

BMJ Open

BMJ Open is committed to open peer review. As part of this commitment we make the peer review history of every article we publish publicly available.

When an article is published we post the peer reviewers' comments and the authors' responses online. We also post the versions of the paper that were used during peer review. These are the versions that the peer review comments apply to.

The versions of the paper that follow are the versions that were submitted during the peer review process. They are not the versions of record or the final published versions. They should not be cited or distributed as the published version of this manuscript.

BMJ Open is an open access journal and the full, final, typeset and author-corrected version of record of the manuscript is available on our site with no access controls, subscription charges or pay-per-view fees (<http://bmjopen.bmj.com>).

If you have any questions on BMJ Open's open peer review process please email info.bmjopen@bmj.com

BMJ Open

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

Journal:	<i>BMJ Open</i>
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

SCHOLARONE™
Manuscripts



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.

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

200 **Sang-Ah Lee^{1,2*}, Sung Ok Kwon¹, Hyerim Park¹, Xiao-Ou Shu², Jong-Koo Lee³, Daehee Kang⁴**

203 ¹Department of Preventive Medicine, School of Medicine, Kangwon National University, Chuncheon, Republic
204 of Korea.

205 ²Division of Epidemiology, Vanderbilt Epidemiology Center, Vanderbilt University Medical Center, Nashville,
206 TN, USA.

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

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

211 **ABSTRACT**

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

214 **Design** Prospective cohort study.

215 **Setting** the Health Examinees (HEXA) cohort.

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

217 **Outcome measures** The data and cause of death occurring until December 31, 2015, were confirmed by death
218 statistics from the National Statistical Office. We conducted the advanced analysis after stratification by
219 NCD_{history} and the sensitivity analysis after excluding death before 1 or 2 years from recruitment. Cox
220 proportional hazard and restricted cubic spline models were used to assess the association.

221 **Results** The association between serum *hsCRP* and the risk of all-cause mortality was observed with strong
222 linearity in both genders, which was not influenced by NCD_{history}. Otherwise, the association of serum *hsCRP*
223 with cancer-mortality risk was not observed in women with NCD_{history}, but the association with the risk of
224 cardiovascular disease (CVD) mortality was predominantly observed in men with NCD_{history}.

225 **Conclusions** This study suggested the dose-response association of *hsCRP* with mortality risk, including
226 cancer and CVD mortality, in Korean with low serum *hsCRP*, although the association with cancer and CVD-
227 mortality risk could be influenced by gender and NCD_{history}.

230 **Strengths and limitations of this study**

- 231 • This is the large population-based prospective study.
- 232 • We examined the effect of very high *hsCRP* concentration on mortality risk.
- 233 • The *hsCRP* level of present study was measured within 18 hours in a single institution to minimize error/bias.

1
2
3
4 234 · Due to due to random fluctuations of *hsCRP*, using the single measurement of *hsCRP* at baseline could reflect
5
6 235 the inaccurate status of blood *hsCRP* levels in the study participants and increase the instability of *hsCRP*.
7
8 236 · This study lacked information on medication use at recruitment and during the follow-up period, and
9
10 237 information on hormone-replacement therapy (HRT) among women.
11
12 238
13 239

14 240 *Correspondence to: Sang-Ah Lee, Ph.D.

15 241 Department of Preventive Medicine, School of Medicine, Kangwon National University,

16 242 Chuncheon, Gangwon, Republic of Korea.

17 243 Tel: +82 33 250 8871

18 244 E-mail: sangahlee@kangwon.ac.kr
19 245
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

266 INTRODUCTION

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

274 Serum *hsCRP* represents a low-grade inflammation state that is generally involved in the process of aging[9].
275 Several large cohorts, including Study of Women's Health Across the Nation (SWAN)[10], the Women's
276 Health Study[11] and the Dallas Heart Study[12], reported significant differences in *hsCRP* levels by race and
277 gender. In two studies of multiethnic populations residing in the USA[10, 13], the median *hsCRP* level in East
278 Asians was less than half the concentration in Caucasians. Even among East Asian populations, the geometric
279 mean of *hsCRP* levels varied depending on ethnic background[14]. In addition, a meta-analysis[11] reported
280 the *hsCRP* levels among women of various ethnic groups living in the United States (from the Women's Health
281 Study) on the association between *hsCRP* and the mortality risk; the association was observed in only men
282 supported by the results from two cohort studies[15, 16] reported in Korea. On the other hand, the increased
283 *hsCRP* may be influenced by comorbidity itself because inflammation has emerged as an important factor in the
284 progression of non-communicable diseases (NCDs), including CVD[17], cancer[18], chronic obstructive
285 pulmonary disease (COPD)[19], type 2 diabetes[20] and fractures[21], which contribute to increased morbidity
286 and mortality.

287 This study aimed to examine the association of serum *hsCRP* with the risk of mortality in Koreans with low
288 serum *hsCRP* and to evaluate the attenuated effect of non-communicable disease history ($NCD_{history}$) on the
289 association.

290

291

292

293

294

295 **METHODS**

296 **Study population**

297 Details on the main objectives, rationale, study design and baseline characteristics of the Health Examinees
298 (HEXA) study have been published elsewhere[22]. Considering the homogeneity and comparability of
299 participants, we created a qualified dataset called HEXA-G (Health Examinees-Gem) from previously published
300 HEXA studies[23]. In the new HEXA-G data, a total of 141 968 participants remained after the exclusion of
301 withdrawers ($n=12$). In addition, 19 887 were excluded due to missing information ($n=19 876$) or small sample
302 size ($n=11$) on any *hsCRP* components at the baseline survey. Ultimately, 122 081 subjects, including 41 070
303 men and 81 011 women, remained in the final analysis (Fig. 1). All study participants provided informed
304 consent prior to entering the study. The Institutional Review Board of the Seoul National University Hospital,
305 Seoul, Korea, approved it for statistical analysis (IRB No. E-1503-103-657).

307 **Laboratory measurements**

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

314 **Follow-up and ascertainment of mortality**

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

322

323 **Baseline variables**

324 Trained interviewers collected information on demographic, socioeconomic and lifestyle factors.
325 Anthropometric measurements were obtained using standardized methods. Body mass index (BMI) was
326 calculated, and all participants were defined into four classes based on the World Health Organization
327 classification of BMI for Asian adults[24]: underweight (BMI <18.5 kg/m²), normal (18.5 ≤ BMI <23.0 kg/m²),
328 overweight (23.0 ≤ BMI <25.0 kg/m²), obesity (25.0 ≤ BMI <29.9 kg/m²), and severe obesity (BMI ≥30.0 kg/m²).
329 The current study defined metabolic syndrome using the National Cholesterol Education Program Adult
330 Treatment Panel III (NCEP-ATP III)[25], modified for the Asian guideline for waist circumference (WC ≥90 and
331 ≥80 cm for men and women, respectively). Nonsmokers were defined as those who had smoked less than 400
332 cigarettes over the course of their lifetime. Participants who had smoked were categorized into two groups:
333 noncurrent (never/former) and current smoker. Noncurrent drinkers were defined as those who had never
334 consumed an alcoholic drink over the course of their lifetime or those who had not consumed alcohol at
335 recruitment, while current drinkers were defined as those who persisted in consuming alcohol. Regular exercise
336 was classified into two groups (yes/no) as follows: “Do you currently engage in regular exercise strenuous enough
337 to cause you to break into a sweat at least once per week?” Furthermore, considering the attenuated effect of the
338 NCD_{history} on the association between serum *hsCRP* and the risk of mortality, we performed advanced analysis
339 after stratification by NCD_{history}. We considered six main non-communicable diseases (hypertension, diabetes,
340 hyperlipidemia, cancer, cardiovascular and cerebrovascular diseases, and respiratory disease) to classify healthy
341 subjects vs. subjects with NCD_{history}.

342

343 **Statistical analysis**

344 For the categorical analysis, we created nine categories based on the distribution of *hsCRP* levels in our
345 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,
346 and >10.0 mg/L. For the advanced analysis after stratification by the NCD_{history}, the *hsCRP* levels were
347 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
348 each subgroup. The concentrations of *hsCRP* were log-transformed for analyses because of the skewed
349 distribution.

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

1
2
3
4 353 *hsCRP* and all-cause mortality, as well as cancer and CVD mortality, were analyzed by Cox proportional hazard
5
6 354 models (aHR) and included adjustment for age, gender, demographic factors (education, marital status, job, BMI
7
8 355 and *NCD_{history}*), and lifestyle factors (smoking, alcohol consumption and exercise). In addition, we conducted a
9
10 356 sensitivity analysis to avoid latent period bias after excluding death before 1 year (aHR_{1year}) or 2 years (aHR_{2year})
11
12 357 since recruitment. We employed restricted cubic splines (RCSs) to evaluate the possibility of complex (i.e.,
13
14 358 nonlinear) hazard functions[26] using continuous values of *hsCRP* (aHR_{continuous}). We selected five *hsCRP*
15
16 359 concentration values as knots based on *hsCRP* concentration percentiles, tested the linear and nonlinear associa-
17
18 360 tions between knots using a cubic function, and presented the integrated graph smoothly. All statistical analyses
19
20 361 were performed using SAS version 9.3 (SAS Institute Inc., Cary, NC, USA) and RCS analysis was carried out
21
22 362 using the SAS LGTPHCURV9 macro. The *P*-values <0.05 were defined as indicating statistical significance.
23
24 363

25 364 **Patient and public involvement**

26
27 365 No patients and public were involved in the design, conducting, reporting, and dissemination plans of the present
28
29 366 study.
30
31 367

32 368

33 369 **RESULTS**

34
35 370 The association of demographic and lifestyle factors with the risk of all-cause mortality is presented in Table
36
37 371 1. During the follow-up period (average 6.8 years), 1 365 men and 864 women died. The median levels of
38
39 372 *hsCRP* were 0.77 and 0.59 mg/L for men and women, respectively. The risk of all-cause mortality was inversely
40
41 373 associated with female gender (aHR=0.38), high educated (aHR=0.65), overweight (aHR=0.81) or obesity
42
43 374 (aHR=0.83), current alcohol consumption (aHR=0.81) and regular exercise (aHR=0.83), but was positively
44
45 375 associated with single marital status (aHR=1.23), *NCD_{history}* (aHR=1.57), underweight (aHR=2.05) and current
46
47 376 smoking (aHR=1.97).
48
49 377

50
51 378
52
53 379
54
55 380
56
57 381
58
59
60

382 **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)
<i>P</i> -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)

383 NCD_{history}: Non-communicable disease history384 ^a Adjusted for age, gender, education, job, marital status, BMI and non-communicable disease history385 ^b Compared to white-colored worker

386

387

388

389

390

391

392

393

394

1
2
3
4 395 The risk of all-cause mortality was inclined with a dose-dependent pattern as increased serum *hsCRP* level
5
6 396 ($P_{trend}<0.001$, Supplement 1), regardless of gender ($P_{trend}<0.001$ in both genders), even in the sensitivity analysis
7
8 397 ($P_{trend}<0.001$ for aHR_{1year} in both genders). The increased risk of female mortality with increased *hsCRP* levels
9
10 398 was observed in both premenopausal ($P_{trend}=0.020$) and postmenopausal women ($P_{trend}<0.001$), although the
11
12 399 statistical significance in premenopausal women disappeared after sensitivity analysis ($P_{trend}=0.150$ for aHR_{2year} ,
13
14 400 Supplement 1). The integrated graph, based on the restricted cubic spline analyses, indicated a strong and linear
15
16 401 association of serum *hsCRP* level with all-cause mortality in both genders ($aHR_{continuous}=1.019$ and 1.013 in men
17
18 402 and women, respectively, Fig. 2 (a)).

19 403 The dose-response association between *hsCRP* level and the risk of all-cause mortality was not influenced by
20
21 404 $NCD_{history}$ (Supplement 2). After stratification by gender, however, the attenuated effect by $NCD_{history}$ on the
22
23 405 association was observed only in women; the linearity of the relationship was observed in healthy women
24
25 406 ($P_{trend}=0.001$ for aHR_{2year}) but disappeared in women with $NCD_{history}$, particularly after sensitivity analysis with
26
27 407 the exclusion of a 2-year follow-up time ($P_{trend}=0.084$ for aHR_{2year}). Based on the restricted cubic spline
28
29 408 analyses, otherwise, the pattern of increase in the association was different depending on the $NCD_{history}$ (Fig. 2
30
31 409 (b)(c)). In the healthy subjects, the risk of all-cause mortality was increased with a gradual slope (strength) until
32
33 410 3.0 mg/L *hsCRP*, with a very steep slope until 4.5 mg/L and finally with a reduced and flattened slope after 4.5
34
35 411 mg/L (Fig. 2 (b)). On the other hand, the slope of the association fluctuated as the *hsCRP* level increased in the
36
37 412 subjects with $NCD_{history}$; the slope increased up to 3.0 mg/L *hsCRP* but decreased until 4.5 mg/L and rapidly
38
39 413 increased after 4.5 mg/L (Fig. 2 (c)).

40 414 The association of serum *hsCRP* with the risk of cancer-mortality was not influenced by $NCD_{history}$
41
42 415 ($P_{trend}<0.001$ regardless of $NCD_{history}$) (Table 2). Otherwise, after stratification by gender, the association was
43
44 416 not observed in women with $NCD_{history}$ ($P_{trend}=0.856$); however, the association was not influenced by $NCD_{history}$
45
46 417 in men ($P_{trend}<0.001$ and 0.002 for aHR in both healthy and $NCD_{history}$) (Table 2). Although the risk of CVD
47
48 418 mortality was linearly associated with increasing *hsCRP* levels, the association was dominant in men
49
50 419 ($P_{trend}=0.002$) and in subjects with $NCD_{history}$ ($P_{trend}=0.001$, Table 3) after stratified by gender and $NCD_{history}$,
51
52 420 respectively. After stratification by gender and $NCD_{history}$, otherwise, the association only appeared in
53
54 421 individuals of both genders with $NCD_{history}$ ($P_{trend}=0.015$ and 0.035 in men and women with $NCD_{history}$,
55
56 422 respectively); no association between *hsCRP* level and CVD mortality risk was found in either healthy men or
57
58 423 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
<i>P</i> -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
<i>P</i> -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
<i>P</i> -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
<i>P</i> -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
<i>P</i> -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
<i>P</i> -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

424 DISCUSSION

425 This study suggests that the risk of all-cause mortality was associated with elevated *hsCRP* levels with a
426 dose-response manner in both gender among Asian who have reported low *hsCRP* levels compared to other
427 races, and was not influenced by $NCD_{history}$. Otherwise, the association was influenced by gender and $NCD_{history}$
428 although a dose-response association of *hsCRP* with the risk of cancer- and CVD-mortality was also observed in
429 this population. The level of *hsCRP* was not associated with the risk of cancer- mortality among women with
430 $NCD_{history}$. The risk effect of high *hsCRP* level on CVD mortality was predominantly observed in men with
431 $NCD_{history}$.

432 Several large cohorts[10-12, 14] have suggested that serum *hsCRP* levels may differ according to ethnic
433 background, with the highest concentrations seen in African Americans, followed by Hispanic, White, Chinese
434 and Japanese individuals. Although the reason for this ethnic difference is not clearly resolved, genetic
435 diversity[27], the relatively low BMI in Asian populations and ethnic differences in diet and lifestyle[28] have
436 been suggested. Although the extent to which these findings adopt to Asian populations has been unclear,
437 several recent studies[11, 16] conducted in Asia reported a positive association of *hsCRP* with mortality risk.
438 In this population, the *hsCRP* level was associated with the risk of all-cause mortality in a dose-dependent
439 manner, even though the level of *hsCRP* was lower than that in the western population. A meta-analysis[29] and
440 large cohort studies[3-6] supported the robustness of the association regardless of adjusted confounders, the cut-
441 off point of CRP level and exclusion deaths within the first 2 years of follow-up.

442 The reason for the discrepancy in *hsCRP* levels with respect to gender is not clearly resolved, although
443 several studies suggested different lifestyle and metabolic risk factors between men and women[30] and genetic
444 diversity[27]. A high level of serum *hsCRP* in our population was positively related to the increased risk of all-
445 cause mortality in both genders, supported by several previous studies[8, 16, 31]. Nevertheless, several studies
446 reported no association of *hsCRP* levels with all-cause mortality was observed in women[7, 16]. In particular,
447 the association was shown in postmenopausal women only, which might suggest the protective effect of
448 endogenous female hormones on the low level of *hsCRP*[32]; the average *hsCRP* level was 0.48 and 0.68 mg/L
449 for premenopausal and postmenopausal women in this study. The protective effect could be supported by the
450 proposition that estrogen or progesterone might to some extent repress the detrimental effects of chronic
451 inflammation on tissue damage[33].

452 Inflammation has emerged as an important factor in the processes of NCD, including CVD[17], cancer[18],
453 type 2 diabetes[20], COPD[19, 34] and fracture[21]. In addition, medications that had taken to treat any specific

1
2
3
4 454 NCD, such as rennin–angiotensin system inhibitors[35] and statins and thiazolidinedione[36], could influence
5
6 455 the level of *hsCRP*. The association between *hsCRP* and the mortality risk was not attenuated by $NCD_{history}$ in
7
8 456 either gender in this study, but the statistical significance of the association disappeared in women after
9
10 457 sensitivity analysis (aHR_{2year}). A dose-response relationship between *hsCRP* level and all-cause mortality risk
11
12 458 was pronounced in both genders. On the other hand, the positive association of *hsCRP* with the risk of all-cause
13
14 459 mortality risk was significantly observed in only men with $NCD_{history}$ but not in women with $NCD_{history}$. The
15
16 460 attenuated effect of $NCD_{history}$ on the association between *hsCRP* and the risk of cancer-mortality was not
17
18 461 observed in men, consistent with results from several studies which reported the associations among healthy
19
20 462 men[3] or cancer patients[37, 38] only. Most studies[3, 4, 6, 7, 15, 16, 31, 39] supported that CVD mortality
21
22 463 increased with elevated *hsCRP* levels, predominantly in men[4, 7, 15, 16]. Although *hsCRP* levels are lower in
23
24 464 our population than in other races, the level of *hsCRP* was positively associated with CVD mortality in men but
25
26 465 not in women, similar to previous studies[7, 15, 16, 31, 39]. After stratification by gender and $NCD_{history}$, the
27
28 466 association between *hsCRP* and the risk of CVD mortality was dominant in subjects with $NCD_{history}$ in this
29
30 467 study.

31 468 This study has several strengths because of the large population-based prospective study; it makes possible 1)
32
33 469 to adjust for confounders; 2) to examine sensitivity analysis after excluding death before 1 or 2 years from
34
35 470 recruitment; 3) to assess an advanced analysis after stratification by gender and $NCD_{history}$; 4) to examine the
36
37 471 association using various cut-off points of *hsCRP* considering low serum *hsCRP* levels in Asian populations;
38
39 472 and 5) to evaluate the complex (i.e., nonlinear) hazard functions using restricted cubic splines on the association
40
41 473 between continuous *hsCRP* levels and the risk of mortality. In particular, most previous studies excluded
42
43 474 subjects with more than 10 mg/L *hsCRP* because of their relatively low sample size or reflecting acute phase
44
45 475 reactions of severe inflammation, but we examined the effect of very high *hsCRP* concentration on the risk of
46
47 476 mortality because it is possible to be more concerning for these subjects in the future. The *hsCRP* level of this
48
49 477 study, in addition, was measured within 18 hours in a single institution to minimize measurement error/bias
50
51 478 from institutional variation to avoid bias from measurement or long-term storage before analysis.

52 479 Despite of those strengths, it is also has several limitations. First, the use of a single measurement of *hsCRP* at
53
54 480 baseline could reflect the inaccurate status of blood *hsCRP* levels in the study participants and increase the
55
56 481 instability of *hsCRP* due to random fluctuations over time. Nevertheless, a report [40] on the long-term *hsCRP*
57
58 482 variability suggested that the *hsCRP* variability within individual is relatively small and that the variability
59
60 483 could not account for the association. Second, our study lacked information on medication use at recruitment

1
2
3
4 484 and during the follow-up period. Several medications related to NCDs, including statins, angiotensin-converting
5
6 485 enzyme inhibitors, fibrates, niacin, thiazolidinedione and estrogen/progestogen hormone, could influence the
7
8 486 *hsCRP* level[37]; however, we tried to overcome this limitation through advanced analysis after stratification by
9
10 487 *NCD_{history}*. Third, because there is no available information on hormone-replacement therapy (HRT) among
11
12 488 women, which could not examine the influence of HRT on the association of *hsCRP* with the risk of hormone-
13
14 489 related cancer or CVD mortality among women, we could not suggest the effect of female hormones on the
15
16 490 association.

17
18 491 In conclusion, the association of *hsCRP* level is dose-responsively increased with the risk of all-cause
19
20 492 mortality in men and women (particularly postmenopausal women), which was not influenced by the association
21
22 493 was not observed in women with *NCD_{history}*. Otherwise, the association of *hsCRP* level with the risk of cancer-
23
24 494 and CVD-mortality could be attenuated by gender or *NCD_{history}*.

25 495

26 496

27 497 **Contributors**

28
29
30 498 SAL, XS and DK: designed and conducted the research, SAL and SOK: analyzed the data and performed the
31
32 499 statistical analyses; HP and JKL: managed data mining and collection; SAL: wrote the manuscript and had primary
33
34 500 responsibility for the final content of the manuscript; and all authors: read and approved the final manuscript.

35 501

36
37
38
39 502 **Funding** None.

40 503

41
42
43 504 **Competing interests** None declared.

44 505

45
46
47
48 506 **Patient consent for publication** Not required.

49 507

50
51
52
53 508 **Ethics approval** The Institutional Review Board of the Seoul National University Hospital, Seoul, Korea,
54
55 509 approved it for statistical analysis (IRB No. E-1503-103-657).

56 510

57
58
59 511 **Provenance and peer review** Not commissioned; externally peer reviewed.

60

1
2
3
4 512 **Data availability statement**

5
6 513 No additional data available.
7
8 514
9
10 515

11
12 516 **REFERENCES**

- 13 517 1 Pepys MB, Hirschfield GM. C-reactive protein: a critical update. *The Journal of clinical*
14 518 *investigation* 2003;**111**:1805-12.
- 15
16 519 2 Elias-Smale SE, Kardys I, Oudkerk M, *et al.* C-reactive protein is related to extent and
17 520 progression of coronary and extra-coronary atherosclerosis; results from the Rotterdam study.
18 521 *Atherosclerosis* 2007;**195**:e195-202.
- 19
20 522 3 Koenig W, Khuseyinova N, Baumert J, *et al.* Prospective study of high-sensitivity C-reactive
21 523 protein as a determinant of mortality: results from the MONICA/KORA Augsburg Cohort Study,
22 524 1984-1998. *Clinical chemistry* 2008;**54**:335-42.
- 23
24 525 4 Ahmadi-Abhari S, Luben RN, Wareham NJ, *et al.* Seventeen year risk of all-cause and
25 526 cause-specific mortality associated with C-reactive protein, fibrinogen and leukocyte count in men
26 527 and women: the EPIC-Norfolk study. *European journal of epidemiology* 2013;**28**:541-50.
- 27
28 528 5 Kuoppamaki M, Salminen M, Vahlberg T, *et al.* High sensitive C-reactive protein (hsCRP),
29 529 cardiovascular events and mortality in the aged: a prospective 9-year follow-up study. *Archives of*
30 530 *gerontology and geriatrics* 2015;**60**:112-7.
- 31
32 531 6 Zuo H, Ueland PM, Ulvik A, *et al.* Plasma Biomarkers of Inflammation, the Kynurenine
33 532 Pathway, and Risks of All-Cause, Cancer, and Cardiovascular Disease Mortality: The Hordaland
34 533 Health Study. *American journal of epidemiology* 2016;**183**:249-58.
- 35
36 534 7 Nisa H, Hirata A, Kohno M, *et al.* High-Sensitivity C-Reactive Protein and Risks of All-
37 535 Cause and Cause-Specific Mortality in a Japanese Population. *Asian Pacific journal of cancer*
38 536 *prevention : APJCP* 2016;**17**:2643-8.
- 39
40 537 8 Li Y, Zhong X, Cheng G, *et al.* Hs-CRP and all-cause, cardiovascular, and cancer mortality
41 538 risk: A meta-analysis. *Atherosclerosis* 2017;**259**:75-82.
- 42
43 539 9 Vasto S, Candore G, Balistreri CR, *et al.* Inflammatory networks in ageing, age-related
44 540 diseases and longevity. *Mechanisms of ageing and development* 2007;**128**:83-91.
- 45
46 541 10 Kelley-Hedgpeath A, Lloyd-Jones DM, Colvin A, *et al.* Ethnic differences in C-reactive
47 542 protein concentrations. *Clinical chemistry* 2008;**54**:1027-37.
- 48
49 543 11 Albert MA, Glynn RJ, Buring J, *et al.* C-reactive protein levels among women of various
50 544 ethnic groups living in the United States (from the Women's Health Study). *The American journal of*
51 545 *cardiology* 2004;**93**:1238-42.
52
53
54
55
56
57
58
59
60

- 1
2
3
4 546 12 Khera A, McGuire DK, Murphy SA, *et al.* Race and gender differences in C-reactive protein
5 547 levels. *Journal of the American College of Cardiology* 2005;**46**:464-9.
- 6
7 548 13 Lakoski SG, Cushman M, Criqui M, *et al.* Gender and C-reactive protein: data from the
8 549 Multiethnic Study of Atherosclerosis (MESA) cohort. *American heart journal* 2006;**152**:593-8.
- 9
10 550 14 Matthews KA, Sowers MF, Derby CA, *et al.* Ethnic differences in cardiovascular risk factor
11 551 burden among middle-aged women: Study of Women's Health Across the Nation (SWAN). *American*
12 552 *heart journal* 2005;**149**:1066-73.
- 13
14
15 553 15 Lee JH, Yeom H, Kim HC, *et al.* C-reactive Protein Concentration Is Associated With a
16 554 Higher Risk of Mortality in a Rural Korean Population. *Journal of preventive medicine and public*
17 555 *health = Yebang Uihakhoe chi* 2016;**49**:275-87.
- 18
19 556 16 Sung KC, Ryu S, Chang Y, *et al.* C-reactive protein and risk of cardiovascular and all-cause
20 557 mortality in 268 803 East Asians. *European heart journal* 2014;**35**:1809-16.
- 21
22
23 558 17 Kengne AP, Batty GD, Hamer M, *et al.* Association of C-reactive protein with
24 559 cardiovascular disease mortality according to diabetes status: pooled analyses of 25,979 participants
25 560 from four U.K. prospective cohort studies. *Diabetes care* 2012;**35**:396-403.
- 26
27
28 561 18 Heikkila K, Ebrahim S, Lawlor DA. A systematic review of the association between
29 562 circulating concentrations of C reactive protein and cancer. *Journal of epidemiology and community*
30 563 *health* 2007;**61**:824-33.
- 31
32
33 564 19 Dahl M, Vestbo J, Lange P, *et al.* C-reactive protein as a predictor of prognosis in chronic
34 565 obstructive pulmonary disease. *American journal of respiratory and critical care medicine*
35 566 2007;**175**:250-5.
- 36
37
38 567 20 Wang X, Bao W, Liu J, *et al.* Inflammatory markers and risk of type 2 diabetes: a systematic
39 568 review and meta-analysis. *Diabetes care* 2013;**36**:166-75.
- 40
41 569 21 Ishii S, Cauley JA, Greendale GA, *et al.* C-reactive protein, bone strength, and nine-year
42 570 fracture risk: data from the Study of Women's Health Across the Nation (SWAN). *Journal of bone*
43 571 *and mineral research : the official journal of the American Society for Bone and Mineral Research*
44 572 2013;**28**:1688-98.
- 45
46
47 573 22 Kim Y, Han BG, Ko GESg. Cohort Profile: The Korean Genome and Epidemiology Study
48 574 (KoGES) Consortium. *International journal of epidemiology* 2017;**46**:1350.
- 49
50 575 23 Shin S, Lee HW, Kim CE, *et al.* Egg Consumption and Risk of Metabolic Syndrome in
51 576 Korean Adults: Results from the Health Examinees Study. *Nutrients* 2017;**9**.
- 52
53 577 24 Pan WH, Yeh WT. How to define obesity? Evidence-based multiple action points for public
54 578 awareness, screening, and treatment: an extension of Asian-Pacific recommendations. *Asia Pacific*
55 579 *journal of clinical nutrition* 2008;**17**:370-4.
- 56
57
58 580 25 National Cholesterol Education Program Expert Panel on Detection E, Treatment of High
59 581 Blood Cholesterol in A. Third Report of the National Cholesterol Education Program (NCEP) Expert

- 1
2
3
4 582 Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment
5 Panel III) final report. *Circulation* 2002;**106**:3143-421.
- 6 583
7 584 26 Heinzl H, Kaider A. Gaining more flexibility in Cox proportional hazards regression models
8 with cubic spline functions. *Computer methods and programs in biomedicine* 1997;**54**:201-8.
- 9 585
10 586 27 MacGregor AJ, Gallimore JR, Spector TD, *et al.* Genetic effects on baseline values of C-
11 reactive protein and serum amyloid a protein: a comparison of monozygotic and dizygotic twins.
12 *Clinical chemistry* 2004;**50**:130-4.
- 13 588
14 589 28 Ledue TB, Rifai N. Preanalytic and analytic sources of variations in C-reactive protein
15 measurement: implications for cardiovascular disease risk assessment. *Clinical chemistry*
16 2003;**49**:1258-71.
- 17 590
18 591 29 Emerging Risk Factors C, Kaptoge S, Di Angelantonio E, *et al.* C-reactive protein
19 concentration and risk of coronary heart disease, stroke, and mortality: an individual participant meta-
20 analysis. *Lancet* 2010;**375**:132-40.
- 21 592
22 593 30 Lee YJ, Lee JH, Shin YH, *et al.* Gender difference and determinants of C-reactive protein
23 level in Korean adults. *Clinical chemistry and laboratory medicine* 2009;**47**:863-9.
- 24 594
25 595 31 Doran B, Zhu W, Muennig P. Gender differences in cardiovascular mortality by C-reactive
26 protein level in the United States: evidence from the National Health and Nutrition Examination
27 Survey III. *American heart journal* 2013;**166**:45-51.
- 28 597
29 598 32 Gaskins AJ, Wilchesky M, Mumford SL, *et al.* Endogenous reproductive hormones and C-
30 reactive protein across the menstrual cycle: the BioCycle Study. *American journal of epidemiology*
31 2012;**175**:423-31.
- 32 600
33 601 33 Gilliver SC. Sex steroids as inflammatory regulators. *The Journal of steroid biochemistry*
34 and molecular biology 2010;**120**:105-15.
- 35 602
36 603 34 Man SF, Connett JE, Anthonisen NR, *et al.* C-reactive protein and mortality in mild to
37 moderate chronic obstructive pulmonary disease. *Thorax* 2006;**61**:849-53.
- 38 604
39 605 35 Di Napoli M, Papa F. Angiotensin-converting enzyme inhibitor use is associated with
40 reduced plasma concentration of C-reactive protein in patients with first-ever ischemic stroke. *Stroke*
41 2003;**34**:2922-9.
- 42 606
43 607 36 Sidhu JS, Cowan D, Kaski JC. The effects of rosiglitazone, a peroxisome proliferator-
44 activated receptor-gamma agonist, on markers of endothelial cell activation, C-reactive protein, and
45 fibrinogen levels in non-diabetic coronary artery disease patients. *Journal of the American College of*
46 *Cardiology* 2003;**42**:1757-63.
- 47 608
48 609 37 Heikkila K, Ebrahim S, Rumley A, *et al.* Associations of circulating C-reactive protein and
49 interleukin-6 with survival in women with and without cancer: findings from the British Women's
50 Heart and Health Study. *Cancer epidemiology, biomarkers & prevention : a publication of the*
51
52
53
54
55
56
57
58
59
60

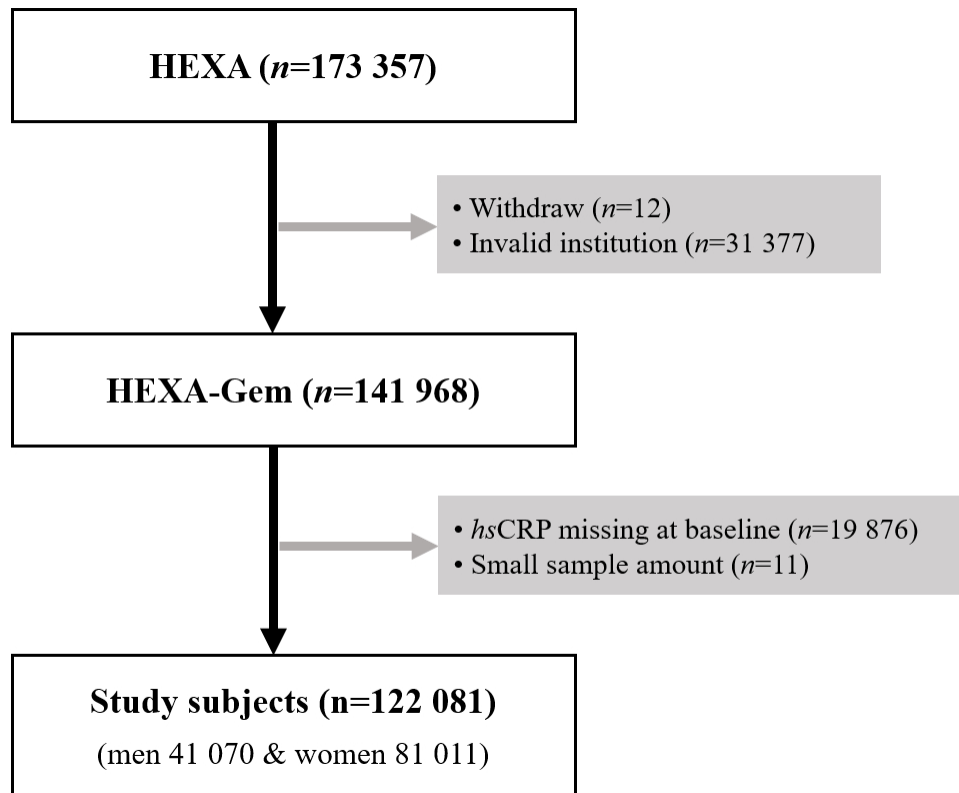
1
2
3
4 617 *American Association for Cancer Research, cosponsored by the American Society of Preventive*
5
6 618 *Oncology* 2007;**16**:1155-9.

7 619 38 Marsik C, Kazemi-Shirazi L, Schickbauer T, *et al.* C-reactive protein and all-cause mortality
8
9 620 in a large hospital-based cohort. *Clinical chemistry* 2008;**54**:343-9.

10 621 39 Proctor MJ, McMillan DC, Horgan PG, *et al.* Systemic inflammation predicts all-cause
11
12 622 mortality: a glasgow inflammation outcome study. *PloS one* 2015;**10**:e0116206.

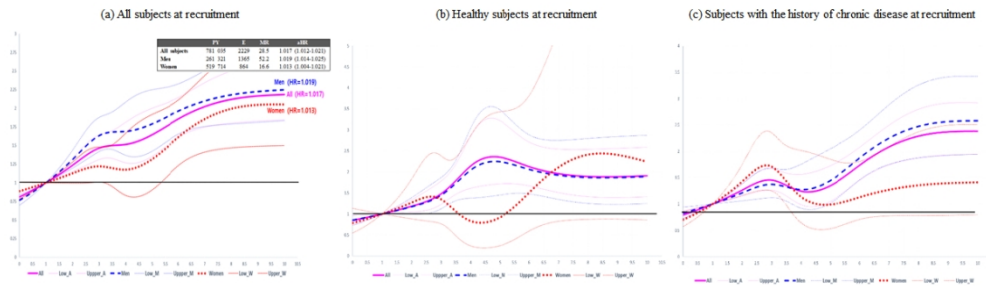
13 623 40 Chen TH, Gona P, Sutherland PA, *et al.* Long-term C-reactive protein variability and
14
15 624 prediction of metabolic risk. *The American journal of medicine* 2009;**122**:53-61.

16
17 625
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60



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 *hsCRP* 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)
<i>P</i> -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)
<i>P</i> -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)
<i>P</i> -trend				<.001	<.001	0.001
Pre-menopause						
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)
<i>P</i> -trend				0.020	0.036	0.150
Post-menopause						
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)
<i>P</i> -trend				<0.001	0.001	0.003

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

1
2
3
4 aHR: Adjusted for age, gender, education, job, marital status, BMI, non-communicable disease history, smoking, alcohol
5 consumption and exercise

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

7 HR_{2year}: aHR after exclude subjects who died within 2 yr f/u time
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

For peer review only

Supplement 2. The association between serum *hsCRP* 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
<i>P</i> -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
<i>P</i> -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
<i>P</i> -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) <i>Cohort study</i> —Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up <i>Case-control study</i> —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 <i>Cross-sectional study</i> —Give the eligibility criteria, and the sources and methods of selection of participants	4
		(b) <i>Cohort study</i> —For matched studies, give matching criteria and number of exposed and unexposed <i>Case-control study</i> —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) <i>Cohort study</i> —If applicable, explain how loss to follow-up was addressed <i>Case-control study</i> —If applicable, explain how matching of cases and controls was addressed	4

		<i>Cross-sectional study</i> —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) <i>Cohort study</i> —Summarise follow-up time (eg, average and total amount)	6
Outcome data	15*	<i>Cohort study</i> —Report numbers of outcome events or summary measures over time	6-10
		<i>Case-control study</i> —Report numbers in each exposure category, or summary measures of exposure	
		<i>Cross-sectional study</i> —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:	<i>BMJ Open</i>
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

SCHOLARONE™
Manuscripts



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.

1
2
3
4 196 **The association of serum high sensitivity C-reactive protein with the risk of mortality in**
5
6 197 **Asian: the Health Examinees cohort**

7 198

8 199

9
10 200 **Sang-Ah Lee^{1,2*}, Sung Ok Kwon¹, Hyerim Park¹, Xiao-Ou Shu², Jong-Koo Lee³, Daehee Kang⁴**

11 201

12 202

13 203 ¹Department of Preventive Medicine, School of Medicine, Kangwon National University, Chuncheon, Republic
14 204 of Korea.15 205 ²Division of Epidemiology, Vanderbilt Epidemiology Center, Vanderbilt University Medical Center, Nashville,
16 206 TN, USA.17 207 ³JW Lee Center for Global Medicine, College of Medicine, Seoul National University, Seoul, Republic of Korea.18 208 ⁴Department of Preventive Medicine, College of Medicine, Seoul National University, Seoul, Republic of Korea.

19 209

20 210

21 211 **ABSTRACT**22 212 **Objectives** This study aimed to examine the association of *hsCRP* with mortality risk and the attenuated effect
23 213 of non-communicable disease history (NCD_{history}) on the association.24 214 **Design** Prospective cohort study.25 215 **Setting** the Health Examinees (HEXA) cohort.26 216 **Participants** A total of 41 070 men and 81 011 women aged ≥ 40 years were involved (follow-up: 6.8 years).27 217 **Outcome measures** The data and cause of death occurring until December 31, 2015, were confirmed by death
28 218 statistics from the National Statistical Office. We conducted the advanced analysis after stratification by
29 219 NCD_{history} and the sensitivity analysis after excluding death before 1 or 2 years from recruitment. Cox
30 220 proportional hazard and restricted cubic spline models were used to assess the association.31 221 **Results** The association between serum *hsCRP* and the risk of all-cause mortality was observed with strong
32 222 linearity in both genders, which was not influenced by NCD_{history}. Otherwise, the association of serum *hsCRP*
33 223 with cancer-mortality risk was not observed in women with NCD_{history}, but the association with the risk of
34 224 cardiovascular disease (CVD) mortality was predominantly observed in men with NCD_{history}.35 225 **Conclusions** This study suggested the dose-response association of *hsCRP* with mortality risk, including
36 226 cancer and CVD mortality, in Korean with low serum *hsCRP*, although the association with cancer and CVD-
37 227 mortality risk could be influenced by gender and NCD_{history}.

38 228

39 229

40 230 **Strengths and limitations of this study**

41 231 • This is the large population-based prospective study.

42 232 • We examined the effect of very high *hsCRP* concentration on mortality risk.43 233 • The *hsCRP* level of present study was measured within 18 hours in a single institution to minimize error/bias.

1
2
3
4 234 • Due to random fluctuations of *hsCRP*, using the single measurement of *hsCRP* at baseline could reflect the
5
6 235 inaccurate status of blood *hsCRP* levels in the study participants and increase the instability of *hsCRP*.
7
8 236 • This study lacked information on medication use at recruitment and during the follow-up period, and
9
10 237 information on hormone-replacement therapy (HRT) among women.
11
12 238
13 239

14 240 *Correspondence to: Sang-Ah Lee, Ph.D.

15 241 Department of Preventive Medicine, School of Medicine, Kangwon National University,

16 242 Chuncheon, Gangwon, Republic of Korea.

17 243 Tel: +82 33 250 8871

18 244 E-mail: sangahlee@kangwon.ac.kr
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

266 INTRODUCTION

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

274 Serum *hsCRP* represents a low-grade inflammation state that is generally involved in the process of aging[9].
275 Several large cohorts, including Study of Women's Health Across the Nation (SWAN)[10], the Women's
276 Health Study[11] and the Dallas Heart Study[12], reported significant differences in *hsCRP* levels by race and
277 gender. In two studies of multiethnic populations residing in the USA[10, 13], the median *hsCRP* level in East
278 Asians was less than half the concentration in Caucasians. Even among East Asian populations, the geometric
279 mean of *hsCRP* levels varied depending on ethnic background[14]. In addition, a meta-analysis[11] reported
280 the *hsCRP* levels among women of various ethnic groups living in the United States (from the Women's Health
281 Study) on the association between *hsCRP* and the mortality risk; the association was observed in only men
282 supported by the results from two cohort studies[15, 16] reported in Korea. On the other hand, the increased
283 *hsCRP* may be influenced by comorbidity itself because inflammation has emerged as an important factor in the
284 progression of non-communicable diseases (NCDs), including CVD[17], cancer[18], chronic obstructive
285 pulmonary disease (COPD)[19], type 2 diabetes[20] and fractures[21], which contribute to increased morbidity
286 and mortality.

287 This study aimed to examine the association of serum *hsCRP* with the risk of mortality in Koreans with low
288 serum *hsCRP* and to evaluate the attenuated effect of non-communicable disease history ($NCD_{history}$) on the
289 association.

290

291

292

293

294

295 **METHODS**

296 **Study population**

297 Details on the main objectives, rationale, study design and baseline characteristics of the Health Examinees
298 (HEXA) study have been published elsewhere[22]. Considering the homogeneity and comparability of
299 participants, we created a qualified dataset called HEXA-G (Health Examinees-Gem) from previously published
300 HEXA studies[23]. In the new HEXA-G data, a total of 141 968 participants remained after the exclusion of
301 withdrawers ($n=12$). In addition, 19 887 were excluded due to missing information ($n=19\ 876$) or small sample
302 size ($n=11$) on any *hsCRP* components at the baseline survey. Ultimately, 122 081 subjects, including 41 070
303 men and 81 011 women, remained in the final analysis (Fig. 1). All study participants provided informed
304 consent prior to entering the study. The Institutional Review Board of the Seoul National University Hospital,
305 Seoul, Korea, approved it for statistical analysis (IRB No. E-1503-103-657).

307 **Laboratory measurements**

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

314 **Follow-up and ascertainment of mortality**

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

322

323 **Baseline variables**

324 Trained interviewers collected information on demographic, socioeconomic and lifestyle factors.
325 Anthropometric measurements were obtained using standardized methods. Body mass index (BMI) was
326 calculated, and all participants were defined into four classes based on the World Health Organization
327 classification of BMI for Asian adults[24]: underweight (BMI <18.5 kg/m²), normal (18.5 ≤ BMI <23.0 kg/m²),
328 overweight (23.0 ≤ BMI <25.0 kg/m²), obesity (25.0 ≤ BMI <29.9 kg/m²), and severe obesity (BMI ≥30.0 kg/m²).
329 The current study defined metabolic syndrome using the National Cholesterol Education Program Adult
330 Treatment Panel III (NCEP-ATP III)[25], modified for the Asian guideline for waist circumference (WC ≥90 and
331 ≥80 cm for men and women, respectively). Nonsmokers were defined as those who had smoked less than 400
332 cigarettes over the course of their lifetime. Participants who had smoked were categorized into two groups:
333 noncurrent (never/former) and current smoker. Noncurrent drinkers were defined as those who had never
334 consumed an alcoholic drink over the course of their lifetime or those who had not consumed alcohol at
335 recruitment, while current drinkers were defined as those who persisted in consuming alcohol. Regular exercise
336 was classified into two groups (yes/no) as follows: “Do you currently engage in regular exercise strenuous enough
337 to cause you to break into a sweat at least once per week?” Furthermore, considering the attenuated effect of the
338 NCD_{history} on the association between serum *hsCRP* and the risk of mortality, we performed advanced analysis
339 after stratification by NCD_{history}. We considered six main non-communicable diseases (hypertension, diabetes,
340 hyperlipidemia, cancer, cardiovascular and cerebrovascular diseases, and respiratory disease) to classify healthy
341 subjects vs. subjects with NCD_{history}.

342

343 **Statistical analysis**

344 For the categorical analysis, we created nine categories based on the distribution of *hsCRP* levels in our
345 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,
346 and >10.0 mg/L. For the advanced analysis after stratification by the NCD_{history}, the *hsCRP* levels were
347 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
348 each subgroup. The concentrations of *hsCRP* were log-transformed for analyses because of the skewed
349 distribution.

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

1
2
3
4 353 *hsCRP* and all-cause mortality, as well as cancer and CVD mortality, were analyzed by Cox proportional hazard
5
6 354 models (aHR) and included adjustment for age, gender, demographic factors (education, marital status, job, BMI
7
8 355 and NCD_{history}), and lifestyle factors (smoking, alcohol consumption and exercise). We used Wald tests to test
9
10 356 for heterogeneity of risk between serum *hsCRP* level groups. The proportional hazards assumption was assessed
11
12 357 on the basis of Schoenfeld residuals, and was not violated for the variables of interest in the adjusted model for
13
14 358 either cancer-mortality or cardiovascular disease mortality ($P>0.05$ for all categories). In addition, we conducted
15
16 359 a sensitivity analysis to avoid latent period bias after excluding death before 1 year (aHR_{1year}) or 2 years
17
18 360 (aHR_{2year}) since recruitment. Based on the Cox proportional hazard models, we made Kaplan-Meier curves and
19
20 361 log-rank analysis. We employed restricted cubic splines (RCSs) to evaluate the possibility of complex (i.e.,
21
22 362 nonlinear) hazard functions[26] using continuous values of *hsCRP* (aHR_{continuous}). We selected five *hsCRP*
23
24 363 concentration values as knots based on *hsCRP* concentration percentiles, tested the linear and nonlinear associa-
25
26 364 tions between knots using a cubic function, and presented the integrated graph smoothly. All statistical analyses
27
28 365 were performed using SAS version 9.3 (SAS Institute Inc., Cary, NC, USA) and RCS analysis was carried out
29
30 366 using the SAS LGTPHCURV9 macro. Two-sided p -values <0.05 were defined as indicating statistical
31
32 367 significance.

33 368

369 **Patient and public involvement**

370 No patients and public were involved in the design, conducting, reporting, and dissemination plans of the present
38
39 371 study.

40 372

41 373

42 374 **RESULTS**

43
44
45
46
47 375 The association of demographic and lifestyle factors with the risk of all-cause mortality is presented in Table
48
49 376 1. During the follow-up period (average 6.8 years), 1 365 men and 864 women died. The median levels of
50
51 377 *hsCRP* were 0.77 and 0.59 mg/L for men and women, respectively. The risk of all-cause mortality was inversely
52
53 378 associated with female gender (aHR=0.38), high educated (aHR=0.65), overweight (aHR=0.81) or obesity
54
55 379 (aHR=0.83), current alcohol consumption (aHR=0.81) and regular exercise (aHR=0.83), but was positively
56
57 380 associated with single marital status (aHR=1.23), NCD_{history} (aHR=1.57), underweight (aHR=2.05) and current
58
59 381 smoking (aHR=1.97).

382 **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)

383 NCD_{history}: Non-communicable disease history384 ^a Adjusted for age, gender, education, job, marital status, BMI and non-communicable disease history385 ^b Compared to white-colored worker

386

387

388

389

390

391

392

393

394

1
2
3
4 395 The risk of all-cause mortality was inclined with a dose-dependent pattern as increased serum *hsCRP* level
5
6 396 ($P_{trend}<0.001$, Supplement 1), regardless of gender ($P_{trend}<0.001$ in both genders), even in the sensitivity analysis
7
8 397 ($P_{trend}<0.001$ for aHR_{1year} in both genders). The increased risk of female mortality with increased *hsCRP* levels
9
10 398 was observed in both premenopausal ($P_{trend}=0.020$) and postmenopausal women ($P_{trend}<0.001$), although the
11
12 399 statistical significance in premenopausal women disappeared after sensitivity analysis ($P_{trend}=0.150$ for aHR_{2year} ,
13
14 400 Supplement 1). The integrated graph, based on the restricted cubic spline analyses, indicated a strong and linear
15
16 401 association of serum *hsCRP* level with all-cause mortality in both genders ($aHR_{continuous}=1.019$ and 1.013 in men
17
18 402 and women, respectively, Fig. 2).

19 403 The dose-response association between *hsCRP* level and the risk of all-cause mortality was not influenced by
20
21 404 $NCD_{history}$ (Supplement 2). After stratification by gender, however, the attenuated effect by $NCD_{history}$ on the
22
23 405 association was observed only in women; the linearity of the relationship was observed in healthy women
24
25 406 ($P_{trend}=0.001$ for aHR_{2year}) but disappeared in women with $NCD_{history}$, particularly after sensitivity analysis with
26
27 407 the exclusion of a 2-year follow-up time ($P_{trend}=0.084$ for aHR_{2year}). Based on the restricted cubic spline
28
29 408 analyses, otherwise, the pattern of increase in the association was different depending on the $NCD_{history}$ (Fig.
30
31 409 3,4). In the healthy subjects, the risk of all-cause mortality was increased with a gradual slope (strength) until
32
33 410 3.0 mg/L *hsCRP*, with a very steep slope until 4.5 mg/L and finally with a reduced and flattened slope after 4.5
34
35 411 mg/L (Fig. 3). On the other hand, the slope of the association fluctuated as the *hsCRP* level increased in the
36
37 412 subjects with $NCD_{history}$; the slope increased up to 3.0 mg/L *hsCRP* but decreased until 4.5 mg/L and rapidly
38
39 413 increased after 4.5 mg/L (Fig. 4).

40 414 The association of serum *hsCRP* with the risk of cancer-mortality was not influenced by $NCD_{history}$
41
42 415 ($P_{trend}<0.001$ regardless of $NCD_{history}$) (Table 2 and Fig. 5-9). Otherwise, after stratification by gender, the
43
44 416 association was not observed in women with $NCD_{history}$ ($P_{trend}=0.856$); however, the association was not
45
46 417 influenced by $NCD_{history}$ in men ($P_{trend}<0.001$ and 0.002 for aHR in both healthy and $NCD_{history}$) (Table 2).
47
48 418 Although the risk of CVD mortality was linearly associated with increasing *hsCRP* levels, the association was
49
50 419 dominant in men ($P_{trend}=0.002$) and in subjects with $NCD_{history}$ ($P_{trend}=0.001$, Table 3) after stratified by gender
51
52 420 and $NCD_{history}$, respectively (Fig. 10-14). After stratification by gender and $NCD_{history}$, otherwise, the association
53
54 421 only appeared in individuals of both genders with $NCD_{history}$ ($P_{trend}=0.015$ and 0.035 in men and women with
55
56 422 $NCD_{history}$, respectively); no association between *hsCRP* level and CVD mortality risk was found in either
57
58 423 healthy men or women.
59
60

Table 2. The association between serum *hsCRP* 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
<i>P</i> -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
<i>P</i> -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
<i>P</i> -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 *hsCRP* 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
<i>P</i> -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
<i>P</i> -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
<i>P</i> -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

424 DISCUSSION

425 This study suggests that the risk of all-cause mortality was associated with elevated *hsCRP* levels with a
426 dose-response manner in both gender among Asian who have reported low *hsCRP* levels compared to other
427 races, and was not influenced by *NCD_{history}*. Otherwise, the association was influenced by gender and *NCD_{history}*
428 although a dose-response association of *hsCRP* with the risk of cancer- and CVD-mortality was also observed in
429 this population. The level of *hsCRP* was not associated with the risk of cancer- mortality among women with
430 *NCD_{history}*. The risk effect of high *hsCRP* level on CVD mortality was predominantly observed in men with
431 *NCD_{history}*.

432 Several large cohorts[10-12, 14] have suggested that serum *hsCRP* levels may differ according to ethnic
433 background, with the highest concentrations seen in African Americans, followed by Hispanic, White, Chinese
434 and Japanese individuals. Although the reason for this ethnic difference is not clearly resolved, genetic
435 diversity[27], the relatively low BMI in Asian populations and ethnic differences in diet and lifestyle[28] have
436 been suggested. Although the extent to which these findings adopt to Asian populations has been unclear,
437 several recent studies[11, 16] conducted in Asia reported a positive association of *hsCRP* with mortality risk.
438 In this population, the *hsCRP* level was associated with the risk of all-cause mortality in a dose-dependent
439 manner, even though the level of *hsCRP* was lower than that in the western population. A meta-analysis[29] and
440 large cohort studies[3-6] supported the robustness of the association regardless of adjusted confounders, the cut-
441 off point of CRP level and exclusion deaths within the first 2 years of follow-up.

442 The reason for the discrepancy in *hsCRP* levels with respect to gender is not clearly resolved, although
443 several studies suggested different lifestyle and metabolic risk factors between men and women[30] and genetic
444 diversity[27]. A high level of serum *hsCRP* in our population was positively related to the increased risk of all-
445 cause mortality in both genders, supported by several previous studies[8, 16, 31]. Nevertheless, several studies
446 reported no association of *hsCRP* levels with all-cause mortality was observed in women[7, 16]. In particular,
447 the association was shown in postmenopausal women only, which might suggest the protective effect of
448 endogenous female hormones on the low level of *hsCRP*[32]; the average *hsCRP* level was 0.48 and 0.68 mg/L
449 for premenopausal and postmenopausal women in this study. The protective effect could be supported by the
450 proposition that estrogen or progesterone might to some extent repress the detrimental effects of chronic
451 inflammation on tissue damage[33].

452 Inflammation has emerged as an important factor in the processes of NCD, including CVD[17], cancer[18],
453 type 2 diabetes[20], COPD[19, 34] and fracture[21]. In addition, medications that had taken to treat any specific

1
2
3
4 454 NCD, such as rennin–angiotensin system inhibitors[35] and statins and thiazolidinedione[36], could influence
5
6 455 the level of *hsCRP*. The association between *hsCRP* and the mortality risk was not attenuated by $NCD_{history}$ in
7
8 456 either gender in this study, but the statistical significance of the association disappeared in women after
9
10 457 sensitivity analysis (aHR_{2year}). A dose-response relationship between *hsCRP* level and all-cause mortality risk
11
12 458 was pronounced in both genders. On the other hand, the positive association of *hsCRP* with the risk of all-cause
13
14 459 mortality risk was significantly observed in only men with $NCD_{history}$ but not in women with $NCD_{history}$. The
15
16 460 attenuated effect of $NCD_{history}$ on the association between *hsCRP* and the risk of cancer-mortality was not
17
18 461 observed in men, consistent with results from several studies which reported the associations among healthy
19
20 462 men[3] or cancer patients[37, 38] only. Most studies[3, 4, 6, 7, 15, 16, 31, 39] supported that CVD mortality
21
22 463 increased with elevated *hsCRP* levels, predominantly in men[4, 7, 15, 16]. Although *hsCRP* levels are lower in
23
24 464 our population than in other races, the level of *hsCRP* was positively associated with CVD mortality in men but
25
26 465 not in women, similar to previous studies[7, 15, 16, 31, 39]. After stratification by gender and $NCD_{history}$, the
27
28 466 association between *hsCRP* and the risk of CVD mortality was dominant in subjects with $NCD_{history}$ in this
29
30 467 study. Although many interventional studies have been conducted recently on anti-inflammatory drugs for the
31
32 468 prevention of cardiovascular disease, the results are controversial. According to the results of our study, elevated
33
34 469 inflammatory markers in people with chronic disease were associated with an increased risk of CVD mortality.
35
36 470 This suggests that CVD-mortality in people with chronic diseases might be reduced by use of anti-inflammatory
37
38 471 medication.

39 472 This study has several strengths because of the large population-based prospective study; it makes possible 1)
40
41 473 to adjust for confounders; 2) to examine sensitivity analysis after excluding death before 1 or 2 years from
42
43 474 recruitment; 3) to assess an advanced analysis after stratification by gender and $NCD_{history}$; 4) to examine the
44
45 475 association using various cut-off points of *hsCRP* considering low serum *hsCRP* levels in Asian populations;
46
47 476 and 5) to evaluate the complex (i.e., nonlinear) hazard functions using restricted cubic splines on the association
48
49 477 between continuous *hsCRP* levels and the risk of mortality. In particular, most previous studies excluded
50
51 478 subjects with more than 10 mg/L *hsCRP* because of their relatively low sample size or reflecting acute phase
52
53 479 reactions of severe inflammation, but we examined the effect of very high *hsCRP* concentration on the risk of
54
55 480 mortality because it is possible to be more concerning for these subjects in the future. The *hsCRP* level of this
56
57 481 study, in addition, was measured within 18 hours in a single institution to minimize measurement error/bias
58
59 482 from institutional variation to avoid bias from measurement or long-term storage before analysis.
60

1
2
3
4 483 Despite of those strengths, it is also several limitations. First, the use of a single measurement of *hsCRP* at
5
6 484 baseline could reflect the inaccurate status of blood *hsCRP* levels in the study participants and increase the
7
8 485 instability of *hsCRP* due to random fluctuations over time. Nevertheless, a report [40] on the long-term *hsCRP*
9
10 486 variability suggested that the *hsCRP* variability within individual is relatively small and that the variability
11
12 487 could not account for the association. Second, our study lacked information on medication use at recruitment
13
14 488 and during the follow-up period. Several medications related to NCDs, including statins, angiotensin-converting
15
16 489 enzyme inhibitors, fibrates, niacin, thiazolidinedione and estrogen/progestogen hormone, could influence the
17
18 490 *hsCRP* level[37]; however, we tried to overcome this limitation through advanced analysis after stratification by
19
20 491 $NCD_{history}$. Third, because there is no available information on hormone-replacement therapy (HRT) among
21
22 492 women, which could not examine the influence of HRT on the association of *hsCRP* with the risk of hormone-
23
24 493 related cancer or CVD mortality among women, we could not suggest the effect of female hormones on the
25
26 494 association. In addition, further studies are needed on the effects of obesity although the inverse relationship
27
28 495 between all-cause mortality with obesity in our population was consistent to Wei's report in Asian[41]. On the
29
30 496 other hand, the inverse association of alcohol drinking with all-cause mortality couldn't interpret directly
31
32 497 because our report wasn't separated the distinguish between mild drinkers and abuse alcohol drinker, which
33
34 498 requires additional research for our population in the future.

35 499 In conclusion, the association of *hsCRP* level is dose-responsively increased with the risk of all-cause
36
37 500 mortality in men and women (particularly postmenopausal women), which was not influenced by the association
38
39 501 was not observed in women with $NCD_{history}$. Otherwise, the association of *hsCRP* level with the risk of cancer-
40
41 502 and CVD-mortality could be attenuated by gender or $NCD_{history}$.

42 503

43 504

44 505 **Figure 1** Flow diagram of analytical sample in current study using Health Examinees cohort.

45 506 **Figure 2** A dose-response association between serum *hsCRP* level and risk of all-cause mortality in all
46 507 subjects at recruitment.

47 508 **Figure 3** A dose-response association between serum *hsCRP* level and risk of all-cause mortality in healthy
48 509 subjects at recruitment.

49 510 **Figure 4** A dose-response association between serum *hsCRP* level and risk of all-cause mortality in subjects
50 511 with non-communicable disease history ($NCD_{history}$) at recruitment.

1
2
3
4 512 **Figure 5** Kaplan-Meier crude survival curves for cancer-mortality according to serum *hsCRP* level in all
5
6 513 subjects at recruitment.

7
8 514 **Figure 6** Kaplan-Meier crude survival curves for cancer-mortality according to serum *hsCRP* level in men at
9
10 515 recruitment.

11
12 516 **Figure 7** Kaplan-Meier crude survival curves for cancer-mortality according to serum *hsCRP* level in women
13
14 517 at recruitment.

15
16 518 **Figure 8** Kaplan-Meier crude survival curves for cancer-mortality according to serum *hsCRP* level in healthy
17
18 519 subjects at recruitment.

19
20 520 **Figure 9** Kaplan-Meier crude survival curves for cancer-mortality according to serum *hsCRP* level in subjects
21
22 521 with non-communicable disease history (NCD_{history}) at recruitment.

23
24 522 **Figure 10** Kaplan-Meier crude survival curves for cardiovascular disease mortality according to serum *hsCRP*
25
26 523 level in all subjects at recruitment.

27
28 524 **Figure 11** Kaplan-Meier crude survival curves for cardiovascular disease mortality according to serum *hsCRP*
29
30 525 level in men at recruitment.

31
32 526 **Figure 12** Kaplan-Meier crude survival curves for cardiovascular disease mortality according to serum *hsCRP*
33
34 527 level in women at recruitment.

35
36 528 **Figure 13** Kaplan-Meier crude survival curves for cardiovascular disease mortality according to serum *hsCRP*
37
38 529 level in healthy subjects at recruitment.

39
40 530 **Figure 14** Kaplan-Meier crude survival curves for cardiovascular disease mortality according to serum *hsCRP*
41
42 531 level in subjects with non-communicable disease history (NCD_{history}) at recruitment.

43 532

44 533

45
46 534 **Contributors**

47
48 535 SAL, XS and DK: designed and conducted the research, SAL and SOK: analyzed the data and performed the
49
50 536 statistical analyses; HP and JKL: managed data mining and collection; SAL: wrote the manuscript and had primary
51
52 537 responsibility for the final content of the manuscript; and all authors: read and approved the final manuscript.

53
54 538

55
56 539 **Funding** None.

57
58 540

59
60 541 **Competing interests** None declared.

542 **Patient consent for publication** Not required.

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

545

546 **Provenance and peer review** Not commissioned; externally peer reviewed.

547 **Data availability statement**

548 No additional data available.

549

550

551 REFERENCES

552 1 Pepys MB, Hirschfield GM. C-reactive protein: a critical update. *The Journal of clinical*
553 *investigation* 2003;**111**:1805-12.

554 2 Elias-Smale SE, Kardys I, Oudkerk M, *et al.* C-reactive protein is related to extent and
555 progression of coronary and extra-coronary atherosclerosis; results from the Rotterdam study.
556 *Atherosclerosis* 2007;**195**:e195-202.

557 3 Koenig W, Khuseyinova N, Baumert J, *et al.* Prospective study of high-sensitivity C-reactive
558 protein as a determinant of mortality: results from the MONICA/KORA Augsburg Cohort Study,
559 1984-1998. *Clinical chemistry* 2008;**54**:335-42.

560 4 Ahmadi-Abhari S, Luben RN, Wareham NJ, *et al.* Seventeen year risk of all-cause and
561 cause-specific mortality associated with C-reactive protein, fibrinogen and leukocyte count in men
562 and women: the EPIC-Norfolk study. *European journal of epidemiology* 2013;**28**:541-50.

563 5 Kuoppamaki M, Salminen M, Vahlberg T, *et al.* High sensitive C-reactive protein (hsCRP),
564 cardiovascular events and mortality in the aged: a prospective 9-year follow-up study. *Archives of*
565 *gerontology and geriatrics* 2015;**60**:112-7.

566 6 Zuo H, Ueland PM, Ulvik A, *et al.* Plasma Biomarkers of Inflammation, the Kynurenine
567 Pathway, and Risks of All-Cause, Cancer, and Cardiovascular Disease Mortality: The Hordaland
568 Health Study. *American journal of epidemiology* 2016;**183**:249-58.

569 7 Nisa H, Hirata A, Kohno M, *et al.* High-Sensitivity C-Reactive Protein and Risks of All-
570 Cause and Cause-Specific Mortality in a Japanese Population. *Asian Pacific journal of cancer*
571 *prevention : APJCP* 2016;**17**:2643-8.

572 8 Li Y, Zhong X, Cheng G, *et al.* Hs-CRP and all-cause, cardiovascular, and cancer mortality
573 risk: A meta-analysis. *Atherosclerosis* 2017;**259**:75-82.

574 9 Vasto S, Candore G, Balistreri CR, *et al.* Inflammatory networks in ageing, age-related
575 diseases and longevity. *Mechanisms of ageing and development* 2007;**128**:83-91.

- 1
2
3
4 576 10 Kelley-Hedgepeth A, Lloyd-Jones DM, Colvin A, *et al.* Ethnic differences in C-reactive
5 577 protein concentrations. *Clinical chemistry* 2008;**54**:1027-37.
- 7 578 11 Albert MA, Glynn RJ, Buring J, *et al.* C-reactive protein levels among women of various
8 579 ethnic groups living in the United States (from the Women's Health Study). *The American journal of*
9 580 *cardiology* 2004;**93**:1238-42.
- 12 581 12 Khera A, McGuire DK, Murphy SA, *et al.* Race and gender differences in C-reactive protein
13 582 levels. *Journal of the American College of Cardiology* 2005;**46**:464-9.
- 15 583 13 Lakoski SG, Cushman M, Criqui M, *et al.* Gender and C-reactive protein: data from the
16 584 Multiethnic Study of Atherosclerosis (MESA) cohort. *American heart journal* 2006;**152**:593-8.
- 18 585 14 Matthews KA, Sowers MF, Derby CA, *et al.* Ethnic differences in cardiovascular risk factor
19 586 burden among middle-aged women: Study of Women's Health Across the Nation (SWAN). *American*
20 587 *heart journal* 2005;**149**:1066-73.
- 23 588 15 Lee JH, Yeom H, Kim HC, *et al.* C-reactive Protein Concentration Is Associated With a
24 589 Higher Risk of Mortality in a Rural Korean Population. *Journal of preventive medicine and public*
25 590 *health = Yebang Uihakhoe chi* 2016;**49**:275-87.
- 28 591 16 Sung KC, Ryu S, Chang Y, *et al.* C-reactive protein and risk of cardiovascular and all-cause
29 592 mortality in 268 803 East Asians. *European heart journal* 2014;**35**:1809-16.
- 31 593 17 Kengne AP, Batty GD, Hamer M, *et al.* Association of C-reactive protein with
32 594 cardiovascular disease mortality according to diabetes status: pooled analyses of 25,979 participants
33 595 from four U.K. prospective cohort studies. *Diabetes care* 2012;**35**:396-403.
- 36 596 18 Heikkila K, Ebrahim S, Lawlor DA. A systematic review of the association between
37 597 circulating concentrations of C reactive protein and cancer. *Journal of epidemiology and community*
38 598 *health* 2007;**61**:824-33.
- 40 599 19 Dahl M, Vestbo J, Lange P, *et al.* C-reactive protein as a predictor of prognosis in chronic
41 600 obstructive pulmonary disease. *American journal of respiratory and critical care medicine*
42 601 2007;**175**:250-5.
- 45 602 20 Wang X, Bao W, Liu J, *et al.* Inflammatory markers and risk of type 2 diabetes: a systematic
46 603 review and meta-analysis. *Diabetes care* 2013;**36**:166-75.
- 48 604 21 Ishii S, Cauley JA, Greendale GA, *et al.* C-reactive protein, bone strength, and nine-year
49 605 fracture risk: data from the Study of Women's Health Across the Nation (SWAN). *Journal of bone*
50 606 *and mineral research : the official journal of the American Society for Bone and Mineral Research*
51 607 2013;**28**:1688-98.
- 55 608 22 Kim Y, Han BG, Ko GESg. Cohort Profile: The Korean Genome and Epidemiology Study
56 609 (KoGES) Consortium. *International journal of epidemiology* 2017;**46**:1350.
- 58 610 23 Shin S, Lee HW, Kim CE, *et al.* Egg Consumption and Risk of Metabolic Syndrome in
59 611 Korean Adults: Results from the Health Examinees Study. *Nutrients* 2017;**9**.

- 1
2
3
4 612 24 Pan WH, Yeh WT. How to define obesity? Evidence-based multiple action points for public
5 613 awareness, screening, and treatment: an extension of Asian-Pacific recommendations. *Asia Pacific*
6 614 *journal of clinical nutrition* 2008;**17**:370-4.
7
8 615 25 National Cholesterol Education Program Expert Panel on Detection E, Treatment of High
9 616 Blood Cholesterol in A. Third Report of the National Cholesterol Education Program (NCEP) Expert
10 617 Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment
11 618 Panel III) final report. *Circulation* 2002;**106**:3143-421.
12
13 619 26 Heinzl H, Kaider A. Gaining more flexibility in Cox proportional hazards regression models
14 620 with cubic spline functions. *Computer methods and programs in biomedicine* 1997;**54**:201-8.
15
16 621 27 MacGregor AJ, Gallimore JR, Spector TD, *et al.* Genetic effects on baseline values of C-
17 622 reactive protein and serum amyloid a protein: a comparison of monozygotic and dizygotic twins.
18 623 *Clinical chemistry* 2004;**50**:130-4.
19
20 624 28 Ledue TB, Rifai N. Preanalytic and analytic sources of variations in C-reactive protein
21 625 measurement: implications for cardiovascular disease risk assessment. *Clinical chemistry*
22 626 2003;**49**:1258-71.
23
24 627 29 Emerging Risk Factors C, Kaptoge S, Di Angelantonio E, *et al.* C-reactive protein
25 628 concentration and risk of coronary heart disease, stroke, and mortality: an individual participant meta-
26 629 analysis. *Lancet* 2010;**375**:132-40.
27
28 630 30 Lee YJ, Lee JH, Shin YH, *et al.* Gender difference and determinants of C-reactive protein
29 631 level in Korean adults. *Clinical chemistry and laboratory medicine* 2009;**47**:863-9.
30
31 632 31 Doran B, Zhu W, Muennig P. Gender differences in cardiovascular mortality by C-reactive
32 633 protein level in the United States: evidence from the National Health and Nutrition Examination
33 634 Survey III. *American heart journal* 2013;**166**:45-51.
34
35 635 32 Gaskins AJ, Wilchesky M, Mumford SL, *et al.* Endogenous reproductive hormones and C-
36 636 reactive protein across the menstrual cycle: the BioCycle Study. *American journal of epidemiology*
37 637 2012;**175**:423-31.
38
39 638 33 Gilliver SC. Sex steroids as inflammatory regulators. *The Journal of steroid biochemistry*
40 639 *and molecular biology* 2010;**120**:105-15.
41
42 640 34 Man SF, Connett JE, Anthonisen NR, *et al.* C-reactive protein and mortality in mild to
43 641 moderate chronic obstructive pulmonary disease. *Thorax* 2006;**61**:849-53.
44
45 642 35 Di Napoli M, Papa F. Angiotensin-converting enzyme inhibitor use is associated with
46 643 reduced plasma concentration of C-reactive protein in patients with first-ever ischemic stroke. *Stroke*
47 644 2003;**34**:2922-9.
48
49 645 36 Sidhu JS, Cowan D, Kaski JC. The effects of rosiglitazone, a peroxisome proliferator-
50 646 activated receptor-gamma agonist, on markers of endothelial cell activation, C-reactive protein, and
51
52
53
54
55
56
57
58
59
60

- 1
2
3
4 647 fibrinogen levels in non-diabetic coronary artery disease patients. *Journal of the American College of*
5 648 *Cardiology* 2003;**42**:1757-63.
- 7 649 37 Heikkila K, Ebrahim S, Rumley A, *et al.* Associations of circulating C-reactive protein and
8 650 interleukin-6 with survival in women with and without cancer: findings from the British Women's
9 651 Heart and Health Study. *Cancer epidemiology, biomarkers & prevention : a publication of the*
10 652 *American Association for Cancer Research, cosponsored by the American Society of Preventive*
11 653 *Oncology* 2007;**16**:1155-9.
- 15 654 38 Marsik C, Kazemi-Shirazi L, Schickbauer T, *et al.* C-reactive protein and all-cause mortality
16 655 in a large hospital-based cohort. *Clinical chemistry* 2008;**54**:343-9.
- 18 656 39 Proctor MJ, McMillan DC, Horgan PG, *et al.* Systemic inflammation predicts all-cause
19 657 mortality: a glasgow inflammation outcome study. *PloS one* 2015;**10**:e0116206.
- 21 658 40 Chen TH, Gona P, Sutherland PA, *et al.* Long-term C-reactive protein variability and
22 659 prediction of metabolic risk. *The American journal of medicine* 2009;**122**:53-61.
- 25 660 41 Zheng W, McLerran DF, Rolland B, *et al.* Association between Body-Mass Index and Risk
26 661 of Death in More Than 1 Million Asians, *N Engl J Med* 2011; 364:719-729.
- 28 662

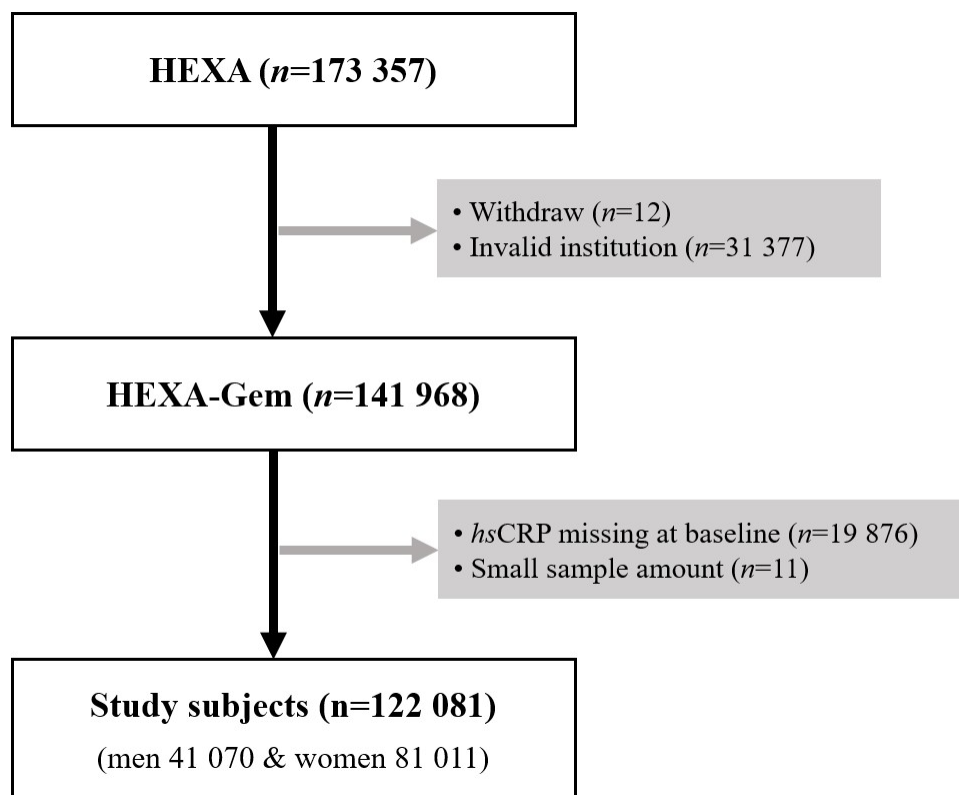


Figure 1 Flow diagram of analytical sample in current study using Health Examinees cohort.
HEXA: Health Examinees, hsCRP: High sensitivity C-reactive protein

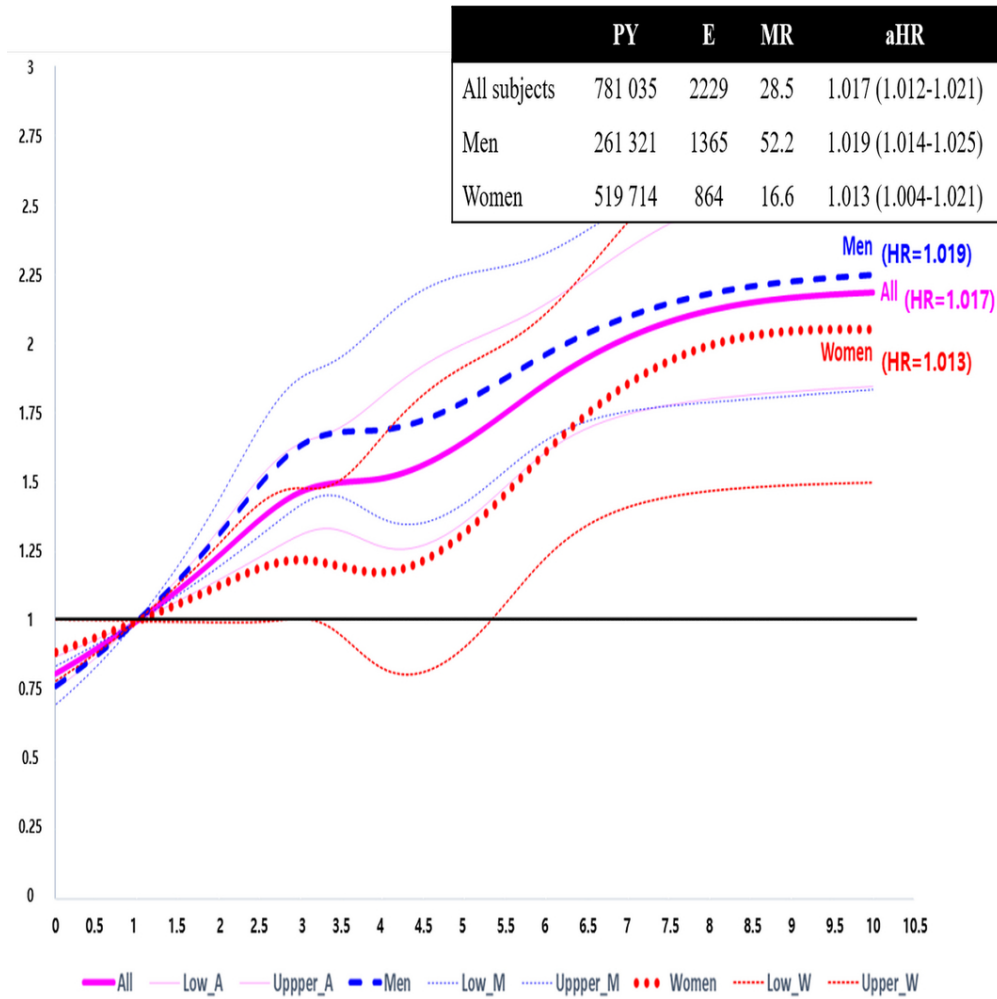


Figure 2 A dose-response association between serum hsCRP level and risk of all-cause mortality in all subjects at recruitment.

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)

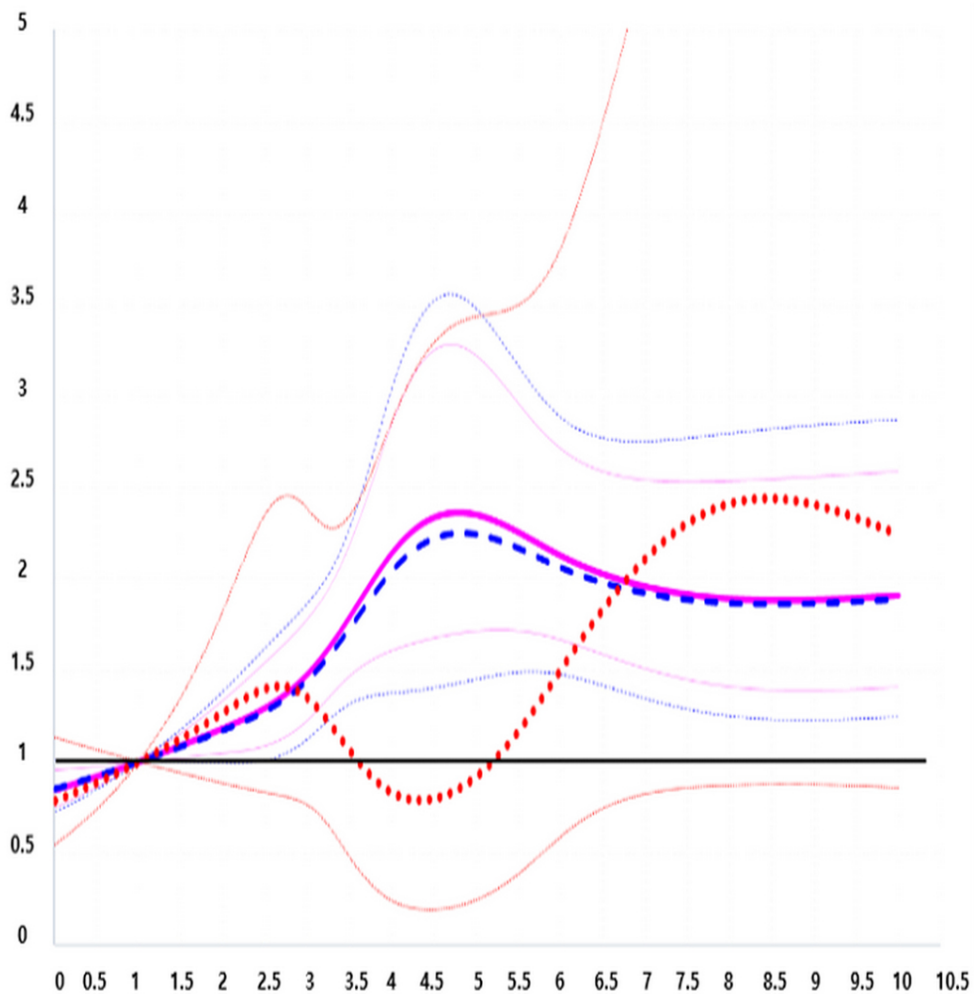


Figure 3 A dose-response association between serum hsCRP level and risk of all-cause mortality in healthy subjects at recruitment.

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)

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

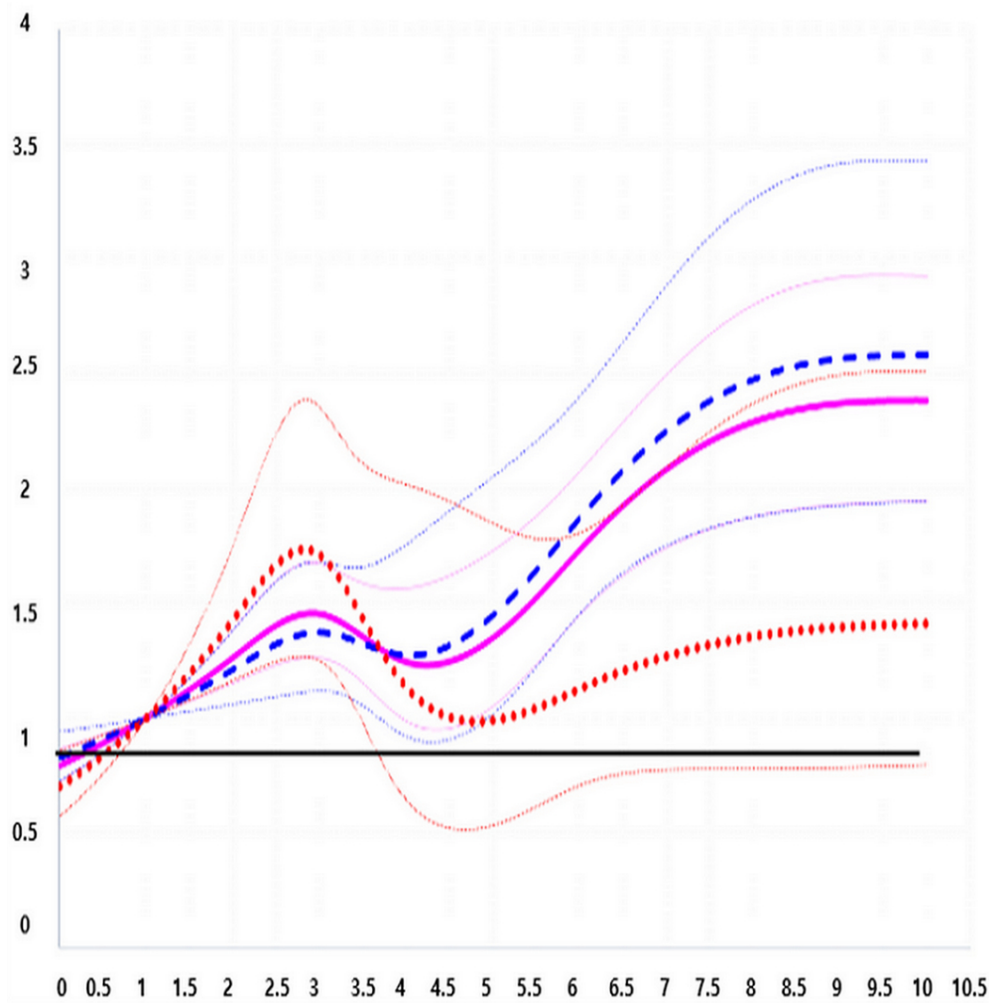


Figure 4 A dose-response association between serum hsCRP level and risk of all-cause mortality in subjects with non-communicable disease history (NCDhistory) at recruitment.
Low_A and Upper_A: 95%CI for all subjects
Low_M and Upper_M: 95%CI for men
Low_W and Upper_W: 95%CI for women
90x90mm (300 x 300 DPI)

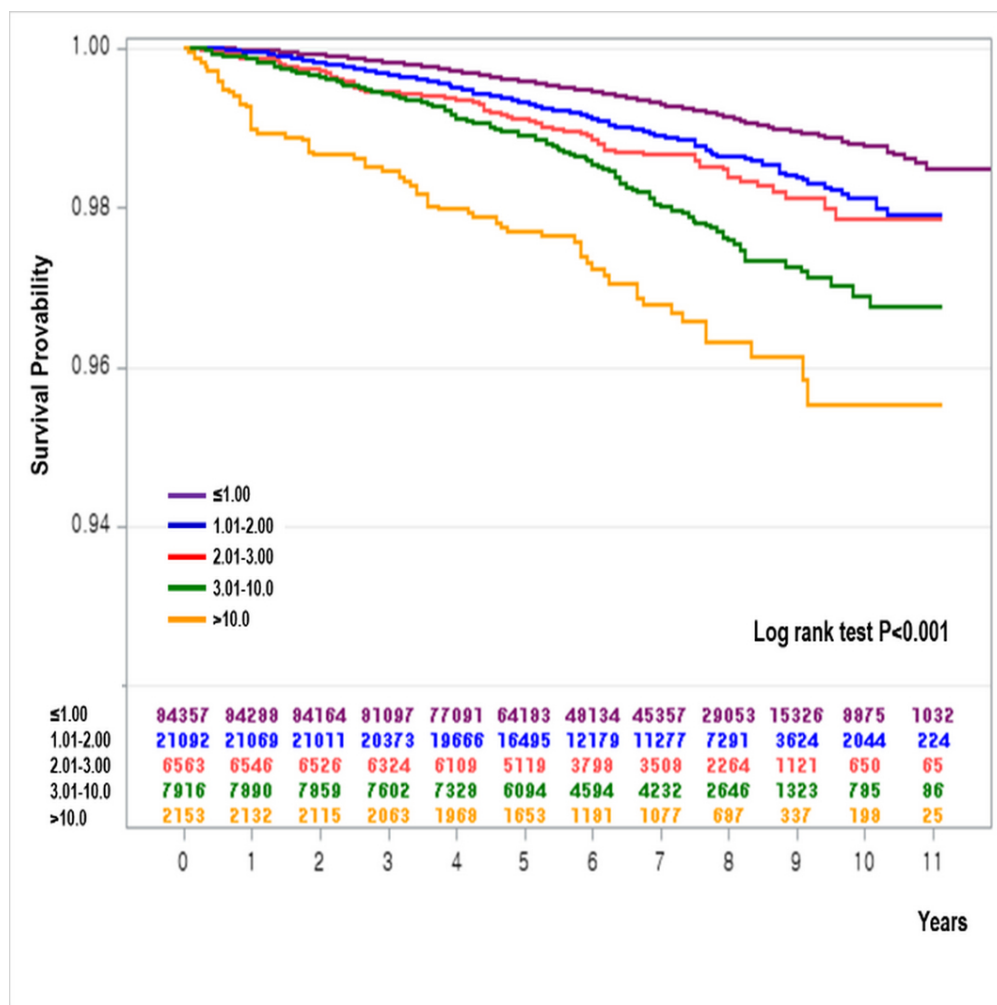


Figure 5 Kaplan-Meier crude survival curves for cancer-mortality according to serum hsCRP level in all subjects at recruitment.

90x90mm (300 x 300 DPI)

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

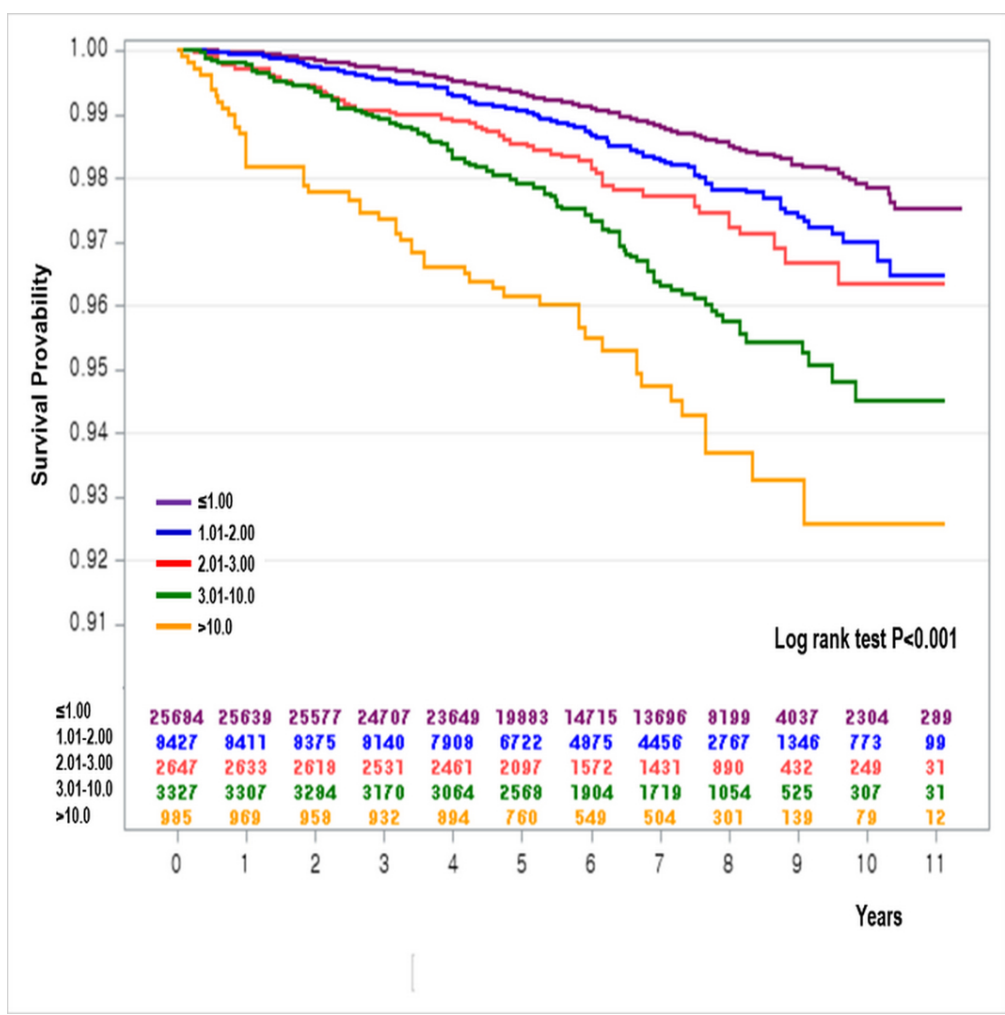


Figure 6 Kaplan-Meier crude survival curves for cancer-mortality according to serum hsCRP level in men at recruitment.

90x90mm (300 x 300 DPI)

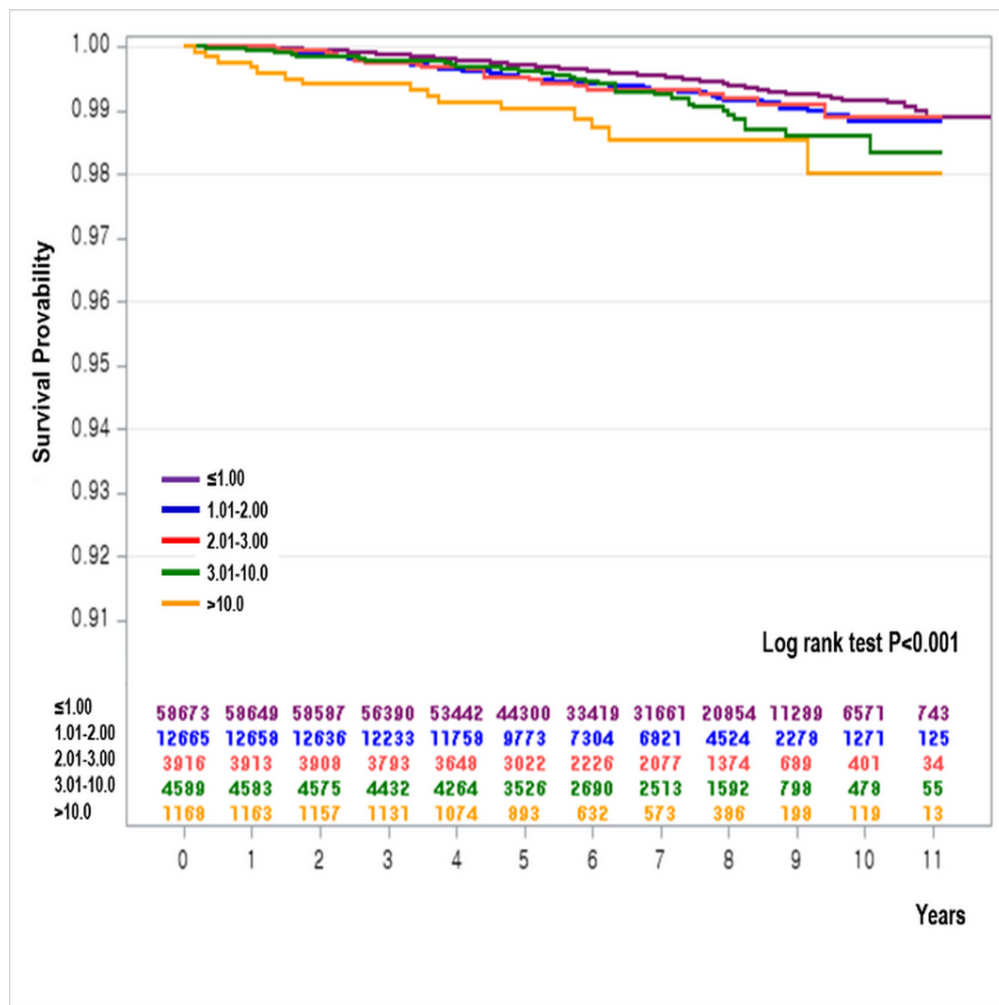


Figure 7 Kaplan-Meier crude survival curves for cancer-mortality according to serum hsCRP level in women at recruitment.

90x90mm (300 x 300 DPI)

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

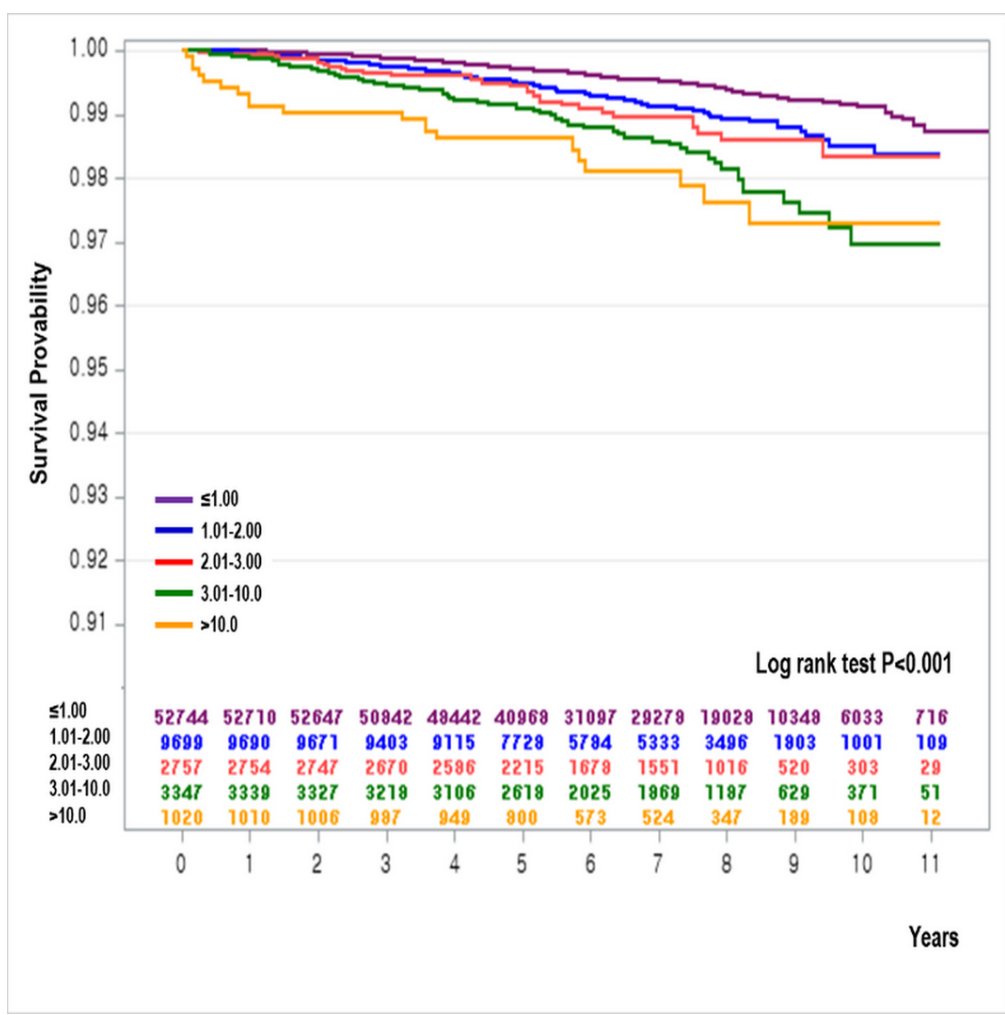


Figure 8 Kaplan-Meier crude survival curves for cancer-mortality according to serum hsCRP level in healthy subjects at recruitment.

90x90mm (300 x 300 DPI)

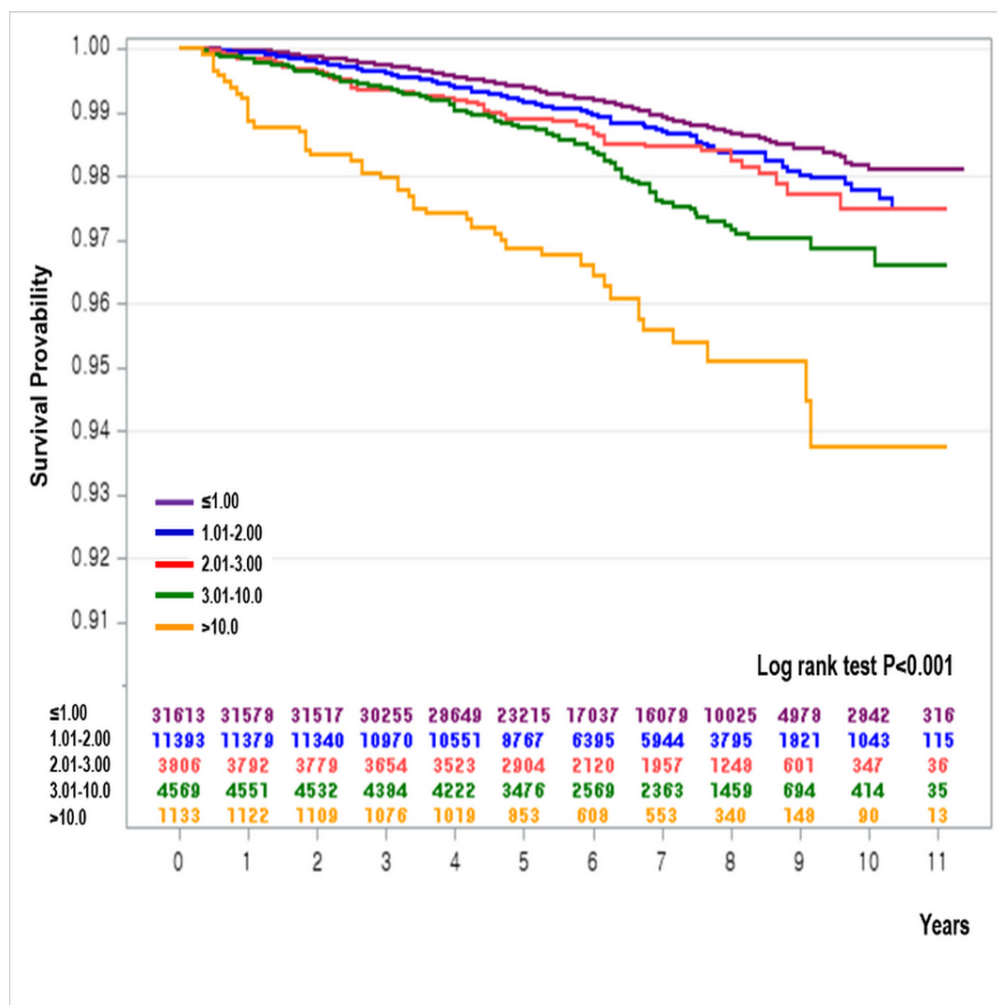


Figure 9 Kaplan-Meier crude survival curves for cancer-mortality according to serum hsCRP level in subjects with non-communicable disease history (NCDhistory) at recruitment.

90x90mm (300 x 300 DPI)

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

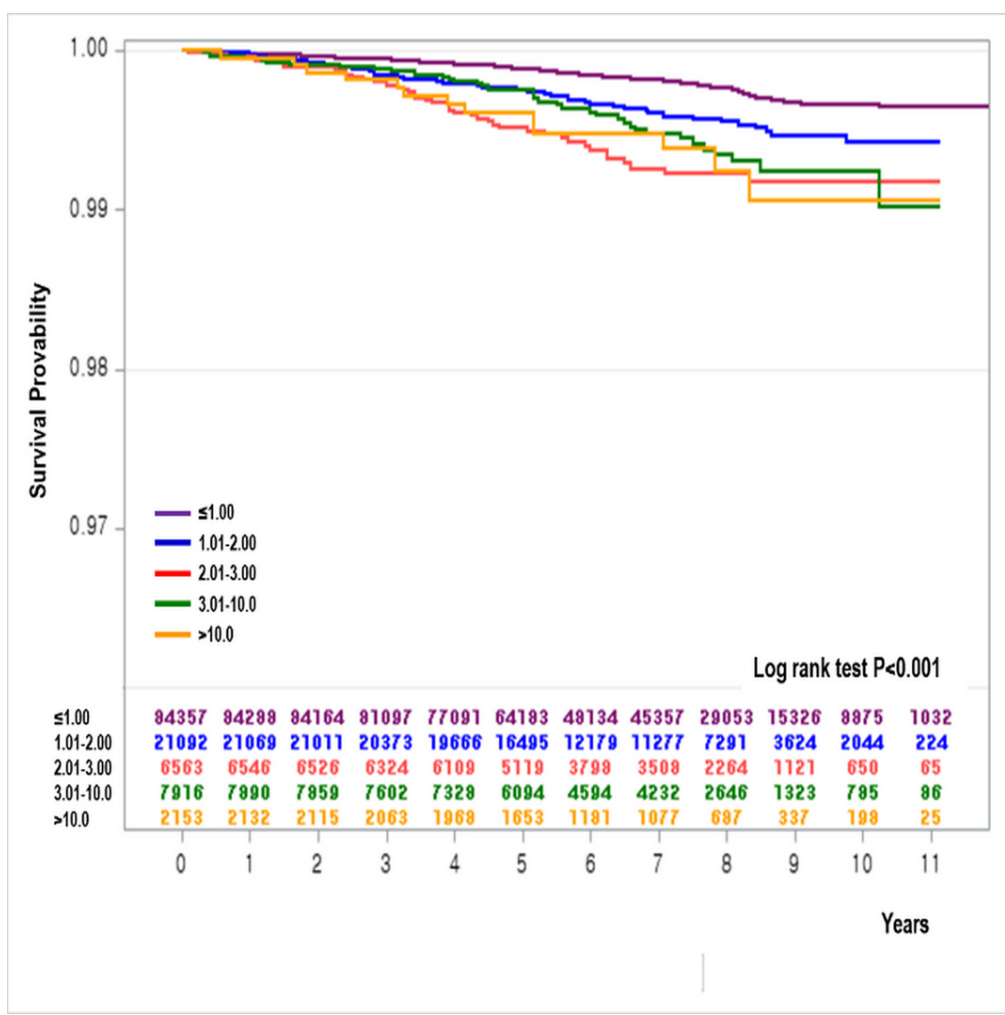


Figure 10 Kaplan-Meier crude survival curves for cardiovascular disease mortality according to serum hsCRP level in all subjects at recruitment.

90x90mm (300 x 300 DPI)

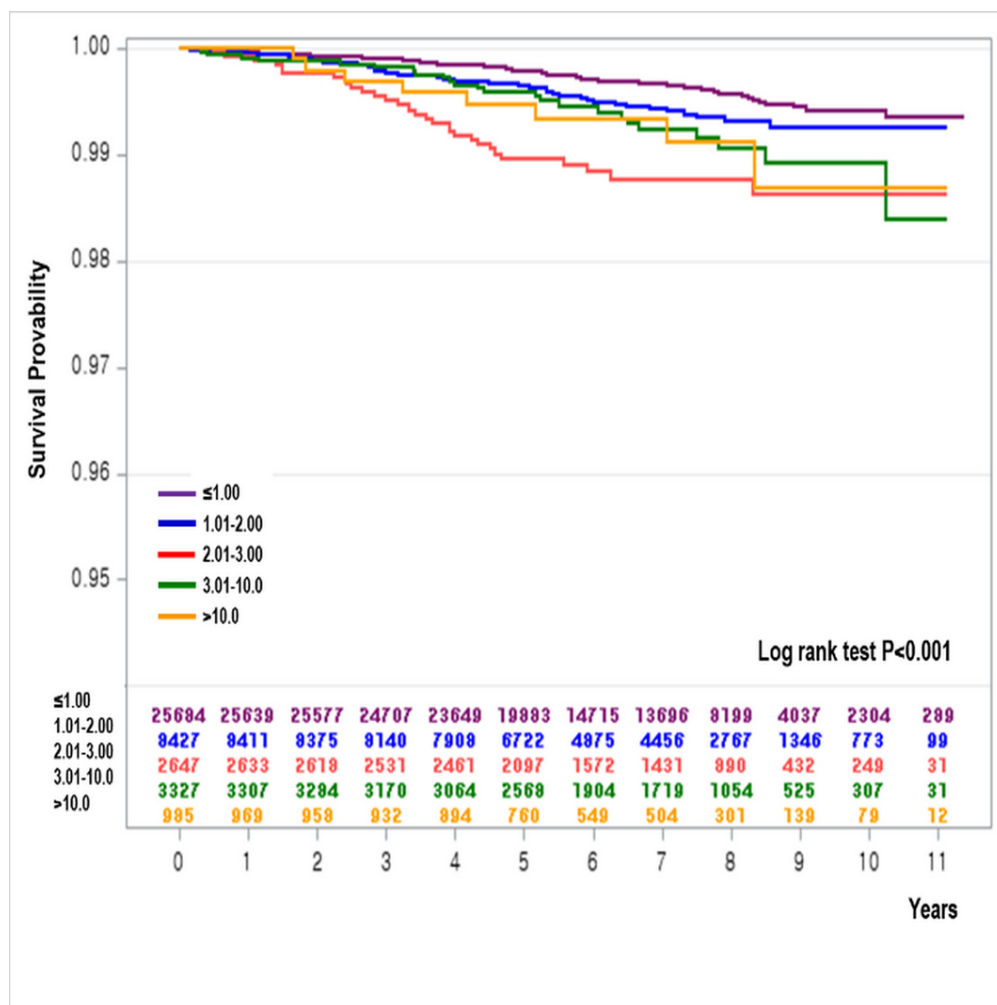


Figure 11 Kaplan-Meier crude survival curves for cardiovascular disease mortality according to serum hsCRP level in men at recruitment.

90x90mm (300 x 300 DPI)

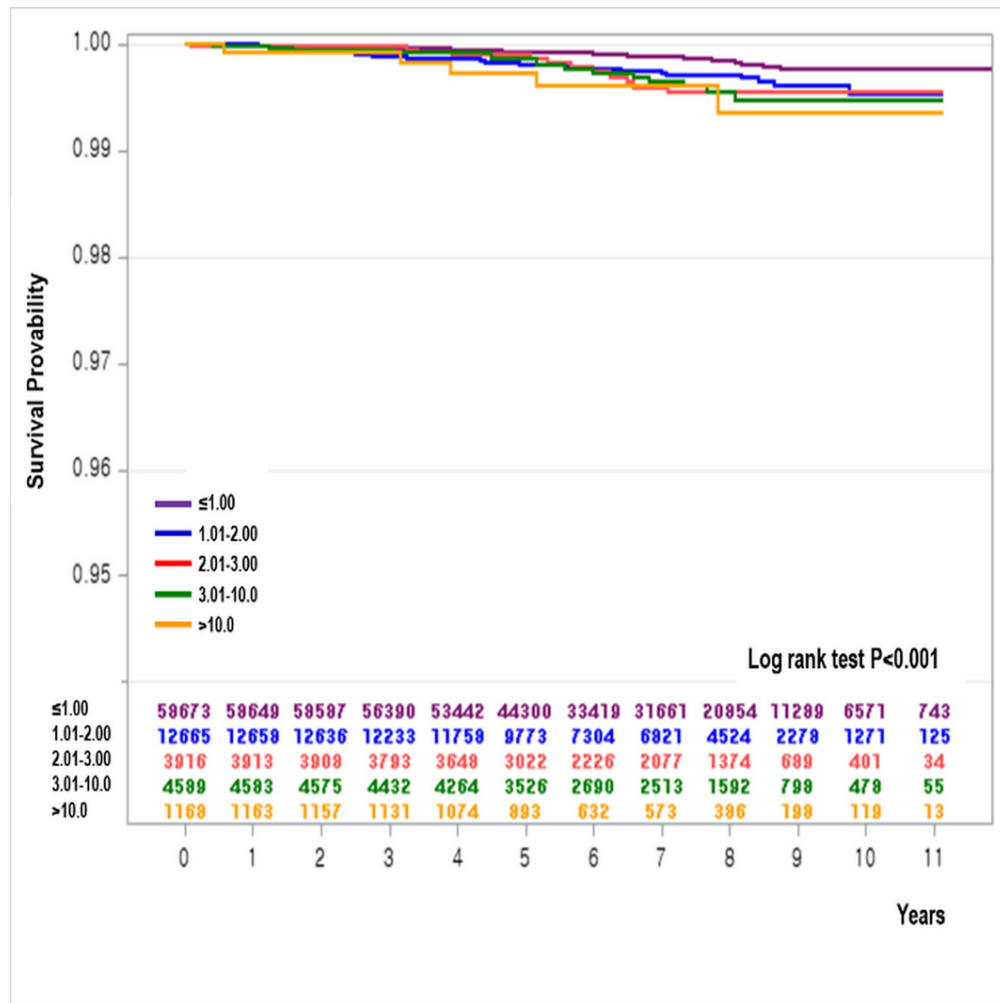


Figure 12 Kaplan-Meier crude survival curves for cardiovascular disease mortality according to serum hsCRP level in women at recruitment.

90x90mm (300 x 300 DPI)

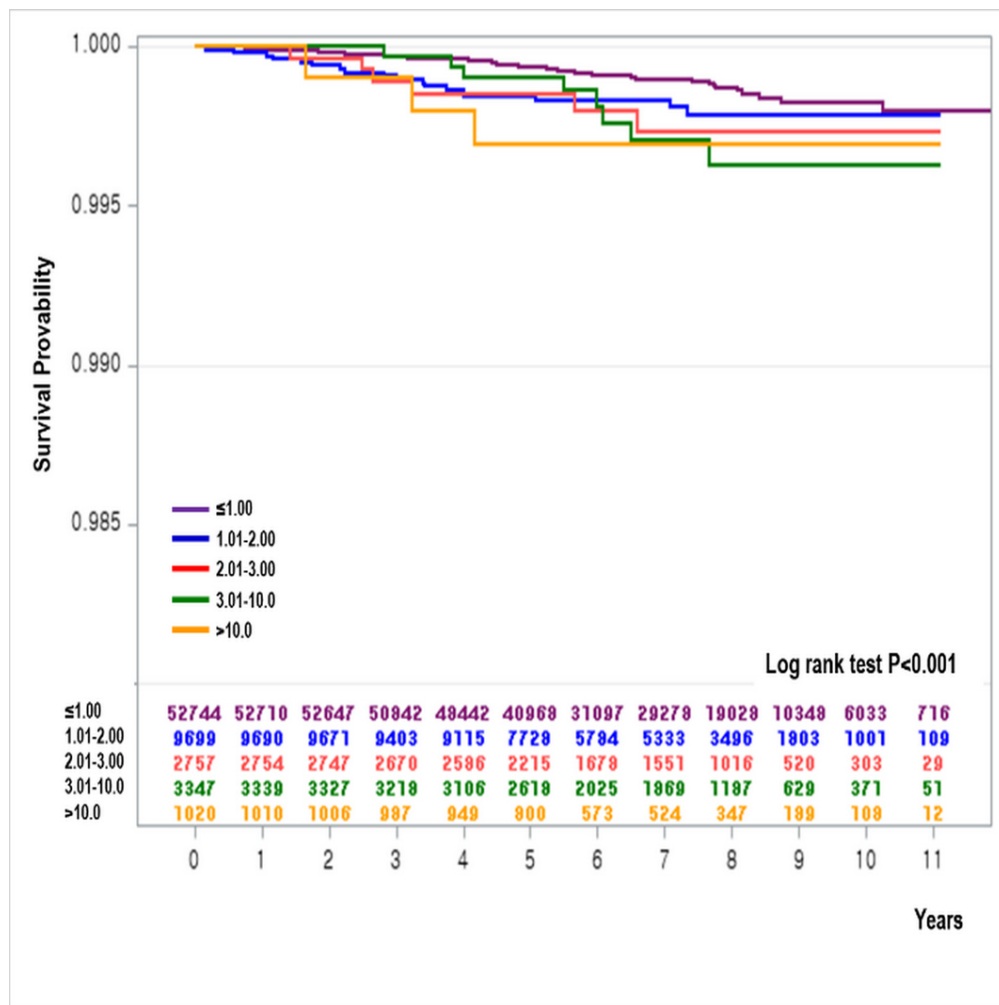


Figure 13 Kaplan-Meier crude survival curves for cardiovascular disease mortality according to serum hsCRP level in healthy subjects at recruitment.

90x90mm (300 x 300 DPI)

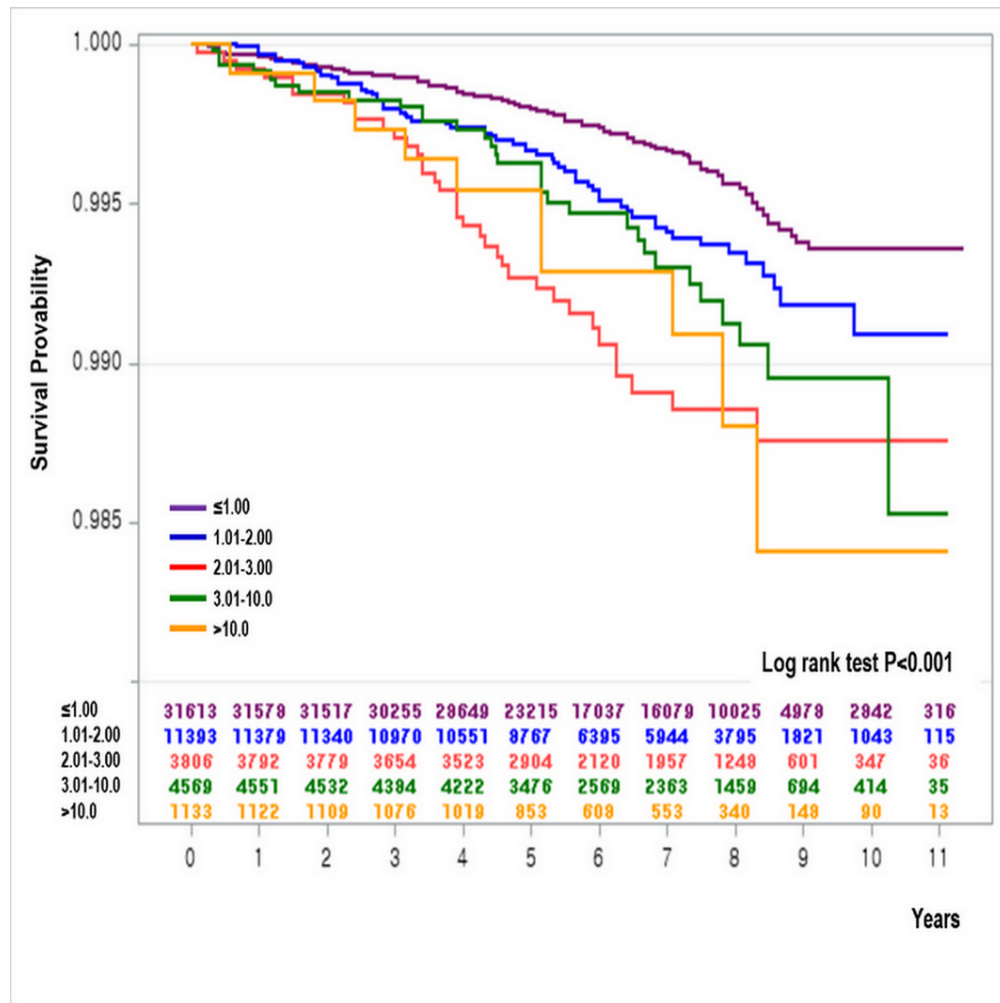


Figure 14 Kaplan-Meier crude survival curves for cardiovascular disease mortality according to serum hsCRP level in subjects with non-communicable disease history (NCDhistory) at recruitment.

90x90mm (300 x 300 DPI)

Supplement 1. The association of serum *hsCRP* 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)
<i>P</i> -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)
<i>P</i> -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)
<i>P</i> -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)
<i>P</i> -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)
<i>P</i> -trend				<0.001	0.001	0.003

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

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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

For peer review only

Supplement 2. The association between serum *hsCRP* 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
<i>P</i> -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
<i>P</i> -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
<i>P</i> -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) <i>Cohort study</i> —Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up <i>Case-control study</i> —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 <i>Cross-sectional study</i> —Give the eligibility criteria, and the sources and methods of selection of participants	4
		(b) <i>Cohort study</i> —For matched studies, give matching criteria and number of exposed and unexposed <i>Case-control study</i> —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) <i>Cohort study</i> —If applicable, explain how loss to follow-up was addressed <i>Case-control study</i> —If applicable, explain how matching of cases and controls was addressed	4

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46

		<i>Cross-sectional study</i> —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) <i>Cohort study</i> —Summarise follow-up time (eg, average and total amount)	6
Outcome data	15*	<i>Cohort study</i> —Report numbers of outcome events or summary measures over time	6-10
		<i>Case-control study</i> —Report numbers in each exposure category, or summary measures of exposure	Not Applicable
		<i>Cross-sectional study</i> —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:	<i>BMJ Open</i>
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

SCHOLARONE™
Manuscripts



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.

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

200 Sang-Ah Lee^{1,2*}, Sung Ok Kwon¹, Hyerim Park¹, Xiao-Ou Shu², Jong-Koo Lee³, Daehee Kang⁴

203 ¹Department of Preventive Medicine, School of Medicine, Kangwon National University, Chuncheon, Republic
204 of Korea.

205 ²Division of Epidemiology, Vanderbilt Epidemiology Center, Vanderbilt University Medical Center, Nashville,
206 TN, USA.

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

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

211 **ABSTRACT**

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

214 **Design** Prospective cohort study.

215 **Setting** the Health Examinees (HEXA) cohort.

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

217 **Outcome measures** The data and cause of death occurring until December 31, 2015, were confirmed by death
218 statistics from the National Statistical Office. We conducted the advanced analysis after stratification by
219 NCD_{history} and the sensitivity analysis after excluding death before 1 or 2 years from recruitment. Cox
220 proportional hazard and restricted cubic spline models were used to assess the association.

221 **Results** The association between serum *hsCRP* and the risk of all-cause mortality was observed with strong
222 linearity in both genders, which was not influenced by NCD_{history}. Otherwise, the association of serum *hsCRP*
223 with cancer-mortality risk was not observed in women with NCD_{history}, but the association with the risk of
224 cardiovascular disease (CVD) mortality was predominantly observed in men with NCD_{history}.

225 **Conclusions** This study suggested the dose-response association of *hsCRP* with mortality risk, including
226 cancer and CVD mortality, in Korean with low serum *hsCRP*, although the association with cancer and CVD-
227 mortality risk could be influenced by gender and NCD_{history}.

230 **Strengths and limitations of this study**

- 231 • This is the large population-based prospective study.
- 232 • We examined the effect of very high *hsCRP* concentration on mortality risk.
- 233 • The *hsCRP* level of present study was measured within 18 hours in a single institution to minimize error/bias.

1
2
3
4 234 • Due to random fluctuations of *hsCRP*, using the single measurement of *hsCRP* at baseline could reflect the
5
6 235 inaccurate status of blood *hsCRP* levels in the study participants and increase the instability of *hsCRP*.
7
8 236 • This study lacked information on medication use at recruitment and during the follow-up period, and
9
10 237 information on hormone-replacement therapy (HRT) among women.
11
12 238
13 239

14 240 *Correspondence to: Sang-Ah Lee, Ph.D.

15 241 Department of Preventive Medicine, School of Medicine, Kangwon National University,

16 242 Chuncheon, Gangwon, Republic of Korea.

17 243 Tel: +82 33 250 8871

18 244 E-mail: sangahlee@kangwon.ac.kr
19 245
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

266 INTRODUCTION

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

274 Serum *hsCRP* represents a low-grade inflammation state that is generally involved in the process of aging[9].
275 Several large cohorts, including Study of Women's Health Across the Nation (SWAN)[10], the Women's
276 Health Study[11] and the Dallas Heart Study[12], reported significant differences in *hsCRP* levels by race and
277 gender. In two studies of multiethnic populations residing in the USA[10, 13], the median *hsCRP* level in East
278 Asians was less than half the concentration in Caucasians. Even among East Asian populations, the geometric
279 mean of *hsCRP* levels varied depending on ethnic background[14]. In addition, a meta-analysis[11] reported
280 the *hsCRP* levels among women of various ethnic groups living in the United States (from the Women's Health
281 Study) on the association between *hsCRP* and the mortality risk; the association was observed in only men
282 supported by the results from two cohort studies[15, 16] reported in Korea. On the other hand, the increased
283 *hsCRP* may be influenced by comorbidity itself because inflammation has emerged as an important factor in the
284 progression of non-communicable diseases (NCDs), including CVD[17], cancer[18], chronic obstructive
285 pulmonary disease (COPD)[19], type 2 diabetes[20] and fractures[21], which contribute to increased morbidity
286 and mortality.

287 This study aimed to examine the association of serum *hsCRP* with the risk of mortality in Koreans with low
288 serum *hsCRP* and to evaluate the attenuated effect of non-communicable disease history ($NCD_{history}$) on the
289 association.

290

291

292

293

294

295 **METHODS**

296 **Study population**

297 Details on the main objectives, rationale, study design and baseline characteristics of the Health Examinees
298 (HEXA) study have been published elsewhere[22]. Considering the homogeneity and comparability of
299 participants, we created a qualified dataset called HEXA-G (Health Examinees-Gem) from previously published
300 HEXA studies[23]. In the new HEXA-G data, a total of 141 968 participants remained after the exclusion of
301 withdrawers ($n=12$). In addition, 19 887 were excluded due to missing information ($n=19 876$) or small sample
302 size ($n=11$) on any *hsCRP* components at the baseline survey. Ultimately, 122 081 subjects, including 41 070
303 men and 81 011 women, remained in the final analysis (Fig. 1). All study participants provided informed
304 consent prior to entering the study. The Institutional Review Board of the Seoul National University Hospital,
305 Seoul, Korea, approved it for statistical analysis (IRB No. E-1503-103-657).

307 **Laboratory measurements**

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

314 **Follow-up and ascertainment of mortality**

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

322

323 **Baseline variables**

324 Trained interviewers collected information on demographic, socioeconomic and lifestyle factors.
325 Anthropometric measurements were obtained using standardized methods. Body mass index (BMI) was
326 calculated, and all participants were defined into four classes based on the World Health Organization
327 classification of BMI for Asian adults[24]: underweight (BMI <18.5 kg/m²), normal (18.5 ≤ BMI <23.0 kg/m²),
328 overweight (23.0 ≤ BMI <25.0 kg/m²), obesity (25.0 ≤ BMI <29.9 kg/m²), and severe obesity (BMI ≥30.0 kg/m²).
329 The current study defined metabolic syndrome using the National Cholesterol Education Program Adult
330 Treatment Panel III (NCEP-ATP III)[25], modified for the Asian guideline for waist circumference (WC ≥90 and
331 ≥80 cm for men and women, respectively). Nonsmokers were defined as those who had smoked less than 400
332 cigarettes over the course of their lifetime. Participants who had smoked were categorized into two groups:
333 noncurrent (never/former) and current smoker. Noncurrent drinkers were defined as those who had never
334 consumed an alcoholic drink over the course of their lifetime or those who had not consumed alcohol at
335 recruitment, while current drinkers were defined as those who persisted in consuming alcohol. Regular exercise
336 was classified into two groups (yes/no) as follows: “Do you currently engage in regular exercise strenuous enough
337 to cause you to break into a sweat at least once per week?” Furthermore, considering the attenuated effect of the
338 NCD_{history} on the association between serum *hsCRP* and the risk of mortality, we performed advanced analysis
339 after stratification by NCD_{history}. We considered six main non-communicable diseases (hypertension, diabetes,
340 hyperlipidemia, cancer, cardiovascular and cerebrovascular diseases, and respiratory disease) to classify healthy
341 subjects vs. subjects with NCD_{history}.

342

343 **Statistical analysis**

344 For the categorical analysis, we created nine categories based on the distribution of *hsCRP* levels in our
345 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,
346 and >10.0 mg/L. For the advanced analysis after stratification by the NCD_{history}, the *hsCRP* levels were
347 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
348 each subgroup. The concentrations of *hsCRP* were log-transformed for analyses because of the skewed
349 distribution.

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

1
2
3
4 353 *hsCRP* and all-cause mortality, as well as cancer and CVD mortality, were analyzed by Cox proportional hazard
5
6 354 models (aHR) and included adjustment for age, gender, demographic factors (education, marital status, job, BMI
7
8 355 and NCD_{history}), and lifestyle factors (smoking, alcohol consumption and exercise). We used Wald tests to test
9
10 356 for heterogeneity of risk between serum *hsCRP* level groups. The proportional hazards assumption was assessed
11
12 357 on the basis of Schoenfeld residuals, and was not violated for the variables of interest in the adjusted model for
13
14 358 either cancer-mortality or cardiovascular disease mortality ($P>0.05$ for all categories). In addition, we conducted
15
16 359 a sensitivity analysis to avoid latent period bias after excluding death before 1 year (aHR_{1year}) or 2 years
17
18 360 (aHR_{2year}) since recruitment. Based on the Cox proportional hazard models, we made Kaplan-Meier curves and
19
20 361 log-rank analysis after adjustment for age, gender, demographic factors (education, marital status, job, BMI and
21
22 362 NCD_{history}), and lifestyle factors (smoking, alcohol consumption and exercise). We employed restricted cubic
23
24 363 splines (RCSs) to evaluate the possibility of complex (i.e., nonlinear) hazard functions[26] using continuous
25
26 364 values of *hsCRP* (aHR_{continuous}). We selected five *hsCRP* concentration values as knots based on *hsCRP* concen-
27
28 365 tration percentiles, tested the linear and nonlinear associations between knots using a cubic function, and
29
30 366 presented the integrated graph smoothly. All statistical analyses were performed using SAS version 9.3 (SAS
31
32 367 Institute Inc., Cary, NC, USA) and RCS analysis was carried out using the SAS LGTPHCURV9 macro. Two-
33
34 368 sided *p*-values <0.05 were defined as indicating statistical significance.

35 369

370 **Patient and public involvement**

38
39 371 No patients and public were involved in the design, conducting, reporting, and dissemination plans of the present
40
41 372 study.

42 373

43 374

44 375

45 376

46 377

47 378

48 379

49 380

50 381

51 382

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 *hsCRP* 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).

412 **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)
<i>P</i> -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)

413 NCD_{history}: Non-communicable disease history414 ^a Adjusted for age, gender, education, job, marital status, BMI and non-communicable disease history415 ^b Compared to white-colored worker

416

417

418

419

420

421

422

423

424

1
2
3
4 425 The risk of all-cause mortality was inclined with a dose-dependent pattern as increased serum *hsCRP* level
5
6 426 ($P_{trend}<0.001$, Supplement 1), regardless of gender ($P_{trend}<0.001$ in both genders), even in the sensitivity analysis
7
8 427 ($P_{trend}<0.001$ for aHR_{1year} in both genders). The increased risk of female mortality with increased *hsCRP* levels
9
10 428 was observed in both premenopausal ($P_{trend}=0.020$) and postmenopausal women ($P_{trend}<0.001$), although the
11
12 429 statistical significance in premenopausal women disappeared after sensitivity analysis ($P_{trend}=0.150$ for aHR_{2year} ,
13
14 430 Supplement 1). The integrated graph, based on the restricted cubic spline analyses, indicated a strong and linear
15
16 431 association of serum *hsCRP* level with all-cause mortality in both genders ($aHR_{continuous}=1.019$ and 1.013 in men
17
18 432 and women, respectively, Fig. 2 (a)).

19 433 The dose-response association between *hsCRP* level and the risk of all-cause mortality was not influenced by
20
21 434 $NCD_{history}$ (Supplement 2). After stratification by gender, however, the attenuated effect by $NCD_{history}$ on the
22
23 435 association was observed only in women; the linearity of the relationship was observed in healthy women
24
25 436 ($P_{trend}=0.001$ for aHR_{2year}) but disappeared in women with $NCD_{history}$, particularly after sensitivity analysis with
26
27 437 the exclusion of a 2-year follow-up time ($P_{trend}=0.084$ for aHR_{2year}). Based on the restricted cubic spline
28
29 438 analyses, otherwise, the pattern of increase in the association was different depending on the $NCD_{history}$ (Fig. 2
30
31 439 (b), (c)). In the healthy subjects, the risk of all-cause mortality was increased with a gradual slope (strength)
32
33 440 until 3.0 mg/L *hsCRP*, with a very steep slope until 4.5 mg/L and finally with a reduced and flattened slope after
34
35 441 4.5 mg/L (Fig. 2 (b)). On the other hand, the slope of the association fluctuated as the *hsCRP* level increased in
36
37 442 the subjects with $NCD_{history}$; the slope increased up to 3.0 mg/L *hsCRP* but decreased until 4.5 mg/L and rapidly
38
39 443 increased after 4.5 mg/L (Fig. 2 (c)).

40 444 The association of serum *hsCRP* with the risk of cancer-mortality was not influenced by $NCD_{history}$
41
42 445 ($P_{trend}<0.001$ regardless of $NCD_{history}$) (Table 2 and Fig. 3 (a-e)). Otherwise, after stratification by gender, the
43
44 446 association was not observed in women with $NCD_{history}$ ($P_{trend}=0.856$); however, the association was not
45
46 447 influenced by $NCD_{history}$ in men ($P_{trend}<0.001$ and 0.002 for aHR in both healthy and $NCD_{history}$) (Table 2).
47
48 448 Although the risk of CVD mortality was linearly associated with increasing *hsCRP* levels, the association was
49
50 449 dominant in men ($P_{trend}=0.002$) and in subjects with $NCD_{history}$ ($P_{trend}=0.001$, Table 3) after stratified by gender
51
52 450 and $NCD_{history}$, respectively (Fig. 4 (a-e)). After stratification by gender and $NCD_{history}$, otherwise, the association
53
54 451 only appeared in individuals of both genders with $NCD_{history}$ ($P_{trend}=0.015$ and 0.035 in men and women with
55
56 452 $NCD_{history}$, respectively); no association between *hsCRP* level and CVD mortality risk was found in either
57
58 453 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
<i>P</i> -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
<i>P</i> -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
<i>P</i> -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 *hsCRP* 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
<i>P</i> -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
<i>P</i> -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
<i>P</i> -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 *hsCRP* levels with a dose-response manner in both gender among Asian who have reported low *hsCRP* 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 *hsCRP* with the risk of cancer- and CVD-mortality was also observed in this population. The level of *hsCRP* was not associated with the risk of cancer- mortality among women with *NCD_{history}*. The risk effect of high *hsCRP* level on CVD mortality was predominantly observed in men with *NCD_{history}*.

Several large cohorts[10-12, 14] have suggested that serum *hsCRP* 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 *hsCRP* with mortality risk. In this population, the *hsCRP* level was associated with the risk of all-cause mortality in a dose-dependent manner, even though the level of *hsCRP* 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 *hsCRP* 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 *hsCRP* 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 *hsCRP* 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 *hsCRP*[32]; the average *hsCRP* 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].

1
2
3
4 482 Inflammation has emerged as an important factor in the processes of NCD, including CVD[17], cancer[18],
5
6 483 type 2 diabetes[20], COPD[19, 34] and fracture[21]. In addition, medications that had taken to treat any specific
7
8 484 NCD, such as rennin–angiotensin system inhibitors[35] and statins and thiazolidinedione[36], could influence
9
10 485 the level of *hsCRP*. The association between *hsCRP* and the mortality risk was not attenuated by $NCD_{history}$ in
11
12 486 either gender in this study, but the statistical significance of the association disappeared in women after
13
14 487 sensitivity analysis (aHR_{2year}). A dose-response relationship between *hsCRP* level and all-cause mortality risk
15
16 488 was pronounced in both genders. On the other hand, the positive association of *hsCRP* with the risk of all-cause
17
18 489 mortality risk was significantly observed in only men with $NCD_{history}$ but not in women with $NCD_{history}$. The
19
20 490 attenuated effect of $NCD_{history}$ on the association between *hsCRP* and the risk of cancer-mortality was not
21
22 491 observed in men, consistent with results from several studies which reported the associations among healthy
23
24 492 men[3] or cancer patients[37, 38] only. Most studies[3, 4, 6, 7, 15, 16, 31, 39] supported that CVD mortality
25
26 493 increased with elevated *hsCRP* levels, predominantly in men[4, 7, 15, 16]. Although *hsCRP* levels are lower in
27
28 494 our population than in other races, the level of *hsCRP* was positively associated with CVD mortality in men but
29
30 495 not in women, similar to previous studies[7, 15, 16, 31, 39]. After stratification by gender and $NCD_{history}$, the
31
32 496 association between *hsCRP* and the risk of CVD mortality was dominant in subjects with $NCD_{history}$ in this
33
34 497 study. Although many interventional studies have been conducted recently on anti-inflammatory drugs for the
35
36 498 prevention of cardiovascular disease, the results are controversial. According to the results of our study, elevated
37
38 499 inflammatory markers in people with chronic disease were associated with an increased risk of CVD mortality.
39
40 500 This suggests that CVD-mortality in people with chronic diseases might be reduced by use of anti-inflammatory
41
42 501 medication.

43 502 This study has several strengths because of the large population-based prospective study; it makes possible 1)
44
45 503 to adjust for confounders; 2) to examine sensitivity analysis after excluding death before 1 or 2 years from
46
47 504 recruitment; 3) to assess an advanced analysis after stratification by gender and $NCD_{history}$; 4) to examine the
48
49 505 association using various cut-off points of *hsCRP* considering low serum *hsCRP* levels in Asian populations;
50
51 506 and 5) to evaluate the complex (i.e., nonlinear) hazard functions using restricted cubic splines on the association
52
53 507 between continuous *hsCRP* levels and the risk of mortality. In particular, most previous studies excluded
54
55 508 subjects with more than 10 mg/L *hsCRP* because of their relatively low sample size or reflecting acute phase
56
57 509 reactions of severe inflammation, but we examined the effect of very high *hsCRP* concentration on the risk of
58
59 510 mortality because it is possible to be more concerning for these subjects in the future. The *hsCRP* level of this
60

1
2
3
4 511 study, in addition, was measured within 18 hours in a single institution to minimize measurement error/bias
5
6 512 from institutional variation to avoid bias from measurement or long-term storage before analysis.
7

8 513 Despite of those strengths, it is also several limitations. First, the use of a single measurement of *hsCRP* at
9
10 514 baseline could reflect the inaccurate status of blood *hsCRP* levels in the study participants and increase the
11
12 515 instability of *hsCRP* due to random fluctuations over time. Nevertheless, a report [40] on the long-term *hsCRP*
13
14 516 variability suggested that the *hsCRP* variability within individual is relatively small and that the variability
15
16 517 could not account for the association. Second, our study lacked information on medication use at recruitment
17
18 518 and during the follow-up period. Several medications related to NCDs, including statins, angiotensin-converting
19
20 519 enzyme inhibitors, fibrates, niacin, thiazolidinedione and estrogen/progestogen hormone, could influence the
21
22 520 *hsCRP* level[37]; however, we tried to overcome this limitation through advanced analysis after stratification by
23
24 521 *NCD_{history}*. Third, because there is no available information on hormone-replacement therapy (HRT) among
25
26 522 women, which could not examine the influence of HRT on the association of *hsCRP* with the risk of hormone-
27
28 523 related cancer or CVD mortality among women, we could not suggest the effect of female hormones on the
29
30 524 association. In addition, further studies are needed on the effects of obesity although the inverse relationship
31
32 525 between all-cause mortality with obesity in our population was consistent to Wei's report in Asian[41]. On the
33
34 526 other hand, the inverse association of alcohol drinking with all-cause mortality couldn't interpret directly
35
36 527 because our report wasn't separated the distinguish between mild drinkers and abuse alcohol drinker, which
37
38 528 requires additional research for our population in the future.

39 529 In conclusion, the association of *hsCRP* level is dose-responsively increased with the risk of all-cause
40
41 530 mortality in men and women (particularly postmenopausal women), which was not influenced by the association
42
43 531 was not observed in women with *NCD_{history}*. Otherwise, the association of *hsCRP* level with the risk of cancer-
44
45 532 and CVD-mortality could be attenuated by gender or *NCD_{history}*.

46 533

47 534

50 535 **Figure 1** Flow diagram of analytical sample in current study using Health Examinees cohort.

52 536 **Figure 2** A dose-response association between serum *hsCRP* level and risk of all-cause mortality in all (a),
53
54 537 healthy subjects at recruitment (b), and subjects with non-communicable disease history (*NCD_{history}*) at
55
56 538 recruitment (c).

58 539 **Figure 3** Kaplan-Meier crude survival curves for cancer-mortality according to serum *hsCRP* level in all (a)

1
2
3
4 540 men (b), women (c), healthy subjects at recruitment (d), and subjects with non-communicable disease history
5
6 541 (NCD_{history}) at recruitment (e).

7
8 542 **Figure 4** Kaplan-Meier crude survival curves for cardiovascular disease mortality according to serum *hsCRP*
9
10 543 level in all (a), men (b), women (c), healthy subjects at recruitment (d), and subjects with non-communicable
11
12 544 disease history (NCD_{history}) at recruitment (e).

13
14 545

15
16 546

17 547 **Contributors**

18
19 548 SAL, XS and DK: designed and conducted the research, SAL and SOK: analyzed the data and performed the
20
21 549 statistical analyses; HP and JKL: managed data mining and collection; SAL: wrote the manuscript and had primary
22
23 550 responsibility for the final content of the manuscript; and all authors: read and approved the final manuscript.

24
25 551

26
27 552 **Funding** None.

28
29 553

30
31 554 **Competing interests** None declared.

32
33 555 **Patient consent for publication** Not required.

34
35 556 **Ethics approval** The Institutional Review Board of the Seoul National University Hospital, Seoul, Korea,
36
37 557 approved it for statistical analysis (IRB No. E-1503-103-657).

38
39 558

40
41 559 **Provenance and peer review** Not commissioned; externally peer reviewed.

42
43 560 **Data availability statement**

44
45 561 No additional data available.

46
47 562

48
49 563

50
51 564 **REFERENCES**

52 565 1 Pepys MB, Hirschfield GM. C-reactive protein: a critical update. *The Journal of clinical*
53
54 566 *investigation* 2003;**111**:1805-12.

55
56 567 2 Elias-Smale SE, Kardys I, Oudkerk M, *et al*. C-reactive protein is related to extent and
57
58 568 progression of coronary and extra-coronary atherosclerosis; results from the Rotterdam study.

59 569 *Atherosclerosis* 2007;**195**:e195-202.

60

- 1
2
3
4 570 3 Koenig W, Khuseyinova N, Baumert J, *et al.* Prospective study of high-sensitivity C-reactive
5 571 protein as a determinant of mortality: results from the MONICA/KORA Augsburg Cohort Study,
6 572 1984-1998. *Clinical chemistry* 2008;**54**:335-42.
- 9 573 4 Ahmadi-Abhari S, Luben RN, Wareham NJ, *et al.* Seventeen year risk of all-cause and
10 574 cause-specific mortality associated with C-reactive protein, fibrinogen and leukocyte count in men
11 575 and women: the EPIC-Norfolk study. *European journal of epidemiology* 2013;**28**:541-50.
- 14 576 5 Kuoppamaki M, Salminen M, Vahlberg T, *et al.* High sensitive C-reactive protein (hsCRP),
15 577 cardiovascular events and mortality in the aged: a prospective 9-year follow-up study. *Archives of*
16 578 *gerontology and geriatrics* 2015;**60**:112-7.
- 18 579 6 Zuo H, Ueland PM, Ulvik A, *et al.* Plasma Biomarkers of Inflammation, the Kynurenine
20 580 Pathway, and Risks of All-Cause, Cancer, and Cardiovascular Disease Mortality: The Hordaland
21 581 Health Study. *American journal of epidemiology* 2016;**183**:249-58.
- 23 582 7 Nisa H, Hirata A, Kohno M, *et al.* High-Sensitivity C-Reactive Protein and Risks of All-
24 583 Cause and Cause-Specific Mortality in a Japanese Population. *Asian Pacific journal of cancer*
25 584 *prevention : APJCP* 2016;**17**:2643-8.
- 28 585 8 Li Y, Zhong X, Cheng G, *et al.* Hs-CRP and all-cause, cardiovascular, and cancer mortality
29 586 risk: A meta-analysis. *Atherosclerosis* 2017;**259**:75-82.
- 31 587 9 Vasto S, Candore G, Balistreri CR, *et al.* Inflammatory networks in ageing, age-related
32 588 diseases and longevity. *Mechanisms of ageing and development* 2007;**128**:83-91.
- 34 589 10 Kelley-Hedgpeath A, Lloyd-Jones DM, Colvin A, *et al.* Ethnic differences in C-reactive
35 590 protein concentrations. *Clinical chemistry* 2008;**54**:1027-37.
- 37 591 11 Albert MA, Glynn RJ, Buring J, *et al.* C-reactive protein levels among women of various
38 592 ethnic groups living in the United States (from the Women's Health Study). *The American journal of*
39 593 *cardiology* 2004;**93**:1238-42.
- 42 594 12 Khera A, McGuire DK, Murphy SA, *et al.* Race and gender differences in C-reactive protein
43 595 levels. *Journal of the American College of Cardiology* 2005;**46**:464-9.
- 45 596 13 Lakoski SG, Cushman M, Criqui M, *et al.* Gender and C-reactive protein: data from the
46 597 Multiethnic Study of Atherosclerosis (MESA) cohort. *American heart journal* 2006;**152**:593-8.
- 48 598 14 Matthews KA, Sowers MF, Derby CA, *et al.* Ethnic differences in cardiovascular risk factor
49 599 burden among middle-aged women: Study of Women's Health Across the Nation (SWAN). *American*
50 600 *heart journal* 2005;**149**:1066-73.
- 53 601 15 Lee JH, Yeom H, Kim HC, *et al.* C-reactive Protein Concentration Is Associated With a
54 602 Higher Risk of Mortality in a Rural Korean Population. *Journal of preventive medicine and public*
55 603 *health = Yebang Uihakhoe chi* 2016;**49**:275-87.
- 58 604 16 Sung KC, Ryu S, Chang Y, *et al.* C-reactive protein and risk of cardiovascular and all-cause
59 605 mortality in 268 803 East Asians. *European heart journal* 2014;**35**:1809-16.

- 1
2
3
4 606 17 Kengne AP, Batty GD, Hamer M, *et al.* Association of C-reactive protein with
5
6 607 cardiovascular disease mortality according to diabetes status: pooled analyses of 25,979 participants
7
8 608 from four U.K. prospective cohort studies. *Diabetes care* 2012;**35**:396-403.
- 9 609 18 Heikkila K, Ebrahim S, Lawlor DA. A systematic review of the association between
10
11 610 circulating concentrations of C reactive protein and cancer. *Journal of epidemiology and community*
12
13 611 *health* 2007;**61**:824-33.
- 14 612 19 Dahl M, Vestbo J, Lange P, *et al.* C-reactive protein as a predictor of prognosis in chronic
15
16 613 obstructive pulmonary disease. *American journal of respiratory and critical care medicine*
17
18 614 2007;**175**:250-5.
- 19 615 20 Wang X, Bao W, Liu J, *et al.* Inflammatory markers and risk of type 2 diabetes: a systematic
20
21 616 review and meta-analysis. *Diabetes care* 2013;**36**:166-75.
- 22 617 21 Ishii S, Cauley JA, Greendale GA, *et al.* C-reactive protein, bone strength, and nine-year
23
24 618 fracture risk: data from the Study of Women's Health Across the Nation (SWAN). *Journal of bone*
25
26 619 *and mineral research : the official journal of the American Society for Bone and Mineral Research*
27
28 620 2013;**28**:1688-98.
- 29 621 22 Kim Y, Han BG, Ko GESg. Cohort Profile: The Korean Genome and Epidemiology Study
30
31 622 (KoGES) Consortium. *International journal of epidemiology* 2017;**46**:1350.
- 32 623 23 Shin S, Lee HW, Kim CE, *et al.* Egg Consumption and Risk of Metabolic Syndrome in
33
34 624 Korean Adults: Results from the Health Examinees Study. *Nutrients* 2017;**9**.
- 35 625 24 Pan WH, Yeh WT. How to define obesity? Evidence-based multiple action points for public
36
37 626 awareness, screening, and treatment: an extension of Asian-Pacific recommendations. *Asia Pacific*
38
39 627 *journal of clinical nutrition* 2008;**17**:370-4.
- 40 628 25 National Cholesterol Education Program Expert Panel on Detection E, Treatment of High
41
42 629 Blood Cholesterol in A. Third Report of the National Cholesterol Education Program (NCEP) Expert
43
44 630 Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment
45
46 631 Panel III) final report. *Circulation* 2002;**106**:3143-421.
- 47 632 26 Heinzl H, Kaider A. Gaining more flexibility in Cox proportional hazards regression models
48
49 633 with cubic spline functions. *Computer methods and programs in biomedicine* 1997;**54**:201-8.
- 50 634 27 MacGregor AJ, Gallimore JR, Spector TD, *et al.* Genetic effects on baseline values of C-
51
52 635 reactive protein and serum amyloid a protein: a comparison of monozygotic and dizygotic twins.
53
54 636 *Clinical chemistry* 2004;**50**:130-4.
- 55 637 28 Ledue TB, Rifai N. Preanalytic and analytic sources of variations in C-reactive protein
56
57 638 measurement: implications for cardiovascular disease risk assessment. *Clinical chemistry*
58
59 639 2003;**49**:1258-71.
60

- 1
2
3
4 640 29 Emerging Risk Factors C, Kaptoge S, Di Angelantonio E, *et al.* C-reactive protein
5 641 concentration and risk of coronary heart disease, stroke, and mortality: an individual participant meta-
6 642 analysis. *Lancet* 2010;**375**:132-40.
7
8
9 643 30 Lee YJ, Lee JH, Shin YH, *et al.* Gender difference and determinants of C-reactive protein
10 644 level in Korean adults. *Clinical chemistry and laboratory medicine* 2009;**47**:863-9.
11
12 645 31 Doran B, Zhu W, Muennig P. Gender differences in cardiovascular mortality by C-reactive
13 646 protein level in the United States: evidence from the National Health and Nutrition Examination
14 647 Survey III. *American heart journal* 2013;**166**:45-51.
15
16
17 648 32 Gaskins AJ, Wilchesky M, Mumford SL, *et al.* Endogenous reproductive hormones and C-
18 649 reactive protein across the menstrual cycle: the BioCycle Study. *American journal of epidemiology*
19 650 2012;**175**:423-31.
20
21
22 651 33 Gilliver SC. Sex steroids as inflammatory regulators. *The Journal of steroid biochemistry*
23 652 *and molecular biology* 2010;**120**:105-15.
24
25 653 34 Man SF, Connett JE, Anthonisen NR, *et al.* C-reactive protein and mortality in mild to
26 654 moderate chronic obstructive pulmonary disease. *Thorax* 2006;**61**:849-53.
27
28 655 35 Di Napoli M, Papa F. Angiotensin-converting enzyme inhibitor use is associated with
29 656 reduced plasma concentration of C-reactive protein in patients with first-ever ischemic stroke. *Stroke*
30 657 2003;**34**:2922-9.
31
32
33 658 36 Sidhu JS, Cowan D, Kaski JC. The effects of rosiglitazone, a peroxisome proliferator-
34 659 activated receptor-gamma agonist, on markers of endothelial cell activation, C-reactive protein, and
35 660 fibrinogen levels in non-diabetic coronary artery disease patients. *Journal of the American College of*
36 661 *Cardiology* 2003;**42**:1757-63.
37
38
39 662 37 Heikkila K, Ebrahim S, Rumley A, *et al.* Associations of circulating C-reactive protein and
40 663 interleukin-6 with survival in women with and without cancer: findings from the British Women's
41 664 Heart and Health Study. *Cancer epidemiology, biomarkers & prevention : a publication of the*
42 665 *American Association for Cancer Research, cosponsored by the American Society of Preventive*
43 666 *Oncology* 2007;**16**:1155-9.
44
45
46 667 38 Marsik C, Kazemi-Shirazi L, Schickbauer T, *et al.* C-reactive protein and all-cause mortality
47 668 in a large hospital-based cohort. *Clinical chemistry* 2008;**54**:343-9.
48
49
50 669 39 Proctor MJ, McMillan DC, Horgan PG, *et al.* Systemic inflammation predicts all-cause
51 670 mortality: a glasgow inflammation outcome study. *PloS one* 2015;**10**:e0116206.
52
53
54 671 40 Chen TH, Gona P, Sutherland PA, *et al.* Long-term C-reactive protein variability and
55 672 prediction of metabolic risk. *The American journal of medicine* 2009;**122**:53-61.
56
57
58 673 41 Zheng W, McLerran DF, Rolland B, *et al.* Association between Body-Mass Index and Risk
59 674 of Death in More Than 1 Million Asians, *N Engl J Med* 2011; 364:719-729.
60 675

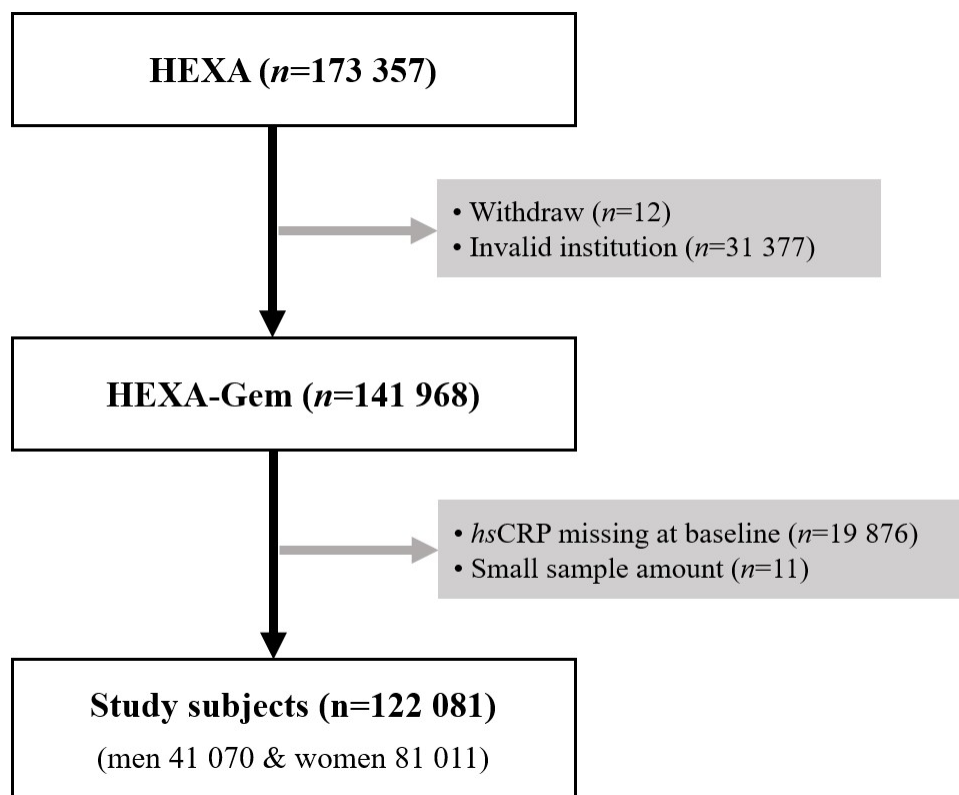


Figure 1 Flow diagram of analytical sample in current study using Health Examinees cohort.
HEXA: Health Examinees, hsCRP: High sensitivity C-reactive protein

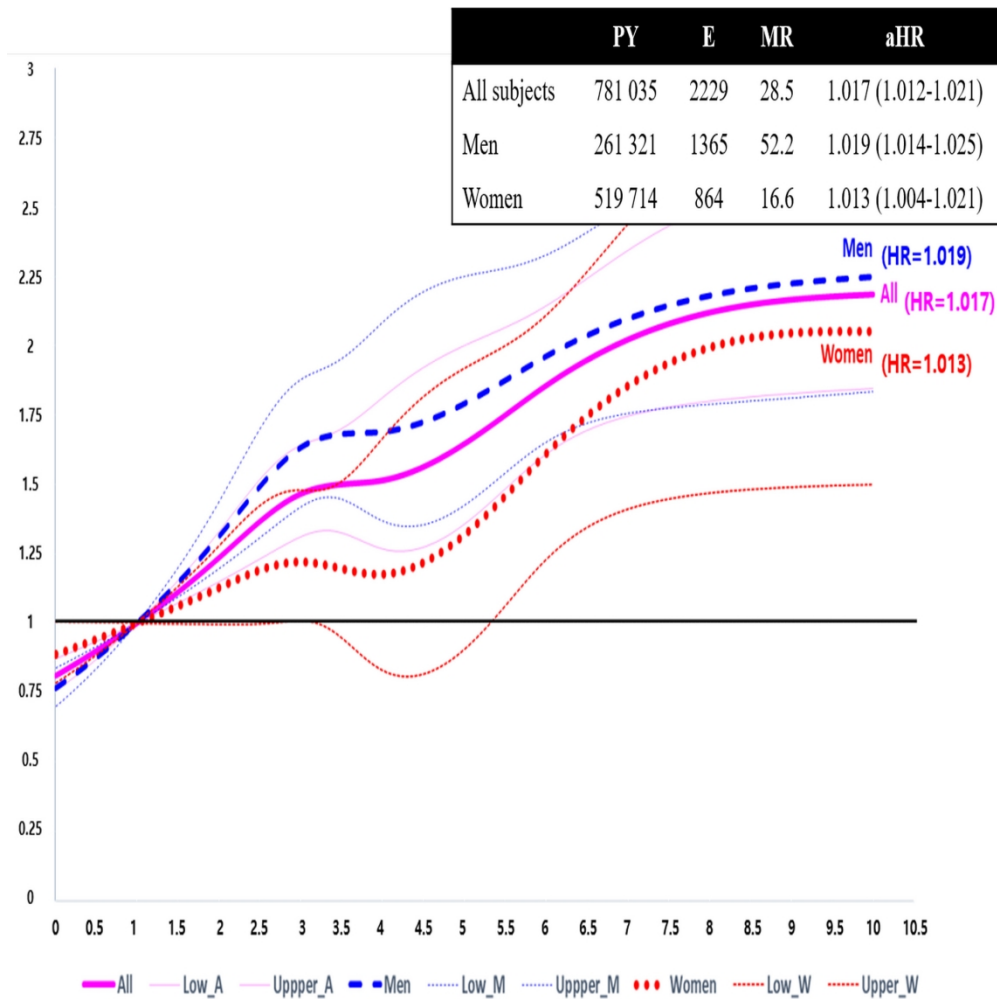


Figure 2 (a) A dose-response association between serum hsCRP level and risk of all-cause mortality in all subjects at recruitment. PY: Person-year, E: Number of death, MR: Mortality rate (10 000 person year) aHR: Adjusted for age, gender, education, job, marital status, BMI, non-communicable disease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

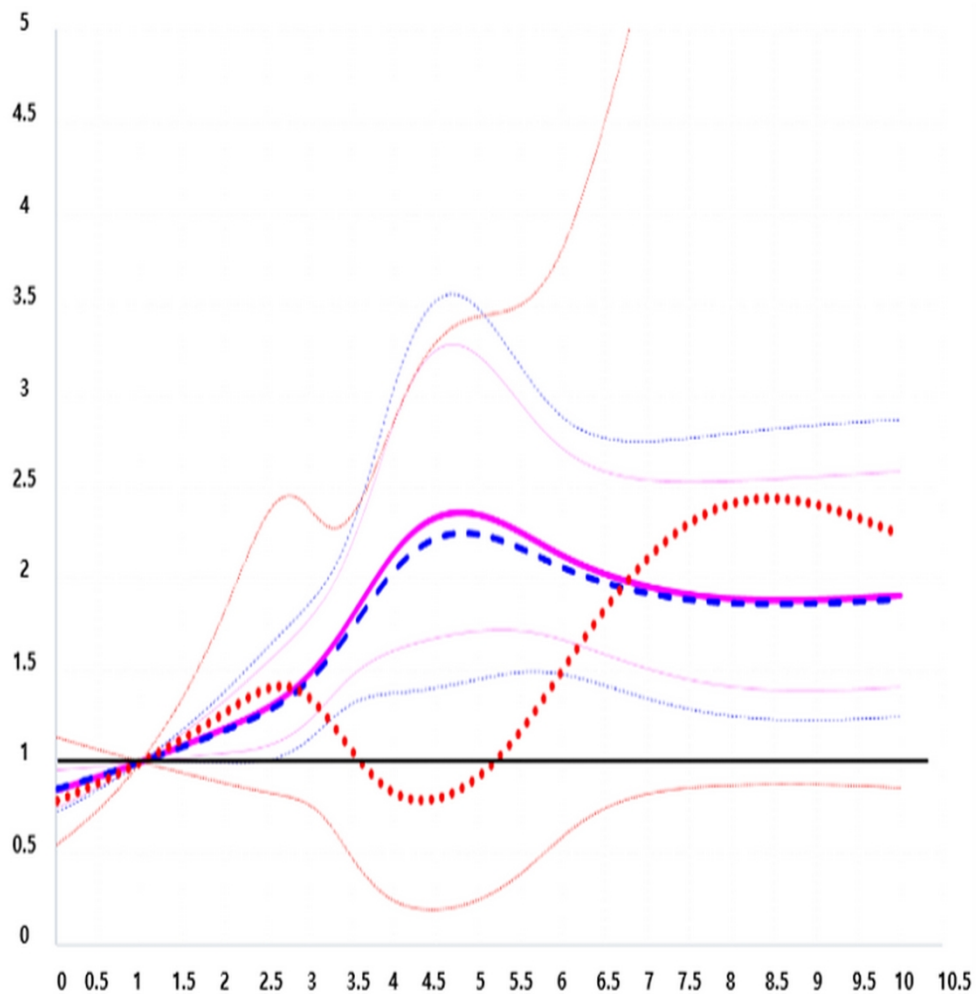


Figure 2 (b) A dose-response association between serum hsCRP level and risk of all-cause mortality in healthy subjects at recruitment. Low_A and Upper_A: 95%CI for all subjects Low_M and Upper_M: 95%CI for men Low_W and Upper_W: 95%CI for women

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

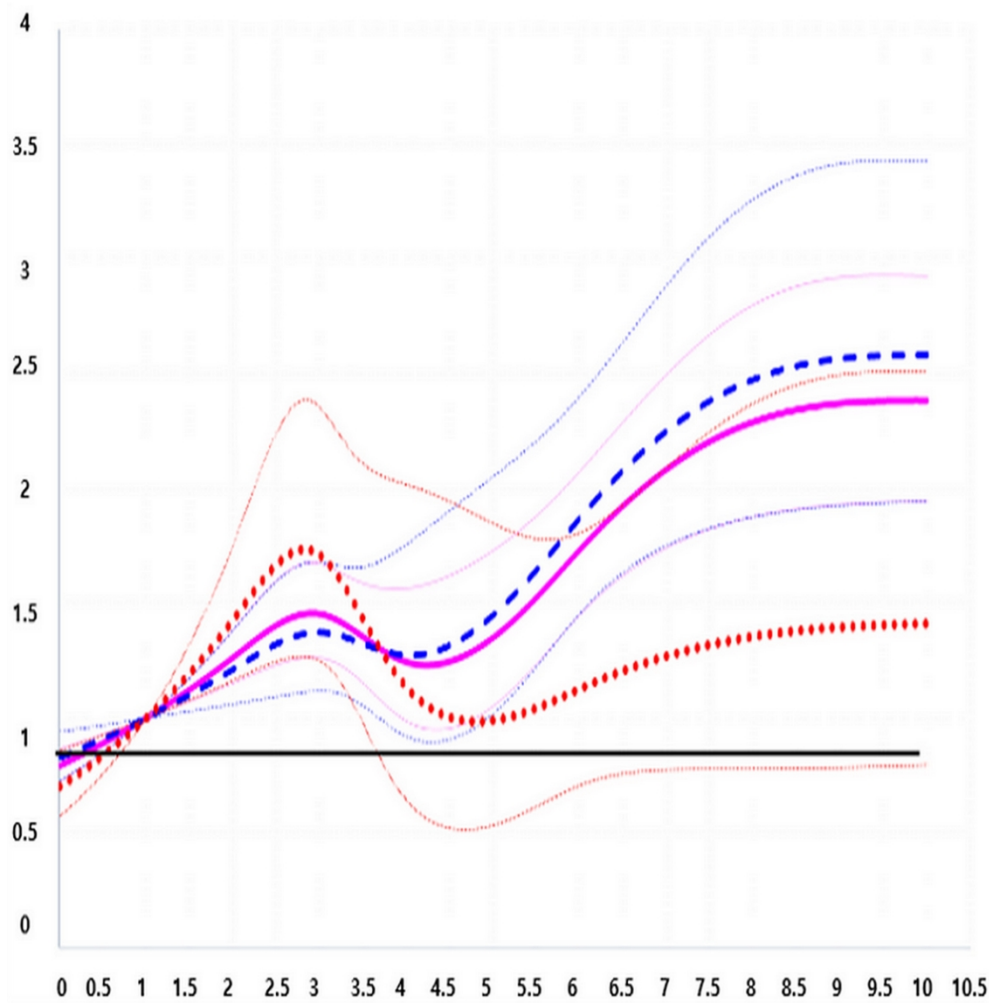


Figure 2 (c) A dose-response association between serum hsCRP level and risk of all-cause mortality in subjects with non-communicable disease history (NCDhistory) at recruitment. Low_A and Upper_A: 95%CI for all subjects Low_M and Upper_M: 95%CI for men Low_W and Upper_W: 95%CI for women

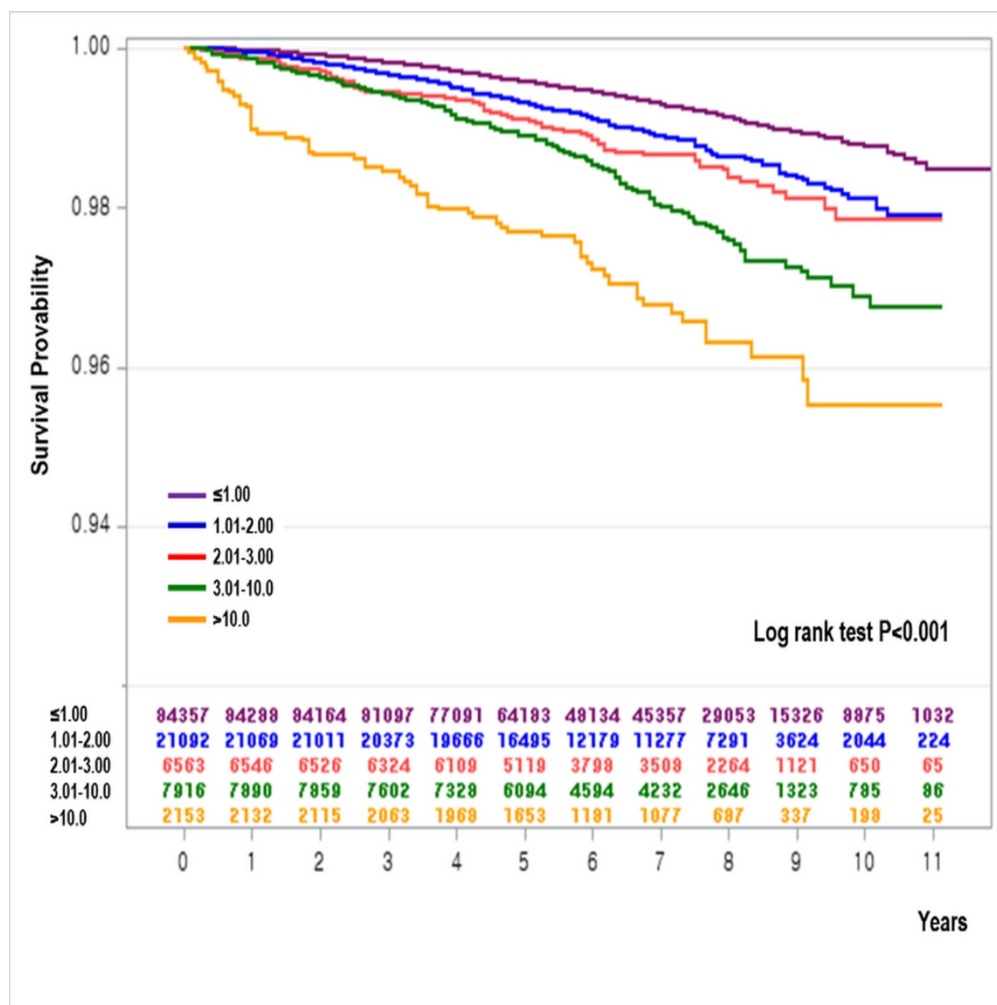


Figure 3 (a) Kaplan-Meier crude survival curves for cancer-mortality according to serum hsCRP level in all subjects at recruitment.

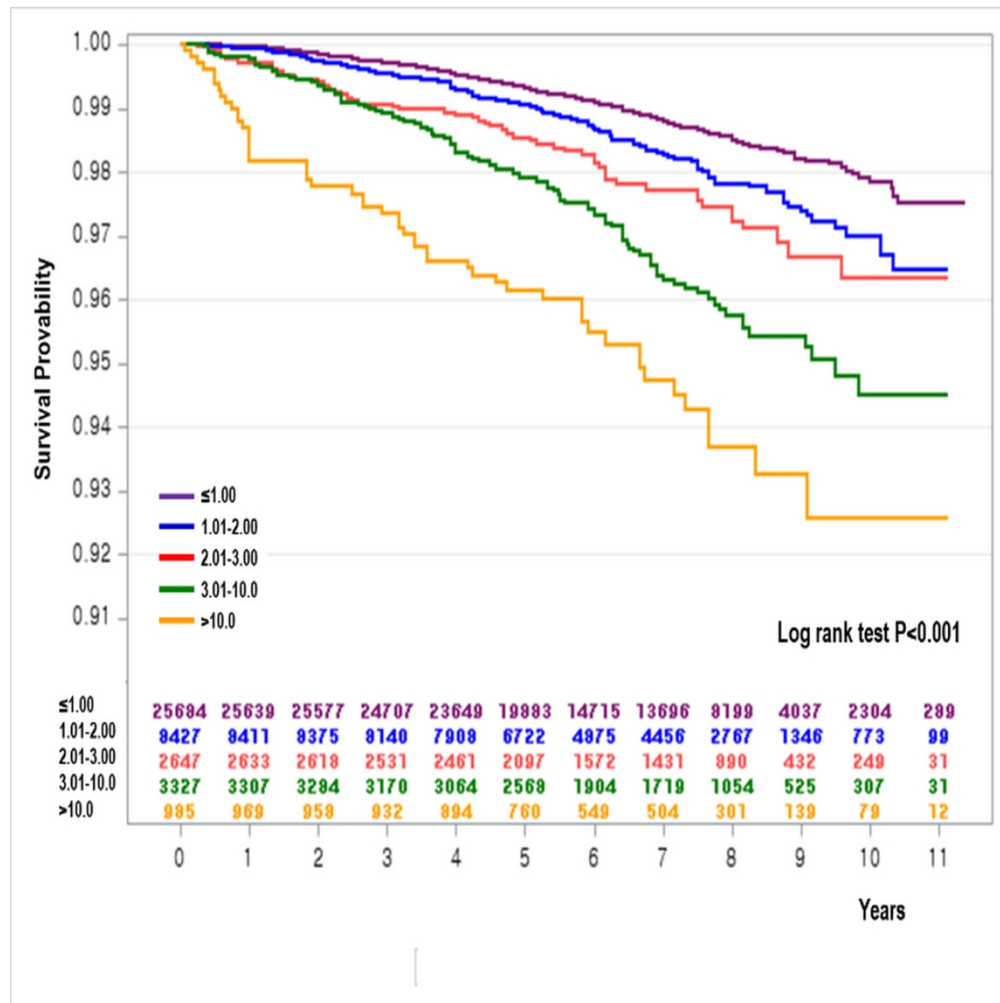


Figure 3 (b) Kaplan-Meier crude survival curves for cancer-mortality according to serum hsCRP level in men at recruitment.

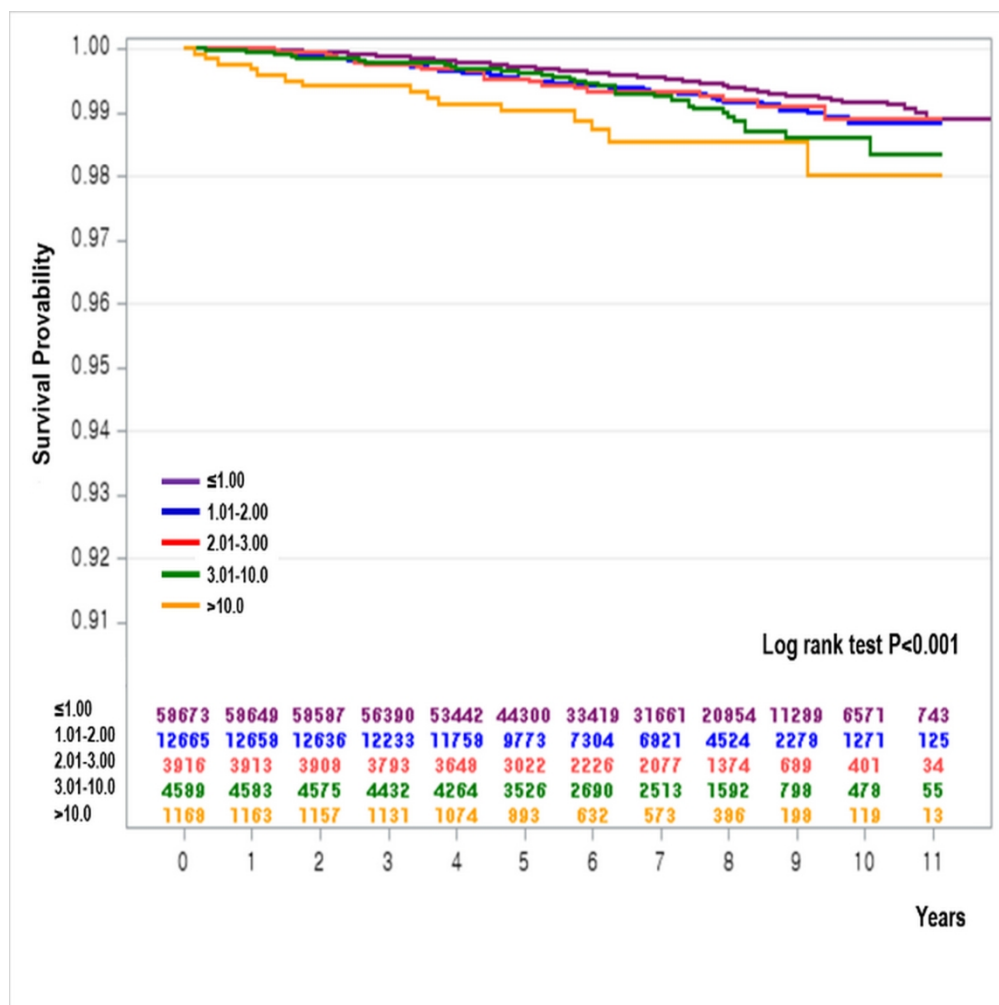


Figure 3 (c) Kaplan-Meier crude survival curves for cancer-mortality according to serum hsCRP level in women at recruitment.

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

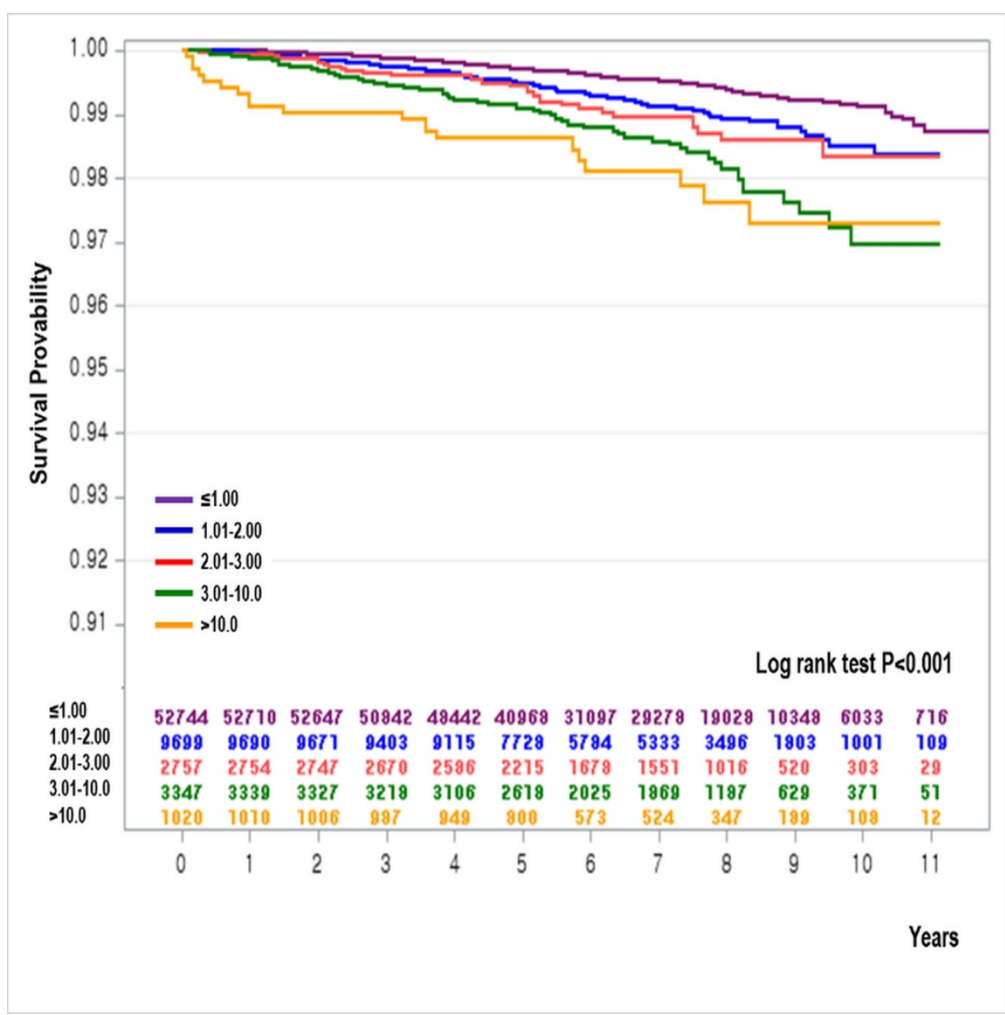


Figure 3 (d) Kaplan-Meier crude survival curves for cancer-mortality according to serum hsCRP level in healthy subjects at recruitment.

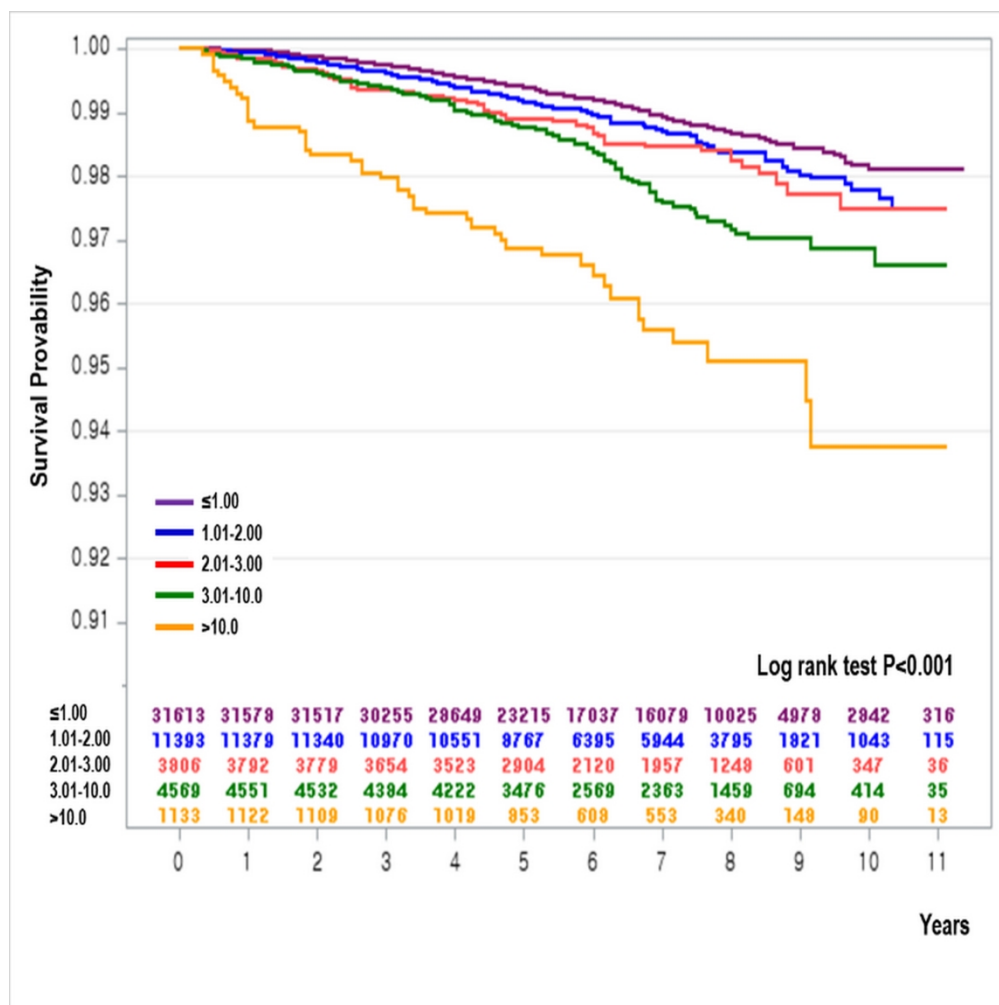


Figure 3 (e) Kaplan-Meier crude survival curves for cancer-mortality according to serum hsCRP level in subjects with non-communicable disease history (NCDhistory) at recruitment.

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

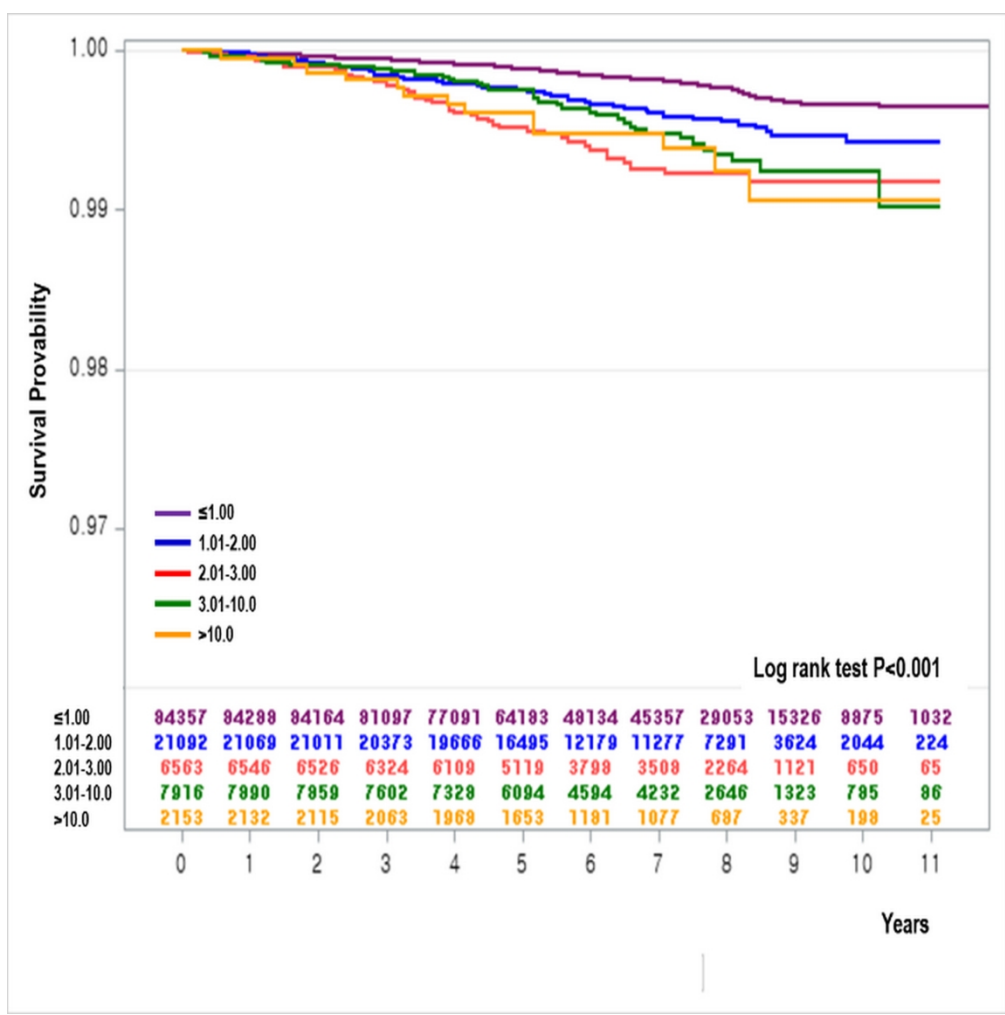


Figure 4 (a) Kaplan-Meier crude survival curves for cardiovascular disease mortality according to serum hsCRP level in all subjects at recruitment.

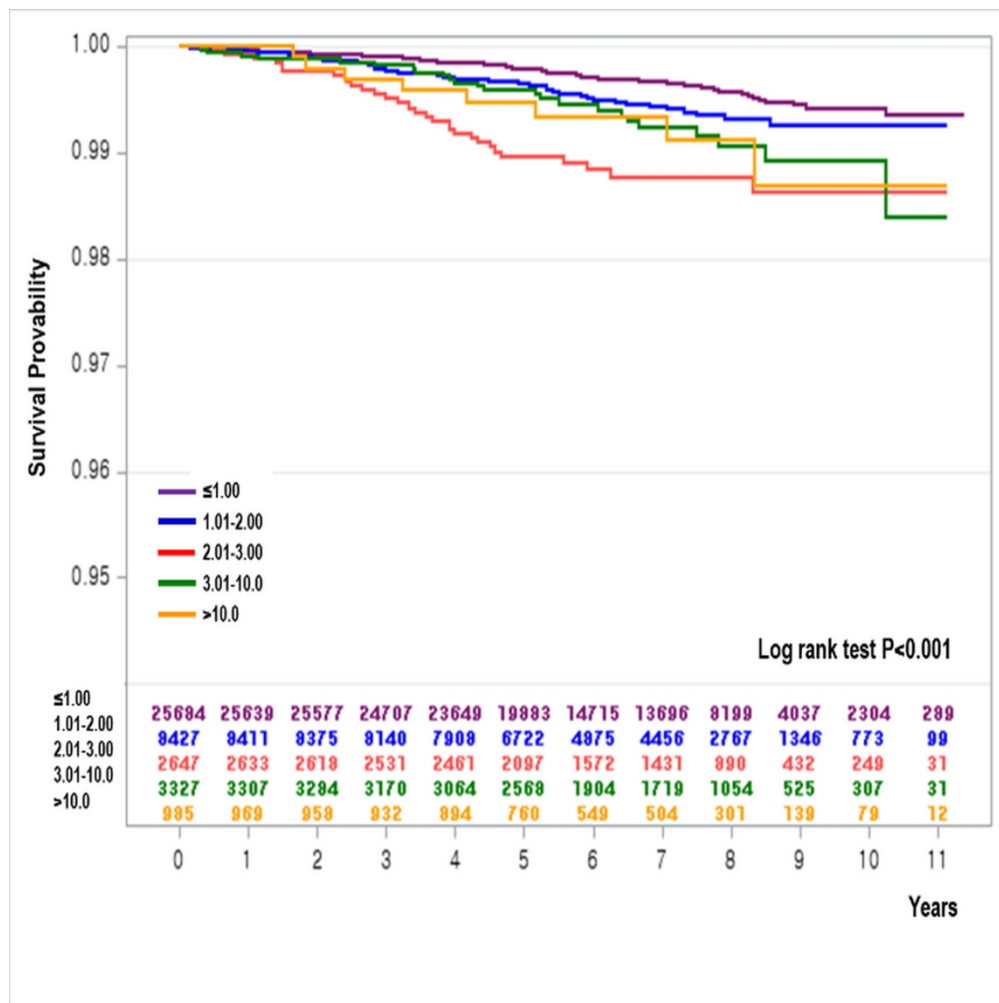


Figure 4 (b) Kaplan-Meier crude survival curves for cardiovascular disease mortality according to serum hsCRP level in men at recruitment.

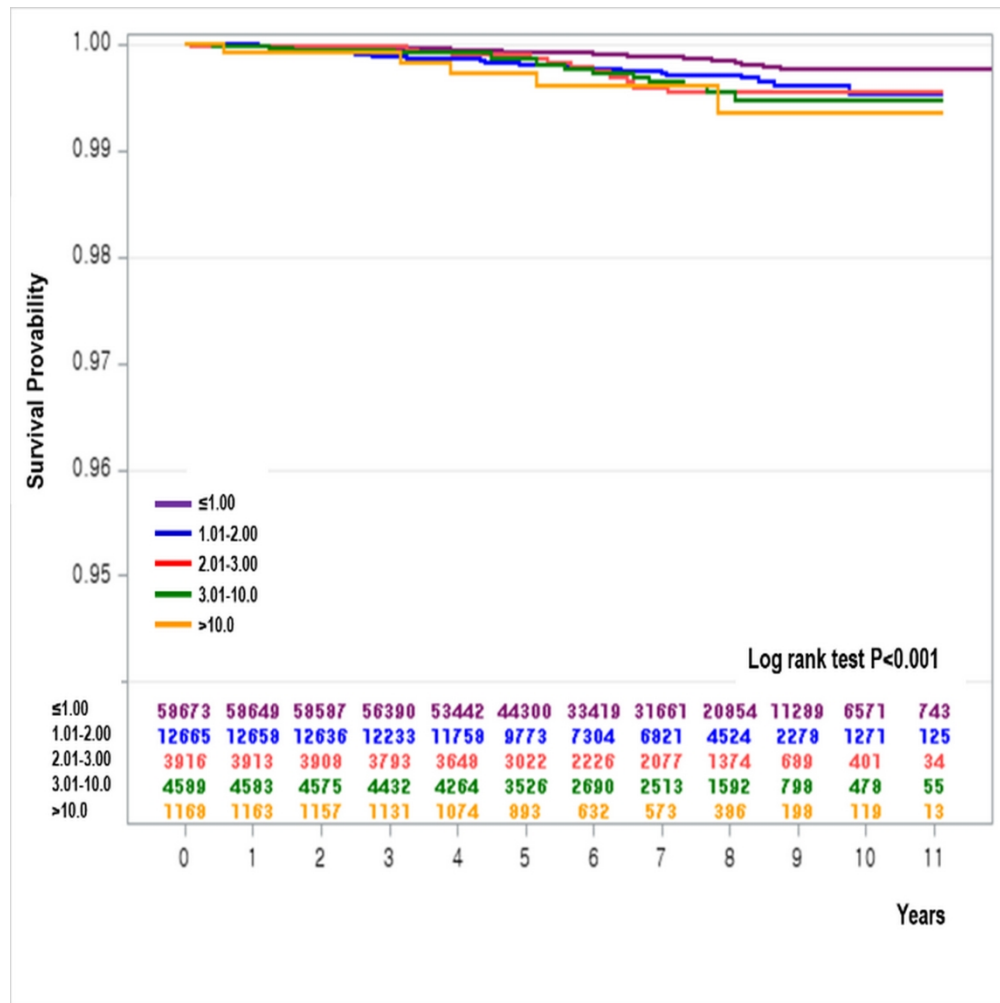


Figure 4 (c) Kaplan-Meier crude survival curves for cardiovascular disease mortality according to serum hsCRP level in women at recruitment.

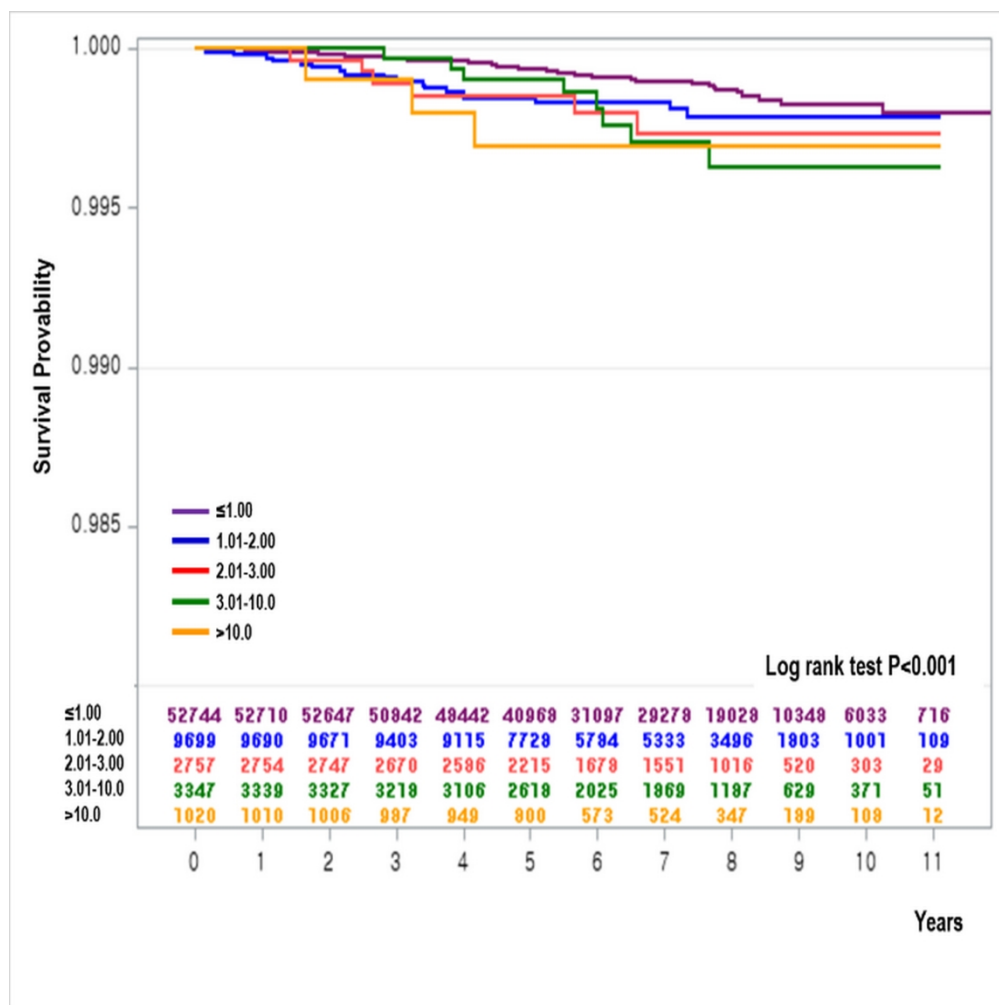


Figure 4 (d) Kaplan-Meier crude survival curves for cardiovascular disease mortality according to serum hsCRP level in healthy subjects at recruitment.

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

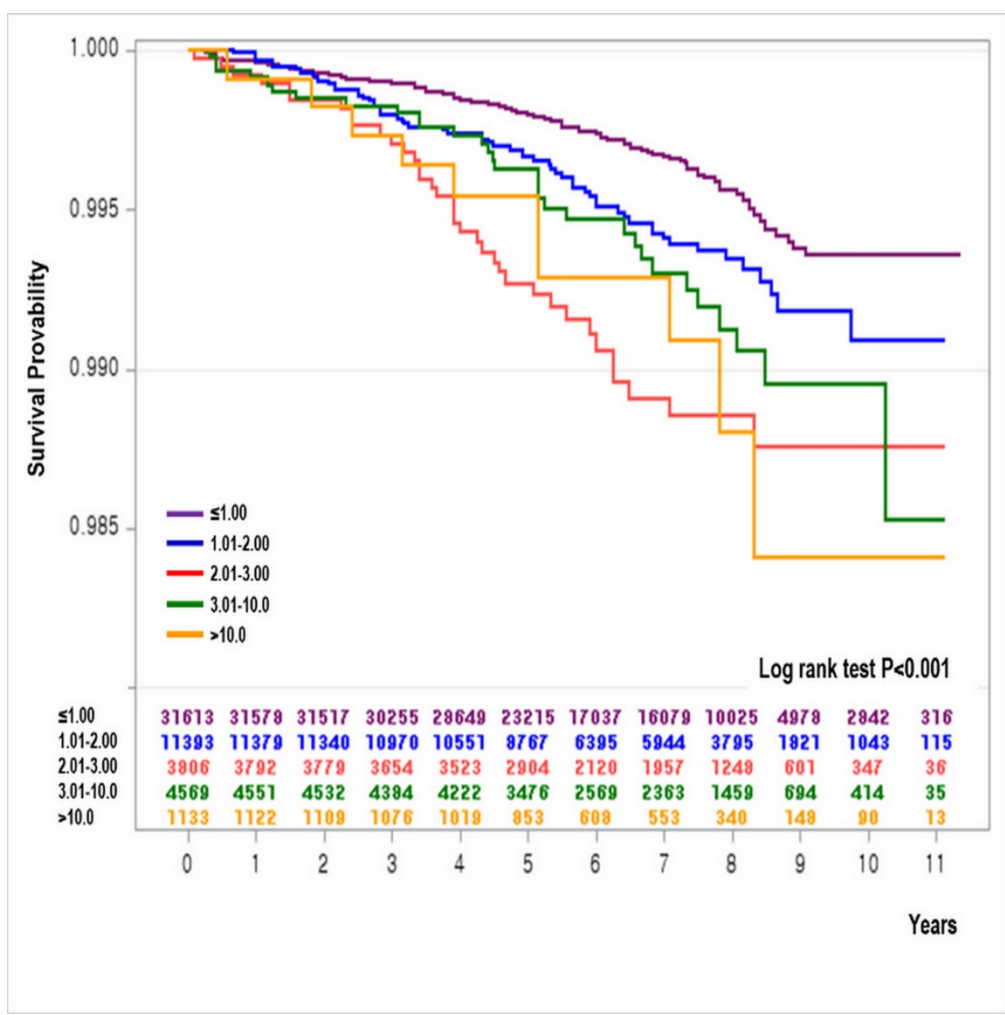


Figure 4 (e) Kaplan-Meier crude survival curves for cardiovascular disease mortality according to serum hsCRP level in subjects with non-communicable disease history (NCDhistory) at recruitment.

Supplement 1. The association of serum *hsCRP* 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)
<i>P</i> -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)
<i>P</i> -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)
<i>P</i> -trend				<.001	<.001	0.001
Pre-menopause						
≤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)
<i>P</i> -trend				0.020	0.036	0.150
Post-menopause						
≤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)
<i>P</i> -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

For peer review only

Supplement 2. The association between serum *hsCRP* 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
<i>P</i> -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
<i>P</i> -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
<i>P</i> -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) <i>Cohort study</i> —Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up <i>Case-control study</i> —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 <i>Cross-sectional study</i> —Give the eligibility criteria, and the sources and methods of selection of participants	4
		(b) <i>Cohort study</i> —For matched studies, give matching criteria and number of exposed and unexposed <i>Case-control study</i> —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) <i>Cohort study</i> —If applicable, explain how loss to follow-up was addressed <i>Case-control study</i> —If applicable, explain how matching of cases and controls was addressed	4

		<i>Cross-sectional study</i> —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) <i>Cohort study</i> —Summarise follow-up time (eg, average and total amount)	6
Outcome data	15*	<i>Cohort study</i> —Report numbers of outcome events or summary measures over time	6-10
		<i>Case-control study</i> —Report numbers in each exposure category, or summary measures of exposure	Not Applicable
		<i>Cross-sectional study</i> —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.