Sex differences in inflammatory markers: what is the contribution of visceral adiposity?1–3

Amélie Cartier, Mélanie Côté, Isabelle Lemieux, Louis Pérusse, Angelo Tremblay, Claude Bouchard, and Jean-Pierre Després

ABSTRACT
Background: C-reactive protein (CRP) concentrations have been found to be higher in premenopausal women than in men, whereas interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α) concentrations have been reported to be lower in women than in men.

Objective: The objective was to determine whether the sex difference in body fat distribution accounts for the observed sex differences in inflammatory markers.

Design: Plasma CRP, IL-6, and TNF-α concentrations were measured in 208 healthy men (age: 42.2 ± 15.2 y) and in 145 healthy women (age: 36.8 ± 11.1 y).

Results: Compared with men, premenopausal women had higher CRP concentrations [1.24 (25th percentile: 0.54; 75th percentile: 3.04) compared with 0.94 (0.51, 2.40) mg/L; P < 0.05] and lower plasma TNF-α concentrations [1.50 (25th percentile: 1.23; 75th percentile: 1.82) compared with 1.71 (1.40, 2.05) pg/mL; P < 0.001]. No sex difference in IL-6 concentrations was noted. Regression analyses indicated that the relation between CRP or IL-6 concentrations and visceral adipose tissue (VAT) and subcutaneous AT (SAT) was sex-specific; a significantly steeper slope was observed in women than in men (P < 0.05). Sex differences in CRP concentrations were abolished after SAT was adjusted for. In a multivariate model of the whole sample, we found that both SAT and VAT and the sex × SAT interaction term were significant correlates of CRP and IL-6 concentrations. Finally, whereas CRP concentrations were largely influenced by visceral adiposity in men, subcutaneous adiposity was the key correlate of CRP in women.

Conclusion: The higher CRP concentrations found in women appear to be due to their greater accumulation of subcutaneous fat than that observed in men. Am J Clin Nutr 2009;89:1307–14.

INTRODUCTION

In industrialized countries, the prevalence and incidence of cardiovascular disease (CVD) is higher in men than in women until menopause (1). Compared with men, relative CVD risk in women is increased to a greater extent by some traditional risk factors (eg, diabetes, hypertension, hypercholesterolemia, and obesity) (2). The metabolic syndrome represents a new "multiplex" modifiable risk entity for the development of CVD (3–5), and sex differences in the prevalence of this condition may contribute to sex differences in CVD (6). In addition, it has been shown that the relative contribution of various metabolic abnormalities to the metabolic syndrome is different between men and women (7).

It is now well recognized that obesity, especially visceral obesity, is associated with a low-grade inflammatory state (13). It was recently suggested that the overexpression of adipokines, such as interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α), by adipose tissue (AT) (14) in the context of obesity could be due to macrophage infiltration (15). C-reactive protein (CRP), the most studied marker of inflammation, is released mainly from the liver after cytokine stimulation (16). CRP has been shown to independently predict cardiovascular events in both men and women (17, 18). However, significant sex differences in CRP concentrations have been reported by several groups.

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2 The Québec Family Study was supported by multiple grants from the Medical Research Council of Canada (now the Canadian Institutes of Health Research) and by the Canadian Diabetes Association. J-PD is the Scientific Director of the International Chair on Cardiometabolic Risk, which is supported by an unrestricted grant awarded to Université Laval by Sanofi Aventis. CB was supported in part by the George A Bray Chair in Nutrition. AT was supported in part by the Canada Research Chair in Physical Activity, Nutrition and Energy Balance. AC was a recipient of a scholarship from the Merck Frosst/CHIR Research Chair in Obesity.

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For instance, CRP concentrations have been found to be higher in premenopausal women than in men, presumably because of the increasing effect of estrogens on CRP concentrations (19). The latter finding is also compatible with the known effect of hormone replacement therapy, which has been shown to increase CRP concentrations (26, 27). On the other hand, plasma IL-6 and TNF-α concentrations have been found to be lower in women than in men, possibly because of the inhibitory effect of estrogens on the expression of inflammatory marker genes (28, 29).

Because body fat distribution is very different between men and premenopausal women, the aim of the present study was to investigate the contribution of body fat distribution, particularly abdominal visceral and subcutaneous adiposity to sex-related variation in inflammatory markers.

SUBJECTS AND METHODS

Subjects
Two hundred eight men aged 19–72 y and 145 premenopausal women aged 18–61 y were recruited from the Québec city area. Recruitment started in January 1990 by solicitation through the media. The subjects were free of metabolic diseases that would require treatment (diabetes, hypertension, and coronary heart disease). No subjects were taking antiinflammatory drugs, either before or at the time of the study, or were taking aspirin chronically. Finally, all participants signed an informed consent document, and the study was approved by the Medical Ethics Committee of Université Laval. As suggested by the Centers for Disease Control and Prevention/American Heart Association, individuals with high-sensitivity CRP (hs-CRP) concentrations >10 mg/L were excluded (30).

Anthropometric measurements
The hydrostatic weighing technique (31) was used to measure body density, which was obtained from the mean of 6 measurements. Pulmonary residual volume was measured before immersion in the hydrostatic tank, with use of the helium dilution method of Meneely and Kalbtreider (32). Percentage body fat was derived from body density by using the equation of Siri (33). Fat mass (FM) was obtained by multiplying body weight by percentage body fat. Height, body weight (34), and waist circumference (35) were measured following standardized procedures.

Computed tomography
Visceral AT accumulation was assessed by computed tomography, which was performed with a Somatom DRH scanner (Siemens, Erlanger, Germany) following previously described procedures (36). Briefly, each subject was examined in the supine position with both arms stretched above the head. The scan was performed at the abdominal level (between L4 and L5 vertebrae) with the use of an abdominal scout radiograph to standardize the position of the scan to the nearest millimeter. Total AT area was calculated by delineating the abdominal scan with a graph pen and then computing the AT surface with an attenuation range of −190 to −30 Hounsfield units (36). The abdominal visceral AT (VAT) area was measured by drawing a line within the muscle wall surrounding the abdominal cavity.

The abdominal subcutaneous AT (SAT) area was calculated by subtracting the VAT area from the total abdominal AT area.

Plasma lipoprotein and lipid variables
Blood samples were collected from an antecubital vein into evacuated tubes containing EDTA (Miles Pharmaceuticals, Rexdale, Canada), after the subjects fasted overnight for 12 h, for the measurement of plasma lipid and lipoprotein concentrations. Cholesterol and triglyceride concentrations were measured in plasma and lipoprotein fractions by using a Technicon RA-500 (Bayer Corporation, Tarrytown, NY), and enzymatic reagents were obtained from Randox (Crumlin, United Kingdom). The HDL fraction was obtained after precipitation of LDL in the infranatant (density > 1.006 g/mL) with heparin and magnesium chloride (37). Cholesterol and triglyceride concentrations in the infranatant were measured before and after the precipitation step.

Oral-glucose-tolerance test
A 75-g oral-glucose-tolerance test (OGTT) was performed in the morning after the subjects fasted overnight. Blood samples were collected into EDTA-containing tubes through a venous catheter placed in an antecubital vein at −15, 0, 15, 30, 45, 60, 90, 120, 150, and 180 min for the measurement of plasma glucose and insulin concentrations. Plasma glucose was measured enzymatically (38), whereas plasma insulin was measured by radioimmunoassay with polyethylene glycol separation (39). The total glucose and insulin areas under the curve during the OGTT were determined by using the trapezoid method.

Measurement of CRP, TNF-α, and IL-6 concentrations
Concentrations of CRP were measured in deeply frozen plasma samples (−80°C) with a highly sensitive immunoassay that used a monoclonal antibody coated with polystyrene particles; the assay was performed with a Behring BN-ProsPect (Dade Behring, Marburg, Germany) according to the methods described by the manufacturer (40). Plasma IL-6 and TNF-α concentrations were measured by a high-sensitivity enzyme-linked immunosorbent assay (ELISA) for human TNF-α and IL-6 (R&D Systems Inc, Minneapolis, MN). The run-to-run CVs were <5%, <10%, and <10% for hs-CRP, IL-6, and TNF-α, respectively.

Statistical analyses
The normality of distribution of each variable was verified by using the Shapiro-Wilk test, and logarithmic transformations were performed if necessary. Pearson’s correlation coefficients were used to quantify the univariate associations among variables. One-factor analysis of variance (ANOVA) adjusted for age was used to evaluate statistically significant differences in physical and metabolic characteristics between men and women. A separate linear regression analyses for each body-composition index (VAT, SAT, or FM) with CRP or IL-6 as dependent variables were performed, and the slopes and intercepts of the regression lines were compared between men and women. After individual pairing of men and women for either abdominal VAT or SAT area (within a variation of 5 cm²) or FM (within a variation of 0.5 kg), sex differences were analyzed with Student’s paired \( t \) tests. A 2-
factor ANOVA adjusted for age and a post hoc Tukey’s test for multiple comparisons was used to examine the effect of VAT or SAT, sex, and their interaction terms on inflammatory markers. To assess the contribution of total and abdominal adiposity as independent variables on CRP, IL-6, and TNF-α concentrations as dependent variables, multivariable linear regression models were performed for men and women separately. Regression models were also performed for all subjects, with sex and interaction terms of body-composition indexes and sex as additional covariates. The results were declared significant at the 0.05 level. All analyses were performed with the statistical package SAS (version 9.1; SAS Institute, Cary, NC).

**RESULTS**

Anthropometric and metabolic characteristics of the 208 men and 145 premenopausal women are presented in **Table 1**. Because men were slightly older than premenopausal women, the data were adjusted for age. Despite similar body mass index (BMI; in kg/m²) values between women and men (26.0 compared with 26.6), men had a much higher waist circumference (92.1 cm compared with 80.5 cm) and accumulation of VAT (125 cm² compared with 82 cm²) than did women. In contrast, women had a greater total-body FM and significantly more SAT than did men. Overall, men were characterized by a more deteriorated metabolic risk profile than women because they had a lower HDL-cholesterol concentration, higher triglyceride concentration, higher ratio of cholesterol to HDL cholesterol, and higher level of insulin resistance than did women. Premenopausal women were characterized by higher CRP concentrations (1.93 ± 1.79 compared with 1.67 ± 1.81 mg/L; \( P = 0.03 \)) and lower plasma TNF-α concentrations (1.58 ± 0.59 compared with 1.85 ± 0.97 pg/mL; \( P = 0.001 \)) than men, whereas IL-6 concentrations did not differ significantly between the 2 groups.

The relation between VAT, SAT or FM, and inflammatory markers (CRP and IL-6) is shown in **Figure 1** for men and women. Highly significant associations were found between VAT and plasma CRP (\( r = 0.44, P < 0.0001 \)) and IL-6 (\( r = 0.41, P < 0.0001 \)) concentrations and between subcutaneous AT and plasma CRP (\( r = 0.51, P < 0.0001 \)) and IL-6 (\( r = 0.50, P < 0.0001 \)) concentrations in premenopausal women. The regression slopes for CRP and IL-6 were significantly steeper in premenopausal women than in men for both VAT and SAT (\( P < 0.05 \)). The intercepts for CRP and IL-6 concentrations according to VAT were not different between men and women. However, the intercept values of the relations between SAT and both CRP (\( P < 0.05 \)) and IL-6 (\( P < 0.0001 \)) were different between sexes. Moreover, univariate correlation coefficients were computed for all anthropometric and metabolic variables with plasma CRP, IL-6, and TNF-α concentrations (**Table 2**).

To further examine the role of visceral adiposity on the sex variation in inflammatory markers, 99 men and 99 premenopausal women were individually matched on the basis of VAT accumulation. The subgroup of women still had significantly higher CRP concentrations than did men (2.01 ± 1.92 compared with 1.36 ± 1.54 mg/L; \( P < 0.01 \) (**Figure 2A**) and lower TNF-α concentrations than did men (1.59 ± 0.61 compared with 1.80 ± 0.79 mg/L; \( P < 0.05 \)); no difference was noted in IL-6 concentrations (data not shown). Similar analyses were performed by individually matching men and women with similar accumulations of SAT (Figure 2B) and FM (Figure 2C). Differences in CRP concentrations were no longer observed between men and women after adjustment for either SAT or FM.

**TABLE 1**

Physical and metabolic characteristics of the sample of men and women in the study

<table>
<thead>
<tr>
<th>Variables</th>
<th>Men (( n = 208 ))</th>
<th>Women (( n = 145 ))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>42.2 ± 15.2(^1)</td>
<td>36.8 ± 11.1</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>26.6 ± 4.3</td>
<td>26.0 ± 5.2</td>
</tr>
<tr>
<td>Fat mass (kg)</td>
<td>19.0 ± 9.0</td>
<td>21.9 ± 10.5(^2)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>79.7 ± 14.6</td>
<td>68.1 ± 14.9(^3)</td>
</tr>
<tr>
<td>Waist girth (cm)</td>
<td>92.1 ± 13.2</td>
<td>80.5 ± 13.0(^4)</td>
</tr>
<tr>
<td>Adipose tissue accumulation (cm²)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Visceral</td>
<td>125 ± 71</td>
<td>82 ± 46(^5)</td>
</tr>
<tr>
<td>Subcutaneous</td>
<td>216 ± 120</td>
<td>300 ± 144(^6)</td>
</tr>
<tr>
<td>Total</td>
<td>341 ± 172</td>
<td>381 ± 177(^2)</td>
</tr>
<tr>
<td>Cholesterol (mmol/L)</td>
<td>5.01 ± 1.01</td>
<td>4.71 ± 0.96</td>
</tr>
<tr>
<td>LDL cholesterol (mmol/L)</td>
<td>3.19 ± 0.88</td>
<td>2.85 ± 0.83(^4)</td>
</tr>
<tr>
<td>HDL cholesterol (mmol/L)</td>
<td>1.11 ± 0.27</td>
<td>1.33 ± 0.31(^3)</td>
</tr>
<tr>
<td>Cholesterol/HDL cholesterol</td>
<td>4.72 ± 1.34</td>
<td>3.71 ± 1.03(^4)</td>
</tr>
<tr>
<td>Triglycerides (mmol/L)</td>
<td>1.40 (0.92, 2.02)(^5)</td>
<td>1.10 (0.84, 1.46)(^4)</td>
</tr>
<tr>
<td>Fasting insulin (pmol/L)</td>
<td>56 (41, 80)</td>
<td>53 (35, 77)(^6)</td>
</tr>
<tr>
<td>Fasting glucose (mmol/L)</td>
<td>5.32 ± 0.55</td>
<td>5.07 ± 0.40(^2)</td>
</tr>
<tr>
<td>Insulin area (pmol · min/L/min × 10⁻³)</td>
<td>77.9 ± 56.6</td>
<td>69.7 ± 38.3</td>
</tr>
<tr>
<td>Glucose area (mmol · L/min × 10⁻³)</td>
<td>1.23 ± 0.25</td>
<td>1.12 ± 0.20(^2)</td>
</tr>
<tr>
<td>C-reactive protein (mg/L)</td>
<td>0.94 (0.51, 2.40)(^5)</td>
<td>1.24 (0.54, 3.04)(^4)</td>
</tr>
<tr>
<td>Interleukin-6 (pg/mL)</td>
<td>1.28 (0.95, 1.97)</td>
<td>1.20 (0.81, 1.87)</td>
</tr>
<tr>
<td>Tumor necrosis factor-α (pg/mL)</td>
<td>1.71 (1.40, 2.05)</td>
<td>1.50 (1.23, 1.82)(^2)</td>
</tr>
</tbody>
</table>

\(^1\) Median ± IQR (all such values).
\(^2\) - 4\) Significantly different from men (one-factor ANOVA adjusted for age): \(^2\) \( P < 0.01 \), \(^3\) \( P < 0.0001 \), \(^4\) \( P < 0.05 \).
\(^5\) Median; interquartile range in parentheses for skewed variables (all such values).
The entire cohort was then stratified into tertiles of visceral adiposity to compare the effect of any given VAT accumulation on plasma CRP, IL-6, and TNF-α concentrations. In the upper 2 tertiles of VAT, women had significantly higher CRP concentrations than did men, and both VAT and sex significantly contributed to variations in CRP concentrations (Figure 3A). However, when similar analyses were conducted using tertiles of SAT, there was no difference in CRP concentrations between men and premenopausal women in each tertile of SAT. However, the CRP concentrations also tended to increase across tertiles of SAT (Figure 3B). A similar analysis was conducted for IL-6 (Figure 3C), which showed that only VAT significantly contributed to the variation in IL-6 concentrations with a statistically significant sex V AT interaction term. However, variation in TNF-α was related to sex but not to visceral adiposity, because women tended to have lower TNF-α concentrations than did men (Figure 3D).

Finally, to determine the relative contribution of total and abdominal adiposity to concentrations of inflammatory markers, multiple regression analyses were conducted in the whole study sample and then by sex. In analyses of the whole study sample (Table 3), variables such as sex, total-body FM, VAT accumulation, sex × VAT, and sex × FM interaction terms were included in model 1. As shown in Table 3, FM (P < 0.0001), VAT (P < 0.001), and the sex × FM interaction term (P < 0.05) contributed independently to the variance in IL-6 concentrations (total $R^2 = 21\%$), whereas FM (P < 0.0001), VAT (P < 0.05), the sex × FM interaction term (P < 0.01), and sex (P < 0.01) contributed independently to the variance in IL-6 (total $R^2 = 19\%$). Sex (P < 0.0001) and FM (P < 0.01) were the only variables that were weakly but significantly and independently associated with TNF-α (total $R^2 = 5.9\%$). When SAT was used instead of FM (model 2), SAT (P < 0.0001), VAT (P < 0.0001), and the sex × SAT interaction term (P < 0.01) explained the variance in CRP for a total of 21%. Regarding IL-6, VAT (P < 0.0001) explained the largest percentage of its variability, followed by SAT (P < 0.0001), the sex × SAT interaction term (P < 0.0001), and sex (P < 0.01) (total $R^2 = 19\%$). For TNF-α, adiposity variables had a small contribution to its variation. Nevertheless, sex (P < 0.01) and VAT (P < 0.01) explained a low but significant proportion (total $R^2 = 5.6\%$) of its variation.

As for the analyses conducted by sex (Table 4), age, FM, VAT, and SAT were included in the model for men and women. For CRP, the variable with the highest partial $R^2$ was VAT (16.0%) in men, whereas SAT (25.8%) explained the largest percentage of variability in CRP in women. For IL-6, age (P < 0.001) and FM (P < 0.001) explained 16.5% of its variance in men, whereas SAT (P < 0.001) contributed to 25.5% of the variability of IL-6 concentrations in women.

**DISCUSSION**

One of the main objectives of the present study was to determine whether the well-known sex difference in body fat distribution could account for differences in inflammatory markers between men and women. To the best of our knowledge, our
study provides for the first time evidence that CRP concentrations seem to be influenced to a greater extent by visceral than by subcutaneous adiposity in men, as opposed to subcutaneous adiposity in women. Moreover, there was a significant sex difference in the association of VAT and SAT with CRP and IL-6, as reflected by significantly different regression slopes between men and women. We also found that women had higher CRP and lower TNF-α concentrations than did men after adjustment for VAT. However, sex differences in CRP concentrations between men and women were no longer significant after SAT and FM were adjusted for. In a multivariate model, we also found that both SAT and VAT and the sex × SAT interaction term were significant correlates of CRP and IL-6 concentrations.

Several mechanisms could explain the sex differences in inflammatory markers. The well-documented sex differences in body fat distribution and systemic sex hormone concentrations could represent major factors in the sex dimorphism that we observed (41, 42). In particular, women generally have a higher percentage of body fat than do men. Furthermore, women store more fat in the gluteal-femoral region, whereas men store more fat in the abdominal and visceral depot (10). However, women who have reached menopause tend to accumulate more fat in the visceral depot (43). The mechanisms responsible for sex-related differences in body fat distribution could be attributable to differences in fatty acid mobilization, oxidation, and storage between male and female subjects (44). Our results agree with these findings, because women had higher levels of total-body FM and SAT than did men, whereas men had higher values for waist girth and VAT, which reflects the well-known sex difference in abdominal adiposity.

Only a few studies have examined sex differences in the associations between measures of body composition and markers of inflammation. Markers of inflammation strongly correlate with measures of adiposity, and this association has been reported to be generally stronger in women than in men, especially for CRP (45, 46) and IL-6 (45, 47). We observed similar associations between body fatness indexes and both CRP and IL-6 concentrations, and the correlation coefficients were greater in women than in men for all measures of adiposity. However, different relations between sex and CRP may be observed across different

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**TABLE 2**

Pearson correlation coefficients between concentrations of proinflammatory cytokines with indexes of adiposity and metabolic risk variables in men and women.

<table>
<thead>
<tr>
<th></th>
<th>Men</th>
<th>Women</th>
<th>Men</th>
<th>Women</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>HDL cholesterol</td>
<td>0.34[^2]</td>
<td>0.53[^2]</td>
<td>0.27[^2]</td>
<td>0.52[^2]</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Fasting glucose</td>
<td>NS</td>
<td>0.18[^2]</td>
<td>0.15[^2]</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Glucose (120 min)</td>
<td>0.21[^7]</td>
<td>0.19[^2]</td>
<td>0.28[^2]</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
</tbody>
</table>

[^1] CRP, C-reactive protein; IL-6, interleukin-6; TNF-α, tumor necrosis factor-α.
[^2] P ≤ 0.0001.
[^3] P < 0.001.
[^4] P < 0.05.

**FIGURE 2.** Plasma C-reactive protein (CRP) concentrations in men and premenopausal women individually matched on the basis of similar visceral adipose tissue (AT; A), subcutaneous AT (B), and fat mass (C). Because the variables were skewed, P values of the log-transformed variables are presented. Differences were tested with a Student’s paired t test.
levels of obesity. In fact, no sex differences in CRP have been reported in lean populations (48). In the present study, except for the intercept values, which were not different between sexes for CRP and IL-6 concentrations, the slopes of the regression lines of CRP and of IL-6 concentrations to visceral adiposity were steeper in women than in men. Thus, CRP concentrations increased more rapidly as a function of visceral adiposity in women than in men. For instance, as shown in Figure 3A, women had significantly higher CRP concentrations than did men in the 2 top VAT tertiles but not in the lowest VAT tertile, which included nonobese subjects. Therefore, both VAT and sex significantly contributed to the variation in CRP concentrations.

On the other hand, the increase in CRP concentrations across tertiles of SAT was not significantly different between men and women (Figure 3B). This result is slightly at variance with the results shown in Figure 1, which suggests a significant sex × SAT interaction term. The use of categories rather than the analyses of the adiposity indexes as continuous variables is a less powerful approach, which probably explains the differences in the results obtained. Nevertheless, when we compared

**TABLE 3**
Multiple regression analyses showing the independent contributions of sex, visceral adipose tissue (VAT), subcutaneous adipose tissue (SAT), total fat mass (FM), sex × VAT interaction, sex × SAT interaction, and sex × FM interaction terms to the variation in plasma inflammatory markers†

<table>
<thead>
<tr>
<th>Dependent variable</th>
<th>Model 1</th>
<th>Model 2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Independent variables</td>
<td>$R^2$</td>
</tr>
<tr>
<td>LogCRP</td>
<td>FM 0.18 + VAT 0.19 + Sex × FM 0.21</td>
<td>0.18</td>
</tr>
<tr>
<td></td>
<td>SAT 0.059</td>
<td>0.059</td>
</tr>
<tr>
<td>LogIL-6</td>
<td>FM 0.16 + VAT 0.17 + Sex × FM 0.17 + Sex 0.19</td>
<td>0.17</td>
</tr>
<tr>
<td></td>
<td>+ Sex × SAT 0.16</td>
<td>0.16</td>
</tr>
<tr>
<td>LogTNF-α</td>
<td>Sex 0.04 + FM 0.059</td>
<td>0.04</td>
</tr>
</tbody>
</table>

† CRP, C-reactive protein; IL-6, interleukin-6; TNF-α, tumor necrosis factor-α; $R^2$, percentage of variance in the dependent variable that is explained by the independent variable.

2 Variables included in model 1 ($n = 341$) were sex, VAT, total FM, and sex × VAT interaction and sex × FM interaction terms.

3 Variables included in model 2 ($n = 353$) were sex, VAT, SAT, and sex × VAT interaction and sex × SAT interaction terms.
men and women with similar VAT accumulation, women had higher CRP concentrations than did men; however, no sex differences in CRP concentrations were observed when we compared men and women with similar SAT or FM values. Thus, the sex difference in subcutaneous adiposity is probably an important factor explaining the sex differences in CRP and IL-6 concentrations.

In the investigation of inflammatory markers, only a few studies have used direct measures of abdominal obesity, such as magnetic resonance imaging or computed tomography in men and women (49, 50). Recently, a study by Pou et al (51) reported associations of both SAT and VAT with inflammatory markers such as CRP and IL-6. Moreover, similarly to our observations, they observed a significant sex interaction for the association of SAT and VAT with CRP. In addition, we also found a significant sex interaction term regarding the association of SAT and VAT with IL-6. However, when SAT and VAT were both included in the model, only the sex × SAT interaction term remained significantly associated with CRP and IL-6. Our sample size was much smaller than the Framingham cohort, but we performed sex-specific analyses of CRP, IL-6, and TNF-α concentrations.

Nevertheless, both studies clearly showed that both abdominal SAT and VAT have a role in inflammation. We (52) and others (53) previously reported that high concentrations of CRP were related to increased accumulation of both visceral and subcutaneous fat depots measured by computed tomography. Our present results agree with these findings and suggest that IL-6 is an important mediator of the relation between abdominal obesity and CRP concentrations in both men and women.

Our study had limitations, including its use of cross-sectional data, from which we were unable to prove a causal relation between SAT, VAT, and inflammatory markers. In addition, the results of the present study cannot be generalized to other ethnic groups or to more obese groups, because our results were obtained in white men and women and our cohort had a lower BMI than did the average US or Canadian population.

In summary, the results of the present study indicate that the observed sex difference in CRP concentrations cannot be explained by the greater amount of VAT generally observed in men than in women. Rather, our study suggests that the higher CRP concentrations found in women could have been due to the greater accumulation of subcutaneous fat in women than in men. CRP concentrations increased more rapidly as a function of visceral or subcutaneous adiposity in women than in men. Finally, whereas CRP concentrations were largely influenced by visceral adiposity in men, subcutaneous adiposity was the key correlate of CRP in women. Because premenopausal women generally have a lower risk of CVD than do men, the contribution of the sex difference in subcutaneous adiposity and in CRP to the sex difference in CVD risk will need to be properly addressed in future studies.

We express our gratitude to the Québec Family Study subjects for their excellent collaboration and to the staff of the Hôpital Laval Research Centre. We especially thank Germain Thériault, Guy Fournier, Lucie Allard, Claude Leblanc, and Monique Chagnon for their help with the data collection.

The authors’ responsibilities were as follows—AC: reviewed the literature, performed the laboratory measurements and statistical analyses, interpreted the data, and wrote the manuscript; MC: assisted with the laboratory measures and the data analysis and interpretation; LP, AT, and CB: responsible for the study design and data collection; and J-PP: supervised the research, directed the data analysis and interpretation, and assisted with the manuscript preparation. All of the authors revised the manuscript. None of the authors had a personal or professional conflict of interest.

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10. Lemieux S, Prud’homme D, Bouchard C, Tremblay A, Despres JP. C-reactive protein, interleukin-6; TNF-α, tumor necrosis factor-α; $R^2$, percentage of variance in the dependent variable that is explained by the independent variable.

TABLE 4 Multivariate regression analyses showing the independent contribution of age, visceral adipose tissue (VAT), total fat mass (FM), and subcutaneous adipose tissue (SAT) to the variations in plasma inflammatory markers in men and women.

<table>
<thead>
<tr>
<th>Dependent variable</th>
<th>Independent variables</th>
<th>Regression $\beta$ coefficient $\pm$ SE ($\times 10^{-3}$)</th>
<th>$P$</th>
<th>Independent variables</th>
<th>Regression $\beta$ coefficient $\pm$ SE ($\times 10^{-3}$)</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>LogCRP</td>
<td>VAT</td>
<td>0.06 3.78 ± 1.0</td>
<td>&lt;0.001</td>
<td>SAT</td>
<td>0.26 1.87 ± 0.70</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>Age</td>
<td>0.19 13.9 ± 4.7</td>
<td>&lt;0.01</td>
<td>+ VAT</td>
<td>0.28 8.66 ± 2.48</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>LogIL-6</td>
<td>Age</td>
<td>0.11 10.3 ± 2.67</td>
<td>&lt;0.001</td>
<td>+ SAT</td>
<td>0.32 −23.5 ± 7.74</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td></td>
<td>FM</td>
<td>0.17 15.8 ± 4.43</td>
<td>&lt;0.001</td>
<td>SAT</td>
<td>0.25 2.51 ± 0.36</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LogTNF-α</td>
<td>FM</td>
<td>0.02 5.17 ± 2.64</td>
<td>&lt;0.05</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

1. Variables included in the analyses were age, total FM, VAT, and SAT. CRP, C-reactive protein; IL-6, interleukin-6; TNF-α, tumor necrosis factor-α; $R^2$, percentage of variance in the dependent variable that is explained by the independent variable.

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