Published in final edited form as:
Am J Cardiol. 2012 December 15; 110(12): 1735–1741. doi:10.1016/j.amjcard.2012.07.044.

Risk Factors for Coronary Artery Calcium Among Patients with Chronic Kidney Disease (From the Chronic Renal Insufficiency Cohort Study)

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Abstract

Cardiovascular disease is the leading cause of death in patients with chronic kidney disease (CKD). We examined the cross-sectional association between novel risk factors and coronary artery calcium (CAC) measured by electron-beam computed tomography or multidetector computed tomography among 2,018 patients with CKD. Based on total Agatston scores, participants were classified as no (0), moderate (>0–100) or high (>100) CAC. After adjustment for age, sex, race, study sites, cigarette smoking, prior cardiovascular disease, hypertension, and diabetes, use of lipid-lowering drugs, body-mass index, waist circumference, and cystatin C, several novel risk factors were significantly associated with high CAC. For example, odds ratios (95% confidence interval) of high CAC associated with one standard deviation higher levels of risk factors were 1.20 (1.04, 1.38) for serum calcium, 1.21 (1.04, 1.41) for serum phosphate, 0.83 (0.71, 0.97) for log (total parathyroid hormone), 1.21 (1.03, 1.43) for log (HOMA-insulin resistance), and 1.23 (1.04, 1.45) for hemoglobin A1c. Additionally, the multivariable-adjusted odds ratio for one standard deviation higher level of cystatin C was 1.31 (1.14, 1.50). Serum high-

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Conflict of interest: none declared

sensitive C-reactive protein, interleukin-6, tumor necrosis factor-α, and homocysteine were not statistically significantly associated with high CAC. In conclusion, these data indicate that abnormal calcium and phosphate metabolism, insulin resistance, and declined kidney function were associated with the prevalence of high CAC independent of traditional risk factors in patients with CKD. Further studies are warranted to examine the causal effect of these risk factors on CAC in CKD patients.

Keywords

calcium; chronic kidney disease; coronary artery calcium; cystatin C; insulin-resistance; phosphate; total parathyroid hormone

Prospective cohort studies have documented that cardiovascular disease (CVD) is the major cause of premature death in patients with chronic kidney disease (CKD).[1–3] Coronary arterial calcium (CAC) independently predicts the risk of CVD over and above traditional risk factors in the general population.[4] CAC is more common and severe in patients with CKD[5,6] and is more strongly associated with increased risk of CVD in patients with end-stage renal disease (ESRD) compared to the general population.[7,8] In a meta-analysis of 30 cohort studies with 218,080 subjects, the presence of CAC was associated with a 3- to 4-fold higher risk of CVD in the overall population and more than 6-fold higher risk among patients with ESRD.[8] In the general population, cigarette smoking, obesity, dyslipidemia, hypertension, diabetes, and inflammation are all associated with increased risk of CAC.[9–11] These risk factors are common in CKD patients and might partially contribute to increased risk of CAC.[12,13] However, there are sparse data on novel risk factors for CAC in pre-dialysis CKD patients.[14] The Chronic Renal Insufficiency Cohort (CRIC) study included a large group of CKD patients with a broad spectrum of renal function and comorbid conditions. More than half of CRIC participants received an electron-beam computed tomography (EBCT) or multidetector CT (MDCT), which provided an exceptional opportunity to examine the traditional and novel risk factors for CAC in CKD patients.

Methods

The CRIC study includes a racially and ethnically diverse group of men and women aged 21 to 74 years with mild-to-moderate CKD [age-based estimated glomerular filtration rate (eGFR) entry criteria 20–70 mL/min/1.73m^2], and approximately half of the cohort has diabetes. A total of 3,612 CRIC participants were recruited between May 2003 and August 2008 from seven clinical centers in the US.[15] Patients with cirrhosis, HIV infection, polycystic kidney disease, and renal cell carcinoma, those on dialysis or who have received a kidney transplant, and those taking immunosuppressant drugs were excluded from the CRIC study. Additionally, patients with a history of coronary artery revascularization were excluded from EBCT/MDCT. Of the CRIC study participants, 1,142 were randomly selected from the entire cohort stratified by age, gender, race/ethnicity, diabetes status, and eGFR level for EBCT/MDCT. In addition, EBCT/MDCT was performed in all eligible CRIC participants from 3 clinical centers for an ancillary study. A total of 2,018 CRIC participants had CAC data and were included in the current analysis.

The CRIC study was approved by the Institutional Review Boards from each of the participating clinical centers, as well as the scientific and data coordinating center. Written informed consent was obtained from all participants. This study also conformed to the Health Insurance Portability and Accountability Act (HIPAA) guidelines.

All CRIC study data were collected by trained study staff during the baseline and annual clinical visits. All data collection procedures and equipment were standardized across study sites. A baseline medical history questionnaire was administered to obtain information on demographic characteristics, lifestyle risk factors, previous history of CVD, and use of medications. Cigarette smokers were defined as participants who smoked >100 cigarettes in their lifetime. Alcohol drinkers were defined as participants who had a drink of any kind of alcoholic beverage in the past 12 months. Body weight and height were measured and body mass index (BMI) was calculated as an index for obesity. Waist circumference was measured at the uppermost lateral border of the iliac crest with a Gulick II tape measure. Three seated blood pressure (BP) measurements were obtained by trained and certified staff after at least 5 minutes of quiet rest. These measurements were performed according to a standard protocol using an aneroid sphygmomanometer, and the average of 3 measurements was used for analysis.[16] Hypertension was defined as systolic BP≥140 mm Hg and/or diastolic BP≥90 mm Hg and/or current use of antihypertensive medications.

Glucose, cholesterol, triglycerides, glycated hemoglobin (HbA1c), phosphate, calcium, total parathyroid hormone (PTH), uric acid, hemoglobin, and alkaline phosphatase were measured using standard laboratory methods. High-sensitive C-reactive protein (hsCRP), interleukin-6, tumor necrosis factor (TNF)-α, homocysteine, and cystatin C were measured by the particle enhanced immunonephelometry method. Fibrinogen was measured using the immunchemical reaction method. Urinary albumin was measured by radioimmunoassay (RIA). Diabetes was defined as a fasting glucose ≥126 mg/dL, random glucose ≥200 mg/dL, and/or use of insulin or other anti-diabetic medication. eGFR was calculated using the four-variable Modification of Diet in Renal Disease equation after calibrating serum creatinine measurements to Cleveland Clinic Foundation reference values.[17] A homeostasis model assessment (HOMA) was calculated to evaluate insulin resistance using the following formula: [fasting serum insulin (μU/ml) × fasting plasma glucose (mmol/L)]/22.5.[18] All laboratory measurements were performed in a centralized laboratory at the University of Pennsylvania.

As a part of the CRIC protocol, a sub-cohort of participants underwent measurement of CAC with either EBCT or MDCT at the year 1 visit. Trained and certified technologists scanned all participants twice over phantoms of known physical calcium concentration. A cardiologist read all computed tomographic scans at a central reading center (Los Angeles Biomedical Research Institute at Harbor–UCLA Medical Center in Torrance, California). The total Agatston score, which is a pseudo-continuous variable derived from plaque densities and their areas in all coronary arteries, was computed.[19] We used average Agatston score from the 2 scans in all analyses. Based on the distribution of Agatston score in our study participants, we divided the CRIC participants into no (0), moderate (>0–100) or high (>100) CAC.

Baseline characteristics of participants were summarized as means [standard deviation (SD)] for continuous variables and percentages for categorical variables by CAC status. Statistical significance was tested using ANOVA for continuous variables and χ^2 tests for categorical variables. Logarithmic transformation was performed for severely skewed variables to stabilize variances and normalize distributions.

The adjusted odds ratios of moderate and high CAC associated with risk factors were estimated using a multinomial logistic regression model. For the multivariable analysis of traditional risk factors, the backward elimination method was used, and only covariates that were significant ($p<0.05$) were retained in the final model. For the multivariable analysis of novel risk factors, age, gender, race, and significant covariates (cigarette smoking, history of hypertension, diabetes, and use of lipid-lowering drugs, BMI, and waist circumference) from

the final traditional risk factor model, as well as prior CVD, were adjusted for each novel risk factor in separate models. Furthermore, serum cystatin C level was adjusted in the multivariable model to control for the confounding effect of kidney function. Odds ratios and 95% confidence intervals (CI) of moderate and high CAC associated with categorical variables or one SD increase in continuous variables were presented. In a sensitivity analysis, the two-part model in which binary CAC (0 vs. >0) was modeled using Poisson regression with robust variance estimation and log (CAC+1) was modeled using linear regression among those with a CAC>0 was employed.[20] All analyses were conducted using SAS v9.1 (Cary, NC). All p-values were two-sided, and statistical significance was defined as $p<0.05$.

Results

Compared to those without CAC, participants with moderate or high CAC were more likely to be older, male, and current or former smokers, and have a history of clinical CVD, hypertension, diabetes, or use of lipid-lowering medications and less likely to be physically active (Table 1). On average, participants with CAC had higher levels of systolic BP, BMI, and waist circumference, and lower levels of HDL-cholesterol, LDL-cholesterol, and eGFR. In addition, participants with CAC had higher average levels of serum phosphate, HOMA-insulin resistance, HbA1c, uric acid, homocysteine, fibrinogen, log (interleukin-6), and cystatin C.

In the age-sex-race-adjusted model, current and former cigarette smoking, history of hypertension, diabetes, and use of lipid-lowering medications, systolic BP, BMI, and waist circumference were positively associated with odds of CAC, while HDL-cholesterol, LDL-cholesterol, and eGFR had an inverse association (Table 2). In the final model selected by backward elimination, cigarette smoking, history of hypertension, diabetes, and lipid-lowering medications, and waist circumference were positively and significantly associated with odds of CAC, while BMI was inversely and significantly associated with odds of CAC.

The age-gender-race-adjusted and multivariable-adjusted odds ratios of CAC associated with novel risk factors are shown in Table 3. After adjusting for age, gender, and race, higher levels of serum phosphate, log (HOMA-insulin resistance), HbA1c, uric acid, homocysteine, fibrinogen, log (interleukin-6), log (TNF-α), cystatin C, and 24-hour urinary excretion of albumin were all significantly associated with greater odds of CAC. In addition, serum alkaline phosphatase was significantly associated with greater odds of high CAC. After adjusting for multiple traditional risk factors, serum phosphate and cystatin C remained significantly associated with overall odds of CAC. In addition, log (HOMA-insulin resistance), HbA1c, homocysteine, and fibrinogen were significantly associated with greater odds of high CAC.

In the multivariable model including cystatin C, higher levels of calcium, phosphate, log (HOMAinsulin resistance), and HbA1c were positively and log (PTH) was inversely associated with greater odds of high CAC. In the sensitivity analysis using the two-part model, the presence of CAC (total Agatston score >0) was positively and significantly associated with one SD higher levels of phosphate (odds ratio=1.05; 95% CI 1.02, 1.08; p=0.001), log (HOMA-insulin resistance) (odds ratio=1.05; 95% CI 1.01, 1.08; p=0.004), HbA1c (odds ratio=1.05; 95% CI 1.02, 1.09; p=0.001), fibrinogen (odds ratio=1.03; 95% CI 1.00, 1.06; p=0.03), and cystatin C (odds ratio=1.04; 95% CI 1.01, 1.07; p=0.01) after adjusting for multiple covariables in Poisson regression; and log (CAC + 1) was positively and significantly associated with one SD higher levels of phosphate (β=0.19; 95% CI 0.07, 0.30; p=0.001), homocysteine (β=0.13; 95% CI 0.02, 0.24; p=0.02), and cystatin C (β=0.21;

95% CI 0.11, 0.30; p<0.0001) among participants with CAC>0 after adjustment for multiple covariables in linear regression.

Discussion

This study contributes to our understanding of the etiology of coronary artery calcium among CKD patients in several ways. First, the findings from the present study indicate that, like in the general population, cigarette smoking, hypertension, diabetes mellitus, dyslipidemia, and obesity are related to increased risk of CAC among CKD patients. Secondly, this study shows that calcium and phosphate metabolism may play an important etiological role in CAC among CKD patients. Furthermore, this study reveals that elevated levels of insulin resistance and HbA1c are associated with increased risk of CAC. Finally, this study finds that cystatin C, a measure of kidney function, is independently associated with elevated CAC.

Our study findings are worthwhile because they are based on data from a large sample of CKD patients. The study outcome (CAC) and numerous traditional and novel CVD risk factors were carefully measured with rigorous quality control. Therefore, our study should provide an accurate estimate of the association between risk factors and CAC. A major limitation of this analysis is its cross-sectional nature; therefore, the temporal relationship between risk factors and CAC cannot be established. Use of subclinical measurement (CAC) in our study, however, should minimize the cross-sectional bias due to change in risk factors as a result of diagnosis of clinical disease. Furthermore, it is unlikely that CAC caused the elevated traditional CVD risk factors, serum calcium and phosphate levels, insulin resistance or serum cystatin C levels, in CKD patients with CAC.

Patients with advanced CKD usually develop hyperphosphatemia due to impaired renal phosphate excretion.[14] Elevated serum levels of calcium, phosphate and calcium phosphate product were associated with higher CAC in ESRD patients receiving hemodialysis[7] and pre-dialysis CKD patients.[21,22] Garland et al reported that serum calcium level was correlated with CAC scores in 119 patients with CKD.[21] Adeney et al reported that serum phosphate concentration was associated with a 21% greater prevalence of CAC in 439 CKD patients from the Multi-Ethnic Study of Atherosclerosis.[22] Our study, with a large sample size, documented the positive and independent associations of serum calcium and phosphate levels with CAC. In addition, we found an inverse and independent association between serum total PTH, an important hormone regulating calcium-phosphate metabolism, and CAC. Tsuchihashi et al reported that hypoparathyroidism was associated with a higher serum calcium level and coronary artery disease among 48 ESRD patients.[23] The findings from our study and others provide strong evidence that abnormal calcium-phosphate metabolism is probably the most important pathogenetic factor in vascular calcification among CKD patients.[13,22]

Insulin resistance and hemoglobin A1c are associated with higher CAC in the general population and in patients with diabetes.[24,25] In a small clinical study, Kobayashi S and colleagues reported that HOMA-insulin resistance was higher in 17 CKD patients with total Agatston scores >600 compared to those with a score <600.[26] In this large study in CKD patients, we found that HOMA-insulin resistance and hemoglobin A1c were positively and independently associated with higher CAC. These findings support the notion that insulin resistance and hyperglycemia are important risk factors for coronary artery disease in CKD patients.

Recent investigations suggest that cystatin C may be a better filtration marker than creatinine, especially at higher levels of GFR.[27] Serum cystatin C has been associated with

an increased risk of CVD.[28] Maahs DM et al reported that cystatin C was modestly predictive of CAC progression in 509 adults with type-1 diabetes.[29] However, Ix et al reported that cystatin C was not independently associated with CAC in 6,749 participants of the Multi-Ethnic Study of Atherosclerosis.[30] We identified a strong, independent, and dose-response association between cystatin C and CAC in this CKD patient population. These findings suggested that kidney function, measured by cystatin C, is an independent risk factor for CAC.

Acknowledgments

The CRIC study was supported by the National Institute of Diabetes and Digestive and Kidney Diseases under a cooperative agreement (5U01DK060990, 5U01DK060984, 5U01DK06102, 5U01DK061021, 5U01DK061028, 5U01DK60980, 5U01DK060963, and 5U01DK060902). In addition, the CRIC study was partially supported by the following institutional Clinical Translational Science Awards and other National Institutes of Health grants: Johns Hopkins University UL1 RR-025005, University of Maryland GRCR M01 RR-16500, Case Western Reserve University Clinical and Translational Science Collaborative UL1 RR-024989, University of Michigan GCRC M01 RR-000042 and CTSA UL1 RR-024986, University of Illinois at Chicago Clinical Research Center, M01 RR-013987-06, Tulane/LSU Clinical and Translational Research, Education, and Commercialization Project (CTRECP), and Kaiser NIH/NCRR UCSF-CTSI UL1 RR-024131 and 5K24DK002651. Additional support for the CRIC study was provided by the National Center for Minority Health and Health Disparities, National Institutes of Health. This work was partially supported by R01 DK074615 from the National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD.

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Table 1

Baseline Characteristics of Study Participants According to Coronary Artery Calcium Score

Variable	Total Agatston Score			P-value
	0 (n=689)	>0–100 (n=578)	>100 (n=751)	
Age (years)	51.9 (12.3)	59.1 (10.2)	63.9 (8.1)	<0.0001
Men	41.9%	53.3%	63.6%	<0.0001
Race				
White	47.2%	45.2%	51.3%	
Black	37.4%	36.3%	32.1%	0.10
Other	15.4%	18.5%	16.6%	
High school graduation	83.7%	78.7%	80.4%	0.06
Physical activity (MET/week)	6.2 (22.0)	5.0 (19.2)	3.6 (16.3)	0.04
Cigarette smoke				
Current	9.0%	10.4%	10.5%	
Former	31.8%	37.7%	49.1%	<0.0001
Never	59.2%	51.9%	40.3%	
Alcohol consumption	65.0%	62.2%	59.2%	0.08
Prior cardiovascular disease	11.8%	21.6%	40.9%	<0.0001
Prior peripheral arterial disease	2.3%	2.2%	10.1%	<0.0001
Prior congestive heart failure	3.3%	5.5%	10.7%	<0.0001
Prior stroke	4.5%	9.3%	13.4%	<0.0001
Prior myocardial infarction	4.5%	8.7%	25.3%	<0.0001
Hypertension	76.4%	89.1%	94.3%	<0.0001
Diabetes mellitus	29.6%	46.2%	62.5%	<0.0001
Use of lipid–lowering drugs	43.4%	60.2%	77.0%	<0.0001
Systolic blood pressure (mm Hg)	122.4 (20.1)	127.0 (21.4)	129.4 (21.2)	<0.0001
Body Mass Index (kg/m^2)	30.4 (6.9)	31.5 (6.7)	31.5 (6.5)	0.002
Waist circumference (cm)	99.9 (16.1)	104.3 (15.7)	106.7 (15.1)	<0.0001
HDL–cholesterol (mg/dL)	51.9 (17.3)	47.9 (15.0)	47.0 (14.5)	<0.0001
LDL–cholesterol (mg/dL)	109.8 (36.5)	104.6 (34.4)	95.8 (32.2)	<0.0001
Calcium (mg/dL)	9.3 (0.5)	9.3 (0.5)	9.3 (0.5)	0.96
Phosphate (mg/dL)	3.6 (0.7)	3.7 (0.7)	3.8 (0.7)	0.002
Alkaline phosphatase (U/L)	89.2 (32.2)	93.1 (33.7)	92.9 (37.5)	0.07
Total parathyroid hormone (pg/mL)	66.9 (64.5)	67.0 (57.9)	72.1 (81.8)	0.28
Log (total parathyroid hormone, pg/mL)	4.0 (0.7)	4.0 (0.7)	4.0 (0.7)	0.3439
HOMA–insulin resistance *	5.0 (6.4)	6.1 (7.4)	6.8 (7.7)	<0.0001
Log (HOMA–insulin resistance)	1.5 (0.6)	1.7 (0.6)	1.8 (0.7)	<0.0001
Hemoglobin A1c (%)	6.2 (1.5)	6.5 (1.5)	6.8 (1.5)	<0.0001
Uric acid (mg/dL)	6.9 (1.9)	7.2 (1.8)	7.4 (1.9)	<0.0001
Homocysteine (μmol/L)	13.2 (5.3)	14.3 (6.5)	15.5 (6.0)	<0.0001
Fibrinogen (mg/dL)	3.9 (1.1)	4.1 (1.2)	4.2 (1.1)	<0.0001

Variable	Total Agatston Score			P-value
	0 (n=689)	>0–100 (n=578)	>100 (n=751)	
High–sensitive C–reactive protein (mg/L)	4.7 (7.8)	5.0 (9.3)	4.6 (6.9)	0.57
Log (high sensitive C–reactive protein, mg/L)	1.3 (0.8)	1.3 (0.9)	1.3 (0.8)	0.78
Interleukin–6 (mg/dL)	2.9 (12.5)	4.8 (21.8)	4.0 (15.7)	0.13
Log (interleukin–6, mg/dL)	1.0 (0.6)	1.1 (0.7)	1.2 (0.6)	<0.0001
Tumor necrosis factor–α (mg/dL)	3.5 (15.1)	3.2 (6.5)	2.8 (2.4)	0.40
Log (tumor necrosis factor–α, mg/dL)	1.2 (0.6)	1.2 (0.5)	1.2 (0.4)	0.06
Estimated glomerular filtration rate (ml/min/1.73m^2)	44.4 (16.5)	42.5 (14.7)	39.2 (13.5)	<0.0001
Cystatin C (mg/L)	1.4 (0.5)	1.5 (0.5)	1.6 (0.5)	<0.0001
24–hour urine albumin, g/24 hour	0.6 (1.4)	0.8 (2.0)	0.7 (1.8)	0.28
Log (24–hour urine albumin, g/24 hour)	0.3 (0.5)	0.3 (0.6)	0.3 (0.5)	0.61

Mean (standard deviation) or percentage.

*The homeostasis model assessment (HOMA) insulin resistance = [fasting serum insulin (μU/ml) × fasting plasma glucose (mmol/L)]/22.

Table 2

Multivariate-adjusted Odds Ratios (95% Confidence Intervals)* of Moderate (>0–100) and Severe (>100) Coronary Artery Calcium Associated with Traditional Risk Factors

Variable	Age-sex-race-adjusted OR (95% CI)			Multivariable-adjusted OR (95% CI)†		
	Moderate (>0–100)	High (>100)	P-value for trends	Moderate (>0–100)	High (>100)	P-value for trends
High school graduation	0.86 (0.62, 1.17)	0.94 (0.68, 1.30)	0.61			
Physical activity (19.2 MET/week)	1.00 (0.89, 1.11)	0.95 (0.84, 1.09)	0.74			
Current smoking	1.37 (0.91, 2.06)	1.98 (1.30, 3.01)		1.51 (0.97, 2.34)	2.31 (1.45, 3.70)	
			0.006			0.004
Former smoking	0.98 (0.76, 1.27)	1.34 (1.04, 1.74)		0.97 (0.74, 1.27)	1.31 (0.98, 1.74)	
Alcohol consumption	0.95 (0.74, 1.22)	0.77 (0.60, 1.00)	0.11			
Hypertension	2.11 (1.50, 2.97)	4.06 (2.70, 6.11)	<0.0001	1.77 (1.22, 2.57)	2.24 (1.43, 3.51)	0.0004
Diabetes mellitus	2.10 (1.64, 2.68)	4.60 (3.55, 5.95)	<0.0001	1.65 (1.26, 2.16)	3.25 (2.44, 4.34)	<0.0001
Use of lipid-lowering drugs	1.66 (1.31, 2.11)	3.37 (2.60, 4.35)	<0.0001	1.37 (1.06, 1.78)	2.56 (1.92, 3.40)	<0.0001
Systolic blood pressure (21.1 mm Hg)	1.15 (1.02, 1.31)	1.30 (1.15, 1.48)	0.0002			
Body mass index (6.7 kg/m^2)	1.21 (1.07, 1.36)	1.32 (1.17, 1.49)	<0.0001	0.89 (0.69, 1.14)	0.69 (0.53, 0.90)	0.02
Waist circumference (15.9 cm)	1.26 (1.11, 1.42)	1.49 (1.31, 1.68)	<0.0001	1.29 (1.00, 1.66)	1.66 (1.27, 2.17)	0.001
HDL cholesterol (15.8 mg/dL)	0.80 (0.70, 0.91)	0.79 (0.69, 0.90)	0.0002			
LDL cholesterol (34.9 mg/dL)	0.93 (0.83, 1.04)	0.75 (0.66, 0.85)	<0.0001			
Estimated glomerular filtration rate (15.1 ml/min/1.73m^2)	0.90 (0.80, 1.01)	0.70 (0.62, 0.79)	<0.0001			

*Odds ratios were calculated using multinomial logistic regression models.

†Variables with p-value <0.05 were kept in final model using backward selection.

Table 3

Multivariate-adjusted Odds Ratios (95% Confidence Intervals)* of Moderate (>0–100) and Severe (>100) Coronary Artery Calcium Associated with Novel Risk Factors

Variable	Age-sex-race-adjusted			Multivariable-adjusted †			Multivariable-adjusted ‡		
	Moderate (>0–100)	High (>100)	P-value for trends	Moderate (>0–100)	High (>100)	P-value for trends	Moderate (>0–100)	High (>100)	P-value for trends
Calcium (0.54 mg/dL)	0.99 (0.87, 1.11)	0.97 (0.86, 1.10)	0.89	1.05 (0.92, 1.19)	1.13 (0.98, 1.29)	0.23	1.07 (0.94, 1.22)	1.20 (1.04, 1.38)	0.04
Phosphate (0.67 mg/dL)	1.26 (1.11, 1.43)	1.66 (1.45, 1.90)	<0.0001	1.11 (0.97, 1.27)	1.30 (1.13, 1.50)	0.001	1.09 (0.94, 1.25)	1.21 (1.04, 1.41)	0.04
Alkaline phosphatase (34.7 U/L)	1.11 (0.98, 1.25)	1.15 (1.02, 1.30)	0.07	1.01 (0.89, 1.15)	1.01 (0.88, 1.15)	0.99	0.99 (0.86, 1.13)	0.94 (0.82, 1.08)	0.67
Log (total parathyroid hormone, 0.68 pg/mL)	1.03 (0.92, 1.17)	1.11 (0.98, 1.26)	0.24	0.96 (0.85, 1.09)	1.00 (0.87, 1.14)	0.78	0.90 (0.77, 1.05)	0.83 (0.71, 0.97)	0.07
Log (HOMA-insulin resistance, 0.65)	1.37 (1.20, 1.56)	1.69 (1.48, 1.93)	<0.0001	1.13 (0.96, 1.31)	1.20 (1.03, 1.41)	0.08	1.13 (0.96, 1.31)	1.21 (1.03, 1.43)	0.06
Hemoglobin A1c (1.54 %)	1.36 (1.20, 1.55)	1.82 (1.59, 2.08)	<0.0001	1.10 (0.93, 1.29)	1.22 (1.03, 1.44)	0.07	1.10 (0.93, 1.30)	1.23 (1.04, 1.45)	0.05
Uric acid (1.88 mg/dL)	1.09 (0.96, 1.23)	1.19 (1.05, 1.35)	0.02	0.98 (0.86, 1.12)	1.03 (0.89, 1.18)	0.80	0.95 (0.82, 1.09)	0.94 (0.81, 1.09)	0.66
Homocysteine (5.96 μmol/L)	1.14 (0.99, 1.32)	1.32 (1.14, 1.52)	0.0006	1.03 (0.90, 1.19)	1.14 (1.00, 1.31)	0.15	1.01 (0.87, 1.16)	1.03 (0.89, 1.20)	0.90
Fibrinogen (1.14 mg/dL)	1.25 (1.10, 1.41)	1.43 (1.26, 1.63)	<0.0001	1.11 (0.97, 1.26)	1.17 (1.01, 1.34)	0.09	1.09 (0.95, 1.25)	1.09 (0.94, 1.26)	0.41
Log (high-sensitivity C-reactive protein, 0.83 mg/L)	1.05 (0.93, 1.18)	1.06 (0.93, 1.19)	0.63	1.01 (0.89, 1.15)	1.01 (0.88, 1.17)	0.98	1.00 (0.88, 1.14)	0.99 (0.86,1.14)	0.97
Log (interleukin-6, 0.63 mg/dL)	1.20 (1.06, 1.37)	1.29 (1.13, 1.48)	0.0006	1.11 (0.97, 1.26)	1.12 (0.97, 1.29)	0.23	1.09 (0.95, 1.25)	1.06 (0.91, 1.22)	0.45
Log (tumor necrosis factor-α, 0.51 mg/dL)	1.14 (1.00, 1.28)	1.17 (1.03, 1.33)	0.04	1.07 (0.94, 1.21)	1.04 (0.91, 1.19)	0.59	1.04 (0.91, 1.18)	0.94 (0.81, 1.08)	0.30
Cystatin C (0.53 mg/L)	1.24 (1.10, 1.41)	1.62 (1.43, 1.84)	<0.0001	1.10 (0.97, 1.26)	1.31 (1.14, 1.50)	0.0005			
24-hour urine albumin (1.72 g/24 hour)	1.26 (1.10, 1.45)	1.35 (1.17, 1.56)	0.0002	1.12 (0.98, 1.28)	1.08 (0.93, 1.26)	0.27	1.10 (0.96, 1.27)	1.01 (0.86, 1.18)	0.25

*Odds ratios were calculated using multinomial logistic regression models.

†Adjusted for age, sex, race, cigarette smoking, prior clinical cardiovascular disease, hypertension and diabetes, use of lipid-lowering drugs, body mass index, and waist circumference.

‡Adjusted for age, sex, race, cigarette smoking, prior clinical cardiovascular disease, hypertension and diabetes, use of lipid-lowering drugs, body mass index, waist circumference, and cystatin C.