Association of Very Highly Elevated C-Reactive Protein Concentration with Cardiovascular Events and All-Cause Mortality

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BACKGROUND: The clinical relevance of very highly increased high-sensitivity C-reactive protein (hsCRP) concentrations (>10 mg/L) is incompletely understood. We examined the association between very highly increased hsCRP and risk of incident cardiovascular disease (CVD) events and all-cause mortality.

METHODS: We recruited 5248 participants free from overt CVD and acute infection [mean age 53.5 (SD 12.4) years, 55.5% women] from the Scottish Health Survey, a representative sample of community-dwelling adults. hsCRP and other conventional risk factors were measured at baseline.

RESULTS: Over an average of 7 years’ follow-up, there were a total of 259 incident CVD events (including myocardial infarction, coronary artery bypass, percutaneous coronary angioplasty, stroke, heart failure) and 357 all-cause deaths. Very highly increased hsCRP was associated with CVD events after adjustment for Framingham risk score (FRS), body mass index (BMI), central obesity, and hormone replacement therapy (HRT) (hazard ratio 2.40, 95% CI 1.51–3.81) and also with all-cause death (hazard ratio 3.64, 95% CI 2.57–5.15). With the addition of CRP scores to the conventional Framingham model, 7.4% of participants were reclassified into a high-risk (>20% FRS) CVD category. Very highly increased hsCRP was also associated with several modifiable risk factors, including smoking, HDL cholesterol, and central obesity.

CONCLUSIONS: hsCRP >10 mg/L was a stronger predictor of clinical events than a conventional cut point of 3 mg/L. Very highly increased hsCRP may provide clinically meaningful prognostic information.

The utility of high-sensitivity C-reactive protein (hsCRP) as a disease biomarker, especially in relation to cardiovascular disease (CVD) risk, has been extensively studied. Debate continues about the clinical utility of different hsCRP cut points. A hsCRP concentration of 3–10 mg/L has been established to identify high-risk individuals, although these findings were not replicated in the Framingham Offspring Study. The aim of the present study was to examine the association between very highly increased hsCRP (>10 mg/L) and risk of CVD events and all-cause mortality.

Materials and Methods

STUDY DESIGN AND PARTICIPANTS
For the present analyses, we used data from the Scottish Health Survey (SHS), which is a periodic survey (typically every 3–5 years) that draws a nationally representative sample of the general population living in households. We combined data from the 1998 and 2003 SHS in adults aged 30–95 years old, as described. The surveys were linked to a patient-based database of CVD hospital admissions and deaths (Information Services Division, Edinburgh, Scotland) to perform prospective analyses on CVD events. Participants gave full informed consent to participate in the study, and ethics approval was obtained from the London Research Ethics Council. The SHS is funded by the Scottish Executive, although the funders had no role in the study design; the collection, analysis and interpretation of data; the writing of the report; or the decision to submit the paper for publication.

BASELINE ASSESSMENT
Survey interviewers visited eligible households and collected data on basic demographics. On a separate visit, nurses collected clinical information to calculate individual Framingham risk scores (FRSs) for first CVD events based on sex-specific multivariable risk functions including age, total and HDL cholesterol, systolic blood pressure, treatment for hypertension, smoking, etc.

1 Nonstandard abbreviations: hsCRP, high-sensitivity C-reactive protein; CVD, cardiovascular disease; SHS, Scottish Health Survey; FRS, Framingham risk score; BMI, body mass index; ICD-9, International Classification of Diseases, Revision 9; HRT, hormone replacement therapy; OR, odds ratio; NHANES, National Health and Nutrition Examination Survey.
and diabetes status (6). In addition, height and weight were measured for the calculation of body mass index (BMI), and waist circumference for estimating central obesity (defined as ≥102 cm in men, ≥88 cm women). Peripheral blood was collected in serum tubes and centrifuged at room temperature. All serum samples were frozen at −70 °C until assay. We analyzed hsCRP concentrations from serum using the N Latex hsCRP mono immunoassay on the Behring Nephelometer II analyzer. The limit of detection was 0.17 mg/L and the CV was <6% for this assay. We measured total cholesterol and HDL cholesterol using cholesterol oxidase assays on an Olympus 640 analyzer. All analyses were carried out in the same laboratory according to standard operating procedures by State-Registered Medical Laboratory scientific officers.

**Statistical Analysis**

We categorized hsCRP according to previously defined cut points (2) but with the addition of a very high group: low (<1 mg/L), medium (1 to <3 mg/L), high (3–10 mg/L), very high (>10 mg/L). We used Cox proportional hazards models with months as the time scale to estimate the risk of CVD events and all-cause mortality according to hsCRP category. Fatal and nonfatal CVD events were combined and included myocardial infarction, coronary artery bypass, percutaneous coronary angioplasty, stroke, and heart failure. Mortality from cardiovascular causes was coded according to *International Classification of Diseases, Revision 9* (ICD-9) (390–459) and ICD-10 (I01–I99). The data were censored to December 2007 in participants that survived. We examined the proportional hazards assumption by comparing the cumulative hazard plots grouped on exposure, although no appreciable violations were noted. In a basic multivariate model, we adjusted for age and sex. In further models, we adjusted for FRS, BMI, central obesity, and use of hormone replacement therapy (HRT). We performed multivariate logistic regression analyses to determine independent associations between CVD risk factors and high hsCRP (>10 mg/L).

The FRS and CRP categories (<1 mg/L, 0 points; 1 to <3 mg/L, 1 point; 3–10 mg/L, 2 points; >10 mg/L, 3 points) were used to construct ROC curves with corresponding areas under the curve (neutral value 0.50 = risk prediction by pure chance) and 95% CIs, with CVD events as the outcome. All analyses were performed using SPSS (version 15), and all tests of statistical significance were based on 2-sided probability.

**Results**

After the removal of participants with clinically confirmed CVD (n = 163) and those reporting an acute infection (influenza, bronchitis, pneumonia, and upper respiratory tract infections) within 3 weeks before clinical assessment (n = 593), the sample consisted of 5248 participants [mean age 53.5 (SD 12.4) years, 55.5% women]. Over an average of 7 years’ follow-up, there were a total of 259 incident CVD events and 357 all-cause deaths. Very high hsCRP concentrations (>10 mg/L) were recorded in 5.6% of the sample. In relation to participants with hsCRP <1 mg/L, those with hsCRP >10 mg/L were more likely to be smokers [odds ratio (OR) 3.15, 95% CI 2.40–4.15], have HDL cholesterol concentrations <1.5 mmol/L (OR 4.25, 95% CI 3.22–5.61), be centrally obese (OR 6.82, 95% CI 5.19–8.95), be HRT users (OR 2.21, 95% CI 1.30–3.75), have hypertension (OR 2.03, 95% CI 1.53–2.09), and have diabetes (OR 2.37, 95% CI 1.19–4.73) after adjustment for age and sex.

Very highly increased hsCRP was a predictor of incident CVD events after adjustment for FRS, BMI, central obesity, and HRT (see Table 1). Highly and very highly increased hsCRP concentration was also predictive of all-cause mortality after adjustment for age and sex (hsCRP 3–10 mg/L, hazard ratio 1.55, 95% CI 1.15–2.09; hsCRP >10 mg/L, hazard ratio 3.64, 95% CI 2.57–5.15). This association persisted after excluding 66 deaths occurring within the first 2 years of follow-

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**Table 1. Cox proportional hazard regression models for CRP and risk of cardiovascular events.**

<table>
<thead>
<tr>
<th>Table 1.</th>
<th>Cox proportional hazard regression models for CRP and risk of cardiovascular events.</th>
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<tbody>
<tr>
<td>hsCRP category, mg/L</td>
<td>Events (total 259/5248)</td>
</tr>
<tr>
<td>&lt;1</td>
<td>47/1817</td>
</tr>
<tr>
<td>≥1 to &lt;3</td>
<td>80/1857</td>
</tr>
<tr>
<td>3–10</td>
<td>95/1278</td>
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<tr>
<td>&gt;10</td>
<td>37/296</td>
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<td>Test for trend</td>
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* Model 1 was adjusted for age and sex.
* Model 2 was adjusted for FRS, BMI category (<18.5, 18.5–25, 25–30, 30–35, 35–40, ≥40 kg/m²), central obesity (≥102 cm men, ≥88 cm women), and HRT.
Discussion

The results of the present study suggest that a very highly increased hsCRP concentration (>10 mg/L) is a robust predictor of incident CVD events in a representative sample of community-dwelling adults, which confirms previous findings (3). Our data suggest that very highly increased hsCRP is a stronger prognostic indicator of both CVD events and all-cause mortality than hsCRP concentrations between 3 and 10 mg/L, although the additive prognostic value of using CRP was not confirmed in ROC analyses. Nevertheless, 7.4% of participants were reclassified into the higher-risk category (>20% FRS) CVD category with the addition of CRP to the conventional FRS. Because the data also infer associations with all-cause mortality, hsCRP might provide prognostic information beyond CVD risk, and some evidence has indicated an association between hsCRP and cancer (7). Numerous other studies have confirmed associations between hsCRP and all-cause mortality, which might indicate a nonspecific immune response to the overexpression of various cytokines involved in disease processes (8).

Very highly increased hsCRP was associated with other modifiable risk factors such as smoking, HDL cholesterol, and central obesity, confirming our previous findings in a cohort of older English adults (9). Data from the National Health and Nutrition Examination Survey (NHANES) also showed that socioeconomic variation in hsCRP occurred only at very high concentrations of CRP (>10.0 mg/L) and could be explained by differential health behaviors (10). In the present study, conventional risk factors appeared to partly explain the association between hsCRP and CVD events, because the associations were somewhat attenuated after adjustment for FRS, BMI, central adiposity, and HRT. Nevertheless, the associations of very high hsCRP and CVD persisted after full adjustments. Taken together, our data suggest that hsCRP can add relevant prognostic information to established risk factors, which is consistent with some (11) but not other (12) data.

We removed participants with common acute infections from our analyses although we cannot rule out the possibility of other unidentified infections and the role of pathogen burden caused by persistent exposure to infection, which might also contribute to very highly increased hsCRP and is thought to play a role in atherosclerosis (13). People of Scottish ancestry appear to demonstrate a markedly higher prevalence of autoimmune and inflammatory disorders (14), possibly related to genetic susceptibility or to the unusual pattern of exposure to infections in small, sparsely populated island communities. Nevertheless, the prevalence of very highly increased hsCRP in the present sample was largely comparable to that observed in a cohort of US women (3).

We have collected hsCRP at only 1 point in time, which represents a limitation of our study since repeated testing has been recommended to confirm very highly increased hsCRP (2). However, hsCRP is thought to be sufficiently stable for use in long-term risk prediction, since its stability over 12 years’ follow-up was similar to that of blood pressure and serum cholesterol (1).

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