C-reactive protein and risk of cardiovascular and all-cause mortality in 268 803 East Asians

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Received 7 September 2013; revised 23 November 2013; accepted 28 January 2014; online publish-ahead-of-print 25 February 2014

See page 1776 for the editorial comment on this article (doi:10.1093/eurheartj/ehu115)

Aims
C-reactive protein concentrations are decreased in Asians compared with people of white European ethnicity. It is uncertain whether C-reactive protein is a robust biomarker of cardiovascular disease (CVD) in Asians. This study aimed to determine the association between C-reactive protein and CVD and all-cause mortality in a large population of Koreans.

Methods and results
Mortality outcomes for 268 803 Koreans enrolled in a health screening programme with measurements of C-reactive protein at baseline and median follow-up of 4.49 years (1 155 930 person-years) were analysed. A subset (48%) of subjects had a repeat C-reactive protein measurement during follow-up. The median (interquartile) baseline C-reactive protein values were higher in men than in women [0.6 (0.3–1.3) vs. 0.4 (0.1–1.1), P < 0.001]. Only 8.6% of men and 6.2% of women met the standard cut point for C-reactive protein >3 mg/L, which represents the top tertile in white populations. During a median follow-up of 4.49 years (1 155 930 person-years), 1047 died; 187 died of CVD causes. In men but not women, baseline C-reactive protein quartiles were linearly associated with both CVD and all-cause mortality (P < 0.001), even after adjustment for known CVD risk factors. Regardless of baseline C-reactive protein concentration, any increase or decrease in C-reactive protein over time did not affect the HR for all-cause, or CVD mortality. Models with C-reactive protein yielded a net reclassification improvement for CVD mortality of 24.9% (P = 0.04) for individuals with intermediate risk.

Conclusions
C-reactive protein concentrations are substantially lower in Koreans than reported for whites populations. Nonetheless, C-reactive protein levels are associated with CVD and all-cause mortality in Korean men. Standard cut points for C-reactive protein may under-represent Asians at risk for CVD.

Keywords
C-reactive protein ● Cardiovascular risk factors ● Cardiovascular and all-cause mortality

Introduction
Inflammation has been suggested to play a role in the development and progression of atherosclerosis as well as other disease processes.1–3 Although several markers of inflammation exist, C-reactive protein remains a widely used biomarker of inflammation and cardiovascular disease (CVD) risk.4–6 Several recent meta-analyses of prospective studies have shown that C-reactive protein can be a predictor of CVD.7–9 However, a limitation of these studies is that a majority of the participants were white of European or North American ancestry.7–9 Therefore, the relevance of C-reactive protein in non-white populations remains unclear.

C-reactive protein concentrations have been shown to vary by ethnic groups with lower levels seen in East Asian populations.10,11 In two studies of multiethnic populations residing in the USA,10,11 the median C-reactive protein level in East Asians was less than half the concentration in whites. In addition, in the Study of Women’s Health Across the Nation (SWAN), the cut point for the top quartile of C-reactive protein was 1.6 in Chinese women and 1.1 in Japanese women compared with 4.1 mg/L in white women.10 Some of the ethnic differences in C-reactive protein concentration have been attributed to lower body mass index (BMI) in East Asians compared with whites.10 On the other hand, at the same BMI, risk for...
CVD and mortality have been reported to be higher in East Asians than white counterparts.\textsuperscript{12,13} These observations raise two questions related to the association between C-reactive protein levels and CVD in East Asians. First, C-reactive protein may be a less robust biomarker of CVD in East Asians compared with whites. Alternatively, C-reactive protein levels may predict CVD at lower C-reactive protein concentrations than seen in whites.

We evaluated these two questions in our unique cohort of 268 803 Koreans with measurement of baseline C-reactive protein and follow-up on CVD and all-cause mortality. In addition, unlike previous studies, we also had C-reactive protein measurements during follow-up in 48% of the population, providing the opportunity to evaluate the role of change in C-reactive protein on mortality. This population represents the largest cohort of East Asians with data on C-reactive protein and mortality.

Methods

Study population

The study population consisted of individuals who participated in a comprehensive health screening programme at Kangbuk Samsung Hospital, Seoul, Korea from 2002 to 09 (N = 278 528). The purpose of the screening programme was to promote health through early detection of chronic diseases and their risk factors. Additionally, the Korean Industrial Safety and Health Law requires working individuals to participate in an annual or biennial health examination. About 60% of the participants were employees of companies or local governmental organizations and their spouses; remaining participants registered individually for the programme.

For the study, individuals were excluded if they did not have measurement of C-reactive protein at baseline (n = 6928). Individuals were also excluded for pre-existing history of malignancy (n = 2627). As some individuals met more than one exclusion criteria, the total number of eligible subjects for the study was 268 803.

This study was approved by the Institutional Review Board of Kangbuk Samsung Hospital. Requirement for informed consent was waived as de-identified information was retrieved retrospectively.

Measurements

As part of the health screening programme, individuals completed questionnaires related to their medical and social history and medication use. Individuals were asked about duration of education, frequency of exercise, smoking history (never, former, or current), and alcohol consumption (frequency per week, amount).

Trained staff also collected anthropometric measurements and vital statistics. Body weight was measured in light clothing with no shoes to the nearest 0.1 kg using a digital scale. Height was measured to the nearest 0.1 cm. Body mass index was calculated as weight in kilograms divided by height in meters squared. Blood pressure was measured using standard mercury sphygmomanometers.

Blood samples were collected after at least 10 h of fasting and analysed in the same core clinical laboratory. The core clinical laboratory has been accredited and participates annually in inspections and surveys by the Korean Association of Quality Assurance for Clinical Laboratories. Plasma glucose was measured by the hexokinase method and lipoprotein concentrations by an enzymatic colorimetric assay using Bayer Reagent Packs on an automated chemistry analyzer (Advia 1650\textsuperscript{TM} Autoanalyzer; Bayer Diagnostics, Leverkusen, Germany). Insulin was measured with an immunoradiometric assay (Biosource, Nivelle, Belgium). High sensitivity-C reactive protein was analysed by particle-enhanced immunonephelometry with the BNII\textsuperscript{TM} System (Dade Behring, Marburg, Germany) with a lower detection limit of 0.1 mg/L.

Calculation

Systemic Coronary Risk Evaluation (SCORE) was calculated for each individual based on age, sex, smoking habits, systolic blood pressure, and total cholesterol.\textsuperscript{14} The low-risk chart was used to calculate 10-year risk of cardiovascular death. Individuals were further stratified as low (SCORE <1%), intermediate (1 to <5%), and high risk (≥5%) for CVD mortality.\textsuperscript{15}

Ascertainment of mortality

The National Statistical Office maintains death records of all Koreans. Kangbuk Samsung Hospital provided the Office with a list of the study population with necessary identifiers including resident identification numbers. The Office confirmed death of individuals and provided cause and day of death. Resident identification numbers were removed prior to information being received by study personnel. Abstractors coded the causes of death according to the International Classification of Diseases, 10th revision.

Statistical analyses

The statistical analysis was performed using STATA version 11.2 (StataCorp LP, College Station, TX, USA). Reported P-values were two-tailed, and P < 0.05 was considered statistically significant. The distribution of continuous variables was evaluated, and transformations were conducted for non-parametric variables. One-way ANOVA and χ²-tests were used to compare the characteristics of study participants at baseline by sex-specific quartiles of C-reactive protein.

Cox proportional hazards models were used to estimate adjusted hazard ratios (and 95% confidence intervals) for mortality in men and women. The lowest C-reactive protein quartile was used as the reference. The models were initially adjusted for age. Further adjustments were made for BMI, education level, smoking status, alcohol intake, and history of hypertension, diabetes, and coronary artery disease (Model 1). Model 2 also adjusted for measured variables including systolic blood pressure and concentration of glucose, low-density lipoprotein cholesterol (LDL-C), high density lipoprotein cholesterol (HDL-C), and triglyceride. For testing linear risk trends, we used the quartile rank as a continuous variable in the regression models. We checked the proportional hazards assumption by examining graphs of estimated log (− log) survival. Kaplan–Meier curves were used to display mortality rates.

Repeat C-reactive protein measurements within the follow-up period was available in nearly half of the population (n = 129 344, 48%). Therefore, the effect of C-reactive protein change on mortality was also evaluated. C-reactive protein change (follow-up C-reactive protein minus baseline C-reactive protein) was defined as being decreased (C-reactive protein change <0) or stable/increased (C-reactive protein change ≥0).

For the purposes of this analysis, individuals were also separated by baseline C-reactive protein as having low (<median baseline C-reactive protein) or high (≥median) C-reactive protein. Thus, four groups were compared: (i) low baseline C-reactive protein and <0 C-reactive protein change (reference), (ii) low C-reactive protein and ≥0 change, (iii) high C-reactive protein and <0 change, and (iv) high C-reactive protein and ≥0 change.

Finally, to understand the clinical utility of C-reactive protein, we evaluated whether C-reactive protein can meaningfully change the risk prediction in individuals at intermediate CVD mortality risk based on SCORE (1–<5%)—the group for which reclassification to low or high risk may be most useful. We first assessed the C-statistic for CVD mortality.
C-reactive protein, cardiovascular, and all-cause mortality

Results

Tables 1 and 2 show baseline clinical and laboratory characteristics by C-reactive protein quartiles in men (n = 151 962) and women (n = 116 841), respectively. The population was relatively young with mean age of 40 years in both sexes. Women comprised 43% of the population. The median (interquartile range) C-reactive protein was higher in men than women [0.6 (0.3–1.3) vs. 0.4 (0.1–1.1), P < 0.001], and sex-specific C-reactive protein quartiles were used. Only 8.6% of men and 6.2% of women met the conventional cut point for C-reactive protein >3 mg/L, which represents the top tertile of C-reactive protein concentration in white populations.

Focusing first on men, BMI increased from 23.2 kg/m² in the lowest C-reactive protein quartile (Q1) to 25.3 kg/m² in the highest quartile (Q4) (Table 1). In addition to increased BMI, higher C-reactive protein quartiles were also associated with less education and unhealthier lifestyle habits including increased current smoking, and greater alcohol intake. Higher C-reactive protein quartiles were also associated with other CVD risk factors including higher blood pressure and higher glucose and lipid values. Accordingly, history of hypertension and diabetes doubled from the lowest C-reactive protein quartile to the highest. History of coronary artery disease and SCORE also increased.

Women overall had a lower mean BMI than men (22.4 ± 3.1 vs. 24.4 ± 2.9, P < 0.001) (Table 2). Nevertheless, BMI increased progressively with increasing C-reactive protein quartiles; the magnitude of increase in BMI between women in C-reactive protein Q1 and Q4 was greater than in men (2.9 vs. 2.1 kg/m²). Likewise, the relative increase from C-reactive protein Q1 to Q4 in history of diabetes (4.9-fold) and hypertension (5.5-fold) was greater in women than in men. Similar to men, prevalence of coronary artery disease and SCORE increased with C-reactive protein quartiles, as well as measured CVD risk factors including blood pressure and lipids. Women smoked and drank less alcohol than men, and the direction of the association between C-reactive protein and these lifestyle habits was less apparent in women.

Median length of follow-up for the population was 4.49 years (range 0–7.99, 1 155 930 person-years at risk). During this time, 1047 deaths occurred (771 men and 276 women). The causes of death are listed in Supplementary material online, Table S1. One hundred eighty-seven deaths (18%) were attributable to CVD causes. Figure 1 illustrates the Kaplan–Meier curves for all-cause death (A, B) and CVD death (C, D) in men and women by C-reactive protein quartiles. Although overall mortality rates were low, there was a progressive increase in all-cause mortality and CVD mortality by C-reactive protein quartile, especially in men. As seen in Tables 3 and 4, there was a significant association between C-reactive protein quartiles and adjusted HRs for both all-cause and CVD mortality in men but not in women. The differences between men and women were more pronounced for CVD death (P = 0.012 for interaction between C-reactive protein and sex in the fully adjusted model, Table 4). Thus, the multivariate HR for CVD death was three-fold greater in men in the highest C-reactive protein quartile (Q4) compared with the lowest (Q1), but there was no increase in HR across quartiles in women.

We also evaluated the effect of C-reactive protein change on all-cause and CVD mortality in the subgroup of individuals with repeat C-reactive protein during follow-up (n = 129 344, 48%). The baseline median C-reactive protein (interquartile) in this subgroup (both men and women) was 0.5 (0.2–1.1) and the follow-up C-reactive protein was 0.6 (0.2–1.3). Within this subgroup, 37.7% of individuals had a decrease in C-reactive protein (C-reactive protein change <0 and 62.3% had stable or increased C-reactive protein (C-reactive protein change ≥0) from baseline. Regardless of whether individuals had low (<median) or high (≥median) C-reactive protein at baseline, there was no effect of C-reactive protein change on all-cause and CVD mortality in the total group (Supplementary material online, Tables S2 and S3).

Finally, to better understand the clinical utility of C-reactive protein, we isolated individuals with intermediate CVD mortality risk based on SCORE (1–<5%). There were 35 242 men and 12 379 women who qualified as having intermediate risk; however, majority (55.1%) had SCORE ≥2%. When C-reactive protein was added to the risk prediction model in this intermediate-risk subset, the C-statistic did not significantly improve (0.715–0.717, P = 0.33). There was a significant net reclassification improvement with 24.9% of individuals being more appropriately reclassified (P = 0.04, see Supplementary material online, Table S4). However, the integrative discrimination index for C-reactive protein was very small (0.01%, P = 0.23), suggesting that most of the net reclassification was occurring immediately adjacent to the thresholds.

Discussion

This study shows in a large population of Korean individuals that although C-reactive protein levels are lower than reported for white populations, C-reactive protein concentrations remain significantly associated with CVD risk factors in both men and women. More importantly, C-reactive protein was also significantly associated with CVD mortality as well as all-cause mortality in men after adjustment for traditional CVD risk factors. Therefore, our study demonstrates for the first time that C-reactive protein levels independently predict CVD mortality in East Asians.

A scientific statement from the American Heart Association and Centers for Disease Control in 2003 set C-reactive protein cut points for CVD risk as follows: low risk <1 mg/L; average risk 1–3 mg/L; and high risk >3 mg/dL. The authors of the statement noted that these cut points were based on approximate tertiles of C-reactive protein in >15 populations involving >40 000 persons. Although not specifically described, a majority of the populations included in the analyses were white North Americans or Europeans. Our study illustrates that the distribution of C-reactive protein concentration is clearly lower in Koreans. Only 8.6% of men and 6.2% of women had C-reactive protein concentrations >3 mg/L. In addition, the cut point to define the top quartile in men was 1.3
and in women it was 1.1 mg/L. Similarly other studies have demonstrated lower C-reactive protein values in Chinese (top quartile 1.5 mg/L in men and 1.2 mg/L in women),\textsuperscript{19} Japanese (1.31 mg/L in men and 1.2 mg/L in women),\textsuperscript{18} and Korean (1.4 mg/L in combined population and low absolute mortality rates in women. In older, predominantly white women, C-reactive protein has been associated with prevalent\textsuperscript{21} and incident CVD.\textsuperscript{22} These findings support the guidelines by the European Society of Cardiology which recommends that measurement of C-reactive protein should be reserved for individuals at moderate, but not low, risk for CVD.\textsuperscript{23} In the current study, C-reactive protein did not improve risk prediction in the intermediate group but was modestly useful in reclassifying risk category up or down. Therefore, C-reactive protein may be a better risk modifier than a risk factor, per se.

In contrast to women, the significant association between C-reactive protein and mortality in equally young men is striking and likely reflect the higher CVD risk burden in men compared with women. For example, 45% of Korean men were current smokers compared with 4.5% of women. Previous studies evaluating the association between C-reactive protein and mortality have predominately been in populations with mean age of 50 or above.\textsuperscript{7,20,24} In addition, this is the first study to demonstrate this association in a large population of East Asians. One recent study in 92,500 Koreans showed that C-reactive protein in combination with

\begin{table}
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\begin{tabular}{lcccccc}
\hline
 & \multicolumn{5}{c}{C-reactive protein} & \\
 & \textbf{Quartile 1} & \textbf{Quartile 2} & \textbf{Quartile 3} & \textbf{Quartile 4} & \textbf{P for trend} \\
\hline
\textbf{Age (years)} & 40.0 (9.6) & 39.0 (8.9) & 40.4 (9.2) & 40.4 (9.7) & 40.6 (10.4) & <0.001 \\
\textbf{BMI (kg/m\textsuperscript{2})} & 24.4 (2.9) & 23.2 (2.5) & 24.5 (2.6) & 25.0 (2.8) & 25.3 (3.1) & <0.001 \\
\textbf{Systolic BP (mmHg)} & 118.1 (13.6) & 116.0 (12.8) & 117.9 (13.5) & 119.0 (13.9) & 120.0 (14.0) & <0.001 \\
\textbf{Diastolic BP (mmHg)} & 77.2 (9.5) & 75.9 (9.0) & 77.4 (9.4) & 77.8 (9.8) & 78.1 (9.8) & <0.001 \\
\textbf{Higher education (%)} & 77.5 & 78.6 & 77.6 & 77.3 & 75.9 & <0.001 \\
\textbf{Regular exercise (%)} & 16.9 & 17.0 & 17.0 & 16.7 & 16.7 & 0.697 \\
\textbf{Smoking status (%)} & & & & & & \\
\textbf{Never smoker} & 27.5 & 30.8 & 27.6 & 26.3 & 24.7 & <0.001 \\
\textbf{Former smoker} & 27.4 & 27.3 & 28.6 & 27.5 & 26.3 & <0.001 \\
\textbf{Current smoker} & 45.1 & 42.0 & 43.9 & 46.2 & 49.0 & <0.001 \\
\textbf{Alcohol intake (%)} & & & & & & \\
\textbf{0 g/day} & 18.8 & 18.5 & 18.5 & 18.6 & 19.6 & <0.001 \\
\textbf{10 g/day} & 58.3 & 60.9 & 57.5 & 57.7 & 56.4 & <0.001 \\
\textbf{20 g/day} & 22.9 & 20.6 & 24.0 & 23.7 & 24.0 & <0.001 \\
\textbf{Laboratory} & & & & & & \\
\textbf{Glucose (mmol/L)} & 5.4 (1.0) & 5.2 (0.8) & 5.3 (1.0) & 5.4 (1.1) & 5.5 (1.3) & <0.001 \\
\textbf{Total cholesterol (mmol/L)} & 5.2 (0.9) & 5.0 (0.8) & 5.2 (0.9) & 5.3 (0.9) & 5.2 (1.0) & <0.001 \\
\textbf{LDL-C (mmol/L)} & 3.1 (0.8) & 2.9 (0.7) & 3.1 (0.7) & 3.1 (0.8) & 3.1 (0.8) & <0.001 \\
\textbf{HDL-C (mmol/L)} & 1.3 (0.3) & 1.4 (0.3) & 1.3 (0.3) & 1.3 (0.3) & 1.3 (0.3) & <0.001 \\
\textbf{Triglycerides (mmol/L)} & 1.4 (1.0–2.1) & 1.2 (0.9–1.7) & 1.5 (1.1–2.1) & 1.6 (1.1–2.3) & 1.6 (1.1–2.2) & <0.001 \\
\textbf{Hx of diabetes mellitus (%)} & 3.0 & 2.0 & 2.7 & 3.2 & 4.0 & <0.001 \\
\textbf{Hx of hypertension (%)} & 8.5 & 5.5 & 8.0 & 9.4 & 11.5 & <0.001 \\
\textbf{Hx of coronary artery disease (%)} & 4.2 & 3.6 & 3.7 & 4.4 & 5.2 & <0.001 \\
\textbf{Glucose ≥7 mmol/L (%)} & 5.0 & 2.7 & 4.3 & 5.7 & 7.5 & <0.001 \\
\textbf{BP ≥140/90 (%)} & 21.9 & 16.2 & 21.7 & 24.1 & 26.8 & <0.001 \\
\textbf{SCORE (%)} & 1.2 (1.5) & 1.0 (1.2) & 1.1 (1.4) & 1.3 (1.5) & 1.5 (1.7) & <0.001 \\
\hline
\textbf{Data are mean (standard deviation), median (interquartile range), or percentage.}
\textbf{BMI, body mass index; BP, blood pressure; HDL-C, high-density lipoprotein-cholesterol; LDL-C, low-density lipoprotein cholesterol. § ≥ 1 time per week.}
\end{tabular}
\end{table}
HDL-C predicted mortality but the association between C-reactive protein alone and mortality was not evaluated.²⁰

Most studies that have reported on the association between C-reactive protein and mortality have used a single measurement of C-reactive protein at baseline.⁷,²⁰,²⁴ In addition, studies that have evaluated the effect of C-reactive protein change on CVD have generally been in the context of an intervention, such as initiation of statin therapy.²⁵,²⁶ Therefore, the effect of interim change in C-reactive protein may not have been substantial in our population, given no systematic intervention. Our findings may also suggest that monitoring C-reactive protein levels during follow-up may not aid in CVD risk stratification.

Table 2  Baseline characteristics of women by C-reactive protein quartile

<table>
<thead>
<tr>
<th></th>
<th>N = 116 841</th>
<th>Overall</th>
<th>C-reactive protein</th>
<th>P for trend</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Quartile 1</td>
<td>Quartile 2</td>
<td>Quartile 3</td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
<td>40.8 (10.5)</td>
<td>37.6 (7.9)</td>
<td>40.6 (9.8)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td></td>
<td>22.4 (3.1)</td>
<td>20.9 (2.3)</td>
<td>22.1 (2.6)</td>
</tr>
<tr>
<td>Systolic BP (mmHg)</td>
<td></td>
<td>110.7 (15.1)</td>
<td>107.3 (12.4)</td>
<td>110.0 (14.4)</td>
</tr>
<tr>
<td>Diastolic BP (mmHg)</td>
<td></td>
<td>70.7 (9.8)</td>
<td>68.8 (8.7)</td>
<td>70.5 (9.6)</td>
</tr>
<tr>
<td>Higher education (%)</td>
<td></td>
<td>54.8</td>
<td>62.5</td>
<td>55.9</td>
</tr>
<tr>
<td>Regular exercise (%)</td>
<td></td>
<td>16.6</td>
<td>16.3</td>
<td>17.4</td>
</tr>
<tr>
<td>Smoking status (%)</td>
<td>Never smoker</td>
<td>92.0</td>
<td>91.6</td>
<td>93.2</td>
</tr>
<tr>
<td>Alcohol intake (%)</td>
<td>Never smoker</td>
<td>68.9</td>
<td>64.4</td>
<td>69.5</td>
</tr>
<tr>
<td></td>
<td>10 g/day</td>
<td>29.4</td>
<td>33.8</td>
<td>29.0</td>
</tr>
<tr>
<td></td>
<td>20 g/day</td>
<td>1.7</td>
<td>1.8</td>
<td>1.5</td>
</tr>
<tr>
<td>Laboratory</td>
<td>Glucose (mmol/L)</td>
<td>5.1 (0.8)</td>
<td>5.0 (0.5)</td>
<td>5.1 (0.7)</td>
</tr>
<tr>
<td></td>
<td>Total cholesterol (mmol/L)</td>
<td>4.9 (0.9)</td>
<td>4.7 (0.8)</td>
<td>4.9 (0.9)</td>
</tr>
<tr>
<td></td>
<td>LDL-C (mmol/L)</td>
<td>2.8 (0.8)</td>
<td>2.6 (0.7)</td>
<td>2.8 (0.7)</td>
</tr>
<tr>
<td></td>
<td>HDL-C (mmol/L)</td>
<td>1.5 (0.3)</td>
<td>1.6 (0.3)</td>
<td>1.6 (0.3)</td>
</tr>
<tr>
<td></td>
<td>Triglycerides (mmol/L)</td>
<td>0.9 (0.7–1.3)</td>
<td>0.8 (0.6–1.0)</td>
<td>0.9 (0.7–1.3)</td>
</tr>
<tr>
<td></td>
<td>Hx of diabetes mellitus (%)</td>
<td>2.0</td>
<td>0.7</td>
<td>1.5</td>
</tr>
<tr>
<td></td>
<td>Hx of hypertension (%)</td>
<td>6.6</td>
<td>2.0</td>
<td>5.0</td>
</tr>
<tr>
<td></td>
<td>Hx of coronary artery disease (%)</td>
<td>5.1</td>
<td>3.8</td>
<td>4.4</td>
</tr>
<tr>
<td></td>
<td>Glucose ≥ 7 mmol/L (%)</td>
<td>3.0</td>
<td>0.8</td>
<td>2.0</td>
</tr>
<tr>
<td></td>
<td>BP ≥ 140/90 (%)</td>
<td>12.4</td>
<td>4.7</td>
<td>10.4</td>
</tr>
<tr>
<td></td>
<td>SCORE (%)</td>
<td>0.4 (0.7)</td>
<td>0.1 (0.4)</td>
<td>0.3 (0.6)</td>
</tr>
</tbody>
</table>

Data are mean (standard deviation), median (interquartile range), or percentage.
BMI, body mass index; BP, blood pressure; HDL-C, high-density lipoprotein-cholesterol; LDL-C, low-density lipoprotein cholesterol. § ≥ 1 time per week.

Body mass index is significantly correlated with C-reactive protein²⁷,²⁸ and implicated as one factor in ethnic differences related to C-reactive protein concentrations.¹⁰,²⁹ However, differences in C-reactive protein levels exist between East and South Asians who have similar BMI distributions.³⁰ In addition, recent meta-analysis of 221 287 people from 89 studies found that ethnic differences remained even when C-reactive protein was adjusted for BMI.³¹ Thus East Asians had a median C-reactive protein of 1.05 compared with 2.17 in South Asians and 1.9 in Whites. Therefore, ethnic differences in C-reactive protein concentrations cannot be simply due to differences in BMI.

There are limitations of this study. This was a retrospective study of mostly working individuals enrolled in a health screening programme. Therefore, the study population was biased to individuals with access to health care. While a select population, it allowed for consistent follow-up in 268 803 individuals from a single ethnic group. The total number of individuals in our study is greater than the number...
Figure 1 Kaplan–Meier curves for all-cause (A and B) and cardiovascular mortality (C and D).

Table 3 Risk of death from all causes according to baseline C-reactive protein quartiles

<table>
<thead>
<tr>
<th>C-reactive protein quartiles (mg/L)</th>
<th>Person-years</th>
<th>Number of events</th>
<th>Mortality rate (10,000 person-year)</th>
<th>Age-adjusted HR (95% CI)</th>
<th>Multivariate HRa (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Model 1</td>
<td>Model 2</td>
</tr>
<tr>
<td>Men (N = 151,962)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Q1 (&lt;0.4)</td>
<td>209,854.9</td>
<td>141</td>
<td>6.7</td>
<td>1.00 (reference)</td>
<td>1.00 (reference)</td>
</tr>
<tr>
<td>Q2 (0.4–0.6)</td>
<td>158,332.1</td>
<td>139</td>
<td>8.8</td>
<td>1.13 (0.89–1.43)</td>
<td>1.20 (0.93–1.55)</td>
</tr>
<tr>
<td>Q3 (0.7–1.3)</td>
<td>160,445.1</td>
<td>204</td>
<td>12.7</td>
<td>1.50 (1.21–1.86)</td>
<td>1.47 (1.15–1.87)</td>
</tr>
<tr>
<td>Q4 (≥1.4)</td>
<td>152,802.1</td>
<td>287</td>
<td>18.8</td>
<td>1.95 (1.59–2.39)</td>
<td>1.87 (1.48–2.36)</td>
</tr>
<tr>
<td>P for trend</td>
<td></td>
<td></td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Women (N = 116,841)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Q1 (&lt;0.2)</td>
<td>126,818.4</td>
<td>43</td>
<td>3.4</td>
<td>1.00 (reference)</td>
<td>1.00 (reference)</td>
</tr>
<tr>
<td>Q2 (0.2–0.4)</td>
<td>147,854.4</td>
<td>62</td>
<td>4.2</td>
<td>0.88 (0.59–1.30)</td>
<td>0.85 (0.54–1.32)</td>
</tr>
<tr>
<td>Q3 (0.5–1.1)</td>
<td>107,645.6</td>
<td>83</td>
<td>7.7</td>
<td>1.20 (0.82–1.76)</td>
<td>1.14 (0.73–1.78)</td>
</tr>
<tr>
<td>Q4 (≥1.2)</td>
<td>92,147.5</td>
<td>88</td>
<td>9.6</td>
<td>1.41 (0.96–2.07)</td>
<td>1.30 (0.81–2.06)</td>
</tr>
<tr>
<td>P for trend</td>
<td></td>
<td></td>
<td>0.011</td>
<td>0.095</td>
<td>0.227</td>
</tr>
<tr>
<td>P for interaction by gender</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Cox proportional hazard models were used to estimate HRs and 95 percent confidence intervals (95% CIs).

aModel 1: adjustment for age, BMI, smoking status, alcohol intake, regular exercise, education level, history of hypertension, history of diabetes, and history of coronary disease; model 2: model 1 plus adjustment for concentration of glucose, LDL-cholesterol, triglyceride, HDL-cholesterol and systolic blood pressure.
of people included in a recent meta-analysis of 54 prospective studies. While the characteristics of our study population may have minimized the association between C-reactive protein and mortality in women, our results also emphasize that the association between C-reactive protein and CVD risk factors occurs at a relatively young age, and in this ethnic group, the association between C-reactive protein and all-cause and cardiovascular mortality is present in relatively young men.

In conclusion, this study demonstrates that C-reactive protein concentrations, although lower than reported in white populations, are significantly associated with CVD risk factors in relatively young Korean men and women. In addition, C-reactive protein concentrations appear to independently predict CVD and all-cause mortality in men. Regardless of the level of C-reactive protein at baseline, any increase or decrease in C-reactive protein concentration over time was not associated with change in risk of all-cause and CVD mortality. These data suggest that C-reactive protein is an important biomarker in East Asians, and current cut points for C-reactive protein may underrepresent Asians at risk for CVD. Finally, there may be differences between men and women that are worthy of further study.

### Supplementary material

Supplementary material is available at European Heart Journal online.

### Funding

This study was partially supported by Samsung Biomedical Research Institute Grant SBRi-C-B1-114-1. CDB is supported in part by the Southampton National Institute for Health Research Biomedical Research Centre.

### Table 4 Risk of death from cardiovascular disease according to baseline C-reactive protein quartiles

<table>
<thead>
<tr>
<th>C-reactive protein quartiles (mg/L)</th>
<th>Person-years</th>
<th>Number of events</th>
<th>Mortality rate (10 000 person-year)</th>
<th>Age-adjusted HR (95% CI)</th>
<th>Multivariate HR* (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men (N = 151,962)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Q1 (&lt;0.4)</td>
<td>209,854.9</td>
<td>15</td>
<td>0.7</td>
<td>1.00 (reference)</td>
<td>1.00 (reference)</td>
</tr>
<tr>
<td>Q2 (0.4–0.6)</td>
<td>158,332.1</td>
<td>27</td>
<td>1.7</td>
<td>2.07 (1.10–3.88)</td>
<td>2.46 (1.16–2.18)</td>
</tr>
<tr>
<td>Q3 (0.7–1.3)</td>
<td>160,445.1</td>
<td>39</td>
<td>2.4</td>
<td>2.68 (1.47–4.86)</td>
<td>2.69 (1.29–5.59)</td>
</tr>
<tr>
<td>Q4 (≥1.4)</td>
<td>152,802.1</td>
<td>59</td>
<td>3.9</td>
<td>3.71 (2.10–6.57)</td>
<td>4.01 (1.99–8.09)</td>
</tr>
<tr>
<td><strong>P for trend</strong></td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
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<td>Women (N = 116,841)</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Q1 (&lt;0.2)</td>
<td>126,818.4</td>
<td>8</td>
<td>0.6</td>
<td>1.00 (reference)</td>
<td>1.00 (reference)</td>
</tr>
<tr>
<td>Q2 (0.2–0.4)</td>
<td>147,854.4</td>
<td>9</td>
<td>0.6</td>
<td>0.61 (0.23–1.60)</td>
<td>0.92 (0.32–2.66)</td>
</tr>
<tr>
<td>Q3 (0.5–1.1)</td>
<td>107,645.6</td>
<td>16</td>
<td>1.5</td>
<td>1.02 (0.42–2.48)</td>
<td>1.17 (0.40–3.44)</td>
</tr>
<tr>
<td>Q4 (≥1.2)</td>
<td>92,147.5</td>
<td>14</td>
<td>1.5</td>
<td>0.97 (0.38–2.44)</td>
<td>1.32 (0.43–4.07)</td>
</tr>
<tr>
<td><strong>P for trend</strong></td>
<td>0.635</td>
<td></td>
<td></td>
<td>0.503</td>
<td>0.924</td>
</tr>
<tr>
<td><strong>P for interaction by gender</strong></td>
<td>0.052</td>
<td></td>
<td></td>
<td>0.034</td>
<td>0.012</td>
</tr>
</tbody>
</table>

Cox proportional hazard models were used to estimate HRs and 95 percent confidence intervals (95% CIs).

*Model 1: adjustment for age, sex, BMI, smoking status, alcohol intake, regular exercise, education level, history of hypertension, history of diabetes, and history of coronary disease; model 2: model 1 plus adjustment for concentration of glucose, LDL-cholesterol, triglyceride, HDL-cholesterol and systolic blood pressure.

### Conflict of interest

none declared.

### References


