Association of 25-hydroxyvitamin D with incident coronary heart disease in the Reasons for Geographic and Racial Differences in Stroke (REGARDS) study

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Abstract Background Low circulating 25-hydroxyvitamin D (25[OH]D) has been associated with increased risk of coronary heart disease (CHD), but whether this association differs by race is unclear.

Methods We examined the association of 25[OH]D with incident CHD in the Reasons for Geographic and Racial Differences in Stroke (REGARDS) study, a prospective cohort study of black and white adults ≥45 years of age enrolled between 2003 and 2007 with follow-up through December 31, 2011. Using a case-cohort design, we measured 25[OH]D in 829 participants who developed incident CHD (cases) and in 813 participants without CHD randomly selected from the REGARDS cohort (comparison subcohort). Cox proportional hazards models were used to examine associations of 25[OH]D with incident CHD adjusting for established CHD risk factors in the study sample overall and stratified by race.

Results In the fully adjusted model, lower quintiles of 25[OH]D were associated with a greater risk of incident CHD (25[OH]D > 33.6 ng/mL reference; 25[OH]D > 27.1-33.6 ng/mL, hazard ratio [HR] 2.79, 95% CI 1.64-4.76; 25[OH]D > 22.4-27.1 ng/mL, HR 2.77, 95% CI 1.57-4.89; 25[OH]D > 16.5-22.4 ng/mL, HR 5.52, 95% CI 3.21-9.50; 25[OH]D ≤ 16.5 ng/mL, HR 7.46, 95% CI 4.19-13.25). The results were similar when 25[OH]D was examined on a continuous scale (HR per 10-ng/mL decrement in 25[OH]D 2.04, 95% CI 1.65-2.52). The results did not statistically differ by race whether 25[OH]D was examined as a categorical or continuous variable ($P_{interaction} > .10$).

Conclusions Lower plasma 25(OH)D concentrations were associated with higher risk of incident CHD. In contrast to prior studies, these associations did not differ by race. (Am Heart J 2019;217:140-7.)

Low circulating concentrations of 25-hydroxyvitamin D (25[OH]D) are associated with increased risk of ischemic heart disease. Several studies have reported that the magnitude and strength of these associations differ by race. The Multi-Ethnic Study of Atherosclerosis (MESA) and Atherosclerosis Risk in Communities (ARIC) study found that lower 25(OH)D concentrations were associated with greater risk of coronary heart disease (CHD) events in white individuals but not in black individuals,[1,2] suggesting that circulating 25(OH)D concentrations may be less informative for assessing heart disease risk in black than in white individuals. Although possible, mean 25(OH)D concentrations are substantially lower in black than in white adults,[3] and accounting for these differences may be important for assessing whether the association of 25(OH)D concentrations with health outcomes differs by race. For example, we reported that lower plasma 25(OH)D concentrations were more strongly associated with incident stroke and cognitive decline in black individuals than in white individuals when using race-specific strata of baseline 25(OH)D but not when using identical strata in both blacks and whites.[4,5] Prior studies were also limited by having relatively few CHD events in black participants, potentially impairing the ability to detect more modest associations at the very low end of the distribution of 25(OH)D concentrations. Accordingly, in the current study, we examined the association of 25(OH)D with CHD in black and white participants of the REGARDS study. Our major goal was to examine whether there were racial differences in the association of 25(OH)D

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with CHD risk when examining a broader distribution of 25(OH)D concentrations in blacks and whites than was available in prior studies.

Methods

The REGARDS study is a population-based investigation of stroke incidence in black and white US adults ≥45 years of age. Details of the study design have been reviewed elsewhere.[6] Briefly, the study was designed to provide approximately equal representation of men and women and oversampled individuals who were black as well as individuals living in the Southeastern United States. Trained interviewers conducted a computer-assisted telephone interview to obtain information including participants' sociodemographics; cardiovascular risk factors; and use of antihypertensive, antiglycemic, and cholesterol-lowering medication. Following this call, health professionals conducted an in-home study visit that included an electrocardiograph (ECG) recording; blood pressure, height, and weight measurements; inventory of medications; and collection of blood and urine samples. Overall, 30,239 individuals were enrolled between January 2003 and October 2007 (42% black, 55% women). Follow-up is by computer-assisted telephone interview every 6 months for suspected medical events (or proxy-reported in case of participants unable to respond). The REGARDS study protocol was approved by the Institutional Review Boards governing research in human subjects at the participating centers, and all participants provided informed consent. Financial support was provided by cooperative agreement U01 NS041588 co-funded by the National Institute of Neurological Disorders and Stroke (NINDS) and the National Institute on Aging (NIA), National Institutes of Health, Department of Health and Human Service.

Primary exposure

The exposure of interest was 25(OH)D concentrations measured in baseline plasma samples using a commercially available enzyme-linked immunosorbent assay (Immunodetection Systems, Fountain Hills, AZ). The assay range was 5-150 ng/mL. Intraassay coefficients of variation were 8.8%-12.5%.

Outcome of interest

The outcome of interest was incident CHD. Medical records were retrieved for suspected CHD events and were reviewed by 2 expert adjudicators to validate potential events using published guidelines,[7,8] as detailed previously.[9] Briefly, for suspected myocardial infarctions, records were examined for signs or symptoms of ischemia; a rising and/or falling pattern in cardiac troponin or creatine phosphokinase-MB concentration over 6 or more hours with a peak concentration greater than twice the upper limit of normal; and ECG changes consistent with ischemia. *Definite myocardial infarctions* were defined as those with diagnostic enzymes or ECG, and probable myocardial infarctions were defined as those with equivocal diagnostic enzymes with a positive but not diagnostic ECG, or, if enzymes were missing, with a positive ECG in the presence of ischemic signs or symptoms. Only definite or probable myocardial infarctions were included as CHD events in this study. For fatal events, the medical history, hospital records, autopsy reports, interviews with next of kin or proxies, and death certificates or National Death Index data were reviewed to adjudicate the cause of death, with definite or probable CHD death used in this analysis.

Covariates of interest

Age, sex, race, body mass index, waist circumference, smoking history, annual family income, and educational attainment were determined by self-report. *Systolic and diastolic blood pressures* were defined as the average of 2 seated measures taken after a 5-minute rest. *History of CHD* was defined as having any of the following: evidence of myocardial infarction on the baseline ECG, self-report of a prior history of a cardiac procedure (coronary artery bypass surgery or percutaneous coronary intervention), or self-reported history of myocardial infarction. *Diabetes* was defined as self-reported use of insulin or oral hypoglycemic agents, fasting blood glucose concentration of 126 mg/dL or higher, or a nonfasting blood glucose concentration of 200 mg/dL or higher. History of atrial fibrillation was ascertained from self-report or by detection in ECG recordings obtained during the baseline study visit. Left ventricular hypertrophy was classified using ECG criteria. High-sensitivity C-reactive protein (hsCRP) was measured by particle-enhanced immunonephelometry (BNII nephelometer, Dade Behring). Total cholesterol, high-density lipoprotein cholesterol (HDL-C), and triglycerides were measured by colorimetric reflectance spectrophotometry. Serum intact parathyroid hormone (PTH) concentrations were measured using a commercially available enzyme-linked immunosorbent assay (Roche Elecsys 2010, Roche Diagnostics, Indianapolis, IN). Estimated glomerular filtration rate (eGFR) was determined from isotope dilution mass spectrometry (IDMS)-traceable serum creatinine measurements using the Chronic Kidney Disease (CKD) Epidemiology Collaboration equation.[10] Urine albumin measured by the BNII ProSpec nephelometer (Siemens AG) and urine creatinine measured by the rate Jaffé method (Roche/Hitachi, Basel, Switzerland) were used to calculate urine albumin to creatinine ratio (ACR). *CKD* was defined as an eGFR <60 mL/min/1.73 m^2 or an ACR ≥30 mg/g.

Derivation of case cohort

We used a case-cohort study design. This approach provides an unbiased estimate of the relative hazard of an outcome(s) without requiring measurement of biomarkers in all participants and without compromising the power of large cohort studies.[11] Cases included all participants who developed an incident CHD during follow-up through December 31, 2011. The cohort random sample (comparison group) was selected using stratified sampling to ensure sufficient representation of high-risk groups.[12] All participants with at least 1 follow-up contact (n = 29,653) were categorized into 20 strata based on age (45-54, 55-64, 65-74, 75-84, ≥85 years), race (black or white), and sex (male or female). In each stratum, participants were randomly selected to fulfill the desired distribution: 50% black, 50% white, 50% female, 50% male, 20% age 45-54, 20% age 55-64, 25% age 65-74, 25% age 75-84, and 10% age ≥85. For the purpose of this analysis, we excluded individuals with prevalent CHD in the cohort random sample.

Statistical analysis

Descriptive statistics were used to compare participant characteristics within the cohort random sample overall and across quintiles of 25(OH)D using appropriate weights to account for the stratified sampling design.

After confirming the proportionality of hazards, in sequential models, Cox regression models for case-cohort studies were used to estimate the hazard ratio (HR) of incident CHD as a function of baseline 25(OH)D. Model 1 adjusted for age, sex, and race. Model 2 adjusted for variables in model 1 plus season of blood draw; body mass index; systolic blood pressure; diastolic blood pressure; diabetes status; income; current cigarette smoking; left ventricular hypertrophy; and use of aspirin, statins, angiotensin II receptor blockers, angiotensin-converting enzyme inhibitors, or spironolactone. Model 3 further adjusted for laboratory factors (eGFR, natural log-transformed ACR, hsCRP, intact PTH, triglycerides, HDL-C, and total cholesterol). Covariates included in multivariable models were chosen if they were established CHD risk factors and had a plausible biologic link with circulating 25(OH)D. In all models, 25(OH)D was analyzed in quintiles, with the highest quintile (>33.6 ng/mL) serving as the referent group, and on a continuous scale. In prespecified secondary analyses, we examined the association of 25(OH)D with incident CHD in strata of race (black vs white). We examined effect modification by race by testing the statistical significance of interaction terms in fully adjusted models. Given wide variability in the distribution of 25(OH)D concentrations by race, we also examined the same associations using race-specific quintiles of 25(OH)D in black and white participants, separately. A 2-tailed P value <.05 was considered statistically significant, except for analyses in which interaction terms were tested where a P value <.10 was considered statistically significant.

Results

Study population characteristics

After excluding 124 individuals missing 25(OH)D concentrations and 224 individuals who had a history of CHD at baseline, we included a total of 829 individuals who developed incident CHD during follow-up (cases) and 813 individuals in the random subcohort.

Baseline characteristics of study participants in the random subcohort overall and stratified by quintiles of plasma 25(OH)D concentrations are depicted in Table I. Participants with lower plasma 25(OH)D concentrations were more likely to be black; had higher blood pressure and body mass index; had lower educational achievement and income; were more likely to be currently smoking, physically inactive, and have a history of diabetes and CKD; and had higher PTH and hsCRP concentrations.

Associations of 25(OH)D with incident CHD

Table II depicts associations of baseline 25(OH)D concentrations with incident CHD events. There was a graded increase in the HR of incident CHD with decreasing quintiles of 25(OH)D in the model adjusted for age, sex, and race (25[OH]D > 33.6 ng/mL reference, 25[OH]D > 27.1-33.6 ng/mL, HR 1.93, 95% CI 1.26-2.96; 25[OH]D > 22.4-27.1 ng/mL, HR 2.58, 95% CI 1.69-3.93; 25[OH]D > 16.5-22.4 ng/mL, HR 4.08, 95% CI 2.67-6.23; 25[OH]D ≤ 16.5 ng/mL, HR 6.84, 95% CI 4.36-10.74). This relationship did not meaningfully change when further adjusted for demographic and clinical variables (model 2) or in the fully adjusted model that added laboratory parameters (model 3: 25[OH]D > 33.6 ng/mL reference, 25[OH]D > 27.1-33.6 ng/mL, HR 2.79, 95% CI 1.64-4.76; 25[OH]D > 22.4-27.1 ng/mL, HR 2.77, 95% CI 1.57-4.89; 25[OH]D > 16.5-22.4 ng/mL, HR 5.52, 95% CI 3.21-9.50; 25[OH]D ≤ 16.5 ng/mL, HR 7.46, 95% CI 4.19-13.25). The results were similar when 25(OH)D was examined on a continuous scale (HR per 10-ng/mL decrement 2.04, 95% CI 1.65-2.25, in the fully adjusted model).

Race-stratified analyses

The magnitude and strength of the association of 25(OH)D with incident CHD did not statistically differ by race in the full multivariable-adjusted model whether 25(OH)D was examined as a categorical variable ($P_{\text{interaction}}$ = .33) or on a continuous scale ($P_{\text{interaction}}$ = .12). In analyses using race-specific quintiles of 25(OH)D, the results were qualitatively the same in both black and white participants. However, the magnitude of the association between lower 25(OH)D and higher risk of incident CHD was greater in whites as compared to

Table I. Baseline characteristics of participants in the random subcohort overall and by quintiles of 25(OH)D

	Overall	Quintile 1 (< 16.5 ng/mL)	Quintile 2 (16.5-22.4 ng/mL)	Quintile 3 (>22.4-27.1 ng/mL)	Quintile 4 (>27.1-33.6 ng/mL)	Quintile 5 (>33.6 ng/mL)
Weighted n*	27,970	5561	5535	5605	5632	5637
Age, y	65.0 (64.5-65.6)	63.7 (62.6-64.7)	65.7 (64.4-66.9)	65.5 (64.3-66.7)	65.5 (64.3-66.7)	64.7 (63.5-65.9)†
Male sex	45	32	45	43	40	45†
Black	41	79	54	33	23	17†
BMI, kg/m^2	29.2 (28.7-29.6)	31.6 (30.4-32.8)	30.1 (29.3-30.9)	28.9 (28.1-29.7)	28.1 (27.3-28.9)	27.1 (26.3-28.0) †
SBP, mm Hg	127.2 (126.1128.4)	130.7 (127.8133.6)	128.1 (125.7130.5)	127.0 (124.6129.4)	125.9 (123.5128.3)	124.5(121.9127.1) †
DBP, mm Hg	76.3 (75.7-76.9)	78.5 (76.9-80.1)	77.3 (75.9-78.5)	76.1 (74.8-77.6)	75.1 (73.6-76.6)	74.6 (72.9-76.2) †
<HS graduate	12	18	19	12	6	6†
Income <$20 K	16	25	21	11	11	11†
Smoking (current)	14	24	11	12	4	17†
Exercise (none)	34	49	36	29	27	28†
Comorbidities						
Diabetes	21	29	31	24	11	10†
CKD	20	23	22	23	13	17†
CPD	9	8	8	9	11 †	8
Medications						
Aspirin	39	40	31	36	42	46†
RAAS inhibitor	29	37	28	31	25	23†
Statins	27	28	33	24	28	24†
25(OH)D, ng/mL	25.8 (25.0-26.5)	12.9 (12.5-13.2)	19.4 (19.1-19.7)	24.7 (24.5-24.9)	30.1 (29.8-30.4)	41.5 (40.3-42.8) †
PTH, pg/mL	45.6 (43.9-47.4)	63.4 (58.0-68.5)	45.2 (42.1-48.4)	42.6 (39.5-45.8)	40.3 (37.7-42.9)	36.4 (33.6-39.2) †
HDL-C, mg/dL	52.6 (51.3-53.9)	54.1 (50.7-57.5)	50.6 (48.1-53.1)	48.2 (45.7-50.6)	54.4 (51.4-57.4)	55.6 (52.3-58.9)
Triglycerides, mg/dL	131.0 (124.9137.1)	115.9 (107.7124.3)	130.8 (11.7143.9)	143.5 (127.4159.6)	132.9 (118.8147.2)	132.3(117.9146.6) †
Total cholesterol, mg/dL	192.9 (189.7196.2)	196.1 (188.6203.5)	188.9 (182.2195.6)	188.2 (180.9195.4)	188.5 (181.5195.6)	202.7(195.7209.7) †
hsCRP, mg/L	2.2 [0.9-4.9]	2.8 [1.2-7.3]	2.4 [0.9-4.8]	2.0 [1.0-4.8]	1.9 [0.9-4.5]	1.7 [0.8-4.2] †

Results are depicted as means (95% CIs), median [interquartile range], or frequencies.
BMI, body mass index; *SBP*, systolic blood pressure; *DBP*, diastolic blood pressure; *HS*, high school; *CKD*, chronic kidney disease (defined as an eGFR <60 mL/min/1.73 m^2 or a spot urine ACR ≥30 mg/g); *CPD*, chronic pulmonary disease; *RAAS*, renin-angiotensin-aldosterone system.
*Weighted back to the original REGARDS cohort.
† $P < .05$ for comparison across quintiles of 25(OH)D.

blacks both when 25(OH)D was modeled in quintiles and on a continuous scale (Table III and Figure 1). (See Fig. 1.)

Discussion

In this cohort of community-dwelling adults, lower plasma 25(OH)D concentrations were associated with higher risk of incident CHD independently of established CHD risk factors. Further, the magnitude and strength of the associations did not statistically differ by race.

Numerous prior studies have examined the association of 25(OH)D with risk of myocardial infarction or fatal CHD events, but only a few population-based studies had sufficient representation of multiracial groups to examine whether the association of 25(OH)D with CHD differed by race. In a study of 6,436 participants of MESA, lower 25(OH)D concentrations were associated with higher risk of incident CHD (defined as myocardial infarction, angina, cardiac arrest of CHD death) in white and Chinese participants but not in black or Hispanic participants.[2] Similarly, the ARIC study found that lower circulating 25 (OH)D concentrations were associated with higher risk of CHD (defined as definite or probable hospitalized myocardial infarction or definite fatal CHD) in white but not black participants.[1] The current study in REGARDS found that the associations of 25(OH)D with incident CHD did not differ by race. The reasons for these discrepancies are unclear. There are important differences in REGARDS participant characteristics as compared to MESA and ARIC that might provide some clues. The REGARDS study population is on average older and had a higher prevalence of comorbidities at baseline than MESA or ARIC. Accordingly, it is possible that part of the reasons for the differences in these results may be that the REGARDS population is generally less healthy than other cohorts, potentially amplifying an association of low 25 (OH)D with CHD risk. Next, in MESA, there were only 94 CHD events in black individuals in total, and of these, only 52 were related to myocardial infarction or CHD mortality; as such, it is possible that the types of ischemic heart disease in black participants of REGARDS were different than those captured in MESA. Furthermore, only 37 CHD events were observed in the very low range of 25 (OH)D concentrations (bottom 2 quintiles) in black

Table II. Hazard ratio (95% CI) of incident CHD as a function of baseline 25(OH)D concentrations

	# Events	Model 1*	Model 2†	Model 3‡§
25(OH)D categories		HR (95% CI)	HR (95% CI)	HR (95% CI)
>33.6 ng/mL	59	Ref	Ref	Ref
>27.1-33.6 ng/mL	117	1.93 (1.26-2.96)	1.91 (1.19-3.04)	2.79 (1.64-4.76)
>22.4-27.1 ng/mL	156	2.58 (1.69-3.93)	2.08 (1.26-3.43)	2.77 (1.57-4.89)
>16.5-22.4 ng/mL	220	4.08 (2.67-6.23)	3.91 (2.44-6.25)	5.52 (3.21-9.50)
≤ 16.5 ng/mL	277	6.84 (4.36-10.74)	6.05 (3.72-9.85)	7.46 (4.19-13.25)
Per 10-ng/mL decrement	829	2.08 (1.75-2.46)	2.00 (1.66-2.41)	2.04 (1.65-2.52)

*Model 1 is adjusted for age, sex and black race.
† Model 2 is adjusted for covariates in model 1 and season of blood draw, systolic blood pressure, diastolic blood pressure, body mass index, income, current smoking, diabetes status, left ventricular hypertrophy, and medication use (statins, aspirin, angiotensin II receptor blockers, angiotensin-converting enzyme inhibitors, spironolactone).
‡ Model 3 is adjusted for covariates in model 2 and eGFR, log-transformed urine ACR, log-transformed hsCRP, intact PTH, triglycerides, HDL-C, and total cholesterol.
§ In the full multivariable-adjusted model, the *P* value for the interaction term between 25(OH)D and race was .33 when 25(OH)D was examined as a categorical variable and .12 when 25(OH)D was examined on a continuous scale.

Table III. Hazard ratio (95% CI) of incident CHD as a function of baseline 25(OH)D concentrations, stratified by race-specific tertiles

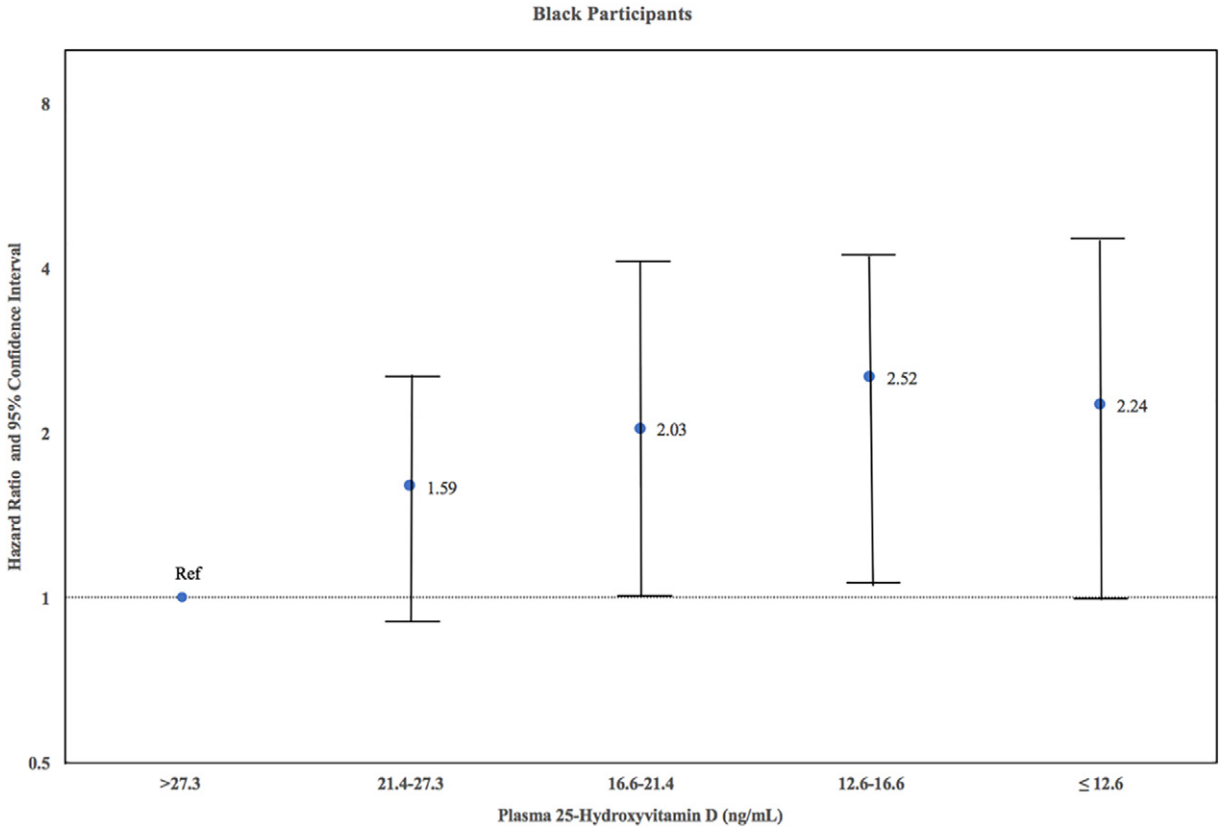
	# Events	Model 1*	Model 2†	Model 3‡
Whites				
25(OH)D categories		HR (95% CI)	HR (95% CI)	HR (95% CI)
>36.0 ng/mL	34	Ref	Ref	Ref
>30.2-36.0 ng/mL	57	1.54 (0.86-2.76)	1.26 (0.64-2.46)	1.77 (0.47-6.73)
>25.7-30.2 ng/mL	87	2.49 (1.41-4.37)	1.76 (0.91-3.41)	3.31 (1.09-9.99)
>21.6-25.7 ng/mL	110	3.02 (1.73-5.28)	2.56 (1.32-4.95)	3.03 (1.09-8.36)
≤21.6 ng/mL	186	5.43 (3.12-9.44)	4.85 (2.62-8.98)	4.21 (1.62-10.94)
Per 10-ng/mL decrement	474	2.15 (1.68-2.74)	2.28 (1.74-2.97)	2.98 (2.04-4.35)
Blacks				
25(OH)D categories		HR (95% CI)	HR (95% CI)	HR (95% CI)
>27.3 ng/mL	29	Ref	Ref	Ref
>21.4-27.3 ng/mL	57	1.93 (1.11-3.36)	1.72 (0.93-3.19)	1.59 (0.83-3.04)
>16.6-21.4 ng/mL	75	2.71 (1.58-4.65)	1.78 (0.93-3.39)	2.03 (1.01-4.09)
>12.6-16.6 ng/mL	78	3.21 (1.84-5.58)	2.53 (1.34-4.76)	2.52 (1.24-5.13)
≤12.6 ng/mL	116	5.07 (2.94-8.73)	3.41 (1.81-6.41)	2.24 (1.00-4.96)
Per 10-ng/mL decrement	355	2.05 (1.61-2.61)	1.76 (1.35-2.29)	1.46 (1.10-1.94)

*Model 1 is adjusted for age and sex.
† Model 2 is adjusted for covariates in model 1 and season of blood draw, systolic blood pressure, diastolic blood pressure, body mass index, income, current smoking, diabetes status, left ventricular hypertrophy, and medication use (statins, aspirin, angiotensin II receptor blockers, angiotensin-converting enzyme inhibitors, spironolactone).
‡ Model 3 is adjusted for covariates in model 2 and eGFR, log-transformed urine ACR, log-transformed hsCRP, intact PTH, triglycerides, HDL-C, and total cholesterol.

participants of MESA versus 194 in the current study. The ARIC study had more CHD events in black participants than MESA, including in the very low range of 25(OH)D. However, most of these events were captured from a single site (Jackson, MS), and many of them occurred in the late 1990s, when prevention of ischemic heart disease may have been different than the standards of practice that were in place during follow-up of REGARDS participants.

There remains great uncertainty about whether lower 25(OH)D concentrations are causally related to the development of CHD. The Vitamin D and Omega-3 Trial (VITAL) reported no effect of cholecalciferol supplementation on the development of major cardiovascular disease events (including myocardial infarction) in a large, randomized controlled study, strongly arguing against a causal relationship between lower 25(OH)D and higher risk of CHD.[13] Furthermore, no randomized controlled studies have shown that vitamin D supplementation ameliorates major risk factors for the development of heart disease such as dyslipidemia, diabetes, or hypertension. In addition, Mendelian randomization studies have failed to show an association of genetically determined 25(OH)D concentrations with risk of coronary artery disease,[14,15] suggesting that the association of lower 25(OH)D with higher CHD risk is accounted for by other factors. Possible factors include vitamin D binding protein, which is the major circulating carrier protein for 25(OH)D and strongly impacts circulating 25(OH)D concentrations and bioavailability. Studies have shown that vitamin D binding protein is associated with CHD risk independently of 25(OH)D concentrations.[1,16] Unfortunately, we did not have measures of vitamin D binding protein in this study, and so we could not determine the association of vitamin D binding protein with CHD in the current study. In addition, there is

Figure 1



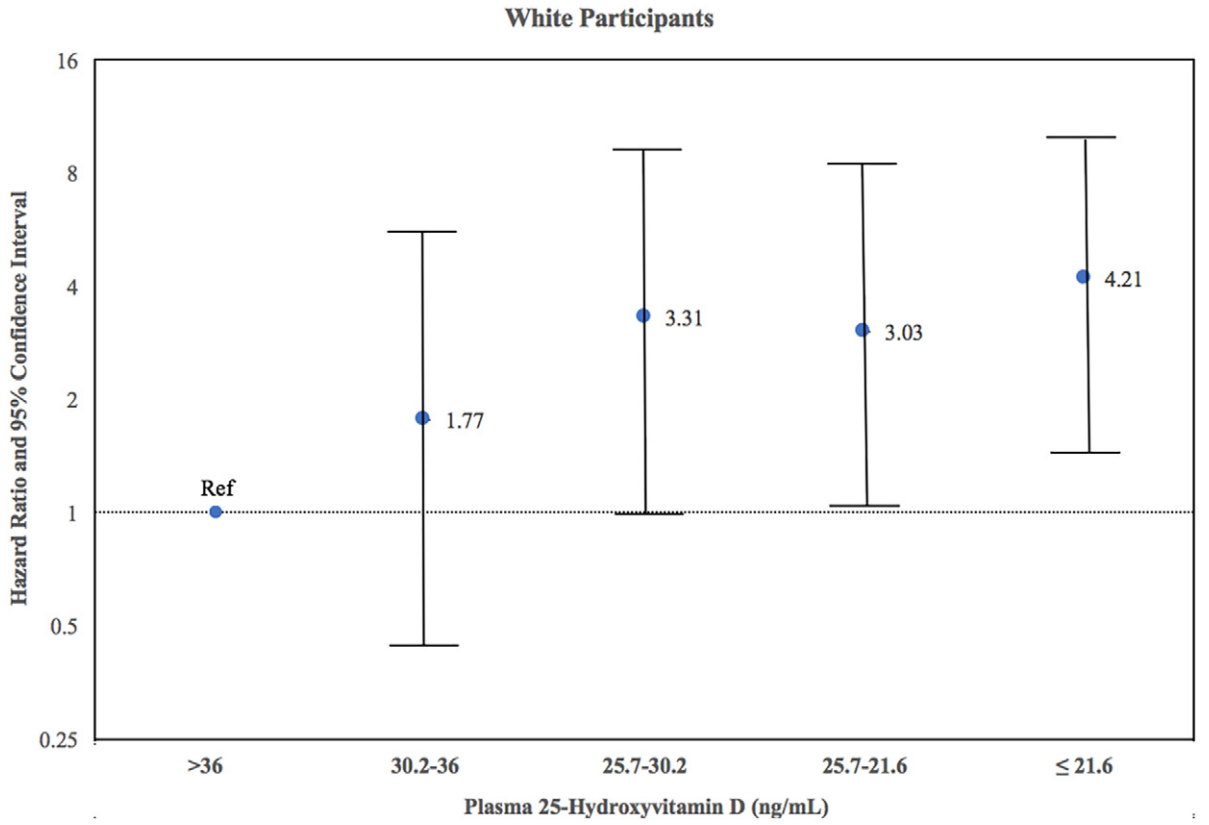
Association between race-specific quintiles of 25(OH)D and incident CHD in black (A) and white (B) REGARDS participants. This is a graphical representation of the estimates from the adjusted model, reported fully in Table III. Hazard ratios were determined from a Cox proportional hazards model adjusted for age, sex, season of blood draw, systolic blood pressure, diastolic blood pressure, body mass index, income, current smoking, diabetes status, left ventricular hypertrophy, medication use (statins, aspirin, angiotensin II receptor blockers, angiotensin-converting enzyme inhibitors, spironolactone), eGFR, log-transformed urine ACR, log-transformed hsCRP, intact PTH, triglycerides, HDL-C, and total cholesterol.

evidence that 25(OH)D may act as an acute phase reactant, with circulating concentrations dropping in settings of acute or chronic illness.[17] To this end, lower 25(OH)D may be a marker of generalized illness, accounting for the inverse association of 25(OH)D with CHD risk. In addition, 25(OH)D modulates several cellular components of the cardiovascular system linked to traditional risk factors for CVD such as lipids, blood pressure control, and insulin sensitivity.[18] These data combined with VITAL study results suggest that 25(OH)D measurements may represent an integrated marker of CVD risk but not a modifiable risk factor in and of itself. Given the robust association of 25(OH)D with CHD in the REGARDS population, understanding factors that may explain this association may uncover novel biomarkers for CHD risk in the general population.

This study had limitations. Serum 25(OH)D concentration was measured at 1 single time point, which may have led to exposure misclassification for some study participants. We did not have 25(OH)D measurements done via liquid chromatography–mass spectrometry, which some suggest is the best method to measure 25(OH)D in blood samples; nonetheless, the assay used to measure 25(OH)D in the current study has been validated against liquid chromatography–mass spectrometry.[19] Next, we measured total 25(OH)D in this study. Associations of free or bioavailable 25(OH)D may differ from associations of total 25(OH)D with CHD. The inclusion of only black or white participants may limit the generalizability of these results to other races and ethnicities in the United States.

In conclusion, lower 25(OH)D concentrations were associated with higher risk of CHD in community-dwelling adults with no statistically significant differences in the magnitude or strength of the association by race. The implications for these data are clouded by the lack of randomized controlled trial data and genetic epidemiologic data supporting a causal role of lower vitamin D in the pathophysiology of heart disease. To this end,

Figure 1



A, Fully adjusted HR (95% CI) of incident CHD by race-specific quintiles of 25(OH)D in black participants.**B**, Fully adjusted HR (95% CI) of incident CHD by race-specific quintiles of 25(OH)D in white participants.

understanding factors that might explain the association of lower 25(OH)D with higher risk of CHD may uncover novel biomarkers of CHD risk in the general population.

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