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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 (*hs*CRP) with mortality risk and the attenuated effect of non-communicable disease history ($NCD_{history}$) 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 $NCD_{history}$ 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 *hs*CRP and risk of all-cause mortality was observed with strong linearity in both genders and was not influenced by $NCD_{history}$. The association of serum *hs*CRP with risk of cancer mortality was not observed in women with $NCD_{history}$, but the association with risk of cardiovascular disease (CVD) mortality was predominantly observed in men with $NCD_{history}$.

Conclusions This study suggests a dose–response association of *hs*CRP with mortality risk, including cancer and CVD mortality, in Koreans with low serum *hs*CRP, although the association with cancer and CVD mortality risk could be influenced by gender and $NCD_{history}$.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This is a large population-based prospective study.
⇒ We examined the effect of very high-sensitivity C reactive protein (*hs*CRP) concentration on mortality risk.
⇒ The *hs*CRP level in the present study was measured within 18 hours at a single institution to minimise error/bias.
⇒ Due to random fluctuations in *hs*CRP, using a single measurement of *hs*CRP at baseline could reflect inaccurate status of blood *hs*CRP level in study participants and increase the instability of *hs*CRP.
⇒ This study lacked information on medication use at recruitment and during the follow-up period, as well as information on hormone replacement therapy among women.

INTRODUCTION

High-sensitivity C reactive protein (*hs*CRP) is an acute-phase response protein synthesised by the liver and is the most sensitive and dynamic marker of inflammation.[1] Since *hs*CRP has been reported as a candidate marker of generalised atherosclerosis and cardiovascular disease (CVD),[2] many studies[3–7] have investigated the role of *hs*CRP level as a predictor of mortality risk. A recent meta-analysis[8] reported the predictive role of serum *hs*CRP in all-cause and CVD mortality in the general population. Nevertheless, it is controversial whether the predictive role of *hs*CRP could be applied to the risk of mortality in Asians, whose *hs*CRP levels are lower than those of individuals in Western countries.

Serum *hs*CRP represents a low-grade inflammation state that is generally involved in the process of ageing.[9] Several large cohorts, including the Study of Women's Health Across the Nation,[10] the Women's Health Study[11] and the Dallas Heart Study,[12] reported significant differences in *hs*CRP level by race and gender. In two studies of multiethnic populations residing in the USA,[10 13] the median *hs*CRP level in East Asians was less than half the concentration in Caucasians. Even among East Asian populations, the geometric mean of *hs*CRP levels varied depending on ethnic background.[14] In addition, a meta-analysis[11] reported the *hs*CRP levels among women of various ethnic groups living in the USA (from the Women's Health Study) and the association between *hs*CRP and risk of mortality; the association was observed only in men, supported by the results from two cohort studies[15 16] reported in Korea. On the other

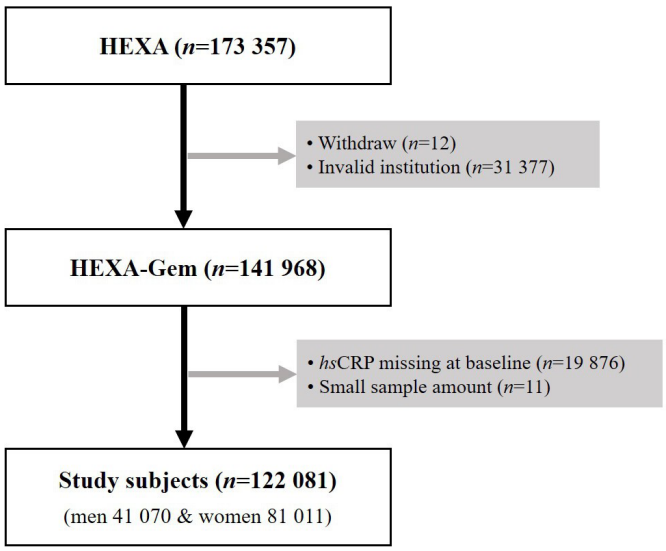

Figure 1 Flow diagram of the analytical sample in the current study using the HEXA cohort. HEXA, Health Examinees; *hs*CRP, high-sensitivity C reactive protein.

hand, increased *hs*CRP may be influenced by comorbidity itself because inflammation has emerged as an important factor in the progression of non-communicable diseases (NCDs), including CVD,[17] cancer,[18] chronic obstructive pulmonary disease (COPD),[19] type 2 diabetes[20] and fractures,[21] which contribute to increased morbidity and mortality.

This study aimed to examine the association of serum *hs*CRP with risk of mortality in Koreans with low serum *hs*CRP 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.[23] In the new HEXA-G data, a total of 141 968 participants remained after exclusion of withdrawers (n=12). In addition, 19 887 were excluded due to missing information (n=19 876) or small sample size (n=11) on any *hs*CRP 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. *hs*CRP 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/m^2), normal (18.5 ≤ BMI <23.0 kg/m^2), overweight (23.0 ≤ BMI <25.0 kg/m^2), obesity (25.0 ≤ BMI <29.9 kg/m^2) and severe obesity (BMI ≥30.0 kg/m^2). 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 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 *hs*CRP 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 *hs*CRP 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 *hs*CRP 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 *hs*CRP 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 *hs*CRP 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 *hs*CRP 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_{1year}) or 2 years (aHR_{2years}) 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[26] using continuous values of *hs*CRP ($aHR_{continuous}$). We selected five *hs*CRP concentration values as knots based on *hs*CRP 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 V.9.3 and RCS analysis was carried out using the SAS LGTPHCURV9 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 *hs*CRP 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=0.83), 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 *hs*CRP level (p_{trend} <0.001; online supplemental material 1), regardless of gender (p_{trend} <0.001 in both genders), even in the sensitivity analysis (p_{trend} <0.001 for aHR_{1year} in both genders). The increased risk of female mortality with increased *hs*CRP level was observed in both premenopausal (p_{trend}=0.020) and postmenopausal (p_{trend} <0.001) women, although the statistical significance in premenopausal women disappeared after sensitivity analysis (p_{trend}=0.150 for aHR_{2years}; online supplemental material 1). The integrated graph, based on the RCS analyses, indicated a strong and linear association of serum *hs*CRP level with all-cause mortality in both genders ($aHR_{continuous}$=1.019 and 1.013 in men and women, respectively; figure 2A).

The dose–response association between *hs*CRP 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_{trend}=0.001 for aHR_{2years}) but disappeared in women with $NCD_{history}$, particularly after sensitivity analysis with exclusion of a 2-year follow-up time (p_{trend}=0.084 for aHR_{2years}). 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 *hs*CRP, 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 *hs*CRP level increased in subjects with $NCD_{history}$; the slope increased up to 3.0 mg/L *hs*CRP but decreased until 4.5 mg/L and rapidly increased after 4.5 mg/L (figure 2C).

The association of serum *hs*CRP with risk of cancer mortality was not influenced by $NCD_{history}$ (p_{trend} <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_{trend}=0.856); however, the association was not influenced by $NCD_{history}$ in men (p_{trend} <0.001 and p_{trend}=0.002 for aHR in both healthy and $NCD_{history}$) (table 2). Although the risk of CVD mortality was linearly associated with increasing *hs*CRP levels, the association was dominant in men (p_{trend}=0.002) and in subjects with $NCD_{history}$ (p_{trend}=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_{trend}=0.015 and p_{trend}=0.035 in men and women with $NCD_{history}$, respectively); no association between *hs*CRP

Table 1 Baseline characteristics of participants by all-cause mortality

			All-cause mortality	
	All (N=122 081)	Death (n=2229)	Age and gender adjusted	Adjusted HR*
Age	53.1±8.3	59.7±8.8		
Female	66.4	38.8	0.40 (0.36–0.43)	0.38 (0.33–0.44)
Education (≥10 years, %)	68.2	55.4	0.67 (0.60–0.75)	0.65 (0.56–0.75)
Blue-collar worker† (%)	32.3	33.8	1.46 (1.26–1.68)	1.16 (0.99–1.35)
Marital status (single, %)	11.0	13.3	1.35 (1.19–1.54)	1.23 (1.07–1.40)
$NCD_{history}$ (yes, %)	32.4	53.6	1.51 (1.39–1.65)	1.57 (1.42–1.72)
Hypertension	18.9	31.5	1.18 (1.08–1.30)	1.22 (1.11–1.35)
Diabetes	6.5	17.1	1.81 (1.62–2.03)	1.77 (1.57–2.00)
Hyperlipidaemia	9.2	7.6	0.73 (0.62–0.86)	0.78 (0.66–0.92)
Cancer	3.2	8.8	2.69 (2.31–3.12)	2.66 (2.27–3.11)
Cerebral and cardiovascular diseases	3.7	10.2	1.50 (1.30–1.73)	1.43 (1.23–1.66)
Respiratory disease	2.4	4.3	1.37 (1.12–1.68)	1.32 (1.06–1.64)
Body mass index (%)				
<18.5	1.8	3.7	2.14 (1.69–2.69)	2.05 (1.61–2.62)
18.5–22.9	38.1	34.9	1.00 (ref)	1.00 (ref)
23.0–24.9	27.8	26.0	0.82 (0.73–0.91)	0.81 (0.72–0.91)
25.0–29.9	29.5	32.5	0.90 (0.81–1.00)	0.83 (0.74–0.93)
≥30.0	2.8	2.9	1.08 (0.83–1.39)	0.81 (0.61–1.08)
P trend			0.0118	<0.0001
Metabolic syndrome (yes, %)	22.0	28.4	1.13 (1.03–1.24)	1.07 (0.96–1.19)
Current smoker (%)	11.7	22.7	2.04 (1.79–2.33)	1.97 (1.71–2.27)
Current drinker (%)	44.0	43.8	0.86 (0.77–0.95)	0.81 (0.73–0.91)
Regular exercise (yes, %)	53.4	49.1	0.76 (0.70–0.83)	0.83 (0.76–0.91)

*Adjusted for age, gender, education, job, marital status, BMI and $NCD_{history}$.
†Compared with white-collar worker.
BMI, body mass index; $NCD_{history}$, non-communicable disease history; ref, reference.

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 *hs*CRP levels in a dose–response manner in both genders among Asians who have reported low *hs*CRP levels compared with other races and was not influenced by $NCD_{history}$. The association was influenced by gender and $NCD_{history}$, although a dose–response association of *hs*CRP with risk of cancer and CVD mortality was also observed in this population. The level of *hs*CRP was not associated with risk of cancer mortality among women with $NCD_{history}$. The risk effect of high *hs*CRP level on CVD mortality was predominantly observed in men with $NCD_{history}$.

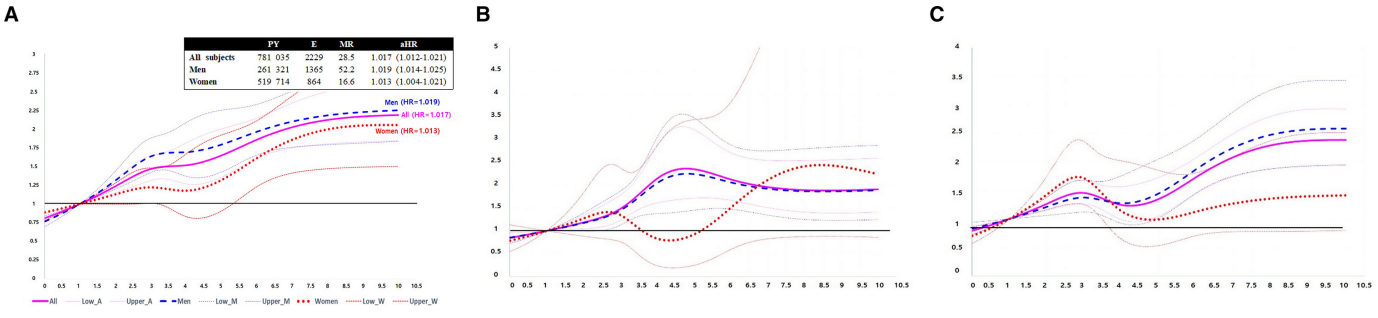

Figure 2 Dose–response association between serum *hs*CRP level and risk of all-cause mortality in all (A), healthy subjects at recruitment (B) and subjects with non-communicable disease history at recruitment (C). aHR, adjusted hazard ratio (adjusted for age, gender, education, job, marital status, BMI,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

Table 2 Association between serum *hs*CRP 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_{1year}	HR_{2years}	E	MR	aHR	HR_{1year}	HR_{2years}	E	MR	aHR	HR_{1year}	HR_{2years}
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			0.002	0.009	0.015
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_{1year}: aHR after excluding subjects who died within 1-year follow-up time.
HR_{2years}: 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); $NCD_{history}$, non-communicable disease history; Ref, reference.

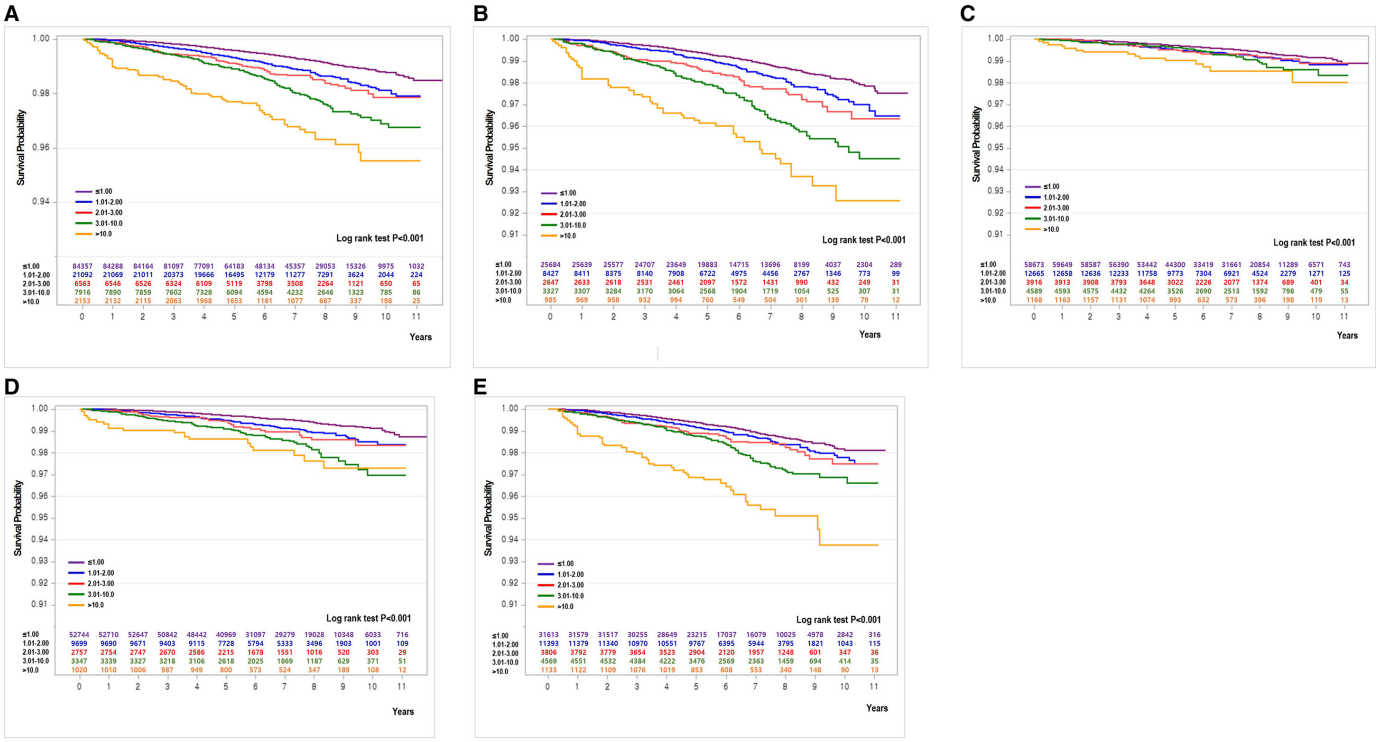

Figure 3 Kaplan-Meier crude survival curves for cancer mortality according to serum *hs*CRP level in all (A), men (B), women (C), healthy subjects at recruitment (D) and subjects with non-communicable disease history at recruitment (E). *hs*CRP, high-sensitivity C reactive protein.

Several large cohorts[10–12 14] have suggested that serum *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,[27] the relatively low BMI in Asian populations, and ethnic differences in diet and lifestyle[28] have been suggested. Although the extent to which these findings adopt to Asian populations has been unclear, several recent studies[11 16] conducted in Asia reported a positive association of *hs*CRP with mortality risk. In this population, the *hs*CRP level was associated with risk of all-cause mortality in a dose-dependent manner, even though the level of *hs*CRP was lower than in the Western population. A meta-analysis[29] and large cohort studies[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 *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[30] and genetic diversity.[27] A high level of serum *hs*CRP in our population was positively related to the increased risk of all-cause mortality in both genders, supported by several previous studies.[8 16 31] Nevertheless, several studies reported no association of *hs*CRP level with all-cause mortality was observed in women.[7 16] 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 *hs*CRP;[32] the average *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.[33]

Inflammation has emerged as an important factor in the processes of NCD, including CVD,[17] cancer,[18] type 2 diabetes,[20] COPD[19 34] and fracture.[21] In addition, medications that had taken to treat any specific NCD, such as renin–angiotensin system inhibitors[35] and statins and thiazolidinedione,[36] could influence the level of *hs*CRP. The association between *hs*CRP and mortality risk was not attenuated by $NCD_{history}$ in either gender in this study, but the statistical significance of the association disappeared in women after sensitivity analysis (aHR_{2years}). A dose–response relationship between *hs*CRP level and all-cause mortality risk was pronounced in both genders. On the other hand, the positive association of *hs*CRP with risk of all-cause mortality was significantly observed only in men with $NCD_{history}$ but not in women with $NCD_{history}$. The attenuated effect of $NCD_{history}$ on the association between *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[3] or patients with cancer[37 38] only. Most studies[3 4 6 7 15 16 31 39] supported that CVD mortality increased with elevated *hs*CRP levels, predominantly in men.[4 7 15 16] Although *hs*CRP levels are

Table 3 Association between serum *hs*CRP level and cardiovascular disease mortality by gender and $NCD_{history}$ at recruitment

	Cardiovascular disease mortality					Healthy subjects at recruitment					Subjects with $NCD_{history}$ at recruitment				
	E	MR	aHR	HR_{1year}	HR_{2years}	E	MR	aHR	HR_{1year}	HR_{2years}	E	MR	aHR	HR_{1year}	HR_{2years}
Total															
≤1.00	167	3.1	Ref	Ref	Ref	58	1.7	Ref	Ref	Ref	109	5.5	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	25	2.7	Ref	Ref	Ref	64	8.9	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	33	1.3	Ref	Ref	Ref	45	6.3	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	1.65	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, $NCD_{history}$, smoking, alcohol consumption and exercise.
HR_{1year}: aHR after excluding subjects who died within 1-year follow-up time.
HR_{2years}: 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); $NCD_{history}$, non-communicable disease history; Ref, reference.

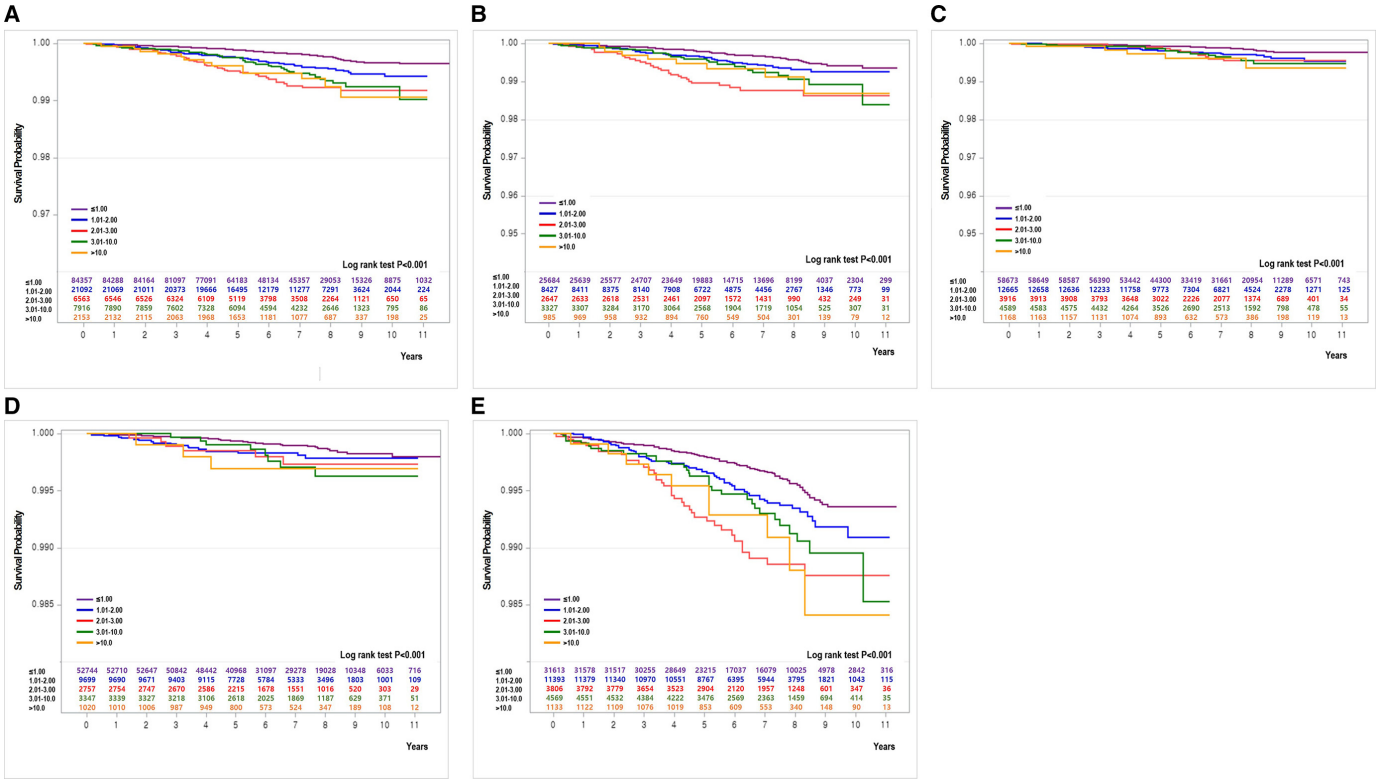

Figure 4 Kaplan-Meier crude survival curves for cardiovascular disease mortality according to serum *hs*CRP level in all (A), men (B), women (C), healthy subjects at recruitment (D) and subjects with non-communicable disease history at recruitment (E). *hs*CRP, high-sensitivity C reactive protein.

lower in our population than in other races, the level of *hs*CRP was positively associated with CVD mortality in men but not in women, similar to previous studies.[7 15 16 31 39] After stratification by gender and $NCD_{history}$, the association between *hs*CRP 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 *hs*CRP considering low serum *hs*CRP levels in Asian populations; and (5) evaluate the complex (ie, non-linear) hazard functions using RCS on the association between continuous *hs*CRP levels and risk of mortality. In particular, most previous studies excluded subjects with more than 10 mg/L *hs*CRP due to their relatively low sample size or reflecting acute-phase reactions of severe inflammation, but we examined the effect of very high *hs*CRP concentration on the risk of mortality because it is possible that studies focusing on patient with *hs*CRP of 10 or higher could be conducted. In addition, the *hs*CRP 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 *hs*CRP at baseline could reflect an inaccurate status of blood *hs*CRP levels in study participants and increase the instability of *hs*CRP due to random fluctuations over time. Nevertheless, a report[40] on long-term *hs*CRP variability suggested that *hs*CRP 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 *hs*CRP level;[37] 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 *hs*CRP 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.[41] 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 *hs*CRP level is dose-responsively increased with the risk of all-cause mortality in men and women (particularly postmenopausal women). Otherwise, the association of *hs*CRP level with risk of cancer and CVD mortality could be attenuated by gender or $NCD_{history}$.

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Patient consent for publication Not required.

Ethics approval 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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