition, small sample size and different biomarker categorizations and model specifications may also explain these inconsistent results.

Contrary to studies of independent associations of 25(OH)D and PTH with cardiometabolic biomarkers, data on their joint associations are limited and have generally been analyzed using their ratio, subgroup analyses by broad categorizations of 25(OH)D and PTH, or adjusted parameter estimates. A

case-control study consisting of 15 obese and 15 matched normal-weight adolescent girls suggested a joint association of high PTH and low 25(OH)D with high hs-CRP, which is similar to our results for black women, but in the opposite direction (38). In our stratified analysis by BMI (<25 compared with ≥25) in black women, the association of 25(OH)D with hs-CRP was positive in those with normal weight, synergistically with PTH. This could be, at least partly, due to *1*) limited variability of hs-CRP among normal-weight black women compared with the women with overweight/obesity; and *2*) the presence of extreme values. In line with our findings, the Korean national survey data showed a nonlinear trend for PTH across eGFR tertiles, after accounting for 25(OH)D and other covariates in Korean women (34). A recent hospital-based case-control study among 225 elderly Greek patients found that participants with vitamin D deficiency and high PTH (third tertile) had the highest HOMA-IR but no changes in HOMA-B compared with all other groups with either vitamin D sufficiency or lower PTH (39). The small sample size with grouped vitamin D/PTH data may have limited their ability to identify joint associations of vitamin D and PTH with HOMA-B.

The reciprocal relation between 25(OH)D and PTH is dynamic, complex, and very sensitive to racial background (13). To account for their nonlinear race-specific relations and their possible interactions with CVD biomarkers, we used novel model-based color contour plots to delineate their joint associations with each biomarker. We found consistent linear associations of higher PTH and lower 25(OH)D with higher HOMA-IR in both white and black women, but black–white differences in their associations with HOMA-B, hs-CRP, and eGFR. Although our results could be explained by the calcium-dependent effects of PTH on insulin release by pancreatic islets (40), the linear relation of higher PTH and lower 25(OH)D with higher HOMA-B is contrary to the existing biological evidence linking the vitamin D–PTH system to pancreatic β-cell function. HOMA-B may not be a reliable or sensitive surrogate of β-cell function alone (22, 41, 42). Its strong correlations with fasting glucose or insulin concentrations reflect insulin resistance to varying extents depending on population characteristics. Contrary to the joint associations of 25(OH)D and PTH with hs-CRP in black women, the independent association between PTH and hs-CRP in white women suggests that the anti-inflammatory property of PTH may be more active in white women than in black women.

Racial differences in associations of 25(OH)D and PTH with eGFR may explain racial disparities in inflammation-related cardiovascular health. The existing evidence, mainly focusing on their independent associations, cannot fully address the racial heterogeneity of their synergistic relations (18, 43, 44). CKD has been described as a state of stagnant vitamin D metabolism with decreased vitamin D catabolism; in this study, the joint associations of 25(OH)D and PTH with eGFR were linear in white women and nonlinear in black women. Our findings may suggest biological differences between whites and blacks in altered vitamin D catabolism related to impaired kidney function. Overall, our findings contribute to a better understanding of racial differences in complex associations of vitamin D and PTH with CVD risk and may thus inform the design of future clinical interventions to reduce racial disparities related to CVD.

Our findings may be explained by the pleiotropic effects of the vitamin D–PTH endocrine system on the cardiovascular system via their receptors in vascular smooth muscle and endothelium. Vitamin D stimulates insulin secretion and action, regulates the RAAS, and inhibits proinflammatory cytokine production, which can induce insulin resistance and inflammation-linked vascular endothelial dysfunction (1–3). PTH also plays an important role in the RAAS, endothelial function, and systemic inflammation independently or jointly with vitamin D (45, 46). Elevated PTH concentrations may increase hepatic production of C-reactive protein by stimulating the release of the cytokine IL-6 (47–49). PTH also affects glucose/insulin metabolism directly or indirectly (50).

This study has several strengths. The well-characterized biracial cohort allowed us to thoroughly examine racial disparities in the associations of total 25(OH)D and PTH with a panel of core cardiometabolic biomarkers. Further, we used a novel analytic approach to visually elucidate possible differences in their complex concurrent associations between whites and blacks, by simultaneously considering nonlinear relations and interactions, as well as controlling confounding. Our study also has some limitations. First, as surrogate measures of insulin resistance and β-cell function, the HOMA model may underestimate insulin sensitivity and overestimate β-cell function, without incorporating proinsulin secretion (22, 42). Further research with a more reliable and feasible marker is needed to confirm our results. Second, free and bioavailable 25(OH)D, which may better reflect vitamin D activity than total 25(OH)D, were not measured. However, their different assays have not been rigorously validated for large populations. Third, our cross-sectional design cannot address cause-to-effect relations. Finally, the lack of data on other racial groups limits the generalizability of the findings.

In conclusion, we found a similar pattern of joint associations of total 25(OH)D and PTH with insulin resistance between US postmenopausal white and black women, but black–white differences in their associations with biomarkers of β-cell function, systemic inflammation, and kidney function. Future longitudinal studies are warranted to determine race-specific thresholds of both 25(OH)D and PTH concentrations and their trajectories in relation to future risk of cardiometabolic diseases.

The authors' responsibilities were as follows—YS: designed and implemented the research, acquired funding for the research, and had primary responsibility for the final content of the manuscript; JX and YS: developed the study conception and interpreted the data; YS and JEM: conducted data acquisition; JX and WT: analyzed the data; JX: drafted the manuscript; and all authors: made major contributions in revising the manuscript and read and approved the final manuscript. JEM was a recipient of NIH funding to conduct VITAL (Vitamin D and Omega-3 Trial), a large-scale randomized trial of vitamin D and omega-3s in the prevention of cancer and cardiovascular disease. The vitamin D study pills were donated by Pharmavite LLC (Northridge, CA). All other authors report no conflicts of interest.

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