Title

How Clinically Relevant Is C-Reactive Protein for Blacks with Metabolic Syndrome to Predict Microalbuminuria?

Journal

Metabolic Syndrome and Related Disorders, 19(1)

ISSN

1540-4196

Authors

Sinha, Satyesh K
Shaheen, Magda
Singh, Vikash R
et al.

Publication Date

2021-02-01

DOI

10.1089/met.2019.0121

Peer reviewed

METABOLIC SYNDROME AND RELATED DISORDERS
Volume 19, Number 1, 2021

Pp. 39–47
DOI: 10.1089/met.2019.0121

How Clinically Relevant Is C-Reactive Protein for Blacks with Metabolic Syndrome to Predict Microalbuminuria?

Satyesh K. Sinha, PhD,[1,2] Magda Shaheen, PhD, MPH, MS,[1,2] Vikash R. Singh, MPhil,[3]
Tripathi B. Rajavashisth, PhD,[1,4] Deyu Pan, MS,[2] Ling Sun, MD,[5]
Keith C. Norris, MD, PhD,[1] and Susanne B. Nicholas, MD, MPH, PhD[1]

Abstract

Background: The metabolic syndrome (MetS) is associated with elevated urinary albumin (UA) excretion and C-reactive protein (CRP). However, potential differences in CRP levels on the association between individual components of the MetS and microalbuminuria (MA; 30–300 μg/mL) and/or UA (0–300 μg/mL) by race/ethnicity is unknown.
Methods: We analyzed National Health and Nutrition Examination Surveys (NHANES) data, (1999–2010) for adults (≥20 years of age) with the MetS ($N = 5700$). The Sobel–Goodman mediation test examined the influence of CRP on the association between individual MetS components and both MA and UA by race/ethnicity. We applied machine learning models to predict UA.
Results: CRP mediated the association between waist circumference (WC) and MA in Whites and Hispanics but not in Blacks. However, in general, the proportion of the total effect of MetS components on UA, mediated by CRP, was: 11% for high-density lipoprotein cholesterol (HDL-C) and 40% for WC ($P < 0.001$). In contrast to MA, the mediation effect of CRP for WC and UA was highest for Blacks (94%) compared with Whites (55%) or Hispanics (18%), $P < 0.05$. The prediction of an elevated UA concentration was increased in Blacks ($\sim$51%) with the MetS when CRP was added to the random forest model.
Conclusions: CRP mediates the association between UA and both HDL-C and WC in Whites and Blacks and between UA and WC in Hispanics. Moreover, the machine learning approach suggests that the incorporation of CRP may improve model prediction of UA in Blacks. These findings may favor screening for CRP in persons with the MetS, particularly in Blacks.

Keywords: CRP, metabolic syndrome, urinary albumin, race, ethnicity

Introduction

The metabolic syndrome (MetS) is a serious health condition that affects more than 25% of adults in the United States (US)[1] and places them at higher risk of premature cardiovascular disease (CVD) and chronic kidney disease (CKD).[2–4] Prevalence of the MetS among US adults varies by race/ethnicity and sex.[1,5] For instance, in the Northern Manhattan Study, appearance of the MetS among racial/ethnic groups was higher in Hispanics compared with Whites or Blacks and its association with stroke risk was greater among women than men.[5]

Several studies have shown that the MetS is associated with microalbuminuria (MA),[6,7] which is an early clinical marker of CKD[8,9] and an independent risk for CVD.[8] A rise in the risk of MA with increasing MetS traits has been reported.[10,11] Some recent studies have found that elevated urinary albumin (UA) levels, even in the normal range, were also associated with MetS and cardiometabolic risk factors,[12–16] challenging the notion that ACR <30 μg/mg is synonymous with ''normal'' albumin excretion.[17]

Inflammation has been posited as an important link between the MetS and MA and may represent a triggering factor in the genesis of the MetS. In support of this, several

[1]Department of Medicine, David Geffen School of Medicine, University of California Los Angeles, Los Angeles, California, USA.
[2]Department of Internal Medicine, Charles R. Drew University of Medicine and Science, Los Angeles, California, USA.
[3]Datareach LLC, Los Angeles, California, USA.
[4]Molecular Biology Unit, Institute of Medical Sciences, Banaras Hindu University, Varanasi, India.
[5]Division of Nephrology, Xuzhou Central Hospital, Medical College of Southeast University, Xuzhou, China.

studies have shown that inflammation, as measured by C-reactive protein (CRP) is associated with the MetS,[18,19] whereas others found a significant correlation between CRP and MA itself.[20,21] In a multivariate analysis, Kshirsagar et al. reported an association between elevated CRP levels and MA in National Health and Nutrition Examination Surveys (NHANES), 1999 to 2004 dataset (odds ratio [OR] = 1.33, 95% CI = 1.08–1.65, $P = 0.009$).[20] Similarly, serum CRP levels were found to be a significant predictor for MA (OR = 1.35, 95% CI = 1.06–1.73; $P < 0.05$ for men: OR = 1.23, 95% CI = 1.03–1.47; $P < 0.05$ for women) in a Japanese population.[21]

Exploring the inter-relationships between individual components of the MetS, MA (30–300 μg/mL) and UA (0–300 μg/mL), as well as inflammation may identify potential causal pathways and determine differences by race/ethnicity. Therefore, the aim of this study is to assess the clinical utility of CRP for the prediction of MA (''including within the clinically defined normal range'') in patients with the MetS from different racial/ethnic groups.

Methods

Study population

The study included participants from NHANES 1999 to 2010, conducted by the National Center for Health Statistics (NCHS) of the Centers for Disease Control and Prevention (CDC). The NHANES sample was recruited using a multistage, stratified probability sampling design ($N = 64,356$) and employed oversampling of the elderly ($N = 9877$), Blacks ($N = 14,955$), and Hispanics ($N = 20,667$). NHANES combined race/ethnicity as one variable. The survey was designed to produce results that are representative of the civilian, noninstitutionalized U.S. population. The participants were interviewed at home and were invited to attend the mobile examination center, where they were asked to complete additional questionnaires, to undergo various examinations, and to provide a blood sample. Descriptions of the survey, sampling procedures, and details of the laboratory tests evaluated can be found on the CDC website (www.cdc.gov/nchs/nhanes/nh3rrm.htm#refman).

The analysis was limited to adults ≥20 years with the MetS. We selected to use the Adult Treatment Panel III (ATP III) definition for diagnosis of the MetS, which provides waist circumference (WC) for males and females. Using the ATP III clinical criteria for the MetS, subjects were classified as having the MetS if they had at least three of the following components: abdominal obesity defined by increased WC (≥40 inches for men or ≥35 inches for women), elevated serum triglyceride (TG) levels (≥150 mg/dL), reduced levels of high-density lipoprotein cholesterol (HDL-C; men ≤40 mg/dL, women ≤50 mg/dL), elevated blood pressure (BP; ≥130 mmHg systolic or ≥85 mmHg diastolic), or fasting plasma glucose (FPG; ≥110 mg/dL).

The total analytic sample was 5700 adults with the MetS. There were some missing data in the study sample, which were different for each variable, ranging from 14 to 36. The number of imputations for WC, estimated glomerular filtration rate (eGFR), hemoglobin A1c (HbA1c), FPG, uric acid, and white blood cell (WBC) were 36, 22, 14, 21, 21, and 15, respectively. To minimize the effect of missing data and increase the power of our study, we imputed for missing data at random (in STATA) for these observed data. In particular, we compared three methods: single unit (certainty), single unit (scaled), and single unit (centered) and observed minimal differences. As such, we used the single unit (centered) option as it is the most conservative method among these three. Since the dataset is publicly available and not considered a protected health information, it is exempt from the need for approval for Human Subjects Research.

Study variables

The dependent variables were UA and MA. The main independent variables were MetS components: WC, elevated TG, reduced HDL-C level, elevated BP, and elevated FPG. The other independent variables were age in years, gender, race/ethnicity, education [<= high school, college and up], smoking status [never, past and current smokers], alcohol intake [yes/no], CVD comorbidity [yes/no (including stroke, heart attack, and coronary heart disease)], low-density lipoprotein cholesterol (LDL-C), total cholesterol, inflammatory markers (CRP, uric acid, WBC), and eGFR.

Data analysis

We analyzed the data using descriptive statistics to depict the sample characteristics and tested the normality of the distribution of the continuous variables. The normality was tested using histograms with normal distribution and the Shapiro–Wilk test for normality. Bivariate analysis of the categorical variables was conducted using the chi-squared test. For continuous variables with normal distribution (variables without normal distribution were log transformed), we used *t*-test for comparison of two groups and analysis of variance for comparing three or more groups. We used multiple logistic regression to assess the independent relationship between individual MetS components and MA adjusting for demographics (age, gender, and race/ethnicity) and eGFR. We fit a logistic model for all the MetS components to determine the association of each component, adjusting for the other components as well as the other confounding variables.

To test for the effect modification of the relationship by CRP, we included the interaction of CRP with each component of the MetS in the multiple regression model and tested the significance of the interaction term. Data were presented as adjusted odds ratio and 95% confidence interval (CI). *P* value <0.05 was considered statistically significant.

We performed the Sobel–Goodman mediation test to examine the extent of how CRP influenced the effect of individual MetS components on MA for the total population and for each racial/ethnic group; and the extent of how CRP influenced the effect of MetS components on the level of UA as a continuous variable for the total population and for each racial/ethnic group. We estimated the indirect effect, direct effect, total effect, and the proportion of the total effect mediated by CRP.

Data were analyzed using SAS (Release V.9.4, 2002–2012; SAS, Inc.) and the survey module of STATA (Release V.14, 1984e2007 Statistics/Data Analysis; StataCorp) taking into consideration the sample weights and sample design. Sample weights, provided by the NCHS, were used to correct for differential selection probabilities and to adjust for noncoverage and nonresponse.

Table 1. Demographic and Clinical Characteristics of Participants (≥20 Years of Age) with the Metabolic Syndrome, Based on Normoalbuminuria and Microalbuminuria

	Total (n = *5700*)	*Normoalbuminuria (UA <30 μg/mL)* (n = *4583; 84.7%*)	*Microalbuminuria (UA 30–300 μg/mL)* (n = *1117; 15.3%*)	P-*value*
Age	55.2 ± 15.5	54.5 ± 15.7	59.2 ± 14.0	<0.001
Sex				
Male	2801 (49.8%)	2174 (48.7%)	627 (55.7%)	0.008
Female	2899 (50.2%)	2409 (51.3%)	490 (44.4%)	
Race/ethnicity				
Whites	3073 (78.3%)	2545 (79.8%)	528 (70.4%)	<0.001
Blacks	1026 (9.9%)	772 (9.0%)	254 (14.9%)	
Hispanics	1601 (11.8%)	1266 (11.2%)	335 (14.7%)	
Education				
≤High school	3488 (52.8%)	2766 (51.7%)	722 (59.1%)	0.001
College and up	2200 (47.2%)	1808 (48.3%)	392 (40.9%)	
Smoking				
Never smoked	2708 (47.5%)	2217 (48.2%)	491 (43.6%)	0.151
Past smoker	1919 (32.6%)	1508 (32.1%)	411 (35.2%)	
Current smoker	1069 (19.9%)	854 (19.7%)	213 (21.2%)	
Alcohol				
No	3740 (82.4%)	3038 (82.7%)	702 (80.7%)	0.285
Yes	874 (17.6%)	695 (17.3%)	179 (19.3%)	
CVD				
No	4674 (85.0%)	3826 (86.2%)	848 (77.9%)	<0.001
Yes	1026 (15.0%)	757 (13.8%)	269 (22.1%)	
MetS components				
Elevated TG				
No	1348 (23.5%)	1080 (23.5%)	268 (23.5%)	
Yes	4352 (76.5%)	3503 (76.5%)	849 (76.5%)	0.988
Reduced HDL-C				
No	2872 (47.8%)	2298 (48.0%)	574 (46.7%)	
Yes	2828 (52.2%)	2285 (52.0%)	543 (53.3%)	0.582
Elevated BP (or taking medications)				
No	1214 (24.4%)	1068 (25.8%)	146 (16.5%)	<0.001
Yes	4486 (75.6%)	3515 (74.2%)	971 (83.5%)	
Elevated FPG (or taking Medications)				
No	1181 (23.9%)	1022 (25.4%)	159 (15.9%)	<0.001
Yes	4519 (76.1%)	3561 (74.6%)	958 (84.1%)	
WC				
No	802 (12.7%)	657 (12.9%)	145 (11.3%)	0.280
Yes	4898 (87.3%)	3926 (87.1%)	972 (88.7%)	
Clinical variables				
TG (mg/dL)	191.8 ± 163.3	188.6 ± 145.7	209.5 ± 220.8	0.065
HDL-C (mg/dL)	46.6 ± 13.6	46.8 ± 13.9	45.6 ± 12.5	0.081
BP (mmHg)				
Systolic	129.2 ± 18.3	128.2 ± 18.0	134.7 ± 18.6	<0.001
Diastolic	72.9 ± 14.2	71.9 ± 14.2	71.6 ± 14.1	0.722
FPG (mg/dL)	118.4 ± 41.7	115.0 ± 36.7	137.2 ± 55.1	<0.001
WC (cm)	108.3 ± 13.8	107.7 ± 13.6	111.6 ± 14.0	<0.001
UA (μg/mL)	20.7 ± 35.4	9.4 ± 6.7	83.2 ± 50.9	<0.001
eGFR (mL/min/1.73 m^2)	75.7 ± 19.4	76.0 ± 19.3	74.4 ± 19.9	0.091
HbA1c (%)	5.9 ± 1.1	5.8 ± 1.0	6.5 ± 1.5	<0.001
LDL-C (mg/dL)	118.3 ± 37.2	119.7 ± 37.9	109.8 ± 33.5	<0.001
Total cholesterol (mg/dL)	201.4 ± 44.7	202.8 ± 44.6	193.8 ± 44.5	0.003
BMI (kg/m^2)	32.0 ± 6.2	31.9 ± 6.2	33.0 ± 6.3	0.002
Inflammatory markers				
CRP (mg/dL)	0.5 ± 0.8	0.5 ± 0.8	0.7 ± 1.1	<0.001
Uric acid (mg/dL)	6.0 ± 1.4	5.9 ± 1.4	6.1 ± 1.3	0.012
WBC count ($10^3/\mu L$)	7.1 ± 2.2	7.1 ± 2.2	7.4 ± 2.2	0.024

UA, urinary albumin; CVD, cardiovascular disease (including stroke, heart attack, and coronary heart disease); TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; BP, blood pressure; FPG, fasting plasma glucose; WC, waist circumference; eGFR, estimated glomerular filtration rate; HbA1c, hemoglobin A1c; LDL-C, low-density lipoprotein cholesterol; BMI, body mass index; CRP, C-reactive protein; WBC, white blood cell.

Machine learning models

Machine learning models were created using Python's Sci-kit Learn library, one of the most popular open source frameworks for developing machine learning models. Linear regression models were built using the default framework parameters, while the random forest model was built using 100 estimators along with default parameters. The models were created for each of the racial/ethnic subgroups both including and excluding CRP as a feature, along with WC, TG, HDL-C, systolic and diastolic BP, and FPG. Ten-fold crossvalidation was performed for each model, and the change in the coefficient of determination (R^2) was calculated between the predicted values and observed values (UA concentration) over all of the testing set samples.

Results

Overall study population characteristics

Of the 5700 subjects with the MetS and normoalbuminuria or MA, and complete data, the average age was 55.2 ± 15.5 years. MA status varied significantly by age, sex, race/ethnicity, education, history of CVD, elevated BP, and FPG level ($P<0.05$). Overall, 76.5% had elevated TG; 52.2% had reduced HDL-C levels; 75.6% had elevated BP; 76.1% had elevated FPG, and 87.3% had central obesity. Clinically, patients with MA had significantly higher levels of systolic BP, FPG, higher WC, UA, HbA1c, LDL-C, total cholesterol, and BMI, as well as the inflammatory markers: CRP, uric acid, and WBC, $P<0.05$ (Table 1).

CRP is not an effect modifier except in Hispanics with reduced HDL-C

In a multivariable analysis, we found that the association between individual MetS components and MA differed by racial/ethnic group. Overall, every component of the MetS, except elevated TG and increased WC, was associated with MA ($P<0.05$). When examined by race/ethnicity, MA was associated with elevated FPG and reduced HDL-C in Whites ($P<0.05$), while with increased WC, elevated BP, elevated TG, and reduced HDL-C in Hispanics ($P<0.05$). However, there was no association observed in Blacks. None of the interaction terms of MetS components and CRP was statistically significant in the overall sample and by race/ethnicity, except in Hispanics where the interaction of CRP and reduced HDL-C was statistically significant, which indicated that CRP is an effect modifier in Hispanics with reduced HDL-C but not an effect modifier in Whites and Blacks (Table 2).

CRP mediates the association between MetS components and UA

As reported above, in the multivariate model, CRP, as well as WC, BP, FPG, and HDL-C, were independent predictors of MA, but CRP was not an effect modifier except in Hispanics with reduced HDL-C. We then performed the Sobel–Goodman mediation test to examine the extent of how CRP influenced the effect of individual MetS components on MA (mediation effects). Our results showed that the proportion of the total effect of the MetS components on MA, mediated by CRP, was: 7% for HDL-C ($z=2.970$,

Table 2. Adjusted Odds Ratio and 95% Confidence Interval of the Relationship Between Microalbuminuria and Individual Metabolic Syndrome Components ($N=5700$)

	Total *AOR* *(95% CI)*	P-*value*	*Whites* *AOR* *(95% CI)*	P-*value*	*Blacks* *AOR* *(95% CI)*	P-*value*	*Hispanics* *AOR* *(95% CI)*	P-*value*
Increased WC	1.32 (0.95–1.84)	0.098	1.23 (0.80–1.89)	0.332	1.64 (0.78–3.44)	0.185	2.50 (1.54–4.07)	<0.001
Elevated BP	1.62 (1.13–2.33)	0.009	1.9 (0.95–2.33)	0.081	1.71 (0.65–4.49)	0.272	2.30 (1.51–3.49)	<0.001
Elevated FPG	1.84 (1.35–2.53)	<0.001	2.11 (1.41–3.15)	<0.001	1.17 (0.56–2.44)	0.666	1.39 (0.93–2.07)	0.102
Elevated TG	1.19 (0.83–1.68)	0.338	1.12 (0.69–1.81)	0.636	1.37 (0.84–2.21)	0.202	1.78 1.13–2.83)	0.015
Reduced HDL-C	1.46 (1.11–1.92)	0.007	1.62 (1.32–2.37)	0.007	1.00 (0.59–1.68)	0.998	1.45 (1.04–2.01)	0.029
CRP	2.10 (0.59–7.41)	0.246	1.26 (0.25–6.32)	0.781	1.95 (0.22–17.02)	0.539	11.89 (2.08–67.99)	0.006
Interactions								
Reduced HDL-C and CRP	0.99 (0.68–1.45)	0.994	1.34 (0.83–2.15)	0.223	0.69 (0.31–1.54)	0.358	0.41 (0.23–0.72)	0.003
Elevated BP and CRP	0.93 (0.56–1.55)	0.783	0.90 (0.48–1.71)	0.755	1.84 (0.50–6.74)	0.349	0.76 (0.41–1.42)	0.388
Increased WC and CRP	1.15 (0.54–2.42)	0.717	1.55 (0.60–4.00)	0.363	0.69 (0.17–2.81)	0.596	0.45 (0.12–1.64)	0.222
Elevated FPG and CRP	0.72 (0.42–1.21)	0.212	0.68 (0.31–1.49)	0.336	0.86 (0.34–2.15)	0.740	0.90 (0.47–1.72)	0.745
Elevated TG and CRP	0.77 (0.46–1.31)	0.340	0.82 (0.38–1.75)	0.597	0.58 (0.26–1.28)	0.171	0.74 (0.34–1.60)	0.439

Reference group; normoalbuminuria.

Model: adjusted for age, sex, other components of the MetS, estimated glomerular filtration rate (eGFR), and inflammatory makers (uric acid, white blood cells).

AOR, adjusted odds ratio.

$P=0.003$) and 4% for FPG ($z=2.225$, $P=0.026$), and 15% for WC ($z=3.465$, $P=0.001$). The mediation effect of CRP for WC and MA was significant in Whites (10%, $z=2.078$, $P=0.038$) and Hispanics (16%, $z=2.196$, $P=0.028$), but in Blacks it did not reach statistical significance, despite having the highest effect (Table 3a). However, when the analysis was performed to evaluate the mediation effect between individual components of the MetS and UA, we observed that the proportion of the total effect of MetS components on UA (0–300 μg/mL), mediated by CRP, was: 11% for HDL-C ($z=3.610$, $P<0.001$) and 40% for WC ($z=4.857$, $P<0.001$). These levels varied by race/ethnicity. The mediation effect of CRP for WC and UA was highest for Blacks (94%, $z=2.155$, $P=0.030$), compared with Whites (55%, $z=3.831$, $P<0.001$) or Hispanics (18%, $z=2.316$ $P=0.007$) (Table 3b). This suggests that Blacks, with increased WC, are differently affected by CRP in terms of UA level.

CRP increases the predictive value of MetS in predicting UA, particularly in blacks

We used both linear regression and random forest models to predict UA concentration in all racial/ethnic groups using MetS components both with and without CRP as a feature. The coefficient of determination (R^2) was the highest for Blacks in both models. In the linear regression model, the R^2 value was 0.064, 0.061, and 0.113 in Whites, Blacks, and Hispanic, respectively. The addition of CRP in the model increased the R^2 the most in Blacks (0.072, 18.96%) followed by Whites (0.068, 7.22%) and Hispanics (0.113, 0.39%). Similarly, addition of CRP in the random forest model increased R^2 highest in Blacks (51.87%) followed by Whites (18.79%), while there was no effect in Hispanics (Table 4). This indicates that CRP is more sensitive as a predictor of UA in Blacks with MetS.

Discussion

We reported in this study for the first time that: (a) CRP, as a measure of inflammation, mediates the association between individual components of the MetS and UA levels (0–300 μg/mL) differently by racial/ethnic group, and (b) the addition of CRP strengthened the predictive value of the MetS (for UA) in Blacks.

Our results, from a nationally representative sample of the noninstitutionalized US population, are divergent from findings of other studies that examined independent aspects of this association. For example, Stuveling et al. found that CRP modified the relationship between BP and MA in a sample of nearly 9000 inhabitants in the Netherlands with a positive interaction that was significant for persons with a mean arterial pressure ≥90 mmHg, but not for those with a mean arterial pressure <90 mmHg.[22] Ridker et al. who analyzed nearly 15,000 participants in the Women's Health Study found that higher CRP levels were associated with

Table 3a. Sobel–Goodman Test for Mediation of C-Reactive Protein to the Relationship Between Microalbuminuria and Individual Metabolic Syndrome Components

			Total population						
Independent variable-mediator outcome	*Indirect effect (SE)*	P-*value*	*Direct effect (SE)*	P-*value*	*Total effect (SE)*	P-*value*	*Proportion of total effect mediated (%)*	*Sobel Z-test*	P *value*
HDL-CRP-MA	0.004 (0.001)	0.003	0.053 (0.015)	<0.001	0.057 (0.015)	<0.001	0.069 (07)	2.970	0.003
BP-CRP-MA	0.001 (0.001)	0.284	0.053 (0.017)	0.002	0.053 (0.017)	0.002	0.021 (02)	1.071	0.284
FPG-CRP-MA	0.003 (0.001)	0.026	0.060 (0.014)	<0.001	0.062 (0.014)	0.540	0.044 (04)	2.225	0.026
TG-CRP-MA	0.002 (0.002)	0.163	0.112 (0.015)	0.467	0.0096 (0.016)	0.540	0.170 (17)	1.397	0.163
WC-CRP-MA	0.007 (0.002)	0.001	0.042 (0.018)	0.018	0.049 (0.018)	<0.001	0.146 (15)	3.465	0.001
Whites									
HDL-CRP-MA	0.003 (0.001)	0.055	0.073 (0.017)	<0.001	0.076 (0.017)	<0.001	0.037 (04)	1.917	0.055
BP-CRP-MA	0.000 (0.001)	0.939	0.037 (0.019)	0.046	0.037 (0.019)	0.049	0.002 (00)	0.077	0.939
FPG-CRP-MA	0.002 (0.001)	0.181	0.066 (0.016)	<0.001	0.068 (0.016)	<0.001	0.023 (02)	1.338	0.181
TG-CRP-MA	0.001 (0.001)	0.234	0.012 (0.020)	0.556	0.010 (0.020)	0.606	0.133 (13)	1.190	0.234
WC-CRP-MA	0.005 (0.002)	0.038	0.039 (0.023)	0.082	0.044 (0.022)	0.051	0.103 (10)	2.078	0.038
Blacks									
HDL-CRP-MA	0.008 (0.006)	0.231	0.030 (0.041)	0.474	0.022 (0.040)	0.586	0.000 (00)	1.197	0.231
BP-CRP-MA	0.005 (0.005)	0.303	0.101 (0.046)	0.027	0.106 (0.046)	0.023	0.000 (00)	1.025	0.305
FPG-CRP-MA	0.006 (0.005)	0.237	0.006 (0.040)	0.873	0.012 (0.040)	0.759	0.475 (48)	1.183	0.237
TG-CRP-MA	0.002 (0.003)	0.424	0.009 (0.040)	0.820	0.011 (0.040)	0.779	0.189 (19)	0.799	0.424
WC-CRP-MA	0.015 (0.012)	0.218	0.058 (0.052)	0.268	0.072 (0.050)	0.148	0.200 (20)	1.233	0.218
Hispanics									
HDL-CRP-MA	0.006 (0.004)	0.165	0.009 (0.029)	0.768	0.015 (0.029)	0.612	0.402 (40)	1.390	0.165
BP-CRP-MA	0.007 (0.005)	0.178	0.094 (0.035)	0.007	0.100 (0.036)	0.005	0.066 (07)	1.347	0.178
FPG-CRP-MA	0.008 (0.006)	0.190	0.047 (0.030)	0.115	0.055 (0.029)	0.106	0.139 (14)	1.312	0.190
TG-CRP-MA	0.003 (0.004)	0.483	0.061 (0.030)	0.046	0.058 (0.031)	0.058	0.049 (05)	0.701	0.483
WC-CRP-MA	0.018 (0.008)	0.028	0.096 (0.033)	0.004	0.113 (0.033)	0.001	0.158 (16)	2.196	0.028

Analyses were adjusted for sex, age, race/ethnicity (for total population), BMI, eGFR, and MetS components.
MetS, metabolic syndrome; MA, microalbuminuria.

Table 3b. Sobel–Goodman Test to Determine Mediation Effect of C-Reactive Protein on Relationship Between Urinary Albumin and Individual Components of the Metabolic Syndrome

Independent variable-mediator outcome	*Total population*								
	Indirect effect (SE)	P-*value*	*Direct effect (SE)*	P-*value*	*Total effect (SE)*	P-*value*	*Proportion of total effect mediated (%)*	*Sobel Z-test*	P *value*
HDL-CRP-UA	0.018 (0.005)	<0.001	0.147 (0.044)	<0.001	0.165 (0.044)	<0.001	0.107 (11)	3.610	<0.001
BP-CRP-UA	0.001 (0.003)	0.658	0.166 (0.051)	0.002	0.164 (0.052)	0.002	0.000 (00)	0.440	0.658
FPG-CRP-UA	0.002 (0.004)	0.701	0.229 (0.042)	<0.001	0.230 (0.042)	<0.001	0.000 (00)	0.380	0.701
TG-CRP-UA	0.007 (0.004)	0.090	0.010 (0.049)	0.783	0.017 (0.049)	0.673	0.048 (05)	1.689	0.090
WC-CRP-UA	0.053 (0.011)	<0.001	0.079 (0.061)	0.345	0.132 (0.059)	0.064	0.400 (40)	4.857	<0.001
Whites									
HDL-CRP-UA	0.018 (0.006)	0.004	0.193 (0.051)	<0.001	0.211 (0.050)	<0.001	0.086 (09)	2.877	0.004
BP-CRP-UA	0.003 (0.004)	0.396	0.110 (0.062)	0.076	0.107 (0.063)	0.091	0.000 (00)	0.849	0.396
FBG-CRP-UA	0.002 (0.005)	0.718	0.254 (0.050)	<0.001	0.256 (0.049)	<0.001	0.007 (00)	0.361	0.718
TG-CRP-UA	0.010 (0.006)	0.076	0.003 (0.064)	0.964	0.013 (0.064)	0.839	0.777 (78)	1.776	0.076
WC-CRP-UA	0.049 (0.013)	<0.001	0.039 (0.076)	0.609	0.088 (0.076)	0.245	0.552 (55)	3.831	<0.001
Blacks									
HDL-CRP-UA	0.032 (0.015)	0.036	0.013 (0.101)	0.890	0.019 (0.102)	0.842	0.000 (00)	2.095	0.036
BP-CRP-UA	0.003 (0.011)	0.821	0.411 (0.126)	<0.001	0.408 (0.127)	<0.001	0.000 (00)	0.226	0.821
FBG-CRP-UA	0.006 (0.008)	0.496	0.099 (0.105)	0.317	0.105 (0.104)	0.285	0.054 (05)	0.680	0.496
TG-CRP-UA	0.003 (0.008)	0.683	0.076 (0.085)	0.335	0.073 (0.084)	0.353	0.000 (00)	0.408	0.683
WC-CRP-UA	0.075 (0.035)	0.030	0.005 (0.119)	0.964	0.790 (0.123)	0.459	0.940 (94)	2.155	0.030
Hispanics									
HDL-CRP-UA	0.005 (0.007)	0.290	0.048 (0.071)	0.416	0.043 (0.070)	0.461	0.000 (00)	0.698	0.290
BP-CRP-UA	0.007 (0.007)	0.243	0.302 (0.083)	<0.001	0.309 (0.081)	<0.001	0.217 (22)	0.914	0.243
FPG-CRP-UA	0.003 (0.008)	0.756	0.164 (0.078)	0.006	0.162 (0.077)	0.007	0.000 (00)	0.311	0.756
TG-CRP-UA	0.001 (0.006)	0.915	0.092 (0.099)	0.226	0.093 (0.099)	0.224	0.006 (00)	0.106	0.915
WC-CRP-UA	0.056 (0.024)	0.007	0.259 (0.084)	<0.001	0.315 (0.088)	<0.001	0.178 (18)	2.316	0.007

Analyses were adjusted for sex, age, race/ethnicity (for total population), BMI, eGFR, and MetS components.
UA, urinary albumin.

increased CVD risk and that the impact was greater with added components of the MetS.[23] Kurella et al. reported a higher risk for CKD with accumulating MetS traits among 10,096 participants in the Atherosclerosis Risk in Communities study, but they studied more advanced stages of CKD and did not examine the role of inflammation.[11] Although, another study, in a cohort of Turkish kidney transplant recipients, demonstrated that the MetS was not related to increased prevalence of MA, even when combined with high CRP.

Table 4. Machine Learning Model's Performance Across Racial/Ethnic Subgroups With and Without C-Reactive Protein

Race	R^2 without CRP	R^2 with CRP	% increase in R^2
Linear regression model			
Whites	0.064	0.068	7.22
Blacks	0.061	0.072	18.96
Hispanics	0.113	0.113	0.39
Random forest model			
Whites	0.038	0.045	18.79
Blacks	0.037	0.056	51.87
Hispanics	0.087	0.076	−12.93

R^2 (coefficient of determination) measures the percentage in variability in the outcome variable (albumin concentration) that can be explained by the predictions of the model.

Our study further differed from these studies in that we examined the association of individual components of the MetS by race/ethnicity and determined the mediation effect of CRP on the association between MetS components and both MA and UA. While considering UA as a categorical outcome (30–300 μg/mL), the mediation effect of CRP on the association between WC and MA was not significant in Blacks. However, when UA was considered as a continuous outcome (0–300 μg/mL), the mediation effect of CRP on the association between WC and UA was greatest in Blacks (94%) compared with Whites or Hispanics. This suggests a different relationship between inflammation and low UA levels in Blacks with the MetS. Vyssoulis and colleagues found that even low-grade UA (*i.e.*, within the normal range) was significantly associated with the prevalence of the MetS in 6650 hypertensive patients.[12] Two studies also showed low-grade UA to be positively associated with the MetS in middle-aged/elderly Chinese and middle-aged Korean men, respectively.[15,16] UA, within the normal range, was associated with the high prevalence of MetS in the Korean population.[24] Increased levels of UA in the normal range, were associated with the development of macroalbuminuria in patients with DM.[23] However, none of these studies examined the mediation effect of inflammation on these associations and thus missing additional insights into a possible mechanistic explanation.

We also examined the effects of uric acid and WBC, as additional markers of inflammation[25] in our studies and found only borderline significance of WBC on MA. Elevated

levels of these inflammatory markers have been previously examined in NHANES III analysis and showed positive and independent association with insulin resistance.[26] Other studies have suggested that uric acid may cause microvascular complications through endothelial dysfunction and may induce the inflammatory cascade, including increased CRP levels.[27] On the other hand, uric acid may also act as an antioxidant and elevated plasma uric acid has been associated with providing a compensatory role in response to increased oxidative stress in CVD.[28,29] Based on these prior reports we adjusted for both uric acid and WBC in the multivariate analyses.

Recent investigations support the notion that chronic inflammation may be a common etiological mechanism in the MetS[30,31] and that adipose tissue macrophages (ATMs) may play a central role in coordinating the metabolic and inflammatory aspects of MetS.[32,33] Higher WC, elevated BP, and reduced HDL-C are often accompanied by low-grade systemic inflammation and these apparently disparate phenomena are linked by ATMs.[30,34,35] Adipocytes are known to secrete proinflammatory cytokines and chemokines, as well as CRP.[36–38] The proinflammatory ATMs may significantly increase the adipose tissue production of these proinflammatory and acute-phase molecules, and thereby contribute to the pathophysiological consequences of obesity.[39] Adipocytes contribute to HDL-C levels through the ATP-binding cassette transporter 1-mediated cholesterol efflux,[40] which declines with the increase in central obesity.[41] HDL-C has potent anti-inflammatory properties that can significantly be decreased with impaired adipocytes in obesity.[42] Although, this is an epidemiological study and we cannot directly implicate these findings into our discussion, they provide possible mechanisms through which inflammation might contribute to the related pathology in patients with MetS, like CVD and CKD. Therefore, in combination with these previous basic findings, our epidemiological outcomes provide a foundation to explore the benefits of the treatment of inflammation in patients with MetS, especially in Blacks, to reduce the possibility of progression to advanced CKD.

Limitations and strengths of the study

This is a cross-sectional study and can provide only associations and not causation. Despite the efforts of NHANES to enroll a random representative noninstitutionalized sample of the US population, persons attending the study visits may differ from those not attending in subtle ways that may affect the results of this study and the generalizability of the findings. Although we tried to control for potentially confounding variables, there is still a possibility of residual confounding. Furthermore, data on risk factors were ascertained only at baseline; therefore, we could not systematically control for differences in the severity of risk factors over time. While CRP is a widely used marker of inflammation, the test is not established to be highly sensitive or specific to CKD and the lack of data on other inflammatory markers, such as interleukins and TNF-α,[43] may limit our ability to interpret a broader assignment of inflammation to the observed effects on the association of components of MetS and MA. Because only a single urine sample (and not replicates) was used to assess the persistence of UA, we may have overestimated its prevalence.[44] Furthermore, data regarding prior history of CKD, not due to DM were not available for the study population, therefore, these data were not included. One important limitation is the small sample size of Blacks, which could affect the internal validity of the results. Balanced against these limitations, the strength of this study lies in the analysis for CRP (the most widely used clinical marker for inflammation) and numerous covariates in a large nationwide population-based sample, which includes a well-validated approach to interviews, laboratory, and physical examination. For the predictive models, we generally observe lower R^2 values, since there is a multitude of factors that can contribute to the UA concentration, which are not captured by the components of MetS and CRP.

Conclusion

Taken together, these findings suggest that CRP mediates the association between WC and UA more strongly in Blacks followed by Whites and then Hispanics, and thus may be an early marker for the onset of CKD and/or CVD in patients with the MetS.

Our predictive models also suggest that CRP increased the ability of the MetS to predict UA concentration in Blacks suggesting that it is more important in this racial/ethnic group. Indeed, in the clinical setting, screening for CRP in Blacks with MetS seems to be important even if their UA falls within the normal range. In summary, our data support the future study of inflammation as a potential target in the management of the MetS and its consequences with coexisting UA, especially in Black patients. Prospective studies are needed to validate the potential causality of these associations.

Author Disclosure Statement

V.R.S. is CEO of Datareach LLC, a California-based company actively involved in the area of artificial intelligence and health care. This research was done as a collaboration with Datareach LLC, with no external commercial interests. The other authors declare no conflicts of interest.

Funding Information

Research reported in this publication/press was supported by the National Institute on Minority Health and Health Disparities of the National Institutes of Health under award number U54MD008149 (RTRN small grant program to S.K.S.). S.B.N. was supported by NIH UL1TR000124. T.B.R. was supported by a Ramalingaswami Fellowship from the Department of Biotechnology, GOI. K.C.N. was supported by NIH grants UL1TR000124 and P30AG021684.

References

1. Beltrán-Sánchez H, Harhay MO, Harhay MM, et al. Prevalence and Trends of Metabolic Syndrome in the Adult U.S. Population, 1999–2010. *J Am Coll Cardiol* 2013;62:697–703.
2. Agrwal S, Shlipak MG, Kramer H, et al. The Association of Chronic Kidney Disease and Metabolic Syndrome with Incident Cardiovascular Events: Multiethnic Study of Atherosclerosis. *Cardiol Res Pract* 2012;2012:806102.
3. Hao Z, Konta T, Takasaki S, et al. The Association between Miroalbuminuria and Metabolic Syndrome in the General

Population in Japan: The Takahata Study. *Intern Med* 2007; 46:341–346.
4. Reaven GM. Role of insulin resistance in human disease. *Diabetes* 1988;37:1595–1607.
5. Boden-Albala B, Sacco RL, Lee HS, et al. Metabolic syndrome and ischemic stroke risk: Northern Manhattan Study. *Stroke* 2008;39:30–35.
6. Palaniappan L, Carnethon M, Fortmann SP. Association between microalbuminuria and the metabolic syndrome: NHANESIII. *Am J Hypertens* 2003;16:952–958.
7. Lin CC, Liu CS, Li TC, et al. Microalbuminuria and the metabolic syndrome and its components in the Chinese population. *Eur J Clin Invest* 2007;37:783–790.
8. Stehouwer Coen DA, Smulders YM. Microalbuminuria and risk for cardiovascular disease: Analysis of potential mechanisms. *JASN* 2007;17:2106–2111.
9. Raikou VD, Gavriil S. Metabolic syndrome and chronic renal disease. *Diseases* 2018,24:6.
10. Chen J, Muntner P, Hamm LL, et al. The metabolic syndrome and chronic kidney disease in U.S. adults. *Ann Intern Med* 2004:140:167–174.
11. Kurella M, Lo JC, Chertow GM. Metabolic syndrome and the risk for chronic kidney disease among nondiabetic adults. *J Am Soc Nephrol* 2005;16:2134–2140.
12. Vyssoulis G, Karpanou E, Spanos P, et al. Urine albumin excretion, within normal range, reflects increasing prevalence of metabolic syndrome in patients with essential hypertension. *J Clin Hypertens (Greenwich)* 2010;12:597–602.
13. Li MF, Tu YF, Li LX, et al. Low-grade albuminuria is associated with early but not late carotid atherosclerotic lesions in community-based patients with type 2 diabetes. *Cardiovasc Diabetol* 2013,12:110.
14. Janssen WM, Hillege H, Pinto-Sietsma SJ, et al. Low levels of urinary albumin excretion are associated with cardiovascular risk factors in the general population. *Clin Chem Lab Med* 2000;38:1107–1110.
15. Oh CM, Park SK, Kim HS, et al. High-normal albuminuria predicts metabolic syndrome in middle-aged Korean men: A prospective cohort study. *Maturitas* 2014;77:149–154.
16. Zhang J, Chen Y, Xu Y, et al. Low-grade albuminuria is associated with metabolic syndrome and its components in middle-aged and elderly Chinese population. *PLoS One* 2013;8:e65597.
17. Arnlov J, Evans JC, Meigs JB, et al. Low-grade albuminuria and incidence of cardiovascular disease events in nonhypertensive and nondiabetic individuals: The Framingham Heart Study. *Circulation* 2005;112:969–975.
18. Voils SA, Cooper-DeHoff RM. Association between high sensitivity C-reactive protein and metabolic syndrome in subjects completing the National Health and Nutrition Examination Survey (NHANES) 2009–10. Diabetes & Metabolic Syndrome: *Clin Res Rev* 2014;8: 88–90.
19. Sigdel M, Kumar A, Gyawali P, et al. Association of high sensitivity C-reactive protein with the components of metabolic syndrome in diabetic and non-diabetic individuals. *J Clin Diagn Res* 2014;8:CC11–CC13.
20. Kshirsagar AV, Bomback AS, Bang H, et al. Association of C-reactive protein and microalbuminuria (from the National Health and Nutrition Examination Surveys, 1999 to 2004). *Am J Cardiol* 2008;101:401–406.
21. Nakamura M, Onoda T, Itai K, et al. Association between serum C-reactive protein levels and microalbuminuria: A population-based cross-sectional study in northern Iwate, Japan. *Intern Med* 2004;43:919–925.
22. Stuveling EM, Bakker SJ, Hillege HL, et al. C-reactive protein modifies the relationship between blood pressure and microalbuminuria. *Hypertension* 2004;43:791–796.
23. Ridker PM, Buring JE, Cook NR, et al. C-reactive protein, the metabolic syndrome, and risk of incident cardiovascular events: An 8-year follow-up of 14719 initially healthy American women. *Circulation* 2003;107:391–397.
24. Park S-Y, Park Y-K, Cho K-H, et al. Normal Range Albuminuria and Metabolic Syndrome in South Korea: The 2011–2012 Korean National Health and Nutrition Examination Survey. *PLoS One* 2015;10:e0125615.
25. Yoon SS, Dillon CF, Carroll M, et al. Effects of statins on serum inflammatory markers: the U.S. National Health and Nutrition Examination Survey 1999-2004. *J Atheroscler Thromb* 2010;17:1176–1182.
26. Chen J, Wildman RP, Hamm LL, et al. Association between inflammation and insulin resistance in U.S. nondiabetic adults: Results from the Third National Health and Nutrition Examination Survey. *Diabetes Care* 2004;27: 2960–2965.
27. Jalal DI, Maahs DM, Hovind P, et al. Uric acid as a mediator of diabetic nephropathy. *Semin Nephrol* 2011;31: 459–465.
28. Nieto FJ, Iribarren C, Gross MD, et al. Uric acid and serum antioxidant capacity: A reaction to atherosclerosis? *Atherosclerosis* 2000;148:131–139.
29. Sautin YY, Johnson RJ. Uric acid: The oxidant-antioxidant paradox. *Nucleosides Nucleotides Nucleic Acids* 2008;27: 608–619.
30. Hotamisligil GS. Inflammation and metabolic disorders. *Nature* 2006;444:860–867.
31. Marsland AL, McCaffery JM, Muldoon MF, et al. Systemic inflammation and the metabolic syndrome among middle-aged community volunteers. *Metabolism* 2010;59:1801–1808.
32. Weisberg SP, McCann D, Desai M, et al. Obesity is associated with macrophage accumulation in adipose tissue. *J Clin Invest* 2003;112:1796–1808.
33. Xu H, Barnes GT, Yang Q, et al. Chronic inflammation in fat plays a crucial role in the development of obesity-related insulin resistance. *J Clin Invest* 2003;112:1821–1130.
34. Boschmann M, Engeli S, Adams F, et al. Adipose tissue metabolism and CD11b expression on monocytes in obese hypertensives. *Hypertension* 2005;46:130–136.
35. He J, Xu X, Francisco A, et al. Markers of adipose tissue macrophage content are negatively associated with serum HDL-C concentrations. *Atherosclerosis* 2011;215: 243–246.
36. Charrière G, Cousin B, Arnaud E, et al. Preadipocyte conversion to macrophage; evidence of plasticity. *J Biol Chem* 2003;278:9850–9855.
37. Hotamisligil GS, Shargill NS, Spiegelman BM. Adipose expression of tumor necrosis factor-alpha: direct role in obesity-linked insulin resistance. *Science* 1993;259:87–91.
38. Visser M, Bouter LM, McQuillan GM, et al. Elevated C-reactive protein levels in overweight and obese adults. *JAMA* 1999;282:2131–2135.
39. Fuentes L, Roszer T, and Ricote M. Inflammatory mediators and insulin resistance in obesity: Role of nuclear receptor signaling in macrophages. *Mediators Inflamm* 2010; 2010:219583.

40. McGillicuddy FC, Reilly MP, Rader DJ. Adipose modulation of high-density lipoprotein cholesterol: Implications for obesity, high-density lipoprotein metabolism, and cardiovascular disease. *Circulation* 2011;124:1602–1605.
41. M Xu M, Zhou H, Wang J, et al. The expression of ATP-binding cassette transporter A1 in Chinese overweight and obese patients. *Int J Obes* 2009;33:851–856.
42. De Nardo D, Labzin LI, Kono H, et al. High-density lipoprotein mediates anti-inflammatory reprogramming of macrophages via the transcriptional regulator ATF3. *Nat Immunol* 2014;15:152–160.
43. Shankar A, Sun L, Klein BEK, et al. Markers of inflammation predict the long-term risk of developing chronic kidney disease: A population-based cohort study. *Kidney Int* 2011;80:1231–1238.
44. Coresh J, Astor BC, Greene T, et al. Prevalence of chronic kidney disease and decreased kidney function in the adult US population: Third National Health and Nutrition Examination Survey. *Am J Kidney Dis* 2003;41:1–12.

Address correspondence to:
Satyesh K. Sinha, PhD
Department of Medicine
David Geffen School of Medicine
University of California Los Angeles
10833 Le Conte, 7-155 Factor Building
Los Angeles, CA 90095
USA

E-mail: sksinha@mednet.ucla.edu

Susanne B. Nicholas, MD, MPH, PhD
Department of Medicine
David Geffen School of Medicine
University of California Los Angeles
10833 Le Conte, 7-155 Factor Building
Los Angeles, CA 90095
USA

E-mail: sunicholas@mednet.ucla.edu