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Inflammation and Cardiovascular Events in Individuals with and without Chronic Kidney Disease

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Abstract

Inflammation and chronic kidney disease (CKD) predict cardiovascular events. Little is known about the interaction of inflammation and CKD. We evaluated inflammation markers (fibrinogen, albumin, white blood cell (WBC) count) in individuals with and without CKD to assess: 1) inflammation as a risk factor for adverse events; 2) synergy between inflammation and CKD; and 3) prognostic ability of these markers relative to c-reactive protein (CRP).

Using Atherosclerosis Risk in Communities and Cardiovascular Health Study data, inflammation was defined by 2 of 3 criteria: lowest albumin quartile and highest fibrinogen and race-specific WBC quartiles. CKD was defined as estimated glomerular filtration rate of 0.25-1 mL/sec/1.73m^2. In Cox models, inflammation was assessed as a risk factor for a composite of cardiac events, stroke and mortality as well as components of this composite.

Among 20,413 individuals, mean WBC count was 6.2±2.0/L^3, albumin 41±3 g/L, and fibrinogen 9.1±1.9 μmol/L. Inflammation was defined in 3,594 subjects and CKD in 1,649. In multivariable analyses, while both inflammation and CKD predicted all outcomes, their interaction was non-significant. In those with CRP measurements (Cardiovascular Health Study only, n=5,597), inflammation and elevated CRP had similar hazard ratios. When focusing only on worst quartile of WBC and albumin, results remained consistent.

CKD and inflammation are associated with an increased risk of adverse events but do not exhibit synergy. The composite of albumin, WBC count and fibrinogen as well as the composite of only albumin and WBC count have a similar association with adverse events as CRP.

INTRODUCTION

Individuals with chronic kidney disease (CKD) are at increased risk of cardiovascular disease (CVD) and all-cause mortality, and it is hypothesized that both traditional and non-

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traditional CVD risk factors may account for this increased risk (1–3). One non-traditional risk factor is inflammation (4, 5).

Inflammation is a systemic condition, mediated by the interplay of multiple factors, including cytokines, complement and white blood cells (WBC). For example, c-reactive protein (CRP), a non-specific acute phase reactant marking inflammation, requires interleukin-6 and either interleukin-1 or tumor necrosis factor alpha for upregulation, while a second acute phase reactant, fibrinogen, requires interleukin-6 for upregulation but is inhibited by interleukin-1 and tumor necrosis factor alpha (6). Elevated fibrinogen is generally a later but more sustained phenomenon in the setting of inflammation than elevated CRP (6). Other acute phase responses, leukocytosis and hypoalbuminemia, occur early following an inflammatory stimuli, and changes may be sustained in chronic inflammatory states (6).

Individuals with CKD have several potential inflammatory stimuli including ischemia, infection and the uremic milieu. An imbalance in pro- and anti-oxidant agents in CKD, perhaps mediated by impaired pro-inflammatory cytokine clearance, may contribute (7). In the general population, inflammation is an established risk factor for CVD, with leukocytosis and CRP both independently associated with cardiovascular outcomes (4, 8, 9). Several studies have shown an association between inflammatory markers and outcomes in CKD populations (10, 11). Although it is hypothesized that inflammation may be the unifying concept between kidney disease and the enhanced CVD risk in CKD (12), the interaction between inflammation and CKD has not been compared in a general population study.

In this study, we examined the effects of inflammation on cardiovascular and mortality outcomes, using established inflammatory markers (fibrinogen, albumin, WBC count) in individuals with and without chronic kidney disease to assess: 1) inflammation as a risk factor for adverse events; 2) synergy between inflammation and CKD to evaluate potential differences in the importance of inflammation among individuals with and without CKD; and 3) importance of these markers relative to CRP in individuals with and without CKD.

RESULTS

Among 20,413 individuals, mean age was 59.3 ± 10.2 years; 1,649 (8.1%) had CKD, 4,732 (23.2%) were African American, 3,471 (17.0%) had prior CVD and 1,970 (9.7%) were diabetic. Mean WBC count was 6.2 ± 2.0 thousand cells/mm^3, mean serum albumin was 41 ± 3 g/L (4.1 ± 0.3 g/dL), and mean fibrinogen was 9.1 ± 1.9 μmol/L (309 ± 66 mg/dL). There were 3,594 (17.6% individuals) with two of three and 740 (3.4%) individuals with all three characteristics in the worst quartile. Individuals with inflammation were older, more often African American and male, and more likely to have hypertension, diabetes and CKD (Table 1). There were 2,483 (12.4%) cardiac events and 4,958 (24.8%) composite events over 105 ± 30 months of follow-up in individuals with complete data (Table 2). Events were significantly more common in those with inflammation ($p<0.001$).

In univariate and multivariable analyses, elevated WBC count, reduced serum albumin and increased fibrinogen were all associated with adverse outcomes (Table 2). The composite variable that defined inflammation by being in the worst quartile of two of these three inflammatory markers was also associated with all adverse outcomes in univariate and multivariable analyses (Table 2). This composite term for inflammation was associated with lower Akaike information criterion (AIC) values and higher hazard ratios than any of the individual components of the composite when examining the same number of individuals (data not shown). The hazard ratios (95% confidence intervals) associated with CKD in multivariable models that also adjusted for inflammation were 1.12 (1.10, 1.26), 1.24 (1.06, 1.46), 1.50 (1.36, 1.65) and 1.22 (1.13, 1.33) for cardiac, stroke, mortality and composite outcomes, respectively. The proportional hazards assumption was met for multivariable models.

Inflammation and Reduced Kidney Function

There were 1,570 (95.2%) individuals with CKD with complete data for multivariable analyses (the majority without complete data were missing electrocardiograms to determine LVH). Although inflammation was more common in individuals with CKD (12.9% versus 7.1%, $p<0.001$), inflammation was a statistically significant risk factor for only mortality and composite events in this subpopulation (Table 3). The addition of inflammation to models did not affect overall predictive ability despite statistical significance (data not shown). Reclassifying WBC count using non-race specific values did not change results (data not shown). Interaction terms defining the relationship between inflammation and CKD were non-significant with beta coefficients of negative sign, implying that, while CKD and inflammation both are associated with an increased risk of adverse events, they are primarily additive rather than synergistic and may even incorporate some similar risks (Table 4).

CRP and Other Inflammation Markers

We examined CRP and the inflammation composite in the 5,597 individuals from CHS with CRP and other inflammatory marker data at baseline. As 23% of the CHS population was defined as having inflammation by the composite inflammation variable, we defined elevated CRP by the highest 23% of CRP values (CRP ≥3.6 mg/L). There was significant collinearity between these 2 variables (phi coefficient=0.27, $p<0.001$), even though only 44% of individuals with ‘inflammation’ had high CRP. The inflammation composite and elevated CRP were statistically significant risk factors for adverse outcomes and were of similar magnitude in all models (Table 5). However, in the CKD subgroup, neither the inflammation composite nor elevated CRP were statistically significant risk factors for adverse outcomes ($p>0.3$ for all except $p=0.08$ for CRP with composite outcomes); this may be a power issue as the interaction term for CKD with inflammatory markers was non-significant in all models. In sensitivity analyses, we used first used CRP ≥3 mg/L and then CRP ≥10 mg/L to define individuals with inflammation. We then varied the criteria for cutpoints for the inflammation composite term, with similar numbers seen for elevated CRP and the inflammation composite with stratification of inflammatory markers at the worst tertile (for CRP ≥3 mg/L) and worst 15% (for CRP ≥10 mg/L) of two of three inflammatory

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markers. Results for elevated CRP and the modified inflammation composites remained similar to those presented (data not shown).

Finally, as albumin and WBC count are routinely obtained in medical practice, we re-defined the inflammation composite as being in both the upper quartile of race-specific WBC count and the lower quartile of albumin in the CHS cohort, resulting in 472 (8.4%) of individuals defined with inflammation. We then defined elevated CRP as >9.0 mg/L (n=484, 8.6%) by taking a similar percentage of individuals. There again was significant agreement between inflammation indicators (phi coefficient=0.16, p<0.001) despite only 23% of individuals with 'inflammation' having high CRP. In multivariable models, the magnitude of risk associated with the inflammation composite and elevated CRP was very similar (Table 6). Notably in the CKD subgroup, the inflammation composite, but not elevated CRP, was associated with cardiac events in multivariable models [$HR_{inflammation}$=1.41 (1.02,1.96) versus HR_{CRP}=1.00(0.71,1.39)], although hazards for the composite outcome were similar [$HR_{inflammation}$=1.26 (1.00,1.59) versus HR_{CRP}=1.30(1.04,1.63)].

DISCUSSION

In this study, we confirm the association between markers of inflammation and mortality and cardiovascular outcomes in a community-based population, regardless of the presence or absence of reduced kidney function. In exploring this relationship, we found that, although both CKD and inflammation are associated with an increased risk of adverse events, these factors do not exhibit synergy. Additionally, we demonstrate that, regardless of kidney function, a composite of reduced serum albumin, elevated fibrinogen and elevated WBC count and a composite of only the more common measures (albumin and WBC count) both predict adverse events in an elderly population to a similar degree as CRP.

Markers of inflammation have previously been evaluated in several studies of the general population. CRP, evaluated in a nested case-control study within a subset of ARIC, was a risk factor for coronary outcomes; however this effect was attenuated by accounting for other markers of inflammation, including WBC count and fibrinogen (13). Other inflammatory markers, including fibrinogen, were evaluated in other studies of the ARIC population (14). Investigators found an independent relationship between both fibrinogen and metabolic syndrome with cardiac and mortality events; notably, this relationship was additive rather than synergistic. Finally, again within ARIC, Saito et al investigated the subpopulation of 1,676 diabetic subjects and found that low albumin, and high WBC count, fibrinogen, von Willenbrand factor and Factor VIII activity predicted incident coronary disease (1). WBC count has also been evaluated as a coronary artery disease risk factor. One study described an association between high WBC count and angiographic coronary disease in the absence of a similar association for elevated CRP (15). Further, the Baltimore Longitudinal Study of Aging described a near linear relationship between WBC count and cardiovascular events (16).

Other studies have specifically focused on inflammatory markers in CKD. Shlipak et al investigated non-traditional CVD risk factors in the CHS population and, in fully adjusted multivariable models, found that both fibrinogen and CRP were associated with increased absolute risk of cardiovascular mortality only in individuals who did not have CKD (although CRP trended to increased risk in those with CKD) (17). In NHANES III, the cross-sectional association between inflammation, marked by elevated CRP, and metabolic syndrome was significant regardless of kidney function (18).

This study expands on current knowledge by: 1) using multiple indicators together to indicate inflammation; 2) evaluating for a unique role of inflammation in CKD as compared to the general population; and 3) comparing the utility of two very common and inexpensive laboratory tests to CRP as a risk factor for adverse outcomes in individuals with and without CKD. Notably, the addition of these variables to models in the entire population or just in those with CKD did not have a substantial effect on overall predictive ability despite statistical significance. This phenomenon is expected when adding variables to multivariable models that are already well fit (19, 20).

An interaction term in statistical models can test whether the impact of a risk factor is modified by the presence of a second risk factor. When the beta coefficient for an interaction term between two risk factors is positive, it implies that these two risk factors have more than additive risk. Less clear is the interpretation of a statistically significant interaction term of negative magnitude. In a model without collinearity, this finding would imply that the presence of these two risk factors in conjunction is protective versus the presence of one of these alone. However, in a model with collinearity, the implication is that these factors include common risk, implying perhaps that the effects of one risk factor may be mediated through effects of the second risk factor. The finding that the interaction term for CKD and inflammation had beta coefficients that were negative in magnitude for the study outcomes with trends toward statistical significance suggests that CKD and inflammation in part identify common risk and supports the finding that heightened inflammation accompanies reduced kidney function (12).

Finally, we demonstrate that two very commonly measured analytes, WBC count and albumin, have associations with events comparable to that of CRP, regardless of kidney function; this finding questions whether there is a significant role for CRP in clinical risk stratification in older adults.

This study has several weaknesses. Most notably, we lack data on proteinuria. We do not have CRP data in ARIC, preventing overall investigation of this inflammatory marker in comparison to more common measures like reduced serum albumin and WBC count. Additionally, the CRP assay used was not a high sensitivity assay, meaning we lack the ability to discriminate at the lowest CRP levels.

This study also has multiple strengths. We evaluate a relatively large stage 3 CKD population with African American representation that likely has generalizability to the US population. Additionally, for wider applicability, we indirectly calibrated albumin and serum creatinine to NHANES III samples. This allows accurate assessment of these labs within our study as well as reproducibility in other community-based populations. We also use race-specific WBC values as normal WBC levels can differ dramatically by race. In general, this was not done in other studies examining WBC count and cardiovascular outcomes. Further, we evaluate multiple outcomes, including stroke, coronary disease and mortality, to assess the overall impact of inflammatory markers on outcomes.

In conclusion, both CKD and inflammation are associated with an increased risk of cardiovascular, stroke and mortality events, but do not exhibit synergy. A composite indicator of inflammation, using data on albumin, fibrinogen and WBC count, as well as a more parsimonious indicator, using data on only albumin and WBC count, is associated with adverse events to a similar degree as CRP.

METHODS

Study Design

This study is a secondary evaluation of two community-based, longitudinal, limited-access datasets designed to evaluate CVD: the Atherosclerosis Risk in Communities Study (ARIC) and Cardiovascular Health Study (CHS).

Study population—Between 1987 and 1989, ARIC enrolled 15,792 participants aged 45–64 years from four communities. The Mississippi cohort is entirely African-American and comprises over 80% of the African-Americans in ARIC. CHS is a population-based study of 5,201 subjects 65 years and older randomly selected from Medicare eligibility files in four communities during 1989 and 1990. CHS recruited an additional 687 African-Americans in 1992 and 1993 (21, 22).

Ascertainment of Level of Kidney Function—Baseline serum creatinine levels were assessed in 15,582 (99%) and 5,716 (97%) subjects in ARIC and CHS, respectively. Kidney function was quantified using estimated glomerular filtration rate (eGFR) derived from the 4-variable Modification of Diet in Renal Disease (MDRD) study equation (23, 24). Because serum creatinine assays vary across laboratories, we calibrated the ARIC and CHS laboratories indirectly using NHANES III data (25, 26). We defined CKD as eGFR below 1 mL/sec/1.73m^2 (60 ml/min/1.73m^2) (27). Subjects with stage 5 CKD (GFR < 0.25 mL/sec/1.73m^2 (15 ml/min/1.73m^2)) were excluded.

Markers of Inflammation: WBC Count, Albumin, Fibrinogen and CRP—White blood cell count was measured in citrated samples in CHS and ARIC in local laboratories on fresh specimens. Although both ARIC and CHS used the bromocresol green method to assess serum albumin, results appeared discrepant by study as mean serum albumin was significantly higher in CHS than ARIC. Discrepancies in albumin measurements may relate to different processing times, non-specific interference from binding to non-albumin proteins, or laboratory calibration differences (28, 29). Therefore, we indirectly calibrated both ARIC and CHS serum albumin levels to NHANES III levels (also measured with a bromocresol green method) using a regression equation that accounted for albumin, age and sex. This resulted in 2.3 g/L (0.23 g/dL) being added to ARIC values, 0.3 g/L (0.03 g/dL) added to values in the CHS original cohort, and no change to values in the CHS African American cohort. In ARIC, plasma fibrinogen was measured by the thrombin-time titration method with reagents and calibration materials (Fibriquik) obtained from General Diagnostics (Organon-Technika Co). In CHS, fibrinogen was measured in a BBL fibrometer

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(Becton Dickinson, Cockeysville, MD). Based on comparisons to NHANES III data, calibration was not necessary for plasma fibrinogen (data not shown). CRP was available only in CHS and was measured in plasma using an automated assay on the BNII nephelometer (Dade Behring Inc).

Baseline Covariates—These included demographics (age, sex, race); medical history (baseline CVD, diabetes mellitus, smoking); physical findings (systolic blood pressure, left ventricular hypertrophy, body mass index (BMI), diastolic blood pressure); and laboratory variables (total cholesterol, high density lipoprotein (HDL) cholesterol, hemoglobin). The methods employed for collection of baseline data by each of these studies have been previously described (21, 22).

Race was white or African American. Education level was dichotomized by high school graduation. Cigarette smoking and alcohol use were dichotomized as current users and non-users. Diabetes was defined by insulin use, oral hypoglycemic medication use, or fasting glucose level ≥7 mmol/L (126 mg/dL). Hypertension was defined as systolic blood pressure ≥140 mm Hg, diastolic ≥90 mm Hg or antihypertensive medication use. BMI was calculated using the formula: weight [kg]/ height^2 [m]. Left ventricular hypertrophy was defined using resting 12-lead electrocardiogram in all studies in subjects meeting voltage criteria and having characteristic S-T segment or T wave changes (30). Baseline CVD included a history of both recognized and silent myocardial infarction (MI), angina, angioplasty and coronary bypass procedures, stroke, transient ischemic attack and intermittent claudication as defined by consensus committees for the respective studies. Baseline CVD also included a history of congestive heart failure in CHS (not coded in ARIC). The methods employed to define CVD outcomes are extensively described elsewhere (21, 22).

Exposures

Because we were interested in examining inflammation, we used the available inflammatory markers in both CHS and ARIC, namely serum albumin, plasma fibrinogen and WBC count. We defined inflammation as being in the worst quartile of any 2 of these 3 variables (lowest albumin, highest fibrinogen and highest WBC count). Quartile of WBC count was race specific as African Americans typically have lower WBC counts than whites (31). Sensitivity analyses using non-race specific WBC count were performed.

Outcomes

The primary study outcome was a composite of MI, coronary revascularization procedure, stroke and all-cause mortality. MI was defined by both clinically recognized and silent infarctions, with ascertainment of silent MI by screening electrocardiogram. Secondary outcomes were cardiac events (fatal coronary heart disease, MI, coronary revascularization), stroke, and all-cause mortality. Committees within each study adjudicated events. Individuals were censored at 10 years.

Study Population

From an initial population of 21,680, we excluded 575 subjects who had data missing on either age, race, sex, creatinine or were of non-white/non-African American race; 36

subjects with eGFR <15 ml/min/1.73m^2; 93 subjects who did not provide permission to release data; 3 subjects without follow-up data; and 556 subjects with missing baseline CVD data. An additional 4 individuals were missing data on fibrinogen, albumin or WBC count. Among the remaining 20,413 subjects, 1,649 subjects had CKD. Of these, 19,986 individuals in total and 1,570 with CKD had data on all baseline covariates.

Analysis and Statistical Methods

The goal of our analysis was to determine the relationship between markers of inflammation and outcomes in individuals with CKD and compare these to individuals without reduced kidney function. A secondary goal was to compare the association of the composite of serum albumin, WBC count and fibrinogen as well as a composite only including albumin and WBC count to that seen with CRP for adverse outcomes in individuals with CKD in the CHS cohort.

Risk factors were explored using plots, means and percentages. We examined reduced albumin, elevated WBC count and elevated fibrinogen in univariate and multivariable proportional hazards models. We then used the composite definition of inflammation (worst quartile in 2 of 3 markers) and examined hazard ratios for the inflammation composite and its individual components in univariate and multivariable models. Variables *a priori* included in multivariable models were known traditional cardiovascular risk factors (age, sex, diabetes, smoking, LVH and systolic blood pressure, and non-HDL cholesterol) as well as history of prior CVD, race, and a term for study of origin (ARIC versus CHS). When evaluating the entire population, a term for CKD was included in all models; in subgroup analysis that examined only individuals with CKD, eGFR was included in models. The proportional hazards assumption was tested by graphically exploring Schoenfeld residuals.

Multiple interaction terms were tested. Because inflammation may influence effects of CKD on adverse outcomes, the interaction between CKD and inflammation was tested, first in a parsimonious model that included only terms for CKD, inflammation and their interaction, and then in full multivariable models.

Analyses using CRP—We defined elevated CRP (CHS only) as comprising a similar number of individuals as the inflammation composite. Correlation between CRP and other markers of inflammation was assessed with phi statistics. We then repeated the analyses above to evaluate the hazard associated with CRP versus to the hazard associated with the inflammation composite for adverse outcomes in both the entire population and the subgroup with CKD. In sensitivity analyses, we defined high CRP first as ≥3 mg/L and then as ≥10 mg/L and subsequently varied the cutpoints for other inflammatory markers to develop an inflammation composite with similar numbers of individuals for each of these CRP levels. We repeated analyses using these revised definitions.

Finally, as albumin and WBC count are common and inexpensive laboratory tests, we redefined inflammation as the highest quartile of race-specific WBC count and the lowest quartile of serum albumin and redefined elevated CRP as comprising a similar number of individuals as the albumin and WBC count-only inflammation composite. We then examined models including these variables as predictors of adverse events. All analyses were conducted with SAS Version 9.1.

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Table 1

Baseline characteristics and clinical events for the cohort stratified by the presence of absence of inflammation.

	No Inflammation n=16,819 (82.4%)	Inflammation n=3,594 (17.6%)	Total n=20,413
Demographics			
Age	59.0 ± 10.1	61.6 ± 10.9	59.4 ± 10.3
Female	54.7	60.0	55.6
African American	21.2	32.7	23.2
High School Graduate	76.7	67.2	75.0
ARIC	74.3	63.8	72.5
Medical History			
Diabetes	8.0	17.5	9.7
Hypertension	43.9	59.4	46.6
Cardiovascular Disease	15.4	24.4	17.0
Current Smoker	18.8	38.4	22.3
Current Alcohol Use	56.6	45.6	54.6
Clinical Findings			
Systolic Blood Pressure	124.6 ± 20.4	129.4 ± 22.6	125.5 ± 20.9
Diastolic Blood Pressure	73.0 ± 11.2	72.5 ± 12.2	72.9 ± 11.4†
Left ventricular hypertrophy	2.5	4.5	2.8
Body Mass Index	27.0 ± 4.7	28.8 ± 6.0	27.3 ± 5.0
Laboratory Results			
Serum Creatinine	78 ± 20	80 ± 27	79 ± 21
Estimated GFR	1.48 ± 0.35	1.48 ± 0.42	1.48 ± 0.36*
Reduced eGFR	7.1	12.1	8.1
Hemoglobin	139 ± 14	138 ± 16	139 ± 14
Total Cholesterol	5.54 ± 0.39	5.46 ± 1.12	5.53 ± 1.07
HDL Cholesterol	1.37 ± 0.44	1.26 ± 0.39	1.35 ± 0.43
Non-HDL Cholesterol	4.17 ± 1.10	4.20 ± 1.16	4.18 ± 1.11‡
Inflammatory Markers			
Albumin	41 ± 2	39 ± 3	41 ± 3
Fibrinogen	293 ± 53	384 ± 70	309 ± 66
WBC Count	5.8 ± 1.7	8.0 ± 2.6	6.2 ± 2.0
CRP	2.6 ± 4.0	6.9 ± 10.2	3.6 ± 10.3

Inflammation was defined by having two of the following three characteristics: upper quartile of fibrinogen (≥344 mg/dL), upper quartile of WBC count (≥6.7 in African Americans, ≥7.3 in whites), and lower quartile of albumin (<3.9 g/dL).

P-value <0.001 for differences between individuals with and without inflammation except

*p>0.20,

‡p<0.20, and

†p<0.05

All events reflect 10-year incidence. Cardiac events include myocardial infarction, fatal coronary disease, and coronary revascularization. ARIC, Atherosclerosis Risk in Communities; GFR, glomerular filtration rate; HDL, high density lipoprotein; WBC, white blood cell; CRP, c-reactive protein. All measurements are mean ± standard deviation for continuous measures or percent for categorical variables. Blood pressure is mm Hg. Body mass index is kg/m^2. Serum creatinine and fibrinogen measurements are μmol/L. Cholesterol measures are in mmol/L. GFR is in mL/sec/1.73m^2. Hemoglobin and albumin are g/L. WBC count is 10^9 cells/L^3. CRP is mg/L. To convert to mg/dL, divide creatinine by 88.4, fibrinogen by 0.0294, and cholesterol measures by 0.02586. To convert to g/dL, divide albumin and hemoglobin by 10. To convert to mL/min/1.73m^2, multiply eGFR by 60.

Table 2

Unadjusted and adjusted risk of adverse events associated with inflammation as well as individual markers of inflammation.

	Events: n (%)	Cardiac 2,483 (12.4%)	Stroke 1,083 (5.4%)	Death 3,059 (15.3%)	Composite 4,958 (24.8%)
Inflammation Components					
WBC	Univariate	1.15 (1.13,1.17)	1.14 (1.11,1.17)	1.15 (1.13,1.16)	1.14 (1.13,1.16)
Albumin	Univariate	0.90 (0.87,0.94)	0.77 (0.73,0.82)	0.74 (0.71,0.76)	0.82 (0.80,0.85)
Fibrinogen	Univariate	1.33 (1.28,1.37)	1.38 (1.31,1.44)	1.41 (1.37,1.45)	1.36 (1.33,1.39)
WBC	Multivariable	1.06 (1.03,1.09)	1.07 (1.03,1.11)[1]	1.07 (1.05,1.09)	1.07 (1.05,1.08)
Albumin	Multivariable	0.90 (0.87,0.94)	0.87 (0.82,0.92)	0.85 (0.82,0.88)	0.89 (0.86,0.91)
Fibrinogen	Multivariable	1.12 (1.08,1.17)	1.10 (1.04,1.16)[2]	1.16 (1.13,1.20)	1.14 (1.11,1.17)
Inflammation Composite					
Composite	Univariate	1.95 (1.79, 2.12)	2.24 (1.97,2.54)	2.19 (2.03,2.37)	2.00 (1.89, 2.13)
Composite	Multivariable	1.35 (1.23,1.49)	1.46 (1.27,1.67)	1.42 (1.31,1.54)	1.37 (1.28,1.46)

Per standard deviation change: 2×10^9 cells/L^3 (2-thousand cells/mm^3) rise in white blood cell (WBC) count; 2.7 g/L (0.27 g/dL) rise in serum albumin; and 1.9 μmol/L (66 mg/dL) rise in fibrinogen. *Inflammation Composite* refers to having two of the following three characteristics: upper quartile of fibrinogen [≥10.1 μmol/L (344 mg/dL)], upper quartile of WBC count [≥6.7 in African Americans, ≥7.3 in whites], and lower quartile of albumin [<39 g/L (<3.9 g/dL)].

Multivariable models are adjusted for presence or absence of kidney disease, anemia, age, sex, race, prior cardiovascular disease, history of diabetes, history of hypertension, LVH, smoking, alcohol use, high school graduation status, body mass index, systolic blood pressure, non-HDL cholesterol, and study of origin. Number of events and multivariable hazards reflect individuals with complete baseline data (n=19,986).

All p-values <0.0001 except

[1] p=0.0003 and

[2] p=0.002

Table 3

Inflammation and adverse events in individuals with CKD.

Events: n (%)	**Cardiac 392 (25.0%)**	**Stroke 209 (13.3%)**	**Death 671 (42.7%)**	**Composite 841 (53.6%)**
Univariate	1.58 (1.29,1.94)	1.51 (1.14, 1.99)	1.76 (1.51, 2.05)	1.66 (1.45, 1.91)
Multivariable	1.14 (0.91,1.43)	1.14 (0.84, 1.55)	1.24 (1.05,1.47)	1.19 (1.02,1.39)

Multivariable analyses and number of events based on the 1,570 individuals with eGFR <1 mL/sec/1.73m^2 (60 mL/min/1.73m^2) with complete baseline data.

Table 4

CKD, inflammation and the risk of adverse events

		Cardiac Outcome		Stroke Outcome		Mortality Outcome		Composite Outcome	
		Events	**HR (95% CI)**	**Events**	**HR (95% CI)**	**Events**	**HR (95% CI)**	**Events**	**HR (95% CI)**
+ Inflammation + CKD	N=446	131	1.39 (1.15,1.68)	70	1.57 (1.22,2.04)	242	2.01 (1.74,2.31)	292	1.58 (1.39,1.79)
+ Inflammation −CKD	N=3,055	525	1.40 (1.26,1.55)	254	1.56 (1.34,1.82)	669	1.47 (1.34,1.61)	1,048	1.40 (1.30,1.51)
− Inflammation + CKD	N=1,124	261	1.20 (1.04,1.37)	139	1.39 (1.14,1.69)	429	1.57 (1.41,1.76)	549	1.28 (1.16,1.41)
− Inflammation −CKD	N=15,361	1,566	reference	620	reference	1,719	reference	3,069	reference
p-value (interaction)		0.12		0.05		0.13		0.13	

Hazard ratio (95% confidence interval) for adverse events in multivariable models that included the interaction term, CKD*inflammation. Percent of individuals with an event is presented below the hazard ratio. The p-value refers to the interaction term itself, where beta coefficients were −0.18, −0.32, −0.14 and −0.12, respectively.

Multivariable models are adjusted for variables described in Table 2 caption.

Table 5

Inflammation composite and elevated CRP in the subgroup of individuals from CHS.

Event **n (%)**	**Cardiac** **1,222 (21.8%)**	**Stroke** **688 (12.3%)**	**Death** **1,878 (33.6%)**	**Composite** **2,623 (46.9%)**
Univariate				
Inflammation	1.48 (1.31,1.68)	1.40 (1.18,1.66)	1.51 (1.37,1.67)	1.40 (1.28,1.53)
Elevated CRP	1.44 (1.27,1.63)	1.33 (1.12,1.58)	1.46 (1.32,1.62)	1.36 (1.25,1.49)
Multivariable				
Inflammation	1.28 (1.13,1.46)	1.22 (1.03,1.45)	1.25 (1.13,1.38)	1.20 (1.09,1.31)
Elevated CRP	1.29 (1.13,1.47)	1.20 (1.01,1.43)	1.31 (1.18,1.45)	1.26 (1.15,1.38)

The variable, inflammation, refers to having two of the following three characteristics: upper quartile of fibrinogen, upper quartile of race-specific WBC count, and lower quartile of albumin. For this comparison, elevated CRP $\geq$3.6 mg/L.

Multivariable models were adjusted for age, sex, race, CKD, cardiovascular disease, diabetes, hypertension, smoking, systolic blood pressure, and non-HDL cholesterol. Education, race, body mass index and alcohol use were not statistically significant in composite models and therefore were not included in these multivariable models.

Table 6

Abbreviated inflammation composite (based only on reduced albumin and elevated WBC count) and elevated CRP in the subgroup of individuals from CHS.

		Cardiac	Stroke	Death	Composite
Entire Population					
Univariate	[events (%)]	1,222 (21.8%)	688 (12.3%)	1,878 (33.6%)	2,623 (46.9%)
	Inflammation	1.50 (1.25,1.80)	1.39 (1.09,1.78)	1.62 (1.41,1.87)	1.45 (1.28,1.65)
	Elevated CRP	1.45 (1.21,1.73)	1.64 (1.30,2.06)	1.56 (1.35,1.80)	1.45 (1.28,1.64)
Multivariable	Inflammation	1.36 (1.13,1.63)	1.23 (0.96,1.59)	1.34 (1.16,1.55)	1.28 (1.12,1.45)
	Elevated CRP	1.23 (1.02,1.48)	1.46 (1.16,1.85)	1.34 (1.16,1.55)	1.30 (1.15,1.48)
CKD Only					
Multivariable	[events (%)]	338 (27.9%)	191 (15.7%)	608 (50.1%)	749 (61.7%)
	Inflammation	1.41 (1.02,1.96)	1.41 (0.91,2.18)	1.10 (0.84,1.43)	1.26 (1.00,1.59)
	Elevated CRP	1.00 (0.71,1.39)	1.57 (1.05,2.36)	1.14 (0.89,1.45)	1.30 (1.04,1.63)

The variable, inflammation, refers to having both of the following: upper quartile of race-specific WBC count and lowest quartile of albumin among all individuals with CRP levels.

Multivariable models were adjusted for age, sex, race, CKD (or eGFR in CKD only), cardiovascular disease, diabetes, hypertension, smoking, systolic blood pressure, and non-HDL cholesterol. Education, race, body mass index and alcohol use were not statistically significant in composite models and therefore were not included in these multivariable models.