C-Reactive Protein Identifies Low-Risk Metabolically Healthy Obese Persons: The European Prospective Investigation of Cancer–Norfolk Prospective Population Study

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Background—Conflicting data exist about the cardiovascular risk of metabolically healthy obese persons. The prognostic value of C-reactive protein (CRP) in this intriguing group is unknown. We assessed the association between CRP levels and the risk of coronary heart disease (CHD) in metabolically healthy persons with abdominal obesity.

Methods and Results—In the European Prospective Investigation of Cancer–Norfolk prospective cohort, CRP levels and information on metabolic syndrome criteria were available for 7279 participants, of whom 825 (11%) developed CHD during a follow-up period of 10.9±1.8 years. There was a trend toward a higher multivariable-adjusted hazard ratio for CHD in metabolically healthy obese participants with CRP levels >2 mg/L compared with <2 mg/L (hazard ratio 1.59, 95% CI 0.97–2.62, P=0.066). Metabolically unhealthy obese participants had significantly higher CHD risk compared with metabolically healthy obese participants with CRP levels <2 mg/L (hazard ratio 1.88, 95% CI 1.20–2.94, P=0.006). Most important, we found that the risk of CHD among metabolically healthy obese persons with CRP levels <2 mg/L was comparable to that of metabolically healthy nonobese persons (hazard ratio 0.91, 95% CI 0.60–1.39, P=0.674).

Conclusions—Among metabolically healthy obese persons, low CRP levels were associated with a CHD risk comparable to that of metabolically healthy nonobese persons. CRP appears to be an easy and widely available method for identifying a low-risk subpopulation among metabolically healthy obese persons. (J Am Heart Assoc. 2016;5:e002823 doi: 10.1161/JAHA.115.002823)

Key Words: atherosclerosis • inflammation • metabolic syndrome • obesity • risk factor

C-reactive protein (CRP) is an acute-phase protein of the family of the pentraxins and is widely used in clinical settings to monitor chronic and acute inflammatory conditions.¹ The positive association between CRP levels and the risk of future coronary heart disease (CHD) has been studied extensively.²⁻³ The metabolic syndrome (MS) represents a cluster of risk factors for cardiovascular disease and type 2 diabetes mellitus, which coexist more often than by chance alone. It is widely accepted that the spectrum of MS includes abdominal obesity, hypertension, hypertriglyceridemia, low high-density lipoprotein cholesterol (HDL-C), and glucose intolerance, although the exact cutoff values are debated.⁴⁻⁵ Two large meta-analyses have shown that the presence of MS raises CHD risk ≈2-fold.⁶⁻⁷ Experimental and observational evidence suggests that inflammation may play a central role in the pathogenesis of cardiovascular disease.⁸ CRP is associated with all parameters of the MS⁹ and has been acknowledged to be an independent but not causal²⁻¹⁰ risk factor for incident CHD and to add prognostic value for CHD risk on top of the MS criteria.³⁻⁹⁻¹¹⁻¹⁴

The presence of obesity-related metabolic disturbances varies widely among obese persons. Metabolically healthy obese persons are characterized by having excessive body fat while displaying a favorable metabolic profile characterized by high levels of insulin sensitivity; no hypertension; and a favorable lipid, inflammation, hormonal, liver enzyme, and...
CRP Identifies Healthy Obese Persons

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Methods

Study Design

EPIC-Norfolk is a prospective population study of 25 639 male and female inhabitants of Norfolk, United Kingdom, aged 39 to 79 years. Briefly, EPIC-Norfolk is part of the 10-country collaborative EPIC study designed to investigate determinants of cancer. Additional data were obtained to enable assessment of determinants of other diseases such as CHD. At the baseline survey between 1993 and 1997, participants completed a detailed health and lifestyle questionnaire with additional data collection performed by trained nurses at a clinic visit. The study cohort was similar to UK population samples with regard to many characteristics including anthropometry, blood pressure, and lipids but with a lower proportion of smokers. Full details of the population were reported elsewhere.20

MS criteria were defined as described previously, with minor modifications.4 Abdominal obesity, obese persons, and obesity were all defined as an elevated waist circumference ≥102 cm (≥40 in) in men and ≥89 cm (≥35 in) in women. Hypertension was defined as systolic blood pressure ≥130 mm Hg, diastolic blood pressure ≥85 mm Hg, or use of antihypertensive medication.2 Hypertriglyceridemia was defined as triglyceride levels ≥150 mg/dL (1.7 mmol/L), whereas low HDL-C was defined as HDL-C <40 mg/dL (1.03 mmol/L) in men or HDL-C <50 mg/dL (1.30 mmol/L) in women. Hyperglycemia was defined as glycated hemoglobin HbA1c ≥6% or being on antidiabetic medication at inclusion. Participants were considered metabolically healthy when no or 1 MS criterion was present. Metabolically unhealthy was defined as the presence of ≥2 MS criteria. Metabolically healthy abdominally obese persons were defined as having an elevated waist circumference ≥102 cm (≥40 in) in men and ≥89 cm (≥35 in) in women without the presence of any of the other MS criteria.

All participants were flagged for mortality at the UK Office of National Statistics, with vital status ascertained for the entire cohort. The death certificates were coded by trained physicians according to the International Classification of Diseases, 10th revision (ICD-10). In addition, participants were identified using their unique National Health Service numbers through data linkage with the East Norfolk Health Authority (ENCORE) database, which identifies all hospital contacts throughout England and Wales for residents of Norfolk. Participants were identified as having a CHD event if the corresponding ICD-10 code (I20–I25) was recorded as the underlying cause of that hospitalization or mortality. The study complied with the Declaration of Helsinki. The Norwich District Health Ethics committee approved the study, and all participants gave signed informed consent.

Laboratory Measurements

Nonfasting blood samples were drawn into plain and citrate bottles. Blood samples were processed directly at the Department of Clinical Biochemistry, University of Cambridge, or stored at −80°C. Serum levels of total cholesterol, HDL-C, and triglycerides were measured in fresh samples with RA 1000 (Bayer Diagnostics). Low-density lipoprotein cholesterol levels were calculated using the Friedewald formula. Because of limited funding, HbA1c levels were measured for participants from 1995 only; this approximates a random subset of the cohort. HbA1c was measured on fresh EDTA blood samples using high-performance liquid chromatography (Dia-mat Automated Glycated Hemoglobin Analyzer; Bio-Rad Laboratories Ltd). When additional funding became available in 2010, serum concentrations of CRP were measured for all participants with available frozen baseline serum samples using a full-range, high-sensitivity assay on an Olympus AU640 clinical chemistry analyzer (Olympus UK Ltd).

Statistical Analysis

For the current analysis, study participants with missing data for CRP, waist circumference, lipids, blood pressure, HbA1c, or use of antihypertensive or antidiabetic medication were excluded. Summary data are presented as mean±SD for continuous variables with a normal distribution, as median and interquartile range (IQR) for continuous variables with a non-normal distribution, and as percentage (number) for categorical variables. Because triglycerides and CRP were not normally distributed, these parameters were log-transformed before analysis. A 2-sided t test was used to test differences between groups for continuous variables, and a chi-square
test was used for categorical variables. A Cox proportional hazards model was used to assess the association between CRP levels and CHD. Associations were expressed as hazard ratios (HRs) and corresponding 95% CIs per 1-SD increment in (log-transformed) CRP. Participants were censored at the time of the first occurrence of the cardiovascular event analyzed, the time of death, or the end of follow-up, which was March 31, 2008, whichever came first. Three Cox regression models were performed to investigate the relation of CHD event rates, CRP, and (1) metabolically healthy or unhealthy persons, (2) persons with or without abdominal obesity, or (3) metabolically healthy or unhealthy persons with or without abdominal obesity. All models were adjusted for sex and age or for sex, age, smoking status, the use of lipid-lowering medication at baseline, and low-density lipoprotein cholesterol. Subgroup analyses were performed to test for a possible interaction between sex and CRP was performed by the inclusion of an interaction term in the multivariable corrected model. The proportional hazards assumption was met for each variable in the model applied.

The predefined level of significance was set at 0.05. Analyses were performed using IBM SPSS statistics version 20 (IBM Corp).

Results

CRP Levels and the MS Criteria

A complete data set on CRP levels, abdominal obesity, hypertension, hypertriglyceridemia, HDL-C, and HbA1c was available for 7279 participants. Table 1 shows the baseline characteristics according to metabolic phenotype and CRP level for the study participants. The mean age was 58 years, and 57% of participants were women. During follow-up, 825 (11%) CHD events occurred. There was a positive association between CRP level and number of MS criteria. CRP levels for those with 0, 1, 2, 3, or ≥4 MS criteria were 0.8 mg/L (IQR 0.4–1.7 mg/L), 1.2 mg/L (IQR 0.6–2.4 mg/L), 1.5 mg/L (IQR 0.8–3.1 mg/L), 2.2 mg/L (IQR 1.2–4.3 mg/L), and

Table 1. Baseline Characteristics

<table>
<thead>
<tr>
<th>Metabolically Healthy</th>
<th>Metabolically Unhealthy</th>
<th>P Value*</th>
<th>P Value†</th>
<th>P Value‡</th>
<th>All</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRP &lt;2 mg/L</td>
<td>CRP ≥2 mg/L</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Participants, n (%)</td>
<td>2685 (37)</td>
<td>997 (14)</td>
<td></td>
<td></td>
<td>7279</td>
</tr>
<tr>
<td>Age, y</td>
<td>55.7±9.2</td>
<td>58.3±9.0</td>
<td></td>
<td></td>
<td>58.4±9.4</td>
</tr>
<tr>
<td>Women, n (%)</td>
<td>1872 (64)</td>
<td>842 (67)</td>
<td>&lt;0.001</td>
<td>647 (42)</td>
<td>790 (51.3)</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>24.6±3.0</td>
<td>26.5±3.9</td>
<td>&lt;0.001</td>
<td>26.7±3.3</td>
<td>28.6±4.4</td>
</tr>
<tr>
<td>Waist circumference, cm</td>
<td>82.6±10.9</td>
<td>87.0±11.6</td>
<td>&lt;0.001</td>
<td>91.3±11.0</td>
<td>95.6±11.6</td>
</tr>
<tr>
<td>Current smoker, n (%)</td>
<td>293 (10)</td>
<td>175 (14)</td>
<td>&lt;0.001</td>
<td>132 (9)</td>
<td>234 (15)</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>10 (0.3)</td>
<td>8 (0.6)</td>
<td>0.182</td>
<td>55 (3.6)</td>
<td>76 (4.9)</td>
</tr>
<tr>
<td>Myocardial infarction at baseline, n (%)</td>
<td>29 (1.0)</td>
<td>22 (1.7)</td>
<td>0.040</td>
<td>68 (4.4)</td>
<td>104 (6.7)</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>128±16</td>
<td>132±18</td>
<td>&lt;0.001</td>
<td>140±17</td>
<td>143±17</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>79±10</td>
<td>81±11</td>
<td>&lt;0.001</td>
<td>86±11</td>
<td>86±10</td>
</tr>
<tr>
<td>Total cholesterol, mmol/L</td>
<td>5.88±1.01</td>
<td>5.99±1.05</td>
<td>0.002</td>
<td>6.32±1.15</td>
<td>6.39±1.18</td>
</tr>
<tr>
<td>LDL-C, mmol/L</td>
<td>3.72±0.94</td>
<td>3.80±0.98</td>
<td>0.012</td>
<td>4.08±1.03</td>
<td>4.12±1.04</td>
</tr>
<tr>
<td>HDL-C, mmol/L</td>
<td>1.63±0.40</td>
<td>1.61±0.40</td>
<td>0.141</td>
<td>1.23±0.35</td>
<td>1.21±0.34</td>
</tr>
<tr>
<td>Triglycerides, mmol/L</td>
<td>1.1 (0.9–1.5)</td>
<td>1.2 (1.0–1.5)</td>
<td>&lt;0.001</td>
<td>2.2 (1.8–2.7)</td>
<td>2.2 (1.8–2.8)</td>
</tr>
<tr>
<td>HbA1c, %</td>
<td>5.09±0.51</td>
<td>5.18±0.55</td>
<td>&lt;0.001</td>
<td>5.46±0.91</td>
<td>5.76±1.15</td>
</tr>
<tr>
<td>CRP, mg/L</td>
<td>0.7 (0.4–1.2)</td>
<td>3.6 (2.5–6.1)</td>
<td>&lt;0.001</td>
<td>1.0 (0.6–1.4)</td>
<td>4.0 (2.8–6.6)</td>
</tr>
<tr>
<td>Use of lipid-lowering drugs at baseline, n (%)</td>
<td>5 (0)</td>
<td>3 (0)</td>
<td>0.646</td>
<td>55 (3.6)</td>
<td>64 (4.2)</td>
</tr>
<tr>
<td>Hormone replacement therapy, n (%)</td>
<td>344 (11.7)</td>
<td>298 (23.6)</td>
<td>&lt;0.001</td>
<td>78 (5.1)</td>
<td>181 (11.7)</td>
</tr>
</tbody>
</table>

Data are presented as mean±SD or number (percentage). Triglyceride and CRP are presented as median with the 25th to 75th percentiles. CRP indicates C-reactive protein; HbA1c, glycated hemoglobin A1c; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

*P value of comparison within metabolically healthy groups with different levels of CRP.
†P value of comparison within metabolically unhealthy groups with different levels of CRP.
‡P value for comparison between metabolically healthy and unhealthy groups independent of CRP level.
3.0 mg/L (IQR 1.6–5.7 mg/L), respectively (P for trend <0.001). Likewise, CRP levels were significantly higher in participants with versus without abdominal obesity independent of MS criteria (P for trend <0.001). Figure 1 displays the median and the 25th and 75th percentiles of the CRP distribution according to the number of MS criteria and the presence of abdominal obesity.

CRP and CHD Risk in Metabolically Healthy and Unhealthy Persons

HRs for CHD according to the presence or absence of metabolic health, abdominal obesity, and CRP level are shown in Table 2. Among metabolically unhealthy participants, those with CRP ≥2 mg/L had significantly higher CHD risk than those with CRP <2 mg/L (HR 1.37, 95% CI 1.16–1.63, P<0.001). Metabolically healthy participants with CRP levels <2 mg/L had a significantly lower risk than those with abdominal obesity and CRP levels <2 mg/L (HR 0.73, 95% CI 0.58–0.92, P=0.008). Compared with sex- and age-adjusted HRs, additional adjustment for smoking status, lipid-lowering medication at baseline, and low-density lipoprotein cholesterol did not change the results importantly (HR 1.38, 95% CI 1.08–1.75, P=0.010, and HR 0.75, 95% CI 0.59–0.94; P=0.013, respectively).

CRP and CHD in Obese and Nonobese Persons

Among participants with abdominal obesity, those with CRP ≥2 mg/L had significantly higher CHD risk compared with those with a CRP level <2 mg/L (HR 1.45, 95% CI 1.14–1.85, P=0.002). Nonobese participants with CRP levels <2 mg/L had a significantly lower risk than those with abdominal obesity and CRP levels <2 mg/L (HR 0.73, 95% CI 0.58–0.92, P=0.008). Compared with sex- and age-adjusted HRs, additional adjustment for smoking status, lipid-lowering medication at baseline, and low-density lipoprotein cholesterol did not change the results importantly (HR 1.38, 95% CI 1.08–1.75, P=0.010, and HR 0.75, 95% CI 0.59–0.94; P=0.013, respectively).

CRP and CHD in Metabolically Healthy and Unhealthy Obese Persons

The risk of CHD for metabolically unhealthy obese participants with CRP <2 mg/L was significantly higher compared with metabolically healthy obese participants with CRP ≥2 mg/L (HR 1.88, 95% CI 1.20–2.94, P=0.006). The risk of CHD for metabolically healthy obese participants with CRP ≥2 mg/L was higher than that for metabolically healthy participants with CRP <2 mg/L (HR 1.59, 95% CI 0.97–2.62, P=0.066), although this trend did not reach statistical significance. Importantly, metabolically healthy participants without abdominal obesity had CHD risk comparable to metabolically healthy obese participants with CRP levels <2 mg/L (HR 0.91, 95% CI 0.60–1.39, P=0.674, for CRP <2 mg/L; HR 1.22, 0.78–1.91, P=0.387, for CRP >2 mg/L). Because sex is known to influence both CRP levels and CHD risk, we performed a subgroup analysis by sex to investigate a possible interaction between sex and CRP levels for risk of CHD. We did not find a statistical difference for the interaction of sex and CRP in the multivariable adjusted
model \( P=0.511 \). Figure 2 displays CHD event rates according to the number of MS criteria and the presence of abdominal obesity in participants with either high or low CRP levels.

### Table 2. Hazard Ratios of Coronary Heart Disease Depending on Metabolic Phenotype or the Presence of Abdominal Obesity Stratified by C-Reactive Protein Levels

<table>
<thead>
<tr>
<th>CRP, mg/L</th>
<th>n (%)</th>
<th>Model 1</th>
<th>( P ) Value</th>
<th>Model 2</th>
<th>( P ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metabolically healthy</td>
<td>&lt;2</td>
<td>2936 (40)</td>
<td>0.53 (0.43–0.65)</td>
<td>&lt;0.001</td>
<td>0.60 (0.48–0.73)</td>
</tr>
<tr>
<td></td>
<td>≥2</td>
<td>1262 (17)</td>
<td>0.80 (0.64–1.01)</td>
<td>0.056</td>
<td>0.85 (0.68–1.01)</td>
</tr>
<tr>
<td>Metabolically unhealthy</td>
<td>&lt;2</td>
<td>1540 (21)</td>
<td>1 (ref)</td>
<td>—</td>
<td>1 (ref)</td>
</tr>
<tr>
<td></td>
<td>≥2</td>
<td>1541 (21)</td>
<td>1.37 (1.16–1.63)</td>
<td>&lt;0.001</td>
<td>1.31 (1.10–1.56)</td>
</tr>
<tr>
<td>No abdominal obesity</td>
<td>&lt;2</td>
<td>3730 (51)</td>
<td>0.73 (0.58–0.92)</td>
<td>0.008</td>
<td>0.75 (0.59–0.94)</td>
</tr>
<tr>
<td></td>
<td>≥2</td>
<td>1697 (23)</td>
<td>1.10 (0.87–1.39)</td>
<td>0.420</td>
<td>1.03 (0.81–1.30)</td>
</tr>
<tr>
<td>Abdominal obesity</td>
<td>&lt;2</td>
<td>746 (10)</td>
<td>1 (ref)</td>
<td>—</td>
<td>1 (ref)</td>
</tr>
<tr>
<td></td>
<td>≥2</td>
<td>1106 (15)</td>
<td>1.45 (1.14–1.85)</td>
<td>0.002</td>
<td>1.38 (1.08–1.75)</td>
</tr>
<tr>
<td>Metabolically healthy without abdominal obesity</td>
<td>&lt;2</td>
<td>2610 (36)</td>
<td>0.87 (0.57–1.33)</td>
<td>0.524</td>
<td>0.91 (0.60–1.39)</td>
</tr>
<tr>
<td></td>
<td>≥2</td>
<td>925 (13)</td>
<td>1.24 (0.80–1.94)</td>
<td>0.336</td>
<td>1.22 (0.78–1.90)</td>
</tr>
<tr>
<td>Metabolically healthy abdominally obese</td>
<td>&lt;2</td>
<td>326 (5)</td>
<td>1 (ref)</td>
<td>—</td>
<td>1 (ref)</td>
</tr>
<tr>
<td></td>
<td>≥2</td>
<td>337 (5)</td>
<td>1.60 (0.98–2.63)</td>
<td>0.063</td>
<td>1.59 (0.97–2.62)</td>
</tr>
<tr>
<td>Metabolically unhealthy abdominally obese</td>
<td>&lt;2</td>
<td>420 (6)</td>
<td>1.97 (1.26–3.09)</td>
<td>0.003</td>
<td>1.88 (1.20–2.94)</td>
</tr>
<tr>
<td></td>
<td>≥2</td>
<td>769 (11)</td>
<td>2.53 (1.67–3.83)</td>
<td>&lt;0.001</td>
<td>2.29 (1.51–3.47)</td>
</tr>
</tbody>
</table>

Data presented as hazard ratios and corresponding 95% CIs. Model 1 is age and sex corrected. Model 2 is corrected for age, sex, smoking, the use of lipid-lowering medication at baseline, and low-density lipoprotein cholesterol. CRP indicates C-reactive protein.

Discussion

The results of the present study indicated that metabolically healthy obese persons with low CRP levels had a trend toward...
lower risk than metabolically healthy obese persons with elevated levels of CRP. More important, we observed that metabolically healthy obese persons with low CRP levels had a CHD risk similar to that of healthy nonobese persons. These data suggest that among metabolically healthy obese persons, low CRP levels are associated with low CHD risk.

Long-Term Risk for CHD

The positive association between CRP levels and the MS and between the MS and CHD have been studied extensively. Previous studies suggest that those with the MS or with elevated levels of CRP have an increased risk of CHD. However, 2 large recently published meta-analyses assessing the associations of CRP concentration with risk of vascular outcomes did not include the MS in their subgroup analyses. Our data indicate that metabolically unhealthy persons with elevated CRP levels have a significantly higher risk of future CHD compared with metabolically unhealthy persons with CRP levels <2 mg/dL. Ridker et al previously reported an age-adjusted HR of 2.3 (95% CI 1.6–3.3) for women with the MS if CRP levels <3 mg/L were present in contrast to the HR of 4.0 (95% CI 3.0–5.4) if CRP levels >3 mg/L were present. Rutter et al similarly observed that CRP independently predicted CHD above the presence of the MS in the Framingham prospective cohort study. We found similar associations for abdominally obese participants with elevated CRP levels showing an increased risk for CHD compared with abdominally obese participants with low CRP levels. Previous studies linking CRP levels to CHD were performed largely in populations with a lower prevalence of obesity than that of the current US population. In the 2 largest published studies of CRP and CHD disease, the mean body mass index (in kg/m²) of participants ranged from 25 to 26, lower than the recently reported mean of 28.7 in US adults, indicating the clinical need for data regarding CRP in obese populations. The Strong Heart Study examined the relationship between CRP levels and CHD in an obese population with a mean body mass index >30. After multivariable adjustment for traditional risk factors, no significant association was observed between elevated CRP levels (>3 mg/L) and CHD events; however, subgroup analyses examining these relationships in obese and nonobese participants were not performed. Similarly, Gupta et al reported that the association between CRP and atherosclerosis is diminished in obese persons aged 30 to 65 years. The role of interleukin 6 was recently corroborated by 3 mendelian-based association studies. Single-nucleotide polymorphisms associated with decreased interleukin 6 signaling were found to correlate with lower values of acute-phase reactants, such as CRP and fibrinogen, with a concomitant proportional reduction in cardiovascular risk. This lower predictive accuracy of CRP in obese participants may be affected by the close correlation between CRP and adiposity. Interleukin 6 is the principle cytokine that stimulates CRP release from the liver, and up to one-third of circulating interleukin 6 is released from adipose tissue. Despite these data suggesting a weakened association in obese versus nonobese persons, our data showed that obese participants with elevated levels of CRP have a higher risk of future CHD than obese participants with CRP levels <2 mg/dL, suggesting that CRP adds prognostic information for the obese population, although the presence or absence of cardiometabolic risk factors may influence the predictive value of CRP in abdominally obese persons (Figure 2).

This study focused primarily on CRP and the risk of future cardiovascular events among participants recently characterized by Primeau et al: metabolically healthy obese persons. Despite having excessive body fat, these participants displayed a favorable metabolic profile characterized by high levels of insulin sensitivity; no hypertension; and a favorable lipid, inflammation, hormonal, liver enzyme, and immune profile. Previous prospective studies provided mixed findings with regard to the prognosis of future CHD events in the metabolically healthy obese population. Three prospective studies observed that metabolically healthy obese persons have a risk of cardiovascular disease, mortality, and all-cause mortality similar to that of metabolically healthy nonobese persons. In contrast, 2 other studies suggested that, compared with metabolically healthy nonobese persons, metabolically healthy obese persons have a higher risk of cardiovascular mortality and all-cause mortality. More recently, Ortega et al showed that when accounting for fitness, cardiovascular risk was lower for metabolically healthy obese persons compared with metabolically unhealthy obese persons. This study suggested that metabolically healthy obese persons might have decreased cardiovascular risk compared with their metabolically unhealthy peers because the metabolically healthy group is usually more physically fit. Our study showed that metabolically healthy obese participants with low CRP levels had a risk of future CHD similar to that of metabolically healthy nonobese participants as well as that of metabolically healthy nonobese participants with elevated CRP. These data suggest that CRP could help identify those metabolically healthy obese persons who are at low CHD risk.

Limitations and Strengths

When interpreting the results of our study, several aspects need to be taken into account. An important strength of this study is the relatively large number of CHD events occurring during follow-up (n=825). CRP levels and HRs for CHD were similar to those observed in previous publications. The prevalence of metabolic risk criteria was in agreement with other large observational cohort studies, whereas the
prevalence of the metabolically healthy but obese phenotype was somewhat higher in our population compared with previous studies, probably because we defined abdominal obesity by waist circumference, whereas other studies used other measures to determine obesity (e.g., body mass index). It must be noted that in view of the subgroups used in our analyses, differences in our population did not always reach our predefined significance level. This study was not designed and powered for the current analyses; therefore, the results should be considered as hypothesis generating and in need of confirmation in larger populations. In this prospective cohort study, changes in lipid-lowering therapy and diet were not recorded during follow-up. Statins and diet can decrease systemic CRP levels. The use of such medication or changes in diet could have altered CRP levels at different times (e.g., body mass index).

Conclusions

We confirmed a strong association between elevated CRP levels and an increased risk of CHD in abdominally obese or metabolically unhealthy persons. Importantly, our data indicated that among metabolically healthy obese persons, low CRP levels appeared to be associated with CHD risk comparable to that of healthy nonobese persons.

Acknowledgments

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Disclosures

None.

References


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