Racial Differences in Association of Serum Calcium with Mortality and Incident Cardio- and Cerebrovascular Events

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Context: Abnormalities in calcium metabolism may potentially contribute to the development of vascular disease. Calcium metabolism may be different in African American (AA) vs white individuals, but the effect of race on the association of serum calcium with clinical outcomes remains unclear.

Objective: This study sought to examine race-specific associations of serum calcium levels with mortality and with major incident cardiovascular events.

Design and Setting: This was a historical cohort study in the U.S. Department of Veterans Affairs health care facilities.

Participants: Participants included veterans (n = 1 967 622) with estimated glomerular filtration rate ≥ 60 mL/min/1.73 m^2.

Main Outcome Measures: The association between serum calcium levels with all-cause mortality, incident coronary heart disease (CHD), and ischemic stroke incidence was examined in multivariable adjusted Cox proportional hazards models, including an interaction term for calcium and race.

Results: The association of calcium with all-cause mortality was U-shaped in both AA and white patients, but race modified the association of calcium with all-cause mortality. Compared with white patients, AA patients experienced lower risk of mortality when calcium was ≥ 8.8 mg/dL, with a statistically significant interaction ($P < .001$). Conversely, AA vs white race was associated with higher mortality when calcium was < 8.8 mg/dL. Calcium showed no significant association with ischemic stroke or CHD in both races; and race did not modify these associations ($P = .37$ and 0.11, respectively for interaction term).

Conclusions: Race modified the U-shaped association between calcium and all-cause mortality. Serum calcium is not associated with incident stroke or CHD in either AA or white patients. The race-specific difference in the association of calcium levels with mortality warrants further examination. (***J Clin Endocrinol Metab*** **101: 4851–4859, 2016)**

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Abbreviations: AA, African American; BMD, bone mineral density; BMI, body mass index; BP, blood pressure; CHD, coronary heart disease; CI, confidence interval; CKD, chronic kidney disease; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; CPT, Current Procedural Terminology; CSC, corrected serum calcium; eGFR, estimated glomerular filtration rate; ICD-9, International Classification of Diseases, Ninth Revision; PS, propensity score; PY, patient-year; RCAV, Racial and Cardiovascular Risk Anomalies; VA, Veterans Affairs.

Calcium as a nutrient aroused public attention more than 50 years ago (1, 2). Calcium or vitamin D supplementation to postmenopausal women was extensively studied in 1990s (3). Given that calcium is the major component of bone and teeth, initial investigations focused primarily on bone mass density or fractures. More recently, vascular calcification has become a focal point (4), with studies examining the relationship between calcium intake (5, 6) or serum calcium (7, 8) with the various clinical outcomes. Most studies focused on the associations between calcium or vitamin D supplementation with vascular calcification, but the effect of these nutritional interventions on cardiovascular events has been less well studied. Even less is known about the association of serum calcium with vascular calcification, bone health, or deaths related to occlusive vascular events. Studies have recently uncovered significant differences in calcium homeostasis between African American (AA) and white individuals. AA individuals have higher bone mineral density (BMD) (9, 10), increased intestinal calcium absorption (11, 12), and low urine calcium secretion (13), and also experience higher incidence of strokes (14) and mortality (15, 16). It is unclear whether differences in calcium and vitamin D metabolism affect race-associated differences in vascular calcification and consequently cardiovascular events.

To clarify whether there is an association between serum calcium level and clinical outcomes, and whether such associations are different in AA vs white individuals, we examined the association of various serum calcium levels with all-cause mortality and with major incident vascular events in a large national cohort of U.S. veterans with estimated glomerular filtration rate (eGFR) of at least 60 mL/min/1.73 m^2.

Materials and Methods

Study population

Our study subjects were selected from a historical cohort examining risk factors and outcomes of incident chronic kidney disease (CKD) (Racial and Cardiovascular Risk Anomalies in CKD (RCAV) study). The RCAV study population was previously described (17, 18). The algorithm for our analytical cohort definition is shown in Figure 1. We included veterans who received Veterans Affairs medical services between October 1, 2004 and September 30, 2006 (baseline period), and who had an outpatient eGFR at least 60 mL/min/1.73 m^2 and available outpatient serum calcium measurements during the same time period. eGFR was calculated by using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation (19). Corrected serum calcium (CSC) was calculated by adjusting serum calcium for serum albumin levels by using the following equation: corrected calcium = measured calcium (mg/dL) + 0.8 [4.0 − serum albumin (g/dL)]. After excluding patients with extremely high or low CSC (>20 mg/dL or <5 mg/dL), those with a diagnosis of primary hyperparathyroidism and patients starting dialysis during the enrollment period, our final cohort consisted of 1 967 622 patients. The mean of all available CSCs during the baseline period was used as a predictor in this study. We divided mean CSCs into eight a priori defined categories with 0.3 mg/dL increments starting from less than 8.5 mg/dL, and used the 9.1–<9.4 mg/dL category as referent in all analyses. In sensitivity analyses we further subdivided hypo- and hypercalcemia into categories of <7.9, 7.9–<8.2 and 8.2–<8.5, and 10.3–<10.6, 10.6–<10.9, 10.9–<11.2, and at least 11.2 mg/dL, respectively.

Patients' age, sex, race, and blood pressure (BP) were obtained from the VA Corporate Data Warehouse, as previously described (20, 21). Information on race was cross referenced with data obtained from Medicare through the VA-Medicare data merge project (22). Information on prevalent comorbidities was

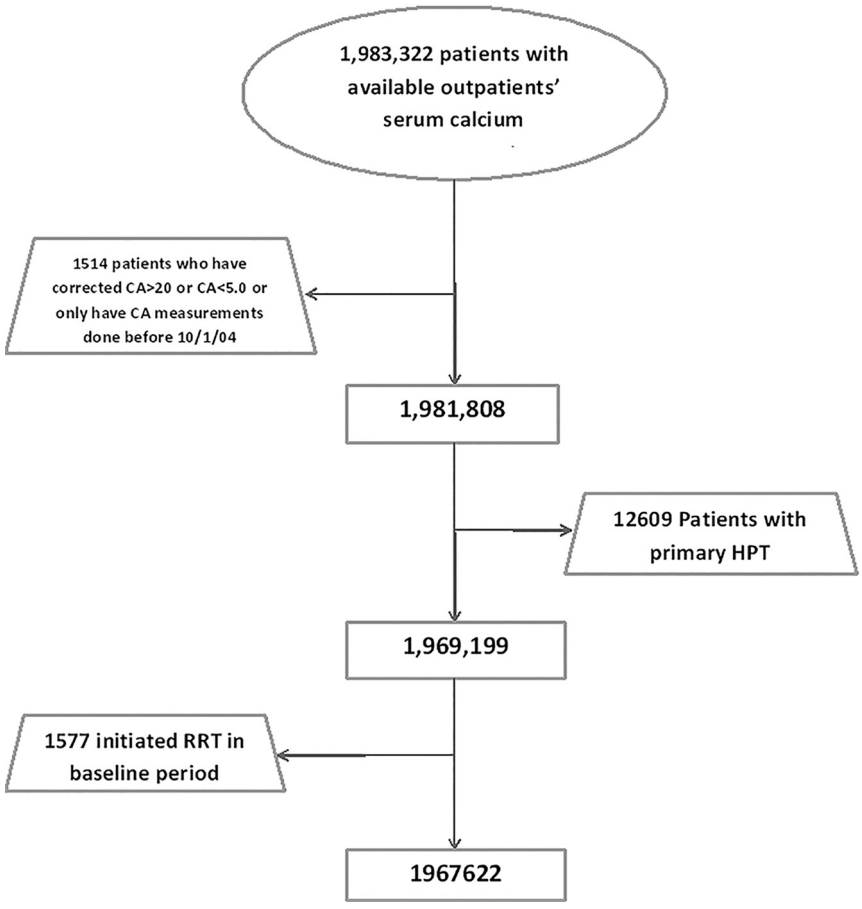

Figure 1. Cohort definition: Algorithm used to define the study cohort.

extracted from the VA Inpatient and Outpatient Medical SAS Datasets (23) using International Classification of Diseases, Ninth Revision (ICD-9) diagnostic and procedure codes and Current Procedural Terminology (CPT) codes recorded during the baseline period.

Incident coronary heart disease (CHD) was defined as a composite outcome of a first occurrence of an ICD-9-CM or CPT code for acute myocardial infarction, coronary artery bypass grafting, or percutaneous angioplasty after October 1, 2006 in patients without such diagnoses prior to this date. Incident ischemic stroke was defined as the first occurrence of an ICD-9-CM code of ischemic stroke after October 1, 2006 in patients without cerebrovascular diseases during the baseline period (24). Data related to baseline medication exposure including calcium or vitamin D supplements, antihypertensive medications, anticoagulation medication, and diuretics was collected from VA Pharmacy dispensation records (25). To minimize random variation we used the respective means of all body mass index (BMI) and BP recordings from the first 90 days after cohort entry as baseline values for these variables in our analyses. Information about all-cause mortality was obtained from the VA Vital Status Files, which contain dates of death until July 26, 2013 from all available sources in the VA system. The sensitivity and specificity of the Vital Status Files using the National Death index as gold standard were shown to be very high (98.3 and 99.8%, respectively) (26).

Statistical analyses

Descriptive analyses were performed by using means ± SD, medians (interquartile range) and proportions as appropriate. Event rates were calculated using the patient-year (PY) approach. Cox proportional hazards models with adjustment for potential confounders were used for examining the association of mean baseline CSCs with all-cause mortality and with incident CHD and strokes. Effect modification by race was examined by testing the significance of the interactive term between race and CSC, and then estimated in hazard ratios and 95% confidence intervals (CI) for the eight a priori defined CSC categories in AA and in white patients using white patients with CSC 9.1–<9.4 mg/dL as referent. Patients were followed in survival analyses from the date of the baseline eGFR until death or were censored at the date of the last health care documented in the VA Vital Status Files, or on July 26, 2013. For incident CHD or ischemic stroke events, the follow-up period started from October 1, 2006 to avoid immortal time bias (27), and lasted until the first event date, death, or last encounter. Patients with cardiovascular disease at baseline were excluded from the analysis for incident CHD outcome, to avoid the uncertainty of a repeat ICD9 code signaling a new event vs merely a history of an earlier one. Similarly, patients with a baseline stroke diagnosis were excluded for incident ischemic stroke outcome.

The effect of potential confounders on outcomes was analyzed by multivariable adjustments including baseline age, sex, BMI, baseline BP, per capita income, marital status, comorbid conditions [(cardiovascular disease, cerebrovascular disease, hypertension, congestive heart failure, rheumatologic disease, malignancy, depression, liver disease, chronic lung disease, HIV, and the Deyo-modified Charlson Comorbidity Index (28)] and medications (calcium and vitamin D supplements, loop diuretics, thiazide diuretics, potassium-sparing diuretics, anticoagulants, and antiplatelet medications), and baseline eGFR.

The associations of CSC with all outcomes were also examined in a propensity score (PS) –matched cohort, which was created by calculating PSs for the likelihood of AA vs white race through logistic regression including all variables in multivariable models and performing a 1:1 nearest-neighbor matching. To make the results of all-cause mortality more comparable with incident CHD/ischemic stroke outcomes, the association of CSC with mortality was re-examined in a sensitivity analysis after excluding patients with baseline cardio- or cerebra-vascular disease. In addition, all outcomes were also analyzed separately in the two race groups.

Statistical analyses were performed using Stata MP Version 12 (StataCor,). The study was approved by the institutional review boards at the Memphis and Long Beach VA Medical Centers.

Results

The mean age of the cohort was 60.6 ± 13.5 years, 15.5% (n = 305 164) were AA, and 93.5% (n = 1 839 698) were male. The mean BMI was 29.3 ± 5.7 kg/m^2, and the mean eGFR was 83.3 ± 15.4 mL/min/1.73 m^2 Baseline characteristics of AA vs white patients categorized by their mean baseline CSC levels are described in Table 1. African Americans were younger than whites, and had higher baseline eGFR levels, lower median income, and lower percentage of married status. African Americans also had slightly lower prevalence of cardiovascular and cerebrovascular diseases. Furthermore, more AAs vs whites were taking calcium or vitamin D supplements, and diuretics except for loop diuretics.

Mortality

White (n = 299,113; 21.1%) and AA (n = 47 775; 15.7%) patients died (mortality rate: 29.9/1000 PY; 95% confidence interval [CI], 29.8–30.0 vs 21.6/1000 PY; 95% CI, 21.4–21.8, respectively). Figure 2 and Table 2 describe the race-specific multivariable adjusted association of mean baseline CSC categories with all-cause mortality in the overall cohort. Both higher and lower CSC levels were associated with higher mortality in both races. AA patients experienced significantly lower mortality compared with white patients in every CSC category above 8.8 mg/dL ($P < .001$), similar mortality for CSC 8.5–<8.8 ($P = .50$), and higher mortality in the CSC less than 8.5 mg/dL group ($P = .02$) (Figure 2). The same associations were consistently present in the PS matched cohort (Supplemental Figure 1), when analyzing AA and white patients as separate subgroups (Supplemental Figure 2), and when subdividing abnormally low and high CSC levels into more granular categories (Supplemental Figure 3). The results remained essentially unchanged in sensitivity analyses excluding patients with baseline coronary and cerebrovascular disease (Supplemental Table 1).

Table 1. Baseline Characteristics of 1 967 622 U.S. Veterans with eGFR ≥ 60 mL/min/1.73 m^2 Divided by their Baseline Mean Corrected Serum Calcium

	CSC, mg/dL							
No. of patients	**<8.5**	**8.5–<8.8**	**8.8–<9.1**	**9.1–<9.4**	**9.4–<9.7**	**9.7–<10**	**10–<10.3**	**≥10.3**
White	11 347	56 494	212 619	494 113	384 567	162 498	72 584	26 261
AA	1869	8327	32 766	90 181	91 889	48 357	22 984	8791
Age, y								
White	64 ± 13	63 ± 13	63 ± 13	62 ± 13	61 ± 13	61 ± 13	61 ± 13	61 ± 13
AA	58 ± 13	56 ± 13	56 ± 13	55 ± 13	55 ± 13	56 ± 13	55 ± 13	57 ± 13
Sex, No. (% male)								
White	10 819 (95)	53 868 (95)	202 724 (95)	470 369 (95)	363 933 (95)	152 757 (94)	67 740 (93)	24 388 (93)
AA	1738 (93)	7600 (91)	29 613 (90)	81 830 (91)	83 177 (91)	43 693 (90)	20 724 (90)	7919 (90)
Marital status, No. (% married)								
White	5772 (51)	31 317 (55)	121 126 (57)	283 414 (57)	216 303 (56)	89 985 (55)	39 633 (54)	14 015 (52)
AA	598 (32)	2921 (35)	12 457 (38)	35 683 (40)	36 991 (40)	19 321 (40)	9245 (40)	3413 (39)
Median income, $								
White	22 046	24 502	24 826	24 920	24 410	23 938	23 472	23 162
AA	15 128	15 342	16 998	17 140	17 274	17 109	17 057	16 608
eGFR (EPI), mL/min/1.73 m^2								
White	82.4 ± 14.7	81.5 ± 14.2	81.5 ± 14.0	81.8 ± 14.0	81.8 ± 14.2	81.6 ± 14.4	81.8 ± 14.7	81.6 ± 14.8
AA	91.9 ± 20.1	91.4 ± 19.3	91.2 ± 18.9	91.4 ± 18.6	91.2 ± 18.6	90.7 ± 18.8	90.6 ± 18.9	90.4 ± 19.1
SBP, mm Hg								
White	134 ± 20	134 ± 19	135 ± 19	135 ± 19	136 ± 19	136 ± 19	136 ± 19	137 ± 20
AA	137 ± 21	137 ± 21	136 ± 20	136 ± 20	137 ± 20	138 ± 21	138 ± 21	139 ± 21
DBP, mm Hg								
White	76 ± 12	76 ± 12	76 ± 11	77 ± 11	77 ± 12	77 ± 12	77 ± 12	77 ± 12
AA	79 ± 13	79 ± 13	79 ± 13	80 ± 13	80 ± 13	80 ± 13	80 ± 13	81 ± 13
BMI, kg/m^2								
White	29.2 ± 6.1	29.6 ± 5.9	29.6 ± 5.8	29.4 ± 5.7	29.4 ± 5.7	29.3 ± 5.8	29.2 ± 5.7	29.0 ± 5.7
AA	28.2 ± 6.3	29.2 ± 6.5	29.4 ± 6.2	29.3 ± 6.0	29.2 ± 6.0	29.1 ± 6.1	28.8 ± 5.9	28.3 ± 6.0
Serum albumin, g/dL								
White	4.0 ± 0.8	4.0 ± 0.6	4.0 ± 0.5	4.1 ± 0.5	4.1 ± 1.1	4.1 ± 1.0	4.2 ± 0.9	4.2 ± 1.2
AA	3.8 ± 0.6	3.9 ± 0.5	4.0 ± 3.1	4.0 ± 0.5	4.0 ± 0.6	4.0 ± 0.6	4.1 ± 0.6	4.1 ± 0.8
CCI								
White	1 (0, 2)	1 (0, 2)	1 (0, 2)	1 (0, 2)	1 (0, 2)	1 (0, 2)	1 (0, 2)	1 (0, 2)
AA	1 (0, 3)	1 (0, 2)	1 (0, 2)	1 (0, 2)	1 (0, 2)	1 (0, 2)	1 (0, 2)	1 (0, 2)
CHF								
White	1020 (9.0%)	3763 (6.7%)	12 137 (5.7%)	24 006 (4.9%)	19 209 (5.0%)	8777 (5.4%)	3616 (5.0%)	1489 (5.7%)
AA	169 (9.0%)	605 (7.3%)	1937 (5.9%)	4348 (4.8%)	4375 (4.8%)	2413 (5.0%)	1090 (4.7%)	468 (5.3%)
Cardiovascular disease								
White	2006 (17.7%)	8608 (15.2%)	31 061 (14.6%)	68 500 (13.9%)	54 619 (14.2%)	23 566 (14.5%)	9761 (13.4%)	3508 (13.4%)
AA	188 (10.1%)	822 (9.9%)	2942 (9.0%)	7121 (7.9%)	7388 (8.0%)	4106 (8.5%)	1765 (7.7%)	717 (8.2%)
Cerebrovascular Disease								
White	1156 (10.2%)	4351 (7.7%)	15 370 (7.2%)	33 487 (6.8%)	27 391 (7.1%)	12 149 (7.5%)	5182 (7.1%)	1978 (7.5%)
AA	166 (8.9%)	598 (7.2%)	2089 (6.4%)	5108 (5.7%)	5554 (6.0%)	3267 (6.8%)	1526 (6.6%)	647 (7.4%)
Malignancy								
White	1893 (16.7%)	7129 (12.6%)	23 992 (11.3%)	52 640 (10.7%)	43 393 (11.3%)	20 074 (12.4%)	8891 (12.2%)	3952 (15.0%)
AA	350 (18.7%)	947 (11.4%)	3287 (10.0%)	8457 (9.4%)	9439 (10.3%)	5594 (11.6%)	2781 (12.1%)	1405 (16.0%)
Liver disease								
White	121 (1.1%)	344 (0.6%)	1075 (0.5%)	2061 (0.4%)	2085 (0.5%)	1140 (0.7%)	510 (0.7%)	230 (0.9%)
AA	27 (1.4%)	40 (0.5%)	129 (0.4%)	247 (0.3%)	344 (0.4%)	261 (0.5%)	143 (0.6%)	69 (0.8%)
Rheumatologic disease								
White	207 (1.8%)	972 (1.7%)	3510 (1.7%)	7757 (1.6%)	6488 (1.7%)	2991 (1.8%)	1240 (1.7%)	455 (1.7%)
AA	16 (0.9%)	102 (1.2%)	414 (1.3%)	1189 (1.3%)	1283 (1.4%)	734 (1.5%)	357 (1.5%)	122 (1.4%)
Lung disease								
White	2978 (26.2%)	13 102 (23.2%)	46 336 (21.8%)	101 125 (20.5%)	81 352 (21.1%)	36 236 (22.3%)	15 451 (21.3%)	5893 (22.4%)
AA	363 (19.4%)	1505 (18.0%)	5581 (17.0%)	14 418 (16.0%)	14 928 (16.2%)	7998 (16.5%)	3681 (16.0%)	1501 (17.1%)
Depression								
White	1257 (11.1%)	5733 (10.1%)	21 965 (10.3%)	48 577 (9.8%)	39 294 (10.2%)	17 051 (10.5%)	7543 (10.4%)	2750 (10.5%)
AA	183 (9.8%)	1036 (12.4%)	3759 (11.5%)	10 199 (11.3%)	10 410 (11.3%)	5410 (11.2%)	2424 (10.5%)	821 (9.3%)
Hypertension								
White	7046 (62.1%)	34 245 (60.6%)	131 325 (61.8%)	308 217 (62.4%)	248 705 (64.7%)	109 004 (67.1%)	48 489 (66.8%)	18 020 (68.6%)
AA	1227 (65.7%)	5320 (63.9%)	21 141 (64.5%)	58 357 (64.7%)	62 030 (67.5%)	34 200 (70.7%)	16 265 (70.8%)	6449 (73.4%)
Peptic ulcer								
White	368 (3.2%)	1326 (2.3%)	4455 (2.1%)	9731 (2.0%)	7803 (2.0%)	3424 (2.1%)	1412 (1.9%)	554 (2.1%)
AA	61 (3.3%)	258 (3.1%)	813 (2.5%)	2077 (2.3%)	2114 (2.3%)	1057 (2.2%)	504 (2.2%)	229 (2.6%)
HIV/AIDS								
White	66 (0.6%)	249 (0.4%)	1007 (0.5%)	2298 (0.5%)	1816 (0.5%)	779 (0.5%)	242 (0.3%)	85 (0.3%)
AA	69 (3.7%)	289 (3.5%)	930 (2.8%)	2204 (2.4%)	2313 (2.5%)	1208 (2.5%)	453 (2.0%)	137 (1.6%)
Vitamin D/calcium supplements								
White	3255 (28.7%)	13 666 (24.2%)	47 939 (22.5%)	103 852 (21.0%)	82 022 (21.3%)	35 874 (22.1%)	15 669 (21.6%)	5664 (21.6%)
AA	645 (34.5%)	2679 (32.2%)	10 296 (31.4%)	26 045 (28.9%)	26 483 (28.8%)	14 373 (29.7%)	6660 (29.0%)	2502 (28.5%)

(*Continued*)

Table 1. Continued

	CSC, mg/dL							
No. of patients	**<8.5**	**8.5–<8.8**	**8.8–<9.1**	**9.1–<9.4**	**9.4–<9.7**	**9.7–<10**	**10–<10.3**	**≥10.3**
Anticoagulants								
White	3377 (29.8%)	14 656 (25.9%)	51 507 (24.2%)	107 826 (21.8%)	84 214 (21.9%)	35 661 (21.9%)	14 682 (20.2%)	5181 (19.7%)
AA	657 (35.2%)	2548 (30.6%)	8761 (26.7%)	21 535 (23.9%)	21 961 (23.9%)	12 049 (24.9%)	5407 (23.5%)	2035 (23.1%)
Anti-platelet agents								
White	1320 (11.6%)	6457 (11.4%)	25 032 (11.8%)	57 241 (11.6%)	46 018 (12.0%)	19 804 (12.2%)	8513 (11.7%)	2922 (11.1%)
AA	131 (7.0%)	668 (8.0%)	2618 (8.0%)	6761 (7.5%)	7184 (7.8%)	3951 (8.2%)	1815 (7.9%)	642 (7.3%)
K-sparing diuretics								
White	1349 (11.9%)	6027 (10.7%)	21 922 (10.3%)	48 496 (9.8%)	39 584 (10.3%)	18 006 (11.1%)	7776 (10.7%)	2969 (11.3%)
AA	336 (18.0%)	1274 (15.3%)	5040 (15.4%)	12 745 (14.1%)	13 290 (14.5%)	7173 (14.8%)	3315 (14.4%)	1333 (15.2%)
Thiazide diuretics								
White	3523 (31.0%)	16 939 (30.0%)	66 064 (31.1%)	158 078 (32.0%)	130 732 (34.0%)	58 405 (35.9%)	26 135 (36.0%)	9567 (36.4%)
AA	832 (44.5%)	3658 (43.9%)	14 601 (44.6%)	41 243 (45.7%)	44 766 (48.7%)	24 440 (50.5%)	11 567 (50.3%)	4407 (50.1%)
Loop diuretics								
White	3871 (34.1%)	14 960 (26.5%)	50 616 (23.8%)	105 068 (21.3%)	84 847 (22.1%)	38 461 (23.7%)	16 165 (22.3%)	6549 (24.9%)
AA	618 (33.1%)	2212 (26.6%)	7343 (22.4%)	17 705 (19.6%)	18 471 (20.1%)	10 598 (21.9%)	4747 (20.7%)	1978 (22.5%)

Abbreviations: CCI, Charlson comorbidity index; CHF, congestive heart failure; CVD, cardiovascular disease; DBP, diastolic blood pressure; SBP, systolic blood pressure.

Values expressed as No. (%), mean ± SD, or median (25th percentile, 75th percentile).

Incident CHD and incident ischemic stroke events

Incident CHD events occurred in 34 304 white (event rate: 5.0/1000 PY; 95% CI, 4.9–5.0) and 6175 AA patients (event rate: 3.7/1000 PY; 95% CI, 3.6–3.8). Incident strokes occurred in 30 300 white patients (event rate: 4.0/1000 PY; 95% CI, 4.0–4.1) and 8129 AA patients (event rate: 4.8/1000 PY; 95% CI, 4.7–4.9). There was no consistent association between CSC levels and either incident CHD (Table 2 and Figure 3) or ischemic strokes (Table 2 and Figure 4) in either AA or white patients. Compared with white patients, AA patients experienced lower incident CHD in all CSC categories except for CSC less than 8.5 mg/dL (Figure 3; $P = .11$), and higher stroke rates in all CSC categories (Figure 4; $P = .37$). Results were similar in PS-matched cohorts when analyzing AA and white patients as separate subgroups (Supplemental Figures 4 and 5), and when subdividing abnormally low and high CSC levels into more granular categories (Supplemental Figures 6 and 7).

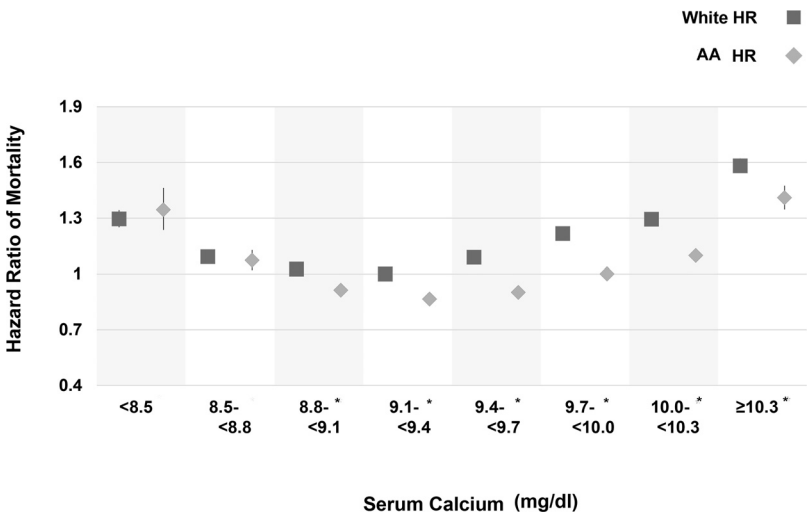

Figure 2. Race-specific associations of CSC with mortality: Multivariable adjusted hazard ratios (95% CIs) of all-cause mortality associated with African American and white race in various mean baseline CSC categories using multivariable adjusted Cox models. Adjustment were made for age, sex, income, BMI, marital status, comorbidities, medications, baseline eGFR, and baseline BPs. White patients with CSC 9.1–<9.4 mg/dL served as referent. Models included a multiplicative interaction term for race and CSC. Signficant differences for AA vs white in the CSC categories marked with "*" are < 0.01.

Discussion

We examined the effect of race on the association between corrected serum calcium and all-cause mortality, incident CHD, and ischemic strokes in a large cohort of AA vs white U.S. veterans with low comorbidity burden and eGFR at least 60 mL/min/1.73 m^2. We describe a U-shaped association of CSC with all-cause mortality in both races, but no association with incident vascular events (CHD or strokes). Even though the association of CSC levels with mortality was U-shaped for both AA and white patients, we describe subtle differences in these associations, in that compared with white patients AA patients experienced relatively higher mortality when CSC was low (<8.5 mg/dL), and relatively lower mortality when CSC was normal or elevated. We detected no significant race-related effect modifications in the association of CSC levels with occlusive cardiovascular events (CHD and stroke). As we (24) and others (29, 30) have

Table 2. Hazard Ratios of AA Versus White for three clinical outcomes in different CSC categories

		All-cause Mortality			CHD			Ischemic Stroke		
CSC Categories, mg/dL	Race	HR	95% CI	*P*	HR	95% CI	*P*	HR	95% CI	*P*
<8.5	White	1.30	1.25–1.34	0	0.95	0.84–1.07	.370	0.98	0.87–1.11	.799
	AA	1.35	1.24–1.46	0	0.92	0.70–1.21	.551	1.15	0.90–1.49	.269
8.5–<8.8	White	1.09	1.07–1.11	0	0.92	0.87–0.98	.010	0.94	0.89–1.00	.054
	AA	1.07	1.02–1.13	0	0.79	0.68–0.91	.001	1.05	0.92–1.20	.449
8.8–<9.1	White	1.03	1.01–1.04	0	0.99	0.96–1.03	.596	0.97	0.94–1.00	.110
	AA	0.91	0.89–0.94	.006	0.74	0.68–0.80	0	1.16	1.09–1.25	0
9.1–<9.4	White	1	1		1	1		1	1	
	AA	0.86	0.85–0.88	0	0.73	0.69–0.77	0	1.11	1.06–1.16	0
9.4–<9.7	White	1.09	1.08–1.1	0	1.02	0.99–1.05	.130	1.03	1.00–1.06	.055
	AA	0.90	0.88–0.92	0	0.77	0.73–0.81	0	1.12	1.07–1.17	0
9.7–<10.0	White	1.22	1.20–1.23	0	1.02	0.99–1.06	.230	1.12	1.08–1.16	0
	AA	1.00	0.98–1.02	.988	0.71	0.66–0.76	0	1.20	1.13–1.27	0
10.0–<10.3	White	1.29	1.27–1.32	0	1.04	0.99–1.09	.141	1.04	0.99–1.10	.131
	AA	1.10	1.06–1.13	0	0.79	0.72–0.86	0	1.22	1.12–1.32	0
≥10.3	White	1.58	1.54–1.62	0	0.97	0.90–1.06	.520	1.09	1.00–1.19	.041
	AA	1.41	1.35–1.47	0	0.68	0.58–0.80	0	1.23	1.08–1.41	.002

Abbreviation: HR, hazard ratio.

previously described, AA veterans experienced overall lower mortality and incident CHD rates, and slightly higher ischemic stroke rates compared with white patients. These findings are different from the higher mortality observed in AA vs white individuals in the general population (24), and could be the result of the beneficial effects of the VA healthcare system combined with biological (eg, genetic) differences between races, or selection bias (24).

Our results confirm findings from prior studies that showed higher mortality associated with both higher and lower serum calcium levels (31–33). Most studies concentrated on populations with chronic illnesses, such as CKD or End Stage Renal Disease and examined various other clinical outcomes besides mortality, such as incident coronary artery disease (34), calcified coronary atherosclerotic plaque (35), intracranial atherosclerosis (36), carotid artery plaque (8), kidney function decline (37), and heart failure (38). Similar to ours, most previous studies have also reported that adverse outcomes associated with lower or higher serum calcium were not just limited to frank hypocalcemia or hypercalcemia, but were also associated with the upper or lower limits of normal calcium levels (8.5–10.2 mg/dL). Our study also adds to the findings from previous literature by extending knowledge about associations of serum calcium with clinical outcomes to individuals without substantial chronic disease burden.

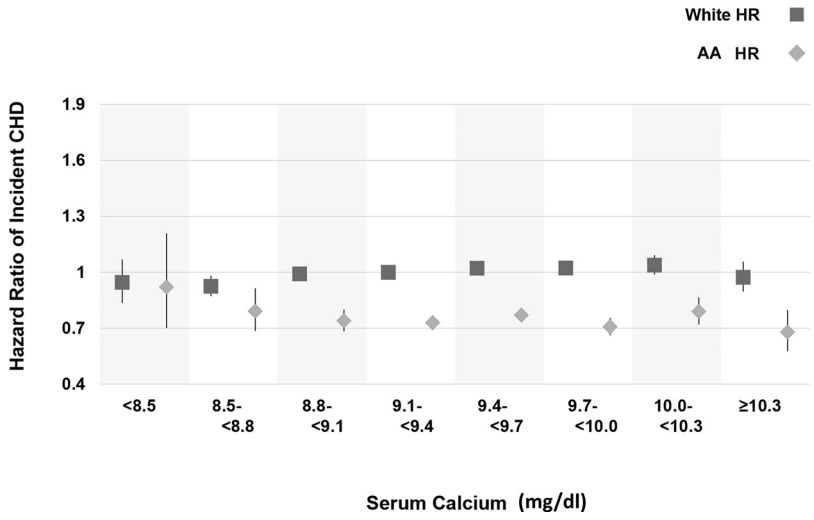

Figure 3. Race-specific associations of CSC with CHD: Multivariable adjusted hazard ratios (95% CIs) of incident CHD (including incident acute myocardial infarction, coronary artery bypass grafting, or percutaneous coronary intervention) associated with African American and white race in various mean baseline CSC categories using multivariable adjusted Cox models. Adjustment were made for age, sex, income, BMI, marital status, comorbidities, medications, baseline estimated GFR, and baseline BPs. White patients with CSC 9.1–<9.4 mg/dL served as referent. Models included a multiplicative interaction term for race and CSC.

The observed associations of both higher and lower serum calcium levels with mortality could be explained by the complex physiologic roles played by calcium, and their alterations in the context of lower and higher serum levels, respectively. Calcium plays a crucial role in the electrophysiologic stability of excitable cells' membranes, and low serum calcium can predispose to abnormal neuromuscular excitability (39). Indeed, calcium has been shown to affect cardiac myocytes function (40), heart failure (41), the QT interval (42), and other arrhythmias (43), such as

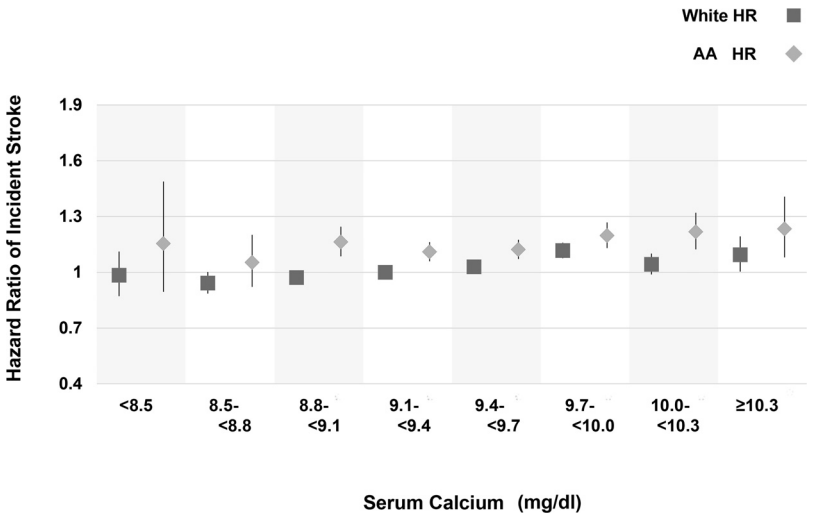

Figure 4. Race-specific associations of CSC with ischemic stroke: Multivariable adjusted hazard ratios (95% CIs) of the incident ischemic strokes associated with AA and white race in various mean baseline CSC categories using multivariable adjusted Cox models. Adjustment were made for age, sex, income, BMI, marital status, comorbidities, medications, baseline eGFR, and baseline BPs. White patients with CSC 9.1–<9.4 mg/dL served as referent. Models included a multiplicative interaction term for race and CSC.

atrial fibrillation (44). It is thus possible that the associations of low serum calcium levels with mortality may be explained by a higher incidence of arrhythmias (45); this will have to be determined in future studies by examining cause-specific mortality.

Conversely, higher serum calcium levels may represent a propensity toward increased vascular calcification and atherosclerosis, which could result in higher cardiovascular death rates. Based on this hypothesis there is an apparent inconsistency between the positive associations with all-cause mortality and the lack of associations with major occlusive cardiovascular events in our study. One potential explanation is that vascular calcification is a complex process that could manifest as both microcalcification and macrocalcification, resulting in completely different clinical manifestations and outcomes (46). It can be hypothesized that higher serum calcium levels may affect such processes in ways that result in adverse outcomes unrelated to occlusive vascular events, such as increased arterial stiffness. Such potential mechanisms will need to be further examined in future studies.

The race-associated differences in mortality in our study may be linked to racial differences in calcium and bone-mineral metabolism (47, 48), which have attracted more and more attention recently (49). Compared with white patients, AA individuals have higher intestinal absorption and lower urine excretion of calcium. Their BMD is also higher than in other races (50), despite lower serum total 25(OH)D levels; the latter could be related to genetic traits affecting vitamin D–binding protein levels (51). Such differences may underlie the reasons for relatively lower mortality in AA individuals with elevated calcium levels, although we could not substantiate race-specific differences in the association between calcium levels and occlusive cardiovascular events. Conversely, AA race may be associated with a genetic predisposition to cardiac arrhythmias (52, 53) which could explain their propensity for relatively higher mortality in the face of low calcium levels.

Our study has limitations that must be acknowledged. Our study was observational, and hence its results cannot be used to infer causality. Most of our patients were male U.S. veterans; hence, the results may not apply to women or to the general U.S. population. Although we adjusted serum calcium levels for serum albumin levels, this method is inferior to measuring ionized calcium level, which could better reflect biologically active calcium level in circulation. We did not have data related to causes of death, so we could only speculate about potential underlying mechanisms of action. Many previous studies investigated the relationship between calcium or vitamin D supplements with clinical outcomes (5). In our study design, we only adjusted for baseline prescribed calcium/vitamin D supplements but did not take into account the quantities of such supplements or changes in prescriptions over time. We adjusted for multiple possible confounders that were available in our database, but we cannot rule out the effect of unmeasured confounders on the observed associations. BMD is another relevant clinical outcome which was investigated by several studies with regard to its relationship with calcium intake (54). We did not have information about BMD; therefore, we could not examine it as a separate outcome or combine CSC levels with BMD as a joint predictor. Our study sample was limited to patients with eGFR at least 60 mL/min/1.73 m^2, due to the definition used to generate our source cohort. This makes it difficult to extrapolate results to patients with CKD and low eGFR; however, CKD has a major effect on serum calcium levels and on calcium homeostasis in general; hence, associations between calcium level and outcomes in patients with CKD are best examined in dedicated cohorts.

The association between serum calcium and all-cause mortality in patients with eGFR at least 60 mL/min/1.73 m^2 is U shaped. Compared with whites, AA individuals experience better survival when CSC is greater than 8.8 mg/dL and higher mortality when CSC is less than 8.5

mg/dL. Serum calcium levels are not associated with incident CHD and ischemic stroke in either AA or white individuals.

Acknowledgments

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References

1. **Rodnan G, Johnson H.** Chronic renal failure in association with the excessive intake of calcium and alkali; Report of case and review of pathogenesis. *Gastroenterology*. 1954;27(5):584–597.
2. **Kessler E.** Hypercalcemia and renal insufficiency secondary to excessive milk and alkali intake. *Ann Intern Med*. 1955;42(2):324–338.
3. **Reid IR, Ames RW, Evans MC, Gamble GD, Sharpe SJ.** Effect of calcium supplementation on bone loss in postmenopausal women. *N Engl J Med*. 1993;328(7):460–464.
4. **Goodman WG, Goldin J, Kuizon BD, et al.** Coronary-artery calcification in young adults with end-stage renal disease who are undergoing dialysis. *N Engl J Med*. 2000;342(20):1478–1483.
5. **Chan R, Leung J, Woo J.** A prospective cohort study examining the associations of dietary calcium intake with all-cause and cardiovascular mortality in older Chinese community-dwelling people. *PLoS One*. 2013;8(11):e80895.
6. **Larsson SC, Orsini N, Wolk A.** Dietary calcium intake and risk of stroke: A dose-response meta-analysis. *Am J Clin Nutr*. 2013;97(5):951–957.
7. **Miller JE, Kovesdy CP, Norris KC, et al.** Association of cumulatively low or high serum calcium levels with mortality in long-term hemodialysis patients. *Am J Nephrol*. 2010;32(5):403–413.
8. **Rubin MR, Rundek T, McMahon DJ, Lee HS, Sacco RL, Silverberg SJ.** Carotid artery plaque thickness is associated with increased serum calcium levels: The Northern Manhattan study. *Atherosclerosis*. 2007;194(2):426–432.
9. **Bachrach LK, Hastie T, Wang MC, Narasimhan B, Marcus R.** Bone mineral acquisition in healthy Asian, Hispanic, black, and Caucasian youth: A longitudinal study. *J Clin Endocrinol Metab*. 1999;84(12):4702–4712.
10. **Looker AC, Melton LJ 3rd, Borrud LG, Shepherd JA.** Lumbar spine bone mineral density in US adults: Demographic patterns and relationship with femur neck skeletal status. *Osteoporos Int*. 2012;23(4):1351–1360.
11. **Weaver CM, McCabe LD, McCabe GP, et al.** Vitamin D status and calcium metabolism in adolescent black and white girls on a range of controlled calcium intakes. *J Clin Endocrinol Metab*. 2008;93(10):3907–3914.
12. **Abrams SA, O'Brien KO, Liang LK, Stuff JE.** Differences in calcium absorption and kinetics between black and white girls aged 5–16 years. *J Bone Miner Res*. 1995;10(5):829–833.
13. **Braun M, Palacios C, Wigertz K, et al.** Racial differences in skeletal calcium retention in adolescent girls with varied controlled calcium intakes. *Am J Clin Nutr*. 2007;85(6):1657–1663.
14. **Go AS, Mozaffarian D, Roger VL, et al.** Executive summary: Heart disease and stroke statistics—2014 update: A report from the American Heart Association. *Circulation*. 2014;129(3):399–410.
15. **Minino AM.** Death in the United States, 2011. *NCHS Data Brief*. 2013(115):1–8.
16. **Karter AJ, Gazzaniga JM, Cohen RD, Casper ML, Davis BD, Kaplan GA.** Ischemic heart disease and stroke mortality in African-American, Hispanic, and non-Hispanic white men and women, 1985 to 1991. *West J Med*. 1998;169(3):139–145.
17. **Molnar MZ, Mucsi I, Novak M, et al.** Association of incident obstructive sleep apnoea with outcomes in a large cohort of US veterans. *Thorax*. 2015;70(9):888–895.
18. **Lu JL, Molnar MZ, Naseer A, Mikkelsen MK, Kalantar-Zadeh K, Kovesdy CP.** Association of age and BMI with kidney function and mortality: A cohort study. *Lancet Diabetes Endocrinol*. 2015;3(9):704–714.
19. **Levey AS, Stevens LA, Schmid CH, et al.** A new equation to estimate glomerular filtration rate. *Ann Intern Med*. 2009;150(9):604–612.
20. **Molnar MZ, Alhourani HM, Wall BM, et al.** Association of hepatitis C viral infection with incidence and progression of chronic kidney disease in a large cohort of US veterans. *Hepatology*. 2015;61(5):1495–1502.
21. **Gosmanova EO, Molnar MZ, Alrifai A, et al.** Impact of non-adherence on renal and cardiovascular outcomes in US veterans. *Am J Nephrol*. 2015;42(2):151–157.
22. **Stroupe KT, Tarlov E, Zhang Q, Haywood T, Owens A, Hynes DM.** Use of Medicare and DOD data for improving VA race data quality. *J Rehabil Res Dev*. 2010;47(8):781–795.
23. **US Department of Veterans Affairs VIRC.** VIReC Research User Guide: VHA Medical SAS Inpatient Datasets FY2006. September 2007.
24. **Kovesdy CP, Norris KC, Boulware LE, et al.** Association of race with mortality and cardiovascular events in a large cohort of US veterans. *Circulation*. 2015;132(16):1538–1548.
25. **(VIReC) VIRC.** VIReC Research User Guide: VHA Pharmacy Prescription Data. 2nd ed. 2008.
26. **Sohn MW, Arnold N, Maynard C, Hynes DM.** Accuracy and completeness of mortality data in the Department of Veterans Affairs. *Popul Health Metr*. 2006;4:2.
27. **Liu J, Weinhandl ED, Gilbertson DT, Collins AJ, St Peter WL.** Issues

regarding 'immortal time' in the analysis of the treatment effects in observational studies. *Kidney Int*. 2012;81(4):341–350.
28. **Deyo RA, Cherkin DC, Ciol MA.** Adapting a clinical comorbidity index for use with ICD-9-CM administrative databases. *J Clin Epidemiol*. 1992;45(6):613–619.
29. **Young BA, Maynard C, Boyko EJ.** Racial differences in diabetic nephropathy, cardiovascular disease, and mortality in a national population of veterans. *Diabetes Care*. 2003;26(8):2392–2399.
30. **Jha AK, Shlipak MG, Hosmer W, Frances CD, Browner WS.** Racial differences in mortality among men hospitalized in the Veterans Affairs health care system. *JAMA*. 2001;285(3):297–303.
31. **Kovesdy CP, Kuchmak O, Lu JL, Kalantar-Zadeh K.** Outcomes associated with serum calcium level in men with non-dialysis-dependent chronic kidney disease. *Clin J Am Soc Nephrol*. 2010;5(3):468–476.
32. **Tentori F, Blayney MJ, Albert JM, et al.** Mortality risk for dialysis patients with different levels of serum calcium, phosphorus, and PTH: The Dialysis Outcomes and Practice Patterns Study (DOPPS). *Am J Kidney Dis*. 2008;52(3):519–530.
33. **Leifsson BG, Ahrén B.** Serum calcium and survival in a large health screening program. *J Clin Endocrinol Metab*. 1996;81(6):2149–2153.
34. **West SL, Swan VJ, Jamal SA.** Effects of calcium on cardiovascular events in patients with kidney disease and in a healthy population. *Clin J Am Soc Nephrol*. 2010;5 Suppl 1:S41–S47.
35. **Shin S, Kim KJ, Chang HJ, et al.** Impact of serum calcium and phosphate on coronary atherosclerosis detected by cardiac computed tomography. *Eur Heart J*. 2012;33(22):2873–2881.
36. **Kang K.** Serum calcium and phosphate concentrations and intracranial atherosclerosis. *Atherosclerosis*. 2014;232(1):249–253.
37. **Lim LM, Kuo HT, Kuo MC, et al.** Low serum calcium is associated with poor renal outcomes in chronic kidney disease stages 3–4 patients. *BMC Nephrol*. 2014;15:183.
38. **Lutsey PL, Alonso A, Michos ED, et al.** Serum magnesium, phosphorus, and calcium are associated with risk of incident heart failure: The Atherosclerosis Risk in Communities (ARIC) Study. *Am J Clin Nutr*. 2014;100(3):756–764.
39. **Carafoli E, Penniston JT.** The calcium signal. *Sci Am*. 1985;253(5):70–78.
40. **Qu Z, Nivala M, Weiss JN.** Calcium alternans in cardiac myocytes: Order from disorder. *J Mol Cell Cardiol*. 2013;58:100–109.
41. **Lehnart SE.** Understanding the physiology of heart failure through cellular and in vivo models-towards targeting of complex mechanisms. *Exp Physiol*. 2013;98(3):622–628.
42. **Pepe J, Curione M, Morelli S, et al.** Parathyroidectomy eliminates arrhythmic risk in primary hyperparathyroidism, as evaluated by exercise test. *Eur J Endocrinol*. 2013;169(2):255–261.
43. **Pun PH, Horton JR, Middleton JP.** Dialysate calcium concentration and the risk of sudden cardiac arrest in hemodialysis patients. *Clin J Am Soc Nephrol*. 2013;8(5):797–803.
44. **Jafari Dehkordi A, Nasser Mohebi A, Heidari Soreshjani M.** Frequency of cardiac arrhythmias in high- and low- yielding dairy cows. *Vet Res Forum*. 2014;5(1):1–5.
45. **Hsueh CH, Chen NX, Lin SF, Chen PS, Gattone VH, 2nd, Allen MR, Fishbein MC, Moe SM.** Pathogenesis of arrhythmias in a model of CKD. *J Am Soc Nephrol*. 2014;25(12):2812–2821.
46. **Pugliese G, Iacobini C, Blasetti Fantauzzi C, Menini S.** The dark and bright side of atherosclerotic calcification. *Atherosclerosis*. 2015;238(2):220–230.
47. **Bell NH, Williamson BT, Hollis BW, Riggs BL.** Effects of race on diurnal patterns of renal conservation of calcium and bone resorption in premenopausal women. *Osteoporos Int*. 2001;12(1):43–48.
48. **Cosman F, Shen V, Morgan D, et al.** Biochemical responses of bone metabolism to 1,25-dihydroxyvitamin D administration in black and white women. *Osteoporos Int*. 2000;11(3):271–277.
49. **Redmond J, Palla L, Yan L, Jarjou LM, Prentice A, Schoenmakers I.** Ethnic differences in urinary calcium and phosphate excretion between Gambian and British older adults. *Osteoporos Int*. 2015;26(3):1125–1135.
50. **van Ballegooijen AJ, Robinson-Cohen C, Katz R, et al.** Vitamin D metabolites and bone mineral density: The multi-ethnic study of atherosclerosis. *Bone*. 2015;78:186–193.
51. **Powe CE, Evans MK, Wenger J, et al.** Vitamin D-binding protein and vitamin D status of black Americans and white Americans. *N Engl J Med*. 2013;369(21):1991–2000.
52. **O'Donnell PH, Bush A, Spitz J, et al.** The 1200 patients project: Creating a new medical model system for clinical implementation of pharmacogenomics. *Clin Pharmacol Ther*. 2012;92(4):446–449.
53. **Ackerman MJ, Tester DJ, Jones GS, Will ML, Burrow CR, Curran ME.** Ethnic differences in cardiac potassium channel variants: Implications for genetic susceptibility to sudden cardiac death and genetic testing for congenital long QT syndrome. *Mayo Clin Proc*. 2003;78(12):1479–1487.
54. **Tai V, Leung W, Grey A, Reid IR, Bolland MJ.** Calcium intake and bone mineral density: Systematic review and meta-analysis. *BMJ*. 2015;351:h4183.