Sex Differences in the Relationship between C-Reactive Protein and Body Fat

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Background: C-reactive protein (CRP) levels are significantly influenced by adiposity and are higher in women compared with men. We postulated that there may be sex differences in the relationship between CRP and body fat.

Methods: We measured CRP and body fat parameters in 1166 men and 1413 women ages 30–65 in the population-based Dallas Heart Study. Total fat mass (TFM) was measured using dual-energy x-ray absorptiometry scanning and was subdivided into truncal fat (TrF) and lower body fat (LBF). The TrF/LBF ratio was used to measure fat distribution. Abdominal fat compartments (ip and sc) were measured using magnetic resonance imaging. Log-transformed CRP was used as the outcome variable in sex-combined models with interaction tests.

Results: Median body mass index was higher in women than in men (29.9 *vs*. 28.2 kg/m^2), as was TFM (29.7 *vs*. 20.5 kg) ($P < 0.001$ each). TFM was linearly associated with log CRP in both sexes, with a steeper slope of association in women (P interaction = 0.003). CRP increased to a greater degree with increasing TrF (P interaction = 0.0004) in women compared with men, even after adjustment for TFM; values were similar across sexes for LBF. Fat distribution (TrF/LBF ratio) was more strongly associated with CRP levels in women *vs*. men (R^2 adjusted for TFM = 0.04 *vs*. 0.008). Greater increases in CRP were also observed with increasing ip and sc fat in women compared with men.

Conclusions: The quantity and distribution of body fat influence CRP to a greater extent in women compared with men. Adiposity as a contributor to subclinical inflammation may be particularly relevant in women. **(*J Clin Endocrinol Metab* 94: 3251–3258, 2009)**

Numerous studies have linked higher C-reactive protein (CRP) levels to the development of cardiovascular risk factors including diabetes and hypertension, and to an increased risk of vascular events (1). Adipose tissue serves as an endocrine organ, secreting a host of inflammatory cytokines including IL-6, which stimulates hepatic production of CRP (2). Indeed, measures of obesity are among the strongest correlates of CRP levels, and the close relationship between inflammation and obesity may help explain the greater burden of cardiovascular disease among obese individuals.

Women generally have higher CRP levels than men, but the mechanisms for this observation are unknown (3–5). One explanation is that there are sex differences in the relationship between CRP and obesity such that CRP levels increase to a greater degree with increasing adiposity in women than in men (4). Only a few studies have investigated sex interactions between CRP and obesity (6–11), but they have largely relied on simple anthropometric measures that may provide an inaccurate assessment of the true quantity of adipose tissue (12). None of these studies have used dual-energy x-ray absorptiometry (DEXA) to

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Abbreviations: BMI, Body mass index; CRP, C-reactive protein; DEXA, dual-energy x-ray absorptiometry; HDL, high-density lipoprotein; HDL-C, HDL-cholesterol; HOMA-IR, homeostasis model assessment of insulin resistance index; %IP fat, proportion of ip fat/total body mass; MCP-1, monocyte chemoattractant protein-1; MRI, magnetic resonance imaging; %SC fat, proportion of sc fat/total body mass; TrF/LBF, truncal fat/lower body fat ratio.

directly quantify adipose tissue, and only one has evaluated abdominal fat compartments using advanced imaging techniques (8).

Therefore, using a large, population-based sample with direct measures of adipose tissue quantity and distribution including DEXA and abdominal magnetic resonance imaging (MRI), we sought to determine whether there are sex differences in the relationship between CRP and body fat.

Subjects and Methods

Study population

The Dallas Heart Study is a multiethnic, population-based, probability sample of Dallas County residents, with deliberate oversampling of African-Americans. Details of the study design have been described previously (13). All participants provided informed consent to participate in the study, and the protocol was approved by the Institutional Review Board of the University of Texas Southwestern Medical Center. Briefly, from an initial cohort of 6101 subjects ages 18–65 yr who underwent a detailed in-home survey, 3398 subjects ages 30–65 returned for a second visit to provide blood and urine samples for laboratory testing, and 2971 subsequently returned for a third visit where they underwent various imaging procedures including DEXA (n = 2889) and abdominal MRI imaging for fat quantitation (n = 2665). Subjects who completed each of the three visits had similar medical history, demographic data, and body mass index (BMI); blood pressure and laboratory parameters were similar among those completing the second and third visits (13). The current study is limited to the 2579 subjects from the third visit with valid measurements for CRP, DEXA, and abdominal MRI parameters.

Detailed descriptions of variable definitions for diabetes, hypertension, hypercholesterolemia, hypertriglyceridemia, and low high-density lipoprotein (HDL) have been previously described (14). BMI was calculated as weight (kilograms)/[height (meters)]^2 (15). Race/ethnicity was determined by subject self-report. The homeostasis model assessment of insulin resistance index (HOMA-IR) was calculated as described previously [fasting insulin (μIU/ml) $\times$ fasting glucose (mmol/liter) /22.5] (16).

Biomarker measurements

Blood samples were obtained after an overnight fast and stored in EDTA tubes and were stored for 4 h or less at 4 C before processing. Plasma aliquots were frozen at −80 C until assays were performed. High-sensitivity CRP measurements were performed on thawed samples using the Roche/Hitachi 912 System, Tina-quant assay (Roche Diagnostics, Indianapolis, IN), a latex-enhanced immunoturbidimetric method (4). The minimal detectable range of this assay is 0.1 mg/liter, and the upper limit is 20 mg/liter. Values greater than 20 mg/liter (n = 220, or 6.5%) were treated as 20 mg/liter. The interassay coefficient of variation was 5.0% at a CRP concentration of 4.3 mg/liter and 3.2% at a concentration of 13.2 mg/liter. The methods for measurement of other biomarkers including monocyte chemoattractant protein-1 (MCP-1) (14), soluble CD40 ligand (17), lipoprotein-associated phospholipase A2 mass and activity (18), osteoprotegerin (19), and IL-18 (20) have been previously described.

DEXA measurement of body fat

DEXA measurements were performed as previously described (21). Subjects were scanned using a Delphi W scanner (Hologic Inc., Bedford, MA), and images were analyzed using Hologic Discovery software (version 12.2). DEXA measurements included total fat mass (kilograms), fat-free mass (kilograms), and bone mineral mass (kilograms) of the following body compartments: trunk, upper and lower extremities, and head. Truncal fat was defined by the region below the chin, delineated by vertical lines within the left and right glenoid fossae bordering laterally to the ribs, and by the oblique lines that cross the femoral necks and converge below the pubic symphysis. Lower body fat included all fat below these oblique lines.

MRI measurement of abdominal fat

Abdominal compartment fat mass measures by MRI in the Dallas Heart Study were performed as previously described (21). Participants were imaged using a 1.5 Tesla MRI scanner (Intera; Philips Medical Systems, Best, The Netherlands). The entire abdomen from the diaphragm to the pelvis was scanned using contiguous axial 10-mm slices. We have previously demonstrated that total abdominal compartment fat masses can be accurately predicted using a regression equation fit to values from a single MRI slice at the L2–L3 level, and we used this methodology for the current study (21, 22). Abdominal adipose tissue was distinguished and separated into ip, sc, and retroperitoneal adipose tissue compartments by manually circumscribed contours using anatomical landmarks. Fat volumes were converted to mass using 0.9196 kg/liter as the density of adipose tissue. These MRI methods to measure abdominal fat mass have been validated against cadavers (22, 23). Because the retroperitoneal fat compartment comprises the smallest amount of total body fat and our previous studies have shown that it minimally correlates with metabolic parameters in contrast to ip and sc fat (24), this compartment was excluded from the current analyses.

Statistical analysis

Categorical data are reported as proportions and continuous data as median values with interquartile ranges. Sex comparisons between body fat parameters were performed using the Wilcoxon rank sum test. Median CRP levels were calculated for gender combined total fat tertiles in each sex. Due to its skewed distribution, log CRP (natural logarithm) values were used as outcome variables in all multivariable models. Comparisons between sexes of β coefficients for body fat parameters as the independent variables and log CRP as the dependent variable were performed using gender combined multivariable linear regression models. The β coefficient for the fat parameter represented the change in mean log CRP for a 1 kg change in the particular fat parameter. Terms for race, sex, the fat parameter, and the interaction term for sex*fat parameter were included in the models. These models were further adjusted for: 1) total fat mass; and 2) age, hypertension, hyperlipidemia, smoking, diabetes, low HDL-cholesterol (HDL-C), elevated triglycerides, HOMA-IR, and statin use. Ratio measures of body fat distribution were derived, including truncal fat to lower body fat ratio (TrF/LBF), proportion of ip fat/total body mass (%IP fat), and proportion of sc fat/total body mass (%SC fat). Median CRP levels were calculated for gender-specific total fat tertiles stratified by gender-specific TrF/LBF ratio, %IP fat, and %SC fat. Partial R^2 values of these ratio measures for log CRP levels were assessed in linear

TABLE 1. Baseline characteristics

	Women	Men
n	1413	1166
Age (yr)[a]	45 (37–52)	44 (38–52)
Black race	50.6%	46.1%
Hypertension	34.8%	32.2%
Diabetes	8.6%	8.9%
Hyperlipidemia	12.9%	14.4%
Low HDL-C	44.2%	34.5%
Elevated triglycerides	7.9%	17.2%
Current smoking	24.0%	33.5%
HOMA-IR[a]	3.0 (1.7–5.0)	2.6 (1.5–4.5)
Statin use	6.6%	6.6%
Oral estrogen use	19.4%	
CRP (mg/liter)[a]	3.6 (1.6–8.0)	1.9 (1.0–4.2)

[a] Data are presented as median (25th–75th percentiles).

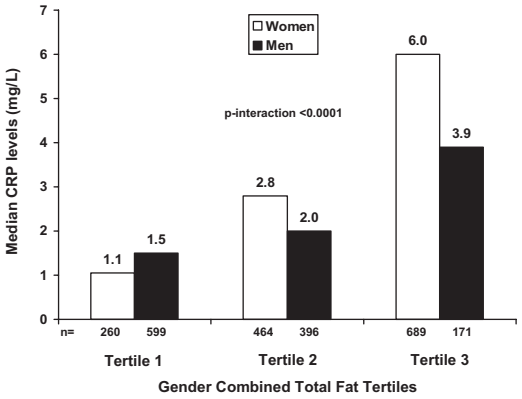

FIG. 1. Gender differences in the relationship between total fat and CRP levels. *P* interaction is adjusted for age, race, hypertension, diabetes, hypercholesterolemia, low HDL-C, elevated triglycerides, smoking, HOMA-IR, and statin use.

regression models adjusted for total fat mass and race. The cohort was also restricted to just black and white subjects, and median CRP levels for race combined total fat tertiles were evaluated, including interaction models assessing the total fat*race interaction on log CRP levels. Models with several other inflammatory biomarkers as the outcome variables were also constructed to evaluate for interactions of sex*total fat mass, with further adjustment for the risk factors above. All statistical analyses were performed using SAS, version 9.1 (SAS Corporation, Cary, NC) statistical software package.

Results

The baseline characteristics of the study cohort, stratified by sex, are presented in Table 1 and demonstrate that women had higher CRP levels than men. Women also had greater total adiposity as measured by BMI and total fat mass, as well as higher values for truncal fat, lower body fat, and sc fat mass (Table 2). In contrast, ip fat mass was greater in men.

Women and men in the lowest tertile of total fat mass had comparable CRP levels, but median CRP increased to a much greater degree with increasing total fat mass in women compared with men (Fig. 1). This sex difference in the relationship between obesity and CRP levels persisted after multivariable adjustment (adjusted *P*-interaction < 0.0001). When the analyses were repeated after excluding users of oral estrogen and when restricting to pre- or postmenopausal women, the findings were unchanged (data not shown). No racial differences were observed in the relationships between total fat mass, truncal fat, ip fat, or sc fat and CRP levels when comparing blacks to whites (*P*-interaction > 0.1 each). However, there was an interaction with race for lower body fat, with variation in lower body fat being more negatively associated with log CRP levels in blacks (−0.096 *vs.* −0.062; *P*-interaction = 0.009).

In contrast to our previous reports using BMI (4), CRP levels were not different between sexes in multivariable models, including traditional risk factors and oral estrogen use, when further adjusting for total fat mass (*P* = 0.09). After additionally adjusting for the interaction term of total fat mass*sex, CRP levels were lower for women than men when total fat mass was equivalent and 33 kg or less, and higher in women for values greater than 33 kg.

Regional fat quantity and CRP levels

Variation in truncal fat was associated with larger increases in log CRP levels in women compared with men (0.092 *vs.* 0.065 mg/liter per 1 kg increase in truncal fat;

TABLE 2. Sex comparisons of fat parameters

	Women	Men	*P* value
n	1413	1166	
BMI (kg/m^2)	29.9 (25.4–35.6)	28.2 (25.0–31.6)	<0.0001
Total body mass (kg)	76.2 (64.9–91.3)	83.9 (74.1–96.4)	<0.0001
Total fat (kg)	29.7 (23.1–39.0)	20.5 (15.1–26.7)	<0.0001
Truncal fat (kg)	14.2 (10.3–19.1)	10.7 (7.6–14.2)	<0.0001
Lower body fat (kg)	11.0 (8.5–14.3)	6.4 (4.6–8.5)	<0.0001
Intraperitoneal fat (kg)	1.1 (0.8–1.5)	1.5 (1.0–2.0)	<0.0001
sc fat (kg)	5.2 (3.6–7.5)	3.2 (2.4–4.4)	<0.0001
Retroperitoneal fat (kg)	0.94 (0.7–1.2)	0.64 (0.5–0.8)	<0.0001

Data are presented as median (25th–75th percentiles).

TABLE 3. Relationship between truncal fat and lower body fat with CRP levels

	Women		Men		
	β coefficient	*P* value	β coefficient	*P* value	*P* interaction
Truncal fat					
Model 1	0.092	<0.0001	0.065	<0.0001	0.0003
Model 2	0.074	<0.0001	0.049	0.0008	0.0006
Model 3	0.049	0.002	0.025	0.1	0.002
Lower body fat					
Model 1	0.101	<0.0001	0.102	<0.0001	0.97
Model 2	−0.069	<0.0001	−0.097	<0.001	0.02
Model 3	−0.046	0.001	−0.076	<0.001	0.02

Model 1 is adjusted for race and age; model 2 for race, age, and total fat mass; and model 3 for race, total fat mass, age, hypertension, hyperlipidemia, smoking, diabetes, low HDL-C, elevated triglycerides, HOMA-IR, and statin use. β coefficient represents change in log CRP levels for 1 kg change in fat parameter.

P interaction = 0.0003) (Table 3). Although the β coefficients were attenuated after additional adjustment for confounding factors with no relationship between CRP and truncal fat observed in men, the sex interaction remained statistically significant ($P = 0.002$). In contrast, no sex difference was observed in the relationship between lower body fat and CRP in race-adjusted analyses. After additionally adjusting for total fat mass, an inverse relationship between increasing lower body fat and log CRP was seen in both sexes, and this inverse association was of greater magnitude in men (*P* interaction = 0.02).

Subcompartments of truncal fat were generally associated with greater changes in CRP levels in women than in men, although the findings were more robust for ip fat. Intraperitoneal fat correlated with CRP for both sexes in all models ($P < 0.0001$ each), and the β coefficients were consistently larger in women (*P* interaction < 0.0001) (Table 4). In men, sc fat was associated with CRP in race-adjusted models, but not after further adjustment for total fat. In women, sc fat remained marginally associated with CRP after adjustment for total fat and other potential confounders. Total fat mass accounted for a greater proportion of the variance in CRP levels than the quantity of fat in either of these subcompartments in women and men (Table 5).

Fat distribution and CRP levels

The relative distribution of fat in the truncal *vs.* lower body regions explained a modest proportion of the variance in CRP levels even after accounting for differences in total fat mass. This relationship was more appreciable in women and was of questionable significance in men (partial R^2 value, 0.027 *vs.* 0.005, respectively) (Table 6 and Fig. 2). The proportion of total body mass deposited as ip fat also contributed to the variance in CRP levels after adjustment for total fat quantity, with a similar association observed for both sexes (Table 6). In contrast, the percentage of sc fat only contributed to CRP levels in women after adjustment for total fat mass (Table 6). Total fat mass accounted for a much greater proportion of the variance in CRP levels than the distribution of fat as assessed by these three parameters. In sensitivity analyses, defining the %IP and %SC fat variables as ratios of total fat mass rather than total body mass, our findings were qualitatively unchanged.

Associations of total fat with other inflammatory biomarkers

In exploratory analyses, no sex-based interactions for the relationship between total fat mass and several other inflammatory biomarkers such as soluble CD40 ligand,

TABLE 4. Relationship between ip and sc fat with CRP levels

	Women		Men		
	β Coefficient	*P* value	β Coefficient	*P* value	*P* interaction
Intraperitoneal fat					
Model 1	0.495	<0.0001	0.427	<0.0001	<0.0001
Model 2	0.301	<0.0001	0.271	<0.0001	<0.0001
Model 3	0.240	<0.0001	0.209	<0.0001	<0.0001
sc fat					
Model 1	0.192	<0.0001	0.165	<0.0001	0.1
Model 2	0.054	0.009	0.008	0.8	<0.001
Model 3	0.044	0.04	−0.0008	1.0	0.02

Model 1 is adjusted for race and age; model 2 for race, age, and total fat mass; and model 3 for race, total fat mass, age, hypertension, hyperlipidemia, smoking, diabetes, low HDL-C, elevated triglycerides, HOMA-IR, and statin use. β coefficient represents change in log CRP levels for 1 kg change in fat parameter.

TABLE 5. Partial R^2 values of abdominal fat quantity measures and total fat mass for CRP levels

	Women		Men	
	Partial R^2 parameter	*P* value	Partial R^2 parameter	*P* value
Model 1				
Intraperitoneal fat mass	0.015	<0.0001	0.015	<0.0001
Total fat mass	0.114	<0.0001	0.019	<0.0001
Model 2				
SC fat mass	0.005	0.006	<0.001	0.5
Total fat mass	0.025	<0.0001	0.024	<0.0001

Each model is adjusted for abdominal fat quantity measure, total fat mass, race, and age.

lipoprotein-associated phospholipase A2 mass and activity, osteoprotegerin, or IL-18 were observed (*P* interaction > 0.05 each). However, whereas MCP-1 levels were lower in women, they increased to a greater degree across total fat mass tertiles in women than in men (*P* interaction = 0.01).

Discussion

In a large, multiethnic population-based cohort we have demonstrated powerful interactions between body composition, sex, and CRP. In this first reported study to include DEXA and MRI assessments of body composition, we observed a much steeper association between total fat mass and CRP levels in women compared with men. Moreover, this sex interaction with CRP levels extended to the quantity and regional distribution of fat in various compartments, including abdominal depots. In contrast, we did not observe similar interactions between sex and body fat for other inflammatory biomarkers, except for a modest interaction with MCP-1, suggesting that body composition has unique influences on CRP.

Sex differences in the relationship between CRP and body fat

We and others have previously described sex differences in the relationship between BMI and CRP (4, 8–10), which may account for the higher CRP levels seen in women (4). However, BMI is a crude measure of adiposity that imprecisely quantifies body fat compared with reference measures (25), and women generally have more body fat than men for the same BMI value (12). In the present study using DEXA scanning, a well-established technique of measuring body composition that has been validated against most other reference measures, we observed a sex-based interaction in the relationship between directly quantified total body fat mass and CRP.

The larger increase in CRP levels in women with increased total fat appeared to be in part driven by opposite relationships with truncal fat and lower body fat. CRP levels were more positively correlated with changes in truncal fat in women but were more negatively correlated with changes in lower body fat in men in models adjusted for total fat mass. Thus, increased fat in these two body compartments with increased total fat mass would create a greater divergence in CRP levels between the sexes. The inverse relationship observed between lower body fat and CRP extends our previous reports showing inverse relationships of lower body fat with traditional cardiovascular risk factors and subclinical atherosclerosis (21, 26). One possible explanation for these findings is that lower body fat may serve as a protective sump for injurious ectopic fat deposition in various organs and in ip depots. Alternatively, greater amounts of lower body fat may simply reflect a lesser quantity of truncal fat for the same total body mass. Although the relative distribution of fat in

TABLE 6. Partial R^2 values of fat distribution measures and total fat mass for CRP levels

	Women		Men	
	Partial R^2 parameter	*P* value	Partial R^2 parameter	*P* value
Model 1				
TrF/LBF ratio	0.027	<0.0001	0.005	0.02
Total fat mass	0.199	<0.0001	0.084	<0.0001
Model 2				
%IP fat	0.022	<0.0001	0.021	<0.0001
Total fat mass	0.221	<0.0001	0.050	<0.0001
Model 3				
%SC fat	0.019	<0.0001	<0.001	0.5
Total fat mass	0.065	<0.0001	0.032	<0.0001

Each model is adjusted for fat distribution measure, total fat mass, race, and age.

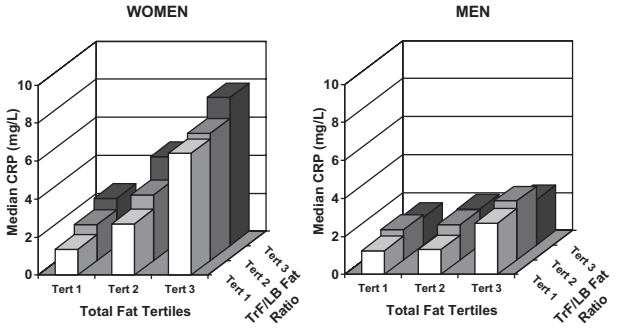

FIG. 2. Impact of TrF/LBF ratio on CRP levels. Median CRP levels by truncal to lower body fat ratio, stratified by gender-specific total fat values. Tert, Tertile.

truncal and lower body stores appeared to influence CRP levels in both sexes, the contribution of fat distribution to CRP was of greater magnitude in women than in men. It should be emphasized, however, that the contribution of fat distribution to CRP was modest compared with the impact of total fat quantity.

Sex differences in the relationship between CRP and increasing quantity of fat for both abdominal subcompartments were qualitatively similar to sex differences in the relationship between CRP and truncal fat. Interestingly, %IP fat contributed to the variance in CRP levels for men and women, whereas %SC fat had no impact on CRP in men after accounting for total fat mass. These findings may in part reflect the greater collinearity between total fat mass and sc fat than with ip fat, thereby statistically diminishing associations with sc fat after adjusting for total fat. On the other hand, ip fat has been more closely implicated in cardiometabolic risk, partly due to the release into the portal circulation of free fatty acids that exert adverse effects on hepatic metabolism (27).

Prior studies evaluating obesity, sex, and CRP

Several previous studies have noted sex differences in the relationship between CRP and obesity (6–11). Most of these studies used simple anthropometric measurements such as BMI and waist circumference to represent the quantity and distribution of body fat (6, 7, 10, 11), which does not accurately reflect fat mass and bias toward higher CRP levels in women (12). One study by Thorand *et al.* (9) used bioelectrical impedance to quantify fat mass in approximately 1200 middle-aged subjects from the KORA study cohort and correlated these measures and anthropometric indices with various inflammatory markers. They observed stronger associations between obesity measures and acute phase reactant proteins including CRP, serum amyloid A, fibrinogen, and IL-6 in women compared with men. Similar to our findings, they reported total body fat as having the greatest impact on CRP levels in women, but also that total body fat and fat distribution contributed similarly in men. These results were consistent with the findings of an earlier study by Festa *et al.* (6) that also used bioelectric impedance and anthropometric indices to assess fat mass and distribution in a triethnic cohort of approximately 1600 subjects. However, fat distribution measures in both studies were limited to waist circumference and waist to hip ratio, rather than directly quantified fat compartments.

Investigators from the Framingham Heart Study recently examined the associations of sc and visceral adipose tissue measured by computed tomography scanning in 1250 participants with serum and urinary markers of inflammation and oxidative stress (8). They observed a significant sex interaction between the quantity of fat in each abdominal depot and CRP levels, but no such interaction for any of the other markers. Although adjustments were made for BMI and waist circumference in the multivariable models, no direct measures of total body fat were obtained to exclude confounding by total fat as an explanation for their observations. Our findings highlight that total fat quantity, rather than fat distribution, has the dominant influence on CRP levels.

Mechanisms of sex differences in the association between fat mass/distribution and CRP

Several possible mechanisms may account for our findings of sex differences in the relationship between CRP and obesity. It may be that in women fat parameters correlate more closely with other determinants of CRP, such as insulin resistance, dyslipidemia, and statin use. However, despite modestly attenuated effect estimates, these gender interactions persisted after adjusting for these variables including HOMA-IR and components of the metabolic syndrome. Another consideration is that these observations may be mediated by the effects of sex hormones because exogenous estrogen is known to increase CRP levels in women (28). In the present study, we observed consistent relationships even after excluding users of oral estrogens and in comparisons with both premenopausal and postmenopausal women.

There is increasing appreciation that adipose tissue is an active endocrine organ producing a variety of hormones and cytokines that may affect CRP levels. Of these, IL-6 is thought to be the principal cytokine involved in CRP release from the liver, and up to one third of circulating IL-6 is derived from adipose tissue (2, 29). It is possible that adipose tissue may be more metabolically active in women compared with men. In the KORA study, fat parameters explained a greater proportion of the variance in IL-6 levels in women compared with men, but there were no sex differences in the Framingham study (8, 9).

Two other adipokines, adiponectin and leptin, are known to be higher in women compared with men (30, 31). We previously described stronger correlations between obesity measures and leptin in women compared with men and an independent association between leptin and CRP only in women (30). These findings suggest that there may be sex-related differences in the inflammatory responses to obesity that in part are mediated by leptin. The mechanisms behind these findings are unknown, but they may reflect direct stimulation of CRP release from the liver by leptin or an indirect mechanism such as leptin-mediated increased production of IL-6.

Obesity-associated inflammation is thought to derive mainly from adipose tissue itself, with a significant contribution from adipocytes. However, macrophage infiltration into adipose tissue now appears to be a key contributor to the inflammatory response (32). Macrophage infiltration is initially promoted by MCP-1 release from preadipocytes and propagated by MCP-1 release from recruited adipose tissue macrophages (33). We observed that plasma MCP-1 levels increased to a greater degree with obesity in women than in men, possibly due to greater macrophage recruitment and infiltration in adipose tissue in women. However, no studies have assessed for quantitative or qualitative sex differences in adipose tissue macrophages. Interestingly, no sex differences were seen in several other inflammatory biomarkers, suggesting that this pattern is not a global one and may be more specific for various biomarkers such as CRP and MCP-1.

Limitations

Several limitations of the current study must be acknowledged. Our cross-sectional study did not permit the assessment of how changes in obesity parameters affect CRP levels. In addition, we did not measure IL-6 levels, so we were unable to assess whether IL-6 impacts the relationship between obesity and CRP. Finally, our abdominal MRI measurements were made from one slice, but we have previously shown the validity of quantifying abdominal values using this approach (22).

Clinical implications

Several studies have shown that women have higher CRP levels than men (3–5). This finding may be due to sex differences in the relationship between CRP and obesity because higher CRP levels in women in our study were contingent upon the amount of total fat mass. Indeed, studies failing to demonstrate differences in CRP levels between the sexes included thinner populations where this sex interaction would not manifest (34, 35). The implications of this sex interaction are unclear. On the one hand, it is possible that subclinical inflammation, which has been linked to the development of cardiovascular risk factors and adverse cardiovascular events, may disproportionately affect women as they become more obese. As such, efforts at weight control may be particularly valuable in women. Alternatively, the cardiovascular signal from CRP may be diluted by the signal from adipose tissue, and the predictive power of CRP for cardiovascular events may diminish in obese populations, particularly obese women. It could be argued that this alternative explanation is supported by the absence of strong sex interactions with other inflammatory biomarkers that have been associated with atherosclerosis in the present study. Further studies evaluating the clinical implications of these findings are warranted.

Conclusions

CRP levels increase to a greater degree with variation in fat quantity and are more affected by fat distribution in women compared with men. Adiposity as a contributor of subclinical inflammation may be particularly relevant in women.

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