Elevated C-Reactive Protein Levels in Overweight and Obese Adults

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Adipose tissue previously was considered a passive storage depot for fat but is now known to play an active role in metabolism. Among the recently discovered compounds expressed in human adipose tissue is the proinflammatory cytokine interleukin 6 (IL-6). Moreover, IL-6 produced in the adipose tissue of healthy humans is released into the circulation. Adipose tissue is estimated to produce about 25% of the systemic IL-6 in vivo. Because of the inflammatory properties of IL-6, including the stimulation of acute-phase protein production in the liver, adipose tissue may induce low-grade systemic inflammation in persons with excess body fat.

A sensitive marker for systemic inflammation is the acute-phase C-reactive protein (CRP). In a meta-analysis of 7 prospective studies, elevated serum CRP concentration was shown to predict future risk of coronary heart disease. C-reactive protein levels well below the conventional clinical upper limit of normal of 1 mg/dL have been associated with a 2- to 3-fold increase in risk of myocardial infarction, ischemic stroke, peripheral arterial disease, and coronary heart disease mortality in healthy men and women.

This study tested whether overweight and obesity are associated with low-grade systemic inflammation as measured by serum CRP concentration.

METHODS
Survey Design and Data Sources
The study included 16,616 adult participants of the Third National Health and Nutrition Examination Survey (NHANES III), 1988-1994. NHANES III was conducted by the National Center for Health Statistics of the Centers for Disease Control and Prevention. The survey had a complex, stratified, multistage probability-cluster design for selecting a sample of approximately 100,000 persons representative of the noninstitutionalized civilian US population. Children younger than 5 years, persons aged 60 years or older, Mexican American persons, and non-Hispanic blacks were sampled at higher rates than others. Eighty-one percent of the non-Hispanic blacks were sampled at higher rates than others. Eighty-one percent of the non-Hispanic blacks were sampled at higher rates than others. Eighty-one percent of the non-Hispanic blacks were sampled at higher rates than others. Eighty-one percent of the non-Hispanic blacks were sampled at higher rates than others. Eighty-one percent of the non-Hispanic blacks were sampled at higher rates than others.
of all eligible adults consented to an initial interview in their household. Of the 20,050 persons aged 17 years or older who were interviewed, 18,162 were subsequently examined in a mobile examination center or in their homes. Persons with missing data on height, body weight, or serum CRP level (n = 1,239) and pregnant women (n = 307, validated by urine pregnancy test) were excluded, leaving 16,016 persons (7,938 men and 8,678 women) available for the statistical analyses.

Body weight and height were measured using standardized procedures. Body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters and used as an indicator of body fat. The 1998 clinical guidelines were used to define overweight (BMI, 25-29.9 kg/m²) and obesity (BMI ≥30 kg/m²).

Waist circumference was measured at the level of the high point of the iliac crest and the circumference at the level of maximum extension of the buttocks. The waist-to-hip ratio, calculated as waist circumference divided by hip circumference, was used as an indicator of abdominal visceral fat.

Serum specimens for the measurement of CRP were stored at −70°C and analyzed within 2 months after phlebotomy. C-reactive protein was analyzed using a modification of the Behring Latex-Enhanced CRP assay on the Behring Nephelometer Analyzer System (Behring Diagnostics, Westwood, Mass) (M.H.W., Phyllis R. Daum, MT [ASCP], G.M.M., unpublished data, 1999). Both within-and between-assy quality control procedures were used and the coefficient of variation of the method was 3.2% to 16.1% through the period (0.1 units) were calculated. Adjustments were made for potential confounders, including age, race, smoking status, estrogen use, inflammatory disease, and other diseases associated with low-grade inflammation, including cardiovascular disease and diabetes mellitus. To assess potential effect modification by age, smoking status, disease status, or estrogen use, the analyses were repeated, restricted to young (aged 17-39 years) healthy non–estrogen-using nonsmokers. Odds ratios do not approximate risk ratios when the prevalence of the outcome variable in the study population is greater than 10%. The calculated OR for elevated CRP concentration therefore should not be interpreted as a risk ratio. Analyses were performed using SAS (SAS Institute Inc, Cary, NC) and SUDAAN (Research Triangle Institute, Research Triangle Park, NC) and incorporated sampling weights to account for oversampling and nonresponse to the household interview and examination. Variance estimates were calculated with SUDAAN, incorporating the complex sampling design of NHANES III.

RESULTS

Elevated CRP levels (≥0.22 mg/dL) were present in 21.8% of men and 33.1% of women, and clinically raised CRP levels (≥1.00 mg/dL) in 4.4% and 8.9%, respectively. Other characteristics of the study population are shown in TABLE 1.

With increasing BMI, the prevalence of elevated CRP level increased...
in both men and women (FIGURE). However, with increasing BMI the prevalence of clinically raised CRP level increased among women only; the prevalence was 4.0% (95% CI, 3.3%-4.8%) in normal-weight women, 7.7% (95% CI, 6.4%-9.4%) in overweight women, and 20.2% (95% CI, 18.1%-22.5%) in obese women.

Obese men were 2.13 times more likely and obese women 6.21 times more likely to have elevated CRP levels compared with their normal-weight counterparts (TABLE 2). Per 1-SD increase in BMI, men were 1.38 and women were 2.04 times more likely to have elevated CRP levels. Among women, BMI was also associated with clinically raised CRP levels. Obese women were 4.76 times more likely to have clinically raised CRP levels. Among women, BMI was also associated with elevated CRP levels (Table 2). The OR for clinically raised CRP levels per 1-SD increase in waist-to-hip ratio was 1.36 in men and 1.28 in women.

The association between BMI and CRP was also investigated after stratification by age group (young = 17-39 years; middle-aged = 40-59 years; old = ≥60 years). Among women, the association between BMI and CRP categories was influenced by age group. Older obese women were less likely to have elevated or clinically raised CRP levels than young obese women. A similar effect modification by age group in women was observed using BMI as a categorical variable. No effect modification by age group was observed in men.

To avoid any potential effect modification by age, inflammatory disease, cardiovascular disease, diabetes mellitus, current smoking, or estrogen use, the analyses were repeated restricted to healthy, nonsmoking, non–estrogen-using persons aged 17 to 39 years. The positive association between BMI category and elevated CRP level remained statistically significant after adjustment for age, race, smoking status (never and former smoking only), and waist-to-hip ratio (TABLE 3). In this restricted analysis, BMI also remained positively associated with clinically raised CRP levels among women.

**COMMENT**

Previous studies in middle-aged and elderly persons have reported a positive association between BMI and CRP concentration.12,26,27 However, in these age groups, the association may have been confounded by disease. Rheumatoid arthritis, diabetes mellitus, and cardiovascular disease are prevalent diseases.

**Figure.** Prevalence of Elevated (≥0.22 mg/dL) Serum C-Reactive Protein Concentration by BMI Category in Men and Women Aged 17 Years or Older

<table>
<thead>
<tr>
<th>BMI, kg/m²</th>
<th>Men (%)</th>
<th>Women (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;25</td>
<td>[n = 662]</td>
<td>[n = 665]</td>
</tr>
<tr>
<td>25-29.9</td>
<td>[n = 729]</td>
<td>[n = 720]</td>
</tr>
<tr>
<td>≥30</td>
<td>[n = 1569]</td>
<td>[n = 1508]</td>
</tr>
</tbody>
</table>

Normal weight was considered a body mass index (BMI) of less than 25 kg/m²; overweight, 25 to 29.9 kg/m²; and obese, 30 kg/m² or more. The prevalence of clinically raised (≥1.00 mg/dL) serum C-reactive protein concentration is indicated in black.
in older persons and are associated with both obesity\textsuperscript{31-33} and increased CRP concentrations.\textsuperscript{8,26-28,34} We carefully controlled for inflammatory disease and other factors known to influence CRP concentrations. A higher prevalence of low-grade systemic inflammation was observed in overweight and obese persons compared with normal-weight persons. Most importantly, our study extends these findings to young adults aged 17 to 39 years, in whom the prevalence of any confounding subclinical disease is generally very low. Of interest is our observation that the distribution of body fat is associated with CRP concentration independent of BMI. A high waist-to-hip ratio, indicative of a large amount of abdominal visceral fat, was associated with low-grade systemic inflammation in men and women.

Our results, together with the evidence of previous studies, have important implications for the health risks of overweight and obese individuals, including those at young ages. Based on NHANES III data, we estimated that 53.9\% of US adults aged 17 years or older are overweight or obese. Overweight, obesity, and a large waist-to-hip ratio pose a considerable health risk, including cardiovascular health.\textsuperscript{33,35-37} Low-grade systemic inflammation has been shown to increase the risk for cardiovascular disease.\textsuperscript{9,11} Some of the increased risk for cardiovascular disease in overweight and obese persons may be explained by our observation that increased CRP concentrations are more prevalent in these persons.

C-reactive protein concentrations well below the conventional clinical upper limit of normal of 1 mg/dL have been associated with a 2- to 3-fold increase in risk of myocardial infarction, ischemic stroke, and peripheral arterial disease in healthy men and women.\textsuperscript{9,13} In addition, elevated CRP levels are predictive of cardiac complications in patients with unstable angina or myocardial infarction\textsuperscript{8,19} and CRP induces the production of tissue factor, a potent procoagulant, in monocytes.\textsuperscript{40} Moreover, elevated CRP concentrations are associated with increased coronary heart disease mortality and total mortality.\textsuperscript{9,41}

Approximately 25\% of circulating IL-6 is estimated to be released by human subcutaneous adipose tissue in vivo,\textsuperscript{2} and IL-6 stimulates the production of acute-phase proteins in the liver.\textsuperscript{8,5} This might explain the observed associations between BMI and CRP. In vitro, human abdominal visceral adipose tissue releases more IL-6 compared with subcutaneous adipose tissue,\textsuperscript{2} possibly explaining our observation that a higher waist-to-hip ratio, after adjustment for BMI and several confounders, was independently associated with elevated CRP level.

Body mass index is an important clinical indicator of overweight and obesity,\textsuperscript{18} but its use as an indicator of body fatness has limitations. At a similar BMI, women have more body fat than men.\textsuperscript{32} This difference was reflected in our data, showing a higher prevalence of elevated and clinically raised CRP levels in women compared with men in overweight and obese persons (Figure). The higher prevalence of elevated and clinically raised CRP levels among obese women compared with obese men could also be due to the fact that women were more likely to be extremely obese: a BMI of 35 to 40 kg/m\textsuperscript{2} was prevalent among 3.4\% of men and 6.4\% of women, and a BMI of 40 kg/m\textsuperscript{2} or more was present among 1.7\% of men and 3.6\% of women. Both phenomena might also explain why BMI was associated with clinically raised CRP levels in women but not men.

Persons with a normal body weight (BMI <25 kg/m\textsuperscript{2}) were used as the reference group. However, this group included a small percentage (1.3\% of men and 3.8\% of women) of underweight persons (BMI <18.5 kg/m\textsuperscript{2}) who might be more likely to be in poor health, with associated higher CRP concentrations. However, when the analyses were

| Table 2. Adjusted Odds Ratios (95% Confidence Intervals) for Elevated and Clinically Raised Serum C-Reactive Protein (CRP) Concentrations in 16 616 Men and Women* |

| E elevated CRP Level (≥0.22 mg/dL)† | Clinically Raised CRP Level (≥1.00 mg/dL)‡ |
|---|---|---|---|---|
| **Men** | **Women** | **Men** | **Women** |
| Body mass index, kg/m\textsuperscript{2} | | | |
| <25 (normal weight) | 1.0 (referent) | 1.0 (referent) | 1.0 (referent) | 1.0 (referent) |
| 25-29.9 (overweight) | 1.41 (1.09-1.81) | 2.23 (1.86-2.67) | 0.90 (0.54-1.51) | 1.65 (1.19-2.28) |
| ≥30 (obese) | 2.13 (1.56-2.91) | 6.21 (4.94-7.81) | 0.84 (0.49-1.41) | 4.76 (3.42-6.61) |
| Per SD increment | 1.38 (1.22-1.55) | 2.04 (1.89-2.20) | 1.08 (0.88-1.33) | 1.69 (1.49-1.92) |
| Waist-to-hip ratio | | | |
| per SD increment | 1.41 (1.17-1.69) | 1.21 (1.07-1.37) | 1.36 (1.01-1.84) | 1.28 (1.07-1.54) |

*Data are adjusted for race, age, smoking status, inflammatory disease, cardiovascular disease, diabetes mellitus, estrogen use (women only), and each other.
†Compared with a CRP level of less than 0.22 mg/dL.
‡Compared with a CRP level of no more than 1.00 mg/dL.

| Table 3. Adjusted Odds Ratios (95% Confidence Intervals) for Elevated and Clinically Raised Serum C-Reactive Protein (CRP) Concentrations in 3303 Young (Aged 17-39 Years), Nonsmoking, Non–Estrogen-Using Men and Women Without Inflammatory Disease, Cardiovascular Disease, or Diabetes Mellitus* |

| Elevated CRP Level (≥0.22 mg/dL)† | Clinically Raised CRP Level (≥1.00 mg/dL)‡ |
|---|---|---|---|---|
| **Men** | **Women** | **Men** | **Women** |
| Body mass index, kg/m\textsuperscript{2} | | | |
| <25 (normal weight) | 1.0 (referent) | 1.0 (referent) | 1.0 (referent) | 1.0 (referent) |
| 25-29.9 (overweight) | 1.35 (0.59-3.11) | 2.87 (1.47-5.58) | 0.11 (0.01-1.03) | 1.42 (0.36-5.64) |
| ≥30 (obese) | 2.85 (1.33-6.10) | 12.90 (5.61-29.65) | 0.64 (0.09-4.68) | 8.56 (2.09-34.95) |
| Per SD increment | 1.61 (1.20-2.16) | 2.46 (1.83-3.32) | 1.17 (0.58-2.37) | 2.26 (1.49-3.41) |
| Waist-to-hip ratio | | | |
| per SD increment | 1.59 (1.06-2.38) | 1.76 (1.13-2.72) | 2.26 (0.89-5.74) | 1.43 (0.75-2.71) |

*Data are adjusted for race, age, smoking status (never and former smoking), and each other.
†Compared with a CRP level of less than 0.22 mg/dL.
‡Compared with a CRP level of less than 1.00 mg/dL.
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repeated after exclusion of underweight people in the reference group, similar results were obtained.

Because the lower detection limit of the CRP assay was 0.22 mg/dL, serum CRP level was used as a categorical variable. It is unlikely that the use of a more sensitive assay would have changed the conclusions of the study. The association between obesity and CRP concentration was observed regardless of the CRP cut point that was used (≥0.22 or >1.00 mg/dL). Second, although the cut point of 1.0 mg/dL has been used in clinical studies, more recent epidemiological studies have shown an increased risk for cardiovascular disease at CRP levels of 0.2 mg/dL and higher. 39-41

We used a single CRP measurement that may not accurately reflect long-term inflammation status. The biological variability of CRP is substantial, with reported values ranging from 10.6% to 63.0%. 41-46 However, because random misclassification due to biological variability will lead to underestimation of true associations, this limitation is unlikely to explain our findings.

Measurements of the serum concentration of IL-6 were not available in the present study. Although the results support the hypothesis that IL-6 produced by the adipocytes increase CRP concentration, direct assessment of IL-6 concentration is needed in future studies to further test this hypothesis.

In conclusion, the results of this large-scale cross-sectional study show that higher BMI is associated with higher CRP concentrations that could not be explained by inflammatory disease or other factors or diseases known to increase CRP concentrations. Because these associations also were observed among young adults aged 17 to 39 years, subclinical disease is unlikely to explain our findings. These data suggest that a state of low-grade systemic inflammation is present in overweight and obese persons.

REFERENCES

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