Association of serum high-sensitivity C reactive protein with risk of mortality in an Asian population: the Health Examinees cohort

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ABSTRACT

Objectives This study aimed to examine the association of high-sensitivity C reactive protein (hsCRP) with mortality risk and the attenuated effect of non-communicable disease history (NCD) on the association.

Design Prospective cohort study.

Setting Health Examinees cohort.

Participants A total of 41 070 men and 81 011 women aged ≥40 years were involved (follow-up: 6.8 years).

Outcome measures Data and cause of death occurring until 31 December 2015 were confirmed by death statistics from the National Statistical Office. We conducted advanced analysis after stratification by NCD and sensitivity analysis after excluding death before 1 or 2 years from recruitment. Cox proportional hazard and restricted cubic spline models were used to assess the association.

Results The association between serum hsCRP and risk of all-cause mortality was observed with strong linearity in both genders and was not influenced by NCD. The association of serum hsCRP with risk of cancer mortality was not observed in women with NCD, but the association with risk of cardiovascular disease (CVD) mortality was predominantly observed in men with NCD.

Conclusions This study suggests a dose–response association of hsCRP with mortality risk, including cancer and CVD mortality, in Koreans with low serum hsCRP, although the association with cancer and CVD mortality risk could be influenced by gender and NCD.

INTRODUCTION

High-sensitivity C reactive protein (hsCRP) is an acute-phase response protein synthesised by the liver and is the most sensitive and dynamic marker of inflammation. Since hsCRP has been reported as a candidate marker of generalised atherosclerosis and cardiovascular disease (CVD), many studies have investigated the role of hsCRP level as a predictor of mortality risk. A recent meta-analysis reported the predictive role of serum hsCRP in all-cause and CVD mortality in the general population. Nevertheless, it is controversial whether the predictive role of hsCRP could be applied to the risk of mortality in Asians, whose hsCRP levels are lower than those of individuals in Western countries.

Serum hsCRP represents a low-grade inflammation state that is generally involved in the process of ageing. Several large cohorts, including the Study of Women’s Health Across the Nation, the Women’s Health Study and the Dallas Heart Study, reported significant differences in hsCRP level by race and gender. In two studies of multiethnic populations residing in the USA, the median hsCRP level in East Asians was less than half the concentration in Caucasians. Even among East Asian populations, the geometric mean of hsCRP levels among women of various ethnic groups living in the USA (from the Women’s Health Study) and the association between hsCRP and risk of mortality; the association was observed only in men, supported by the results from two cohort studies reported in Korea. On the other
hand, increased hsCRP may be influenced by comorbidity itself because inflammation has emerged as an important factor in the progression of non-communicable diseases (NCDs), including cardiovascular disease,17 cancer,18 chronic obstructive pulmonary disease (COPD),19 type 2 diabetes20 and fractures,21 which contribute to increased morbidity and mortality.

This study aimed to examine the association of serum hsCRP with risk of mortality in Koreans with low serum hsCRP and to evaluate the attenuated effect of non-communicable disease history (NCD history) on the association.

**METHODS**

**Study population**
Details on the main objectives, rationale, study design and baseline characteristics of the Health Examinees (HEXA) study have been published elsewhere.22 Considering the homogeneity and comparability of participants, we created a qualified data set called HEXA-G (Health Examinees-Gem) from previously published HEXA studies.25 In the new HEXA-G data, a total of 141,968 participants remained after exclusion of withdrawals (n=12). In addition, 19,887 were excluded due to missing information (n=19,876) or small sample size (n=11) on any hsCRP components at the baseline survey. Ultimately, 122,081 subjects, including 41,070 men and 81,011 women, remained in the final analysis (Figure 1). All study participants provided informed consent prior to entering the study.

**Laboratory measurements**
After at least 10 hours of overnight fasting, blood samples were obtained in the morning. Biospecimens included fasting blood samples that were collected in a serum separator tube and two EDTA tubes. All samples were then transported within 18 hours to the National Biobank of Korea and stored for future research purposes. hsCRP was measured using a turbidimetric immunoassay (ADVIA 1650 and ADVIA 1800; Siemens Healthineers).

**Follow-up and ascertainment of mortality**
All-cause mortality was confirmed by death statistics from the National Statistical Office, which provided the data and causes of all deaths occurring through 31 December 2015. We added the mortality data from Statistics Korea to our data set using each participant’s unique identifier. Information on death and causes of death was obtained from a record link with the national death certificate files in Korea. The main outcome of interest was all-cause mortality (defined as death from any cause), including cancers and CVD mortality. The cause of death was classified according to the International Classification of Diseases, 10th Revision. Deaths were coded as C00-C97 for cancer and I00-I99 for CVD.

**Baseline variables**
Trained interviewers collected information on demographic, socioeconomic and lifestyle factors. Anthropometric measurements were obtained using standardised methods. Body mass index (BMI) was calculated and all participants were defined into four classes based on the WHO classification of BMI for Asian adults.24 Underweight (BMI <18.5 kg/m²), normal (18.5 ≤ BMI <23.0 kg/m²), overweight (23.0 ≤ BMI <25.0 kg/m²), obesity (25.0 ≤ BMI <29.9 kg/m²) and severe obesity (BMI ≥30.0 kg/m²). The current study defined metabolic syndrome using the National Cholesterol Education Program Adult Treatment Panel III,25 modified for Asian guidelines on waist circumference (≥90 cm for men and ≥80 cm for men and women, respectively). Non-smokers were defined as those who had smoked less than 400 cigarettes over the course of their lifetime. Participants who had smoked were categorised into two groups: non-current (never/former) and current smoker. Non-current drinkers were defined as those who had never consumed an alcoholic drink over the course of their lifetime or those who had not consumed alcohol at recruitment, while current drinkers were defined as those who persisted in consuming alcohol. Regular exercise was classified into two groups (yes/no) as follows: ‘Do you currently engage in regular exercise strenuous enough to cause you to break into a sweat at least once per week?’ Furthermore, considering the attenuated effect of NCD history on the association between serum hsCRP and risk of mortality, we performed advanced analysis after stratification by NCD history. We considered six main NCDs (hypertension, diabetes, hyperlipidaemia, cancer, cardiovascular and cerebrovascular diseases, and respiratory disease) to classify healthy subjects versus subjects with NCD history.

**Statistical analysis**
For the categorical analysis, we created nine categories based on the distribution of hsCRP levels in our...
population: ≤1.00 (reference group), 1.01–1.50, 1.51–2.00, 2.01–2.50, 2.51–3.00, 3.01–4.00, 4.01–6.00, 6.01–10.0 and >10.0 mg/L. For the advanced analysis after stratification by NCD history, the hsCRP levels were categorised into ≤1.00, 1.01–2.00, 2.01–3.00, 3.01–10.0 and >10.0 mg/L due to the reduced sample size in each subgroup. The concentrations of hsCRP were log-transformed for analyses due to the skewed distribution.

We calculated a follow-up time for each subject starting from the date of interview until the date of death or 31 December 2015, whichever came first. Using age as the time scale, subjects entered the risk set at the age at which they completed the baseline questionnaire and exited at their event/censoring age. The associations of hsCRP and all-cause mortality, as well as cancer and CVD mortality, were analysed by Cox proportional hazard models (adjusted HR (aHR)) and included adjustment for age, gender, demographic factors (education, marital status, job, BMI and NCD history) and lifestyle factors (smoking, alcohol consumption and exercise). We used Wald test to test for heterogeneity of risk between serum hsCRP level groups. The proportional hazards assumption was assessed on the basis of Schoenfeld residuals and was not violated for the variables of interest in the adjusted model for either cancer mortality or CVD mortality (p>0.05 for all categories). In addition, we conducted a sensitivity analysis to avoid latent period bias after excluding death before 1 year (aHR for 1 year) or 2 years (aHR for 2 years) since recruitment. Based on the Cox proportional hazard models, we made Kaplan-Meier curves and log-rank analysis after adjustment for age, gender, demographic factors (education, marital status, job, BMI and NCD history) and lifestyle factors (smoking, alcohol consumption and exercise). We employed restricted cubic splines (RCS) to evaluate the possibility of complex (ie, non-linear) hazard functions using continuous values of hsCRP (aHR_{rísimo}). We selected five hsCRP concentration values as knots based on hsCRP concentration percentiles, tested the linear and non-linear associations between knots using a cubic function, and presented the integrated graph smoothly. All statistical analyses were performed using SAS V9.3 and RCS analysis was carried out using the SAS LGTPH-CURV9 macro. Two-sided p values <0.05 were defined as indicating statistical significance.

**Patient and public involvement**

No patients and public were involved in the design, conduct, reporting and dissemination plans of the present study.

**RESULTS**

The association of demographic and lifestyle factors with risk of all-cause mortality is presented in table 1. During the follow-up period (average 6.8 years), 1365 men and 864 women died. The median levels of hsCRP were 0.77 mg/L and 0.59 mg/L for men and women, respectively. The risk of all-cause mortality was inversely associated with female gender (aHR=0.38), high education (aHR=0.65), overweight (aHR=0.81) or obesity (aHR=0.85), current alcohol consumption (aHR=0.81) and regular exercise (aHR=0.83), but was positively associated with a single marital status (aHR=1.23), NCD history (aHR=1.57), underweight (aHR=2.05) and current smoking (aHR=1.97).

The risk of all-cause mortality increased in a dose-dependent pattern with serum hsCRP level (p<0.001; online supplemental material 1), regardless of gender (p<0.001 in both genders), even in the sensitivity analysis (p=0.010 for aHR_{p=0.001} in both genders). The increased risk of female mortality with increased hsCRP level was observed in both premenopausal (p=0.020) and postmenopausal (p<0.001) women, although the statistical significance in premenopausal women disappeared after sensitivity analysis (p=0.150 for aHR_{p=0.001}; online supplemental material 1). The integrated graph, based on the RCS analyses, indicated a strong and linear association of serum hsCRP level with all-cause mortality in both genders (aHR_{rísimo}=1.019 and 1.013 in men and women, respectively; figure 2A).

The dose–response association between hsCRP level and risk of all-cause mortality was not influenced by NCD history (online supplemental material 2). After stratification by gender, however, the attenuated effect by NCD history on the association was observed only in women; the linearity of the relationship was observed in healthy women (p=0.001 for aHR_{p=0.001} but disappeared in women with NCD history, particularly after sensitivity analysis with exclusion of a 2-year follow-up time (p=0.084 for aHR_{p=0.001}). Based on the RCS analyses, the pattern of increase in the association was different depending on NCD history (figure 2B,C). In healthy subjects, the risk of all-cause mortality increased with a gradual slope (strength) until 3.0 mg/L hsCRP, with a very steep slope until 4.5 mg/L and finally with a reduced and flattened slope after 4.5 mg/L (figure 2B). On the other hand, the slope of the association fluctuated as the hsCRP level increased in subjects with NCD history, the slope increased up to 3.0 mg/L hsCRP but decreased until 4.5 mg/L and rapidly increased after 4.5 mg/L (figure 2C).

The association of serum hsCRP with risk of cancer mortality was not influenced by NCD history (p<0.001 regardless of NCD history) (table 2 and figure 3A–E). After stratification by gender, the association was not observed in women with NCD history (p=0.856); however, the association was not influenced by NCD history in men (p=0.001 and p=0.002 for aHR in both healthy and NCD history) (table 2). Although the risk of CVD mortality was linearly associated with increasing hsCRP levels, the association was dominant in men (p=0.002) and in subjects with NCD history (p=0.001; table 3) after stratification by gender and NCD history, respectively (figure 4A–E). After stratification by gender and NCD history, the association only appeared in individuals of both genders with NCD history (p=0.015 and p=0.035 in men and women with NCD history, respectively); no association between hsCRP
level and CVD mortality risk was found in either healthy men or women.

**DISCUSSION**

This study suggests that the risk of all-cause mortality was associated with elevated hsCRP levels in a dose–response manner in both genders among Asians who have reported low hsCRP levels compared with other races and was not influenced by NCD<sub>history</sub>. The association was influenced by gender and NCD<sub>history</sub>, although a dose–response association of hsCRP with risk of cancer and CVD mortality was also observed in this population. The level of hsCRP was not associated with risk of cancer mortality among women with NCD<sub>history</sub>. The risk effect of high hsCRP level on CVD mortality was predominantly observed in men with NCD<sub>history</sub>.

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**Figure 2** Dose–response association between serum hsCRP level and risk of all-cause mortality in all (A), healthy subjects at recruitment (B) and subjects with non-communicable disease history at recruitment (C). aHR, adjusted hazard ratio (adjusted for age, gender, education, job, marital status, BMI, NCD<sub>history</sub>, smoking, alcohol consumption and exercise) BMI, body mass index; E, number of death; hsCRP, high-sensitivity C reactive protein; MR, mortality rate; PY, person-year.
Table 2  Association between serum hsCRP level and cancer mortality by gender and NCD history at recruitment

| Cancer mortality | Healthy subjects at recruitment | Subjects with NCD history at recruitment |
|------------------|--------------------------------|-----------------------------------------|
|                  | E    | MR   | aHR  | HR_{year} | HR_{years} | E    | MR   | aHR  | HR_{year} | HR_{years} | E    | MR   | aHR  | HR_{year} | HR_{years} |
|                  |      |      |      |          |            |      |      |      |            |            |      |      |      |            |            |
| Total            |      |      |      |          |            |      |      |      |            |            |      |      |      |            |            |
| ≤1.00            | 590  | 10.9 | Ref  | Ref      | Ref        | 270  | 7.9  | Ref  | Ref      | Ref        | 320  | 16.3 | Ref  | Ref      | Ref        |
| 1.01–2.00        | 232  | 17.1 | 1.25 | 1.23      | 1.17       | 85   | 13.4 | 1.43 | 1.40      | 1.31       | 147  | 20.3 | 1.19 | 1.13      | 1.09       |
| 2.01–3.00        | 86   | 20.4 | 1.32 | 1.24      | 1.19       | 29   | 16.0 | 1.38 | 1.34      | 1.35       | 57   | 23.7 | 1.35 | 1.18      | 1.10       |
| 3.01–10.0        | 149  | 29.4 | 1.83 | 1.76      | 1.72       | 54   | 24.8 | 2.22 | 2.07      | 2.01       | 95   | 33.0 | 1.75 | 1.59      | 1.55       |
| >10.0            | 66   | 48.9 | 2.69 | 2.28      | 1.96       | 20   | 30.6 | 1.85 | 1.59      | 1.57       | 46   | 65.9 | 3.25 | 2.64      | 2.16       |
| P trend          |      |      |      |            |            | <0.001 | <0.001 | <0.001 | <0.001 | <0.001 | <0.001 | <0.001 | <0.001 | <0.001 |
| Men              |      |      |      |            |            |      |      |      |            |            |      |      |      |            |            |
| ≤1.00            | 302  | 18.5 | Ref  | Ref      | Ref        | 169  | 23.6 | Ref  | Ref      | Ref        | 133  | 14.5 | Ref  | Ref      | Ref        |
| 1.01–2.00        | 144  | 26.6 | 1.36 | 1.36      | 1.32       | 95   | 32.6 | 1.40 | 1.38      | 1.34       | 49   | 19.7 | 1.31 | 1.34      | 1.31       |
| 2.01–3.00        | 59   | 34.7 | 1.45 | 1.31      | 1.19       | 40   | 40.4 | 1.54 | 1.37      | 1.16       | 19   | 26.7 | 1.29 | 1.22      | 1.26       |
| 3.01–10.0        | 111  | 52.7 | 2.17 | 2.10      | 2.00       | 77   | 64.5 | 2.26 | 2.24      | 2.12       | 34   | 37.3 | 1.98 | 1.80      | 1.70       |
| >10.0            | 50   | 82.9 | 3.13 | 2.66      | 2.34       | 38   | 114.1| 4.07 | 3.42      | 2.79       | 13   | 46.1 | 1.58 | 1.40      | 1.56       |
| P trend          |      |      |      |            |            | <0.001 | <0.001 | <0.001 | <0.001 | <0.001 | <0.001 | <0.001 | <0.001 | <0.001 |
| Women            |      |      |      |            |            |      |      |      |            |            |      |      |      |            |            |
| ≤1.00            | 288  | 7.7  | Ref  | Ref      | Ref        | 137  | 5.5  | Ref  | Ref      | Ref        | 151  | 12.1 | Ref  | Ref      | Ref        |
| 1.01–2.00        | 88   | 10.8 | 1.13 | 1.08      | 0.99       | 36   | 9.4  | 1.60 | 1.48      | 1.31       | 52   | 12.1 | 0.86 | 0.86      | 0.81       |
| 2.01–3.00        | 27   | 10.7 | 1.16 | 1.17      | 1.2        | 10   | 9.1  | 1.48 | 1.50      | 1.47       | 17   | 12.0 | 0.96 | 0.98      | 1.03       |
| 3.01–10.0        | 38   | 12.9 | 1.31 | 1.24      | 1.29       | 20   | 15.8 | 2.58 | 2.48      | 2.57       | 18   | 10.7 | 0.75 | 0.71      | 0.74       |
| >10.0            | 15   | 20.4 | 1.89 | 1.61      | 1.28       | 7    | 18.9 | 2.16 | 1.75      | 1.42       | 8    | 21.9 | 1.66 | 1.47      | 1.17       |
| P trend          | 0.019 | 0.074 | 0.161 | <0.001 | <0.001 | <0.002 | 0.856 | 0.635 | 0.538 |

aHR: adjusted for age, gender, education, job, marital status, BMI, NCD history, smoking, alcohol consumption and exercise.
HR_{year}: aHR after excluding subjects who died within 1-year follow-up time.
HR_{years}: aHR after excluding subjects who died within 2-year follow-up time.
aHR, adjusted hazard ratio; BMI, body mass index; E, number of death; hsCRP, high-sensitivity C reactive protein; MR, mortality rate (10 000 person-years); NCD history, non-communicable disease history; Ref, reference.
Several large cohorts\textsuperscript{10–12, 14} have suggested that serum \textit{hs}CRP levels may differ according to ethnic background, with the highest concentrations seen in African Americans, followed by Hispanic, white, Chinese and Japanese individuals. Although the reason for this ethnic difference is not clearly resolved, genetic diversity,\textsuperscript{27} the relatively low BMI in Asian populations, and ethnic differences in diet and lifestyle\textsuperscript{28} have been suggested. Although the extent to which these findings adopt to Asian populations has been unclear, several recent studies\textsuperscript{11, 16} conducted in Asia reported a positive association of \textit{hs}CRP with mortality risk. In this population, the \textit{hs}CRP level was associated with risk of all-cause mortality in a dose-dependent manner, even though the level of \textit{hs}CRP was lower than in the Western population. A meta-analysis\textsuperscript{29} and large cohort studies\textsuperscript{3–6} supported the robustness of the association regardless of adjusted confounders, the cut-off point of CRP level and exclusion of deaths within the first 2 years of follow-up.

The reason for the discrepancy in \textit{hs}CRP levels with respect to gender is not clearly resolved, although several studies suggested different lifestyle and metabolic risk factors between men and women\textsuperscript{30} and genetic diversity.\textsuperscript{27} A high level of serum \textit{hs}CRP in our population was positively related to the increased risk of all-cause mortality in both genders, supported by several previous studies.\textsuperscript{16, 31} Nevertheless, several studies reported no association of \textit{hs}CRP level with all-cause mortality was observed in women.\textsuperscript{7} In particular, the association was shown in postmenopausal women only, which might suggest the protective effect of endogenous female hormones on the low level of \textit{hs}CRP.\textsuperscript{32} the average \textit{hs}CRP level was 0.48 mg/L and 0.68 mg/L for premenopausal and postmenopausal women in this study. The protective effect could be supported by the proposition that oestrogen or progesterone might to some extent repress the detrimental effects of chronic inflammation on tissue damage.\textsuperscript{33}

Inflammation has emerged as an important factor in the processes of NCD, including CVD,\textsuperscript{17} cancer,\textsuperscript{18} type 2 diabetes,\textsuperscript{20} COPD\textsuperscript{19, 34} and fracture.\textsuperscript{21} In addition, medications that had taken to treat any specific NCD, such as renin–angiotensin system inhibitors\textsuperscript{35} and statins and thiazolidinedione,\textsuperscript{36} could influence the level of \textit{hs}CRP. The association between \textit{hs}CRP and mortality risk was not attenuated by NCD\textsubscript{history} in either gender in this study, but the statistical significance of the association disappeared in men after sensitivity analysis (aHR\textsubscript{2years}). A dose–response relationship between \textit{hs}CRP level and all-cause mortality risk was pronounced in both genders. On the other hand, the positive association of \textit{hs}CRP with risk of all-cause mortality was significantly observed only in men with NCD\textsubscript{history}, but not in women with NCD\textsubscript{history}. The attenuated effect of NCD\textsubscript{history} on the association between \textit{hs}CRP and risk of cancer mortality was not observed in men, consistent with results from several studies which reported an association among healthy men\textsuperscript{7} or patients with cancer.\textsuperscript{37, 38} only. Most studies\textsuperscript{3, 4, 6, 7, 15–17, 39} supported that CVD mortality increased with elevated \textit{hs}CRP levels, predominantly in men.\textsuperscript{4, 7, 15, 16} Although \textit{hs}CRP levels are

![Figure 3](https://via.placeholder.com/150)

**Figure 3** Kaplan-Meier crude survival curves for cancer mortality according to serum \textit{hs}CRP level in all (A), men (B), women (C), healthy subjects at recruitment (D) and subjects with non-communicable disease history at recruitment (E). \textit{hs}CRP, high-sensitivity C reactive protein.
### Table 3  Association between serum *hs*CRP level and cardiovascular disease mortality by gender and NCD\textsubscript{history} at recruitment

| Cardiovascular disease mortality | Healthy subjects at recruitment | Subjects with NCD\textsubscript{history} at recruitment |
|---------------------------------|-------------------------------|------------------------------------------------------|
| **E** | **MR** | **aHR** | **HR\textsubscript{year}** | **HR\textsubscript{years}** | **E** | **MR** | **aHR** | **HR\textsubscript{year}** | **HR\textsubscript{years}** | **E** | **MR** | **aHR** | **HR\textsubscript{year}** | **HR\textsubscript{years}** |
|---------------------------------|-------------------------------|------------------------------------------------------|
| Total                           |                               |                                                      |
| ≤1.00                           | 167                           | 3.1 Ref                                              | Ref Ref Ref                      | 58   | 1.7 Ref | Ref Ref Ref                      | 109  | 5.5 Ref | Ref Ref Ref                      |
| 1.01–2.00                       | 79                             | 5.8 1.35                                            | 1.37 1.23                       | 18   | 2.8 1.19 | 1.15 0.94                       | 64   | 8.4 1.42 | 1.46 1.36                       |
| 2.01–3.00                       | 42                             | 10.0 2.06                                           | 2.05 2.02                       | 6    | 3.3 1.47 | 1.54 1.46                       | 36   | 15.0 2.28 | 2.25 2.26                       |
| 3.01–10.0                       | 39                             | 7.7 1.45                                            | 1.38 1.44                       | 8    | 3.7 1.44 | 1.50 1.70                       | 31   | 1.08 1.48 | 1.37 1.40                       |
| >10.0                           | 13                             | 9.6 1.81                                            | 1.76 1.59                       | 3    | 4.6 2.02 | 2.10 1.58                       | 10   | 14.3 1.85 | 1.74 1.68                       |
| **P trend**                     | 0.001                          | 0.002 0.004                                         | 0.130 0.100 0.162               | 0.001 | 0.006 0.009 |
| Men                             |                               |                                                      |
| ≤1.00                           | 89                             | 5.5 Ref                                              | Ref Ref Ref                      | 25   | 2.7 Ref | Ref Ref Ref                      | 64   | 8.9 Ref | Ref Ref Ref                      |
| 1.01–2.00                       | 45                             | 8.3 1.33                                            | 1.32 1.25                       | 12   | 4.8 1.30 | 1.22 1.22                       | 33   | 11.3 1.31 | 1.33 1.33                       |
| 2.01–3.00                       | 30                             | 17.6 2.70                                           | 2.67 2.53                       | 3    | 4.2 1.31 | 1.37 1.37                       | 27   | 27.3 3.05 | 2.99 2.99                       |
| 3.01–10.0                       | 24                             | 11.4 1.43                                           | 1.36 1.46                       | 6    | 6.6 1.70 | 1.79 1.79                       | 18   | 15.1 1.42 | 1.21 1.21                       |
| >10.0                           | 8                              | 13.0 1.90                                           | 2.02 1.70                       | 3    | 10.6 3.42 | 3.61 3.61                       | 5    | 15.0 1.59 | 1.62 1.62                       |
| **P trend**                     | 0.002                          | 0.003 0.009                                         | 0.053 0.038 0.062               | 0.015 | 0.027 0.047 |
| Women                           |                               |                                                      |
| ≤1.00                           | 78                             | 2.1 Ref                                              | Ref Ref Ref                      | 33   | 1.3 Ref | Ref Ref Ref                      | 45   | 6.3 Ref | Ref Ref Ref                      |
| 1.01–2.00                       | 34                             | 4.2 1.41                                            | 1.46 1.25                       | 6    | 1.6 1.09 | 1.13 0.62                       | 28   | 9.6 1.60 | 1.66 1.58                       |
| 2.01–3.00                       | 12                             | 4.8 1.26                                            | 1.30 1.44                       | 3    | 2.7 1.67 | 1.70 1.86                       | 9    | 9.1 1.17 | 1.20 1.39                       |
| 3.01–10.0                       | 15                             | 5.1 1.51                                            | 1.45 1.44                       | 2    | 1.6 1.06 | 1.07 1.14                       | 13   | 10.9 1.75 | 1.64 1.65                       |
| >10.0                           | 5                              | 6.8 1.72                                            | 1.35 1.45                       | 0    | – – – – | – – – – | 5    | 15.0 2.51 | 1.91 2.07                       |
| **P trend**                     | 0.092                          | 0.177 0.168                                         | 0.940 0.998 0.922               | 0.035 | 0.092 0.078 |

\(aHR\): adjusted for age, gender, education, job, marital status, BMI, NCD\textsubscript{history}, smoking, alcohol consumption and exercise.

\(HR\textsubscript{year}\): \(aHR\) after excluding subjects who died within 1-year follow-up time.

\(HR\textsubscript{years}\): \(aHR\) after excluding subjects who died within 2-year follow-up time.

\(aHR\), adjusted hazard ratio; BMI, body mass index; E, number of death; \(hs\)CRP, high-sensitivity C reactive protein; MR, mortality rate (10 000 person-years); NCD\textsubscript{history}, non-communicable disease history; Ref, reference.
lower in our population than in other races, the level of hsCRP was positively associated with CVD mortality in men but not in women, similar to previous studies. After stratification by gender and NCD history, the association between hsCRP and risk of CVD mortality was dominant in subjects with NCD history in this study. Although many interventional studies have been conducted recently on anti-inflammatory drugs for prevention of CVD, the results are controversial. According to the results of our study, elevated inflammatory markers in people with chronic disease were associated with an increased risk of CVD mortality. This suggests that CVD mortality in people with chronic diseases might be reduced by use of anti-inflammatory medication.

This study has several strengths. As a large population-based prospective study, it was possible to (1) adjust for confounders; (2) perform a sensitivity analysis after excluding death before 1 or 2 years from recruitment; (3) assess an advanced analysis after stratification by gender and NCD history; (4) examine the association using various cut-off points of hsCRP considering low serum hsCRP levels in Asian populations; and (5) evaluate the complex (ie, non-linear) hazard functions using RCS on the association between continuous hsCRP levels and risk of mortality. In particular, most previous studies excluded subjects with more than 10 mg/L hsCRP due to their relatively low sample size or reflecting acute-phase reactions of severe inflammation, but we examined the effect of very high hsCRP concentration on the risk of mortality because it is possible that studies focusing on patient with hsCRP of 10 or higher could be conducted. In addition, the hsCRP level in this study was measured within 18 hours at a single institution to minimise measurement error/bias from institutional variations and to avoid bias from measurement or long-term storage before analysis.

Despite these strengths, the study also has several limitations. First, the use of a single measurement of hsCRP at baseline could reflect an inaccurate status of blood hsCRP levels in study participants and increase the instability of hsCRP due to random fluctuations over time. Nevertheless, a report on long-term hsCRP variability suggested that hsCRP variability within an individual is relatively small and that the variability could not account for the association. Second, our study lacked information on medication use at recruitment and during the follow-up period. Several medications related to NCDs, including statins, ACE inhibitors, fibrates, niacin, thiazolidinedione and oestrogen/progestogen hormone, could influence hsCRP level; however, we tried to overcome this limitation through advanced analysis after stratification by NCD history. Third, because there is no available information on hormone replacement therapy (HRT) among women and we could not examine the influence of HRT on the association of hsCRP with risk of hormone-related cancer or CVD mortality among women, we could not suggest the effect of female hormones on the association. In addition, further studies are needed on the effects of obesity, although the inverse relationship between all-cause...
mortality and obesity in our population was consistent with Zheng et al’s report in Asians. On the other hand, the inverse association of alcohol drinking with all-cause mortality could not be interpreted directly because we were not able to distinguish between mild drinkers and abusive alcohol drinkers and thus requires additional research in the future.

In conclusion, the association of hsCRP level is dose-responsively increased with the risk of all-cause mortality in men and women (particularly postmenopausal women). Otherwise, the association of hsCRP level with risk of cancer and CVD mortality could be attenuated by gender or NCD history.

Contributors
S-AL, X-OS and DK designed and conducted the research. S-AL and SOK analysed the data and performed the statistical analyses. HP and J-KL managed the data mining and collection. S-AL wrote the manuscript and approved the final version of the submitted manuscript. All authors read and approved the final manuscript.

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None declared.

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Patient consent for publication
Not required.

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This study involves human participants and was approved by the Institutional Review Board of the Seoul National University Hospital, Seoul, Korea (IRB no: E-1503-103-657). Participants gave informed consent to participate in the study before taking part.

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No data are available.

Supplemental material
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