BMJ Open

The association of serum high sensitivity C-reactive protein with the mortality risk in Asian: the Health Examinees cohort

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2021-052630
Article Type:	Original research
Date Submitted by the Author:	20-Apr-2021
Complete List of Authors:	Lee, Sang-Ah; Kangwon National University School of Medicine, Preventive Medicine; Vanderbilt University Medical Center Kwon, Sung Ok; Kangwon National University School of Medicine, Preventive Medicine Park, Hyerim; Kangwon National University School of Medicine, Preventive Medicine Shu, Xiao-Ou ; Vanderbilt University Medical Center Lee, Jong-Koo; JW LEE Center for Global Medicine Kang, Daehee; Seoul National University College of Medicine, Preventive Medicine
Keywords:	PREVENTIVE MEDICINE, EPIDEMIOLOGY, Cardiac Epidemiology < CARDIOLOGY

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

The association of serum high sensitivity C-reactive protein with the mortality risk in Asian: the Health Examinees cohort

Sang-Ah Lee[1,2 *], Sung Ok Kwon[1], Hyerim Park[1], Xiao-Ou Shu[2], Jong-Koo Lee[3], Daehee Kang[4]

[1]Department of Preventive Medicine, School of Medicine, Kangwon National University, Chuncheon, Republic of Korea.

[2]Division of Epidemiology, Vanderbilt Epidemiology Center, Vanderbilt University Medical Center, Nashville, TN, USA.

[3]JW Lee Center for Global Medicine, College of Medicine, Seoul National University, Seoul, Republic of Korea.

[4]Department of Preventive Medicine, College of Medicine, Seoul National University, Seoul, Republic of Korea.

ABSTRACT

Objectives This study aimed to examine the association of *hs*CRP with mortality risk and the attenuated effect of non-communicable disease history ($NCD_{history}$) on the association.

Design Prospective cohort study.

Setting the Health Examinees (HEXA) cohort.

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

Outcome measures The data and cause of death occurring until December 31, 2015, were confirmed by death statistics from the National Statistical Office. We conducted the advanced analysis after stratification by $NCD_{history}$ and the 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 the risk of all-cause mortality was observed with strong linearity in both genders, which was not influenced by $NCD_{history}$. Otherwise, the association of serum *hs*CRP with cancer-mortality risk was not observed in women with $NCD_{history}$, but the association with the risk of cardiovascular disease (CVD) mortality was predominantly observed in men with $NCD_{history}$.

Conclusions This study suggested the dose-response association of *hs*CRP with mortality risk, including cancer and CVD mortality, in Korean 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 the large population-based prospective study.
- We examined the effect of very high *hs*CRP concentration on mortality risk.
- The *hs*CRP level of present study was measured within 18 hours in a single institution to minimize error/bias.

· Due to due to random fluctuations of *hs*CRP, using the single measurement of *hs*CRP at baseline could reflect the inaccurate status of blood *hs*CRP levels in the study participants and increase the instability of *hs*CRP.

· This study lacked information on medication use at recruitment and during the follow-up period, and information on hormone-replacement therapy (HRT) among women.

*Correspondence to: Sang-Ah Lee, Ph.D.
Department of Preventive Medicine, School of Medicine, Kangwon National University,
Chuncheon, Gangwon, Republic of Korea.
Tel: +82 33 250 8871
E-mail: sangahlee@kangwon.ac.kr

INTRODUCTION

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

Serum *hs*CRP represents a low-grade inflammation state that is generally involved in the process of aging[9]. Several large cohorts, including Study of Women's Health Across the Nation (SWAN)[10], the Women's Health Study[11] and the Dallas Heart Study[12], reported significant differences in *hs*CRP levels 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 United States (from the Women's Health Study) on the association between *hs*CRP and the mortality risk; the association was observed in only men supported by the results from two cohort studies[15, 16] reported in Korea. On the other hand, the 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 the 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 dataset 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 the 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 (Fig. 1). All study participants provided informed consent prior to entering the study. The Institutional Review Board of the Seoul National University Hospital, Seoul, Korea, approved it for statistical analysis (IRB No. E-1503-103-657).

Laboratory measurements

After at least 10 hours of overnight fasting, blood samples were obtained in the morning. Bio-specimens included fasting blood samples that were collected in a serum separator tube and two ethylenediaminetetraacetic acid (EDTA) tubes. All samples were then transported to the National Biobank of Korea and stored for future research purposes within 18 hours. *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 December 31, 2015. We added the mortality data from Statistics Korea to our dataset 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 (ICD-10). 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 standardized methods. Body mass index (BMI) was calculated, and all participants were defined into four classes based on the World Health Organization 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 (NCEP-ATP III)[25], modified for the Asian guideline for waist circumference (WC ≥90 and ≥80 cm for men and women, respectively). Nonsmokers were defined as those who had smoked less than 400 cigarettes over the course of their lifetime. Participants who had smoked were categorized into two groups: noncurrent (never/former) and current smoker. Noncurrent 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 the $NCD_{history}$ on the association between serum *hs*CRP and the risk of mortality, we performed advanced analysis after stratification by $NCD_{history}$. We considered six main non-communicable diseases (hypertension, diabetes, hyperlipidemia, cancer, cardiovascular and cerebrovascular diseases, and respiratory disease) to classify healthy subjects vs. 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 the $NCD_{history}$, the *hs*CRP levels were categorized as ≤1.00, 1.01-2.00, 2.01-3.00, 3.01-10.0, and >10.0 mg/L because of the reduced sample size in each subgroup. The concentrations of *hs*CRP were log-transformed for analyses because of the skewed distribution.

We calculated a follow-up time for each subject starting from the date of interview until the date of death or December 31, 2015, whichever came first. Using age as the time scale, subjects enter the risk set at the age at which they completed the baseline questionnaire and exit at their event/censoring age. The associations of

*hs*CRP and all-cause mortality, as well as cancer and CVD mortality, were analyzed by Cox proportional hazard models (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). In addition, we conducted a sensitivity analysis to avoid latent period bias after excluding death before 1 year (aHR_{1year}) or 2 years (aHR_{2year}) since recruitment. We employed restricted cubic splines (RCSs) to evaluate the possibility of complex (i.e., nonlinear) 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 nonlinear associations between knots using a cubic function, and presented the integrated graph smoothly. All statistical analyses were performed using SAS version 9.3 (SAS Institute Inc., Cary, NC, USA) and RCS analysis was carried out using the SAS LGTPHCURV9 macro. The *P*-values <0.05 were defined as indicating statistical significance.

Patient and public involvement

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

RESULTS

The association of demographic and lifestyle factors with the risk of all-cause mortality is presented in Table 1. During the follow-up period (average 6.8 years), 1 365 men and 864 women died. The median levels of *hs*CRP were 0.77 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 educated (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 single marital status (aHR=1.23), $NCD_{history}$ (aHR=1.57), underweight (aHR=2.05) and current smoking (aHR=1.97).

Table 1. Baseline characteristics of participants by all-cause mortality

	All (n=122 081)	Death (n=2229)	All-cause mortality	
			Age,gender adjusted	adj HR[a]
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 year, %)	68.2	55.4	0.67 (0.60-0.75)	0.65 (0.56-0.75)
Blue-colored worker[b] (%)	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)
Diabete	6.5	17.1	1.81 (1.62-2.03)	1.77 (1.57-2.00)
Hyperlipidemia	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 & cardiovascular disease	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	<.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)

$NCD_{history}$: Non-communicable disease history

[a] Adjusted for age, gender, education, job, marital status, BMI and non-communicable disease history

[b] Compared to white-colored worker

The risk of all-cause mortality was inclined with a dose-dependent pattern as increased serum *hs*CRP level (P_{trend}<0.001, Supplement 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 levels was observed in both premenopausal (P_{trend}=0.020) and postmenopausal women (P_{trend}< 0.001), although the statistical significance in premenopausal women disappeared after sensitivity analysis (P_{trend}=0.150 for aHR_{2year}, Supplement 1). The integrated graph, based on the restricted cubic spline 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, Fig. 2 (a)).

The dose-response association between *hs*CRP level and the risk of all-cause mortality was not influenced by $NCD_{history}$ (Supplement 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_{2year}) but disappeared in women with $NCD_{history}$, particularly after sensitivity analysis with the exclusion of a 2-year follow-up time (P_{trend}=0.084 for aHR_{2year}). Based on the restricted cubic spline analyses, otherwise, the pattern of increase in the association was different depending on the $NCD_{history}$ (Fig. 2 (b)(c)). In the healthy subjects, the risk of all-cause mortality was 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 (Fig. 2 (b)). On the other hand, the slope of the association fluctuated as the *hs*CRP level increased in the 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 (Fig. 2 (c)).

The association of serum *hs*CRP with the risk of cancer-mortality was not influenced by $NCD_{history}$ (P_{trend}<0.001 regardless of $NCD_{history}$) (Table 2). Otherwise, 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 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 stratified by gender and $NCD_{history}$, respectively. After stratification by gender and $NCD_{history}$, otherwise, the association only appeared in individuals of both genders with $NCD_{history}$ (P_{trend}=0.015 and 0.035 in men and women with $NCD_{history}$, respectively); no association between *hs*CRP level and CVD mortality risk was found in either healthy men or women.

Table 2. The association between serum *hs*CRP level and cancer-mortality by gender and non-communicable disease history ($NCD_{history}$) at recruitment

	Cancer-mortality					Healthy subjects at recruitment					Subjects with $NCD_{history}$ at recruitment				
	E	MR	aHR	HR_{1year}	HR_{2year}	E	MR	aHR	HR_{1year}	HR_{2year}	E	MR	aHR	HR_{1year}	HR_{2year}
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			<.001	<.001	<.001			<.001	<.001	<.001			<.001	<.001	<.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			<.001	<.001	<.001			<.001	<.001	<.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			<.001	0.001	0.002			0.856	0.635	0.538

E: Number of death, MR: Mortality rate (10 000 person year), Ref: Reference
aHR: Adjusted for age, gender, education, job, marital status, BMI, non-communicable disease history, smoking, alcohol consumption and exercise
HR_{1year}: aHR after exclude subjects who died within 1 yr f/u time
HR_{2year}: aHR after exclude subjects who died within 2 yr f/u time

Table 3. The association between serum *hs*CRP level and cardiovascular disease mortality by gender and non-communicable disease history ($NCD_{history}$) at recruitment

	Cardiovascular disease mortality					Healthy subjects at recruitment					Subjects with $NCD_{history}$ at recruitment				
	E	MR	aHR	HR_{1year}	HR_{2year}	E	MR	aHR	HR_{1year}	HR_{2year}	E	MR	aHR	HR_{1year}	HR_{2year}
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

E: Number of death, MR: Mortality rate (10 000 person year), Ref: Reference
aHR: Adjusted for age, gender, education, job, marital status, BMI, non-communicable disease history, smoking, alcohol consumption and exercise
HR_{1year}: aHR after exclude subjects who died within 1 yr f/u time
HR_{2year}: aHR after exclude subjects who died within 2 yr f/u time

DISCUSSION

This study suggests that the risk of all-cause mortality was associated with elevated *hs*CRP levels with a dose-response manner in both gender among Asian who have reported low *hs*CRP levels compared to other races, and was not influenced by $NCD_{history}$. Otherwise, the association was influenced by gender and $NCD_{history}$ although a dose-response association of *hs*CRP with the risk of cancer- and CVD-mortality was also observed in this population. The level of *hs*CRP was not associated with the 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 $NCD_{history}$.

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 the risk of all-cause mortality in a dose-dependent manner, even though the level of *hs*CRP was lower than that 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 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 levels 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 and 0.68 mg/L for premenopausal and postmenopausal women in this study. The protective effect could be supported by the proposition that estrogen 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 rennin–angiotensin system inhibitors[35] and statins and thiazolidinedione[36], could influence the level of *hs*CRP. The association between *hs*CRP and the 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_{2year}). 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 the risk of all-cause mortality risk was significantly observed in only men with $NCD_{history}$ but not in women with $NCD_{history}$. The attenuated effect of $NCD_{history}$ on the association between *hs*CRP and the risk of cancer-mortality was not observed in men, consistent with results from several studies which reported the associations among healthy men[3] or cancer patients[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 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 the risk of CVD mortality was dominant in subjects with $NCD_{history}$ in this study.

This study has several strengths because of the large population-based prospective study; it makes possible 1) to adjust for confounders; 2) to examine sensitivity analysis after excluding death before 1 or 2 years from recruitment; 3) to assess an advanced analysis after stratification by gender and $NCD_{history}$; 4) to examine the association using various cut-off points of *hs*CRP considering low serum *hs*CRP levels in Asian populations; and 5) to evaluate the complex (i.e., nonlinear) hazard functions using restricted cubic splines on the association between continuous *hs*CRP levels and the risk of mortality. In particular, most previous studies excluded subjects with more than 10 mg/L *hs*CRP because of 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 to be more concerning for these subjects in the future. The *hs*CRP level of this study, in addition, was measured within 18 hours in a single institution to minimize measurement error/bias from institutional variation to avoid bias from measurement or long-term storage before analysis.

Despite of those strengths, it is also has several limitations. First, the use of a single measurement of *hs*CRP at baseline could reflect the inaccurate status of blood *hs*CRP levels in the study participants and increase the instability of *hs*CRP due to random fluctuations over time. Nevertheless, a report [40] on the long-term *hs*CRP variability suggested that the *hs*CRP variability within 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, angiotensin-converting enzyme inhibitors, fibrates, niacin, thiazolidinedione and estrogen/progestogen hormone, could influence the *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, which could not examine the influence of HRT on the association of *hs*CRP with the risk of hormone-related cancer or CVD mortality among women, we could not suggest the effect of female hormones on the association.

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), which was not influenced by the association was not observed in women with $NCD_{history}$. Otherwise, the association of *hs*CRP level with the risk of cancer- and CVD-mortality could be attenuated by gender or $NCD_{history}$.

Contributors

SAL, XS and DK: designed and conducted the research, SAL and SOK: analyzed the data and performed the statistical analyses; HP and JKL: managed data mining and collection; SAL: wrote the manuscript and had primary responsibility for the final content of the manuscript; and all authors: read and approved the final manuscript.

Funding None.

Competing interests None declared.

Patient consent for publication Not required.

Ethics approval The Institutional Review Board of the Seoul National University Hospital, Seoul, Korea, approved it for statistical analysis (IRB No. E-1503-103-657).

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement

No additional data available.

REFERENCES

1 Pepys MB, Hirschfield GM. C-reactive protein: a critical update. *The Journal of clinical investigation* 2003;**111**:1805-12.

2 Elias-Smale SE, Kardys I, Oudkerk M, *et al.* C-reactive protein is related to extent and progression of coronary and extra-coronary atherosclerosis; results from the Rotterdam study. *Atherosclerosis* 2007;**195**:e195-202.

3 Koenig W, Khuseyinova N, Baumert J, *et al.* Prospective study of high-sensitivity C-reactive protein as a determinant of mortality: results from the MONICA/KORA Augsburg Cohort Study, 1984-1998. *Clinical chemistry* 2008;**54**:335-42.

4 Ahmadi-Abhari S, Luben RN, Wareham NJ, *et al.* Seventeen year risk of all-cause and cause-specific mortality associated with C-reactive protein, fibrinogen and leukocyte count in men and women: the EPIC-Norfolk study. *European journal of epidemiology* 2013;**28**:541-50.

5 Kuoppamaki M, Salminen M, Vahlberg T, *et al.* High sensitive C-reactive protein (hsCRP), cardiovascular events and mortality in the aged: a prospective 9-year follow-up study. *Archives of gerontology and geriatrics* 2015;**60**:112-7.

6 Zuo H, Ueland PM, Ulvik A, *et al.* Plasma Biomarkers of Inflammation, the Kynurenine Pathway, and Risks of All-Cause, Cancer, and Cardiovascular Disease Mortality: The Hordaland Health Study. *American journal of epidemiology* 2016;**183**:249-58.

7 Nisa H, Hirata A, Kohno M, *et al.* High-Sensitivity C-Reactive Protein and Risks of All-Cause and Cause-Specific Mortality in a Japanese Population. *Asian Pacific journal of cancer prevention : APJCP* 2016;**17**:2643-8.

8 Li Y, Zhong X, Cheng G, *et al.* Hs-CRP and all-cause, cardiovascular, and cancer mortality risk: A meta-analysis. *Atherosclerosis* 2017;**259**:75-82.

9 Vasto S, Candore G, Balistreri CR, *et al.* Inflammatory networks in ageing, age-related diseases and longevity. *Mechanisms of ageing and development* 2007;**128**:83-91.

10 Kelley-Hedgepeth A, Lloyd-Jones DM, Colvin A, *et al.* Ethnic differences in C-reactive protein concentrations. *Clinical chemistry* 2008;**54**:1027-37.

11 Albert MA, Glynn RJ, Buring J, *et al.* C-reactive protein levels among women of various ethnic groups living in the United States (from the Women's Health Study). *The American journal of cardiology* 2004;**93**:1238-42.

12 Khera A, McGuire DK, Murphy SA, *et al.* Race and gender differences in C-reactive protein levels. *Journal of the American College of Cardiology* 2005;**46**:464-9.

13 Lakoski SG, Cushman M, Criqui M, *et al.* Gender and C-reactive protein: data from the Multiethnic Study of Atherosclerosis (MESA) cohort. *American heart journal* 2006;**152**:593-8.

14 Matthews KA, Sowers MF, Derby CA, *et al.* Ethnic differences in cardiovascular risk factor burden among middle-aged women: Study of Women's Health Across the Nation (SWAN). *American heart journal* 2005;**149**:1066-73.

15 Lee JH, Yeom H, Kim HC, *et al.* C-reactive Protein Concentration Is Associated With a Higher Risk of Mortality in a Rural Korean Population. *Journal of preventive medicine and public health = Yebang Uihakhoe chi* 2016;**49**:275-87.

16 Sung KC, Ryu S, Chang Y, *et al.* C-reactive protein and risk of cardiovascular and all-cause mortality in 268 803 East Asians. *European heart journal* 2014;**35**:1809-16.

17 Kengne AP, Batty GD, Hamer M, *et al.* Association of C-reactive protein with cardiovascular disease mortality according to diabetes status: pooled analyses of 25,979 participants from four U.K. prospective cohort studies. *Diabetes care* 2012;**35**:396-403.

18 Heikkila K, Ebrahim S, Lawlor DA. A systematic review of the association between circulating concentrations of C reactive protein and cancer. *Journal of epidemiology and community health* 2007;**61**:824-33.

19 Dahl M, Vestbo J, Lange P, *et al.* C-reactive protein as a predictor of prognosis in chronic obstructive pulmonary disease. *American journal of respiratory and critical care medicine* 2007;**175**:250-5.

20 Wang X, Bao W, Liu J, *et al.* Inflammatory markers and risk of type 2 diabetes: a systematic review and meta-analysis. *Diabetes care* 2013;**36**:166-75.

21 Ishii S, Cauley JA, Greendale GA, *et al.* C-reactive protein, bone strength, and nine-year fracture risk: data from the Study of Women's Health Across the Nation (SWAN). *Journal of bone and mineral research : the official journal of the American Society for Bone and Mineral Research* 2013;**28**:1688-98.

22 Kim Y, Han BG, Ko GESg. Cohort Profile: The Korean Genome and Epidemiology Study (KoGES) Consortium. *International journal of epidemiology* 2017;**46**:1350.

23 Shin S, Lee HW, Kim CE, *et al.* Egg Consumption and Risk of Metabolic Syndrome in Korean Adults: Results from the Health Examinees Study. *Nutrients* 2017;**9**.

24 Pan WH, Yeh WT. How to define obesity? Evidence-based multiple action points for public awareness, screening, and treatment: an extension of Asian-Pacific recommendations. *Asia Pacific journal of clinical nutrition* 2008;**17**:370-4.

25 National Cholesterol Education Program Expert Panel on Detection E, Treatment of High Blood Cholesterol in A. Third Report of the National Cholesterol Education Program (NCEP) Expert

Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. *Circulation* 2002;**106**:3143-421.

26 Heinzl H, Kaider A. Gaining more flexibility in Cox proportional hazards regression models with cubic spline functions. *Computer methods and programs in biomedicine* 1997;**54**:201-8.

27 MacGregor AJ, Gallimore JR, Spector TD*, et al.* Genetic effects on baseline values of C-reactive protein and serum amyloid a protein: a comparison of monozygotic and dizygotic twins. *Clinical chemistry* 2004;**50**:130-4.

28 Ledue TB, Rifai N. Preanalytic and analytic sources of variations in C-reactive protein measurement: implications for cardiovascular disease risk assessment. *Clinical chemistry* 2003;**49**:1258-71.

29 Emerging Risk Factors C, Kaptoge S, Di Angelantonio E*, et al.* C-reactive protein concentration and risk of coronary heart disease, stroke, and mortality: an individual participant meta-analysis. *Lancet* 2010;**375**:132-40.

30 Lee YJ, Lee JH, Shin YH*, et al.* Gender difference and determinants of C-reactive protein level in Korean adults. *Clinical chemistry and laboratory medicine* 2009;**47**:863-9.

31 Doran B, Zhu W, Muennig P. Gender differences in cardiovascular mortality by C-reactive protein level in the United States: evidence from the National Health and Nutrition Examination Survey III. *American heart journal* 2013;**166**:45-51.

32 Gaskins AJ, Wilchesky M, Mumford SL*, et al.* Endogenous reproductive hormones and C-reactive protein across the menstrual cycle: the BioCycle Study. *American journal of epidemiology* 2012;**175**:423-31.

33 Gilliver SC. Sex steroids as inflammatory regulators. *The Journal of steroid biochemistry and molecular biology* 2010;**120**:105-15.

34 Man SF, Connett JE, Anthonisen NR*, et al.* C-reactive protein and mortality in mild to moderate chronic obstructive pulmonary disease. *Thorax* 2006;**61**:849-53.

35 Di Napoli M, Papa F. Angiotensin-converting enzyme inhibitor use is associated with reduced plasma concentration of C-reactive protein in patients with first-ever ischemic stroke. *Stroke* 2003;**34**:2922-9.

36 Sidhu JS, Cowan D, Kaski JC. The effects of rosiglitazone, a peroxisome proliferator-activated receptor-gamma agonist, on markers of endothelial cell activation, C-reactive protein, and fibrinogen levels in non-diabetic coronary artery disease patients. *Journal of the American College of Cardiology* 2003;**42**:1757-63.

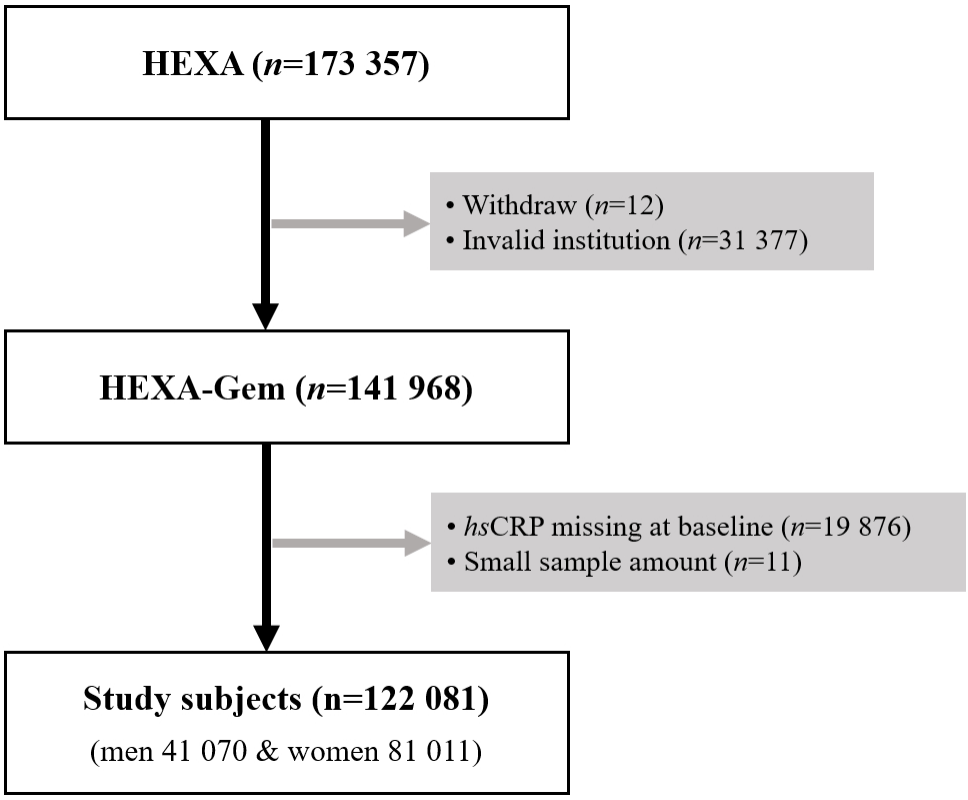
37 Heikkila K, Ebrahim S, Rumley A*, et al.* Associations of circulating C-reactive protein and interleukin-6 with survival in women with and without cancer: findings from the British Women's Heart and Health Study. *Cancer epidemiology, biomarkers & prevention : a publication of the*

American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology 2007;**16**:1155-9.

38 Marsik C, Kazemi-Shirazi L, Schickbauer T*, et al.* C-reactive protein and all-cause mortality in a large hospital-based cohort. *Clinical chemistry* 2008;**54**:343-9.

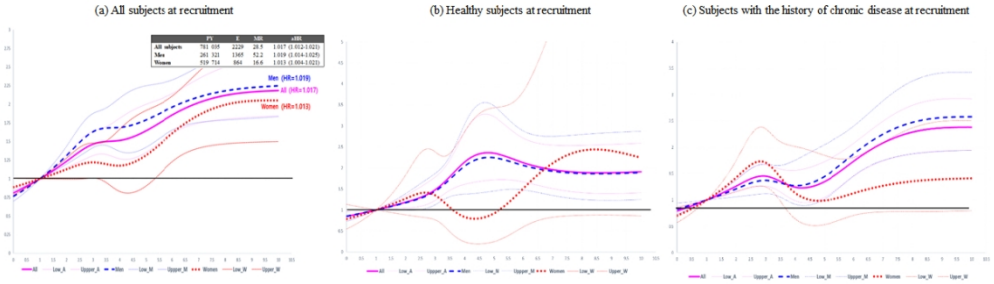
39 Proctor MJ, McMillan DC, Horgan PG*, et al.* Systemic inflammation predicts all-cause mortality: a glasgow inflammation outcome study. *PloS one* 2015;**10**:e0116206.

40 Chen TH, Gona P, Sutherland PA*, et al.* Long-term C-reactive protein variability and prediction of metabolic risk. *The American journal of medicine* 2009;**122**:53-61.



Flow diagram of analytical sample in current study using Health Examinees cohort
HEXA: Health Examinees, hsCRP: High sensitivity C-reactive protein

169x137mm (150 x 150 DPI)



A dose-response association between serum hsCRP level and risk of all-cause mortality by subject.
PY: Person-year, E: Number of death, MR: Mortality rate (10 000 person year)
aHR: Adjusted for age, gender, education, job, marital status, BMI, non-communicable disease history, smoking, alcohol consumption and exercise
Low_A and Upper_A: 95%CI for all subjects
Low_M and Upper_M: 95%CI for men
Low_W and Upper_W: 95%CI for women

330x97mm (96 x 96 DPI)

Supplement 1. The association of serum *hs*CRP level with the risk of all-cause mortality

	PY	E	MR	aHR	HR_{1year}	HR_{2year}
All subjects						
Continuous	781 035	2229	28.5	1.017 (1.012-1.021)	1.015 (1.010-1.020)	1.014 (1.009-1.019)
≤1.00	539 271	1153	21.4	Reference	Reference	Reference
1.01-1.50	90 911	308	33.9	1.26 (1.10-1.45)	1.27 (1.10-1.45)	1.21 (1.04-1.40)
1.51-2.00	44 615	163	36.5	1.28 (1.08-1.53)	1.28 (1.07-1.53)	1.26 (1.04-1.52)
2.01-2.50	25 139	117	46.5	1.53 (1.25-1.89)	1.51 (1.22-1.87)	1.49 (1.19-1.87)
2.51-3.00	16 996	72	42.4	1.39 (1.08-1.80)	1.31 (1.00-1.72)	1.23 (0.92-1.65)
3.01-4.00	19 667	103	52.4	1.61 (1.29-2.01)	1.62 (1.29-2.03)	1.64 (1.30-2.08)
4.01-6.00	17 933	102	56.9	1.84 (1.48-2.28)	1.77 (1.41-2.21)	1.70 (1.34-2.16)
6.01-10.00	13 019	88	67.6	2.02 (1.59-2.56)	1.96 (1.54-2.50)	1.93 (1.49-2.51)
>10.0	13 484	123	91.2	2.59 (2.12-3.16)	2.41 (1.95-2.97)	2.26 (1.80-2.84)
P-trend				<.001	<.001	<.001
Men						
Continuous	261 321	1365	52.2	1.019 (1.014-1.025)	1.017 (1.011-1.023)	1.017 (1.010-1.023)
≤1.00	163 068	638	39.1	Reference	Reference	Reference
1.01-1.50	36 094	190	52.6	1.27 (1.07-1.51)	1.28 (1.07-1.53)	1.22 (1.01-1.47)
1.51-2.00	17 946	103	57.4	1.34 (1.07-1.67)	1.34 (1.07-1.68)	1.35 (1.06-1.72)
2.01-2.50	10 059	77	76.5	1.56 (1.20-2.03)	1.53 (1.16-2.00)	1.47 (1.10-1.96)
2.51-3.00	6959	54	77.6	1.71 (1.27-2.29)	1.57 (1.15-2.15)	1.46 (1.04-2.05)
3.01-4.00	8177	77	94.2	1.88 (1.45-2.43)	1.94 (1.50-2.52)	1.92 (1.46-2.54)
4.01-6.00	7425	75	101.0	2.05 (1.59-2.63)	1.95 (1.49-2.53)	1.91 (1.44-2.52)
6.01-10.00	5456	59	108.1	2.03 (1.52-2.73)	1.96 (1.44-2.66)	1.85 (1.33-2.58)
>10.0	6137	92	149.9	2.84 (2.25-3.58)	2.66 (2.08-3.39)	2.58 (1.99-3.35)
P-trend				<.001	<.001	<.001
Women						
Continuous	519 714	864	16.6	1.013 (1.004-1.021)	1.011(1.002-1.021)	1.010 (0.999-1.021)
≤1.00	376 203	515	13.7	Reference	Reference	Reference
1.01-1.50	54 817	118	21.5	1.28 (1.03-1.59)	1.27 (1.02-1.58)	1.23 (0.97-1.56)
1.51-2.00	26 669	60	22.5	1.23 (0.92-1.64)	1.21 (0.90-1.63)	1.14 (0.83-1.56)
2.01-2.50	15 080	40	26.5	1.52 (1.09-2.14)	1.52 (1.08-2.15)	1.56 (1.09-2.24)
2.51-3.00	10 037	18	17.9	0.84 (0.49-1.44)	0.87 (0.51-1.48)	0.83 (0.46-1.47)
3.01-4.00	11 490	26	22.6	1.16 (0.75-1.81)	1.09 (0.68-1.72)	1.21 (0.76-1.93)
4.01-6.00	10 508	27	25.7	1.48 (0.99-2.22)	1.47 (0.97-2.22)	1.36 (0.86-2.14)
6.01-10.00	7563	29	38.3	2.00 (1.34-2.98)	1.98 (1.32-2.98)	2.10 (1.39-3.19)
>10.0	7347	31	42.2	2.02 (1.36-3.02)	1.84 (1.21-2.81)	1.51 (0.93-2.47)
P-trend				<.001	<.001	0.001
Premenopause						
≤1.00	141 286	96	6.8			
1.01-2.00	20 500	20	9.8	1.52 (0.92-2.52)	1.49 (0.89-2.50)	1.57 (0.90-2.73)
2.01-3.00	5835	6	10.3	1.76 (0.77-4.06)	1.83 (0.79-4.22)	1.42 (0.52-3.93)
3.01-10.0	6886	6	8.7	1.51 (0.66-3.50)	1.31 (0.53-3.25)	1.21 (0.44-3.36)
>10.0	1759	4	22.7	2.57 (0.81-8.14)	2.63 (0.83-8.37)	2.09 (0.51-8.58)
P-trend				0.020	0.036	0.150
Postmenopause						
≤1.00	192 164	366	19.0			
1.01-2.00	52 897	145	27.4	1.26 (1.03-1.55)	1.25 (1.02-1.54)	1.18 (0.95-1.48)
2.01-3.00	16 943	44	26.0	1.11 (0.80-1.56)	1.12 (0.80-1.57)	1.19 (0.83-1.68)
3.01-10.0	19 687	67	34.0	1.49 (1.13-1.97)	1.47 (1.10-1.95)	1.52 (1.13-2.05)
>10.0	4828	27	55.9	2.09 (1.37-3.21)	1.88 (1.19-2.96)	1.56 (0.92-2.63)
P-trend				<0.001	0.001	0.003

PY: Person-year, E: Number of death, MR: Mortality rate (10,000 person year)

2

aHR: Adjusted for age, gender, education, job, marital status, BMI, non-communicable disease history, smoking, alcohol consumption and exercise

HR_{1year}: aHR after exclude subjects who died within 1 yr f/u time

HR_{2year}: aHR after exclude subjects who died within 2 yr f/u time

Supplement 2. The association between serum *hs*CRP level and all-cause mortality by gender and non-communicable disease history ($NCD_{history}$) at recruitment

	Healthy subjects at recruitment					Subjects with $NCD_{history}$ at recruitment				
	E	MR	aHR	HR_{1year}	HR_{2year}	E	MR	aHR	HR_{1year}	HR_{2year}
All										
≤ 1.00	517	15.1	Ref	Ref	Ref	636	32.3	Ref	Ref	Ref
1.01-2.00	145	22.9	1.20	1.19	1.16	326	45.1	1.20	1.19	1.16
2.01-3.00	53	29.3	1.38	1.37	1.32	136	56.6	1.51	1.46	1.41
3.01-10.0	102	46.8	2.22	2.15	2.15	191	66.3	1.62	1.60	1.58
>10.0	40	61.3	2.38	2.23	2.27	83	118.9	2.74	2.54	2.29
P-trend			<.001	<.001	<.001			<.001	<.001	<.001
Men										
≤ 1.00	270	29.5	Ref	Ref	Ref	368	51.4	Ref	Ref	Ref
1.01-2.00	89	35.8	1.11	1.11	1.13	204	70.0	1.40	1.41	1.33
2.01-3.00	33	46.3	1.22	1.17	1.15	98	99.0	1.82	1.73	1.61
3.01-10.0	70	76.8	2.14	2.08	2.03	141	118.1	1.92	1.90	1.83
>10.0	31	110.0	2.60	2.49	2.73	61	183.1	3.05	2.83	2.58
P-trend			<.001	<.001	<.001			<.001	<.001	<.001
Women										
≤ 1.00	247	9.8	Ref	Ref	Ref	268	21.4	Ref	Ref	Ref
1.01-2.00	56	14.6	1.35	1.32	1.20	122	28.3	1.19	1.20	1.19
2.01-3.00	20	18.2	1.61	1.66	1.60	38	26.9	1.06	1.06	1.11
3.01-10.0	32	25.2	2.31	2.23	2.37	50	29.7	1.16	1.14	1.17
>10.0	9	24.3	1.69	1.49	1.12	22	60.3	2.15	1.99	1.68
P-trend			<.001	<.001	0.001			0.018	0.043	0.084

E: Number of death, MR: Mortality rate (10 000 person year)

aHR: Adjusted for age, gender, education, job, marital status, BMI, non-communicable disease history, smoking, alcohol consumption and exercise

HR_{1year}: aHR after exclude subjects who died within 1 yr f/u time

HR_{2year}: aHR after exclude subjects who died within 2 yr f/u time

STROBE 2007 (v4) checklist of items to be included in reports of observational studies in epidemiology*

Checklist for cohort, case-control, and cross-sectional studies (combined)

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	1-2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3
Objectives	3	State specific objectives, including any pre-specified hypotheses	3
Methods			
Study design	4	Present key elements of study design early in the paper	4
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4-5
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	4
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	-
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	5
Bias	9	Describe any efforts to address potential sources of bias	6
Study size	10	Explain how the study size was arrived at	4
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	5-6
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	5-6
		(*b*) Describe any methods used to examine subgroups and interactions	5-6
		(*c*) Explain how missing data were addressed	4
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed	4

		Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	6
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	4
		(b) Give reasons for non-participation at each stage	4
		(c) Consider use of a flow diagram	4
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	6-7
		(b) Indicate number of participants with missing data for each variable of interest	4
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	6
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	6-10
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	6-10
		(*b*) Report category boundaries when continuous variables were categorized	5
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	-
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	8
Discussion			
Key results	18	Summarise key results with reference to study objectives	11
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	12-13
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	11-12
Generalisability	21	Discuss the generalisability (external validity) of the study results	11-12
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	13

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.
Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

The association of serum high sensitivity C-reactive protein with the risk of mortality in Asian: the Health Examinees cohort

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2021-052630.R1
Article Type:	Original research
Date Submitted by the Author:	27-Oct-2021
Complete List of Authors:	Lee, Sang-Ah; Kangwon National University School of Medicine, Preventive Medicine; Vanderbilt University Medical Center Kwon, Sung Ok; Kangwon National University School of Medicine, Preventive Medicine Park, Hyerim; Kangwon National University School of Medicine, Preventive Medicine Shu, Xiao-Ou ; Vanderbilt University Medical Center Lee, Jong-Koo; JW LEE Center for Global Medicine Kang, Daehee; Seoul National University College of Medicine, Preventive Medicine
Primary Subject Heading:	Epidemiology
Secondary Subject Heading:	Epidemiology, Cardiovascular medicine
Keywords:	PREVENTIVE MEDICINE, EPIDEMIOLOGY, Cardiac Epidemiology < CARDIOLOGY

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

The association of serum high sensitivity C-reactive protein with the risk of mortality in Asian: the Health Examinees cohort

Sang-Ah Lee[1,2 *], Sung Ok Kwon[1], Hyerim Park[1], Xiao-Ou Shu[2], Jong-Koo Lee[3], Daehee Kang[4]

[1]Department of Preventive Medicine, School of Medicine, Kangwon National University, Chuncheon, Republic of Korea.

[2]Division of Epidemiology, Vanderbilt Epidemiology Center, Vanderbilt University Medical Center, Nashville, TN, USA.

[3]JW Lee Center for Global Medicine, College of Medicine, Seoul National University, Seoul, Republic of Korea.

[4]Department of Preventive Medicine, College of Medicine, Seoul National University, Seoul, Republic of Korea.

ABSTRACT

Objectives This study aimed to examine the association of *hs*CRP with mortality risk and the attenuated effect of non-communicable disease history ($NCD_{history}$) on the association.

Design Prospective cohort study.

Setting the Health Examinees (HEXA) cohort.

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

Outcome measures The data and cause of death occurring until December 31, 2015, were confirmed by death statistics from the National Statistical Office. We conducted the advanced analysis after stratification by $NCD_{history}$ and the 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 the risk of all-cause mortality was observed with strong linearity in both genders, which was not influenced by $NCD_{history}$. Otherwise, the association of serum *hs*CRP with cancer-mortality risk was not observed in women with $NCD_{history}$, but the association with the risk of cardiovascular disease (CVD) mortality was predominantly observed in men with $NCD_{history}$.

Conclusions This study suggested the dose-response association of *hs*CRP with mortality risk, including cancer and CVD mortality, in Korean 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 the large population-based prospective study.
- We examined the effect of very high *hs*CRP concentration on mortality risk.
- The *hs*CRP level of present study was measured within 18 hours in a single institution to minimize error/bias.

· Due to random fluctuations of *hs*CRP, using the single measurement of *hs*CRP at baseline could reflect the inaccurate status of blood *hs*CRP levels in the study participants and increase the instability of *hs*CRP.

· This study lacked information on medication use at recruitment and during the follow-up period, and information on hormone-replacement therapy (HRT) among women.

*Correspondence to: Sang-Ah Lee, Ph.D.
Department of Preventive Medicine, School of Medicine, Kangwon National University,
Chuncheon, Gangwon, Republic of Korea.
Tel: +82 33 250 8871
E-mail: sangahlee@kangwon.ac.kr

INTRODUCTION

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

Serum *hs*CRP represents a low-grade inflammation state that is generally involved in the process of aging[9]. Several large cohorts, including Study of Women's Health Across the Nation (SWAN)[10], the Women's Health Study[11] and the Dallas Heart Study[12], reported significant differences in *hs*CRP levels 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 United States (from the Women's Health Study) on the association between *hs*CRP and the mortality risk; the association was observed in only men supported by the results from two cohort studies[15, 16] reported in Korea. On the other hand, the 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 the 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 dataset 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 the 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 (Fig. 1). All study participants provided informed consent prior to entering the study. The Institutional Review Board of the Seoul National University Hospital, Seoul, Korea, approved it for statistical analysis (IRB No. E-1503-103-657).

Laboratory measurements

After at least 10 hours of overnight fasting, blood samples were obtained in the morning. Bio-specimens included fasting blood samples that were collected in a serum separator tube and two ethylenediaminetetraacetic acid (EDTA) tubes. All samples were then transported to the National Biobank of Korea and stored for future research purposes within 18 hours. *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 December 31, 2015. We added the mortality data from Statistics Korea to our dataset 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 (ICD-10). 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 standardized methods. Body mass index (BMI) was calculated, and all participants were defined into four classes based on the World Health Organization 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 (NCEP-ATP III)[25], modified for the Asian guideline for waist circumference (WC ≥90 and ≥80 cm for men and women, respectively). Nonsmokers were defined as those who had smoked less than 400 cigarettes over the course of their lifetime. Participants who had smoked were categorized into two groups: noncurrent (never/former) and current smoker. Noncurrent 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 the $NCD_{history}$ on the association between serum *hs*CRP and the risk of mortality, we performed advanced analysis after stratification by $NCD_{history}$. We considered six main non-communicable diseases (hypertension, diabetes, hyperlipidemia, cancer, cardiovascular and cerebrovascular diseases, and respiratory disease) to classify healthy subjects vs. 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 the $NCD_{history}$, the *hs*CRP levels were categorized as ≤1.00, 1.01-2.00, 2.01-3.00, 3.01-10.0, and >10.0 mg/L because of the reduced sample size in each subgroup. The concentrations of *hs*CRP were log-transformed for analyses because of the skewed distribution.

We calculated a follow-up time for each subject starting from the date of interview until the date of death or December 31, 2015, whichever came first. Using age as the time scale, subjects enter the risk set at the age at which they completed the baseline questionnaire and exit at their event/censoring age. The associations of

*hs*CRP and all-cause mortality, as well as cancer and CVD mortality, were analyzed by Cox proportional hazard models (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 tests 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 cardiovascular disease 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_{2year}) since recruitment. Based on the Cox proportional hazard models, we made Kaplan-Meier curves and log-rank analysis. We employed restricted cubic splines (RCSs) to evaluate the possibility of complex (i.e., nonlinear) 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 nonlinear associations between knots using a cubic function, and presented the integrated graph smoothly. All statistical analyses were performed using SAS version 9.3 (SAS Institute Inc., Cary, NC, USA) 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, conducting, reporting, and dissemination plans of the present study.

RESULTS

The association of demographic and lifestyle factors with the risk of all-cause mortality is presented in Table 1. During the follow-up period (average 6.8 years), 1 365 men and 864 women died. The median levels of *hs*CRP were 0.77 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 educated (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 single marital status (aHR=1.23), $NCD_{history}$ (aHR=1.57), underweight (aHR=2.05) and current smoking (aHR=1.97).

Table 1. Baseline characteristics of participants by all-cause mortality

	All (*n*=122 081)	Death (*n*=2229)	All-cause mortality	
			Age,gender adjusted	adj HR[a]
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 year, %)	68.2	55.4	0.67 (0.60-0.75)	0.65 (0.56-0.75)
Blue-colored worker[b] (%)	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)
Diabete	6.5	17.1	1.81 (1.62-2.03)	1.77 (1.57-2.00)
Hyperlipidemia	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 & cardiovascular disease	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	<.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)

$NCD_{history}$: Non-communicable disease history

[a] Adjusted for age, gender, education, job, marital status, BMI and non-communicable disease history

[b] Compared to white-colored worker

The risk of all-cause mortality was inclined with a dose-dependent pattern as increased serum *hs*CRP level (P_{trend}<0.001, Supplement 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 levels was observed in both premenopausal (P_{trend}=0.020) and postmenopausal women (P_{trend}< 0.001), although the statistical significance in premenopausal women disappeared after sensitivity analysis (P_{trend}=0.150 for aHR_{2year}, Supplement 1). The integrated graph, based on the restricted cubic spline 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, Fig. 2).

The dose-response association between *hs*CRP level and the risk of all-cause mortality was not influenced by $NCD_{history}$ (Supplement 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_{2year}) but disappeared in women with $NCD_{history}$, particularly after sensitivity analysis with the exclusion of a 2-year follow-up time (P_{trend}=0.084 for aHR_{2year}). Based on the restricted cubic spline analyses, otherwise, the pattern of increase in the association was different depending on the $NCD_{history}$ (Fig. 3,4). In the healthy subjects, the risk of all-cause mortality was 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 (Fig. 3). On the other hand, the slope of the association fluctuated as the *hs*CRP level increased in the 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 (Fig. 4).

The association of serum *hs*CRP with the risk of cancer-mortality was not influenced by $NCD_{history}$ (P_{trend}<0.001 regardless of $NCD_{history}$) (Table 2 and Fig. 5-9). Otherwise, 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 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 stratified by gender and $NCD_{history}$, respectively (Fig. 10-14). After stratification by gender and $NCD_{history}$, otherwise, the association only appeared in individuals of both genders with $NCD_{history}$ (P_{trend}=0.015 and 0.035 in men and women with $NCD_{history}$, respectively); no association between *hs*CRP level and CVD mortality risk was found in either healthy men or women.

Table 2. The association between serum *hs*CRP level and cancer-mortality by gender and non-communicable disease history ($NCD_{history}$) at recruitment

	Cancer-mortality					Healthy subjects at recruitment					Subjects with $NCD_{history}$ at recruitment				
	E	MR	aHR	HR_{1year}	HR_{2year}	E	MR	aHR	HR_{1year}	HR_{2year}	E	MR	aHR	HR_{1year}	HR_{2year}
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			<.001	<.001	<.001			<.001	<.001	<.001			<.001	<.001	<.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			<.001	<.001	<.001			<.001	<.001	<.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			<.001	0.001	0.002			0.856	0.635	0.538

E: Number of death, MR: Mortality rate (10 000 person year), Ref: Reference
aHR: Adjusted for age, gender, education, job, marital status, BMI, non-communicable disease history, smoking, alcohol consumption and exercise
HR_{1year}: aHR after exclude subjects who died within 1 yr f/u time
HR_{2year}: aHR after exclude subjects who died within 2 yr f/u time

Table 3. The association between serum *hs*CRP level and cardiovascular disease mortality by gender and non-communicable disease history ($NCD_{history}$) at recruitment

	Cardiovascular disease mortality					Healthy subjects at recruitment					Subjects with $NCD_{history}$ at recruitment				
	E	MR	aHR	HR_{1year}	HR_{2year}	E	MR	aHR	HR_{1year}	HR_{2year}	E	MR	aHR	HR_{1year}	HR_{2year}
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

E: Number of death, MR: Mortality rate (10 000 person year), Ref: Reference
aHR: Adjusted for age, gender, education, job, marital status, BMI, non-communicable disease history, smoking, alcohol consumption and exercise
HR_{1year}: aHR after exclude subjects who died within 1 yr f/u time
HR_{2year}: aHR after exclude subjects who died within 2 yr f/u time

DISCUSSION

This study suggests that the risk of all-cause mortality was associated with elevated *hs*CRP levels with a dose-response manner in both gender among Asian who have reported low *hs*CRP levels compared to other races, and was not influenced by $NCD_{history}$. Otherwise, the association was influenced by gender and $NCD_{history}$ although a dose-response association of *hs*CRP with the risk of cancer- and CVD-mortality was also observed in this population. The level of *hs*CRP was not associated with the 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 $NCD_{history}$.

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 the risk of all-cause mortality in a dose-dependent manner, even though the level of *hs*CRP was lower than that 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 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 levels 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 and 0.68 mg/L for premenopausal and postmenopausal women in this study. The protective effect could be supported by the proposition that estrogen 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 rennin–angiotensin system inhibitors[35] and statins and thiazolidinedione[36], could influence the level of *hs*CRP. The association between *hs*CRP and the 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_{2year}). 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 the risk of all-cause mortality risk was significantly observed in only men with $NCD_{history}$ but not in women with $NCD_{history}$. The attenuated effect of $NCD_{history}$ on the association between *hs*CRP and the risk of cancer-mortality was not observed in men, consistent with results from several studies which reported the associations among healthy men[3] or cancer patients[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 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 the 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 the prevention of cardiovascular disease, 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 because of the large population-based prospective study; it makes possible 1) to adjust for confounders; 2) to examine sensitivity analysis after excluding death before 1 or 2 years from recruitment; 3) to assess an advanced analysis after stratification by gender and $NCD_{history}$; 4) to examine the association using various cut-off points of *hs*CRP considering low serum *hs*CRP levels in Asian populations; and 5) to evaluate the complex (i.e., nonlinear) hazard functions using restricted cubic splines on the association between continuous *hs*CRP levels and the risk of mortality. In particular, most previous studies excluded subjects with more than 10 mg/L *hs*CRP because of 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 to be more concerning for these subjects in the future. The *hs*CRP level of this study, in addition, was measured within 18 hours in a single institution to minimize measurement error/bias from institutional variation to avoid bias from measurement or long-term storage before analysis.

Despite of those strengths, it is also several limitations. First, the use of a single measurement of *hs*CRP at baseline could reflect the inaccurate status of blood *hs*CRP levels in the study participants and increase the instability of *hs*CRP due to random fluctuations over time. Nevertheless, a report [40] on the long-term *hs*CRP variability suggested that the *hs*CRP variability within 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, angiotensin-converting enzyme inhibitors, fibrates, niacin, thiazolidinedione and estrogen/progestogen hormone, could influence the *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, which could not examine the influence of HRT on the association of *hs*CRP with the 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 with obesity in our population was consistent to Wei's report in Asian[41]. On the other hand, the inverse association of alcohol drinking with all-cause mortality couldn't interpret directly because our report wasn't separated the distinguish between mild drinkers and abuse alcohol drinker, which requires additional research for our population 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), which was not influenced by the association was not observed in women with $NCD_{history}$. Otherwise, the association of *hs*CRP level with the risk of cancer- and CVD-mortality could be attenuated by gender or $NCD_{history}$.

Figure 1 Flow diagram of analytical sample in current study using Health Examinees cohort.

Figure 2 A dose-response association between serum *hs*CRP level and risk of all-cause mortality in all subjects at recruitment.

Figure 3 A dose-response association between serum *hs*CRP level and risk of all-cause mortality in healthy subjects at recruitment.

Figure 4 A dose-response association between serum *hs*CRP level and risk of all-cause mortality in subjects with non-communicable disease history ($NCD_{history}$) at recruitment.

Figure 5 Kaplan-Meier crude survival curves for cancer-mortality according to serum *hs*CRP level in all subjects at recruitment.

Figure 6 Kaplan-Meier crude survival curves for cancer-mortality according to serum *hs*CRP level in men at recruitment.

Figure 7 Kaplan-Meier crude survival curves for cancer-mortality according to serum *hs*CRP level in women at recruitment.

Figure 8 Kaplan-Meier crude survival curves for cancer-mortality according to serum *hs*CRP level in healthy subjects at recruitment.

Figure 9 Kaplan-Meier crude survival curves for cancer-mortality according to serum *hs*CRP level in subjects with non-communicable disease history ($NCD_{history}$) at recruitment.

Figure 10 Kaplan-Meier crude survival curves for cardiovascular disease mortality according to serum *hs*CRP level in all subjects at recruitment.

Figure 11 Kaplan-Meier crude survival curves for cardiovascular disease mortality according to serum *hs*CRP level in men at recruitment.

Figure 12 Kaplan-Meier crude survival curves for cardiovascular disease mortality according to serum *hs*CRP level in women at recruitment.

Figure 13 Kaplan-Meier crude survival curves for cardiovascular disease mortality according to serum *hs*CRP level in healthy subjects at recruitment.

Figure 14 Kaplan-Meier crude survival curves for cardiovascular disease mortality according to serum *hs*CRP level in subjects with non-communicable disease history ($NCD_{history}$) at recruitment.

Contributors

SAL, XS and DK: designed and conducted the research, SAL and SOK: analyzed the data and performed the statistical analyses; HP and JKL: managed data mining and collection; SAL: wrote the manuscript and had primary responsibility for the final content of the manuscript; and all authors: read and approved the final manuscript.

Funding None.

Competing interests None declared.

Patient consent for publication Not required.

Ethics approval The Institutional Review Board of the Seoul National University Hospital, Seoul, Korea, approved it for statistical analysis (IRB No. E-1503-103-657).

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement

No additional data available.

REFERENCES

1 Pepys MB, Hirschfield GM. C-reactive protein: a critical update. *The Journal of clinical investigation* 2003;**111**:1805-12.

2 Elias-Smale SE, Kardys I, Oudkerk M, *et al.* C-reactive protein is related to extent and progression of coronary and extra-coronary atherosclerosis; results from the Rotterdam study. *Atherosclerosis* 2007;**195**:e195-202.

3 Koenig W, Khuseyinova N, Baumert J, *et al.* Prospective study of high-sensitivity C-reactive protein as a determinant of mortality: results from the MONICA/KORA Augsburg Cohort Study, 1984-1998. *Clinical chemistry* 2008;**54**:335-42.

4 Ahmadi-Abhari S, Luben RN, Wareham NJ, *et al.* Seventeen year risk of all-cause and cause-specific mortality associated with C-reactive protein, fibrinogen and leukocyte count in men and women: the EPIC-Norfolk study. *European journal of epidemiology* 2013;**28**:541-50.

5 Kuoppamaki M, Salminen M, Vahlberg T, *et al.* High sensitive C-reactive protein (hsCRP), cardiovascular events and mortality in the aged: a prospective 9-year follow-up study. *Archives of gerontology and geriatrics* 2015;**60**:112-7.

6 Zuo H, Ueland PM, Ulvik A, *et al.* Plasma Biomarkers of Inflammation, the Kynurenine Pathway, and Risks of All-Cause, Cancer, and Cardiovascular Disease Mortality: The Hordaland Health Study. *American journal of epidemiology* 2016;**183**:249-58.

7 Nisa H, Hirata A, Kohno M, *et al.* High-Sensitivity C-Reactive Protein and Risks of All-Cause and Cause-Specific Mortality in a Japanese Population. *Asian Pacific journal of cancer prevention : APJCP* 2016;**17**:2643-8.

8 Li Y, Zhong X, Cheng G, *et al.* Hs-CRP and all-cause, cardiovascular, and cancer mortality risk: A meta-analysis. *Atherosclerosis* 2017;**259**:75-82.

9 Vasto S, Candore G, Balistreri CR, *et al.* Inflammatory networks in ageing, age-related diseases and longevity. *Mechanisms of ageing and development* 2007;**128**:83-91.

10 Kelley-Hedgepeth A, Lloyd-Jones DM, Colvin A, *et al.* Ethnic differences in C-reactive protein concentrations. *Clinical chemistry* 2008;**54**:1027-37.

11 Albert MA, Glynn RJ, Buring J, *et al.* C-reactive protein levels among women of various ethnic groups living in the United States (from the Women's Health Study). *The American journal of cardiology* 2004;**93**:1238-42.

12 Khera A, McGuire DK, Murphy SA, *et al.* Race and gender differences in C-reactive protein levels. *Journal of the American College of Cardiology* 2005;**46**:464-9.

13 Lakoski SG, Cushman M, Criqui M, *et al.* Gender and C-reactive protein: data from the Multiethnic Study of Atherosclerosis (MESA) cohort. *American heart journal* 2006;**152**:593-8.

14 Matthews KA, Sowers MF, Derby CA, *et al.* Ethnic differences in cardiovascular risk factor burden among middle-aged women: Study of Women's Health Across the Nation (SWAN). *American heart journal* 2005;**149**:1066-73.

15 Lee JH, Yeom H, Kim HC, *et al.* C-reactive Protein Concentration Is Associated With a Higher Risk of Mortality in a Rural Korean Population. *Journal of preventive medicine and public health = Yebang Uihakhoe chi* 2016;**49**:275-87.

16 Sung KC, Ryu S, Chang Y, *et al.* C-reactive protein and risk of cardiovascular and all-cause mortality in 268 803 East Asians. *European heart journal* 2014;**35**:1809-16.

17 Kengne AP, Batty GD, Hamer M, *et al.* Association of C-reactive protein with cardiovascular disease mortality according to diabetes status: pooled analyses of 25,979 participants from four U.K. prospective cohort studies. *Diabetes care* 2012;**35**:396-403.

18 Heikkila K, Ebrahim S, Lawlor DA. A systematic review of the association between circulating concentrations of C reactive protein and cancer. *Journal of epidemiology and community health* 2007;**61**:824-33.

19 Dahl M, Vestbo J, Lange P, *et al.* C-reactive protein as a predictor of prognosis in chronic obstructive pulmonary disease. *American journal of respiratory and critical care medicine* 2007;**175**:250-5.

20 Wang X, Bao W, Liu J, *et al.* Inflammatory markers and risk of type 2 diabetes: a systematic review and meta-analysis. *Diabetes care* 2013;**36**:166-75.

21 Ishii S, Cauley JA, Greendale GA, *et al.* C-reactive protein, bone strength, and nine-year fracture risk: data from the Study of Women's Health Across the Nation (SWAN). *Journal of bone and mineral research : the official journal of the American Society for Bone and Mineral Research* 2013;**28**:1688-98.

22 Kim Y, Han BG, Ko GESg. Cohort Profile: The Korean Genome and Epidemiology Study (KoGES) Consortium. *International journal of epidemiology* 2017;**46**:1350.

23 Shin S, Lee HW, Kim CE, *et al.* Egg Consumption and Risk of Metabolic Syndrome in Korean Adults: Results from the Health Examinees Study. *Nutrients* 2017;**9**.

24 Pan WH, Yeh WT. How to define obesity? Evidence-based multiple action points for public awareness, screening, and treatment: an extension of Asian-Pacific recommendations. *Asia Pacific journal of clinical nutrition* 2008;**17**:370-4.

25 National Cholesterol Education Program Expert Panel on Detection E, Treatment of High Blood Cholesterol in A. Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. *Circulation* 2002;**106**:3143-421.

26 Heinzl H, Kaider A. Gaining more flexibility in Cox proportional hazards regression models with cubic spline functions. *Computer methods and programs in biomedicine* 1997;**54**:201-8.

27 MacGregor AJ, Gallimore JR, Spector TD*, et al.* Genetic effects on baseline values of C-reactive protein and serum amyloid a protein: a comparison of monozygotic and dizygotic twins. *Clinical chemistry* 2004;**50**:130-4.

28 Ledue TB, Rifai N. Preanalytic and analytic sources of variations in C-reactive protein measurement: implications for cardiovascular disease risk assessment. *Clinical chemistry* 2003;**49**:1258-71.

29 Emerging Risk Factors C, Kaptoge S, Di Angelantonio E*, et al.* C-reactive protein concentration and risk of coronary heart disease, stroke, and mortality: an individual participant meta-analysis. *Lancet* 2010;**375**:132-40.

30 Lee YJ, Lee JH, Shin YH*, et al.* Gender difference and determinants of C-reactive protein level in Korean adults. *Clinical chemistry and laboratory medicine* 2009;**47**:863-9.

31 Doran B, Zhu W, Muennig P. Gender differences in cardiovascular mortality by C-reactive protein level in the United States: evidence from the National Health and Nutrition Examination Survey III. *American heart journal* 2013;**166**:45-51.

32 Gaskins AJ, Wilchesky M, Mumford SL*, et al.* Endogenous reproductive hormones and C-reactive protein across the menstrual cycle: the BioCycle Study. *American journal of epidemiology* 2012;**175**:423-31.

33 Gilliver SC. Sex steroids as inflammatory regulators. *The Journal of steroid biochemistry and molecular biology* 2010;**120**:105-15.

34 Man SF, Connett JE, Anthonisen NR*, et al.* C-reactive protein and mortality in mild to moderate chronic obstructive pulmonary disease. *Thorax* 2006;**61**:849-53.

35 Di Napoli M, Papa F. Angiotensin-converting enzyme inhibitor use is associated with reduced plasma concentration of C-reactive protein in patients with first-ever ischemic stroke. *Stroke* 2003;**34**:2922-9.

36 Sidhu JS, Cowan D, Kaski JC. The effects of rosiglitazone, a peroxisome proliferator-activated receptor-gamma agonist, on markers of endothelial cell activation, C-reactive protein, and

fibrinogen levels in non-diabetic coronary artery disease patients. *Journal of the American College of Cardiology* 2003;**42**:1757-63.

37 Heikkila K, Ebrahim S, Rumley A, *et al.* Associations of circulating C-reactive protein and interleukin-6 with survival in women with and without cancer: findings from the British Women's Heart and Health Study. *Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology* 2007;**16**:1155-9.

38 Marsik C, Kazemi-Shirazi L, Schickbauer T, *et al.* C-reactive protein and all-cause mortality in a large hospital-based cohort. *Clinical chemistry* 2008;**54**:343-9.

39 Proctor MJ, McMillan DC, Horgan PG, *et al.* Systemic inflammation predicts all-cause mortality: a glasgow inflammation outcome study. *PloS one* 2015;**10**:e0116206.

40 Chen TH, Gona P, Sutherland PA, *et al.* Long-term C-reactive protein variability and prediction of metabolic risk. *The American journal of medicine* 2009;**122**:53-61.

41 Zheng W, McLerran DF, Rolland B, *et al.* Association between Body-Mass Index and Risk of Death in More Than 1 Million Asians , *N Engl J Med* 2011; 364:719-729.

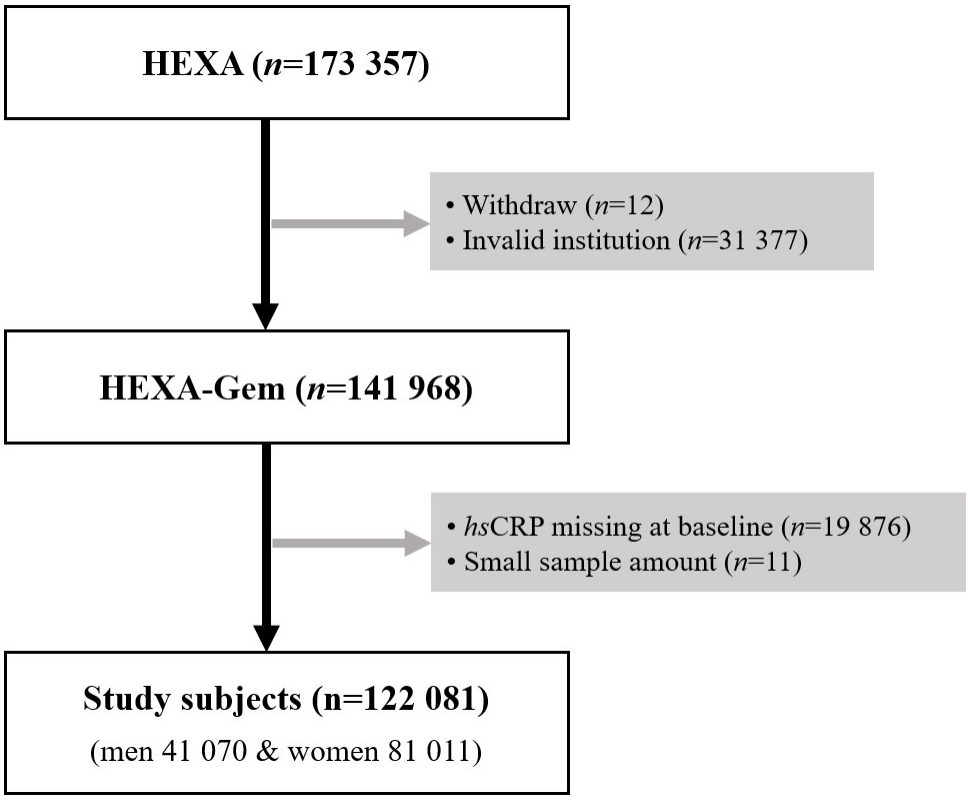


Figure 1 Flow diagram of analytical sample in current study using Health Examinees cohort.
HEXA: Health Examinees, hsCRP: High sensitivity C-reactive protein

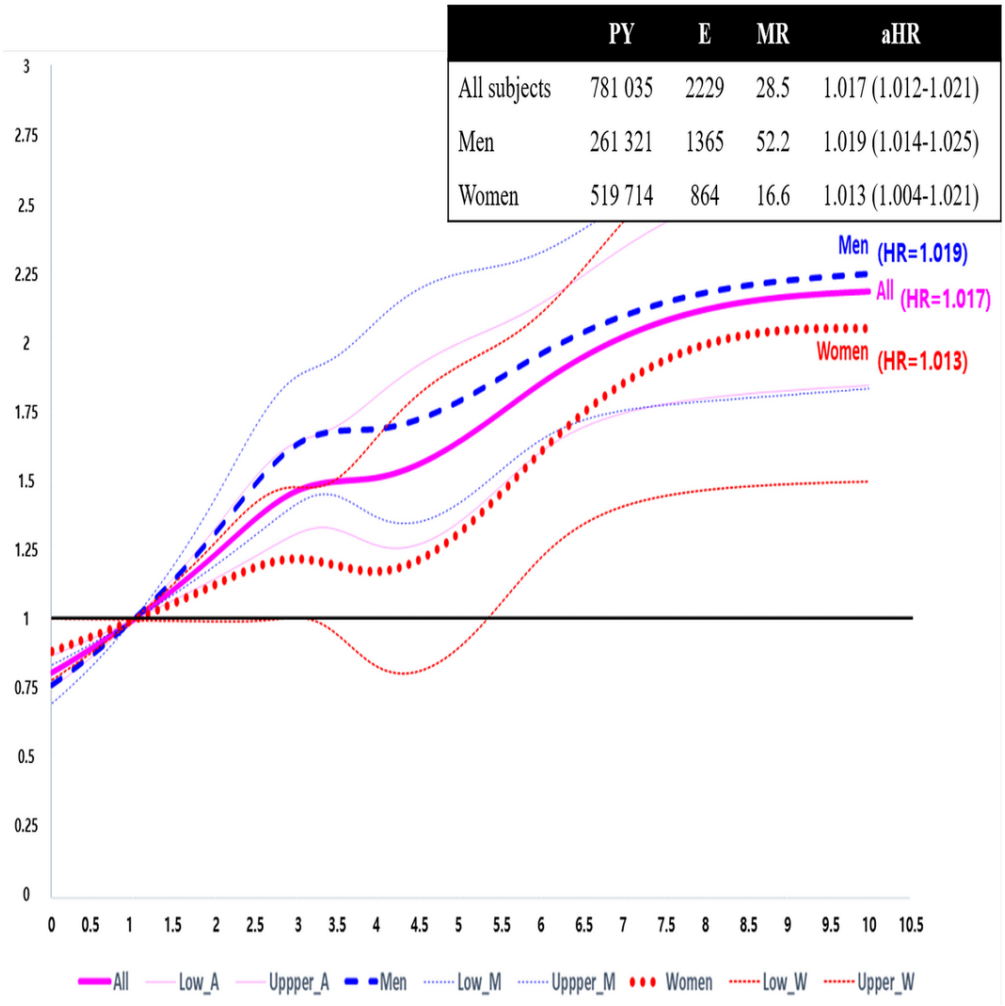


Figure 2 A dose-response association between serum hsCRP level and risk of all-cause mortality in all subjects at recruitment.
PY: Person-year, E: Number of death, MR: Mortality rate (10 000 person year)
aHR: Adjusted for age, gender, education, job, marital status, BMI, non-communicable disease history, smoking, alcohol consumption and exercise
Low_A and Upper_A: 95%CI for all subjects
Low_M and Upper_M: 95%CI for men
Low_W and Upper_W: 95%CI for women

90x90mm (300 x 300 DPI)

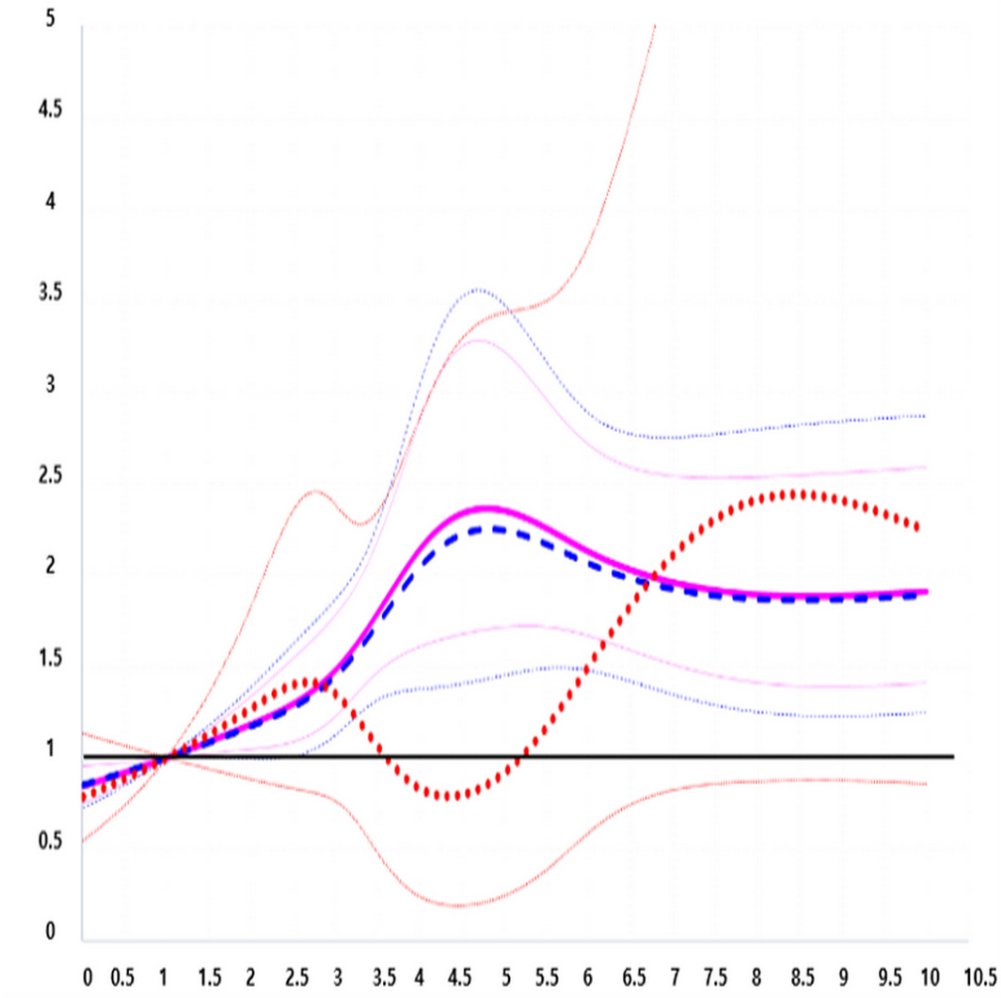


Figure 3 A dose-response association between serum hsCRP level and risk of all-cause mortality in healthy subjects at recruitment.
Low_A and Upper_A: 95%CI for all subjects
Low_M and Upper_M: 95%CI for men
Low_W and Upper_W: 95%CI for women

90x90mm (300 x 300 DPI)

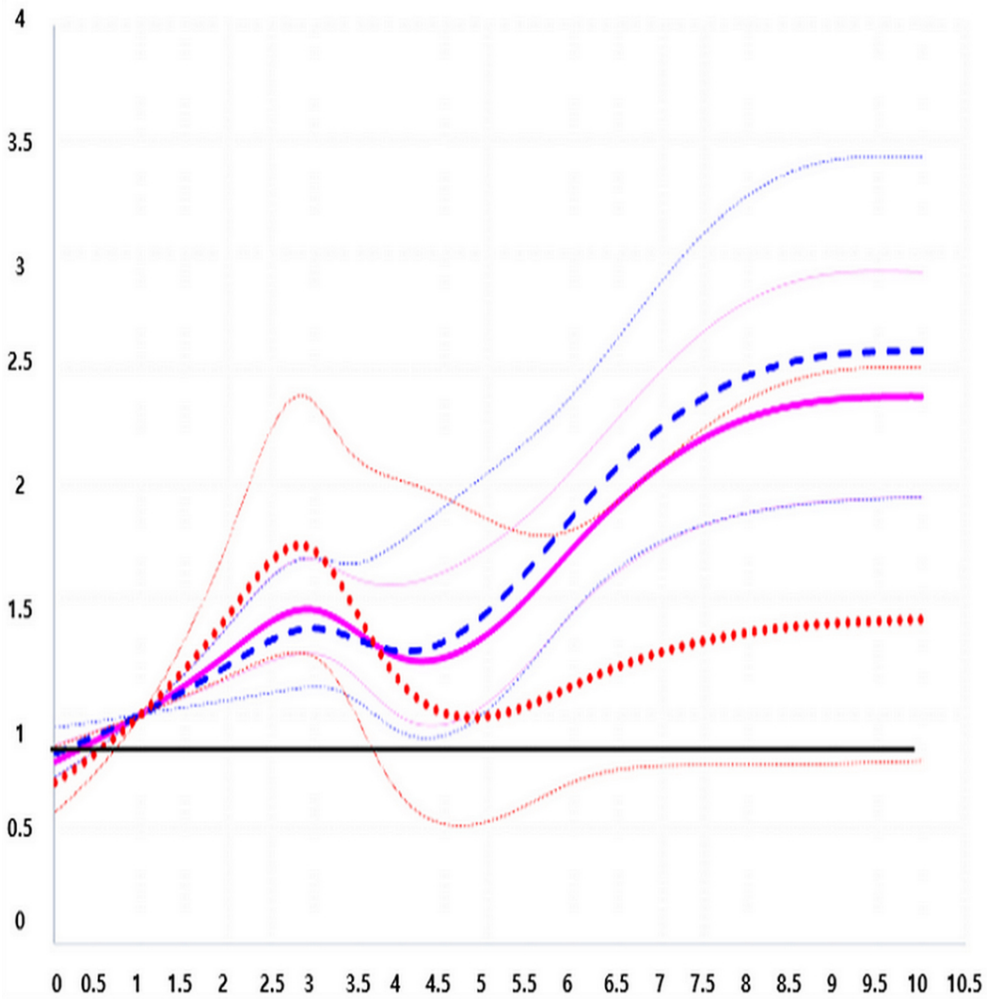


Figure 4 A dose-response association between serum hsCRP level and risk of all-cause mortality in subjects with non-communicable disease history (NCDhistory) at recruitment.
Low_A and Upper_A: 95%CI for all subjects
Low_M and Upper_M: 95%CI for men
Low_W and Upper_W: 95%CI for women

90x90mm (300 x 300 DPI)

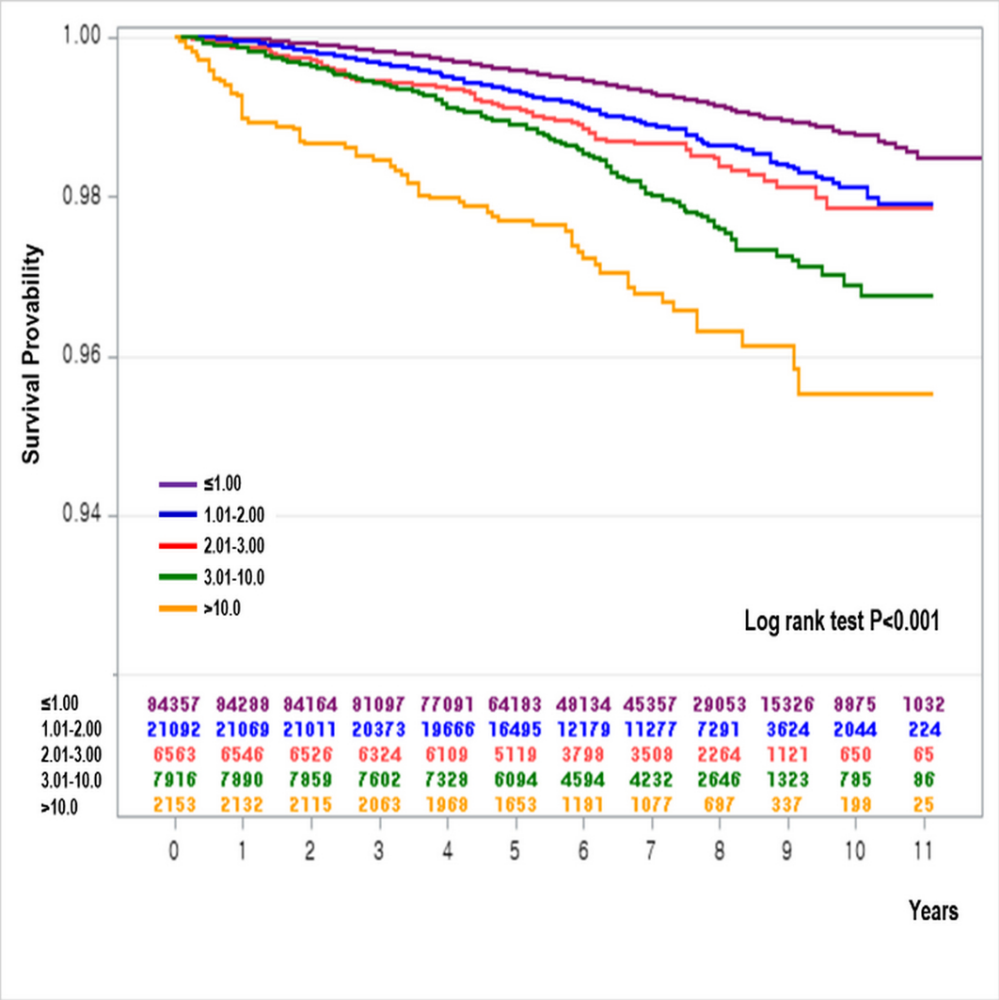


Figure 5 Kaplan-Meier crude survival curves for cancer-mortality according to serum hsCRP level in all subjects at recruitment.

90x90mm (300 x 300 DPI)

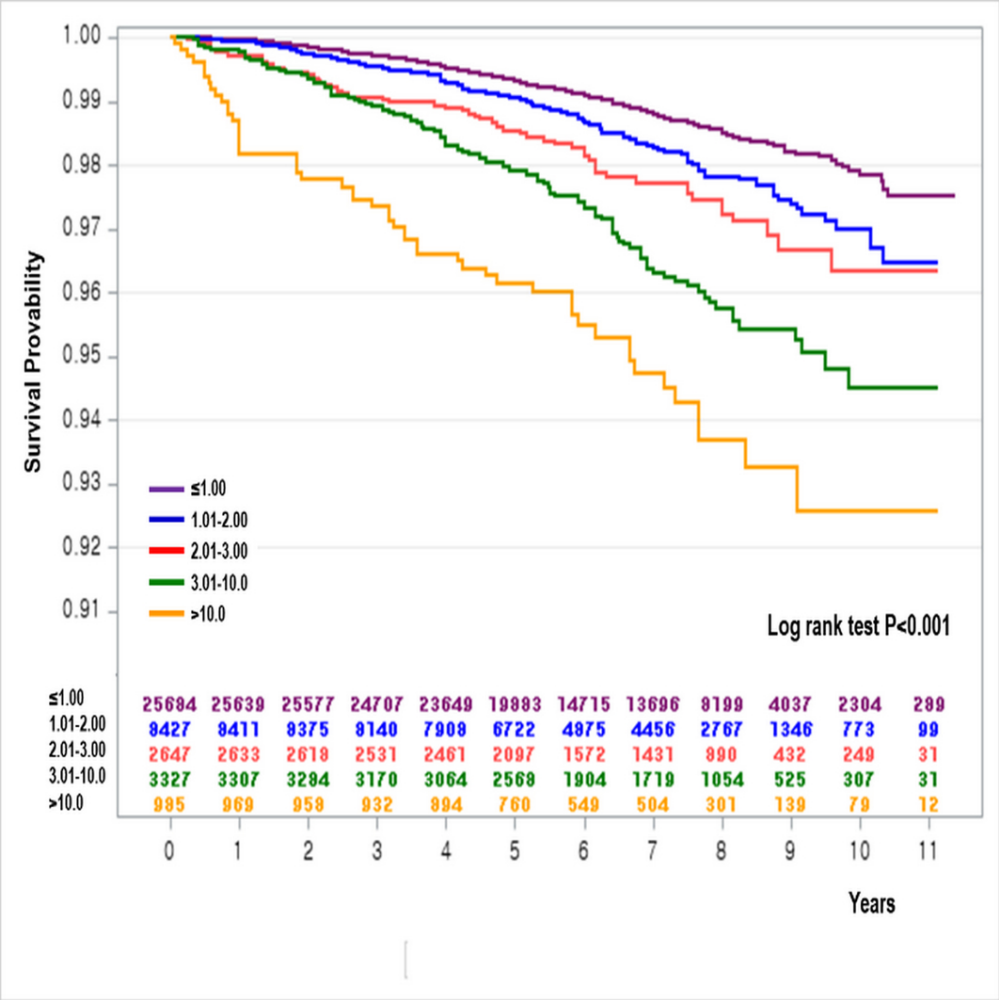


Figure 6 Kaplan-Meier crude survival curves for cancer-mortality according to serum hsCRP level in men at recruitment.

90x90mm (300 x 300 DPI)

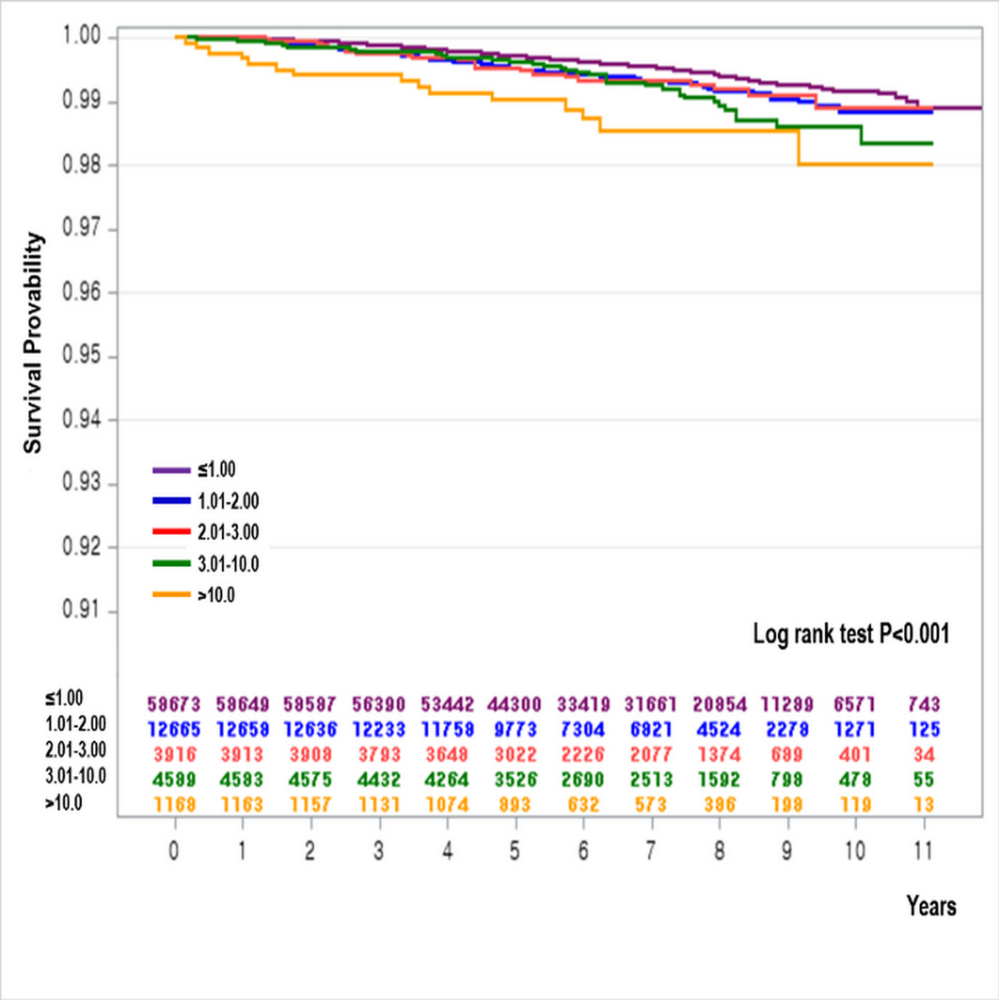


Figure 7 Kaplan-Meier crude survival curves for cancer-mortality according to serum hsCRP level in women at recruitment.

90x90mm (300 x 300 DPI)

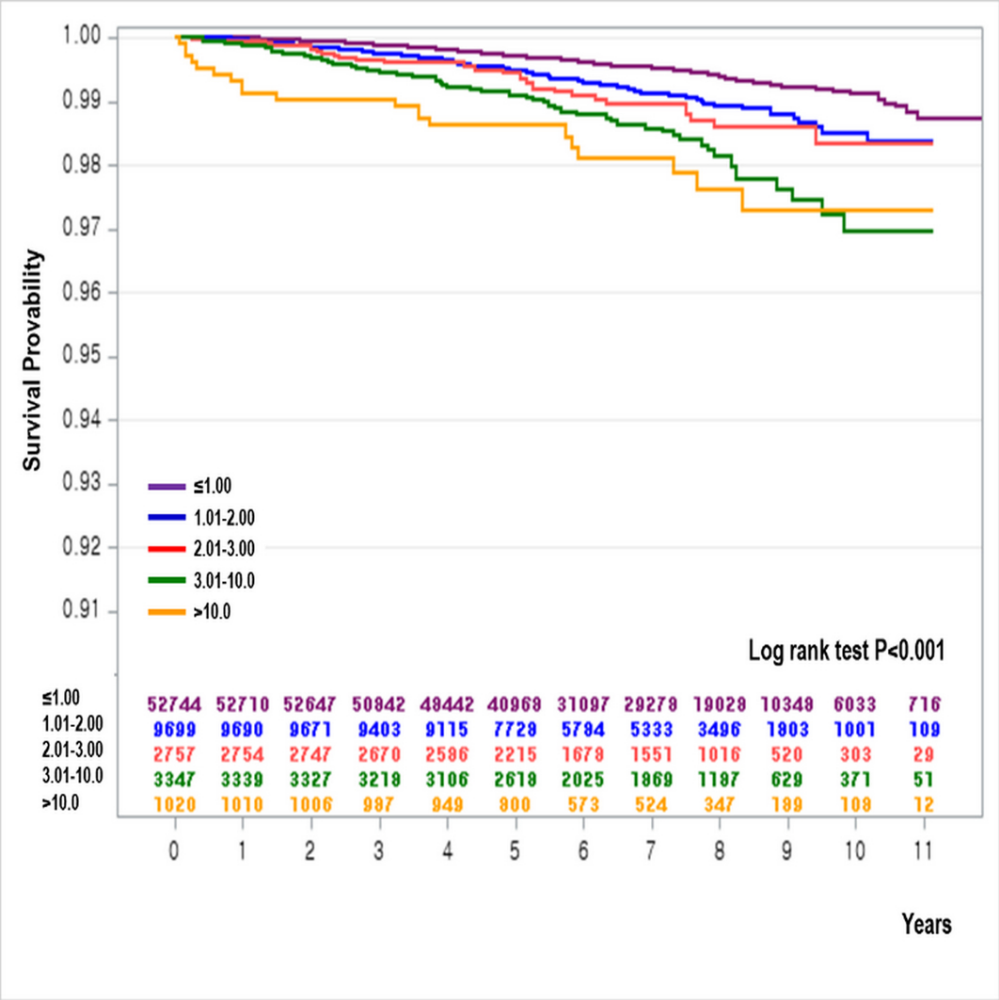


Figure 8 Kaplan-Meier crude survival curves for cancer-mortality according to serum hsCRP level in healthy subjects at recruitment.

90x90mm (300 x 300 DPI)

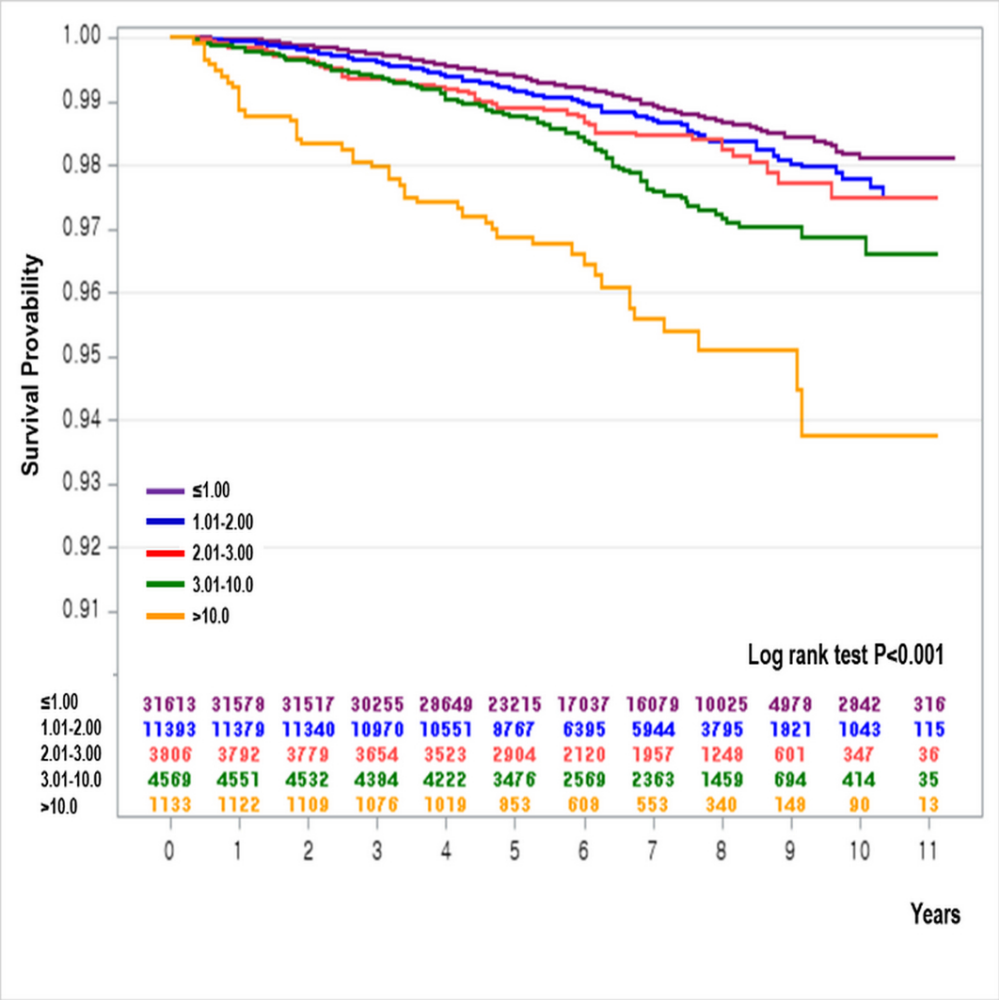


Figure 9 Kaplan-Meier crude survival curves for cancer-mortality according to serum hsCRP level in subjects with non-communicable disease history (NCDhistory) at recruitment.

90x90mm (300 x 300 DPI)

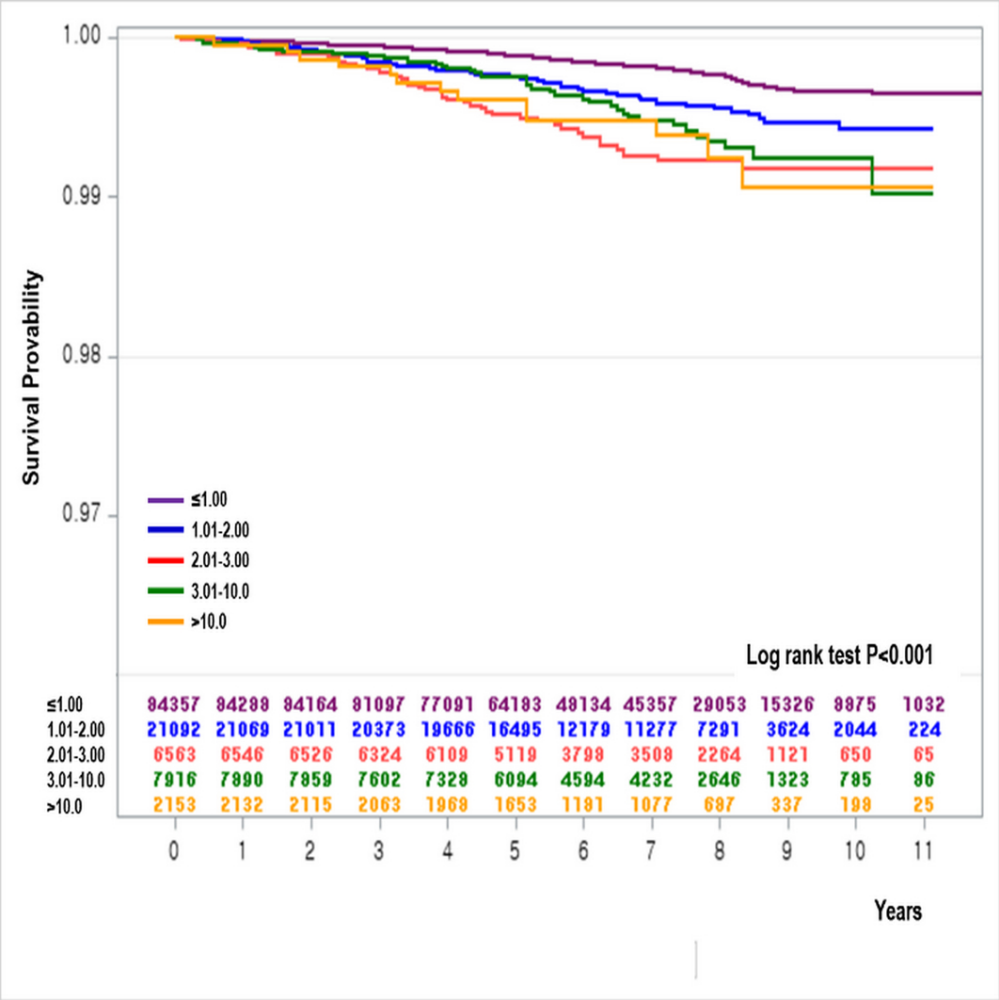


Figure 10 Kaplan-Meier crude survival curves for cardiovascular disease mortality according to serum hsCRP level in all subjects at recruitment.

90x90mm (300 x 300 DPI)

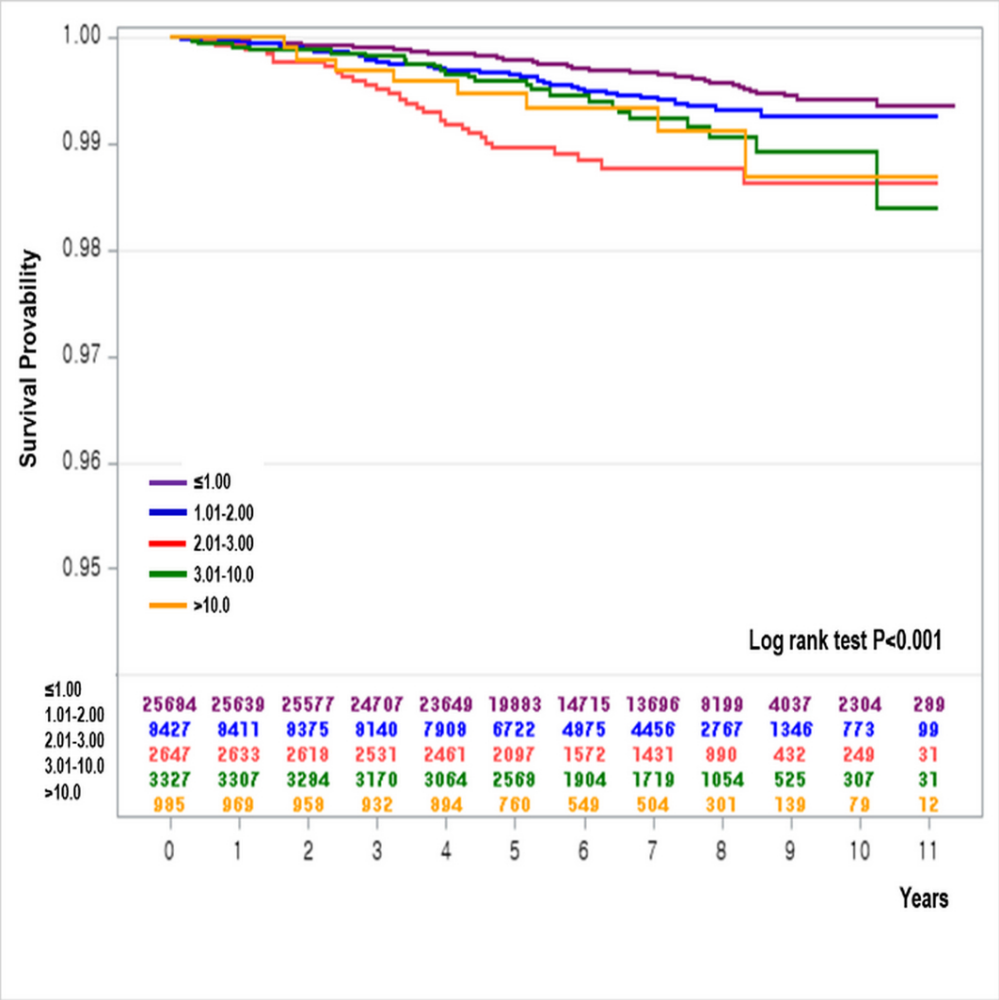


Figure 11 Kaplan-Meier crude survival curves for cardiovascular disease mortality according to serum hsCRP level in men at recruitment.

90x90mm (300 x 300 DPI)

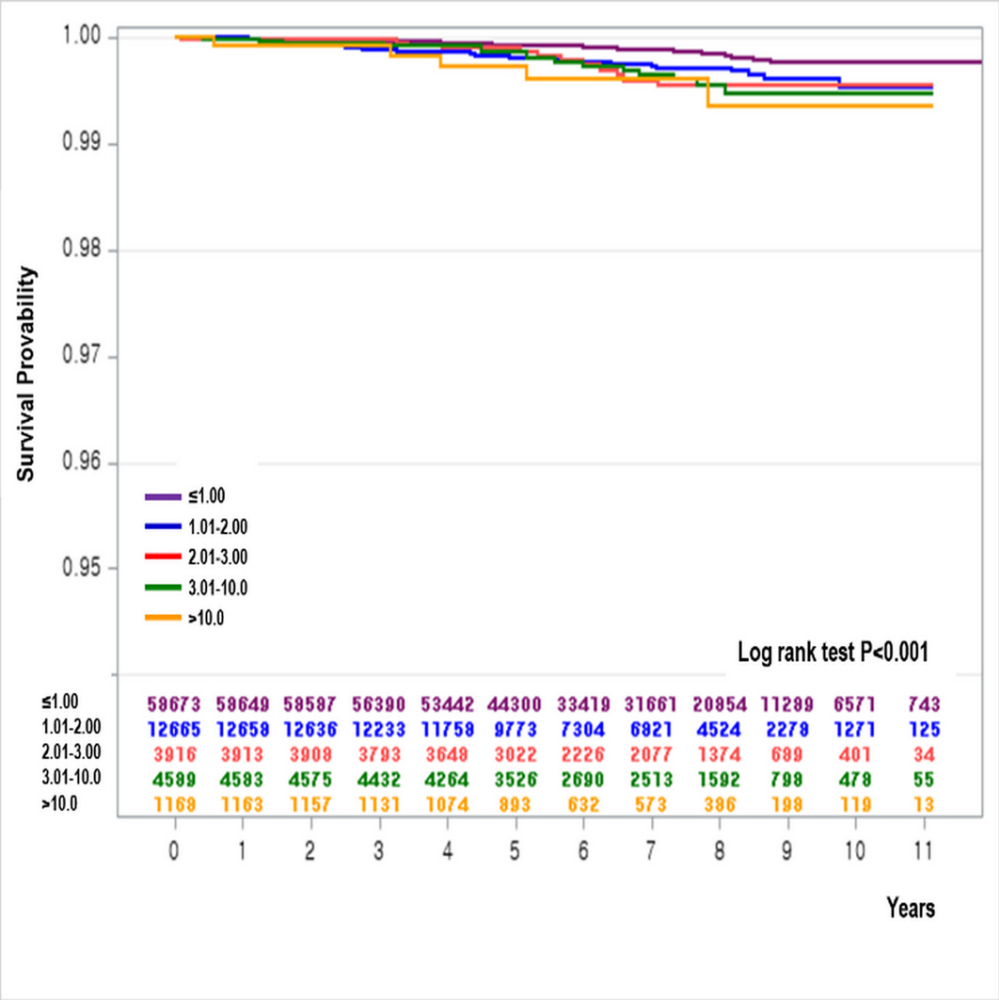


Figure 12 Kaplan-Meier crude survival curves for cardiovascular disease mortality according to serum hsCRP level in women at recruitment.

90x90mm (300 x 300 DPI)

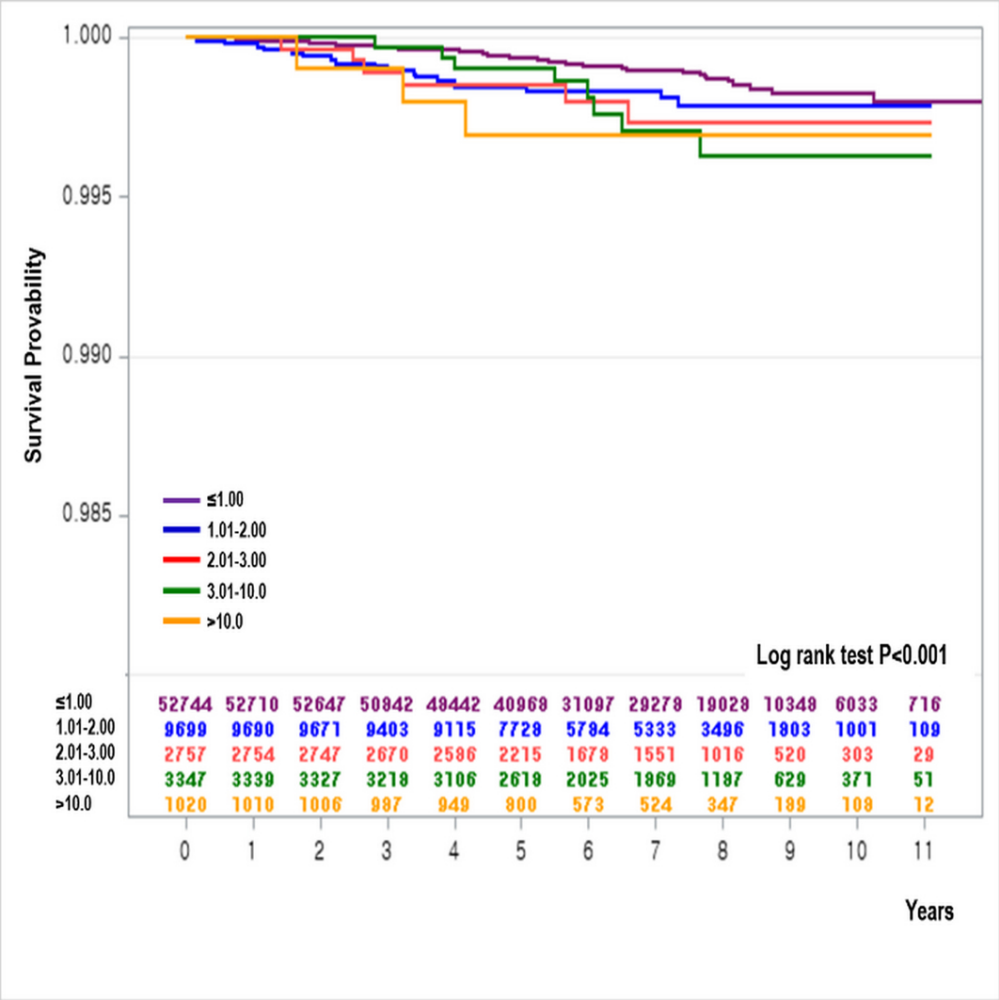


Figure 13 Kaplan-Meier crude survival curves for cardiovascular disease mortality according to serum hsCRP level in healthy subjects at recruitment.

90x90mm (300 x 300 DPI)

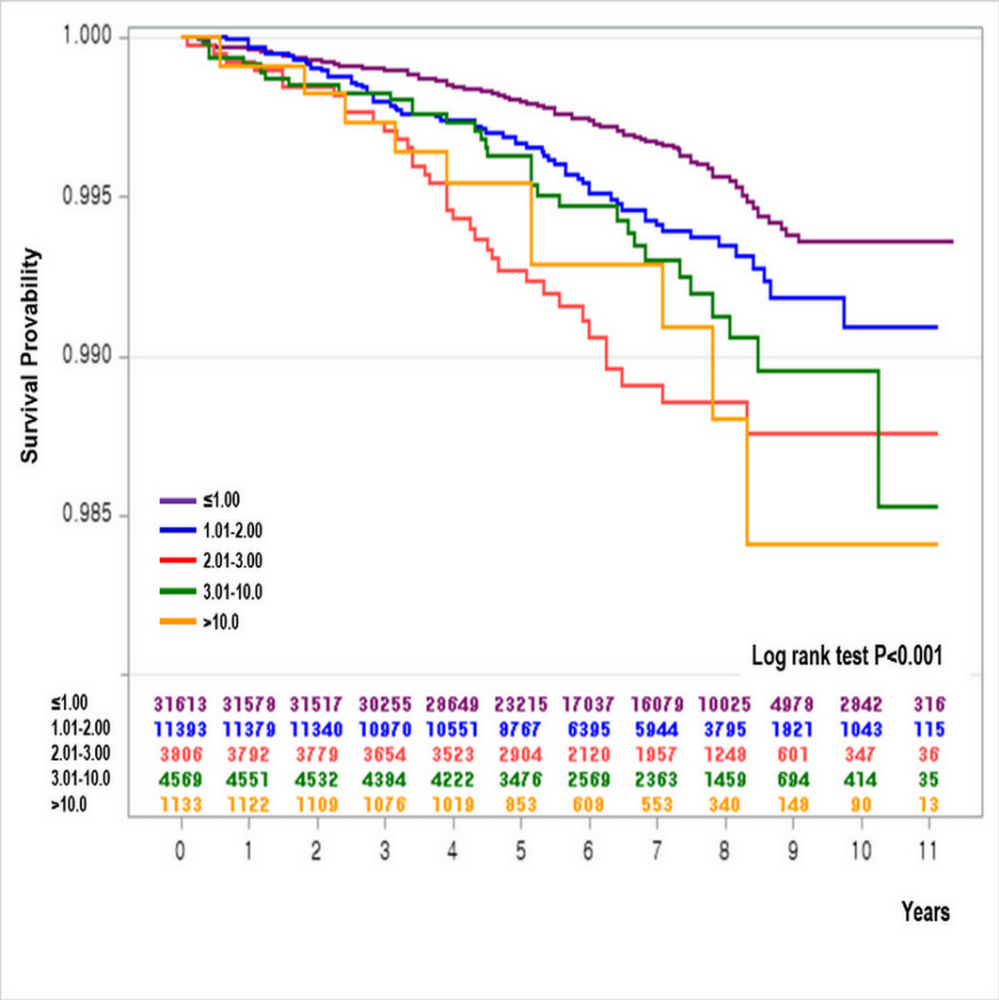


Figure 14 Kaplan-Meier crude survival curves for cardiovascular disease mortality according to serum hsCRP level in subjects with non-communicable disease history (NCDhistory) at recruitment.

90x90mm (300 x 300 DPI)

Supplement 1. The association of serum *hs*CRP level with the risk of all-cause mortality

	PY	E	MR	aHR	HR_{1year}	HR_{2year}
All subjects						
Continuous	781 035	2229	28.5	1.017 (1.012-1.021)	1.015 (1.010-1.020)	1.014 (1.009-1.019)
≤1.00	539 271	1153	21.4	Reference	Reference	Reference
1.01-1.50	90 911	308	33.9	1.26 (1.10-1.45)	1.27 (1.10-1.45)	1.21 (1.04-1.40)
1.51-2.00	44 615	163	36.5	1.28 (1.08-1.53)	1.28 (1.07-1.53)	1.26 (1.04-1.52)
2.01-2.50	25 139	117	46.5	1.53 (1.25-1.89)	1.51 (1.22-1.87)	1.49 (1.19-1.87)
2.51-3.00	16 996	72	42.4	1.39 (1.08-1.80)	1.31 (1.00-1.72)	1.23 (0.92-1.65)
3.01-4.00	19 667	103	52.4	1.61 (1.29-2.01)	1.62 (1.29-2.03)	1.64 (1.30-2.08)
4.01-6.00	17 933	102	56.9	1.84 (1.48-2.28)	1.77 (1.41-2.21)	1.70 (1.34-2.16)
6.01-10.00	13 019	88	67.6	2.02 (1.59-2.56)	1.96 (1.54-2.50)	1.93 (1.49-2.51)
>10.0	13 484	123	91.2	2.59 (2.12-3.16)	2.41 (1.95-2.97)	2.26 (1.80-2.84)
P-trend				<.001	<.001	<.001
Men						
Continuous	261 321	1365	52.2	1.019 (1.014-1.025)	1.017 (1.011-1.023)	1.017 (1.010-1.023)
≤1.00	163 068	638	39.1	Reference	Reference	Reference
1.01-1.50	36 094	190	52.6	1.27 (1.07-1.51)	1.28 (1.07-1.53)	1.22 (1.01-1.47)
1.51-2.00	17 946	103	57.4	1.34 (1.07-1.67)	1.34 (1.07-1.68)	1.35 (1.06-1.72)
2.01-2.50	10 059	77	76.5	1.56 (1.20-2.03)	1.53 (1.16-2.00)	1.47 (1.10-1.96)
2.51-3.00	6959	54	77.6	1.71 (1.27-2.29)	1.57 (1.15-2.15)	1.46 (1.04-2.05)
3.01-4.00	8177	77	94.2	1.88 (1.45-2.43)	1.94 (1.50-2.52)	1.92 (1.46-2.54)
4.01-6.00	7425	75	101.0	2.05 (1.59-2.63)	1.95 (1.49-2.53)	1.91 (1.44-2.52)
6.01-10.00	5456	59	108.1	2.03 (1.52-2.73)	1.96 (1.44-2.66)	1.85 (1.33-2.58)
>10.0	6137	92	149.9	2.84 (2.25-3.58)	2.66 (2.08-3.39)	2.58 (1.99-3.35)
P-trend				<.001	<.001	<.001
Women						
Continuous	519 714	864	16.6	1.013 (1.004-1.021)	1.011(1.002-1.021)	1.010 (0.999-1.021)
≤1.00	376 203	515	13.7	Reference	Reference	Reference
1.01-1.50	54 817	118	21.5	1.28 (1.03-1.59)	1.27 (1.02-1.58)	1.23 (0.97-1.56)
1.51-2.00	26 669	60	22.5	1.23 (0.92-1.64)	1.21 (0.90-1.63)	1.14 (0.83-1.56)
2.01-2.50	15 080	40	26.5	1.52 (1.09-2.14)	1.52 (1.08-2.15)	1.56 (1.09-2.24)
2.51-3.00	10 037	18	17.9	0.84 (0.49-1.44)	0.87 (0.51-1.48)	0.83 (0.46-1.47)
3.01-4.00	11 490	26	22.6	1.16 (0.75-1.81)	1.09 (0.68-1.72)	1.21 (0.76-1.93)
4.01-6.00	10 508	27	25.7	1.48 (0.99-2.22)	1.47 (0.97-2.22)	1.36 (0.86-2.14)
6.01-10.00	7563	29	38.3	2.00 (1.34-2.98)	1.98 (1.32-2.98)	2.10 (1.39-3.19)
>10.0	7347	31	42.2	2.02 (1.36-3.02)	1.84 (1.21-2.81)	1.51 (0.93-2.47)
P-trend				<.001	<.001	0.001
Premenopause						
≤1.00	141 286	96	6.8			
1.01-2.00	20 500	20	9.8	1.52 (0.92-2.52)	1.49 (0.89-2.50)	1.57 (0.90-2.73)
2.01-3.00	5835	6	10.3	1.76 (0.77-4.06)	1.83 (0.79-4.22)	1.42 (0.52-3.93)
3.01-10.0	6886	6	8.7	1.51 (0.66-3.50)	1.31 (0.53-3.25)	1.21 (0.44-3.36)
>10.0	1759	4	22.7	2.57 (0.81-8.14)	2.63 (0.83-8.37)	2.09 (0.51-8.58)
P-trend				0.020	0.036	0.150
Postmenopause						
≤1.00	192 164	366	19.0			
1.01-2.00	52 897	145	27.4	1.26 (1.03-1.55)	1.25 (1.02-1.54)	1.18 (0.95-1.48)
2.01-3.00	16 943	44	26.0	1.11 (0.80-1.56)	1.12 (0.80-1.57)	1.19 (0.83-1.68)
3.01-10.0	19 687	67	34.0	1.49 (1.13-1.97)	1.47 (1.10-1.95)	1.52 (1.13-2.05)
>10.0	4828	27	55.9	2.09 (1.37-3.21)	1.88 (1.19-2.96)	1.56 (0.92-2.63)
P-trend				<0.001	0.001	0.003

PY: Person-year, E: Number of death, MR: Mortality rate (10,000 person year)

aHR: Adjusted for age, gender, education, job, marital status, BMI, non-communicable disease history, smoking, alcohol consumption and exercise
HR_{1year}: aHR after exclude subjects who died within 1 yr f/u time
HR_{2year}: aHR after exclude subjects who died within 2 yr f/u time

Supplement 2. The association between serum *hs*CRP level and all-cause mortality by gender and non-communicable disease history ($NCD_{history}$) at recruitment

	Healthy subjects at recruitment					Subjects with $NCD_{history}$ at recruitment				
	E	MR	aHR	HR_{1year}	HR_{2year}	E	MR	aHR	HR_{1year}	HR_{2year}
All										
≤ 1.00	517	15.1	Ref	Ref	Ref	636	32.3	Ref	Ref	Ref
1.01-2.00	145	22.9	1.20	1.19	1.16	326	45.1	1.20	1.19	1.16
2.01-3.00	53	29.3	1.38	1.37	1.32	136	56.6	1.51	1.46	1.41
3.01-10.0	102	46.8	2.22	2.15	2.15	191	66.3	1.62	1.60	1.58
>10.0	40	61.3	2.38	2.23	2.27	83	118.9	2.74	2.54	2.29
P-trend			<.001	<.001	<.001			<.001	<.001	<.001
Men										
≤ 1.00	270	29.5	Ref	Ref	Ref	368	51.4	Ref	Ref	Ref
1.01-2.00	89	35.8	1.11	1.11	1.13	204	70.0	1.40	1.41	1.33
2.01-3.00	33	46.3	1.22	1.17	1.15	98	99.0	1.82	1.73	1.61
3.01-10.0	70	76.8	2.14	2.08	2.03	141	118.1	1.92	1.90	1.83
>10.0	31	110.0	2.60	2.49	2.73	61	183.1	3.05	2.83	2.58
P-trend			<.001	<.001	<.001			<.001	<.001	<.001
Women										
≤ 1.00	247	9.8	Ref	Ref	Ref	268	21.4	Ref	Ref	Ref
1.01-2.00	56	14.6	1.35	1.32	1.20	122	28.3	1.19	1.20	1.19
2.01-3.00	20	18.2	1.61	1.66	1.60	38	26.9	1.06	1.06	1.11
3.01-10.0	32	25.2	2.31	2.23	2.37	50	29.7	1.16	1.14	1.17
>10.0	9	24.3	1.69	1.49	1.12	22	60.3	2.15	1.99	1.68
P-trend			<.001	<.001	0.001			0.018	0.043	0.084

E: Number of death, MR: Mortality rate (10 000 person year)

aHR: Adjusted for age, gender, education, job, marital status, BMI, non-communicable disease history, smoking, alcohol consumption and exercise

HR_{1year}: aHR after exclude subjects who died within 1 yr f/u time

HR_{2year}: aHR after exclude subjects who died within 2 yr f/u time

STROBE 2007 (v4) checklist of items to be included in reports of observational studies in epidemiology*

Checklist for cohort, case-control, and cross-sectional studies (combined)

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	1-2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3
Objectives	3	State specific objectives, including any pre-specified hypotheses	3
Methods			
Study design	4	Present key elements of study design early in the paper	4
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4-5
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	4
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	Not Applicable
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	5
Bias	9	Describe any efforts to address potential sources of bias	6
Study size	10	Explain how the study size was arrived at	4
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	5-6
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	5-6
		(*b*) Describe any methods used to examine subgroups and interactions	5-6
		(*c*) Explain how missing data were addressed	4
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed	4

		Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	6
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	4
		(b) Give reasons for non-participation at each stage	4
		(c) Consider use of a flow diagram	4
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	6-7
		(b) Indicate number of participants with missing data for each variable of interest	4
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	6
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	6-10
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	Not Applicable
		Cross-sectional study—Report numbers of outcome events or summary measures	Not Applicable
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	6-10
		(*b*) Report category boundaries when continuous variables were categorized	5
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Not Applicable
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	8
Discussion			
Key results	18	Summarise key results with reference to study objectives	11
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	12-13
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	11-13
Generalisability	21	Discuss the generalisability (external validity) of the study results	11-12
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	14

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.
Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

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

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2021-052630.R2
Article Type:	Original research
Date Submitted by the Author:	28-Mar-2022
Complete List of Authors:	Lee, Sang-Ah; Kangwon National University School of Medicine, Preventive Medicine; Vanderbilt University Medical Center Kwon, Sung Ok; Kangwon National University School of Medicine, Preventive Medicine Park, Hyerim; Kangwon National University School of Medicine, Preventive Medicine Shu, Xiao-Ou ; Vanderbilt University Medical Center Lee, Jong-Koo; JW LEE Center for Global Medicine Kang, Daehee; Seoul National University College of Medicine, Preventive Medicine
Primary Subject Heading:	Epidemiology
Secondary Subject Heading:	Epidemiology, Cardiovascular medicine
Keywords:	PREVENTIVE MEDICINE, EPIDEMIOLOGY, Cardiac Epidemiology < CARDIOLOGY

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

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

Sang-Ah Lee[1,2 *], Sung Ok Kwon[1], Hyerim Park[1], Xiao-Ou Shu[2], Jong-Koo Lee[3], Daehee Kang[4]

[1]Department of Preventive Medicine, School of Medicine, Kangwon National University, Chuncheon, Republic of Korea.

[2]Division of Epidemiology, Vanderbilt Epidemiology Center, Vanderbilt University Medical Center, Nashville, TN, USA.

[3]JW Lee Center for Global Medicine, College of Medicine, Seoul National University, Seoul, Republic of Korea.

[4]Department of Preventive Medicine, College of Medicine, Seoul National University, Seoul, Republic of Korea.

ABSTRACT

Objectives This study aimed to examine the association of *hs*CRP with mortality risk and the attenuated effect of non-communicable disease history ($NCD_{history}$) on the association.

Design Prospective cohort study.

Setting the Health Examinees (HEXA) cohort.

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

Outcome measures The data and cause of death occurring until December 31, 2015, were confirmed by death statistics from the National Statistical Office. We conducted the advanced analysis after stratification by $NCD_{history}$ and the 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 the risk of all-cause mortality was observed with strong linearity in both genders, which was not influenced by $NCD_{history}$. Otherwise, the association of serum *hs*CRP with cancer-mortality risk was not observed in women with $NCD_{history}$, but the association with the risk of cardiovascular disease (CVD) mortality was predominantly observed in men with $NCD_{history}$.

Conclusions This study suggested the dose-response association of *hs*CRP with mortality risk, including cancer and CVD mortality, in Korean 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 the large population-based prospective study.
- We examined the effect of very high *hs*CRP concentration on mortality risk.
- The *hs*CRP level of present study was measured within 18 hours in a single institution to minimize error/bias.

· Due to random fluctuations of *hs*CRP, using the single measurement of *hs*CRP at baseline could reflect the inaccurate status of blood *hs*CRP levels in the study participants and increase the instability of *hs*CRP.

· This study lacked information on medication use at recruitment and during the follow-up period, and information on hormone-replacement therapy (HRT) among women.

*Correspondence to: Sang-Ah Lee, Ph.D.
Department of Preventive Medicine, School of Medicine, Kangwon National University,
Chuncheon, Gangwon, Republic of Korea.
Tel: +82 33 250 8871
E-mail: sangahlee@kangwon.ac.kr

INTRODUCTION

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

Serum *hs*CRP represents a low-grade inflammation state that is generally involved in the process of aging[9]. Several large cohorts, including Study of Women's Health Across the Nation (SWAN)[10], the Women's Health Study[11] and the Dallas Heart Study[12], reported significant differences in *hs*CRP levels 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 United States (from the Women's Health Study) on the association between *hs*CRP and the mortality risk; the association was observed in only men supported by the results from two cohort studies[15, 16] reported in Korea. On the other hand, the 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 the 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 dataset 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 the 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 (Fig. 1). All study participants provided informed consent prior to entering the study. The Institutional Review Board of the Seoul National University Hospital, Seoul, Korea, approved it for statistical analysis (IRB No. E-1503-103-657).

Laboratory measurements

After at least 10 hours of overnight fasting, blood samples were obtained in the morning. Bio-specimens included fasting blood samples that were collected in a serum separator tube and two ethylenediaminetetraacetic acid (EDTA) tubes. All samples were then transported to the National Biobank of Korea and stored for future research purposes within 18 hours. *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 December 31, 2015. We added the mortality data from Statistics Korea to our dataset 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 (ICD-10). 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 standardized methods. Body mass index (BMI) was calculated, and all participants were defined into four classes based on the World Health Organization 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 (NCEP-ATP III)[25], modified for the Asian guideline for waist circumference (WC ≥90 and ≥80 cm for men and women, respectively). Nonsmokers were defined as those who had smoked less than 400 cigarettes over the course of their lifetime. Participants who had smoked were categorized into two groups: noncurrent (never/former) and current smoker. Noncurrent 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 the $NCD_{history}$ on the association between serum *hs*CRP and the risk of mortality, we performed advanced analysis after stratification by $NCD_{history}$. We considered six main non-communicable diseases (hypertension, diabetes, hyperlipidemia, cancer, cardiovascular and cerebrovascular diseases, and respiratory disease) to classify healthy subjects vs. 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 the $NCD_{history}$, the *hs*CRP levels were categorized as ≤1.00, 1.01-2.00, 2.01-3.00, 3.01-10.0, and >10.0 mg/L because of the reduced sample size in each subgroup. The concentrations of *hs*CRP were log-transformed for analyses because of the skewed distribution.

We calculated a follow-up time for each subject starting from the date of interview until the date of death or December 31, 2015, whichever came first. Using age as the time scale, subjects enter the risk set at the age at which they completed the baseline questionnaire and exit at their event/censoring age. The associations of

*hs*CRP and all-cause mortality, as well as cancer and CVD mortality, were analyzed by Cox proportional hazard models (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 tests 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 cardiovascular disease 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_{2year}) 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 (RCSs) to evaluate the possibility of complex (i.e., nonlinear) 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 nonlinear associations between knots using a cubic function, and presented the integrated graph smoothly. All statistical analyses were performed using SAS version 9.3 (SAS Institute Inc., Cary, NC, USA) 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, conducting, reporting, and dissemination plans of the present study.

RESULTS

The association of demographic and lifestyle factors with the risk of all-cause mortality is presented in Table 1. During the follow-up period (average 6.8 years), 1 365 men and 864 women died. The median levels of *hs*CRP were 0.77 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 educated (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 single marital status (aHR=1.23), $NCD_{history}$ (aHR=1.57), underweight (aHR=2.05) and current smoking (aHR=1.97).

Table 1. Baseline characteristics of participants by all-cause mortality.

	All (n=122 081)	Death (n=2229)	All-cause mortality	
			Age,gender adjusted	adj HR[a]
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 year, %)	68.2	55.4	0.67 (0.60-0.75)	0.65 (0.56-0.75)
Blue-colored worker[b] (%)	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)
Diabete	6.5	17.1	1.81 (1.62-2.03)	1.77 (1.57-2.00)
Hyperlipidemia	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 & cardiovascular disease	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	<.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)

$NCD_{history}$: Non-communicable disease history

[a] Adjusted for age, gender, education, job, marital status, BMI and non-communicable disease history

[b] Compared to white-colored worker

The risk of all-cause mortality was inclined with a dose-dependent pattern as increased serum *hs*CRP level (P_{trend}<0.001, Supplement 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 levels was observed in both premenopausal (P_{trend}=0.020) and postmenopausal women (P_{trend}< 0.001), although the statistical significance in premenopausal women disappeared after sensitivity analysis (P_{trend}=0.150 for aHR_{2year}, Supplement 1). The integrated graph, based on the restricted cubic spline 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, Fig. 2 (a)).

The dose-response association between *hs*CRP level and the risk of all-cause mortality was not influenced by $NCD_{history}$ (Supplement 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_{2year}) but disappeared in women with $NCD_{history}$, particularly after sensitivity analysis with the exclusion of a 2-year follow-up time (P_{trend}=0.084 for aHR_{2year}). Based on the restricted cubic spline analyses, otherwise, the pattern of increase in the association was different depending on the $NCD_{history}$ (Fig. 2 (b), (c)). In the healthy subjects, the risk of all-cause mortality was 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 (Fig. 2 (b)). On the other hand, the slope of the association fluctuated as the *hs*CRP level increased in the 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 (Fig. 2 (c)).

The association of serum *hs*CRP with the risk of cancer-mortality was not influenced by $NCD_{history}$ (P_{trend}<0.001 regardless of $NCD_{history}$) (Table 2 and Fig. 3 (a-e)). Otherwise, 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 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 stratified by gender and $NCD_{history}$, respectively (Fig. 4 (a-e)). After stratification by gender and $NCD_{history}$, otherwise, the association only appeared in individuals of both genders with $NCD_{history}$ (P_{trend}=0.015 and 0.035 in men and women with $NCD_{history}$, respectively); no association between *hs*CRP level and CVD mortality risk was found in either healthy men or women.

Table 2. The association between serum *hs*CRP level and cancer-mortality by gender and non-communicable disease history ($NCD_{history}$) at recruitment.

	Cancer-mortality					Healthy subjects at recruitment					Subjects with $NCD_{history}$ at recruitment				
	E	MR	aHR	HR_{1year}	HR_{2year}	E	MR	aHR	HR_{1year}	HR_{2year}	E	MR	aHR	HR_{1year}	HR_{2year}
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			<.001	<.001	<.001			<.001	<.001	<.001			<.001	<.001	<.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			<.001	<.001	<.001			<.001	<.001	<.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			<.001	0.001	0.002			0.856	0.635	0.538

E: Number of death, MR: Mortality rate (10 000 person year), Ref: Reference
aHR: Adjusted for age, gender, education, job, marital status, BMI, non-communicable disease history, smoking, alcohol consumption and exercise
HR_{1year}: aHR after exclude subjects who died within 1 yr f/u time
HR_{2year}: aHR after exclude subjects who died within 2 yr f/u time

Table 3. The association between serum *hs*CRP level and cardiovascular disease mortality by gender and non-communicable disease history ($NCD_{history}$) at recruitment.

	Cardiovascular disease mortality					Healthy subjects at recruitment					Subjects with $NCD_{history}$ at recruitment				
	E	MR	aHR	HR_{1year}	HR_{2year}	E	MR	aHR	HR_{1year}	HR_{2year}	E	MR	aHR	HR_{1year}	HR_{2year}
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

E: Number of death, MR: Mortality rate (10 000 person year), Ref: Reference
aHR: Adjusted for age, gender, education, job, marital status, BMI, non-communicable disease history, smoking, alcohol consumption and exercise
HR_{1year}: aHR after exclude subjects who died within 1 yr f/u time
HR_{2year}: aHR after exclude subjects who died within 2 yr f/u time

DISCUSSION

This study suggests that the risk of all-cause mortality was associated with elevated *hs*CRP levels with a dose-response manner in both gender among Asian who have reported low *hs*CRP levels compared to other races, and was not influenced by $NCD_{history}$. Otherwise, the association was influenced by gender and $NCD_{history}$ although a dose-response association of *hs*CRP with the risk of cancer- and CVD-mortality was also observed in this population. The level of *hs*CRP was not associated with the 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 $NCD_{history}$.

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 the risk of all-cause mortality in a dose-dependent manner, even though the level of *hs*CRP was lower than that 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 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 levels 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 and 0.68 mg/L for premenopausal and postmenopausal women in this study. The protective effect could be supported by the proposition that estrogen 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 rennin–angiotensin system inhibitors[35] and statins and thiazolidinedione[36], could influence the level of *hs*CRP. The association between *hs*CRP and the 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_{2year}). 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 the risk of all-cause mortality risk was significantly observed in only men with $NCD_{history}$ but not in women with $NCD_{history}$. The attenuated effect of $NCD_{history}$ on the association between *hs*CRP and the risk of cancer-mortality was not observed in men, consistent with results from several studies which reported the associations among healthy men[3] or cancer patients[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 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 the 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 the prevention of cardiovascular disease, 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 because of the large population-based prospective study; it makes possible 1) to adjust for confounders; 2) to examine sensitivity analysis after excluding death before 1 or 2 years from recruitment; 3) to assess an advanced analysis after stratification by gender and $NCD_{history}$; 4) to examine the association using various cut-off points of *hs*CRP considering low serum *hs*CRP levels in Asian populations; and 5) to evaluate the complex (i.e., nonlinear) hazard functions using restricted cubic splines on the association between continuous *hs*CRP levels and the risk of mortality. In particular, most previous studies excluded subjects with more than 10 mg/L *hs*CRP because of 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 to be more concerning for these subjects in the future. The *hs*CRP level of this

study, in addition, was measured within 18 hours in a single institution to minimize measurement error/bias from institutional variation to avoid bias from measurement or long-term storage before analysis.

Despite of those strengths, it is also several limitations. First, the use of a single measurement of *hs*CRP at baseline could reflect the inaccurate status of blood *hs*CRP levels in the study participants and increase the instability of *hs*CRP due to random fluctuations over time. Nevertheless, a report [40] on the long-term *hs*CRP variability suggested that the *hs*CRP variability within 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, angiotensin-converting enzyme inhibitors, fibrates, niacin, thiazolidinedione and estrogen/progestogen hormone, could influence the *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, which could not examine the influence of HRT on the association of *hs*CRP with the 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 with obesity in our population was consistent to Wei's report in Asian[41]. On the other hand, the inverse association of alcohol drinking with all-cause mortality couldn't interpret directly because our report wasn't separated the distinguish between mild drinkers and abuse alcohol drinker, which requires additional research for our population 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), which was not influenced by the association was not observed in women with $NCD_{history}$. Otherwise, the association of *hs*CRP level with the risk of cancer- and CVD-mortality could be attenuated by gender or $NCD_{history}$.

Figure 1 Flow diagram of analytical sample in current study using Health Examinees cohort.

Figure 2 A 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 ($NCD_{history}$) at recruitment (c).

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 ($NCD_{history}$) at recruitment (e).

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 ($NCD_{history}$) at recruitment (e).

Contributors

SAL, XS and DK: designed and conducted the research, SAL and SOK: analyzed the data and performed the statistical analyses; HP and JKL: managed data mining and collection; SAL: wrote the manuscript and had primary responsibility for the final content of the manuscript; and all authors: read and approved the final manuscript.

Funding None.

Competing interests None declared.

Patient consent for publication Not required.

Ethics approval The Institutional Review Board of the Seoul National University Hospital, Seoul, Korea, approved it for statistical analysis (IRB No. E-1503-103-657).

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement

No additional data available.

REFERENCES

1 Pepys MB, Hirschfield GM. C-reactive protein: a critical update. *The Journal of clinical investigation* 2003;**111**:1805-12.

2 Elias-Smale SE, Kardys I, Oudkerk M, *et al.* C-reactive protein is related to extent and progression of coronary and extra-coronary atherosclerosis; results from the Rotterdam study. *Atherosclerosis* 2007;**195**:e195-202.

3 Koenig W, Khuseyinova N, Baumert J, *et al.* Prospective study of high-sensitivity C-reactive protein as a determinant of mortality: results from the MONICA/KORA Augsburg Cohort Study, 1984-1998. *Clinical chemistry* 2008;**54**:335-42.

4 Ahmadi-Abhari S, Luben RN, Wareham NJ, *et al.* Seventeen year risk of all-cause and cause-specific mortality associated with C-reactive protein, fibrinogen and leukocyte count in men and women: the EPIC-Norfolk study. *European journal of epidemiology* 2013;**28**:541-50.

5 Kuoppamaki M, Salminen M, Vahlberg T, *et al.* High sensitive C-reactive protein (hsCRP), cardiovascular events and mortality in the aged: a prospective 9-year follow-up study. *Archives of gerontology and geriatrics* 2015;**60**:112-7.

6 Zuo H, Ueland PM, Ulvik A, *et al.* Plasma Biomarkers of Inflammation, the Kynurenine Pathway, and Risks of All-Cause, Cancer, and Cardiovascular Disease Mortality: The Hordaland Health Study. *American journal of epidemiology* 2016;**183**:249-58.

7 Nisa H, Hirata A, Kohno M, *et al.* High-Sensitivity C-Reactive Protein and Risks of All-Cause and Cause-Specific Mortality in a Japanese Population. *Asian Pacific journal of cancer prevention : APJCP* 2016;**17**:2643-8.

8 Li Y, Zhong X, Cheng G, *et al.* Hs-CRP and all-cause, cardiovascular, and cancer mortality risk: A meta-analysis. *Atherosclerosis* 2017;**259**:75-82.

9 Vasto S, Candore G, Balistreri CR, *et al.* Inflammatory networks in ageing, age-related diseases and longevity. *Mechanisms of ageing and development* 2007;**128**:83-91.

10 Kelley-Hedgepeth A, Lloyd-Jones DM, Colvin A, *et al.* Ethnic differences in C-reactive protein concentrations. *Clinical chemistry* 2008;**54**:1027-37.

11 Albert MA, Glynn RJ, Buring J, *et al.* C-reactive protein levels among women of various ethnic groups living in the United States (from the Women's Health Study). *The American journal of cardiology* 2004;**93**:1238-42.

12 Khera A, McGuire DK, Murphy SA, *et al.* Race and gender differences in C-reactive protein levels. *Journal of the American College of Cardiology* 2005;**46**:464-9.

13 Lakoski SG, Cushman M, Criqui M, *et al.* Gender and C-reactive protein: data from the Multiethnic Study of Atherosclerosis (MESA) cohort. *American heart journal* 2006;**152**:593-8.

14 Matthews KA, Sowers MF, Derby CA, *et al.* Ethnic differences in cardiovascular risk factor burden among middle-aged women: Study of Women's Health Across the Nation (SWAN). *American heart journal* 2005;**149**:1066-73.

15 Lee JH, Yeom H, Kim HC, *et al.* C-reactive Protein Concentration Is Associated With a Higher Risk of Mortality in a Rural Korean Population. *Journal of preventive medicine and public health = Yebang Uihakhoe chi* 2016;**49**:275-87.

16 Sung KC, Ryu S, Chang Y, *et al.* C-reactive protein and risk of cardiovascular and all-cause mortality in 268 803 East Asians. *European heart journal* 2014;**35**:1809-16.

17 Kengne AP, Batty GD, Hamer M*, et al.* Association of C-reactive protein with cardiovascular disease mortality according to diabetes status: pooled analyses of 25,979 participants from four U.K. prospective cohort studies. *Diabetes care* 2012;**35**:396-403.

18 Heikkila K, Ebrahim S, Lawlor DA. A systematic review of the association between circulating concentrations of C reactive protein and cancer. *Journal of epidemiology and community health* 2007;**61**:824-33.

19 Dahl M, Vestbo J, Lange P*, et al.* C-reactive protein as a predictor of prognosis in chronic obstructive pulmonary disease. *American journal of respiratory and critical care medicine* 2007;**175**:250-5.

20 Wang X, Bao W, Liu J*, et al.* Inflammatory markers and risk of type 2 diabetes: a systematic review and meta-analysis. *Diabetes care* 2013;**36**:166-75.

21 Ishii S, Cauley JA, Greendale GA*, et al.* C-reactive protein, bone strength, and nine-year fracture risk: data from the Study of Women's Health Across the Nation (SWAN). *Journal of bone and mineral research : the official journal of the American Society for Bone and Mineral Research* 2013;**28**:1688-98.

22 Kim Y, Han BG, Ko GESg. Cohort Profile: The Korean Genome and Epidemiology Study (KoGES) Consortium. *International journal of epidemiology* 2017;**46**:1350.

23 Shin S, Lee HW, Kim CE*, et al.* Egg Consumption and Risk of Metabolic Syndrome in Korean Adults: Results from the Health Examinees Study. *Nutrients* 2017;**9**.

24 Pan WH, Yeh WT. How to define obesity? Evidence-based multiple action points for public awareness, screening, and treatment: an extension of Asian-Pacific recommendations. *Asia Pacific journal of clinical nutrition* 2008;**17**:370-4.

25 National Cholesterol Education Program Expert Panel on Detection E, Treatment of High Blood Cholesterol in A. Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. *Circulation* 2002;**106**:3143-421.

26 Heinzl H, Kaider A. Gaining more flexibility in Cox proportional hazards regression models with cubic spline functions. *Computer methods and programs in biomedicine* 1997;**54**:201-8.

27 MacGregor AJ, Gallimore JR, Spector TD*, et al.* Genetic effects on baseline values of C-reactive protein and serum amyloid a protein: a comparison of monozygotic and dizygotic twins. *Clinical chemistry* 2004;**50**:130-4.

28 Ledue TB, Rifai N. Preanalytic and analytic sources of variations in C-reactive protein measurement: implications for cardiovascular disease risk assessment. *Clinical chemistry* 2003;**49**:1258-71.

29 Emerging Risk Factors C, Kaptoge S, Di Angelantonio E, *et al.* C-reactive protein concentration and risk of coronary heart disease, stroke, and mortality: an individual participant meta-analysis. *Lancet* 2010;**375**:132-40.

30 Lee YJ, Lee JH, Shin YH, *et al.* Gender difference and determinants of C-reactive protein level in Korean adults. *Clinical chemistry and laboratory medicine* 2009;**47**:863-9.

31 Doran B, Zhu W, Muennig P. Gender differences in cardiovascular mortality by C-reactive protein level in the United States: evidence from the National Health and Nutrition Examination Survey III. *American heart journal* 2013;**166**:45-51.

32 Gaskins AJ, Wilchesky M, Mumford SL, *et al.* Endogenous reproductive hormones and C-reactive protein across the menstrual cycle: the BioCycle Study. *American journal of epidemiology* 2012;**175**:423-31.

33 Gilliver SC. Sex steroids as inflammatory regulators. *The Journal of steroid biochemistry and molecular biology* 2010;**120**:105-15.

34 Man SF, Connett JE, Anthonisen NR, *et al.* C-reactive protein and mortality in mild to moderate chronic obstructive pulmonary disease. *Thorax* 2006;**61**:849-53.

35 Di Napoli M, Papa F. Angiotensin-converting enzyme inhibitor use is associated with reduced plasma concentration of C-reactive protein in patients with first-ever ischemic stroke. *Stroke* 2003;**34**:2922-9.

36 Sidhu JS, Cowan D, Kaski JC. The effects of rosiglitazone, a peroxisome proliferator-activated receptor-gamma agonist, on markers of endothelial cell activation, C-reactive protein, and fibrinogen levels in non-diabetic coronary artery disease patients. *Journal of the American College of Cardiology* 2003;**42**:1757-63.

37 Heikkila K, Ebrahim S, Rumley A, *et al.* Associations of circulating C-reactive protein and interleukin-6 with survival in women with and without cancer: findings from the British Women's Heart and Health Study. *Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology* 2007;**16**:1155-9.

38 Marsik C, Kazemi-Shirazi L, Schickbauer T, *et al.* C-reactive protein and all-cause mortality in a large hospital-based cohort. *Clinical chemistry* 2008;**54**:343-9.

39 Proctor MJ, McMillan DC, Horgan PG, *et al.* Systemic inflammation predicts all-cause mortality: a glasgow inflammation outcome study. *PloS one* 2015;**10**:e0116206.

40 Chen TH, Gona P, Sutherland PA, *et al.* Long-term C-reactive protein variability and prediction of metabolic risk. *The American journal of medicine* 2009;**122**:53-61.

41 Zheng W, McLerran DF, Rolland B, *et al.* Association between Body-Mass Index and Risk of Death in More Than 1 Million Asians , *N Engl J Med* 2011; 364:719-729.

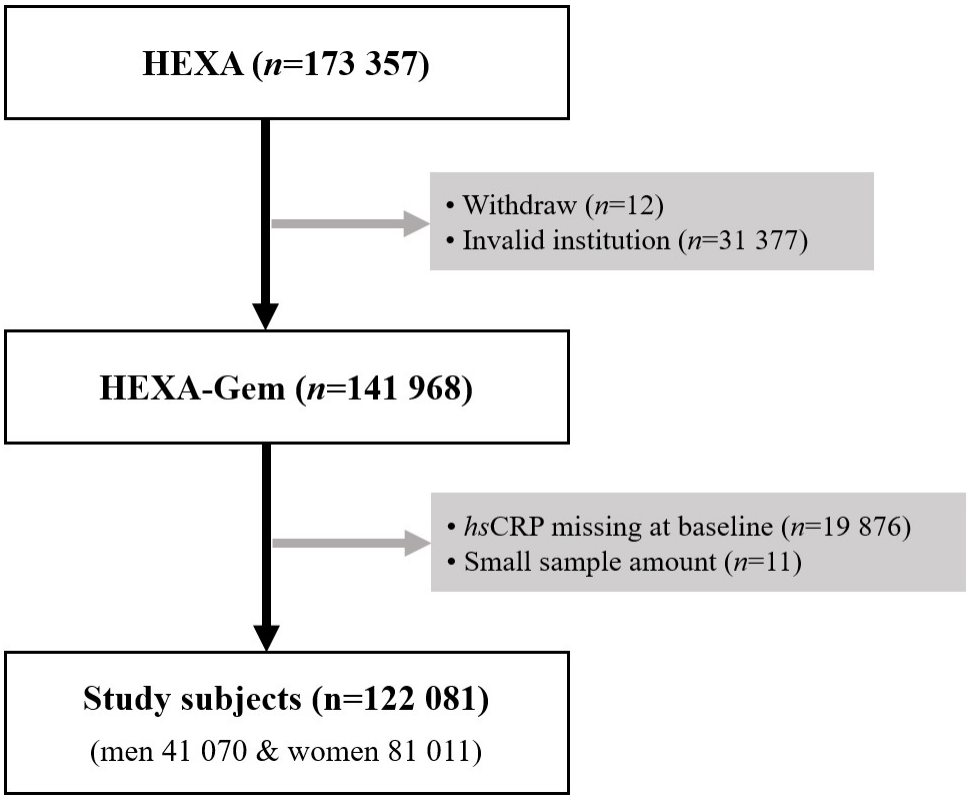


Figure 1 Flow diagram of analytical sample in current study using Health Examinees cohort.
HEXA: Health Examinees, hsCRP: High sensitivity C-reactive protein

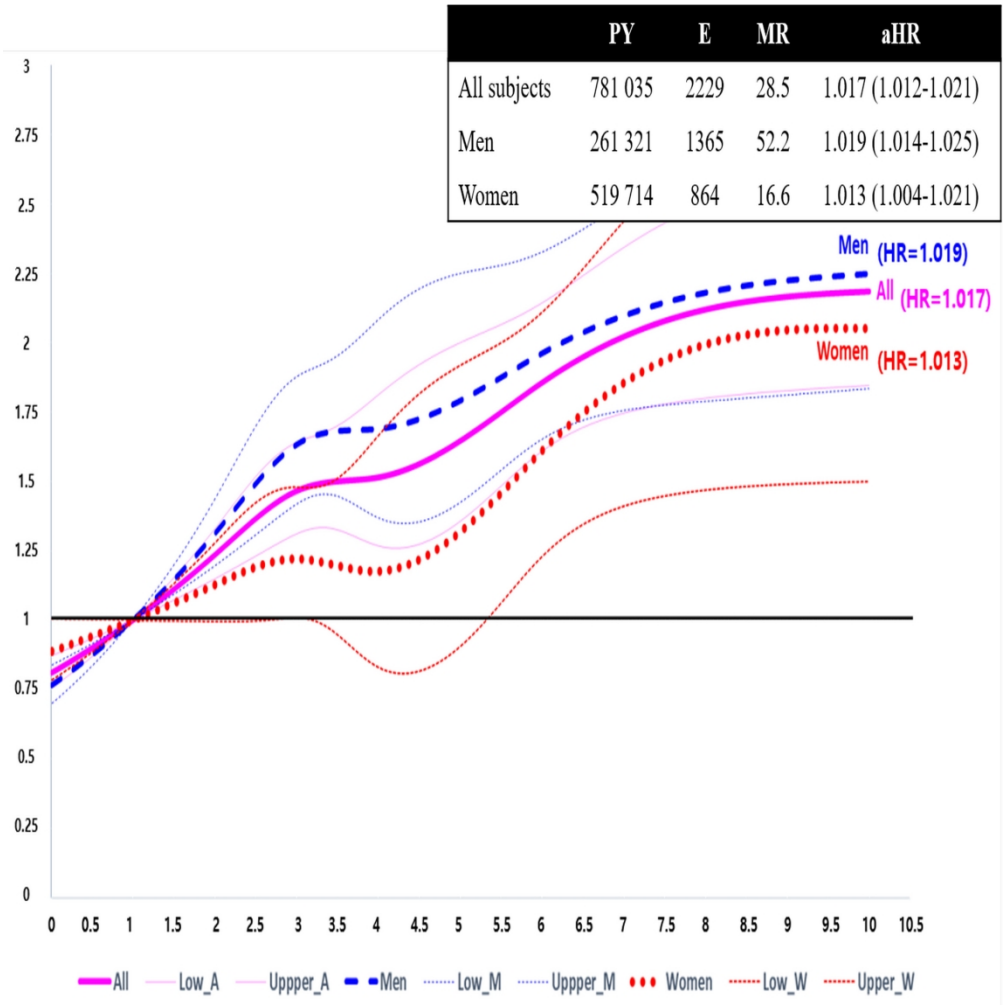


Figure 2 (a) A dose-response association between serum hsCRP level and risk of all-cause mortality in all subjects at recruitment.PY: Person-year, E: Number of death, MR: Mortality rate (10 000 person year)aHR: Adjusted for age, gender, education, job, marital status, BMI, non-communicable disease history, smoking, alcohol consumption and exerciseLow_A and Upper_A: 95%CI for all subjectsLow_M and Upper_M: 95%CI for menLow_W and Upper_W: 95%CI for women

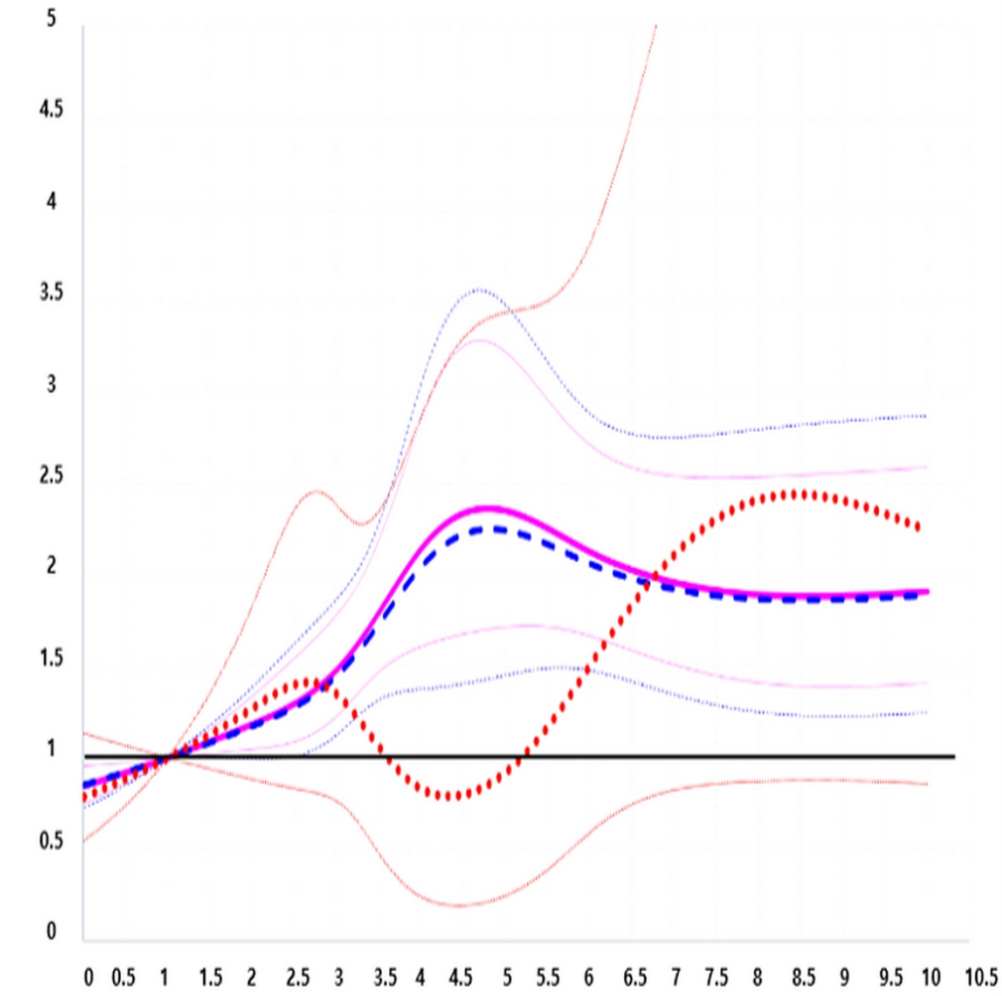


Figure 2 (b) A dose-response association between serum hsCRP level and risk of all-cause mortality in healthy subjects at recruitment.Low_A and Upper_A: 95%CI for all subjects Low_M and Upper_M: 95%CI for menLow_W and Upper_W: 95%CI for women

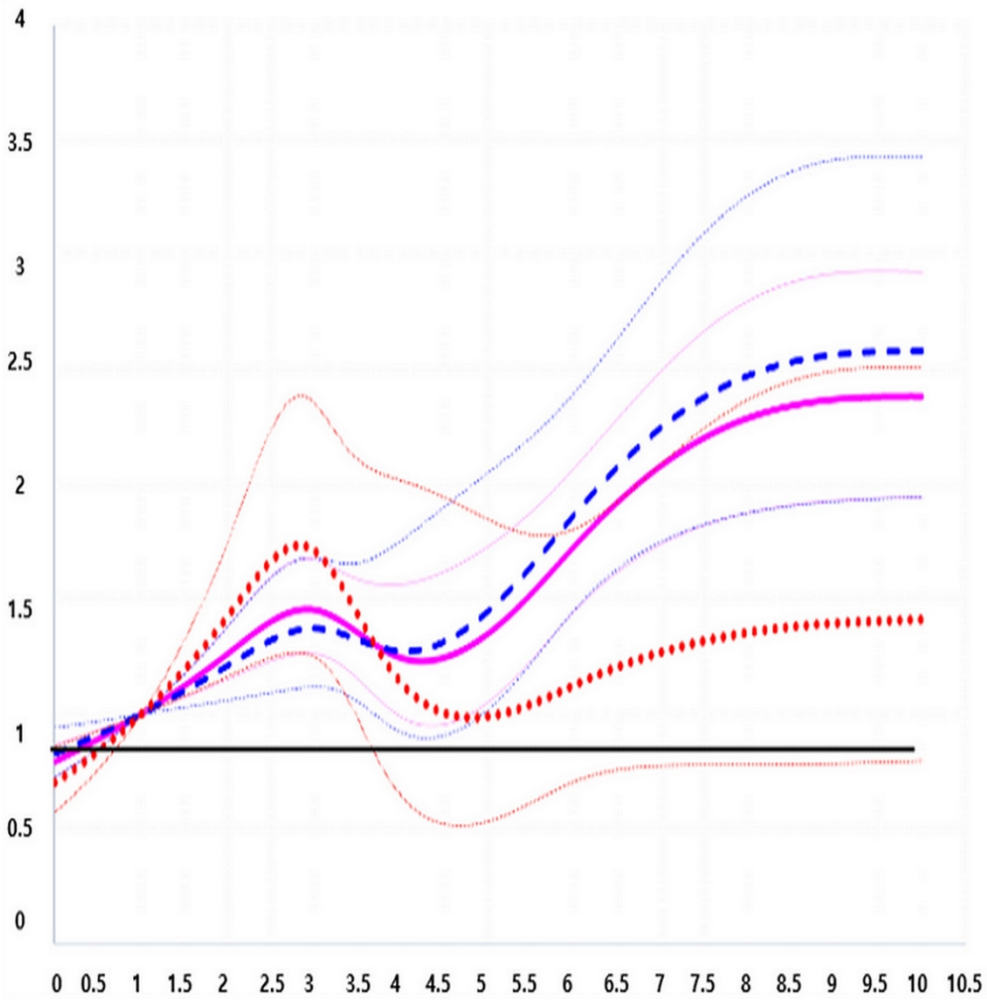


Figure 2 (c) A dose-response association between serum hsCRP level and risk of all-cause mortality in subjects with non-communicable disease history (NCDhistory) at recruitment.Low_A and Upper_A: 95%CI for all subjectsLow_M and Upper_M: 95%CI for menLow_W and Upper_W: 95%CI for women

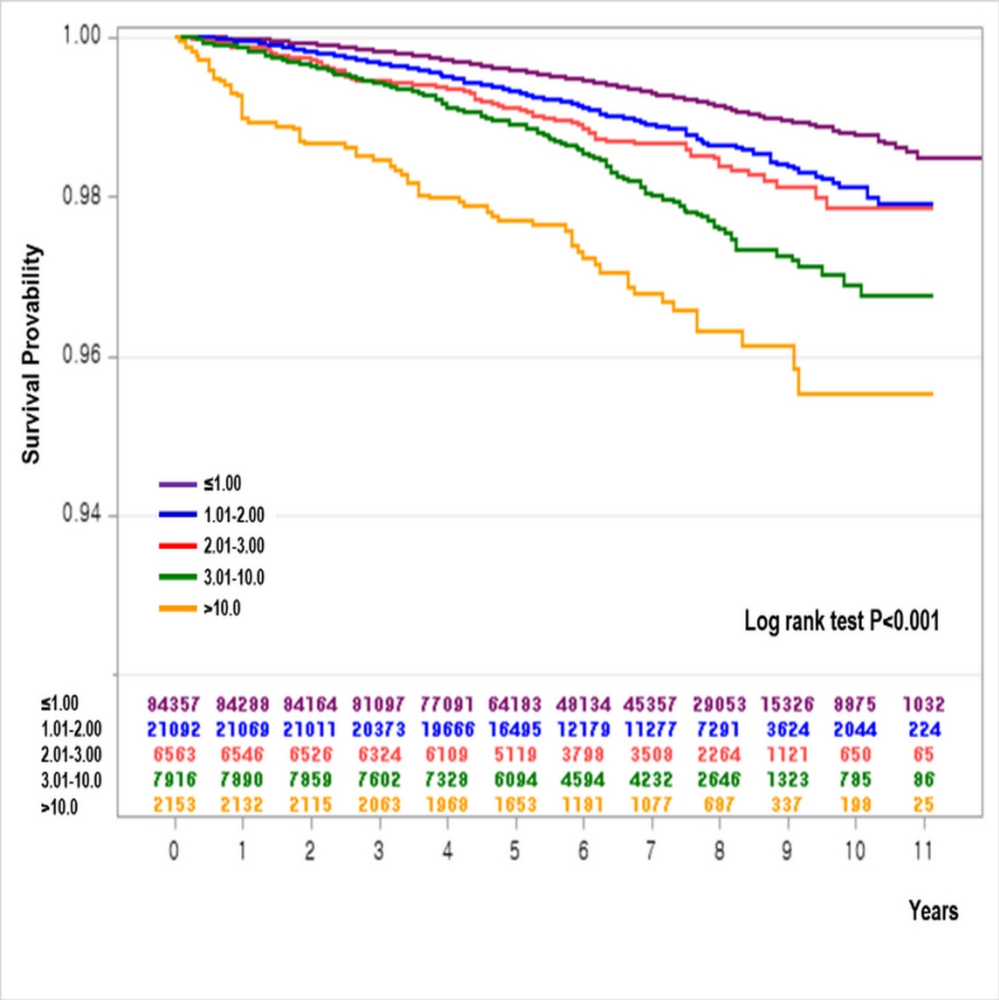


Figure 3 (a) Kaplan-Meier crude survival curves for cancer-mortality according to serum hsCRP level in all subjects at recruitment.

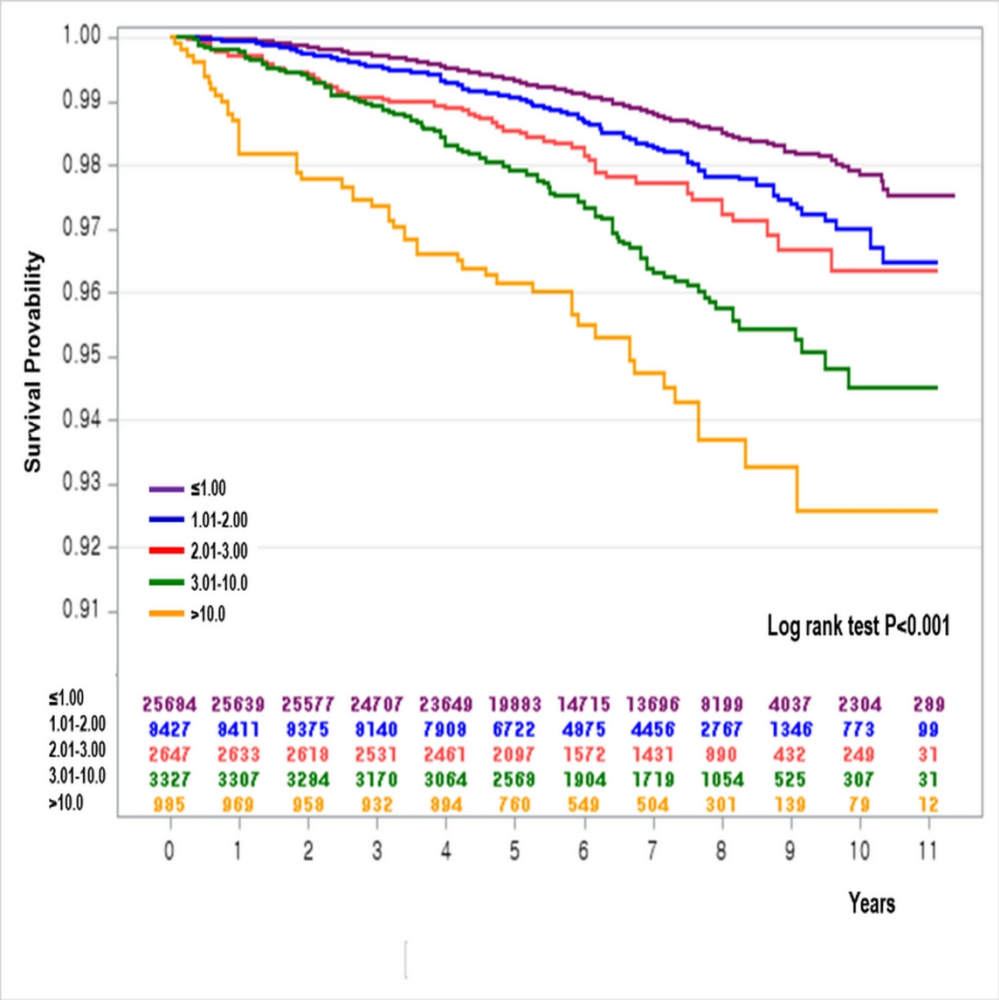


Figure 3 (b) Kaplan-Meier crude survival curves for cancer-mortality according to serum hsCRP level in men at recruitment.

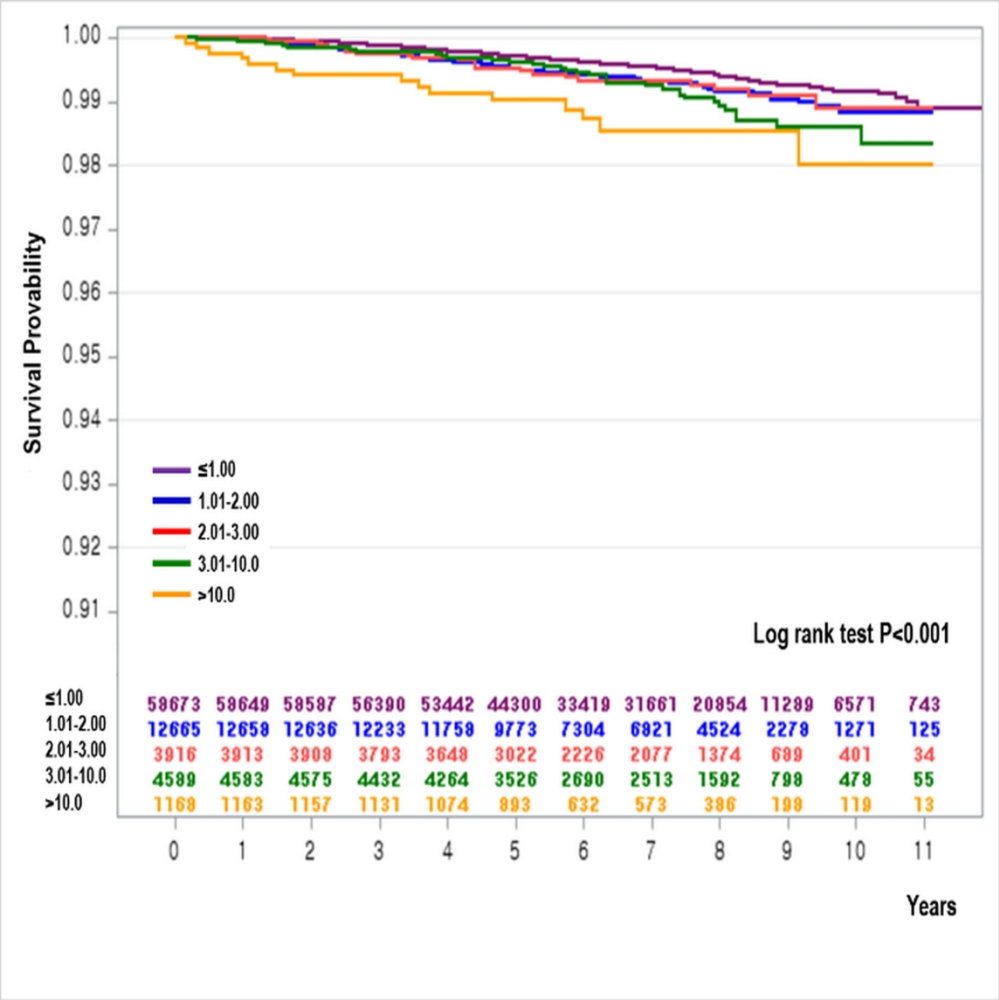


Figure 3 (c) Kaplan-Meier crude survival curves for cancer-mortality according to serum hsCRP level in women at recruitment.

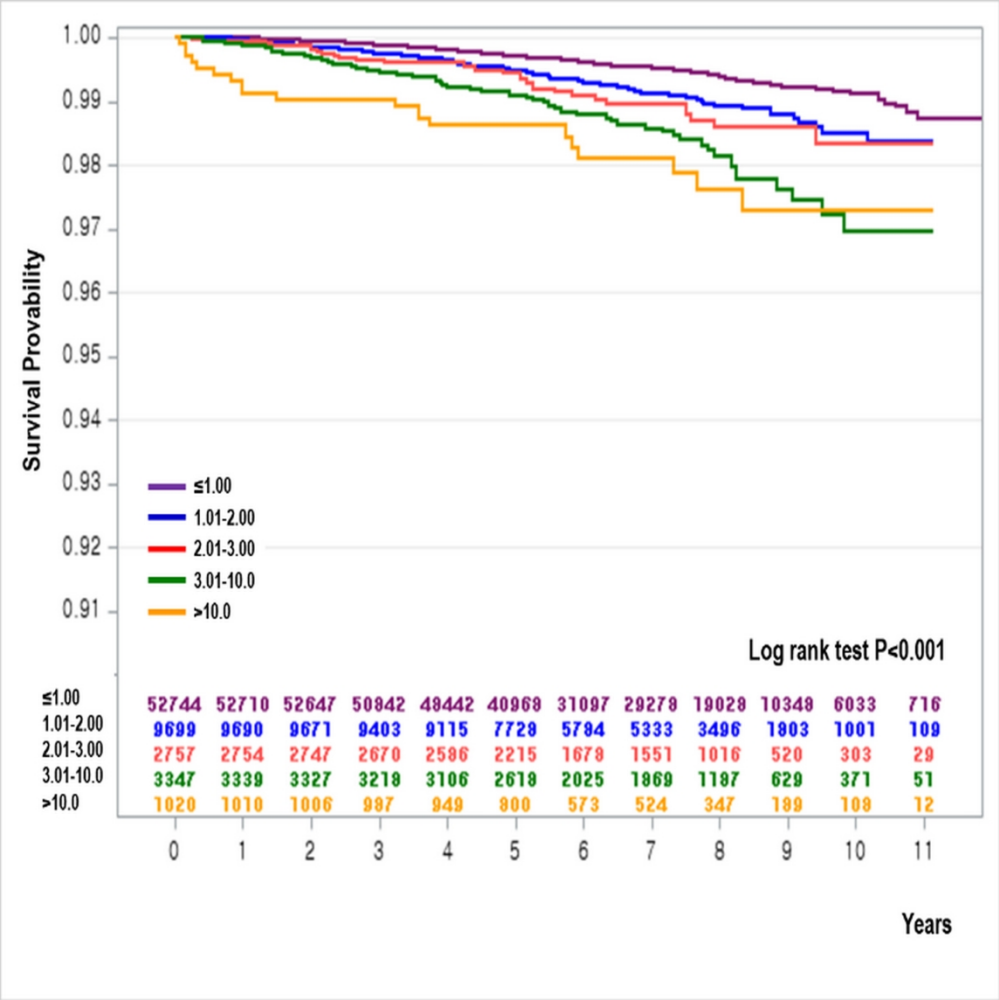


Figure 3 (d) Kaplan-Meier crude survival curves for cancer-mortality according to serum hsCRP level in healthy subjects at recruitment.

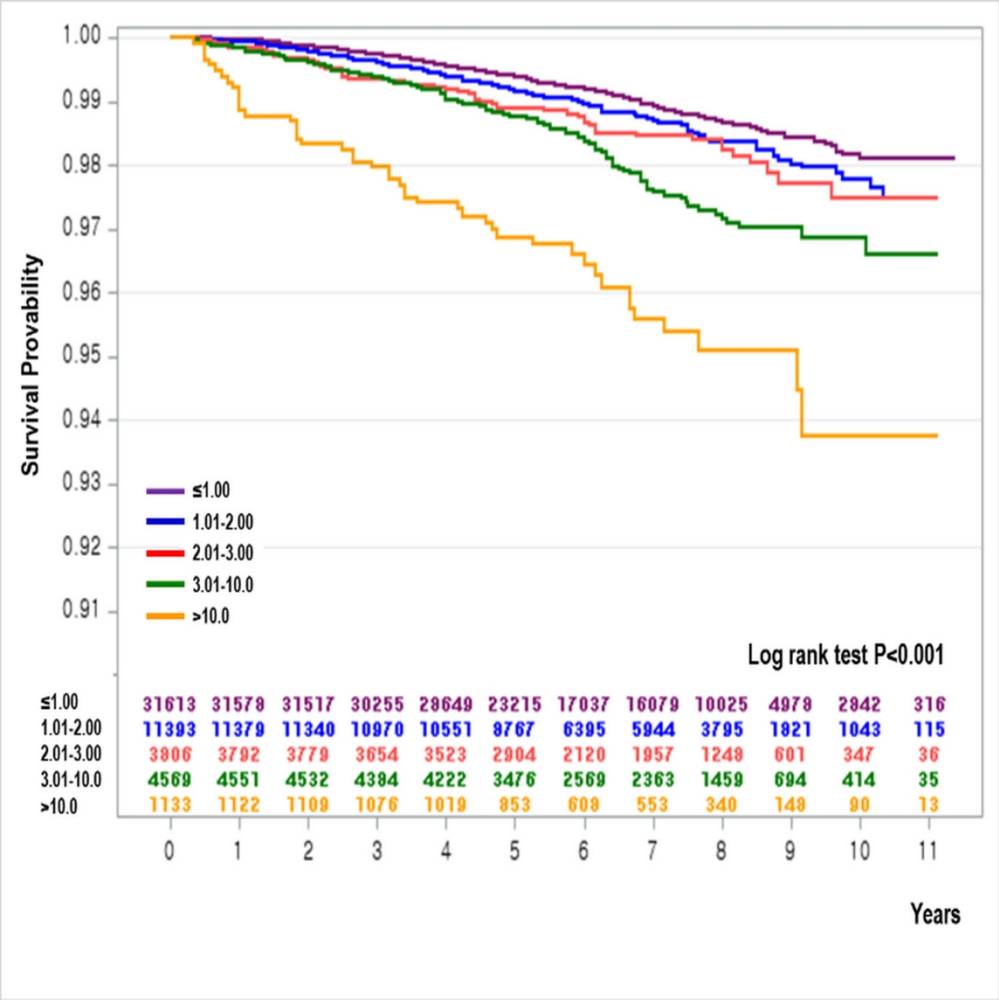


Figure 3 (e) Kaplan-Meier crude survival curves for cancer-mortality according to serum hsCRP level in subjects with non-communicable disease history (NCDhistory) at recruitment.

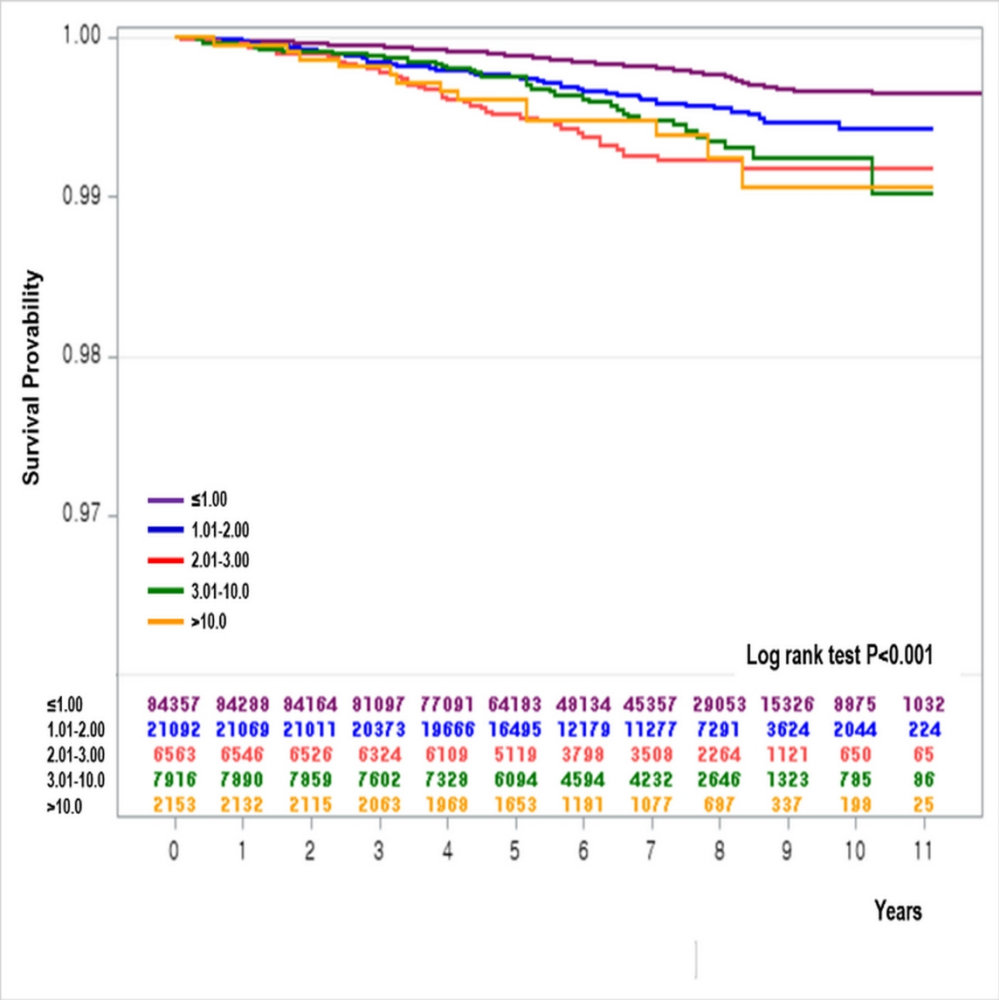


Figure 4 (a) Kaplan-Meier crude survival curves for cardiovascular disease mortality according to serum hsCRP level in all subjects at recruitment.

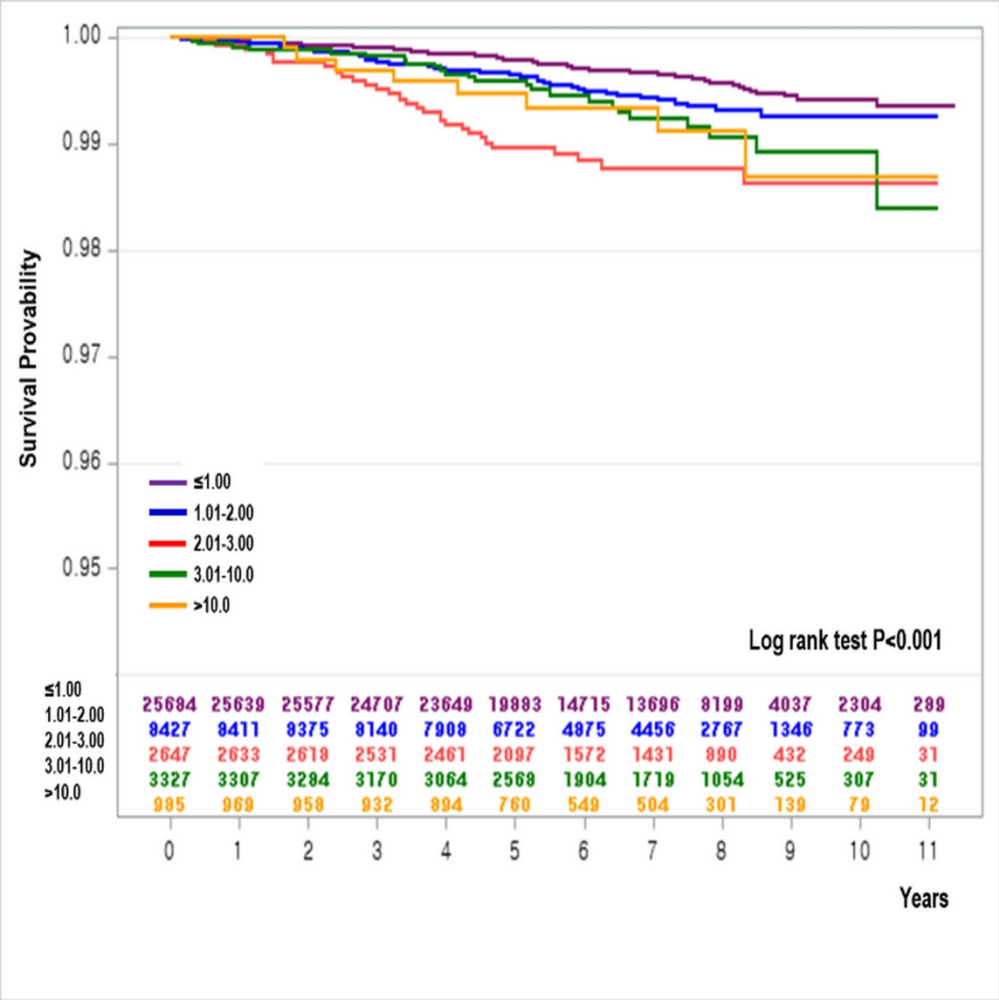


Figure 4 (b) Kaplan-Meier crude survival curves for cardiovascular disease mortality according to serum hsCRP level in men at recruitment.

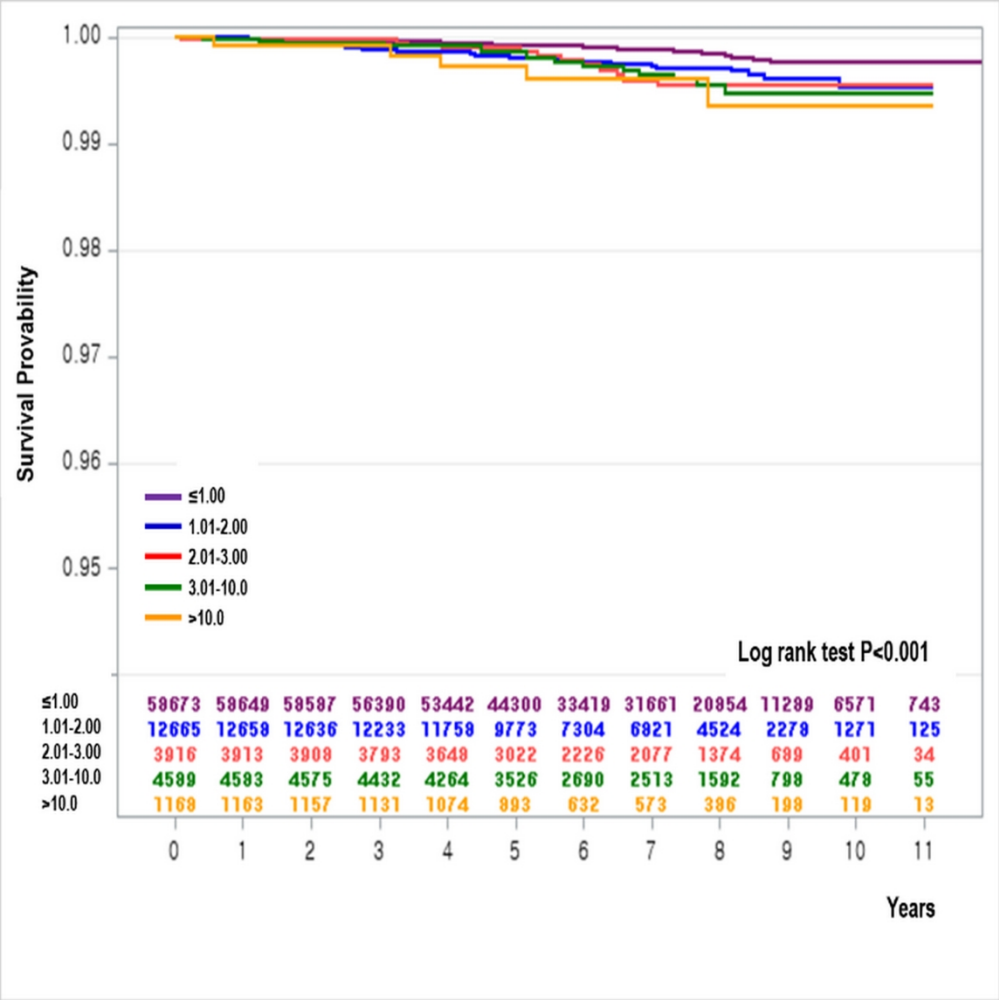


Figure 4 (c) Kaplan-Meier crude survival curves for cardiovascular disease mortality according to serum hsCRP level in women at recruitment.

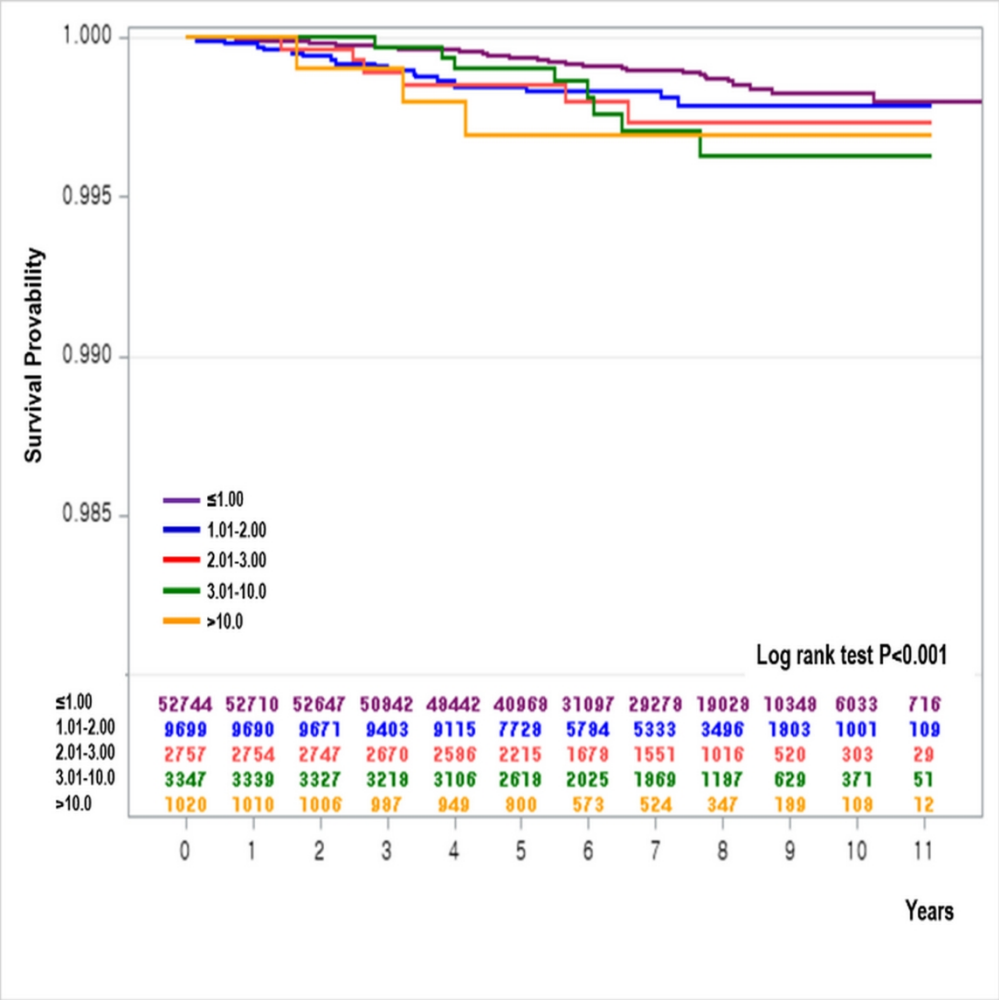


Figure 4 (d) Kaplan-Meier crude survival curves for cardiovascular disease mortality according to serum hsCRP level in healthy subjects at recruitment.

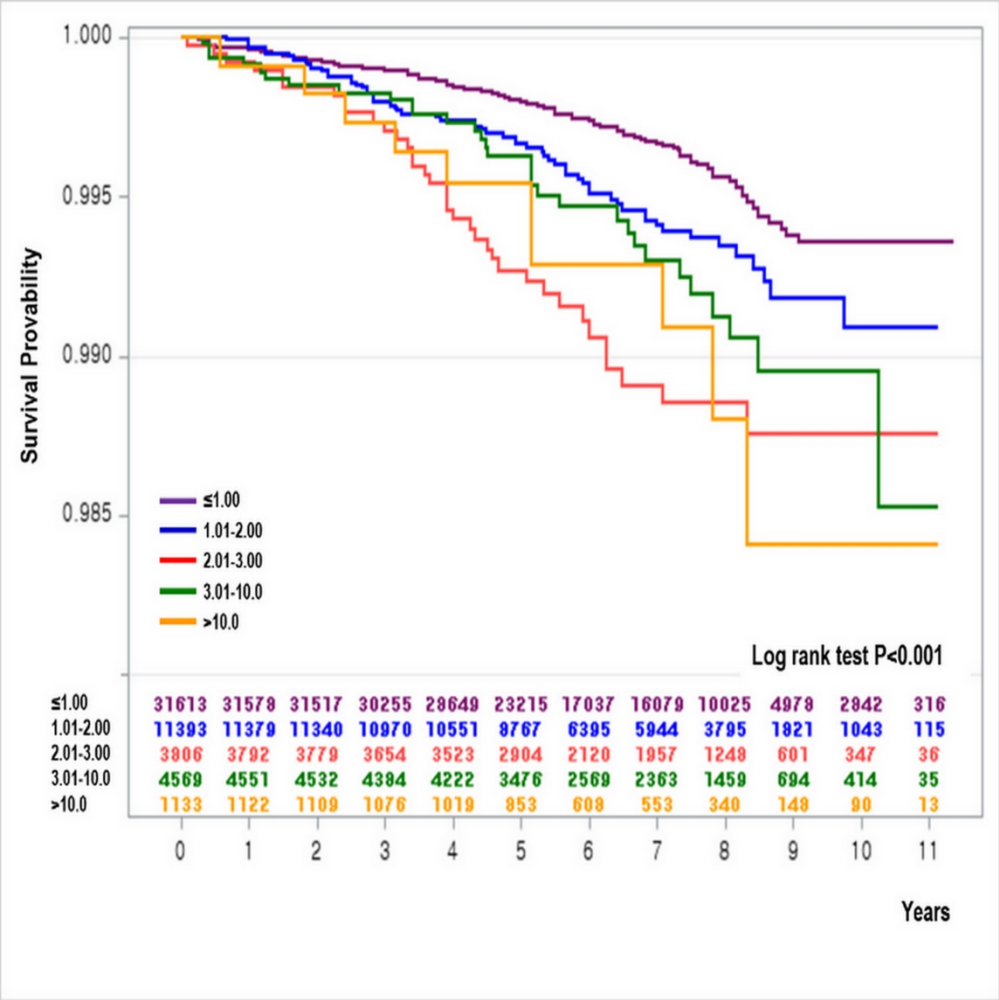


Figure 4 (e) Kaplan-Meier crude survival curves for cardiovascular disease mortality according to serum hsCRP level in subjects with non-communicable disease history (NCDhistory) at recruitment.

Supplement 1. The association of serum *hs*CRP level with the risk of all-cause mortality

	PY	E	MR	aHR	HR_{1year}	HR_{2year}
All subjects						
Continuous	781 035	2229	28.5	1.017 (1.012-1.021)	1.015 (1.010-1.020)	1.014 (1.009-1.019)
≤1.00	539 271	1153	21.4	Reference	Reference	Reference
1.01-1.50	90 911	308	33.9	1.26 (1.10-1.45)	1.27 (1.10-1.45)	1.21 (1.04-1.40)
1.51-2.00	44 615	163	36.5	1.28 (1.08-1.53)	1.28 (1.07-1.53)	1.26 (1.04-1.52)
2.01-2.50	25 139	117	46.5	1.53 (1.25-1.89)	1.51 (1.22-1.87)	1.49 (1.19-1.87)
2.51-3.00	16 996	72	42.4	1.39 (1.08-1.80)	1.31 (1.00-1.72)	1.23 (0.92-1.65)
3.01-4.00	19 667	103	52.4	1.61 (1.29-2.01)	1.62 (1.29-2.03)	1.64 (1.30-2.08)
4.01-6.00	17 933	102	56.9	1.84 (1.48-2.28)	1.77 (1.41-2.21)	1.70 (1.34-2.16)
6.01-10.00	13 019	88	67.6	2.02 (1.59-2.56)	1.96 (1.54-2.50)	1.93 (1.49-2.51)
>10.0	13 484	123	91.2	2.59 (2.12-3.16)	2.41 (1.95-2.97)	2.26 (1.80-2.84)
P-trend				<.001	<.001	<.001
Men						
Continuous	261 321	1365	52.2	1.019 (1.014-1.025)	1.017 (1.011-1.023)	1.017 (1.010-1.023)
≤1.00	163 068	638	39.1	Reference	Reference	Reference
1.01-1.50	36 094	190	52.6	1.27 (1.07-1.51)	1.28 (1.07-1.53)	1.22 (1.01-1.47)
1.51-2.00	17 946	103	57.4	1.34 (1.07-1.67)	1.34 (1.07-1.68)	1.35 (1.06-1.72)
2.01-2.50	10 059	77	76.5	1.56 (1.20-2.03)	1.53 (1.16-2.00)	1.47 (1.10-1.96)
2.51-3.00	6959	54	77.6	1.71 (1.27-2.29)	1.57 (1.15-2.15)	1.46 (1.04-2.05)
3.01-4.00	8177	77	94.2	1.88 (1.45-2.43)	1.94 (1.50-2.52)	1.92 (1.46-2.54)
4.01-6.00	7425	75	101.0	2.05 (1.59-2.63)	1.95 (1.49-2.53)	1.91 (1.44-2.52)
6.01-10.00	5456	59	108.1	2.03 (1.52-2.73)	1.96 (1.44-2.66)	1.85 (1.33-2.58)
>10.0	6137	92	149.9	2.84 (2.25-3.58)	2.66 (2.08-3.39)	2.58 (1.99-3.35)
P-trend				<.001	<.001	<.001
Women						
Continuous	519 714	864	16.6	1.013 (1.004-1.021)	1.011(1.002-1.021)	1.010 (0.999-1.021)
≤1.00	376 203	515	13.7	Reference	Reference	Reference
1.01-1.50	54 817	118	21.5	1.28 (1.03-1.59)	1.27 (1.02-1.58)	1.23 (0.97-1.56)
1.51-2.00	26 669	60	22.5	1.23 (0.92-1.64)	1.21 (0.90-1.63)	1.14 (0.83-1.56)
2.01-2.50	15 080	40	26.5	1.52 (1.09-2.14)	1.52 (1.08-2.15)	1.56 (1.09-2.24)
2.51-3.00	10 037	18	17.9	0.84 (0.49-1.44)	0.87 (0.51-1.48)	0.83 (0.46-1.47)
3.01-4.00	11 490	26	22.6	1.16 (0.75-1.81)	1.09 (0.68-1.72)	1.21 (0.76-1.93)
4.01-6.00	10 508	27	25.7	1.48 (0.99-2.22)	1.47 (0.97-2.22)	1.36 (0.86-2.14)
6.01-10.00	7563	29	38.3	2.00 (1.34-2.98)	1.98 (1.32-2.98)	2.10 (1.39-3.19)
>10.0	7347	31	42.2	2.02 (1.36-3.02)	1.84 (1.21-2.81)	1.51 (0.93-2.47)
P-trend				<.001	<.001	0.001
Premenopause						
≤1.00	141 286	96	6.8			
1.01-2.00	20 500	20	9.8	1.52 (0.92-2.52)	1.49 (0.89-2.50)	1.57 (0.90-2.73)
2.01-3.00	5835	6	10.3	1.76 (0.77-4.06)	1.83 (0.79-4.22)	1.42 (0.52-3.93)
3.01-10.0	6886	6	8.7	1.51 (0.66-3.50)	1.31 (0.53-3.25)	1.21 (0.44-3.36)
>10.0	1759	4	22.7	2.57 (0.81-8.14)	2.63 (0.83-8.37)	2.09 (0.51-8.58)
P-trend				0.020	0.036	0.150
Postmenopause						
≤1.00	192 164	366	19.0			
1.01-2.00	52 897	145	27.4	1.26 (1.03-1.55)	1.25 (1.02-1.54)	1.18 (0.95-1.48)
2.01-3.00	16 943	44	26.0	1.11 (0.80-1.56)	1.12 (0.80-1.57)	1.19 (0.83-1.68)
3.01-10.0	19 687	67	34.0	1.49 (1.13-1.97)	1.47 (1.10-1.95)	1.52 (1.13-2.05)
>10.0	4828	27	55.9	2.09 (1.37-3.21)	1.88 (1.19-2.96)	1.56 (0.92-2.63)
P-trend				<0.001	0.001	0.003

PY: Person-year, E: Number of death, MR: Mortality rate (10,000 person year)

aHR: Adjusted for age, gender, education, job, marital status, BMI, non-communicable disease history, smoking, alcohol consumption and exercise
HR_{1year}: aHR after exclude subjects who died within 1 yr f/u time
HR_{2year}: aHR after exclude subjects who died within 2 yr f/u time

Supplement 2. The association between serum *hs*CRP level and all-cause mortality by gender and non-communicable disease history ($NCD_{history}$) at recruitment

	Healthy subjects at recruitment					Subjects with $NCD_{history}$ at recruitment				
	E	MR	aHR	HR_{1year}	HR_{2year}	E	MR	aHR	HR_{1year}	HR_{2year}
All										
≤ 1.00	517	15.1	Ref	Ref	Ref	636	32.3	Ref	Ref	Ref
1.01-2.00	145	22.9	1.20	1.19	1.16	326	45.1	1.20	1.19	1.16
2.01-3.00	53	29.3	1.38	1.37	1.32	136	56.6	1.51	1.46	1.41
3.01-10.0	102	46.8	2.22	2.15	2.15	191	66.3	1.62	1.60	1.58
>10.0	40	61.3	2.38	2.23	2.27	83	118.9	2.74	2.54	2.29
P-trend			<.001	<.001	<.001			<.001	<.001	<.001
Men										
≤ 1.00	270	29.5	Ref	Ref	Ref	368	51.4	Ref	Ref	Ref
1.01-2.00	89	35.8	1.11	1.11	1.13	204	70.0	1.40	1.41	1.33
2.01-3.00	33	46.3	1.22	1.17	1.15	98	99.0	1.82	1.73	1.61
3.01-10.0	70	76.8	2.14	2.08	2.03	141	118.1	1.92	1.90	1.83
>10.0	31	110.0	2.60	2.49	2.73	61	183.1	3.05	2.83	2.58
P-trend			<.001	<.001	<.001			<.001	<.001	<.001
Women										
≤ 1.00	247	9.8	Ref	Ref	Ref	268	21.4	Ref	Ref	Ref
1.01-2.00	56	14.6	1.35	1.32	1.20	122	28.3	1.19	1.20	1.19
2.01-3.00	20	18.2	1.61	1.66	1.60	38	26.9	1.06	1.06	1.11
3.01-10.0	32	25.2	2.31	2.23	2.37	50	29.7	1.16	1.14	1.17
>10.0	9	24.3	1.69	1.49	1.12	22	60.3	2.15	1.99	1.68
P-trend			<.001	<.001	0.001			0.018	0.043	0.084

E: Number of death, MR: Mortality rate (10 000 person year)

aHR: Adjusted for age, gender, education, job, marital status, BMI, non-communicable disease history, smoking, alcohol consumption and exercise

HR_{1year}: aHR after exclude subjects who died within 1 yr f/u time

HR_{2year}: aHR after exclude subjects who died within 2 yr f/u time

STROBE 2007 (v4) checklist of items to be included in reports of observational studies in epidemiology*

Checklist for cohort, case-control, and cross-sectional studies (combined)

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	1-2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3
Objectives	3	State specific objectives, including any pre-specified hypotheses	3
Methods			
Study design	4	Present key elements of study design early in the paper	4
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4-5
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	4
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	Not Applicable
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	4-5
Bias	9	Describe any efforts to address potential sources of bias	6
Study size	10	Explain how the study size was arrived at	4
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	5-6
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	5-6
		(*b*) Describe any methods used to examine subgroups and interactions	5-6
		(*c*) Explain how missing data were addressed	4
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed	4

		Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	6
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	4
		(b) Give reasons for non-participation at each stage	4
		(c) Consider use of a flow diagram	4
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	6-7
		(b) Indicate number of participants with missing data for each variable of interest	4
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	6
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	6-10
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	Not Applicable
		Cross-sectional study—Report numbers of outcome events or summary measures	Not Applicable
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	7-11
		(*b*) Report category boundaries when continuous variables were categorized	5
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Not Applicable
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	9
Discussion			
Key results	18	Summarise key results with reference to study objectives	12
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	14
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	12-14
Generalisability	21	Discuss the generalisability (external validity) of the study results	12-14
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	15

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.
Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.