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The relation of C-reactive protein to chronic kidney disease in African Americans: the Jackson Heart Study

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Abstract

Background: African Americans have an increased incidence and worse prognosis with chronic kidney disease (CKD - estimated glomerular filtration rate [eGFR] <60 ml/min/1.73 m²) than their counterparts of European descent. Inflammation has been related to renal disease in non-Hispanic whites, but there are limited data on the role of inflammation in renal dysfunction in African Americans in the community.

Methods: We examined the cross-sectional relation of log transformed C-reactive protein (CRP) to renal function (eGFR by Modification of Diet and Renal Disease equation) in African American participants of the community-based Jackson Heart Study’s first examination (2000 to 2004). We conducted multivariable linear regression relating CRP to eGFR adjusting for age, sex, body mass index, systolic and diastolic blood pressure, diabetes, total/HDL cholesterol, triglycerides, smoking, antihypertensive therapy, lipid lowering therapy, hormone replacement therapy, and prevalent cardiovascular disease events. In a secondary analysis we assessed the association of CRP with albuminuria (defined as albumin-to-creatinine ratio > 30 mg/g).

Results: Participants (n = 4320, 63.2% women) had a mean age ± SD of 54.0 ± 12.8 years. The prevalence of CKD was 5.2% (n = 228 cases). In multivariable regression, CRP concentrations were higher in those with CKD compared to those without CKD (mean CRP 3.2 ± 1.1 mg/L vs. 2.4 ± 1.0 mg/L, respectively p < 0.0001). CRP was significantly associated with albuminuria in sex and age adjusted model however not in the multivariable adjusted model (p > 0.05).

Conclusion: CRP was associated with CKD however not albuminuria in multivariable-adjusted analyses. The study of inflammation in the progression of renal disease in African Americans merits further investigation.

Background

The incidence and mortality of chronic kidney disease (CKD) is disproportionately higher in African Americans compared to their white counterparts. In a 12-year follow up cohort study of 9,082 African American and white adults between 30-74 years of age, African Americans’ risk of CKD was 2.7 times higher than that of whites [1]. Although high rates of hypertension, diabetes and obesity in the middle-aged African American population contribute in part to the racial difference, the disparities were not fully accounted for by risk factor burden [1].

Recent data support the concept that C-reactive protein (CRP) is associated with the prevalence, progression and prognosis of renal dysfunction in non-Hispanic whites. Increasing CRP concentrations have been related to both prevalent [2-5] and incident [6] CKD in this group. Also a10-ml/minute/1.73 m² lower estimate GFR [(eGFR) among persons with eGFR <60 ml/minute/1.73 m²] has been associated with an incidence rate ratio of 1.29 (95% confidence interval: 1.06, 1.55) for cardiovascular mortality and a doubling of albuminuria has been associated with an incidence rate ratio of 1.06 (95% confidence interval: 1.04, 1.08) for cardiovascular mortality.
CRP concentrations association with albuminuria may be affected by ethnicity and sex and this may part
the clustering of cardiovascular risk factors and the higher incidence of cardiovascular disease observed in
African Americans [8]. Despite the increased incidence
and poor sequelae from CKD, and the existing research
in non-Hispanic whites relating inflammation to CKD,
there are limited data on the relation of inflammatory
biomarkers to renal function and albuminuria in African
Americans. We hypothesized that renal function and
albuminuria are significantly related to systemic inflam-
ination in African Americans after adjusting for tradi-
tional cardiovascular risk factors.

Methods

Study Cohort and Design

The Jackson Heart Study is a longitudinal community-
based observational cohort that was initiated in 2000 to
prospectively investigate the epidemiology and determi-
ants of cardiovascular disease in African Americans
[9]. Thirty percent of study participants were former
members of the Jackson, Mississippi cohort of the
Atherosclerosis Risk in Communities study, and had
been recruited by random selection from the driver’s
license registry [10]. Among the remaining participants,
23% were recruited by random selection from the
“Accudata” list (a commercial listing that represents the
overall tri-county population). An additional 23% were
members of a constrained volunteer sample, in which
recruitment was distributed among defined demographic
cells in proportions designed to mirror those in the
overall tri-county population. Twenty-four percent of
participants were recruited through the Jackson Heart
Study Family Study, as described [11]. Among the 5,301
participants recruited for Examination 1, we studied
4,320 participants after excluding participants for the fol-
dowing indications: missing CRP measurements (n =
105); those with self-reported malignancy, those using
medications suggesting underlying rheumatologic or
inflammatory disease, and those with a white blood cell
count > 12 suggesting infection (n = 312); missing cov-
arites (n = 523); eGFR <15 ml/min/1.73 m 2 (n = 20);
and missing eGFR (n = 21). The Jackson Heart Study
was approved by the University of Mississippi Medical
Center Institutional Review Board and participants gave
written informed consent.

Measurement of Renal Function

Biochemical testing for serum creatinine was performed
at the University of Mississippi Medical Center Labora-
tory Reading Center using a multi-point enzymatic spec-
trophotometric assay on a Vitros 950 Ortho-Clinical
Diagnostics analyzer. Creatinine values were biochemi-
cally calibrated to Cleveland Clinic-equivalent Minne-
sota Beckman CX3 assay for analysis purposes. Thus,

CKD was defined in the primary analysis as eGFR <60
ml/min/1.73 m 2 [13,14]. In a secondary analysis, CRP
relation to albuminuria [defined as an urinary albumin-
to-creatinine ratio (UACR) of > 30 mg/g on spot or 24-
hour urine collection] was considered. A thorough dis-
cussion of the measurements for CKD and their relation
to interview and medical data in the Jackson Heart
Study has been previously published [15].

CRP measurement

We measured CRP using immunoturbidimetric CRP-
Latex assay from Kamiya Biomedical Company following
manufacturer’s high-sensitivity protocol. The inter-assay
coefficients of variation on control samples repeated in
each assay were 4.5% and 4.4% at CRP concentrations of
0.45 mg/L and 1.56 mg/L respectively. The reliability
coefficient for masked quality control replicates was 0.95
for the CRP assay.

Covariates

Body mass index (BMI) was calculated as the ratio of
fasting weight to height squared (kg/m 2). Obesity was
defined as a BMI ≥30 kg/m 2. We defined hypertension
based on Joint National Commission VII guidelines
(≥140/90 mmHg, or reported use of antihypertensive
medications within two weeks prior to the visit) [16].
Our definition for diabetes was based on the American
Diabetes Association guidelines: participants were con-
sidered to have diabetes if they had one of the following:
fasting serum glucose ≥126 mg/dL or use of diabetic
medications within two weeks of the clinic visit, or his-
tory of physician-diagnosed diabetes [17]. Fasting serum
total to high density lipoprotein (HDL) cholesterol and
triglyceride concentrations were assessed with Roche
enzymatic methods using a Cobras centrifuge analyzer
(Hoffman-La Roche). Smoking status was defined as any
participant who had smoked at least 400 cigarettes in
their lifetime and was currently smoking at their base-
line examination. Prevalent cardiovascular disease was
defined as a stated history of physician-diagnosed myo-
cardial infarction or stroke, electrocardiographic evi-
dence of myocardial infarction, or history of a revascu-
larization procedure (percutaneous transluminal
 coronary angioplasty or coronary artery bypass surgery).

Statistical Analysis

We performed descriptive statistics to determine the
mean, standard deviation (SD) and/or percentages for
study participants’ characteristics. Frequency distribu-
tions were used for categorical data. Descriptive statis-
tics were used to determine the characteristics of

\[
eGFR (\text{ml} / \text{min} / 1.73 \text{ m}^2) = 186 \times \left(\frac{\text{P}\text{BW}}{74.2}\right)^{0.413} \times \left(\frac{\text{Age} - 0.209}{0.375}\right) \times 1.210 \times \{0.85 \text{ if female}\}
\]
participants according to dichotomized CRP concentration (using the lower 75th percentile as cutoff). Descriptive statistics were also used to determine characteristics of Jackson Heart Study participants with and without CKD.

Since its distribution was skewed, CRP concentration was natural log-transformed for clinical correlates analyses [18]. By means of general linear modeling (SAS PROC GLM) age- and sex-adjusted linear regression was used to assess the relation of CRP concentrations (log transformed) to renal function (CKD). Multivariable regression was used to assess the relation of CRP to CKD accounting for cardiovascular disease risk factors including age, sex, body mass index (BMI), systolic and diastolic blood pressure, diabetes, total/HDL cholesterol, triglycerides, smoking, antihypertensive therapy, lipid lowering therapy, hormone replacement therapy, and prevalent cardiovascular disease events. Effect modification test of age, sex, obesity (BMI<30 versus ≥ 30 kg/m²), prevalent CVD and prevalent MI were performed and the analysis was stratified based on significant effect modifiers at the significance level of 0.01.

In a secondary analysis, we investigated the relation of CRP to albuminuria (UACR) by multivariable linear regression adjusting the above mentioned covariates. The presence or absence of albuminuria served as the independent variable in the model. Analyses were conducted with SAS version 9.2 (SAS Institute, Cary, NC). A two-sided p-value < 0.01 was considered statistically significant.

**Results**

Table 1 displays the clinical characteristics of the Jackson Heart Study by CRP (the lower 75th percentile and upper 25th percentile) for the overall study population, for those participants age < 60 years and for those participants age ≥ 60 years. The prevalence of CKD based on eGFR criteria alone was 5.2% (n = 226); mean eGFR among individuals with CKD was 45.9 ± 13.7 ml/min/1.73 m². CKD was more prevalent in those participants > 60 years old and the mean CRP concentration was slightly higher in this group.

Table 2 shows the relation of CRP with CKD in the study population. There was evidence of effect modification by sex (p = 0.0061) therefore the analysis was stratified. For both men and women, CRP concentrations were higher in those with CKD compared to those without CKD. Between the CKD and non-CKD groups,

| Table 1 Characteristics of Study Participants in the Lower 75th and Upper 25th percentile of C-Reactive Protein Stratified by Age 60 years |
|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
|                 | Overall         | Age < 60 years  | Age ≥ 60 years  |
|                 | (< 5.7 mg/L)    | (≥ 5.7 mg/L)    | (< 5.7 mg/L)    | (≥ 5.7 mg/L)    | (< 5.7 mg/L)    | (≥ 5.7 mg/L)    |
| n               | 3254            | 1066            | 2071            | 663             | 1183            | 403             |
| C-reactive protein mg/L | 2.1 ± 1.5 | 14.4 ± 15.2 | 2.0 ± 1.5 | 14.1 ± 10.6 | 2.2 ± 1.5 | 14.9 ± 20.6 |
| Demographic factors | | | | | | |
| Age, years      | 54 ± 13         | 54 ± 12         | 46 ± 9          | 47 ± 8          | 67 ± 6          | 67 ± 6          |
| Male, %         | 42.01           | 18.57           | 45.3            | 184             | 36.3            | 189             |
| Cardiovascular risk factors | | | | | | |
| Body mass index, kg/m² | 30.3 ± 6.1 | 36.1 ± 8.3 | 30.4 ± 6.3 | 37.4 ± 8.3 | 30.1 ± 5.8 | 34.0 ± 7.8 |
| Systolic blood pressure, mmHg | 127 ± 18 | 127 ± 18 | 123 ± 16 | 124 ± 16 | 134 ± 20 | 133 ± 20 |
| Diastolic blood pressure, mmHg | 80 ± 10 | 78 ± 10 | 81 ± 10 | 80 ± 10 | 78 ± 10 | 75 ± 11 |
| Hypertension, % | 57.6            | 69.0            | 46.3            | 57.6            | 77.4            | 87.6            |
| Diabetes, %     | 13.7            | 18.9            | 9.8             | 15.5            | 20.6            | 24.3            |
| Total/HDL cholesterol, ratio | 4.1 ± 1.3 | 4.1 ± 1.4 | 4.2 ± 1.4 | 4.1 ± 1.5 | 4.0 ± 1.2 | 4.1 ± 1.3 |
| Triglyceride, mg/dL | 104 ± 76 | 113 ± 80 | 102 ± 83 | 109 ± 69 | 107 ± 63 | 119 ± 95 |
| Current smoker, % | 12.2           | 14.4            | 14.3            | 15.9            | 8.7             | 12.0            |
| Anti-hypertension therapy, % | 46.8         | 60.1            | 34.3            | 48.9            | 68.6            | 78.5            |
| Lipid lowering therapy, % | 12.0           | 10.5            | 6.8             | 7.8             | 21.1            | 14.9            |
| HRT use in women, % | 11.2           | 24.1            | 10.6            | 22.9            | 12.1            | 26.0            |
| Nutritional factors | | | | | | |
| Total protein   | 79 ± 47         | 77 ± 48         | 86 ± 51         | 86 ± 53         | 66 ± 35         | 64 ± 35         |
| Kidney disease factors | | | | | | |
| Chronic kidney disease, % | 42             | 8.4             | 1.5             | 4.2             | 8.9             | 15.4            |

Values are % or mean ± standard deviation
HRT, hormone replacement therapy, L75th = lower 75th percentile, U25th = upper 25th percentile
Chronic kidney disease is defined as a glomerular filtration rate, 60 ml/min/1.73 m².
there were greater differences in CRP in men compared to women. Therefore, the changes were in the same direction for both sexes, and the type of effect modification by sex was synergist. There was no effect modification by age, obesity, prevalent CVD or prevalent MI. Age-adjusted CRP concentration was significantly associated with CKD for both women (p = 0.02) and men (< 0.0001). After adjusting for age, BMI, systolic and diastolic blood pressure, diabetes, current smoking status, hypertension drugs, lipid lowering drugs, hormone therapy replacement, triglycerides, total cholesterol/HDL ratio, and prevalent cardiovascular disease events in the multivariable regression, CRP remained strongly associated with CKD for both women and men (p < 0.0001 for both). (See Additional file 1 for results of additional sub-analysis).

Secondary analyses
In a secondary analysis we assessed the relation of CRP with albuminuria (based on spot or 24-hour urine values with an UACR > 30 mg/g). (Table 3) The prevalence of albuminuria was 10.8% (n = 298) among the 2,750 participants with urine to calculate UACR. CRP was significantly associated with albuminuria in the age and sex adjusted model (< 0.0001) but was not in the multivariable-adjusted model (p = 0.16). There was no evidence

<table>
<thead>
<tr>
<th>Table 2 Association of C-Reactive Protein with Chronic Kidney Disease (ml/min/1.73 m²) in the Pooled Study Population and Stratified by Sex</th>
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</thead>
<tbody>
<tr>
<td>CKD (eGFR &lt; 60)</td>
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<tr>
<td><strong>Pooled</strong></td>
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<tr>
<td>N</td>
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<tr>
<td>CRP (Geometric Mean ± SE)</td>
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<td><strong>Adjustment</strong></td>
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<td>Age and Sex</td>
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<tr>
<td>Multivariable*</td>
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<td><strong>Women</strong></td>
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<tr>
<td>N</td>
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<tr>
<td>CRP (Geometric Mean ± SE)</td>
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<td><strong>Adjustment</strong></td>
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<tr>
<td>Age</td>
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<tr>
<td>Multivariable*</td>
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<tr>
<td><strong>Men</strong></td>
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<tr>
<td>N</td>
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<tr>
<td>CRP (Geometric Mean ± SE)</td>
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<td><strong>Adjustment</strong></td>
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<td>Age</td>
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<td>Multivariable*</td>
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</tbody>
</table>

* adjusted for age, sex, body mass index, systolic and diastolic blood pressures, diabetes, current smoking status, hypertension drugs, lipid lowering drugs, hormone therapy replacement, triglycerides, total cholesterol/HDL ratio, and prevalent cardiovascular disease events.
** pooled signify both men and women included in the analysis
† sex is excluded from list of covariates since analysis is stratified by sex
CKD, Chronic kidney disease; eGFR, estimated glomerular filtration rate; CRP, C-reactive protein

<table>
<thead>
<tr>
<th>Table 3 Association of C-Reactive Protein with Albuminuria (UACR &gt; 30 mg/g)</th>
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<tbody>
<tr>
<td>Albuminuria Present</td>
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</tr>
<tr>
<td><strong>Pooled</strong> **</td>
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<tr>
<td>N</td>
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<tr>
<td>CRP (Geometric Mean ± SE)</td>
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<tr>
<td><strong>Adjustment</strong></td>
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<tr>
<td>Age and Sex</td>
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<tr>
<td>Multivariable*</td>
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</tbody>
</table>

* adjusted for age, sex, body mass index, systolic and diastolic blood pressures, diabetes, current smoking status, hypertension drugs, lipid lowering drugs, hormone therapy replacement, triglycerides, total cholesterol/HDL ratio, and prevalent cardiovascular disease events.
** pooled signify both men and women included in the analysis
UACR = urinary albumin-to-creatinine ratio; CRP, C-reactive protein
of effect modification by age, sex, obesity, prevalent CVD or prevalent MI on the relation of CRP with albuminuria.

Discussion
Principal Findings
We found a significant association between higher mean CRP concentrations and CKD for women and men after adjusting for multiple traditional cardiovascular risk factors. In the secondary analysis, we found that CRP was significantly associated with albuminuria in age- and sex- adjusted models. CRP was not significantly associated with albuminuria in the multivariable adjusted model. This finding speaks against a glomerular involvement.

We found that the prevalence of CKD using eGFR by MDRD formula was 5.2% in this cohort. This result is somewhat surprising given the prevalence of stage III CKD was estimated at 7.7% in the recent analysis by Coresh et al. in the NHANES 1999-2004 population (a nationally representative sample of non-institutionalized adults aged 20 years or older) [15,19]. This may be affected by a number of factors including that hypertension control in our cohort was greater than that of the AA in NHANES and that differences in sample recruitment between our cohort and that in NHANES may favor a lower percentage of unhealthy individuals and subsequently lower prevalence of CKD in the Jackson Heart Study.

Relation of CRP to CKD: Comparison with Prior Literature
Our finding of a significant association between CRP (as a marker of systemic inflammation) and CKD in the African American population-based cohort of the Jackson Heart Study is similar to that seen in the Netherlands Study (a large population-based cohort consisting of 7,317 non-Hispanic white individuals without diabetes). In a cross-sectional analysis of the cohort, CRP was significantly associated with lower GFR in the multivariable model (OR 1.9;95% CI 1.3 to 2.9) [5]. Two recent smaller studies in individuals with diabetes showed a relation between inflammatory markers and CKD, though in neither study was there a significant association with CRP [20,21] In the Cardiovascular Health Study, a community-based cohort of elderly individuals, CRP and other markers of systemic inflammation remained associated with a rise in creatinine after adjusting for multiple clinical risk factors including race (follow up period of nine years for the original cohort and four years for the more recently recruited African American cohort). Similar results were found for decline in estimated GFR. The decline in eGFR was greater with increasing number of inflammatory or prothrombotic markers that were above the median [22].

Finally, others have shown that higher CRP concentrations are related to reduced kidney cortex width and reduced renal cortex width is related to increased blood pressure [34,35] Hence, CRP may be a marker of kidney dysfunction.
inflammation with increased scarring in the kidney cortex, which may then relate to blood pressure.

**Strengths and Limitations**

There are a number of limitations of our study. First, the study population consists solely of African Americans and so the generalizability of this study to other ethnic groups is unclear. Second, this study is cross-sectional and therefore cause-effect relations cannot be determined. Third, because data are derived from the first visit for the Jackson Heart Study cohort, investigators were unable to assess the effects of longitudinal exposure to environmental factors. Fourth, renal function in the current analysis was estimated using the MDRD eGFR formula (a recommended means of estimating kidney function). MDRD has stronger specificity than sensitivity in predicting kidney problems. The more direct measure of kidney disease (using iothalamate or iohexol clearance to measure GFR) is not feasible in a population-based setting. Balanced against these caveats, the strength of this study lies in the prospective collection of CRP concentrations and covariates in a large population-based cohort of African Americans.

**Conclusion**

Our study found that CRP is significantly related to CKD as defined by eGFR < 60 ml/min/1.73 m² in African Americans. Given the disproportionate burden of renal dysfunction in the African American community, future investigations should focus on the relation of CRP to the development and progression of renal disease and whether lower CRP in longitudinal studies predict improvement in renal function over time. Such findings would suggest that CRP as a marker of systemic inflammation may serve as a potential target for treatment and prevention. Research into genetic factors contributing to CRP variation in African Americans may also provide further understanding of how systemic inflammation relates to renal dysfunction in this group [36].

**References**


**Abbreviations**

BMI denotes body mass index; CKD denotes chronic kidney disease; CRP denotes C-reactive protein; CVD denotes cardiovascular disease; eGFR represents estimated glomerular filtration rate; MDRD: Modification of Diet in Renal Disease; UACR denotes urinary albumin to creatinine ratio.

**Acknowledgements**

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**Authors’ contributions**

EF conceived the study and participated in the design and drafted the manuscript. EB participated in the design of the study and revised the manuscript critically for important intellectual content, DA participated in the design of the study and performed the statistical analysis, HN and JT both participated in the design of the study and drafted the manuscript, MS performed assays on CRP and contributed to revising the manuscript for important intellectual content, AS, MF and CF each participated in the design and revised the manuscript critically for important intellectual content, EA derived key variables important for statistical analysis and participated in the design of the manuscript, RG made significant changes to the statistical analysis section and drafted of the manuscript and HT contributed by making critical revisions to the manuscript for intellectual content. All authors read and approved the final manuscript.

**Competing interests**

The authors declare that they have no competing interests.

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**Additional file 1: Summary Results of Additional Sub-analysis**

Additional sub-analysis was performed examining the association between CRP (log transformed) and CKD status by means of linear regression models. Two set of linear regression models were derived, the first was age and sex-adjusted and the second was multivariable adjusted. CKD status was categorized into normal (eGFR ≥ 90 and absence of albuminuria) and CKD Stages 1 (eGFR ≥ 90 and presence of albuminuria), 2 (60 ≤ eGFR ≥ 89 and presence of albuminuria), and 3 (30 ≤ eGFR ≤ 59). P trend was computed to assess the linear trend in the levels of CRP as one progress from normal to Stage 3 of CKD. Results of the analysis are summarized below (see Table S2a). The geometric means (± standard error) and confidence intervals for the various categories of CKD status are provided in a Table S2a, entitled “Association of C-Reactive Protein with Chronic Kidney Disease (ml/min/1.73 m²)”.

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