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C-reactive protein (CRP) is a risk factor for cardiovascular disease and mortality; it is known to be positively associated with obesity but there is some evidence that this association differs by race or sex. We used nationally representative data of adults aged >50 years to investigate sex and race modifiers of the associations between obesity and CRP in non-Hispanic White males (n=3,517) and females (n=4,658), and non-Hispanic Black males (n=464) and females (n=826). Using multiple linear regression models with the natural logarithm of CRP as the dependent variable, we sequentially included body mass index (BMI), a body shape index (ABSI), and socioeconomic, health and health behavior covariates in the model. The association between BMI and CRP was significantly stronger in females than males. Obese White females had mean CRP values slightly above 3 mg/liter (vs 2 for White males) and Black females had mean CRP values >4 mg/liter (vs 3 for Black males). More than 50% of Black females in the United States have obesity. Continued research into racial and sex differences in the relationship between obesity, inflammation, and health risks may ultimately lead to more personalized weight loss recommendations. *Ethn Dis.* 2016;26(2):197-204; doi:10.18865/ed.26.2.197

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INTRODUCTION

C-reactive protein (CRP) is a marker of chronic inflammation and a risk factor for cardiovascular disease and mortality.¹⁻⁵ C-reactive protein levels are known to vary across demographic groups and metabolic states.⁶⁻⁸ For example, it is known that CRP increases with age and is higher in those with excess adipose tissue.⁹ Adipose tissue contains most types of immune cells making it important to immune cell homeostasis.¹⁰ One pathway to inflammation related to obesity is the inadequate storage of fat in subcutaneous adipose tissue. This leads to an increase in visceral adipose tissue,¹¹ which furthers inflammation.¹²⁻¹⁴

Epidemiological studies have found that, like CRP, fat storage varies across demographic groups.^{13,15} Males, for example, are known to store a greater proportion of fat in visceral tissue.¹³ Racial and ethnic variations have also been shown in regard to fat storage.¹⁷ Non-Hispanic Blacks (hereafter, Black) adults, for example, have been shown in numerous epidemiological studies to store a lower proportion of fat in visceral tissue compared with non-Hispanic

Whites (hereafter, White) adults.¹⁶ One study that characterized fat distribution via dual energy X-ray and computed tomography showed that Black men and women had lower visceral fat than White men and women controlling for age, total body fat, and other covariates.¹⁷

Consistent with these differences in fat storage, there is evidence that the relationship between obesity and CRP varies across demographic groups.⁶ For example, numerous observational studies have shown a stronger positive association between BMI and CRP in females than males. Findings have been inconsistent with regard to race, however, and a systematic review of BMI and CRP concluded that further studies comparing differences are needed.⁶ Of 51 cross-sectional studies in this 2013 review, just one included African Americans (n=315) despite African American women having among the highest levels of obesity in the world. That study found a positive association between obesity and CRP that remained after adjustments for sex and age.¹⁸

We used a large national sample of adults aged >50 years in the United States to investigate sex and race (ie, Black or White) as modifi-

ers of the association between BMI and CRP. Our models included chronic disease and health covariates as well as a new indicator of fat distribution. A body shape index (ABSI) is a recently introduced measure of adiposity that has been presented as an indicator of adipose tissue distribution.¹⁹ In two separate nationally representative data-

We hypothesized that we would find a weaker association between BMI and CRP in demographic groups that store a lower proportion of fat in visceral tissue (eg, women and Black adults) in comparison to groups that store more fat in visceral tissue (eg, men and White adults).

sets (one of the United States and one of Great Britain), the ABSI has been shown to be a better predictor of mortality than BMI, waist circumference, waist to hip ratio, and waist to height ratio.^{19,20} Such information may improve understanding of sex and race differences in the health consequences of obesity and inflammation. This understanding could help to guide work

that is needed to develop obesity guidelines that are more specific to group and individual risk. We hypothesized that we would find a weaker association between BMI and CRP in demographic groups that store a lower proportion of fat in visceral tissue (eg, women and Black adults) in comparison to groups that store more fat in visceral tissue (eg, men and White adults).

METHODS

We investigated cross-sectional associations between obesity and CRP using nationally representative data.

Study Sample

The Health and Retirement Survey (HRS) is an ongoing nationally representative study of US adults aged >50 years.²¹ The sample is constructed from a multi-stage national area probability sample with an oversample of Black adults. Data are collected by home interview. For the analyses reported here, we selected HRS respondents who were aged >50 years at the 2006 or 2008 interview. The 2006 and 2008 interviews included, for the first time, the opportunity to provide blood for measurement of biomarkers, including CRP. One-half of the 2006 sample was randomly preselected. One half of respondents in the preselected sample were invited to provide blood and saliva specimens in 2006 and the other one half of the preselected sample were invited to do so in 2008. For the analyses, we excluded those missing BMI (n=789), who had

sample weights of 0 (n=752), were below normal BMI (n=82), Hispanic (n=951), other races (n=217) or were missing any of the covariates (n=138). Final sample size was 9,465. Sampling weights were used in all analyses. The institutional review board of Indiana University-Purdue University Indianapolis approved the work reported here. Analyses were completed in 2014.

Measures

C-reactive protein was determined from assays of dried blood spot. Because values based on dried blood spot vary by assay, we used the National Health and Nutrition Examination Survey equivalent assay. BMI was computed from height and weight, which were measured at the home interviews. We created normal (18.5-24.9), overweight (25-29.9), obese I (30-34.9), and obese II or III (35 or over) BMI classes. Waist circumference, measured at the height of the participant's navel, was also obtained at the home interviews. The ABSI was computed from BMI and waist circumference using the formula published by Krakauer and Krakauer.²⁰ In Table 1, we provide the ABSI value without adjustment. For analyses, due to the small scale of the ABSI values, we multiplied them by 100 so that the regression coefficient of the ABSI is on the similar order of magnitude to those for other covariates. Variables created from survey questions were: age; sex; race; years of education; household income; household net worth; perceived health; number of chronic conditions (arthritis, dia-

betes, hypertension, heart disease [heart attack, coronary heart disease, congestive heart failure, angina, other], lung disease, cancer other than skin, and stroke); smoking status (never, former, current); and activity level (sedentary, regular moderate activity, and regular vigorous activity). Perceived health was phrased as “In general, would you say your health is (excellent, very good, good, fair, or poor)?” The stem to the chronic condition questions was “Has your doctor ever told you that you have...?” These HRS measures were selected as covariates to adjust for demographic,

economic, chronic disease, and health and health behavior differences in sex and race groups that may contribute to inflammation.²²

Analyses

Descriptive statistics were reported using mean and standard deviation for normally distributed continuous variables, median and interquartile range for non-normally distributed continuous variables, and percent for categorical variables among White male, Black male, White female, and Black female subgroups. Racial differences in covariates among

males and females were compared using regression analysis for continuous variables and Pearson chi-square test for categorical variables.

To estimate modifying effects of sex and race, we first compared BMI and CRP associations across the four sex-by-race subgroups. Second, we introduced ABSI into the model to assess the role fat distribution may play in the modifying effects of sex and race. Finally, we tested whether sex and race persist as modifiers of the BMI and CRP association with demographic, socioeconomic, chronic disease, health, and health behavior factors controlled.

Table 1. Natural logarithm c-reactive protein (logeCRP), body mass index (BMI), sociodemographic, health, illness, and behavior values among White males and females and Black males and females, 2006 and 2008 Health and Retirement Study

| | White Males | Black Males | White Females | Black Females |
|--|-------------|-------------|---------------|---------------|
| Sample size | n=3,533 | n=466 | n=4,680 | n=838 |
| Age (SD) | 65.6 (10.2) | 63.7 (8.0) | 67.0 (10.2) | 64.6 (7.5) |
| Years of education, mean (SD) | 13.6 (2.8) | 11.9 (3.1) | 13.1 (2.4) | 12.0 (2.4) |
| Household income, median (00) (SD) | 6.1 (14.9) | 3.7 (5.7) | 4.3 (11.2) | 2.0 (3.2) |
| Household net worth, median (000) (SD) | 1.3 (14.0) | .1 (4.7) | 1.0 (7.9) | .0 (1.5) |
| Smoking, % | | | | |
| Never smoked | 32 | 30 | 52 | 50 |
| Formerly smoked | 56 | 51 | 36 | 35 |
| Currently smoke | 12 | 19 | 12 | 15 |
| Activity level, % | | | | |
| Sedentary | 13 | 13 | 19 | 27 |
| Some physical activity | 57 | 62 | 61 | 60 |
| Vigorous physical activity | 30 | 25 | 20 | 13 |
| Perceived health, % | | | | |
| Excellent | 12 | 7 | 12 | 4 |
| Very good | 34 | 26 | 35 | 21 |
| Good | 32 | 30 | 32 | 34 |
| Fair | 16 | 28 | 16 | 31 |
| Poor | 6 | 10 | 5 | 10 |
| Number of chronic illnesses, mean (SD) | 1.8 (1.4) | 1.8 (1.2) | 1.8 (1.3) | 2.3 (1.1) |
| CRP, mean (SD) | 3.59 (7.96) | 4.78 (8.30) | 4.36 (7.72) | 6.83 (8.30) |
| logeCRP, mean (SD) | .53 (1.24) | .78 (1.11) | .78 (1.16) | 1.18 (1.02) |
| A body shape index (ABSI), mean (SD) | .084 (0) | .083 (0) | .081 (.01) | .081 (.01) |
| Body mass index (BMI), mean (SD) | 29.4 (5.3) | 29.4 (4.8) | 29.1 (6.3) | 32.2 (5.6) |
| Normal BMI, 18.5<25.0, % | 19 | 22 | 30 | 15 |
| Overweight BMI, 25.0<30.0, % | 42 | 38 | 34 | 26 |
| Obese class I BMI, 30.0<35.0, % | 26 | 27 | 21 | 28 |
| Obese class II & III BMI, ≥35.0, % | 13 | 13 | 15 | 31 |

Specifically, three multiple linear regression models were used to test the association of BMI class with CRP in sex-by-race groups after sequentially adjusting for covariates. Each model included main effects for sex, race, and BMI as well as the interaction of the terms. The first model included only age at data collection as a covariate, the second also included ABSI, while the third model also included years of education, household income, household net worth, perceived health, number of chronic conditions, smoking status, and activity level. From each model, parameter estimates, standard errors and p-values were obtained for each of the covariates. Due to the positive skewness of the CRP levels, the natural logarithm of

CRP (logeCRP) was used as the dependent variable in all models. The exponentiated regression coefficient of an independent variable represents the ratio of the expected geometric mean CRP level when the independent variable increases by one unit. The adjusted mean levels of logeCRP were calculated for each sex, race and BMI combination and the geometric mean of CRP was computed by exponentiating each estimate. The geometric means were plotted for a visual representation of the BMI class association with CRP by sex and race after adjusting for covariates. The overall association of BMI class as well as comparisons of the association of BMI class with logeCRP across race and sex groups were estimated

by constructing appropriate contrasts from the models. All analyses were performed using the SAS 9.4 survey procedures that considered the sample weights and the multi-stage sample design of the HRS.

RESULTS

Descriptive statistics are shown in Table 1 for the four race by sex groups. Black males were youngest followed by Black females, White males, and, finally, White females. White males and females had more years of education, income, and net worth than Black males and females. Slightly more Black males and females smoked currently. Black males and females more often rated their health as fair or poor compared with White males and females and Black females had a greater number of chronic conditions than the other three groups.

BMI, ABSI, and CRP values for the four subgroups are also shown in Table 1. Mean BMI was considerably higher among Black females in comparison to the other three groups; 59% of Black females were obese (class I or greater) compared with 36% of White females, 40% of Black males, and 39% of White males. Mean ABSI, however, was quite similar across the four subgroups and just slightly higher among males (.084 vs .081). Mean CRP was greatest among Black females at 6.8 and lowest among White males at 3.6. LogeCRP for these two groups was 1.18 and .53, respectively.

Age-adjusted geometric mean

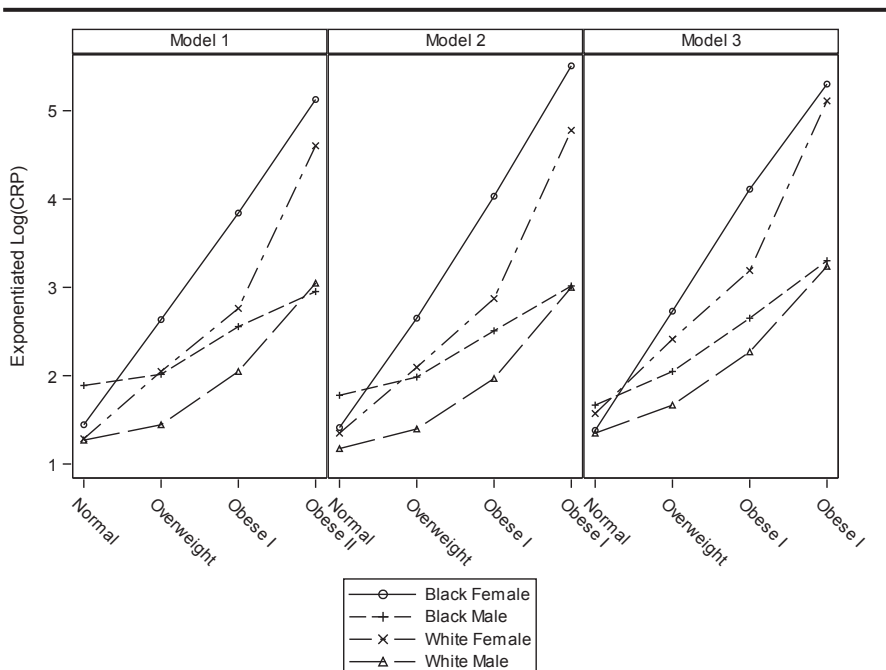


Figure 1. Multivariable adjusted (geometric) mean c-reactive protein by body mass index class for Black females, Black males, White males, and White females, 2006 and 2008 Health and Retirement Study

Model 1 included age; Model 2 included age and ABSI; Model 3 included age, ABSI, demographic variables, chronic disease, health, and health behavior covariates.

Table 2. Parameter estimates and standard errors (SE) for covariates of Models^a 1, 2, and 3 regressed on natural logarithm c-reactive protein (logeCRP), 2006 and 2008 Health and Retirement Study

| | Model 1 | | | Model 2 | | | Model 3 | | |
|---|---------|-----|------|---------|-----|------|---------|-----|------|
| | Est. | SE | P | Est. | SE | P | Est. | SE | P |
| Age | .01 | .00 | <.01 | 0 | 0 | .39 | 0 | 0 | .93 |
| ABSI (x100) | | | | .27 | .02 | <.01 | .19 | .02 | <.01 |
| Years of education | | | | | | | -.02 | .01 | <.01 |
| Household income (00) | | | | | | | 0 | 0 | .69 |
| Household net worth (000) | | | | | | | 0 | 0 | .67 |
| Never smoked (reference category) | | | | | | | | | |
| Formerly Smoked | | | | | | | .09 | .03 | <.01 |
| Currently smoke | | | | | | | .40 | .04 | <.01 |
| Some physical activity (reference category) | | | | | | | | | |
| Sedentary | | | | | | | .09 | .04 | .02 |
| Vigorous physical activity | | | | | | | -.05 | .03 | .14 |
| Perceived health very good (reference category) | | | | | | | | | |
| Perceived health excellent | | | | | | | -.09 | .04 | .04 |
| Perceived health good | | | | | | | .04 | .03 | .21 |
| Perceived health fair | | | | | | | .16 | .05 | <.01 |
| Perceived health poor | | | | | | | .36 | .07 | <.01 |
| Number of chronic illnesses | | | | | | | .02 | .01 | .08 |

a. Models 1, 2, and 3 each included main effects and interaction terms for each race by sex group and BMI class.

CRP levels for each BMI class are shown in Model 1 of Figure 1 separately for the four subgroups. Relative to normal weight BMI, having an overweight or obese BMI was associated with a higher CRP value ($P<.001$). Females experienced a stronger positive association between BMI class and CRP than did males ($P<.001$). In contrast, there was no significant difference in the association between age-adjusted CRP and BMI class between Black and White respondents. Models 2 and 3 of Figure 1 show CRP means adjusted for covariates. Model 2 adjusts for age and ABSI and model 3 adjusts for age, ABSI, socioeconomic, health, behavior, and illness. These covariates had little effect on sex differences in adjusted geometric mean CRP. A significant sex effect remained ($P=.002$ in model

2; $P=.010$ in model 3). As can be seen in Model 3, multivariable adjusted mean CRP exceeded 3.0 for females in obese class I and 5.0 for those in obese class II or higher.

Table 2 shows the parameter estimates for the covariates adjusted in the multiple linear regression models. As shown in Model 1, age had strong positive associations with logeCRP. In Model 2, ABSI had a highly significant positive association with logeCRP. ABSI did not, however, reduce the association between BMI and logeCRP nor did it significantly alter the parameter estimates for the association of BMI with logeCRP (not shown).

Model 3 of Table 2 included socioeconomic covariates along with perceived health, number of chronic illnesses, physical activity level, and smoking status. Among

newly added covariates, fewer years of education, current and former smokers compared to non-smokers, fair or poor perceived health compared to very good health, and sedentary activity level compared to some physical activity were associated with a higher CRP. Neither the variable of income/net worth nor chronic illnesses reached statistical significance in this model.

DISCUSSION

We found a considerably stronger positive association between BMI class and CRP among females, both Black and White. As noted earlier, a systematic review found the association between BMI and CRP was stronger among females than males.⁶ The stronger association

among females was consistent across cultures and race among available epidemiological studies. Available studies did not include a sample of African American men and women, which the study reported here now provides. The reasons for a stronger relationship between BMI and CRP in females are still unknown but the review offered three possible biological reasons: 1) metabolic activity of adipose tissue may differ by sex; 2) females have higher levels of

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leptin; and 3) body fat is higher and distributed differently in females. As a preliminary investigation of the latter hypothesis, we adjusted for ABSI, a new measure of central adiposity. ABSI as measured did not eliminate sex differences in the relationship between BMI and CRP in our analyses. In fact, both ABSI and BMI had significant positive independent associations with CRP.

A stronger association between obesity and CRP among women is of concern for several reasons. First, a recent large pooled analysis showed that adults in the top quintile of CRP had a hazard ratio well

above 2.0 for all-cause mortality and approaching 3.0 for cardiovascular disease mortality and the hazard ratios were largely consistent by sex.² Second, Lakoski et al found a CRP value of 3 mg/liter or greater was associated with increased mortality risk among obese White adults and Black adults.²³ Finally, other authors have concluded that a single CRP value of >3 mg/L is robustly associated with 2-fold greater all-cause mortality risk.⁴ We found obese White females to have an adjusted mean CRP value slightly above 3 mg/L and obese Black females to have an adjusted value slightly above 4 mg/L. Among White and Black males, mean CRP approached 3 mg/L only among those in BMI class II or higher. At obese class II or higher, White females had mean CRP values > 4 mg/L and Black females had mean CRP values > 5 mg/L. The majority of Black females in the United States have class II or higher obesity.²⁴

A recent and large prospective cohort study of Black adults with a socioeconomically matched White sample found obesity as measured by BMI was associated with mortality in middle and older-aged White but not Black adults.²⁵ Lakoski et al found a similar result; an obese BMI was associated with higher mortality in middle and older aged Whites but not Blacks.²³ And, in a recent analysis of BMI class and 10-year mortality in older Nigerians and African Americans, we did not find class I or II BMI to confer any mortality risk above normal BMI class. Adjusting for baseline disease and biomarkers including

CRP did not affect the findings.²⁶ Combined with evidence of higher SAT compared to VAT in Black vs White adults,¹³ these findings suggest the possibility of lower BMI risk among Black compared with White adults.¹³ However, our current analyses do not support this conclusion as we did not find a statistically significant race difference in the association between BMI and CRP. Moreover, parameter estimates of the association between BMI and CRP were little affected by adjustments for socioeconomic factors or comorbidity in any of the four subgroups.

There are important limitations to our report. The work reported here is based on data representative of United States adults aged >50 years in 2006 or 2008 but the analyses are all cross-sectional. Moreover, our characterization of race is based on self-reported identity. Evidence indicates that, for predicting cardiovascular risk, self-identified race produces results similar to biogeographic ancestry but a higher BMI is associated with West African ancestry.²⁷ The dataset used in these analyses lacked important metabolic indicators, such as insulin and lipids, which hindered our ability to further explore the positive association between BMI and CRP or sex differences in that relationship.

CONCLUSION

Recent epidemiological evidence of substantially elevated CRP values among middle and older aged Black obese women, yet limited mortality

risk from elevated BMI, warrants more investigation. This paradox may be an opportunity to improve understanding and guidelines for obesity. Evidence now supports that adipose tissue function is as important as amount.²⁸ Future studies comparing multiethnic samples might investigate the association of metabolic indicators and markers of fat with longer-term cardiovascular disease and mortality outcomes. Such investigations may shed new light on the association between obesity and risk, which may ultimately lead to more personalized obesity guidelines and weight management recommendations.

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CONFLICTS OF INTEREST

No conflicts of interest to report.

AUTHOR CONTRIBUTIONS

Clark, Unroe, Xu, Keith, Callahan, Tu; Research concept and design: Clark, Xu, Keith, Callahan; Acquisition of data: Clark, Unroe, Keith; Data analysis and interpretation: Clark, Xu, Keith, Tu; Manuscript draft: Clark, Unroe, Xu, Keith, Callahan, Tu; Statistical expertise: Clark, Xu, Keith, Tu; Acquisition of funding: Clark, Keith; Administrative: Clark, Keith, Callahan; Supervision: Clark, Unroe, Keith, Callahan

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