

ETHNICITY AND SEX MODIFY THE ASSOCIATION OF SERUM C-REACTIVE PROTEIN WITH MICROALBUMINURIA

Objectives: To study the association between serum C-reactive protein (CRP) and urinary albumin excretion in the Multi-Ethnic Study of Atherosclerosis and to assess whether the association is modified by ethnicity, sex, or systolic blood pressure.

Methods: This was a cross-sectional study of 6675 participants who were free from macroalbuminuria and clinical cardiovascular disease (mean age 62.1 years, 53% female; 39% White, 27% African American, 22% Hispanic, and 12% Chinese). Urinary albumin excretion was measured by spot urine albumin-to-creatinine ratio (ACR). Effect modifications were tested after adjusting for age, diabetes, body mass index, smoking, use of angiotensin-converting enzyme inhibitor or angiotensin-receptor blocker, other antihypertensive drugs, estrogens, statins, and high-density lipoprotein cholesterol and triglyceride levels.

Results: The association between CRP and ACR was modified by ethnicity ($P=.01$) and sex ($P<.001$), but not by systolic blood pressure. After multivariate adjustment, the association remained in Chinese, African American, and Hispanic men and African American women ($P<.02$ for African American men, and $P<.04$ for the other subgroups).

Conclusions: The association between CRP and ACR was modified by ethnicity and sex; it was stronger in non-White men and African American women. These interactions have not been reported before, and future studies should consider them. (*Ethn Dis*. 2008;18:324–329)

Key Words: Albuminuria, C-Reactive Protein, Ethnicity, Sex

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INTRODUCTION

Microalbuminuria predicts cardiovascular morbidity and mortality^{1–5} and progression to renal failure.^{6,7} Serum C-reactive protein (CRP) is also an independent predictor of cardiovascular morbidity and mortality^{8,9} and renal failure.^{10,11} Given that traditional cardiovascular risk factors are associated with the development of microalbuminuria, interest has grown in the association between CRP levels and microalbuminuria. Several cross-sectional^{12–15} and one longitudinal study¹⁶ have reported a significant association. However, whether the strength of the association differs by ethnicity is not known. The only study in a multiethnic population found no evidence of effect modification by ethnicity, but their statistical power was limited.¹²

The population distribution of CRP levels^{17,18} and urinary albumin excretion rates^{19,20} vary by sex. Furthermore, the association of CRP with insulin resistance and the metabolic syndrome²¹ and with carotid atherosclerosis^{22,23} appears to differ by sex. Therefore, whether sex modifies the association between CRP and urinary albumin excretion should be determined.

We studied a large multiethnic cohort, free from clinical cardiovascular disease and macroalbuminuria, to determine whether CRP levels were independently associated with urinary albumin excretion and whether ethnicity and sex modified the association. We also tested whether blood pressure levels modified that relationship, as previously reported.²⁴

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METHODS

Study Sample

The Multi-Ethnic Study of Atherosclerosis (MESA) is a prospective cohort study to investigate the prevalence, correlates, and progression of subclinical cardiovascular disease in individuals without clinical cardiovascular disease.²⁵ Classification of ethnicity was based on self-identification, and it was categorized as White (non-Hispanic), African American (non-Hispanic), Chinese, and Hispanic. The current study used data obtained at the baseline visit of MESA, performed between August 1, 2000, and July 30, 2002. Participants who did not have a urinary albumin and creatinine measurement and those

with macroalbuminuria were excluded from this study. All participants provided informed consent, and the study was approved by the institutional review boards at all participating institutions.

Data Collection

Medication use was assessed by using a validated medication inventory.²⁶ Height and weight were measured to the nearest .1 cm and .5 kg, respectively. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. Resting blood pressure was measured by trained study personnel in the participant's right arm after five minutes in the seated position. An automated oscillometric method (Dinamap Monitor Pro 100, Critikon Inc., Tampa, Fla) was used. Three readings were taken; the second and third readings were averaged to obtain the blood pressure levels used in analyses.

Laboratory Determinations

Blood samples were collected after an overnight fast. CRP (mg/L) was measured by using the BNII nephelometer (N High Sensitivity CRP; Dade Behring Inc., Deerfield, Ill). Total and high-density lipoprotein (HDL) cholesterol (mg/dL) were measured by using a cholesterol oxidase method, and triglycerides were measured by using the Triglyceride GB reagent (both from Roche Diagnostics, Indianapolis, Ind). Serum creatinine (mg/dL) was measured by rate reflectance spectrophotometry by using a thin film adaptation of the creatine amidinohydrolase method on the Vitros analyzer (Johnson & Johnson Clinical Diagnostics, Inc., Rochester, NY).

Urinary albumin ($\mu\text{g}/\text{dL}$) was determined by using the Array 360 CE Protein Analyzer (Beckman Instruments, Inc., Drea, Calif). Urinary creatinine (mg/dL) was measured by using the Vitros 950IRC instrument (Johnson & Johnson Clinical Diagnostics, Inc.).

Definitions

Urinary albumin-to-creatinine ratio (ACR, $\mu\text{g}/\text{mg}$) was calculated from a random morning sample. Urinary albumin excretion was then categorized into normal ACR (<13.0 mg/g in women and <9.0 mg/g in men), high-normal ACR (13.0–24.9 mg/g in women and 9.0–16.9 mg/g in men), microalbuminuria (ACR 25.0–354.9 mg/g in women and 17.0–249.9 mg/g in men), and macroalbuminuria (ACR ≥ 355.0 mg/g in women and ≥ 250.0 mg/g in men).²⁷ Participants with macroalbuminuria were excluded from these analyses.

Statistical Analysis

Variables that did not approximate the normal distribution were log-transformed for the analyses. Differences between ethnic groups and sexes were tested by using analysis of variance and the χ^2 test, as appropriate. Multivariable linear regression was used to assess associations of CRP with ACR. The interaction terms CRP level by sex, CRP level by ethnicity, and CRP level by systolic blood pressure were tested in the full multivariable model. If an interaction was identified, analyses were stratified accordingly. The full model adjusted for age, diabetes mellitus, BMI, current smoking status, angiotensin-converting enzyme (ACE) inhibitor or angiotensin-receptor blocker (ARB) use, other antihypertensive medication use, statin use, estrogen supplementation (in women), HDL cholesterol levels, and triglyceride levels. All those covariates were included in the final model because of known associations with both the exposure and the outcome.²⁸ Other covariates, such as low-density lipoprotein cholesterol and diastolic blood pressure were not included because their addition to the model caused excessive collinearity. For descriptive purposes, the age and multivariable-adjusted geometric mean (95% confidence interval) of the ACR was calculated for three categories of serum CRP: <1 mg/L, 1–3 mg/L, and >3 mg/L.

Statistical analyses were performed by using the R software (The R Foundation for Statistical Computing: <http://www.r-project.org>), version 2.0.1, and SPSS, version 15.0 (SPSS, Chicago, Ill).

RESULTS

Of 6814 participants, 39 did not provide a urine sample, 25 had missing data, and 75 had macroalbuminuria, leaving 6675 participants in the current study. The ethnic composition was 39% White, 27% African American, 22% Hispanic, and 12% Chinese. Mean age was 62.1 (± 10.2) years, and 53% of the participants were women. Microalbuminuria was present in 854 participants (13%).

Minority participants differed from Whites in several relevant characteristics (Table 1). They had higher urine ACR, and higher prevalence of diabetes and were less likely to take statins. African Americans and Hispanics also had higher prevalence of hypertension and smoking and higher BMI, serum CRP levels, and systolic blood pressure, as compared with Whites. They took ACE inhibitors or ARBs more frequently. Chinese participants had lower BMI and serum CRP and were less likely to smoke and to take ACE inhibitors or ARBs than Whites.

There were also significant differences between sexes within each ethnic group. In all ethnic groups, women had lower CRP levels than men ($P<.01$ for Chinese and $P<.001$ for the other ethnic groups) and had higher HDL-cholesterol and lower diastolic blood pressure ($P<.001$ for all ethnicities). White and African American women had a lower prevalence of microalbuminuria than men ($P<.001$ for both); we observed a similar but nonsignificant trend in Chinese and Hispanic patients. African American women had higher BMI and systolic blood pressure than African American men ($P<.001$ and $P=.001$, respectively).

Table 1. Demographic and clinical characteristics, by ethnicity, of participants in the Multi-Ethnic Study of Atherosclerosis, 2000–2002

Characteristic	White (n=2597)*	African American (n=1839)*	Chinese (n=790)*	Hispanic (n=1449)*
Age, year†	62.6±10.2	62.1±10.0	62.3±10.3	61.2±10.3
Male‡	47.9	44.3	48.6	47.5
BMI, kg/m²†	27.8±5.1	30.1±5.8	23.9±3.3	29.4±5.1
SBP, mm Hg†	123.5±20.4	131.3±21.5	124.1±21.3	126.2±21.4
DBP, mm Hg†	70.2±9.9	74.5±10.2	71.8±10.2	71.4±9.9
Hypertension†	37.8	57.7	36.5	40.1
Diabetes†	7.7	19.5	14.7	19.3
Smoking†	11.6	17.8	5.6	13.5
Urine ACR, mg/g†	4.6 (3.1–8.4)	5.4 (3.1–12.1)	6.6 (3.9–12.50)	6.0 (3.7–11.7)
C-reactive protein, mg/L†	1.8 (.8–4.0)	2.5 (1.1–5.6)	.9 (.5–1.8)	2.4 (1.1–4.9)
Creatinine, mg/dL†	.95±.2	1.01±.2	.89±.2	.89±.2
HDL cholesterol, mg/dL†	52.3±15.7	52.4±15.2	49.5±12.7	47.8±13.0
LDL cholesterol, mg/dL§	117.1±30.1	116.6±32.9	115.1±29.0	119.4±32.2
Triglycerides, mg/dL†	132.6±89.2	104.5±68.7	142.4±85.0	155.6±99.1
ACEIs/ARBs†	14.3	22.9	11.8	16.1
Other antihypertensive medications†	12.6	24.5	16.2	13.5
Statins†	16.1	14.9	12.8	11.7

BMI = body mass index, SBP = systolic blood pressure, DBP = diastolic blood pressure, ACR = albumin-to-creatinine ratio, HDL = high-density lipoprotein, LDL = low-density lipoprotein, ACEI = angiotensin-converting enzyme inhibitor, ARB = angiotensin-receptor blocker.

* Data are presented as means plus or minus standard deviations, percentages, or medians (interquartile ranges).

† $P < .001$ for difference.

‡ Nonsignificant.

§ $P < .01$ for difference.

Table 2 summarizes the results of the multivariable linear regression analyses. Systolic blood pressure did not modify the association of CRP with ACR ($P=.4$ for the interaction term). In contrast, sex and ethnicity modified the association between CRP and ACR significantly ($P<.001$ and $P=.01$, respectively). Accordingly, our analyses were stratified by sex and ethnicity. In age-adjusted models, only White and Chinese women did not show a significant association between CRP and ACR. After multivariable adjustment, the association between serum CRP and ACR persisted in all non-White men but only in African American women. In all sex and ethnic subgroups, systolic blood pressure and diabetes mellitus were the most influential covariates (data not shown). Age was also an influential covariate in Whites (both sexes) and in Chinese women.

For descriptive purposes, the adjusted geometric mean ACR (95% confidence interval) was calculated for three

categories of serum CRP commonly used by clinicians: <1 mg/L, 1–3 mg/L, and >3 mg/L, within strata of sex and ethnicity (Table 3). Consistent with the results of linear regression models, we observed an increase in multivariable-adjusted ACR from lower to higher CRP categories in all non-White men and in African American women.

DISCUSSION

In this multiethnic cohort the association between serum CRP levels and urinary albumin excretion was modified by ethnicity. The association appeared to be stronger in non-White participants in general, and in African Americans in particular. To the best of our knowledge, this is the first time this interaction has been reported. The Insulin Resistance Atherosclerosis (IRAS) study did not detect an effect modification by ethnicity, but the number of participants with microalbu-

minuria was relatively small, thus reducing their statistical power.¹² Our finding of a stronger association between CRP and urinary albumin excretion in African Americans is particularly important because we found, as others had, that this ethnic group has a higher prevalence of diabetes mellitus²⁹ and hypertension.³⁰ They also progress more quickly to end-stage renal disease,³¹ have a higher incidence of severe strokes,³² and have a higher mortality after a myocardial infarction.³³ This raises the question whether elevated serum CRP levels and microalbuminuria could be part of the clustering of cardiovascular risk factors this study and others have observed in African Americans—a phenomenon thought to be linked to their higher cardiovascular morbidity and mortality.³⁴ Whether the same reasoning applies to other ethnic minorities is far less clear, as there is paucity of studies in those populations.

We also identified an effect modification by sex. After multivariable adjustment, the association between CRP

Table 2. Results of linear regression models testing the association of serum C-reactive protein (log-transformed) with urine albumin-to-creatinine ratio (log-transformed), by sex and ethnicity, Multi-Ethnic Study of Atherosclerosis, 2000–2002

	White Women (n=1343)		Chinese Women (n=406)		African American Women (n=1012)		Hispanic Women (n=758)	
	β (SE)	P value	β (SE)	P value	β (SE)	P value	β (SE)	P value
Age-adjusted	.008 (.019)	ns	.074 (.046)	ns	.084 (.027)	†	.094 (.033)	†
Multivariable-adjusted	.0003 (.022)	ns	.042 (.045)	ns	.058 (.028)	‡	.016 (.034)	ns

	White Men (n=1239)		Chinese Men (n=382)		African-American Men (n=808)		Hispanic Men (n=685)	
	β (SE)	P value	β (SE)	P value	β (SE)	P value	β (SE)	P value
Age-adjusted	.089 (.024)	*	.173 (.055)	†	.119 (.035)	*	.124 (.036)	*
Multivariable-adjusted	.022 (.025)	ns	.113 (.054)	‡	.085 (.035)	‡	.072 (.034)	‡

* $P < .001$

† $P < .01$

‡ $P < .05$

ns=nonsignificant. Multivariable model adjusted for age, systolic blood pressure, diabetes mellitus, body mass index, current smoking status, angiotensin-converting enzyme inhibitor or angiotensin-receptor blocker use, other antihypertensive medications, statins, estrogen supplementation (in women), high-density lipoprotein cholesterol levels, and triglyceride levels.

and urinary albumin excretion remained significant only in African American women, whereas it persisted in all non-White men. The mechanism mediating this interaction remains unknown. However, the stronger association between serum CRP and albuminuria in men resembles the observation that, in general, men are more susceptible to traditional cardiovascular risk factors than are women of similar age.³⁵ In this sense, another study found that for a given level of any traditional cardiovascular risk factor, urinary albumin excretion was higher in men than in women.³⁶ Our finding of an effect modification by sex is novel and warrants examination in other populations.

Although systolic blood pressure was an influential confounder of the association between CRP and albuminuria, it was not an effect modifier. In contrast, CRP has been shown to modify the association between blood pressure and albuminuria,²⁴ but researchers may have obtained different results for several reasons. First, their cohort was composed exclusively of White participants, and people with diabetes were excluded. Second, they measured urinary albumin excretion in two 24-hour urine samples, a more accurate method than the spot urine sample ACR we used. Third, their recruitment was designed to oversample people with elevated urinary albumin excretion.

Certain limitations are noteworthy. First, this is a cross-sectional study, and it

does not permit inferences about causality or temporality. Second, as previously noted, albuminuria was measured by using a single-spot urine sample. More intensive methods, such as 24-hour or 72-hour urine collection, would probably provide a more accurate measurement of renal albumin excretion. However, assessment of microalbuminuria in a spot urine sample has been accepted as an accurate estimate and a feasible alternative in large epidemiologic studies.¹² Moreover, misclassification of microalbuminuria caused by our spot measurement would not likely differ with respect to the exposures of interest. Finally, our findings of effect modification by sex and ethnicity prompted stratified analyses within eight different

Table 3. Multivariable-adjusted geometric mean ACR and 95% CI (mg/g) within categories of CRP (mg/L), stratified by sex and racial/ethnic group, Multi-Ethnic Study of Atherosclerosis, 2000–2002*

CRP level	White		Chinese		African American		Hispanic	
	Women n=1343	Men n=1239	Women n=406	Men n=382	Women n=1012	Men n=808	Women n=758	Men n=685
<1 mg/L n=1988	6.05 (5.49–6.62)	5.32 (4.89–5.74)	8.09 (7.13–9.06)	6.62 (5.75–7.49)	6.73 (5.74–7.71)	5.94 (5.14–6.73)	8.62 (7.23–10.0)	6.12 (5.33–6.92)
1–3 mg/L n=2259	5.88 (5.43–6.34)	4.99 (4.60–5.38)	9.71 (8.36–11.06)	7.53 (6.09–8.97)	6.73 (5.99–7.46)	5.85 (5.16–6.54)	7.66 (6.81–8.52)	6.65 (5.95–7.35)
>3 mg/L n=2386	5.99 (5.57–6.41)	5.71 (5.13–6.29)	9.72 (7.58–11.87)	8.78 (5.95–11.61)	7.47 (6.86–8.08)	7.29 (6.33–8.26)	8.53 (7.74–9.32)	7.14 (6.31–7.97)

ACR = albumin-to-creatinine ratio, CRP = C-reactive protein, CI = confidence interval.

* Model adjusted for age, systolic blood pressure, diabetes mellitus, body mass index, current smoking status, angiotensin-converting enzyme inhibitor or angiotensin-receptor blocker use, other antihypertensive medications, statins, estrogen supplementation (in women), high-density lipoprotein cholesterol levels, and triglyceride levels.

In this multiethnic cohort, CRP levels were associated with urinary albumin excretion that ranged from normal values to microalbuminuria.

subgroups. This may have resulted in a loss of statistical power to test the association of interest, particularly in Chinese women, the smallest subgroup. A population-based study in Japan reported a multivariate-adjusted association of serum CRP with microalbuminuria in both men and women.¹³

Our study also has notable strengths, such as the large, multiethnic sample that included adequate representation of women and accurately measured data on many pertinent confounders. In addition, we enrolled a sizable subgroup with microalbuminuria, allowing for adequate power to examine associations of interest.

Conclusions

In this multiethnic cohort, CRP levels were associated with urinary albumin excretion that ranged from normal values to microalbuminuria. Ethnicity and sex modified that association: it was stronger among non-White men and African American women. This finding may be important because men and African Americans tend to exhibit clustering of cardiovascular risk factors and higher cardiovascular morbidity and mortality.

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