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# Distribution and metabolic syndrome correlates of plasma C-reactive protein in biracial (black-white) younger adults: the Bogalusa Heart Study

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**Abstract**

The association between plasma C-reactive protein (CRP), a marker of systemic inflammation, and the metabolic syndrome is well recognized. However, information is scant regarding the component of metabolic syndrome that is critical in modulating CRP levels in younger adults. This aspect was examined in a biracial (black-white) community-based sample of 1083 younger adults (mean age, 36.1 years; 71% white, 45% male) enrolled in the Bogalusa Heart Study. Plasma CRP along with metabolic syndrome variables were measured. CRP levels showed a significant race (black > white, $P = .01$) and sex (female > male, $P = .0001$) differences, and related to measures of obesity (body mass index [BMI], waist circumference, and sagittal diameter), blood pressure (systolic, diastolic, and mean arterial blood pressure), lipoproteins (low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglycerides, total cholesterol–high-density lipoprotein cholesterol ratio), glucose homeostasis (insulin, glucose, homeostasis model assessment of insulin resistance), and uric acid, after adjusting for age, race, sex, and cigarette smoking. Furthermore, CRP levels increased with increasing number of metabolic syndrome risk factors, as defined by the National Cholesterol Education Program Adult Treatment Panel III, regardless of race and sex ($P$ for trend $<.0001$). In multivariate analysis, using 3 separate models for different obesity measures, obesity was the major contributor to the explained variance in each model with BMI, waist, and sagittal diameter contributing 17.0%, 13.4%, and 17.1% of the variance, respectively. In contrast, homeostasis model assessment of insulin resistance contributed 1.2%, 0.3%, and 0% to the explained variance in the models with BMI, waist, and sagittal diameter, respectively. In conclusion, CRP levels differ among race and sex groups and correlate to metabolic syndrome variables in younger adults. In addition, these findings strongly suggest that although obesity and insulin resistance are the main underlying features of the metabolic syndrome, the former appears to be the major mediator of CRP levels, which has important health implications.


## 1. Introduction

That inflammation plays a key role in the pathogenesis of cardiovascular (CV) disease is now well recognized [1]. C-reactive protein (CRP), an acute-phase reactant, is a marker of underlying systemic inflammation and a reliable predictor of CV disease beyond what can be estimated by traditional risk factors [2-5]. Furthermore, subclinical inflammatory state is considered as a part of the metabolic syndrome [6-8], a constellation of interrelated conditions of obesity, insulin resistance/hyperinsulinemia, dyslipidemia, and hypertension occurring commonly in the general population [9-12]. Although a number of studies have found association between CRP and the variables of metabolic syndrome in middle-aged and older adults, most of whom are already at high risk for CV disease, only few studies have focused on this aspect in apparently healthy younger adult population [7,13-15]. Both obesity and insulin resistance [9,10], the underlying features of metabolic syndrome, are thought to influence CRP levels [6,7,15,16]. However, regarding obesity, insulin resistance, or both, as independent correlate(s) of excess CRP, these previous studies have yielded mixed results.

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As a part of the Bogalusa Heart Study, a biracial (black-white) community-based investigation of the early natural history of CV disease [17], the present study examines the distribution of CRP and its association with CV risk factor variables of metabolic syndrome in an effort to identify the variable that is critical in modulating plasma CRP levels in younger adults.

## 2. Methods

### 2.1. Study population

Individuals (N = 1203) aged 24 to 43 years, residing in the biracial (65% white, 35% black) community of Bogalusa, LA, were examined in the 2000 to 2001 cross-sectional survey. Of these, 1083 individuals (mean age, 36.1 years; 71% white, 45% male) who had data on plasma CRP along with other variables of metabolic syndrome formed the study sample. Individuals (n = 4) with CRP levels of more than 10 mg/L were excluded to minimize the effect of any acute infection. This study was approved by the Institutional Review Board of the Tulane University Health Sciences Center. All participants gave their informed consent.

### 2.2. General examination

All examinations followed essentially the identical protocols. Subjects were instructed to fast for 12 hours before the screening, with compliance ascertained by an interview on the day of examination. Height and weight were measured twice to the nearest 0.1 cm and 0.1 kg, respectively, and the average values were used to calculate body mass index (BMI = weight in kilograms divided by the square of height in meters) as a measure of overall adiposity. Waist circumference was measured at the center point between the lower border of rib cage and the upper border of iliac crest to the nearest 0.1 cm and was used as an indicator of abdominal visceral fat along with sagittal diameter [18,19]. Sagittal diameter (abdominal height), defined as the thickness of the abdomen at waist level, was measured with a portable sliding beam abdominal caliper in supine position. In the supine position, the body's visceral fat projects the abdomen in a sagittal direction, and gravity moves the subcutaneous fat to the sides [20]. Replicate blood pressure measurements were obtained on the right arm of the subjects in a relaxed, sitting potion. Well-trained observers, using mercury sphygmomanometer, recorded first and fifth Korotkoff phase for systolic and diastolic blood pressures, respectively. Blood pressure levels were reported as a mean of 6 replicate readings.

### 2.3. Laboratory analyses

Cholesterol and triglycerides levels in the serum were assayed using enzymatic procedures on the Hitachi 902 Automatic Analyzer (Roche Diagnostics, Indianapolis, IN). Serum lipoprotein cholesterol levels were analyzed by a combination of heparin-calcium precipitation and agar-agarose gel electrophoresis procedures [21]. The laboratory is being monitored for precision and accuracy of lipid measurements by the Lipid Standardization and Surveillance Program of the Centers for Disease Control and Prevention (Atlanta, GA). A commercial radioimmunoassay kit was used for measuring plasma immunoreactive insulin levels (Phadebas; Pharmacia Diagnostics, Piscataway, NJ). Plasma glucose and uric acid levels were measured as part of a multiple chemistry profile (SMA20) by enzymatic procedures with the multichannel Olympus Au-5000 analyzer

Table 1
Mean ± SD of CRP and other risk factor variables by race and sex: the Bogalusa Heart Study

| Variable | Male | | Female | | $P^a$ | |
|---|---|---|---|---|---|---|
| | White (n = 358) | Black (n = 129) | White (n = 412) | Black (n = 184) | Sex | Race |
| Age (y) | 36.4 ± 4.3 | 36.5 ± 4.4 | 36.3 ± 4.3 | 35.2 ± 4.8 | NS | NS |
| BMI (kg/m$^2$) | 29.2 ± 5.7 | 29.9 ± 7.3 | 27.9 ± 6.4 | 30.4 ± 7.5 | <.0001[b] | <.0001[c] |
| Waist (cm) | 99.7 ± 15.1 | 97.8 ± 17.7 | 86.4 ± 15.8 | 91.9 ± 16.6 | <.0001 | <.0001 |
| Sagittal diameter (cm) | 23.3 ± 3.9 | 24.2 ± 4.4 | 20.7 ± 3.8 | 23.0 ± 4.1 | <.0001 | <.0001 |
| SBP (mm Hg) | 118.5 ± 11.1 | 128.8 ± 16.2 | 110.4 ± 11.0 | 118.1 ± 15.4 | <.0001 | <.0001 |
| DBP (mm Hg) | 80.3 ± 8.1 | 86.9 ± 12.1 | 74.6 ± 8.1 | 79.1 ± 11.0 | <.0001 | <.0001 |
| MAP (mm Hg) | 93.1 ± 8.6 | 100.8 ± 13.0 | 86.5 ± 8.7 | 92.1 ± 12.0 | <.0001 | <.0001 |
| LDL-C (mg/dL) | 128.9 ± 34.3 | 124.5 ± 43.4 | 123.8 ± 32.3 | 115.4 ± 31.3 | .002 | .005 |
| HDL-C (mg/dL) | 40.8 ± 10.8 | 48.9 ± 15.6 | 50.1 ± 12.5 | 51.8 ± 12.7 | <.0001[b] | <.0001[d] |
| TG (mg/dL) | 166.1 ± 130.5 | 130.7 ± 109.3 | 120.6 ± 72.6 | 87.5 ± 37.4 | <.0001 | <.0001 |
| TC/HDL-C ratio | 5.0 ± 1.4 | 4.2 ± 1.5 | 4.0 ± 1.1 | 3.6 ± 1.0 | <.0001 | <.0001 |
| Insulin ($\mu$U/mL) | 13.3 ± 10.1 | 12.4 ± 9.7 | 11.3 ± 8.0 | 13.5 ± 9.4 | <.0001[b] | <.0001[c] |
| Glucose (mmol/L) | 88.6 ± 23.6 | 90.5 ± 32.5 | 82.5 ± 15.6 | 88.0 ± 33.6 | .009 | .02 |
| HOMA-IR | 3.1 ± 3.2 | 2.9 ± 2.7 | 2.4 ± 2.8 | 3.0 ± 2.4 | <.0001[b] | <.0001 |
| Uric acid (mg/dL) | 6.2 ± 1.2 | 6.5 ± 1.5 | 4.4 ± 1.0 | 4.3 ± 1.2 | <.0001 | .04[d] |
| CRP (mg/L) | 1.8 ± 1.9 | 2.3 ± 2.3 | 2.5 ± 2.3 | 2.7 ± 2.4 | .0001 | .01 |

TG indicates triglyceride; SBP, systolic blood pressure; DBP, diastolic blood pressure; TC, total cholesterol; NS, not significant.

[a] Adjusted for age.
[b] Whites only.
[c] Females only.
[d] Males only.

(Olympus, Lake Success, NY). Insulin resistance status was assessed as homeostasis model assessment of insulin resistance (HOMA-IR) according to the formula described previously [22]: HOMA-IR = [insulin ($\mu$U/mL) × glucose (mmol/L)/22.5]. This index of insulin resistance is considered useful for epidemiological studies [23]. Plasma high-sensitivity CRP was measured by latex particle-enhanced immunoturbidimetric assay on Hitachi 902 Automatic Analyzer.

### 2.4. Statistical analysis

All statistical analyses were performed with SAS version 9.1 (SAS Institute, Cary, NC). General linear models were used to examine race and sex differences in risk factor variables. All $P$ values were 2-tailed and adjusted for covariates where appropriate. Wherever race-sex interaction was present, separate models were used by race or sex. Univariate analysis was used to obtain the percentile and frequency distribution of CRP by race and sex. Correlations between CRP and risk factor variables were assessed by Pearson correlation coefficients, adjusted for age, race, sex, and cigarette smoking. Individuals were considered smokers if they reported current use of cigarette or having stopped smoking within the past year. Effect of multiple risk factors of metabolic syndrome on levels of CRP was examined by comparing the mean CRP values of individuals with 0, 1, 2, and 3 or more risk factors. The metabolic syndrome risk

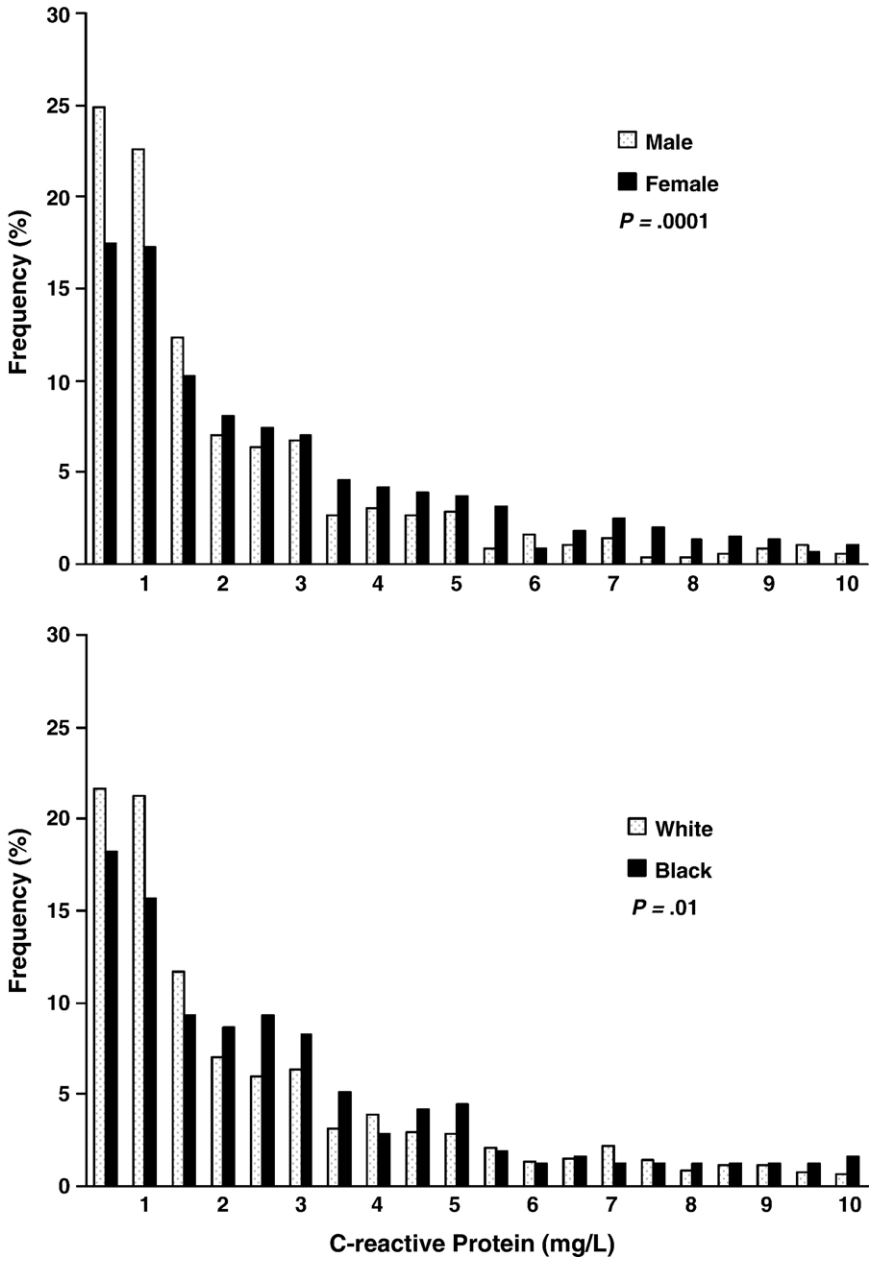


Fig. 1. Frequency distribution of CRP by sex and race: the Bogalusa Heart Study.

Table 2
Pearson correlation coefficients between risk factor variables and CRP in young adults by race and sex: the Bogalusa Heart Study

| Variables | White male[a] | Black male[a] | White female[a] | Black female[a] | Total sample[b] |
|---|---|---|---|---|---|
| BMI | 0.39*** | 0.49*** | 0.46*** | 0.35*** | 0.41*** |
| Waist | 0.41*** | 0.51*** | 0.46*** | 0.39*** | 0.36*** |
| Sagittal diameter | 0.40*** | 0.51*** | 0.52*** | 0.42*** | 0.41*** |
| SBP | 0.16** | 0.25* | 0.26*** | 0.09 | 0.15*** |
| DBP | 0.20*** | 0.24* | 0.23*** | 0.12 | 0.15*** |
| MAP | 0.20*** | 0.25*** | 0.25*** | 0.12 | 0.16*** |
| LDL-C | 0.20* | 0.23* | 0.20*** | 0.23** | 0.16*** |
| HDL-C | −0.17** | −0.39*** | −0.04 | −0.03 | −0.07* |
| TG | 0.16* | 0.31** | 0.38*** | 0.19* | 0.20*** |
| TC/HDLC ratio | 0.21*** | 0.41*** | 0.21*** | 0.18* | 0.15*** |
| Insulin | 0.24*** | 0.42*** | 0.44*** | 0.24** | 0.32*** |
| Glucose | 0.14* | 0.25* | 0.15** | 0.25** | 0.17*** |
| HOMA-IR | 0.24*** | 0.44*** | 0.44*** | 0.30*** | 0.33*** |
| Uric acid | 0.14* | 0.34*** | 0.26*** | 0.10 | 0.07* |

[a] Adjusted for age and smoking.
[b] Adjusted for age, sex, race, and smoking.
* $P \leq .01$.
** $P = .001$.
*** $P \leq .0001$.

factors and cutoff values were used in this analysis as defined by the National Cholesterol Education Program Adult Treatment Panel III [24].

Models assessing the independent relation between risk factor variables and CRP were constructed using stepwise linear regression (significance level to enter and stay, .05). Three separate models including different measures of obesity (BMI, waist circumference, and sagittal diameter) were used to examine the independent contribution of different measures of obesity to the variance in CRP levels. Other independent variables included in these models were age, race, sex, cigarette smoking, mean arterial pressure (MAP = diastolic blood pressure + 1/3 pulse pressure), total cholesterol–high-density lipoprotein cholesterol (HDL-C) ratio, HOMA-IR, and uric acid. The ratio of total cholesterol to HDL-C was chosen as a measure of dyslipidemia because it better relates to insulin resistance, the underlying feature of metabolic syndrome [25]. Values of CRP, HOMA-IR, triglyceride, and uric acid were log transformed in the correlation and regression analyses to improve normality.

## 3. Results

Mean levels of anthropometric, hemodynamic, and metabolic variables along with CRP levels in the study cohort are shown in Table 1 by race and sex. With the exception of age, significant race and sex differences were observed for all the risk variables listed. Blacks had higher BMI (females only), waist circumference, sagittal diameter, systolic and diastolic blood pressures, MAP, HDL-C (males only), glucose, insulin (females only), HOMA-IR, and uric acid (males only), and lower low-density lipoprotein cholesterol (LDL-C), triglycerides, and total cholesterol–HDL-C ratio than whites. With respect to sex differences, males vs females had higher BMI (whites only), waist circumference, sagittal diameter, systolic and diastolic blood pressures, MAP, LDL-C, triglycerides, total cholesterol–HDL-C ratio, glucose insulin (whites only), HOMA-IR (whites only), and

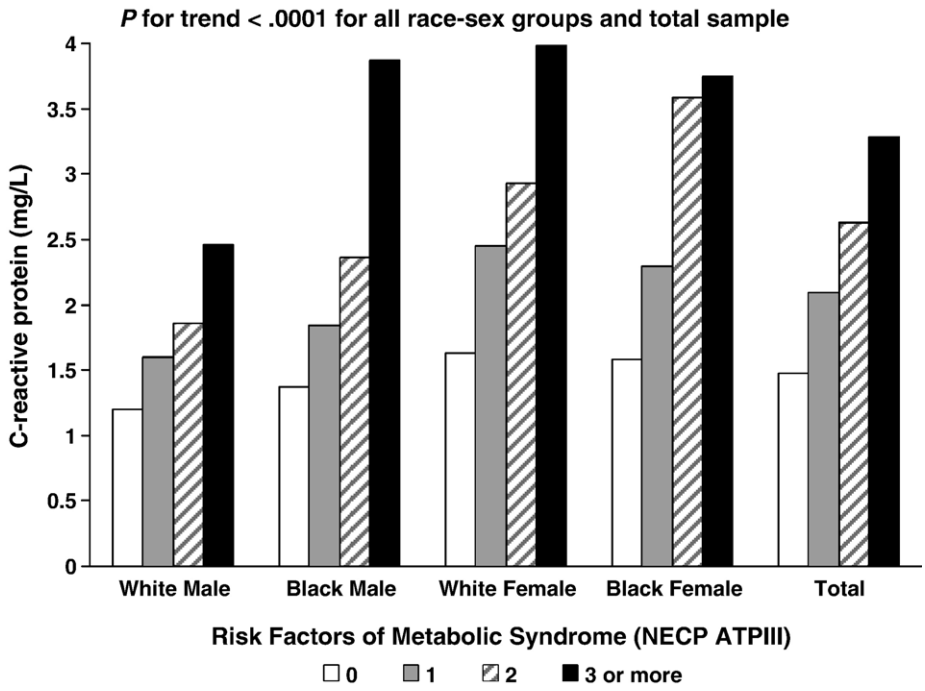


Fig. 2. Mean CRP levels by number of risk factors of metabolic syndrome: the Bogalusa Heart Study.

Table 3
Predictors of CRP levels in young adults by different measures of obesity: the Bogalusa Heart Study

| Model 1 (BMI) | | Model 2 (waist circumference) | | Model 3 (sagittal diameter) | |
|---|---|---|---|---|---|
| Predictors | Partial $R^2$ | Predictors | Partial $R^2$ | Predictors | Partial $R^2$ |
| BMI | 0.170**** | Waist | 0.134**** | Sagittal diameter | 0.171**** |
| Sex (female > male) | 0.029**** | Sex (female > male) | 0.080**** | Sex (female > male) | 0.065**** |
| HOMA-IR | 0.012**** | TC/HDL-C ratio | 0.006** | TC/HDL-C ratio | 0.007*** |
| TC/HDL-C ratio | 0.005** | MAP | 0.005* | | |
| MAP | 0.005** | HOMA-IR | 0.003* | | |
| Model $R^2$ (%) | 22.2 | Model $R^2$ (%) | 23.0 | Model $R^2$ (%) | 24.4 |

Predictor variables are listed in the order of entry ixnto the model. Each model includes age, race, sex, cigarette smoking (yes/no), MAP, TC/HDL-C ratio, HOMA-IR, uric acid, and 1 obesity measure (BMI/waist circumference/sagittal diameter). Abbreviations are explained in Table 1.

* $P < .05$.
** $P < .01$.
*** $P < .001$.
**** $P < .0001$.

lower HDL-C (whites only). With respect to CRP, blacks vs whites and females vs males had significantly higher values. As shown in Fig. 1, the frequency distribution were continuous but highly skewed to the right in all 4 race-sex groups, reflecting the wide difference between the median and mean values for each race-sex group.

Partial correlations between risk factor variables and CRP levels in race-sex groups (adjusted for age and cigarette smoking status) and total sample (adjusted for age, race, sex, and cigarette smoking status) are listed in Table 2. In the total sample and males of both races, CRP was significantly and positively associated with all risk factor variables, except HDL-C, which showed significant inverse correlation. These significant associations were also seen in white females, except for HDL-C; black females showed no significant association with respect to blood pressure variables, HDL-C, and uric acid. In general, the magnitude of correlations was better with obesity measures, insulin, and HOMA-IR than with other variables.

The mean CRP levels for subjects with increasing number of risk factors of metabolic syndrome (0, 1, 2, and $\geq 3$), as defined by the National Education Program Adult Treatment Panel III, are shown by race-sex groups and total sample in Fig. 2. Mean CRP levels increased with increasing number of risk factors in all race-sex groups and total sample ($P$ for trend $<.0001$).

Predictor variables of CRP are listed in Table 3. The effects of independent variables on CRP explained 22.2%, 23.0%, and 24.4% of the variance, respectively, in separate models, which includes BMI, waist circumference, and sagittal diameter as a measure of obesity. In all 3 models, measure of obesity was the major contributor with BMI, waist circumference, and sagittal diameter, explaining 17.0%, 13.4%, and 17.1% of the variance, respectively. In contrast, HOMA-IR explained only 1.2% and 0.3% of the variance in the models that includes BMI and waist circumference, respectively, and nothing in the model with sagittal diameter. Of note, sex (female > male) was the second best independent correlate of CRP in all 3 models and explained 2.9% to 8.0% of the variance.

## 4. Discussion

This community-based study demonstrates that plasma CRP levels of younger adults vary by race and sex and relate adversely to risk variables of metabolic syndrome such as measure of body fatness and glucose homeostasis, lipoprotein variables, blood pressure, and uric acid, either individually or in cluster. These observations are consistent with previous findings made primarily in middle-aged and older populations [7,13-15]. It is noteworthy that of the metabolic syndrome variables, body fatness was the major independent predictor of CRP in this younger adult population, thereby suggesting obesity as a mediator of excess CRP seen in metabolic syndrome.

The observed race (black > white) and sex (female > male) divergences in CRP levels are consistent with previous data [26-30]. However, in a multivariate model, sex but not race was retained as an independent correlate of CRP in this study cohort. It is likely that the black-white difference in CRP may reflect the observed black excess in adiposity, whereas the female excess in CRP may be due to the estrogen effect. Estrogen has been implicated in the transcriptional control, clearance, or cytokine regulation of several liver-produced proteins including CRP [31-34]. Although use of oral contraceptives and postmenopausal estrogen hormone replacement therapy in the form of estrogen is known to markedly influence CRP levels [34-39], the role of premenopausal endogenous estrogen in this regard is not known.

In this study, obesity measured as BMI, waist circumference, or sagittal diameter has been identified as a critical correlate of CRP, independent of other variables of metabolic syndrome, age, race, sex, and cigarette smoking status. In fact, the sagittal diameter, a relatively better indicator of visceral adiposity [18,19,40], accounted for as much as 70% of the total explained variance in the multivariate model (total $R^2$ = 24.4%); BMI, a measure of general adiposity, also yielded similar results. These observations are consistent with previous findings [7,15,16,41-43] and underscore the pathophysiological role of adipose tissue in regulating inflammation. As a major source of proinflammatory cytokines,

adipose tissue produces tumor necrosis factor α and interleukin 6, the latter considered as the main stimulator of CRP synthesis in the liver [43,44].

Previous studies reporting a relationship between adiposity and CRP levels also found an independent association of insulin resistance/hyperinsulinemia with CRP levels [6,7,45,46]. Most of these studies involved relatively older adult population in whom the metabolic sequelae and interrelationships regarding metabolic syndrome variables might already have been well established in clinical terms, whereas in the current younger adult study cohort, insulin resistance assessed as HOMA-IR, although retained in the multivariate model that included BMI or waist circumference, contributed minimally to the CRP variance. Furthermore, in the model that included sagittal diameter, HOMA-IR was not retained as significant correlate of CRP. These results suggest that adiposity, especially visceral adiposity, may be the major regulator of CRP levels in the younger population.

Of note, although insulin resistance is considered to play a pathogenic role in metabolic syndrome [9,10] and the link between obesity and insulin resistance/hyperinsulinemia is well known [47,48], our earlier studies in this cohort showed temporal association between the baseline adiposity and incidence of hyperinsulinemia and the associated metabolic syndrome, independent of baseline insulin level [49,50]. Because adipose tissue also plays a role in the development of insulin resistance through adipocytokines [51,52], it could be a modulator of CRP associated with metabolic syndrome. It is of interest that in the current study CRP levels increased with increasing metabolic syndrome risk factors that included abdominal obesity and hyperglycemia, which is consistent with earlier studies [6,8,13,14].

The present study has certain limitations. This study lacks direct assessments of body fat mass and distribution and in vivo insulin action used in clinical and etiological studies. Instead, we used well-established surrogate measures that are simple and appropriate at population level. Furthermore, this study is observational and cross-sectional in nature and, therefore, cannot prove but only suggest causality of the observed relationships.

In summary, although obesity and insulin resistance are the underlying features of the metabolic syndrome, the former appears to be the major contributing factor to CRP levels in younger adults. When viewed in the context of the upward secular trend in the United States for being obese [53,54] and beneficial effect of weight reduction on CRP levels [45,55,56], these observations underscore the importance of prevention and control of obesity early in life.

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