

# Relationships between leptin and C-reactive protein with cardiovascular disease in the adult general population

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## SUMMARY

**Background** Leptin could be a key regulator of C-reactive protein (CRP) levels, which serve as a marker of systemic inflammation. Both leptin and CRP are predictors of cardiovascular disease (CVD). However, the interactions between leptin and CRP, and their association with CVD, remain unclear. We therefore studied them in a large, multiethnic population.

**Methods** We analyzed leptin and CRP levels, anthropometric variables and cardiovascular risk factor data from 6,251 participants from the Third National Health and Nutrition Examination Survey (NHANES III). Logistic regression was used to estimate the association between leptin, CRP and CVD (defined as history of myocardial infarction or stroke). Receiver operating characteristic curves were created to study the additional value of leptin and CRP for the association with CVD.

**Results** The mean age was  $44.4 \pm 0.21$  years (52.5% women). After adjustment for age, race, dyslipidemia, hypertension, diabetes, smoking, obesity and CRP, high levels of leptin were significantly associated with CVD in men (odds ratio 2.47, 95% CI 1.19–5.19) and in women (odds ratio 3.30, 95% CI 1.47–7.99). After adjustment for leptin, CRP was not associated with CVD. There was a significant correlation between levels of leptin and CRP (Spearman correlation  $\rho = 0.22$  in men and  $\rho = 0.32$  in women, both  $P < 0.0001$ ). The area under the curve, representing the association between cardiovascular risk factors and CVD, increased after the addition of high levels of both leptin and CRP together.

**Conclusion** High leptin levels are independently associated with CVD even after adjustment for CRP; elevated CRP levels are not associated with CVD after adjustment for leptin. However, increased concentrations of both leptin and CRP confer the highest risk for CVD.

**KEYWORDS** C-reactive protein, cardiovascular disease, cardiovascular risk factors, leptin

## INTRODUCTION

Leptin, an adipose tissue-derived hormone that is involved in body weight regulation and insulin homeostasis, has been implicated in contributing to a raised risk of myocardial infarction (MI) and stroke in patients with and without known coronary artery disease.<sup>1–5</sup> Leptin might induce the expression of C-reactive protein (CRP), a marker of systemic inflammation related to cardiovascular disease (CVD), in vascular endothelial cells.<sup>6</sup> This theory is supported by studies reporting a significant correlation between levels of leptin and CRP.<sup>7–9</sup> However, whether leptin influences CVD through its action on CRP expression or through some independent pathway, and to what degree the interactions between leptin and CRP contribute to the prediction of CVD, remain unclear. We investigated, therefore, whether measuring both biomarkers, rather than each biomarker alone, would improve the association with CVD in the general adult population in the US.<sup>10</sup>

## METHODS

### Participants

The National Health and Nutrition Examination Survey (NHANES III) population is assessed by periodic surveys that entail stratified, multistage probability sampling to produce estimates of health that could be generalized to the whole US population.<sup>11</sup> We based our study on the population of the third survey, which was conducted from 1988 to 1994 and involved a sample of the US general population who were not institutionalized. Briefly, of 39,695 people selected for the NHANES III, 33,994 were interviewed and 30,818 underwent an examination by a physician at a mobile examination center. Tests included extensive anthropometric, physiological and laboratory assessments. For our study, we restricted the sample to be studied to adults aged 20–80 years for whom leptin and CRP values were available ( $n = 6,335$ ). We excluded data from 84 pregnant women, resulting in a final sample of 6,251 individuals (2,902 men and 3,349 women).

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### Laboratory assessments

In NHANES III, fasting venous blood samples were collected in the morning. Serum specimens were stored at  $-70^{\circ}\text{C}$  for an average of 8 years. Samples were submitted to at least one freeze–thaw cycle before measurement of leptin concentrations by radioimmunoassay at Linco Research, Inc. (St Charles, MO).<sup>12</sup> The minimum detectable concentration of the assay is 0.5 ng/ml. Variations in coefficients within and between assays were less than 5%.<sup>13</sup> Cholesterol levels were measured quantitatively by a peroxidase-catalyzed reaction and HDL levels were measured following the precipitation of the other lipoproteins with a Hitachi 704 Analyzer (Boehringer Mannheim Diagnostics, Mannheim, Germany). LDL cholesterol concentration was calculated (LDL cholesterol = total cholesterol – [triglycerides/5] – HDL cholesterol). LDL cholesterol was not assessed in NHANES III if the value was missing or if the triglyceride level was above 4.52 mmol/l (400 mg/dl). Fasting plasma glucose was measured using a modified hexokinase enzymatic method (Cobas Mira, Roche, Nutley, NJ). Only fasting, morning samples were used for glucose analyses. CRP levels in serum were measured within 2 months of sample collection, with a modified Behring latex-enhanced CRP assay (Behring Diagnostics, Westwood, MA) as described.<sup>14,15</sup> Serum creatinine concentrations were measured with the modified kinetic Jaffe reaction (Hitachi 737, Boehringer Mannheim Corp, Indianapolis, IN). More detailed methodology and laboratory procedures of NHANES III have been published elsewhere.<sup>16</sup>

### Definition of anthropometric and cardiovascular risk factor variables

Height, weight and waist circumference were measured by trained personnel using standard techniques and equipment and BMI was calculated from these values. Blood pressure was measured after 5 min of quiet rest while the participant was seated. All measurements were made by a board-eligible physician at the NHANES III mobile examination center. Individuals were deemed hypertensive if they were taking antihypertensive medications, if they self-reported a diagnosis of hypertension, if their systolic pressure was above 140 mmHg, if their diastolic pressure was above 90 mmHg, or if a combination of these features was recorded.<sup>17</sup> Similarly, dyslipidemia

was recorded if participants reported current use of cholesterol-lowering medications, self-reported a diagnosis of hypercholesterolemia, had HDL cholesterol levels below 1.036 mmol/l (40 mg/dl) in men and 1.30 mmol/l (50 mg/dl) in women or had LDL cholesterol levels above 4.10 mmol/l (160 mg/dl).<sup>18</sup> Participants were considered to have diabetes if they reported current usage of antidiabetic medications, reported a previous diagnosis of diabetes or had a fasting plasma glucose above 7.0 mmol/l (126 mg/dl).<sup>19</sup> Participants were classified as having ever smoked if they answered yes to the question “Have you ever smoked more than 100 cigarettes in your life?”

### Definition of cardiovascular disease

CVD was defined as MI and/or stroke. Presence of MI was defined as self-reported MI based on the interview question “Has a doctor ever told you that you had a heart attack?” Presence of stroke was defined as self-reported stroke based on the interview question: “Has a doctor ever told you that you had a stroke?”

### Statistical analyses

Data were summarized by calculating means and SE for quantitative variables and number and percentages for qualitative variables. Due to considerably different leptin levels measured in men and women, all analyses were stratified by sex and controlled for age and race. We used logistic regression to calculate the odds ratios and 95% CI to determine the association between leptin and CRP with CVD. As the data were significantly skewed, we used the logarithms of leptin and CRP values.

We defined leptin concentrations as high if they fell in the highest sex-specific quartile of serum leptin ( $\geq 7.6$  ng/ml in men and  $\geq 23.7$  ng/ml in women) when compared with those in the lowest quartile ( $< 2.8$  ng/ml in men and  $< 8.9$  ng/ml in women). We did the same for CRP values (highest quartile  $\geq 0.33$  mg/dl in men and  $\geq 0.50$  mg/dl in women) when compared to the lowest quartile ( $< 0.21$  mg/dl in men and  $< 0.21$  mg/dl in women). We analyzed whether the rates of cardiovascular risk factors in individuals with high leptin and CRP values differed by age, weight and history of CVD from those in people with low leptin and high CRP, high leptin and low CRP, or low leptin and low CRP. We decided to use quartiles instead of absolute values for several reasons. First, the

use of quartiles has clinical applicability, as we can identify the 'cut-off' at which leptin is associated with CVD. Second, significantly different levels for leptin have been reported for men and women. Third, because leptin and CRP are not linear variables, a non-parametric analysis such as quartiles is preferable.

We also analyzed whether individuals with high leptin and high CRP values were at raised risk of CVD after controlling for age, race, dyslipidemia, high blood pressure, diabetes, smoking, total and central obesity, and concentrations of creatinine, leptin (for CRP), and CRP (for leptin) in serum. Because of skewness of leptin and CRP values, we used Spearman's correlation coefficients ( $\rho$ ) between leptin or CRP concentration, age, BMI and waist circumference. There is strong evidence to suggest that BMI alone is not the best measure of obesity to assess cardiovascular outcomes.<sup>20–23</sup> We decided, therefore, to combine measures of total and central obesity (BMI  $\geq 30$  kg/m<sup>2</sup> and/or waist circumference  $\geq 102$  cm in men and  $\geq 88$  cm in women) to explore the effects of leptin and CRP independently of obesity. However, we adjusted for BMI by using standard cut-off values, as well as analyzing it as a continuous variable. This approach did not change the results (data not shown). Finally, receiver operating characteristic curves were created to study the additional value of high leptin and high CRP concentrations for the association with CVD.

Significance was set at  $P < 0.05$ . All analyses were weighted according to NHANES methodology and were performed on Windows versions of SAS<sup>24</sup> and SUDAAN.<sup>25</sup>

## RESULTS

The characteristics, cardiovascular risk factors and adverse outcomes of all participants included are summarized in Table 1. The mean age of the sample population was  $44.4 \pm 0.21$  years; 3,349 (52.5%) of the participants were women. From the total weighted sample, 2.9% had a history of MI, 1.7% had a history of stroke and 4.2% had a history of CVD.

Participants with high concentrations of both leptin and CRP had significantly higher rates of hypertension, dyslipidemia, diabetes and smoking, and were older and heavier than individuals with low leptin and CRP levels ( $P < 0.0001$  for all parameters; Table 2). Furthermore, those with high leptin and CRP concentrations had higher rates of MI, stroke and

**Table 1** Characteristics of the study participants.

Variable	Participants (n = 6,251)
Mean (SE) age (years)	44.4 $\pm$ 0.21
Sex (female)	3,349 (52.5%)
Race	
Non-Hispanic white	2,636 (76.7%)
Non-Hispanic black	1,701 (10.5%)
Mexican American	1,653 (4.9%)
Other	261 (7.7%)
Mean (SE) BMI (kg/m <sup>2</sup> )	26.5 $\pm$ 0.07
Mean (SE) waist circumference (cm)	
All	91.7 $\pm$ 0.18
Men	95.5 $\pm$ 0.25
Women	88.2 $\pm$ 0.26
Dyslipidemia	3,322 (52.5%)
Hypertension	2,330 (34.0%)
Diabetes	598 (6.4%)
Ever smoked	3,124 (54.0%)
CVD	
MI + stroke	340 (4.2%)
MI	225 (2.9%)
Stroke	156 (1.7%)

Abbreviations: CVD, cardiovascular disease; MI, myocardial infarction.

CVD (8.3%, 3.4% and 10.8%, respectively) than participants with low leptin and CRP concentrations (1.4%, 1.0% and 2.3 %, respectively;  $P < 0.0001$  for all parameters; Table 2).

After adjustment for age and race, men and women with high leptin and CRP concentrations had the greatest risk of developing CVD (odds ratio [OR] 2.73,  $P < 0.0001$  and OR 3.82,  $P < 0.0001$ , respectively) compared with individuals with low leptin and CRP concentrations. These associations remained significant after adjustment for total and central obesity in men (OR 2.84,  $P < 0.0001$ ) and in women (OR 3.44,  $P < 0.0001$ ; Figure 1). Leptin and CRP levels correlated significantly with each other ( $\rho = 0.22$  in men and  $\rho = 0.32$  in women, both  $P < 0.0001$ ) and with age, BMI and waist circumference (data not shown).

After adjustment for age, race, dyslipidemia, hypertension, diabetes, smoking, total and central obesity and serum creatinine and CRP levels, the risk of developing CVD was higher among individuals with high leptin than among those with low leptin (OR 2.53,  $P = 0.011$  in men and OR 3.37,  $P = 0.005$  in women; Table 3). By contrast, after adjustment for traditional

**Table 2** Baseline characteristics by leptin and CRP levels.

Variable	<sup>a</sup> Low leptin, low CRP (n=3,737)	Low leptin, high CRP (n=951)	High leptin, low CRP (n=865)	High leptin, high CRP (n=673)
Mean (SE) age (years)	42.1±0.27	49.3±0.55 <sup>b</sup>	46.7±0.55 <sup>b</sup>	51.3±0.61 <sup>b</sup>
Sex (female)	2,001 (53.3%)	514 (52.2%)	449 (46.7%)	378 (57.1%)
Race				
Non-hispanic white	1,636 (78.3%)	347 (70.4%) <sup>b</sup>	369 (76.7%)	274 (73.9%) <sup>b</sup>
Non-hispanic black	927 (9.0%)	248 (14.1%) <sup>b</sup>	238 (10.3%)	243 (16.6%) <sup>b</sup>
Mexican American	1005 (4.9%)	286 (6.4%) <sup>b</sup>	221 (4.7%)	136 (3.7%) <sup>b</sup>
Other	169 (7.7%)	34 (9.0%) <sup>b</sup>	37 (8.1%)	20 (5.7%) <sup>b</sup>
Mean (SE) BMI (kg/m <sup>2</sup> )	24.3±0.05	26.5±0.15 <sup>b</sup>	31.9±0.18 <sup>b</sup>	34.1±0.23 <sup>b</sup>
Mean (SE) waist circumference (cm)				
All	85.9±0.18	93.2±0.41 <sup>a</sup>	105.1±0.44 <sup>b</sup>	110.5±0.50 <sup>b</sup>
Men	90.1±0.22	95.5±0.50 <sup>b</sup>	108.5±0.62 <sup>b</sup>	113.2±0.73 <sup>b</sup>
Women	82.2±0.24	91.2±0.62 <sup>b</sup>	101.3±0.58 <sup>b</sup>	108.6±0.66 <sup>b</sup>
Dyslipidemia	1,762 (46.8%)	574 (63.5%) <sup>b</sup>	520 (59.2%) <sup>b</sup>	453 (70.0%) <sup>b</sup>
Hypertension	1,070 (25.0%)	438 (46.1%) <sup>b</sup>	425 (49.1%) <sup>b</sup>	387 (59.0%) <sup>b</sup>
Diabetes mellitus	213 (3.3%)	152 (11.2%) <sup>b</sup>	100 (10.7%) <sup>b</sup>	128 (15.2%) <sup>b</sup>
Ever smoked	1,796 (51.8%)	547 (65.2%) <sup>b</sup>	407 (53.3%)	366 (58.3%) <sup>b</sup>
CVD				
MI + stroke	122 (2.3%)	67 (6.8%) <sup>b</sup>	70 (6.9%) <sup>b</sup>	80 (10.8%) <sup>b</sup>
MI	78 (1.4%)	47 (5.0%) <sup>b</sup>	39 (4.5%) <sup>b</sup>	60 (8.3%) <sup>b</sup>
Stroke	56 (1.0%)	32 (3.1%) <sup>c</sup>	37 (2.5%) <sup>d</sup>	30 (3.4%) <sup>b</sup>

<sup>a</sup>Low leptin-low CRP serves as the reference group. <sup>b</sup>P<0.0001. <sup>c</sup>P<0.001. <sup>d</sup>P<0.01. Abbreviations: CRP, C-reactive protein; CVD, cardiovascular disease; MI, myocardial infarction.

cardiovascular risk factors, obesity measures, serum creatinine and leptin levels, high CRP concentrations were not associated with a higher risk of developing CVD than low concentrations (Table 3).

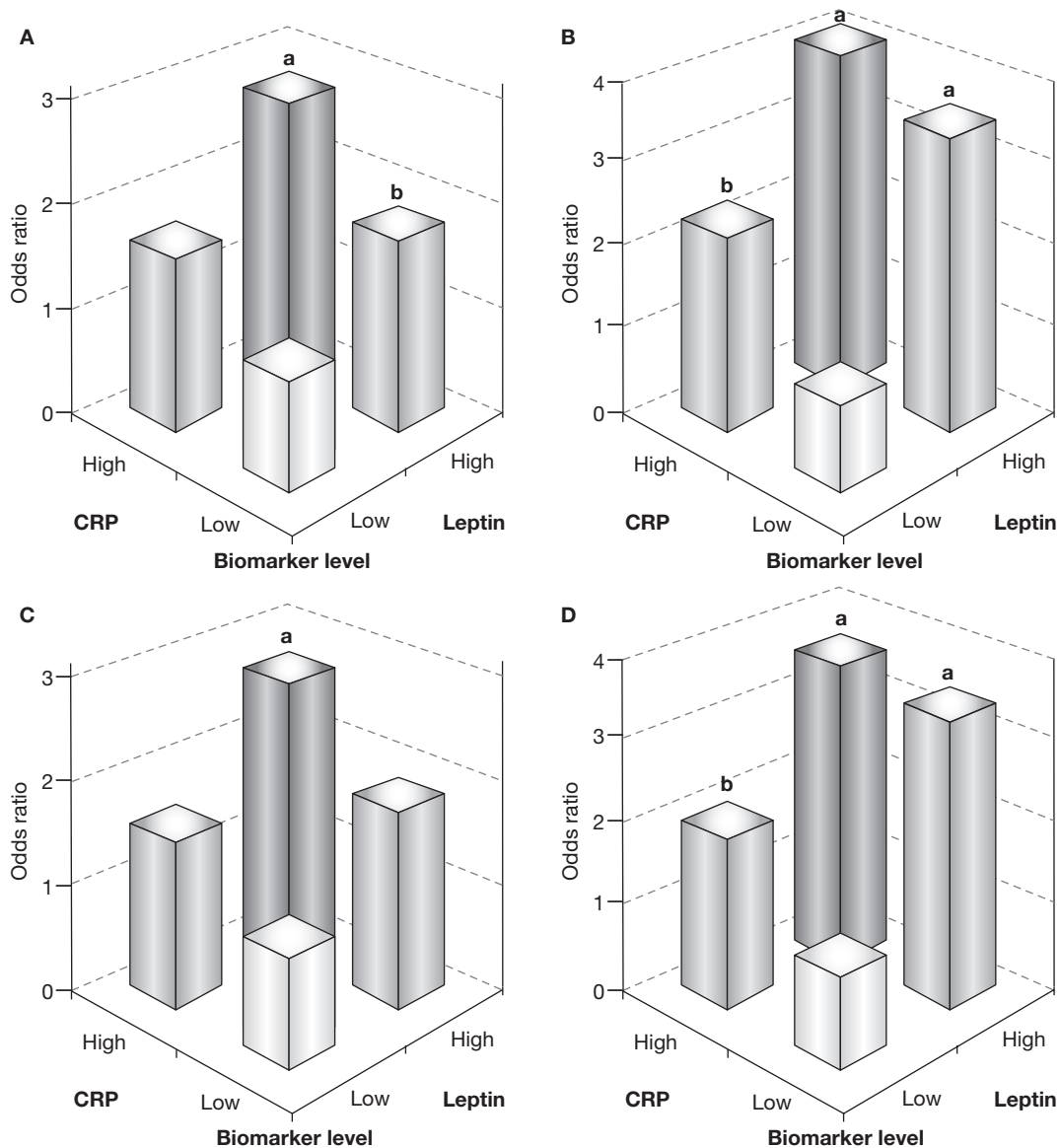
After the addition of high levels of leptin and CRP, the area under the curve for the association between cardiovascular risk factors and CVD improved significantly (Figure 2).

**DISCUSSION**

Our study shows that high leptin and CRP levels and high leptin levels alone are associated with an increased risk of developing CVD, beyond that conferred by raised CRP levels alone, even after adjustment for cardiovascular risk factors and measures of total and central obesity. By contrast, the association between CRP and CVD risk became nonsignificant after adjustment for leptin levels.

Previous studies have reported an association between leptin and MI and between leptin and stroke.<sup>1-5</sup> Only a few studies have, however, evaluated the effects of leptin and its interaction with CRP on the risk of CVD. In a nested case-control

study in moderately hypercholesterolemic men, a correlation between leptin and CRP concentrations was reported that was similar to that noted in our study ( $r=0.24$ ,  $P<0.001$  and  $\rho=0.22$ ,  $P<0.001$ , respectively).<sup>4</sup> A raised leptin level was found to predict the composite outcome of MI, need for revascularization and mortality (relative risk 1.18, 95% CI 1.00-1.39) independent of age, BMI, lipids, systolic blood pressure and CRP.<sup>4</sup> Similarly, in a sample of 382 patients (70% men) with angiographically established coronary artery disease and a follow-up of 4 years, high leptin levels ( $\geq 21.3$  ng/ml) remained associated with a sixfold increased risk of adverse cardiovascular events after adjustment for age, sex, smoking, prior MI, unstable angina or acute MI, blood pressure, LDL/HDL ratio, insulin resistance, vessel stenoses >50 % and fibrinogen and CRP levels.<sup>1</sup> Wolk and colleagues<sup>1</sup> suggested that CRP was no longer associated with adverse cardiovascular events after adjustment for leptin levels. Our results are consistent with theirs and indicate that high CRP levels are not associated with MI or stroke after adjustment for leptin. Notably, however,



**Figure 1** Sex-specific odds ratios for the association between cardiovascular disease with CRP and leptin levels. Data adjusted for age and race in (A) men and (B) women, and adjusted for age, race and total and central obesity in (C) men and (D) women. <sup>a</sup> $P < 0.0001$  and <sup>b</sup> $P < 0.05$  when compared with low leptin and low CRP. Abbreviation: CRP, C-reactive protein.

individuals with high levels of both leptin and CRP were at higher risk of CVD than those with high levels of leptin or CRP alone. In fact, when incorporating high levels of both biomarkers, the risk increased noticeably, as illustrated by the change in area under the curve. This interaction between CRP and leptin might explain the suboptimal performance of CRP when used as a biomarker of cardiovascular risk in some studies.<sup>1,4</sup> On the basis of our results, the role of leptin might be more significant than that of

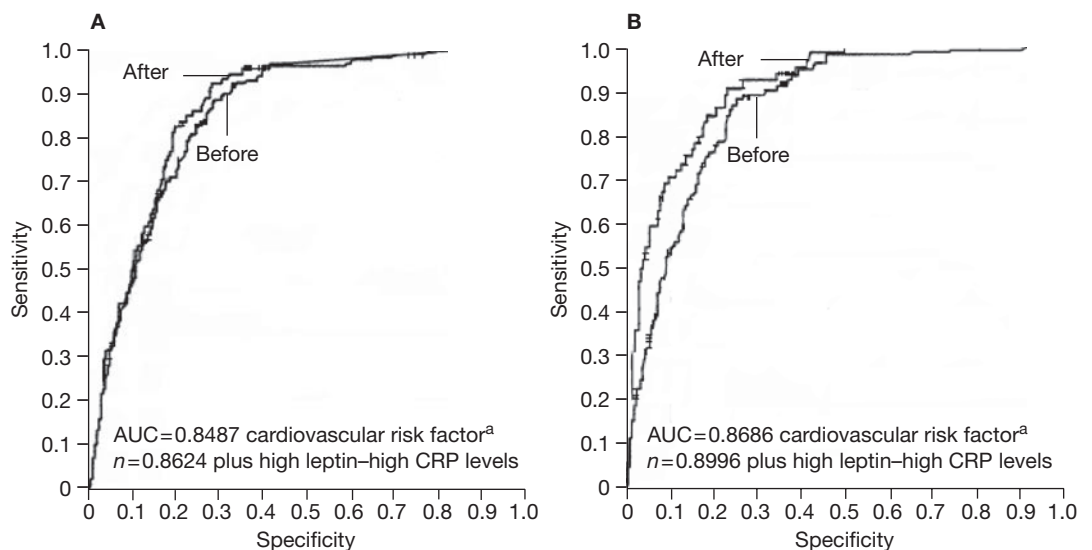
CRP; however, a better association with CVD is achieved when both markers are considered.

Information is limited with regard to the possible differential effects of leptin on CVD in women and men. Wolk *et al.*<sup>1</sup> found that when the data from men and women ( $n = 132$ ; 30% of the sample) were combined, high leptin levels increased the risk of cardiovascular events, reaching a plateau phase in the third and fourth quintiles, after which the risk increased exponentially (highest quintile of leptin).<sup>1</sup> This plateau

**Table 3** Sex-specific odds ratios adjusted for age and race for the association between cardiovascular disease and high leptin and CRP.

Variable	CVD (MI + stroke)			
	Men		Women	
	OR (95% CI)	P	OR (95% CI)	P
High leptin level <sup>a</sup>	2.75 (1.65–4.76)	0.0002	3.37 (1.98–5.94)	<0.0001
Adjusted high leptin level <sup>b</sup>	2.52 (1.21–5.32)	0.011	3.37 (1.49–8.18)	0.005
High CRP level <sup>c</sup>	1.77 (1.29–2.42)	0.0003	2.28 (1.52–3.44)	<0.0001
Adjusted high CRP level <sup>b</sup>	1.38 (0.98–1.95)	0.060	1.55 (0.97–2.48)	0.061

<sup>a</sup>High leptin was defined as the highest sex-specific quartile of serum leptin ( $\geq 7.6$  ng/ml in men and  $\geq 23.7$  ng/ml in women) when compared to the lowest quartile of leptin ( $< 2.8$  ng/ml in men and  $< 8.9$  ng/ml in women). <sup>b</sup>Additionally adjusted for dyslipidemia, hypertension, diabetes, smoking, total and central obesity (BMI  $\geq 30$  kg/m<sup>2</sup> and/or waist circumference  $\geq 102$  cm in men and  $\geq 88$  cm in women), serum creatinine, CRP (for leptin) and leptin (for CRP). <sup>c</sup>High CRP was defined as the highest sex-specific quartile of serum CRP ( $\geq 0.33$  mg/dl in men and  $\geq 0.50$  mg/dl in women) when compared to the lowest quartile of CRP ( $< 0.21$  mg/dl in men and women). Abbreviations: CRP, C-reactive protein; CVD, cardiovascular disease; MI, myocardial infarction.



**Figure 2** Sex-specific receiver operating characteristic curves for the association between cardiovascular risk factors. Total and central obesity and cardiovascular disease (MI and/or stroke) before and after the addition of high leptin and high C-reactive protein levels in (A) men and (B) women. <sup>a</sup>Including total and central obesity. Abbreviations: AUC, area under the curve; CRP, C-reactive protein.

phase has also been reported in the WOSCOPS study,<sup>4</sup> which includes only men. After stratification by sex, however, we have shown that the relationship in women between raised leptin levels and risk of developing CVD became linear, with higher odds ratios than men.<sup>5</sup> We hypothesize that the higher risk in women is related to the presence of higher concentrations of leptin and CRP, as well as the higher proportion of body fat found in women than in men.<sup>5,26</sup>

The mechanisms that link leptin and CRP are complex. Leptin is produced by adipose tissue. Adipocytes are also an important source of

circulating inflammatory cytokines, which contribute to CRP synthesis.<sup>27–29</sup> Evidence suggests that leptin directly influences CRP production in the liver.<sup>30,31</sup> This theory is supported by studies showing that both leptin and CRP are associated with indices of obesity and CVD.<sup>8,32</sup> Furthermore, leptin induces CRP expression in human coronary artery endothelial cells by activating the leptin receptor.<sup>6</sup> Despite the evidence linking the roles of these two biomarkers, the true nature of the association between leptin and CRP observed here is not known.<sup>32</sup>

Our analyses showed that the relationship between leptin and CRP persisted after adjusting for measures of total and central obesity. This finding is relevant to the concept of so-called leptin resistance, which seeks to explain why endogenous hyperleptinemia does not reduce appetite or increase energy expenditure.<sup>33</sup> A role for CRP in the development of leptin resistance has also been suggested, but needs to be studied further.<sup>31,34</sup>

The large sample size used in our study could be considered to be representative of the US population because of the stratified, multi-stage probability sampling design of NHANES. Furthermore, the measurements of total and central obesity recorded in NHANES III enable us to explore the relationship between leptin and CRP with central and total obesity, which are important confounders for any study of leptin as a biomarker of cardiovascular risk. However, separating numerous factors that might be linked by a common pathophysiological mechanism (e.g. obesity, leptin, CRP, lipids) has considerable limitations from a biological standpoint, as the risk calculated from these analyses for leptin and CRP might be different (probably higher) if no adjustment is made for common disease pathways.

Another limitation is the cross-sectional design of the study; MI and stroke events were not prospectively assessed and were self-reported, limiting our ability to determine any causal relation between biomarkers and CVD. Finally, unmeasured variables, such as diet and physical activity could potentially change our risk estimates.

In conclusion, the association between high leptin concentrations and CVD risk is greater than that for CRP alone, even after adjustment for cardiovascular risk factors and measures of total and central obesity. The significant correlation between concentrations of leptin and CRP and the relationship between the highest concentrations of these biomarkers and significantly raised risk of developing CVD might prove useful for risk stratification and assessment of prognosis in the general population. High levels of leptin and CRP seem to confer greater risk of developing CVD in women than in men. However, there is a complex relationship between leptin and CRP that remains to be fully elucidated. New therapies targeted at modifying the effects of leptin might help to reduce the risk of CVD.

## KEY POINTS

- High leptin levels were independently associated with risk of developing CVD, even after adjustment for raised CRP levels
- Elevated CRP levels were no longer significantly associated with CVD after adjustment for raised leptin levels
- Individuals with raised concentrations of both leptin and CRP were at the highest risk of developing CVD
- Women with high levels of leptin might have a higher risk of developing CVD than men, possibly because they have a higher proportion of body fat

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## Competing interests

A Romero-Corral, VK Somers and F Lopez-Jimenez have declared an association with the following company: Select Research Ltd. See the article online for full details of the relationship. The other authors declared no competing interests.

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