EPIDEMIOLOGY/HEALTH SERVICES RESEARCH

Metabolic Syndrome, C-Reactive Protein, and Mortality in U.S. Blacks and Whites: The Reasons for Geographic and Racial Differences in Stroke (REGARDS) Study

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OBJECTIVE

We evaluate associations of metabolic syndrome (MetS), C-reactive protein (CRP), and a CRP-incorporated definition of MetS (CRPMetS) with risk of all-cause mortality in a biracial population.

RESEARCH DESIGN AND METHODS

We studied 23,998 participants in the Reasons for Geographic and Racial Differences in Stroke (REGARDS) cohort, an observational study of black and white adults ≥45 years old across the U.S. Elevated CRP was defined as ≥3 mg/L and MetS by the revised Third Report of the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III; ATP III) criteria (three of five components). CRPMetS was defined as presence of three out of six components, with elevated CRP added to ATP III criteria as a sixth component. Cox models were used to calculate hazard ratios (HRs) for all-cause mortality, and population attributable risk (PAR) was calculated. Stratified analyses based on race and diabetes status were performed.

RESULTS

There were 9,741 participants (41%) with MetS and 12,179 (51%) with CRPMetS at baseline. Over 4.8 years of follow-up, 2,050 participants died. After adjustment for multiple confounders, MetS, elevated CRP, and CRPMetS were each significantly associated with increased mortality risk (HRs 1.26 [95% CI 1.15–1.38], 1.55 [1.41–1.70], and 1.34 [1.22–1.48], respectively). The PAR was 9.5% for MetS, 18.1% for CRP, and 14.7% for CRPMetS. Associations of elevated CRP and of CRPMetS with mortality were significantly greater in whites than blacks, while no differences in associations were observed based on diabetes status.

CONCLUSIONS

By definition, CRPMetS identifies more people at risk than MetS but still maintains a similar mortality risk. Incorporating CRP into the definition for MetS may be useful in identifying additional high-risk populations to target for prevention.

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Metabolic syndrome (MetS), a clustering of cardiometabolic risk factors, is associated with type 2 diabetes and cardiovascular disease (CVD) risk (1,2). It is presumed that obesity and insulin resistance are underlying pathophysiologies of the syndrome, and the importance of lifestyle modification including diet and exercise has been advocated (3,4). MetS is also associated with nonalcoholic steatohepatitis (5–7), chronic kidney disease (8,9), and polycystic ovary syndrome (10). Previous studies revealed conflicting evidence on the association between MetS and all-cause mortality, with five studies showing an association (11–15) and four showing no association (16–19).

C-reactive protein (CRP) is an inflammatory biomarker increasingly used in cardiovascular risk assessment (20–23). Higher CRP is associated with other health outcomes, including all-cause mortality (24–26), insulin resistance (4), diabetes (27), and MetS (28–31). Both categorical MetS and CRP definitions are frequently used in clinical practice. Recent studies suggested that incorporation of inflammatory markers, CRP and interleukin-6, into the MetS definition might improve prediction of cardiovascular events (30,32,33). It is unknown whether a CRP-incorporated definition of MetS (CRPMetS) might be useful in identifying a population at risk for mortality.

In a large cohort study of blacks and whites aged 45 years and older, we contrasted the associations of CRPMetS, MetS, and CRP with mortality. Furthermore, since CRP is higher among those with diabetes and in blacks compared with whites, we also analyzed associations separately by race and diabetes status.

RESEARCH DESIGN AND METHODS

Subjects

The Reasons for Geographic and Racial Differences in Stroke (REGARDS) study is a prospective population-based observational cohort study of black and white adults ≥45 years old across the U.S. and is designed to determine the causes for the excess stroke mortality in the southeastern U.S. and among blacks. The design, rationale, and examination details were described elsewhere (34,35). Briefly, participants were a stratified random sample enrolled between January 2003 and October 2007 with recruitment by mail then telephone, where data on stroke risk factors, sociodemographic, lifestyle, and psychosocial characteristics were collected. Fifty-six percent of participants resided in the stroke belt (NC, SC, GA, AL, MS, TN, AR, and LA) with the rest from the other 40 contiguous states. A total of 30,239 participants were included in the REGARDS study, among which 12,514 were black and 16,632 were women. Written informed consent and physical and physiological measures, including blood pressure and waist circumference, fasting blood samples, and electrocardiogram were collected during an in-home visit. Blood pressures were taken following a standard protocol in the left arm. The average of the two seated blood pressure measurements was used. Waist circumference was measured using a tape measure midway between the lowest rib and the iliac crest with the participant standing. Glucose was measured using the Ortho Vitros Clinical Chemistry System 950IRC instrument (Johnson & Johnson Clinical Diagnostics, Rochester, NY). Participants were followed via telephone at 6-month intervals. Study methods were reviewed and approved by the institutional review boards at each study institution. The authors had full access to and take full responsibility for the integrity of the data.

Outcome Assessment

The primary outcome was all-cause mortality. Death events were ascertained by proxy report on the 6-month telephone contacts and confirmed through other sources such as the Social Security Death Index, LexisNexis searches, and the National Death Index. This analysis included follow-up through 9 January 2011.

Laboratory Methods

Phlebotomy was performed at the participant's home by trained personnel using standard procedures. Participants were asked to fast for 10–12 h, and samples were shipped overnight on ice to the REGARDS central laboratory as previously described (35). Serum total cholesterol, HDL, triglycerides, glucose, insulin, and creatinine were measured. LDL cholesterol was calculated using the Friedewald equation. hs-CRP was measured by particle enhanced immuno-nephelometry using the BNII nephelometer (N High Sensitivity CRP, Dade Behring, Deerfield, IL) with interassay coefficients of variation of 2.1–5.7%. Elevated CRP was defined as ≥3 mg/L (36).

Definitions

MetS was defined using the modified Third Report of the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III; ATP III) criteria (4,37). Subjects were classified as having MetS if they had three or more of the following five characteristics: 1) waist circumference ≥102 cm for men and ≥88 cm for women; 2) triglycerides ≥150 mg/dL; 3) HDL <40 mg/dL in men and <50 mg/dL in women; 4) systolic blood pressure ≥130 mmHg, diastolic blood pressure ≥85 mmHg, or hypertension medication use in participants with diagnosed hypertension; 5) fasting glucose >100 mg/dL or on drug treatment for elevated blood glucose. CRPMetS was defined as presence of three out of six components, with elevated CRP (≥3 mg/L) added to ATP III criteria as a sixth component.

Baseline CVD was defined as a participant self-report of a history of myocardial infarction, stroke, or cardiovascular procedures (carotid endarterectomy, coronary artery bypass graft, percutaneous coronary intervention, or peripheral vascular surgery at baseline) or electrocardiographic evidence of myocardial infarction (34). Atrial fibrillation was defined as either self-report of history or presence of fibrillatory waves on the baseline electrocardiogram.

We excluded 4,098 (14%) participants whose phlebotomy was not fasting, 2,087 (7%) subjects with missing CRP or components of MetS, and 56 others with no follow-up, leaving an analysis cohort of 23,998 subjects.

Statistical Analysis

Baseline characteristics were compared between those with or without MetS using χ^2 tests for discrete variables and t tests for continuous data. The mortality rate in groups based on MetS or elevated CRP was presented as events per 1,000 person-years. Cox proportional hazards models were used to examine the association of MetS and CRPMetS with mortality. Participants were censored at date of last contact or 9 January 2011 (whichever occurred first). To control for confounding, the following

variables were included in multivariable models: age, sex, race, region (stroke belt or not), creatinine, LDL cholesterol, current smoking, alcohol intake (heavy, moderate, or none), atrial fibrillation (self-report or electrocardiogram evidence), and baseline CVD. These variables were known risk factors for death from other research and were prespecified. To examine whether associations differed by race or diabetes status, we added interaction terms between these factors and CRP, MetS, or CRPMetS to the models then performed stratified analyses if the interaction P value was <0.1. To determine whether MetS and elevated CRP increased mortality risk in an additive way, hazard ratios (HRs) of all-cause mortality were calculated for cross-classified groups based on these factors. In order to examine the impact of MetS and CRPMetS in the cohort, population attributable risk (PAR) was calculated. PAR indicates the proportion of cases that would not occur if the factor were eliminated and calculated as follows by using Levin's formula:

$$PAR = \frac{p(r-1)}{p(r-1)+1}$$

where p is the prevalence of the population with the exposure and r is the relative risk. PAR for MetS and CRPMetS was calculated.

A P value of <0.05 was considered significant and 95% CIs were calculated. As interaction tests are often underpowered, a P value of <0.1 was considered significant for interaction testing so as not to falsely accept a null hypothesis (type II error). Statistical analyses were performed using SAS 9.1.3 software for Windows (SAS, Gary, NC).

RESULTS

Baseline characteristics of subjects with and without MetS and with and without CRPMetS are shown in Table 1. There were 9,741 (41%) subjects with MetS and 12,179 (51%) with CRPMetS at baseline. Among 14,257 subjects without MetS, 2,438 (17%) had CRPMetS. Compared with subjects without MetS, those with MetS were more likely to be women, black, reside in the stroke belt, and have higher waist circumference, blood pressure, triglycerides, glucose, and CRP (Table 1). Total cholesterol,

HDL, and LDL were lower in the MetS group. When subjects with and without CRPMetS were compared, patterns of difference were similar to those with versus without MetS, other than age. Basic characteristics stratified based on race, MetS, and CRPMetS are shown in Table 2. There were differences in the way MetS factors accumulated between the races. For example, in participants with MetS, hypertension was more prevalent in blacks and triglycerides were higher in whites.

MetS, CRP, CRPMetS, and All-Cause Mortality

Over a mean of 4.8 years of follow-up, 2,050 participants died. In Table 3 (adjusting for age, sex, race, region, creatinine, LDL cholesterol, smoking status, alcohol intake, atrial fibrillation, and prevalent CVD), MetS, elevated CRP, and CRPMetS were each associated with increased mortality. For MetS, the HR was 1.26 (95% CI 1.15–1.38) overall,

with no difference between blacks and whites (P for interaction = 0.87). The HR of death for elevated CRP was higher in whites than blacks: HR 1.73 (95% CI 1.53–1.95) and 1.32 (1.15–1.53), respectively (P interaction of race and CRP = 0.003). Similarly, the HR of death associated with CRPMetS was higher in whites (1.45 [CI 1.28–1.64]) than blacks (1.23 [CI 1.06–1.42]; P interaction = 0.08). There were no significant differences in the associations of CRP, MetS, or CRPMetS with mortality by diabetes status.

In Table 4, the PAR for death was 9.5% for MetS, 18.1% for CRP, and 14.7% for CRPMetS. When stratified by race, MetS accounted for 10.1% of the cases in blacks and 9.5% in whites. Elevated CRP accounted for 20.9% of the cases in whites and 13.5% in blacks.

Table 5 shows joint associations of MetS and elevated CRP with mortality. Subjects with only MetS had a 17% increased risk of mortality compared with

Table 1—Baseline characteristics of the cohort by MetS and CRPMetS status

	MetS		CRPMetS	
	Absent (n = 14,257)	Present (n = 9,741)	Absent (n = 11,819)	Present (n = 12,179)
Age (years)†	64.5 ± 9.7	64.6 ± 9.0	64.5 ± 9.7	64.7 ± 9.0
Women	53	58	51	59
Black	37	44	34	46
Stroke belt	54	59	54	58
Alcohol intake (heavy or moderate)	43	31	45	32
Education (less than high school)	10	15	8	15
Income (>$75,000)	19	12	21	12
Waist circumference (cm)	90 ± 13	105 ± 14	88 ± 12	104 ± 14
Physical activity (4+ days/week)	33	25	35	25
Hypertension	44	79	40	76
Diabetes	7	40	6	34
Coronary heart disease	14	22	14	21
Stroke	5	8	4	7
Atrial fibrillation	8	10	7	10
Systolic blood pressure (mmHg)	124 ± 16	132 ± 17	123 ± 16	132 ± 17
Diastolic blood pressure (mmHg)	76 ± 9	78 ± 10	75 ± 9	78 ± 10
Current smoking	14	15	13	16
Total cholesterol (mg/dL)	194 ± 38	191 ± 43	194 ± 38	192 ± 42
Triglycerides (mg/dL)	104 ± 55	171 ± 107	101 ± 55	160 ± 101
HDL (mg/dL)	57 ± 16	44 ± 13	58 ± 16	46 ± 14
LDL (mg/dL)	116 ± 34	113 ± 36	116 ± 33	114 ± 36
Glucose (mg/dL)	93 ± 20	116 ± 41	92 ± 18	112 ± 39
CRP (mg/L)‡	3.7 (7.8)	5.9 (9.6)	2.6 (6.1)	6.5 (10.2)
Creatinine (mg/dL)	0.9 ± 0.4	0.9 ± 0.5	0.9 ± 0.3	0.9 ± 0.5

For continuous variables, mean ± SD is shown. For categorical variables, percentage is shown. †P < 0.001 except age between CRPMetS absent versus present (P = NS). ‡Median (interquartile range).

Table 2—Baseline characteristics of the cohort by MetS and CRPMetS status stratified by race

	MetS				CRPMetS			
	Absent		Present		Absent		Present	
	Black (n = 5,231)	White (n = 9,026)	Black (n = 4,285)	White (n = 5,456)	Black (n = 3,977)	White (n = 7,842)	Black (n = 5,539)	White (n = 6,640)
Age (years)	63.7 ± 10	65.0 ± 10	63.7 ± 9	65.4 ± 9	63.7 ± 10	64.9 ± 10	63.7 ± 9	65.4 ± 9
Women	57	51	69	49	53	50	69	50
Stroke belt	50	57	54	62	50	57	53	62
Alcohol intake (heavy or moderate)	32	50	24	36	33	51	25	37
Education (less than high school)	17	6	21	9	15	5	21	9
Income (>$75,000)	11	24	8	16	12	25	8	16
Waist circumference (cm)	91 ± 13	89 ± 13	105 ± 14	104 ± 14	89 ± 12	88 ± 12	104 ± 14	103 ± 14
Physical activity (4+ days/week)	30	36	22	27	31	37	23	27
Hypertension	57	36	87	73	52	33	84	70
Diabetes	11	4	49	32	9	4	42	28
Coronary heart disease	12	16	18	24	12	15	17	23
Stroke	6	4	9	7	6	3	8	6
Atrial fibrillation	6	8	9	10	6	8	9	10
Systolic blood pressure (mmHg)	128 ± 17	122 ± 15	134 ± 17	130 ± 16	127 ± 17	122 ± 15	134 ± 17	130 ± 16
Diastolic blood pressure (mmHg)	78 ± 10	74 ± 9	80 ± 10	77 ± 9	77 ± 9	74 ± 9	80 ± 10	77 ± 9
Current smoking	17	12	17	14	17	11	18	14
Total cholesterol (mg/dL)	196 ± 39	193 ± 37	190 ± 43	192 ± 43	196 ± 39	193 ± 37	192 ± 42	192 ± 42
Triglycerides (mg/dL)	91 ± 51	111 ± 55	135 ± 88	198 ± 112	89 ± 55	107 ± 53	127 ± 81	187 ± 107
HDL (mg/dL)	59 ± 16	56 ± 16	47 ± 14	42 ± 11	60 ± 16	57 ± 16	49 ± 14	44 ± 13
LDL (mg/dL)	119 ± 36	114 ± 32	116 ± 37	111 ± 35	118 ± 36	114 ± 32	118 ± 37	111 ± 35
Glucose (mg/dL)	95 ± 27	92 ± 15	122 ± 46	112 ± 35	94 ± 24	91 ± 14	116 ± 45	109 ± 34
CRP (mg/L)†	4.6 (9.1)	3.2 (6.9)	7.0 (11.2)	4.9 (7.9)	2.9 (6.3)	2.4 (5.9)	7.7 (11.9)	5.6 (8.4)
Creatinine (mg/dL)	0.9 ± 0.5	0.8 ± 0.2	1.0 ± 0.7	0.9 ± 0.4	0.9 ± 0.5	0.8 ± 0.2	1.0 ± 0.6	0.9 ± 0.3

For continuous variables, mean ± SD is shown. For categorical variables, percentage is shown. †Median (interquartile range).

those without MetS or elevated CRP. Subjects with only elevated CRP had a 48% higher risk of mortality. Subjects with both MetS and elevated CRP had an 80% higher risk of mortality compared with those without either risk factor. Stratifying on race, blacks with only elevated CRP had a 19% increased risk of mortality compared with those without MetS or elevated CRP. On the other hand, whites with only elevated CRP had a 71% increased risk of mortality compared with those without MetS or elevated CRP in whites. White participants

with both MetS and elevated CRP had a 104% higher risk of mortality, while black participants with both had a 55% higher risk of mortality, compared with those without either risk factor.

CONCLUSIONS

In this large cohort of geographically dispersed white and black American women and men, MetS, elevated CRP, and CRPMetS were each associated with higher mortality over 5 years. By our definition, CRPMetS must identify more people at risk than MetS (three

out of five positive characteristics will always be among those with three out of six positive characteristics); however, we showed that the addition of CRP to the definition identified this larger group of individuals with marginally higher mortality risk than MetS alone. Correspondingly, the PAR was higher for CRPMetS than MetS alone. Elevated CRP and CRPMetS (but not MetS) were more strongly associated with mortality in whites compared with blacks.

There are conflicting data on the association between MetS and all-cause

Table 3—HRs of mortality by baseline MetS, CRP, and CRPMetS

	Reference	Unadjusted HR (95% CI)	Adjusted* HR (95% CI)	Adjusted* HR stratified by race (95% CI)†		Adjusted* HR stratified by diabetes (95% CI)	
				Blacks	Whites	Diabetes	No diabetes
MetS	No MetS	1.35 (1.24–1.47)	1.26 (1.15–1.38)	1.25 (1.09–1.44)	1.28 (1.13–1.45)	0.94 (0.77–1.15)	1.10 (0.98–1.24)
Elevated CRP	CRP <3 mg/L	1.62 (1.49–1.77)	1.55 (1.41–1.70)	1.32 (1.15–1.53)	1.73 (1.53–1.95)	1.52 (1.28–1.81)	1.51 (1.35–1.69)
CRPMetS	No CRPMetS	1.49 (1.36–1.62)	1.34 (1.22–1.48)	1.23 (1.06–1.42)	1.45 (1.28–1.64)	1.20 (0.93–1.54)	1.19 (1.07–1.33)

*Adjusted for age, sex, race, region, creatinine, LDL, smoking, alcohol intake, atrial fibrillation, and prevalent CVD. †P values for interaction of MetS, CRP, and CRPMetS with race were 0.87, 0.003, and 0.08, respectively.

Table 4—PAR for mortality by MetS in all subjects, blacks, and whites

PAR	All	Blacks	Whites
MetS	9.5%	10.1%	9.5%
Elevated CRP	18.1%	13.5%	20.1%
CRPMetS	14.7%	11.8%	17.1%

mortality, but no study has included a large number of blacks. In agreement with our findings, some studies showed that MetS was associated with increased all-cause mortality (11–15), while others indicated that the risk of all-cause mortality was not increased in those with MetS (16–19). The prevalence of MetS in some of these studies was low, varying from 8 to 27%. Our study is unique in that the prevalence of MetS was very high (41%), ~40% of participants were black, and participants were a national sample of the U.S. population. Hunt et al. (14) showed that ATP III–defined MetS was associated with all-cause mortality in the San Antonio Heart Study. The majority of that cohort was Mexican American, and sample size was modest at 2,815 participants. Hu et al. (12) showed that MetS by a modified World Health Organization definition was associated with all-cause mortality in 11,512 European men and women. In one study of 19,223 men who were primarily white, MetS was associated with all-cause mortality, but not independent of cardiorespiratory fitness (18). The conflicting results might be due to differences in cohort composition by age, race, sex, or other factors, including prevalence of MetS and inclusion of other risk factors for mortality. The current analysis showed that MetS was associated with all-cause mortality in both blacks and whites. We included a large sample of blacks, and findings extend current knowledge to this group, among whom the MetS is more prevalent than among whites.

There has remained a controversy combining MetS and CRP in predicting CVD outcomes. Our results extend previous studies on associations between the MetS, inflammation, and CVD outcomes (32,33,38) to the end point of mortality. One study showed additive effects of MetS and CRP on CVD risk and proposed incorporating CRP into the definition of MetS (32). Another

study in an elderly cohort showed an additive effect of MetS and inflammation markers on heart failure risk (33). MetS was associated with coronary artery calcification independent of CRP in a cross-sectional study (38). The current study showed similar associations among MetS, CRP, and all-cause mortality. However, as in the case of heart failure (33), the HR of death for elevated CRP alone without MetS was larger than for MetS alone. It may be that elevated CRP captures multiple elements of MetS that are less reliably measured, potentially obviating the need to classify people on the basis of MetS. On the other hand, Rutter et al. (39) showed that both MetS and elevated CRP were independently associated with CVD outcomes, but no additive discriminative value was observed when used together. A study by Agarwal et al. (40) performed principal component analysis to provide a continuous definition of MetS in a multiethnic population and found no benefit of adding CRP to the MetS variables in predicting cardiovascular events. These mixed findings could be due to difference in cohorts or in outcomes. Our study may be novel in that we combined MetS and CRP in association with all-cause mortality.

We observed racial differences in the association of elevated CRP and CRPMetS, but not MetS, with mortality. No such difference was observed based on diabetes status. The HR for elevated CRP was weaker in blacks than whites. This may be due to the higher baseline level of CRP in blacks compared with whites (33). These findings suggest that if the goal is to predict death, race-specific cut points for CRP might be needed. We are not aware of other studies that included large enough numbers of blacks to address this issue adequately for any outcomes. We elucidated the racial difference in the association of CRPMetS with mortality. The higher prevalence of hypertension in blacks compared with whites with MetS may partly explain this, but further research is needed.

The strengths of this study include its prospective population-based design and large sample size of whites and blacks that allowed for subgroup analyses. Limitations of our study merit discussion. First, categorization of continuous variables can result in

Table 5—HRs of mortality for MetS and elevated CRP in all subjects, blacks, and whites

MetS	Elevated CRP	All		Blacks		Whites	
		Mortality per 1,000 person-years (95% CI)	Adjusted* HR (95% CI)	Mortality per 1,000 person-years (95% CI)	Adjusted† HR (95% CI)	Mortality per 1,000 person-years (95% CI)	Adjusted† HR (95% CI)
(−)	(−)	12.9 (12.0–14.0)	Reference	16.8 (14.8–19.0)	Reference	11.2 (10.1–12.4)	Reference
(+)	(−)	17.4 (15.8–19.3)	1.17 (1.02–1.33)	19.4 (16.5–22.7)	1.10 (0.89–1.36)	16.4 (14.5–18.7)	1.22 (1.03–1.45)
(−)	(+)	21.6 (19.8–23.7)	1.48 (1.31–1.68)	20.9 (18.2–24.0)	1.19 (0.98–1.45)	22.2 (19.7–25.0)	1.71 (1.45–2.02)
(+)	(+)	24.6 (22.7–26.7)	1.80 (1.59–2.04)	24.4 (21.7–27.4)	1.55 (1.29–1.86)	24.8 (22.1,27.8)	2.04 (1.72–2.40)

*Adjusted for age, sex, race, region, creatinine, LDL, smoking, alcohol intake, atrial fibrillation, and prevalent CVD. †Adjusted for age, sex, region, creatinine, LDL, smoking, alcohol intake, atrial fibrillation, and prevalent CVD.

misclassification of exposures such as the MetS components and CRP. However, the categorical MetS definition and elevated CRP are used in clinical practice (36). Second, we only evaluated a single measurement of risk factors. However, the large sample size compensated for this weakness, and this would bias results toward the null hypothesis. Third, we do not yet have information on cause of death so could not more fully investigate reasons for differences in association by race. Fourth, we did not have white blood count measured on the full cohort so did not assess this as a marker of inflammation to reclassify MetS. This might be more readily available to clinicians than CRP, so further study would be useful. Last, lack of inclusion of other racial/ethnic groups means that findings may not be generalizable to other racial groups.

In summary, in this study, CRPMetS identified more people at risk for death than MetS alone and was associated with marginally higher mortality risk. CRPMetS or CRP alone may be more useful clinically in identifying higher-risk populations for all-cause mortality. Clinical implications of differences observed by race warrant further research.

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