

Prospective Study of High-Sensitivity C-Reactive Protein as a Determinant of Mortality: Results from the MONICA/KORA Augsburg Cohort Study, 1984–1998

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BACKGROUND: C-reactive protein (CRP), an exquisitely sensitive systemic marker of inflammation, has emerged as an independent predictor of cardiovascular diseases (CVD). Because other chronic diseases are also associated with an inflammatory response, we sought to assess the association of high-sensitivity CRP (hsCRP) with total and cause-specific mortality in a large cohort of middle-aged men.

METHODS: We measured hsCRP at baseline in 3620 middle-aged men, randomly drawn from 3 samples of the general population in the Augsburg area (Southern Germany) in 1984–85, 1989–90, and 1994–95. Outcome was defined as all deaths, fatal CVD, fatal coronary heart disease (CHD) including sudden cardiac deaths, and cancer deaths.

RESULTS: During an average follow-up of 7.1 years, 408 deaths occurred (CVD 196, CHD 129, cancer 127). In multivariable Cox regression analysis, subjects with hsCRP >3 mg/L at baseline showed an almost 2-fold increased risk to die vs those with hsCRP <1 mg/L [hazard ratio (HR) 1.88, 95% CI 1.41–2.52]. HRs were 2.15 (95% CI 1.39–3.34) for fatal CVD, 1.74 (1.04–2.92) for fatal CHD, and 1.65 (1.01–2.68) for cancer mortality. In contrast, neither total nor HDL cholesterol significantly predicted all-cause or cancer mortality, and cholesterol had only modest effects on CVD mortality.

CONCLUSIONS: Our results suggest that increased circulating hsCRP concentrations are associated with an increased risk of death from several widespread chronic

diseases. Persistently increased hsCRP is a sensitive and valuable nonspecific indicator of an ongoing disease process that deserves serious and careful medical attention.

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Increased concentrations of high-sensitivity C-reactive protein (hsCRP)⁴ represent an established, unspecific inflammatory risk marker for nonfatal and fatal cardiovascular disease (CVD), as documented in more than 25 prospective population-based studies, but also in patients with stable coronary heart disease (CHD) and the acute coronary syndrome (ACS) (1). Because other major causes of death, such as various malignancies (2) and chronic obstructive pulmonary disease (COPD) (3), are also known to be associated with an inflammatory response, it seems logical to assume that increased hsCRP may also be related to all-cause mortality.

Indeed, increased concentrations of several pro-inflammatory molecules such as interleukin-6 (IL-6) (4–7), and fibrinogen (8, 9), as well as increased white blood cell count (10, 11) and low concentrations of serum albumin, (12) predicted all-cause mortality in various population-based studies, but reports relating hsCRP to all-cause mortality remain inconsistent (5–7, 13–19). One nested case-control study showed an association between increased concentrations of hsCRP and colorectal cancer (20), yet in the Women's Health Study, in middle-aged women, hsCRP did not

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⁴ Nonstandard abbreviations: hsCRP, high-sensitivity C-reactive protein; CVD, cardiovascular disease; CHD, coronary heart disease; ACS, acute coronary syndrome; COPD, chronic obstructive pulmonary disease; IL-6, interleukin-6; MONICA, Monitoring of trend and determinants in Cardiovascular Disease; ICD-9, 9th revision of the International Classification of Diseases; BMI, body mass index; HR, hazard ratio.

predict cancer, in particular breast cancer, or cancer of the ovary and uterus (21, 22).

Thus, we sought to investigate the association between hsCRP concentrations in serum and all-cause mortality as well as deaths from cancer and CVD causes in a large cohort of middle-aged white men of German nationality randomly drawn from the general population.

Materials and Methods

STUDY DESIGN, POPULATION, AND FOLLOW-UP

The population-based Monitoring of trends and determinants in Cardiovascular Disease (MONICA) Augsburg studies (Southern Germany) conducted between 1984 and 1998 were used as database (23). Three independent cross-sectional surveys covering the city of Augsburg and two adjacent counties were conducted in 1984–85 (S1), 1989–90 (S2), and 1994–95 (S3) to estimate the prevalence of cardiovascular risk factors among men and women. Altogether 13 428 Caucasians of German nationality (6725 men, 6703 women, response rate 77%), age 25–74 years, randomly drawn from the general population, participated in at least 1 of the 3 studies. All subjects were prospectively followed within the framework of the Cooperative Health Research in the Region of Augsburg (KORA). The present analysis was restricted to men age 45–74 years (response rate 80%) at the baseline examination ($n = 3667$). Of those, 990 (27%) subjects were from survey S1, 1324 (36%) from S2, and 1353 (37%) from S3. We excluded 47 subjects who had missing hsCRP measurements or other variables. Thus, 3620 subjects were available for the present analysis.

OUTCOME DEFINITION

The end points used in this study were mortality from any CVD, CHD, cancer, and all-cause mortality. Mortality was ascertained by regularly checking the vital status of all sampled persons of the MONICA surveys through the population registries inside and outside the study area; this procedure guaranteed that the vital status of cohort members who had moved out of the study area could also be assessed. Death certificates were obtained from local health departments and coded for the underlying cause of death by a single trained person using the 9th revision of the International Classification of Diseases (ICD-9). During follow-up, there occurred 196 deaths from CVD (ICD-9 390–459, 798), 129 deaths from CHD (ICD-9 410–414, 798), 127 deaths from cancer (ICD-9 140–208), and 408 deaths from any cause (ICD-9 001–999).

SURVEY METHODS

All participants completed a standardized questionnaire, including medical history, lifestyle, and drug his-

tory. Blood pressure, body height (m), body weight (kg), body mass index (BMI, kg/m^2), smoking behavior, and alcohol consumption (g/day) were determined as described (24). The number of education years was calculated on the basis of the highest level of formal education completed.

LABORATORY PROCEDURES

A nonfasting venous blood sample was collected from all participants in a sitting position. Samples for measurement of hsCRP were stored at $-70\text{ }^\circ\text{C}$ until analysis. Serum hsCRP concentrations were measured using a high-sensitivity immunoradiometric assay (range 0.05–10 mg/L) as described (25). The CV for repeated measurements was 12% over all ranges. Total serum and HDL cholesterol were measured in multiple batches by routine enzymatic methods. Corresponding CVs were between 1% and 3% for total cholesterol and between 3% and 4% for HDL.

STATISTICAL ANALYSIS

We analyzed means or proportions for baseline demographic and clinical characteristics by t or χ^2 test for men with and without the respective fatal event. hsCRP was log-transformed, as it followed approximately a log-normal distribution. We assessed differences in hsCRP concentration categories by various characteristics by computing the geometric mean of hsCRP concentration. We used Pearson correlation to describe the association between traditional risk factors, lipid variables, and (log-transformed) hsCRP and estimated the absolute risk of a respective fatal event by the Kaplan-Meier method. Differences in Kaplan-Meier survival curves were tested by log-rank test. We used Person-Years method to estimate crude incident fatal event rates by hsCRP categories and Cox proportional hazards analysis to assess the independent risk for all-cause mortality, cancer mortality, CHD mortality, and CVD mortality separately in established categories of hsCRP ($<1\text{ mg/L}$; $1.0\text{--}3.0\text{ mg/L}$; $>3\text{ mg/L}$) (26). Relative risks for hsCRP were adjusted for age and survey (S1, S2, or S3) and were further adjusted for BMI (according to Bray (7)), current regular smoking (yes vs no), hypertension (blood pressure $<$ vs $\geq 140/90\text{ mmHg}$), education years ($<$ vs ≥ 12 years), alcohol consumption (0, 0.1–39.9, $\geq 40\text{ g/day}$), physical activity (inactive vs active, that is $\geq 1\text{ h}$ in at least 1 season), history of diabetes (yes vs no), and history of dyslipidemia (yes vs no) in all other models. Results are presented as hazard ratios (HRs) together with their 95% CIs. P values are based on Wald statistic. Significance tests are 2-tailed, and P values <0.05 were considered statistically significant. All analyses were per-

Table 1. Demographic and laboratory characteristics of study participants.

Characteristic	All-cause mortality			P value
	Total sample	Alive	Dead	
N	3620	3212	408	
Age, years	57.9 (8.10)	57.4 (8.10)	61.5 (7.40)	<0.0001
Total cholesterol, mmol/L	6.31 (1.17)	6.31 (1.16)	6.31 (1.30)	0.9924
HDL cholesterol, mmol/L	1.31 (0.39)	1.29 (0.39)	1.30 (0.45)	0.8016
TC/HDL ratio ^a	5.0 (1.4)	5.0 (1.4)	5.0 (1.4)	0.8987
hsCRP, mg/L ^a	1.7 (3.0)	1.6 (2.9)	2.8 (3.4)	<0.0001
Systolic blood pressure, mmHg	138.9 (18.7)	138.4 (18.2)	142.7 (21.3)	0.0001
Diastolic blood pressure, mmHg	83.3 (11.4)	83.5 (11.2)	81.6 (12.7)	0.0037
BMI, kg/m ²	27.9 (3.5)	27.8 (3.5)	27.9 (4.0)	0.8043
BMI ^b				
<25 kg/m ²	19.8	19.3	23.5	
25.1–29.9 kg/m ²	57.2	58.2	49.5	0.0038
≥30.0 kg/m ²	23.0	22.5	27.0	
Alcohol intake, %				
0 g/d	17.3	16.9	20.1	0.0569
0.1–39.9 g/d	50.0	50.7	44.6	
≥40 g/d	32.7	32.4	35.3	
History of diabetes, %	7.2	6.3	14.5	<0.0001
Dyslipidemia (total:HDL cholesterol ≥5.0), %	49.8	49.6	51.7	0.4197
Regular smoking, %	23.6	21.9	37.0	<0.0001
Hypertension (≥140/90 mmHg), %	49.9	49.2	56.1	0.0080
Physical activity, %	19.0	19.8	12.0	0.0001
Education <12 years, %	70.1	79.7	68.9	<0.0001

Data are mean (SD) or % unless indicated otherwise.
^a Geometric mean (SD).
^b Category according to Bray (%).

formed using the Statistical Analysis System (version 8.2; SAS Institute Inc.).

Results

BASELINE CHARACTERISTICS

During an average follow-up of 7.1 years, 408 deaths occurred. Men who died were significantly older and more frequently had hypertension, diabetes, and lower education. Also, there were more smokers among those who died, and they were less frequently physically active. Those who died more frequently had BMI <25 kg/m² and >30 kg/m² but a lower prevalence of overweight compared with survivors. Total and HDL cholesterol levels were not different between the 2 groups, but hsCRP was clearly different, with lower concentrations in survivors than in those who died (Table 1).

Subjects who died from cancer also were older, more frequently had BMI <25 kg/m², and less frequently had BMI > 30 kg/m². As expected, the prevalence of regular smoking was more than 2-fold increased in cancer deaths, the subjects were far less physically active, and they showed fewer years of formal education compared with survivors. hsCRP was 3.1 mg/L in those who died from cancer and 1.6 mg/L in survivors. Again, lipids were not different between the 2 groups (data not shown).

Those who died from CVD or CHD were also older, were more frequently obese, and had a history of diabetes and hypertension (borderline significance for CHD deaths). Interestingly, total and HDL cholesterol levels were not different compared with survivors, but the total:HDL cholesterol ratio was slightly higher in CHD deaths. Smoking showed bor-

Table 2. hsCRP concentrations according to traditional cardiovascular risk factors.

Characteristic	% hsCRP, mg/L		
	N	%	Geometric mean (SE)
Age, years			
45–54	1384	38.2	1.36 (1.03)
55–64	1381	38.2	1.73 (1.03) ^b
65–74	855	23.6	2.16 (1.04) ^b
Regular smoker			
Yes	853	23.6	2.55 (1.04) ^b
No	2767	76.4	1.46 (1.02)
BMI ^a			
<25 kg/m ²	716	19.8	1.18 (1.04)
25.1–29.9 kg/m ²	2071	57.2	1.63 (1.02) ^b
≥30.0 kg/m ²	833	23.0	2.36 (1.04) ^b
Alcohol intake			
0 g/d	625	17.3	1.80 (1.05)
0.1–39.9 g/d	1810	50.0	1.53 (1.03) ^c
≥40 g/d	1185	32.7	1.81 (1.03)
History of diabetes			
Yes	261	7.2	2.34 (1.08) ^b
No	3359	92.8	1.62 (1.02)
Dyslipidemia (total:HDL cholesterol ≥5.0)			
Yes	1804	49.8	1.97 (1.02) ^b
No	1816	50.2	1.41 (1.03)
History of hypertension (≥140/90 mmHg)			
Yes	1808	49.9	1.84 (1.03) ^b
No	1812	50.1	1.50 (1.03)
Physically active			
Yes	686	19.0	1.43 (1.02) ^b
No	2934	81.0	1.72 (1.04)
Education <12 years			
Yes	2539	70.1	1.77 (1.03) ^b
No	1081	29.9	1.43 (1.02)

^a Category according to Bray.
^b $P < 0.0001$; ^c $P < 0.001$.

derline significant differences in both groups, and subjects who died were less frequently physically active and had lower education (data not shown).

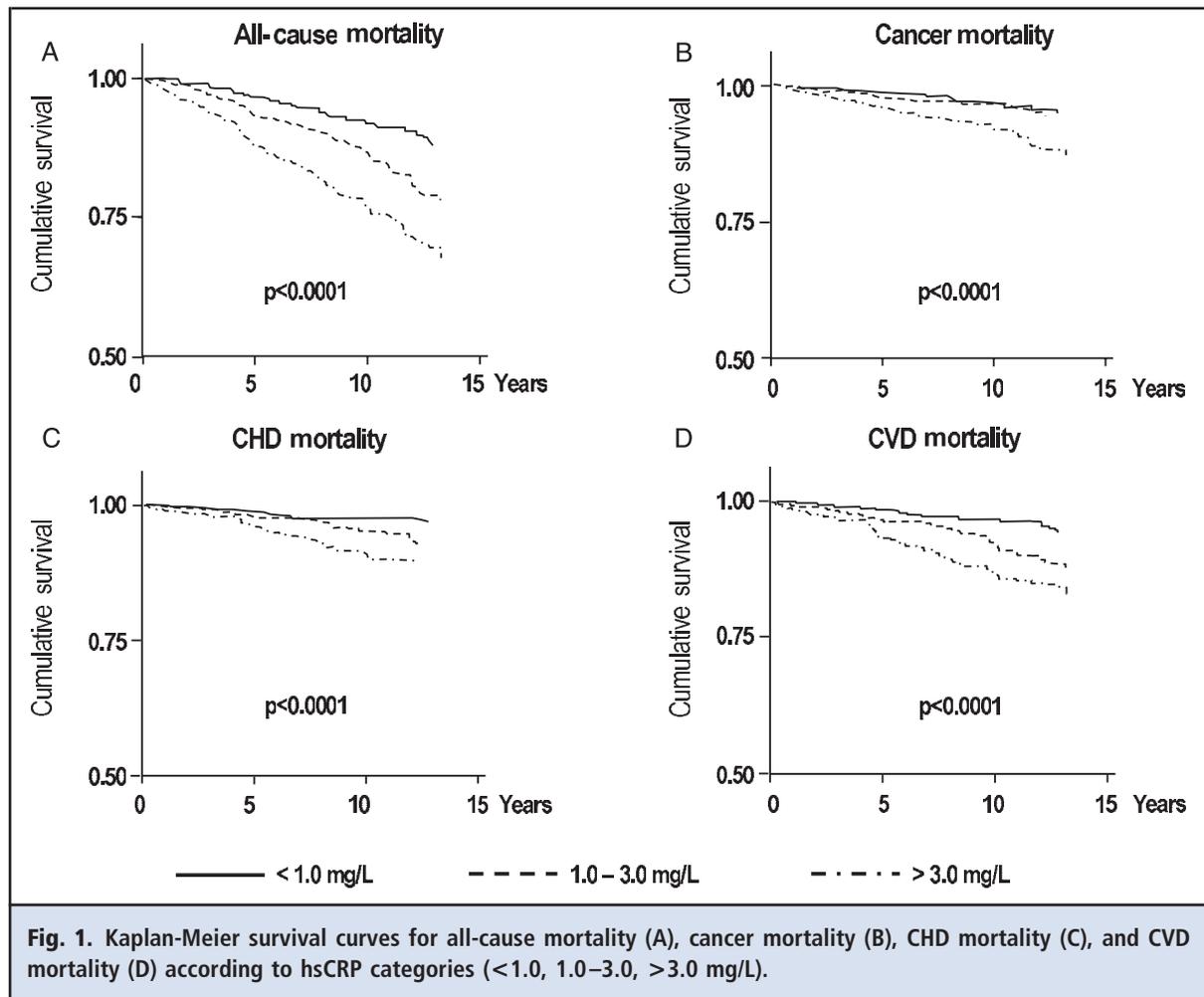
ASSOCIATIONS BETWEEN HSCRP AND CARDIOVASCULAR RISK FACTORS

Table 2 shows the well known associations between hsCRP concentrations and various cardiovascular risk factors. In addition, Pearson correlation coefficients (R) revealed a weak but significant positive correlation between log hsCRP and age ($R = 0.17$, $P < 0.001$), BMI

(0.22, $P < 0.001$), systolic blood pressure (0.13, $P < 0.001$), total cholesterol (0.07, $P < 0.001$), and total:HDL cholesterol ratio (0.15, $P < 0.001$) and a negative correlation with HDL (-0.13 , $P < 0.0001$). No statistically significant correlation was seen with diastolic blood pressure (data not shown).

ASSOCIATION BETWEEN hsCRP AND ALL-CAUSE MORTALITY, CANCER DEATHS, AND CHD, AS WELL AS CVD MORTALITY

Fig. 1A–D shows Kaplan-Meier survival curves for all 4 end points, which are clearly separated according to the



3 hsCRP categories. We further performed Cox proportional hazards analyses to assess the independent contribution of hsCRP measurements on the risk to die from all causes, cancer, CHD, and CVD (Table 3). In multivariable analyses, adjusting for age, survey, BMI, diabetes, regular smoking, hypertension, dyslipidemia, physical activity, and number of formal education years, the probability (HR) to die from all causes associated with increasing categories of hsCRP was 1.35 (95% CI 1.01–1.81) in those with concentrations between 1 and 3 mg/L and 1.88 (95% CI 1.41–2.52) in those whose hsCRP was >3 mg/L, compared with subjects with concentrations <1 mg/L.

For cancer mortality, HRs were slightly smaller and only the top category (>3 mg/L) vs the bottom category was still significant in multivariable analysis, HR 1.65 (95% CI 1.01–2.68). Again, those with hsCRP >3 mg/L had a significantly increased risk of dying from CHD and CVD, HR 1.74 (95% CI 1.04–2.92) and 2.15 (95% CI 1.39–3.34), respectively, compared with subjects with hsCRP levels <1 mg/L.

Discussion

In this prospective, population-based study, including 3620 men age 45–74 years, increased concentrations of hsCRP were strongly and independently associated not only with CHD and CVD mortality, but also with cancer and all-cause mortality, even after adjustment for potential confounders, thereby raising the question whether chronic low-grade systemic inflammation might help to identify individuals at increased risk of death. It is also interesting to note that, despite the large differences in hsCRP concentrations between survivors and nonsurvivors (1.6 vs 2.8 mg/L, respectively, $P < 0.0001$), there was only a minimal difference between these groups with respect to BMI (27.8 vs 27.9 kg/m², $P = 0.8$), so the effect of CRP is not simply due to obesity, as is often suggested.

The relationship of hsCRP with cardiovascular diseases has been firmly established in numerous studies. In the present large study, including middle-aged

Table 3. Cox regression analysis of hsCRP on all-cause, cancer, CHD, and CVD mortality.

	N	Number of deaths	Person-years	Crude incidence rate/1000 person-years	Model 1 ^a HR (95% CI)	Model 2 ^b HR (95% CI)	P
All-cause mortality (ICD 9 001–999)							
hsCRP <1.00 mg/L	1104	70	8252	8.5	1.0	1.0	<0.0001
hsCRP 1.00 to ≤3.00 mg/L	1478	147	9998	14.7	1.50 (1.13–2.00)	1.35 (1.01–1.81)	
hsCRP >3.00 mg/L	1038	191	7298	26.2	2.39 (1.81–3.16)	1.88 (1.41–2.52)	
Cancer mortality (ICD 9 140–208)							
hsCRP <1.00 mg/L	1104	26	8252	3.2	1.0	1.0	0.0157
hsCRP 1.00 to ≤3.00 mg/L	1478	37	9998	3.7	1.02 (0.61–1.68)	0.94 (0.56–1.58)	
hsCRP > 3.00 mg/L	1038	64	7298	8.8	2.18 (1.38–3.47)	1.65 (1.01–2.68)	
CHD mortality (ICD 9 410–414, 798)							
hsCRP <1.00 mg/L	1104	22	8252	2.7	1.0	1.0	0.0437
hsCRP 1.00 to ≤3.00 mg/L	1478	45	9998	4.5	1.40 (0.84–2.34)	1.16 (0.69–1.96)	
hsCRP >3.00 mg/L	1038	62	7298	8.5	2.32 (1.42–3.80)	1.74 (1.04–2.92)	
CVD mortality (ICD 9 390–459, 798)							
hsCRP <1.00 mg/L	1104	29	8252	3.5	1.0	1.0	0.0016
hsCRP 1.00 to ≤3.00 mg/L	1478	73	9998	7.3	1.75 (1.14–2.70)	1.51 (0.97–2.35)	
hsCRP >3.00 mg/L	1038	94	7298	12.9	2.72 (1.79–4.15)	2.15 (1.39–3.34)	

MONICA/KORA Augsburg Cohort Study 1984–1998. N = 3620 men.
^a Adjusted for age and survey.
^b Adjusted for age, survey, physical activity (active/nonactive), education (>/≤12 years), BMI (categories according to Bray), diabetes (yes/no), alcohol (0 g/d and ≥40 g/d vs 0.1–39.9 g/d), regular smoking (yes/no), hypertension (yes/no), and dyslipidemia (yes/no).

men without CVD at baseline, we found an approximately 2-fold increased risk for CHD and CVD mortality in subjects with hsCRP concentrations >3 mg/L compared with those whose hsCRP concentrations were <1 mg/L. These results are consistent with data from other prospective studies (6, 17–19, 27, 28), which also found a 2- to 4-fold increased risk for future CVD death.

The main components of total mortality besides CVD are cancer and, to a lesser extent, COPD or asthma. Thus, the independent associations seen in our study between a low-grade inflammatory process, as reflected by increased concentrations of hsCRP, and all-cause, CVD, and non-CVD deaths are not surprising, since all main contributors of total mortality listed above have been shown to be associated with systemic inflammation. In other words, CHD, various malignancies, and chronic pulmonary diseases are inflammation-associated pathophysiological conditions. Thus, one might assume that increased concentrations of hsCRP associated with total mortality represent an indicator of common hyperreactivity of the organism, probably in a form of a cumulative and nonspecific immune response to overexpression of various cytokines at any anatomic site.

In line with this suggestion are results from a number of studies, which clearly show that increased concentrations of various markers of the acute-phase response are prospectively related to total mortality (4–19). For instance, in 3571 Japanese-American men participating in the Honolulu Heart Program, fibrinogen levels at baseline were associated with all-cause and cause-specific mortality during 4.4 years of follow-up (8). Recently, individual participant metaanalysis from the Fibrinogen Studies Collaboration (9) has shown an approximately 2-fold increased risk of death from all causes per 1 g/L increase in fibrinogen in multivariate models (HR 2.05, 95% CI 1.84–2.29). However, the evidence for such a relationship is not completely homogeneous. Although several studies, including ours, found hsCRP to be a strong predictor of total mortality (5–7, 17–19), two other studies (14, 15) revealed no prognostic value of hsCRP for death from all causes. In both analyses, increased hsCRP concentrations were associated with future total mortality only in unadjusted models, whereas further controlling for conventional risk factors attenuated this association. It should be noted here that these two studies were much smaller than our present study and might not have had enough power to detect any significant association. More re-

cently, Jenny et al. (17) investigated the impact of hsCRP and fibrinogen on early and late total and CVD death in a large cohort of older participants from the Cardiovascular Health Study (CHS) and found that both biomarkers were associated with death within 3 years of measurement. The associations were stronger among men than among women, and prediction of death in men was further improved when the two markers were combined.

Furthermore, several studies have revealed an important role of systemic inflammation in COPD (3), showing that reduced lung function is significantly associated with increased levels of inflammatory markers (29, 30). It has been further demonstrated that increased hsCRP concentrations were able to predict mortality in patients with mild to moderate COPD (31) and in patients with chronic respiratory failure (32).

Several lines of evidence also suggest a link between low-grade chronic systemic inflammation and poor prognosis from various malignant diseases (2). In most cases, however, such an association might have been confounded by socioeconomic and lifestyle factors. So, for instance, the association between hsCRP concentration and lung cancer is highly biased by smoking status (2). Moreover, the ability of hsCRP to predict cancer mortality seems to be sex-dependent, since numerous large population-based prospective studies including only women failed to detect an independent association of hsCRP and the risk of incident cancer or cancer mortality. Indeed, Rifai et al. (21), using a nested case-control design within the Women's Health Study (WHS), investigated the predictive value of hsCRP for any cancer incidence and found that hsCRP levels appeared to independently predict CVD but not cancer in their study sample of middle-aged, low-risk women. Furthermore, Heikkilä et al. (33) investigated the association between hsCRP and survival in women with and without cancer within the British Women's Heart and Health Study (BWHHS) and showed that increased hsCRP concentrations predicted cancer mortality, but only in models that did not include IL-6. Since almost 60% of cancer mortality in the WHS (21) and 40% in the BWHHS (33) was due to hormone-related malignancies such as breast, ovarian, or cervical cancer, one could speculate that such outcomes might be less associated with a low-grade inflammation in women. More recently, Zhang et al. (22), again within the WHS, confirmed this suggestion, demonstrating no association between increased hsCRP and incident breast cancer in women. In contrast to these studies, however, our analysis included only middle-aged men, where serum concentrations of hsCRP >3 mg/L were independently and

strongly associated with a 65% increased risk of overall cancer mortality. In line with our data is the recent report by Il'yasova et al. (34), who found an even stronger association between hsCRP and fatal cancers than with incident cancer in the Health Aging and Body Composition (Health ABC) study, with an average follow-up of 5.5 years. The HRs associated with each increment of hsCRP (1 mg/L) were 1.51 (95% CI 1.19–1.92) for cancer mortality, but only 1.23 (95% CI 1.06–1.43) for incident cancer. In addition, increased concentrations of hsCRP were found to be associated with incident cancer in general as well as with incident cancers of different etiologies in numerous prospective studies, conducted in combined populations (men and women) such as the CLUE II cohort (20), EPIC-Greece (35), the α -Tocopherol, β -Carotene (ATBC) Cancer Prevention Study (36), and the Japan Public Health Center-Based Prospective Study (37).

In summary, our data confirm and extend results from several other studies using different markers of inflammation in a large, representative sample of men from the general population. Our results suggest that increased circulating hsCRP concentrations are associated with an increased risk of death from several widespread diseases. In contrast, neither total nor HDL cholesterol significantly predicted all-cause or cancer mortality, and they had only modest effects on cardiovascular mortality. Thus, persistently increased hsCRP production might represent a sensitive and valuable nonspecific indicator of an ongoing disease process that deserves serious and careful medical attention. Conversely, persistently low hsCRP concentrations seem to be associated with a good health status.

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