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Relationship of Total and Abdominal Adiposity with CRP and IL-6 in Women

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PURPOSE: To examine the relationship between different measures of adiposity as predictors of C-reactive protein (CRP) and interleukin-6 (IL-6) levels.
METHODS: A cross-sectional study of 733 women free from preexisting cardiovascular disease or cancer at baseline.
MEASUREMENTS: Total adiposity, as measured by body mass index (BMI). Abdominal adiposity, as measured by waist circumference (WC) and waist/hip ratio (WHR). High sensitivity CRP levels and IL-6 levels.
RESULTS: BMI, WHR, and WC were all significantly correlated with CRP and IL-6, throughout the anthropometric spectrum. After adjustment for risk factors, the odds ratios (ORs) were 12.2 (95% CI, 6.44–23.0) for elevated CRP (≥75th percentile) and 4.13 (95% CI, 2.37–7.18) for elevated IL-6 (≥75th percentile) in comparisons of extreme BMI quartiles. Among women in the highest WC quartile, the OR for elevated CRP and IL-6 were 8.57 (95% CI, 4.59–16.0) and 4.40 (95%CI, 2.46–7.89), while ORs for the highest WHR quartile were 2.88 (95% CI, 1.60–5.19) and 1.76 (95% CI, 1.03–3.01), respectively. Compared with lean nonusers, women in the highest BMI quartile who did not use hormone therapy (HT) had an OR for elevated CRP of 7.79 (95% CI, 2.08–29.2) vs. 31.6 (95% CI, 7.97–125.6) for current hormone users.
CONCLUSIONS: Indices of both total and abdominal adiposity were strongly associated with significant increased levels of CRP and IL-6. This association was evident across the entire spectrum of BMI.
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KEY WORDS: Obesity, Inflammation, C-reactive Protein, Interleukin-6, Women, Anthropometrics.

INTRODUCTION

The prevalence of obesity has steadily increased over the last several decades, particularly in women (1). While much of the cardiovascular risk attributable to obesity may be mediated through effects on blood pressure, lipids, and glucose tolerance, some of this risk may be mediated by inflammatory pathways. Adipocytes secrete interleukin-6 (IL-6) (2, 3), one of the chief determinants of hepatic C-reactive protein (CRP) production (4). Some have reported that abdominal adipose tissue, as opposed to subcutaneous depots, may have higher secretion levels of IL-6 (5). Higher levels of CRP have been reported in obese individuals (6–8), but the relationship between CRP and body mass index (BMI) in the normal weight range has not been well-characterized. In addition, few studies (6) have examined whether abdominal adiposity is associated more strongly with CRP levels than measures of total adiposity, such as BMI. Additionally, few studies have examined whether IL-6 mediates the risk of elevated CRP associated with obesity.

The purpose of this study was to examine the association between anthropometry and risk of elevated CRP and IL-6 in women, using both measures of total adiposity (BMI) as well as measures of abdominal adiposity, including waist circumference (WC) and waist-hip ratio (WHR). In addition, we wished to determine whether the higher risk of elevated CRP among heavier women might be mediated by IL-6 and whether there was any potential effect modification by postmenopausal hormone therapy (HT).

METHODS

This cross-sectional study was conducted among controls from two plasma substudies in the Women's Health Study, an ongoing randomized, double-blind, placebo-controlled

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trial of 39,876 female health professionals age 45 and older designed to determine the effects of low-dose aspirin and vitamin E in the primary prevention of cardiovascular disease and cancer. The design and cohort of the WHS is described in detail elsewhere (9).

Women enrolled in the WHS completed a baseline questionnaire which included questions on demographics (age, race), health characteristics/behaviors (height, weight, alcohol use, smoking status, physical activity, HT use) menopause (age at menopause and type of menopause) and past medical history (history of hypertension, diabetes mellitus, elevated cholesterol and use of cholesterol-lowering drugs). Postmenopausal status was defined by self-report of permanent cessation of menstrual periods due to natural menopause, complete oophorectomy, radiation, or chemotherapy. In addition, women who reported having a hysterectomy without bilateral oophorectomy were considered postmenopausal when they reached the age at which 95% of the population had experienced natural menopause (56 years).

During the run-in phase of the study when all participants were taking 100 mg of aspirin every other day, blood collection kits were mailed to participants. Thus, all participants had the same aspirin exposure at the time of blood collection. Blood samples were requested to be taken in the fasting state if possible. Blood samples were collected in EDTA tubes from 28,263 women (71% of the WHS total cohort) and were stored in liquid nitrogen freezers until the time of analysis Participants for our study were comprised of controls from two separate substudies. 576 subjects were controls in a study of inflammatory markers and risk of diabetes mellitus (10) and were required not to have a prior history of diabetes before study entry. They were matched to cases by age and whether the samples were taken in the fasting state. In addition, 244 subjects were controls from a study of inflammatory markers and cardiovascular disease (11). These women were matched to cases with cardiovascular disease by age and smoking status.

Exposure Variables

BMI, self-reported weight in kilograms divided by the square of self-reported height in meters (kg/m^2), was the primary measure of total adiposity in this analysis. This index is minimally correlated with height ($r = -0.03$) and highly correlated with absolute fat mass in women ($r = 0.84–0.91$) (12). BMI was categorized into quartiles based on the distribution in this population. Self-reported and directly measured weight were highly correlated ($r = 0.96$) in a validation study in a similar population of female health professionals (13).

WC and WHR were used as measures of abdominal adiposity. Waist and hip circumferences were provided on the 72-month questionnaire. In our study population, 80.5% of women (622/773) provided these measurements (in the total population, 74.1% provided these measures). Waist/hip ratio was calculated as waist circumference divided by hip circumference. WC and WHR were divided into quartiles based on the distribution in the population. In a validation study among female health professionals in the Nurses' Health Study, women reliably reported waist circumference, but underestimated hip circumference by an average of 0.54 inches. Crude Pearson correlation coefficients for reported and measured circumferences for waist, hip and WHR were 0.89, 0.84, and 0.70 respectively (14). The mean change in BMI between baseline and 72 months was 0.94 kg/m^2, and 74.3% of women experienced <5 kg change in weight during this period.

BMI and waist circumference are strongly correlated with weight ($r = 0.93$ for BMI and 0.75 for waist circumference) whereas the correlation between WHR and weight is much weaker ($r = 0.29$). The correlations of BMI with waist circumference and WHR were 0.73 and 0.29, respectively.

Laboratory Procedures

IL-6 assays were performed on thawed plasma samples using a commercially available enzyme-linked immunoabsorbent assay (RandD systems, Minneapolis, Minnesota). C-reactive protein was measured using a high-sensitivity latex enhanced immunophelometric assay on a BN II analyzer (Dade-Behring, Newark, Delaware) (15).

Statistical Analyses

From the cohort of 820 eligible women, women with a history of inflammatory arthritis (dermatomyosistis, scleroderma, systemic lupus erythematosis, and rheumatoid arthritis) were excluded ($n = 10$) as well as women on whom IL-6, BMI or CRP exposure status was missing ($n = 37$), leaving a total sample size of 773. The Chi square statistic was used to test differences in proportions. Due to skewed distributions, natural logarithm transformations of CRP and IL-6 were performed before calculating correlation coefficients. The Jonckheere-Terpstra test (16) was used to test ordered differences in medians across anthropometric quartiles. Quartiles of inflammatory markers were calculated, and those in the highest quartile of CRP ($\geq$0.59 mg/dl) and IL-6 ($\geq$2.05 pg/ml) were defined as having elevated levels. Linear regression was used to model the relationship between continuous measures of inflammatory markers and other risk factors. Logistic regression was used to obtain quartile specific estimates while simultaneously adjusting for age, smoking, BMI, physical activity, alcohol consumption, HT, as well as history of hypertension, diabetes mellitus, and elevated cholesterol. Since randomized treatment assignments to vitamin

E and aspirin were not associated with baseline levels of plasma markers, these were not included in the models.

RESULTS

The characteristics of women with elevated CRP levels (≥75th percentile: ≥0.59 mg/dl) are presented in Table 1. Women with elevated CRP had higher BMI, WC, and WHR. In addition, they were more likely to be current HT users and to have a history of hypertension. Women with elevated IL-6 (≥75th percentile: ≥2.05 pg/ml) had higher BMI, WC, and WHR, and were more likely to smoke and less likely to use HT. They were also more likely to have a history of hypertension.

Figure 1 shows the relationship of CRP with BMI and IL-6 throughout the BMI spectrum. Age-adjusted CRP levels (natural log transformed) were strongly correlated with BMI and waist circumference (r = 0.42 [p = 0.0001] and 0.33 [p = 0.0001], respectively), but more weakly correlated with WHR (r = 0.18 [p = 0.0001]). Likewise, the correlations with IL-6 (natural log transformed) were stronger for BMI and waist (r = 0.33 [p = 0.0001] and 0.29 [p = 0.0001] respectively) than WHR (r = 0.16 [p = 0.0001]). When median levels of CRP and IL-6 were examined by BMI quartiles, there was a strong, direct association with higher levels of both inflammatory markers in each BMI quartile (p trend = 0.0001) (Table 2). The median CRP level was more than 4-fold higher in the highest than the lowest BMI quartile. Median levels of CRP also increased steadily across WC quartiles and WHR quartiles (p trend = 0.0001 for both). Median IL-6 levels also increased steadily across increasing BMI, WC, and WHR quartiles (p trends 0.0001 for each).

Median CRP levels were markedly higher (P < 0.0001) and IL-6 levels were lower (p = 0.04) among HT users than nonusers. As shown in Figures 2a and 2b, CRP and IL-6 levels increased across BMI quartiles for HT users (p trends < 0.0001 for CRP and IL-6) and nonusers (P trends < 0.001 for CRP and IL-6 across quartiles).

Multivariate models predicting the risk of elevated CRP or IL-6 were performed to adjust for multiple covariates (Table 3). For elevated CRP, women in the highest BMI quartile had an OR of 8.47 (95% CI, 4.82–14.9) after adjustment for age, compared with women in the lowest BMI quartile. Adjustment for additional covariates, including

TABLE 1. Baseline characteristics of the population according to CRP and IL-6 status

Characteristic	Normal CRP[a] (n = 576)	Elevated CRP[a] (n = 197)	P value*	Normal IL-6[b] (n = 579)	Elevated IL-6[b] (n = 194)	P value*
Mean age ± SD	56.5 ± 7.8	56.3 ± 7.8	0.73	56.2 ± 7.5	57.3 ± 8.5	0.12
Mean BMI ± SD	24.7 ± 4.2	28.7 ± 6.0	0.0001	24.9 ± 4.1	28.3 ± 6.4	0.0001
Mean WHR ± SD	0.83 ± 0.08	0.86 ± 0.09	0.0003	0.83 ± 0.08	0.86 ± 0.09	0.004
Mean waist ± SD	34.1 ± 5.2	37.9 ± 6.1	0.0001	34.3 ± 5.3	37.4 ± 6.3	0.0001
Postmenopausal %	63.2	66.0	0.48	63.0	66.5	0.39
Smoking %						
Never	52.4	44.7	0.07	52.0	45.9	0.004
Past	33.9	35.5		35.2	31.4	
Current	13.7	19.8		12.8	22.7	
Hormone replacement therapy use %						
Never	47.2	29.4	0.001	40.4	49.5	0.02
Past	11.8	12.2		11.2	13.9	
Current	41.0	58.4		48.4	36.6	
Physical activity %						
<1/wk	57.3	62.9	0.09	54.9	70.1	0.001
1–3 x/wk	30.0	30.0		32.8	21.7	
4+ x/wk	12.7	7.1		12.3	8.3	
Alcohol consumption %						
Rarely/never	54.5	63.5	0.07	55.1	61.9	0.16
Monthly	35.1	26.4		34.7	27.3	
Weekly	10.4	10.2		10.2	10.8	
Family history of CHD %	14.0	11.5	0.37	13.5	12.9	0.84
History of diabetes %	0.35	0.51	1.00	0.35	0.52	1.00
History of hypertension %	23.8	38.3	0.001	23.1	40.8	0.001
History of elevated cholesterol %	27.1	33.7	0.08	27.3	33.0	0.13
Use of cholesterol-lowering drugs %	4.7	2.9	0.25	4.2	3.1	0.49

[a]Normal CRP defined as <75th percentile. Elevated CRP defined as ≥75th percentile (≥0.59 mg/dl).
[b]Normal IL-6 defined as <75th percentile. Elevated IL-6 defined as ≥75th percentile (≥2.05 pg/ml).
*P values from t-test for continuous variables and chi square for categorical variables. Fisher's exact test (2-tailed) used for diabetes, given small cell size.

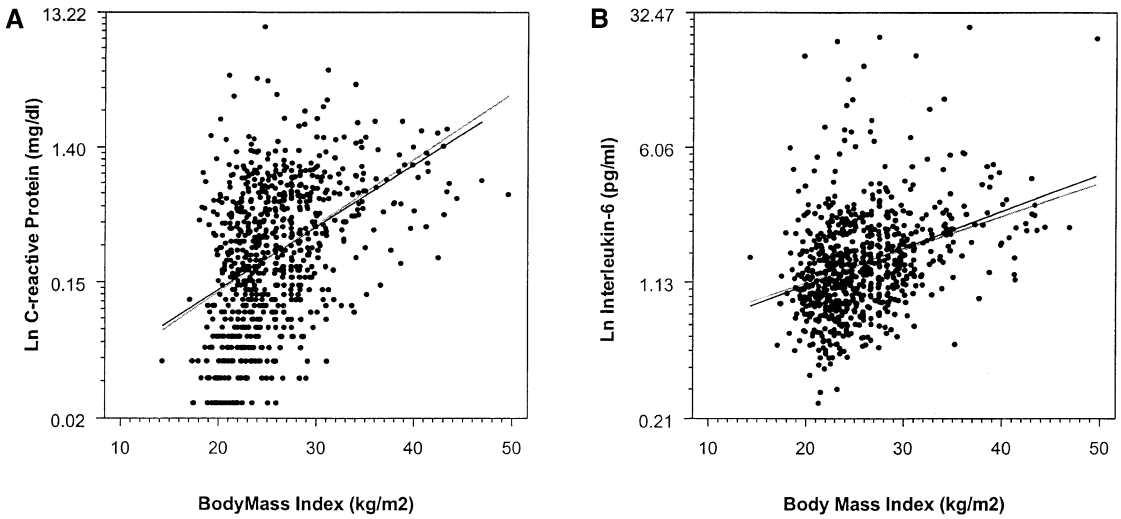

FIGURE 1. Linear regression lines for logarithm-transformed inflammatory biomarkers against body-mass index. Age-adjusted relationships are shown in black; fully adjusted associations are show in gray. Fully adjusted models include age, smoking status, history of hypercholesterolemia, history of hypertension, diabetes, exercise frequency, alcohol consumption, and hormone replacement use.

smoking, HT use, menopausal status, alcohol use, physical activity, history of elevated cholesterol, use of cholesterol-lowering drugs, hypertension and diabetes, augmented the association slightly for CRP, due to an inverse association between HT use and BMI; the odds of having an elevated CRP were 12.2 (95% CI, 6.44–23.0) for comparison of extreme BMI quartiles. In multivariate-adjusted linear models of CRP (Figure 1a), each unit (kg/m^2) of BMI was associated with a parameter estimate of 0.11 ($p < 0.0001$). Additional adjustment for IL-6 resulted in a modest attenuation of the association, with women in the highest BMI quartile having an OR of 9.20 (95% CI, 4.69–18.1) for elevated CRP, suggesting that the risk of increased CRP with obesity is mediated at least partially by IL-6. Adjustment for WC quartiles also attenuated but did not eliminate the association.

TABLE 2. Median (and interquartile range) of inflammatory marker levels by BMI quartile

	BMI Quartile 1 (<22.4)	BMI Quartile 2 (22.4–<24.6)	BMI Quartile 3 (24.6–<28.3)	BMI Quartile 4 (≥28.3)	
Number	193	192	194	194	p trend*
CRP	0.12 (0.05–0.32)	0.18 (0.09–0.40)	0.31 (0.14–0.61)	0.54 (0.25–0.87)	0.0001
IL-6	1.08 (0.84–1.60)	1.18 (0.81–1.72)	1.38 (0.96–2.09)	1.80 (1.26–2.49)	0.0001
	Waist Quartile 1 (<31 in)	Waist Quartile 2 (31–<34 in)	Waist Quartile 3 (34–<39 in)	Waist Quartile 4 (≥39 in)	
Number	129	148	180	165	p trend
CRP	0.11 (0.05–0.32)	0.21 (0.10–0.50)	0.28 (0.12–0.57)	0.54 (0.25–0.88)	0.0001
IL-6	1.06 (0.80–1.62)	1.21 (0.80–1.63)	1.26 (0.95–1.77)	1.84 (1.32–2.62)	0.0001
	WHR Quartile 1 (<0.78)	WHR Quartile 2 (0.78–<0.84)	WHR Quartile 3 (0.84–<0.90)	WHR Quartile 4 (≥0.90)	
Number	149	160	155	157	p trend
CRP	0.19 (0.07–0.47)	0.19 (0.07–0.50)	0.35 (0.15–0.65)	0.40 (0.16–0.77)	0.0001
IL-6	1.24 (0.82–1.79)	1.15 (0.86–1.59)	1.40 (0.98–2.11)	1.55 (1.14–2.38)	0.0001

*p trend by the Jonckheere-Terpstra test.

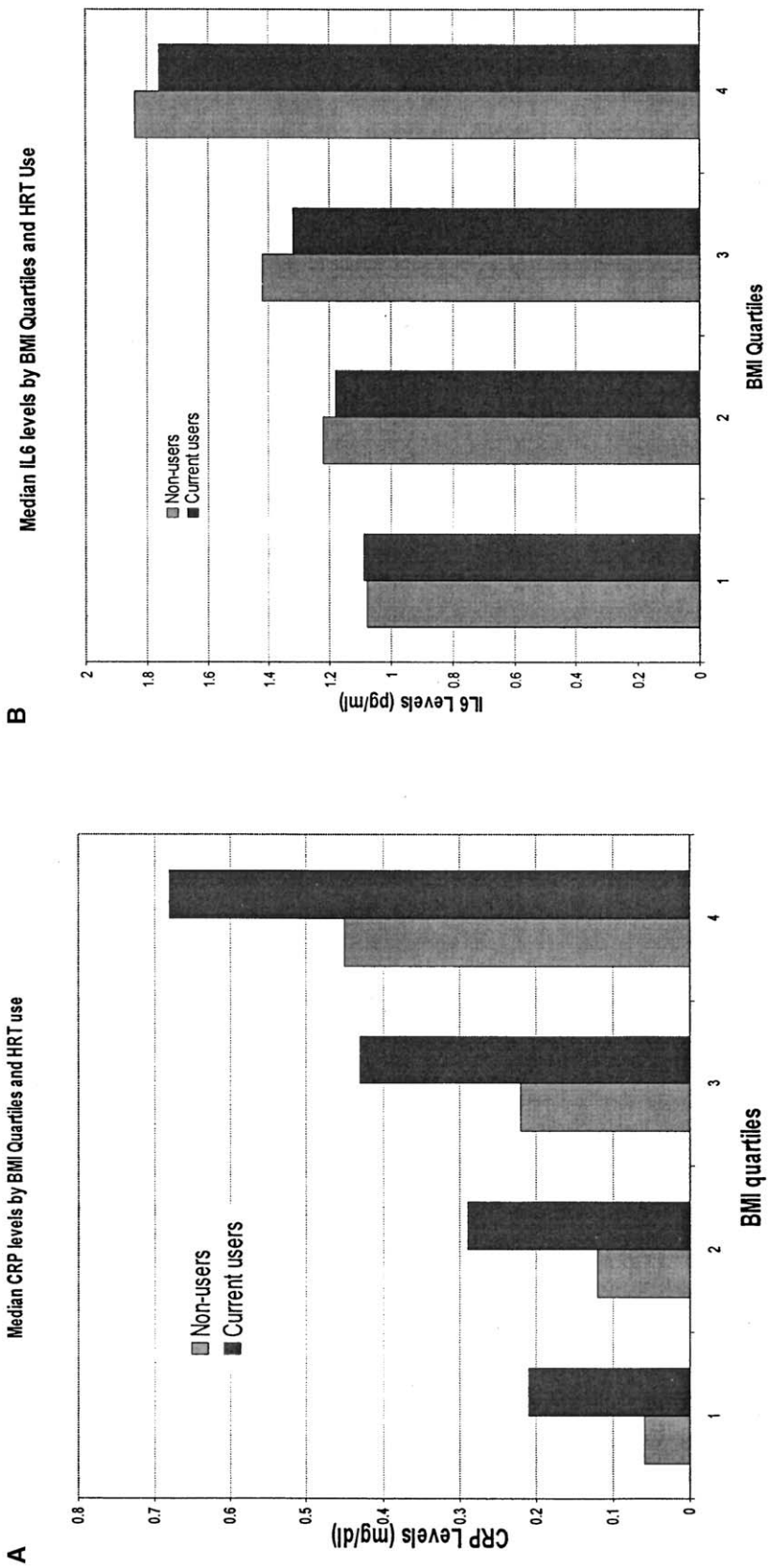

FIGURE 2. Median CRP and IL-6 levels by body mass index (BMI) quartiles and hormone replacement therapy use.

Waist circumference quartiles were also strongly associated with odds of elevated CRP. In multivariate-adjusted models, women in the highest WC (≥39 inches) had an odds of elevated CRP of 8.57 (95% CI, 4.59–16.0). Additional adjustment for BMI eliminated an independent effect. When WHR quartiles were examined, women in the highest WHR quartile (≥0.90) had a multivariate-adjusted odds of 2.88 (95% CI, 1.60–5.19) for elevated CRP; this was no longer significant after adjustment for BMI.

With regard to IL-6, BMI was also strongly associated with elevated levels (Table 3). After adjustment for age, women in the highest quartile had an OR of 4.33 (95% CI, 2.62–7.15) for elevated IL-6. In age-adjusted linear models, each unit of BMI was associated with a parameter estimate of 0.05 ($p < 0.0001$) for IL-6. Adjustment for the additional covariates listed above, attenuated the results slightly with an OR of 4.13 (95% CI, 2.37–7.18) for elevated IL-6 among women in the highest BMI quartile. Additional control for WC quartiles had little effect on the risk estimates. Waist circumference was also associated with elevated IL-6. Women in the highest waist quartile had a multivariate-adjusted odds of 4.40 (95% CI, 2.46–7.89) for elevated IL-6 which was somewhat attenuated after adjustment for BMI. Women in the highest WHR quartile had only a modestly higher risk of elevated IL = 6 (OR 1.76 [1.03–3.01]).

Since HT use has been shown to increase CRP levels and HT users also tend to have lower BMI, we stratified our results by HT use (Table 4). Current HT users were at higher risk of having elevated CRP levels, but at reduced risk of having elevated IL-6 levels. In stratified analyses among postmenopausal women with lean nonusers as the referent group, nonusers in the highest BMI quartile had a multivariate OR for elevated CRP of 7.79 (95% CI, 2.08–29.2) while current hormone users had an OR of 31.6

TABLE 3. Adjusted odds ratios for elevated CRP and IL-6 levels according to body mass index (BMI) quartiles, waist circumference quartiles, and waist/hip ratio quartiles

	Elevated CRP				Elevated IL-6			
	Model 1[a]	Model 2[b]	Model 3[c]	Model 4[d]	Model 1[a]	Model 2[b]	Model 3[c]	Model 4[d]
Number total	773	767	767	617	773	767	767	617
Number elevated	197	195	195	159	194	191	191	151
BMI quartile 1	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
BMI quartile 2	2.16	2.80	2.78	3.36	1.60	1.86	1.47	1.82
	(1.18–3.97)	(1.47–5.33)	(1.40–5.54)	(1.56–7.25)	(0.94–2.74)	(1.06–3.28)	(0.80–2.71)	(0.95–3.49)
BMI quartile 3	3.75	4.43	3.89	5.50	2.07	2.17	1.21	2.21
	(2.10–6.68)	(2.38–8.26)	(2.01–7.52)	(2.58–11.7)	(1.23–3.49)	(1.25–3.79)	(0.66–2.22)	(1.16–4.24)
BMI quartile 4	8.47	12.2	9.20	15.3	4.33	4.13	1.55	4.17
	(4.82–14.9)	(6.44–23.0)	(4.69–18.1)	(6.92–33.8)	(2.62–7.15)	(2.37–7.18)	(0.83–2.90)	(2.14–8.15)
Number total	622	617	617	617	622	617	617	617
Number elevated	161	159	159	159	153	151	151	151
Waist quartile 1	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
Waist quartile 2	1.37	2.30	2.10	1.24	1.11	1.48	0.96	1.17
	(0.69–2.70)	(1.24–4.27)	(1.08–4.08)	(0.62–2.46)	(0.59–2.09)	(0.81–2.71)	(0.50–1.86)	(0.61–2.24)
Waist quartile 3	2.22	1.80	1.69	0.69	1.19	1.29	0.92	0.89
	(1.19–4.15)	(0.95–3.41)	(0.86–3.33)	(0.33–1.46)	(0.65–2.16)	(0.71–2.36)	(0.48–1.76)	(0.45–1.79)
Waist quartile 4	6.33	8.57	5.53	2.04	4.32	4.40	1.73	2.57
	(3.45–11.6)	(4.59–16.0)	(2.85–10.7)	(0.90–4.62)	(2.45–7.63)	(2.46–7.89)	(0.89–3.36)	(1.19–5.55)
Number total	621	616	616	616	621	616	616	616
Number elevated	161	159	159	159	153	151	151	151
WHR quartile 1	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
WHR quartile 2	1.19	1.26	1.48	1.06	0.67	0.56	0.46	0.51
	(0.67–2.11)	(0.68–2.31)	(0.77–2.86)	(0.56–2.02)	(0.38–1.20)	(0.30–1.03)	(0.24–0.90)	(0.27–0.95)
WHR quartile 3	2.21	2.22	2.32	1.29	1.26	1.03	0.66	0.76
	(1.28–3.80)	(1.24–3.97)	(1.24–4.34)	(0.69–2.42)	(0.74–2.14)	(0.59–1.80)	(0.36–1.22)	(0.42–1.36)
WHR quartile 4	2.52	2.88	2.41	1.60	1.98	1.76	1.07	1.30
	(1.48–4.32)	(1.60–5.19)	(1.28–4.53)	(0.85–3.01)	(1.19–3.31)	(1.03–3.01)	(0.59–1.95)	(0.74–2.28)

[a]Model 1: adjusted for age.
[b]Model 2: adjusted for age, smoking, HRT use, menopausal status, alcohol (3 categories), physical activity (<1/wk, 1–3 x/wk, ≥ 4/wk), history of elevated cholesterol, use of lipid lowering drugs, diabetes, and hypertension.
[c]Model 3: adjusted for variables in model 2, as well as ln IL-6 for CRP models, and ln CRP for IL-6 models.
[d]Model 4: adjusted for variables in model 2, as well as BMI quartiles for waist and WHR models, and waist circumference for BMI models.

TABLE 4. Adjusted odds[a] of elevated CRP and IL-6 by BMI, WHR and waist quartiles among postmenopausal women, stratified by HRT use

	Elevated CRP			
	BMI quartile 1	BMI quartile 2	BMI quartile 3	BMI quartile 4
HRT Nonusers	1.0 (Referent)	2.99 (0.73–12.2)	3.14 (0.80–12.4)	7.79 (2.08–29.2)
HRT Users	3.18 (0.83–12.1)	6.85 (1.83–25.6)	10.7 (2.92–39.5)	31.6 (7.97–125.6)
	Waist quartile 1	Waist quartile 2	Waist quartile 3	Waist quartile 4
HRT Nonusers	1.00 (Referent)	1.45 (0.62–3.43)	0.39 (0.14–1.09)	2.31 (1.07–4.99)
HRT Users	1.14 (0.54–2.41)	1.69 (0.81–3.56)	2.27 (1.05–4.89)	7.62 (3.20–18.2)
	WHR quartile 1	WHR quartile 2	WHR quartile 3	WHR quartile 4
HRT Nonusers	1.00 (Referent)	0.37 (0.12–1.14)	0.74 (0.31–1.78)	0.99 (0.47–2.08)
HRT Users	0.95 (0.44–2.08)	1.15 (0.54–2.44)	2.26 (1.14–4.47)	2.92 (1.35–6.31)
	Elevated IL-6			
	BMI quartile 1	BMI quartile 2	BMI quartile 3	BMI quartile 4
HRT Nonusers	1.00 (Referent)	1.60 (0.60–4.27)	2.40 (0.94–6.14)	4.71 (1.85–12.0)
HRT Users	0.83 (0.31–2.27)	1.51 (0.57–3.99)	1.48 (0.56–3.89)	2.93 (1.05–8.18)
	Waist quartile 1	Waist quartile 2	Waist quartile 3	Waist quartile 4
HRT Nonusers	1.00 (Referent)	1.54 (0.68–3.47)	1.11 (0.52–2.34)	4.59 (2.16–9.73)
HRT Users	0.64 (0.29–1.42)	1.00 (0.44–2.24)	0.83 (0.35–1.99)	2.94 (1.26–6.89)
	WHR quartile 1	WHR quartile 2	WHR quartile 3	WHR quartile 4
HRT Nonusers	1.00 (Referent)	0.56 (0.22–1.41)	0.90 (0.41–1.99)	1.85 (0.95–3.60)
HRT Users	0.49 (0.21–1.16)	0.62 (0.27–1.38)	0.93 (0.45–1.93)	1.11 (0.49–2.51)

[a]Adjusted for age, smoking, HRT use, alcohol (rarely/never, 1–3/month, 1–6/week, ⩾1/day), physical activity (<1/wk, 1–3 x/wk, ⩾4/wk), history of elevated cholesterol, use of lipid lowering drugs and hypertension.

(95%CI, 7.97–125.6). Likewise, women in the highest waist quartile had a higher odds ratio of elevated CRP if they were current users (OR = 7.62, 95% CI 3.20–18.2) than nonusers (OR = 2.31, 95% CI 1.07–4.99). In contrast, the relationship between BMI and IL-6 was slightly weaker among women using HT than those not using HT. Nonusers in the highest BMI quartile had an OR of 4.71 (95%CI, 1.85–11.9) compared with 2.93 (95% CI, 1.05–8.18) for current HT users. For women in the highest WC quartile, nonusers had an OR of 4.59 (95% CI, 2.16–9.73) compared with 2.94 (95% CI, 1.26–6.89) for current HT users.

DISCUSSION

We found that both CRP and IL-6 levels were strongly correlated with BMI, not just at higher levels but throughout the full spectrum of BMI. Both inflammatory markers were also strongly associated with waist circumference, but more weakly associated with WHR. Risks associated with measures of abdominal adiposity were not independent of total adiposity, as measured by BMI. Among the adiposity measures that we studied, BMI was the strongest predictor of elevated inflammatory markers. The associations with BMI were dramatic; women in the highest BMI quartile (BMI ⩾ 28.3 kg/m^2) had a more than 12-fold increased risk of having elevated CRP levels and a more than 4-fold increased risk of elevated IL-6 levels; nonetheless higher CRP and IL-6 levels were observed with each increment in BMI.

CRP levels were substantially higher in HT users, but increased across BMI quartiles in both HT users and nonusers. The highest CRP levels were seen among women who both used HT and also were in the highest BMI quartile. Compared with lean women who did not use HT, women in the highest BMI quartile had a 7-fold increased risk of elevated CRP if they did not use hormones and a more than 30-fold increased risk if they were current users. In contrast, IL-6 levels were relatively similar among HT users and nonusers, with a tendency toward lower risk of elevated IL-6 levels among women taking HT.

The increased risk of elevated CRP and IL-6 with higher BMI has potentially important clinical implications. The cutpoints that we used for elevated CRP are similar to those previously reported from our cohort which were associated with a four-fold increased risk of cardiovascular disease

(11) and diabetes (10). Elevated IL-6 levels have been associated with a more than two-fold increased risk of subsequent myocardial infarction (11, 17) and diabetes (10).

Adipocytes secrete IL-6 (2, 3), one of the chief determinants of CRP production by the liver (4). Approximately 30% of circulating IL-6 is estimated to be from adipose tissue (3). Some research has suggested that omental adipose tissue secretes more IL-6 (5) and tumor necrosis factor (18), another proinflammatory mediator, than subcutaneous adipose tissue. However, we found that BMI was the measure most strongly associated with CRP. Whether the same cutpoints for clinically important elevated CRP should be used for obese women and for women on HT has not been fully resolved.

Relatively few studies have compared measures of adiposity and CRP levels in women. In a cross-sectional study of 107 men and women, CRP was more strongly correlated with BMI than WHR, whereas IL-6 was more strongly correlated with WHR than BMI (19). In a Dutch study, the age-adjusted correlations for CRP were 0.54 for BMI, 0.55 for WC, and 0.33 for WHR in women (20). In the largest study, Visser et al. found higher odds ratios for elevated CRP per standard deviation of BMI than for WHR in women (6). Correlations of IL-6 with different adiposity measures have not been well-studied. We found that BMI was the adiposity measure most strongly correlated with CRP and IL-6, although waist circumference was also associated with both inflammatory markers.

Several studies have reported higher CRP levels among men and women with increasing BMI (8, 20–23). The associations between CRP and BMI may be stronger in women than men (6). HT users have been shown to have higher CRP levels in several studies (7, 24, 25). In a recent report, Barinas-Mitchell et al. found that women who used HT and were in the highest quartile of visceral fat had the highest CRP levels. Correlations of CRP with measures of body fat and body fat distribution were stronger among women not taking HT than among HT users (26). Likewise in the Postmenopausal Estrogen/Progestin Interventions (PEPI) Study, treatment with HT diminished the correlation between BMI and CRP (24). We also found that BMI, WC, and WHR were associated with increased risk of elevated CRP in both users and nonusers.

Our findings of higher CRP but not IL-6 levels in HT users supports the hypothesis that HT increases CRP levels independently of IL-6 (27). Our results differ slightly from another study that examined the cross-sectional relationship between IL-6, BMI, and HT. Straub et al. also found that women taking HT had lower IL-6 levels than women not taking HT, but BMI was correlated with IL-6 only among women not taking HT (28). We continue to find a relationship between BMI and IL-6 regardless of HT use, although it was more prominent in nonusers. An IL-6–independent first pass effect of estrogens on hepatic CRP production has been suggested (29). Transdermal estrogens have not been associated with elevated CRP (30, 31), but only 7.5% of our population used transdermal estrogens.

Our study has several strengths. We compared different measures of adiposity with CRP and IL-6 levels and examined interactions by HT-use status. We used a high sensitivity CRP assay that has been suggested as a possible screening tool (32). We had detailed covariate information about factors that have been associated with inflammatory markers. None of the women had known cardiovascular disease at the time of CRP measurement.

We are limited by having only single measures of CRP and IL-6 and by samples not being obtained at a uniform time of day; however, these single measures have been associated with significantly increased risk of cardiovascular disease (11, 17) and diabetes (10). In addition, the weaker association of abdominal adiposity measures with inflammatory markers could possibly be due to measurement issues. Measures of regional fat distribution were available only several years after the measurement of CRP; however, 74% of the women in our population had <5kg weight change between the baseline questionnaire and WHR ascertainment. Redistribution of body fat may have occurred even among those who maintained relatively constant weights. In addition, there may be greater measurement error and misclassification associated with self-measured waist and hip than weight and height.

Our study cannot determine whether obesity causes elevated CRP levels directly, or whether higher CRP levels are a marker of other intermediate conditions such as atherosclerosis or insulin resistance which influence the underlying burden of inflammation among overweight and obese individuals. Clinicians should be aware that obese individuals are at substantially increased risk of having an elevated CRP; whether CRP and IL-6 remain independently predictive of cardiovascular disease and diabetes mellitus among obese individuals remains unclear. The associations of BMI with HT are additive, such that the highest CRP levels were observed among women who were both obese and used HT. Weight loss in obese women has been shown to decrease CRP levels (33, 34). Whether weight loss will result in reduced cardiovascular risk associated with CRP has not been determined.

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REFERENCES

1. Kuczmarski RJ, Flegal KM, Campbell SM, Johnson CL. Increasing prevalence of overweight among US adults. The National Health and Nutrition Examination Surveys, 1960 to 1991. JAMA. 1994;272:205–211.
2. Kern PA, Ranganathan S, Li C, Wood L, Ranganathan G. Adipose tissue tumor necrosis factor and interleukin-6 expression in human obesity and insulin resistance. Am J Physiol Endocrinol Metab. 2001;280:E745–E751.
3. Mohamed-Ali V, Goodrick S, Rawesh A, Katz DR, Miles JM, Yudkin JS, et al. Subcutaneous adipose tissue releases interleukin-6, but not tumor necrosis factor-alpha, in vivo. J Clin Endocrinol Metab. 1997;82:4196–4200.
4. Papanicolaou DA, Wilder RL, Manolagas SC, Chrousos GP. The pathophysiologic roles of interleukin-6 in human disease. Ann Intern Med. 1998; 128:127–137.
5. Fried SK, Bunkin DA, Greenberg AS. Omental and subcutaneous adipose tissues of obese subjects release interleukin-6: depot difference and regulation by glucocorticoid. J Clin Endocrinol Metab. 1998;83:847–850.
6. Visser M, Bouter LM, McQuillan GM, Wener MH, Harris TB. Elevated C-reactive protein levels in overweight and obese adults. JAMA. 1998; 282:2131–2135.
7. Cushman M, Meilahn EN, Psaty BM, Kuller LH, Dobs AS, Tracy RP. Hormone replacement therapy, inflammation, and hemostasis in elderly women. Arterioscler Thromb Vasc Biol. 1999;19:893–899.
8. Mendall MA, Patel P, Ballam L, Strachan D, Northfield TC. C-reactive protein and its relation to cardiovascular risk factors: a population-based cross sectional study. BMJ. 1996;312:1061–1065.
9. Rexrode KM, Lee IM, Cook NR, Hennekens CH, Buring JE. Baseline characteristics of participants in the Women's Health Study. J Women Health Gen-B. 2000;9:19–27.
10. Pradhan AD, Manson JE, Rifai N, Buring JE, Ridker PM. C-reactive protein, interleukin 6, and risk of developing type 2 diabetes mellitus. JAMA. 2001;286:327–334.
11. Ridker PM, Hennekens CH, Buring JE, Rifai N. C-reactive protein and other markers of inflammation in the prediction of cardiovascular disease in women. N Engl J Med. 2000;342:836–843.
12. Spiegelman D, Israel RG, Bouchard C, Willett WC. Absolute fat mass, percent body fat, and body-fat distribution: which is the real determinant of blood pressure and serum glucose? Am J Clin Nutr. 1992;55:1033–1044.
13. Willett W, Stampfer M, Bain C, Lipnick R, Speizer FE, Rosner B, et al. Cigarette smoking, relative weight, and menopause. J Epidemiol. 1983; 117:651–658.
14. Rimm EB, Stampfer MJ, Colditz GA, Chute CG, Litin LB, Willett WC. Validity of self-reported waist and hip circumferences in men and women. Epidemiology. 1990;1:466–473.
15. Rifai N, Tracy RP, Ridker PM. Clinical efficacy of an automated high-sensitivity C-reactive protein assay. Clin Chem. 1999;45:2136–2141.
16. Hollander M, Wolfe DA. Nonparametric Statistical Methods. New York: John Wiley and Sons, Inc.; 1973.
17. Ridker PM, Rifai N, Stampfer MJ, Hennekens CH. Plasma concentration of interleukin-6 and the risk of future myocardial infarction among apparently healthy men. Circulation. 2000;101:1767–1772.
18. Tsigos C, Kyrou I, Chala E, Tsapogas P, Stavridis JC, Raptis SA, et al. Circulating tumor necrosis factor alpha concentrations are higher in abdominal versus peripheral obesity. Metabolism. 1999;48:1332–1335.
19. Yudkin JS, Stehouwer CD, Emeis JJ, Coppack SW. C-reactive protein in healthy subjects: associations with obesity, insulin resistance, and endothelial dysfunction: a potential role for cytokines originating from adipose tissue? Arterioscler Thromb Vasc Biol. 1999;19:972–978.
20. Hak AE, Stehouwer CD, Bots ML, Polderman KH, Schalkwijk CG, Westendrop IC, et al. Associations of C-reactive protein with measures of obesity, insulin resistance, and subclinical atherosclerosis in healthy, middle-aged women. Arterioscler Thromb Vasc Biol. 1999;19:1986–1991.
21. Tracy RP, Lemaitre RN, Psaty BM, Ives DG, Evans RW, Cushman M, et al. Relationship of C-reactive protein to risk of cardiovascular disease in the elderly. Results from the Cardiovascular Health Study and the Rural Health Promotion Project. Arterioscler Thromb Vasc Biol. 1997;17: 1121–1127.
22. Danesh J, Muir J, Wong YK, Ward M, Gallimore JR, Pepys MB. Risk factors for coronary heart disease and acute-phase proteins. A population-based study. Eur Heart J. 1999;20:954–959.
23. Ford ES. Body mass index, diabetes, and C-reactive protein among US adults. Diabetes Care. 1999;22:1971–1977.
24. Cushman M, Legault C, Barrett-Connor E, Stefanick ML, Kessler C, Judd HL, et al. Effect of postmenopausal hormones on inflammation-sensitive proteins: the Postmenopausal Estrogen/Progestin Interventions (PEPI) Study. Circulation. 1999;100:717–722.
25. Ridker PM, Hennekens CH, Rifai N, Buring JE, Manson JE. Hormone replacement therapy and increased plasma concentration of C-reactive protein. Circulation. 1999;100:713–716.
26. Barinas-Mitchell E, Cushman M, Meilahn EN, Tracy RP, Kuller LH. Serum levels of C-reactive protein are associated with obesity, weight gain, and hormone replacement therapy in healthy postmenopausal women. Am J Epidemiol. 2001;153:1094–1101.
27. van Baal WM, Kenemans P, van der Mooren MJ, Kessel H, Emeis JJ, Stehouwer CD. Increased C-reactive protein levels during short-term hormone replacement therapy in healthy postmenopausal women. Thromb Haemost. 1999;81:925–928.
28. Straub RH, Hense HW, Andus T, Scholmerich J, Riegger GA, Schunkert H. Hormone replacement therapy and interrelation between serum interleukin-6 and body mass index in postmenopausal women: a population-based study. J Clin Endocrinol Metab. 2000;85:1340–1344.
29. Weinhold B, Ruther U. Interleukin-6-dependent and -independent regulation of the human C-reactive protein gene. Biochem J. 1997;327:425–429.
30. Sattar N, Perera M, Small M, Lumsden MA. Hormone replacement therapy and sensitive C-reactive protein concentrations in women with type-2 diabetes. Lancet. 1999;354:487–488.
31. Lowe GD, Upton MN, Rumley A, McConnachie A, O'Reilly DS, Watt GC. Different effects of oral and transdermal hormone replacement therapies on factor IX, APC resistance, t-PA, PAI and C-reactive protein–a cross-sectional population survey. Thromb Haemost. 2001;86:550–556.
32. Ridker P. High-sensitivity C-reactive protein: Potential adjunct for global risk assessment in the primary prevention of cardiovascular disease. Circulation. 2001;103:1813–1818.
33. Heilbronn LK, Noakes M, Clifton PM. Energy restriction and weight loss on very-low-fat diets reduce C-reactive protein concentrations in obese, healthy women. Arterioscler Thromb Vasc Biol. 2001;21:968–970.
34. Tchernof A, Nolan A, Sites CK, Ades PA, Poehlman ET. Weight loss reduces C-reactive protein levels in obese postmenopausal women. Circulation. 2002;105:564–569.