Eur J Epidemiol (2013) 28:541–550
DOI 10.1007/s10654-013-9819-6

MORTALITY

Seventeen year risk of all-cause and cause-specific mortality associated with C-reactive protein, fibrinogen and leukocyte count in men and women: the EPIC-Norfolk study

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Received: 14 January 2013 / Accepted: 20 June 2013 / Published online: 3 July 2013

Abstract There is strong evidence from observational studies suggesting serum C-reactive protein (CRP) is associated with cardiovascular and all-cause mortality. However, less is known about whether there are differences in the association of CRP with all-cause or cause specific mortality by sex, smoking, body mass index (BMI), or physical activity. We aimed to investigate these interactions and also investigate and compare the association of CRP and other inflammation markers (i.e., fibrinogen and leukocyte count) with all-cause and cause-specific mortality. Men and women aged 40–79 were recruited in 1993–1997 in the EPIC-Norfolk cohort study. A total of 16,850 participants with high-sensitivity assayed CRP data who had no known cancer, myocardial infarction and stroke at baseline were entered in the analysis to test the association of CRP, fibrinogen and leukocyte count with risk of all-cause and cause specific mortality. A total of, 2,603 all-cause deaths (1,452 in men) including 823 cardiovascular and 1,035 cancer deaths, were observed after 231,000 person-years of follow-up (median 14.3 years). CRP was positively associated with risk of all-cause, cardiovascular, and non-cancer non-cardiovascular mortality independent of established risk factors. The hazard ratio of all-cause mortality (95 % CI) for participants with CRP in the range of 3–10 and >10 mg/l (vs. <0.5 mg/l) was 1.56 (1.26–1.93) and 1.87 (1.43–2.43) respectively in men and 1.34 (1.07–1.68) and 1.98 (1.50–2.63) in women. The association was less positively graded in women with the increased risk being significant only at higher levels of the CRP distribution. The association persisted in never smokers and did not vary by levels of BMI or physical activity. Although fibrinogen and leukocyte count were also positively associated with mortality risk, only CRP remained a significant predictor of mortality when the inflammation markers were adjusted for one another in multivariable models. Serum CRP levels were a long-term predictor of risk of cardiovascular and non-cardiovascular mortality independent of known risk factors, fibrinogen, and leukocyte count.

Keywords Mortality · Cardiovascular disease · Inflammation · Ageing · C-reactive protein · Fibrinogen · Leukocyte count · Cohort study

Electronic supplementary material The online version of this article (doi:10.1007/s10654-013-9819-6) contains supplementary material, which is available to authorized users.

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Introduction

Chronic low-grade inflammation has been proposed to lead to long-term tissue damage and increased mortality risk [1, 2]. C-reactive protein (CRP) and fibrinogen are acute phase reactants and as well as leukocyte count are general systemic markers of inflammation. CRP has both pro-inflammatory and anti-inflammatory properties and is postulated to have a role in immuno-regulation [3]. Elevated serum levels of high-sensitivity assayed CRP are associated with

risk of various conditions such as cardiovascular diseases (CVD) [4–6], cancer [7–9], type-2 diabetes [10], hypertension [11], and chronic obstructive pulmonary disease (COPD) [12]. Serum CRP, fibrinogen and leukocyte count are also correlated with many lifestyle and cardiovascular risk factors such as body size and adiposity [13–18], smoking [13, 17–20], physical activity [21–23], cholesterol levels, and blood pressure [4, 19, 24–27].

Previous prospective studies have reported a positive association between serum CRP [4, 28–31], fibrinogen [26, 27], and leukocyte count [18, 32] with risk of all-cause and cardiovascular mortality. Uncertainties remain about whether the association of CRP with all-cause or cause-specific mortality differ between men and women, or between smokers and non-smokers or vary by subgroups of age, body mass index (BMI) or physical activity. Previous studies were either not sufficiently powered or have not adequately reported on such associations especially regarding subgroups of the population. Moreover, the association of fibrinogen and leukocyte count with non-cardiovascular causes of mortality has been less investigated previously. We aimed to explore these associations in a large prospective cohort study of men and women with long-term follow up.

Methods

Study participants were recruited as part of the European prospective investigation into cancer in Norfolk (EPIC-Norfolk) population study. The details of this ongoing cohort study have been previously described [33]. Briefly, 78,000 men and women aged 40–79, resident in Norfolk, England were randomly selected from the general practice age-sex registers and invited to participate in the study, of which 25,639 participated (participation rate 33 %) and attended the baseline health examination in 1993–1997. The EPIC-Norfolk study was approved by the Norfolk Local Research Ethics Committee, and all volunteers gave written informed consent.

At baseline, extensive demographic, medical, lifestyle, family history and dietary data were collected by asking participants to complete a health and lifestyle questionnaire and trained nurses took anthropometric measurements.

Leukocyte count and cholesterol were measured in non-fasting fresh blood samples using methods previously described [33]. Aliquots of serum used for the CRP analyses were taken at baseline examination, stored in −80 °C freezers, thawed in 2008, and assayed for high-sensitivity CRP using the Olympus AU640 chemistry analyzer. Fibrinogen was measured using the commercial kit Fibriquik (bioMerieux, Lyon, France) on an MDA180 automated analyser, in 2000–2002, in thawed serum samples that were kept frozen in liquid nitrogen at −196 °C since baseline examination. Measurements of CRP, fibrinogen and leukocyte count were performed at different points of time when funding became available and are thus performed on different numbers of participants.

All participants were flagged for death certification at the office for National Statistics, and trained nosologists coded all death certificates up to March 30, 2010. Mortality ascertainment was complete for all participants. Main outcomes of interest were all-cause mortality (defined as death from any cause) or mortality from CVD or cancers as underlying cause, which were defined using the International Classification of Diseases ninth or tenth edition (ICD-9 or ICD-10) codes (CVD mortality ICD-9 401–448, or ICD-10 I10–I79 codes, and cancer mortality ICD-9 140–208 or ICD-10 C00–C97). Mortality from causes other than CVD and cancer was defined as "other causes" of death.

Statistical analysis

The association of CRP, fibrinogen and leukocyte count with all-cause mortality were assessed using Cox proportional hazards regression analysis and with cause-specific mortality using competing risks analysis. In competing risks analysis, mortality from causes other than the one under investigation is considered as a competing risk and is not right censored uninformatively. Follow-up time was calculated for each participant from time of entry to the study to time of death, loss to follow-up (point of last contact for participants for whom contact was lost (<6 % of participants)), or until March 30, 2010. Proportional hazards assumption was reasonably met when tested by plotting ln(−ln(survival)) against ln(time) and Schoenfeld residuals method. The covariates in all multivariate analyses were age, BMI, smoking, alcohol intake, physical activity, cholesterol levels, systolic blood pressure, history of diabetes, social class, and for women only menopausal status and postmenopausal hormone replacement therapy (HRT). To explore possible differences in the shape and magnitude of the associations between men and women, all analyses were sex-specific.

To allow for non-linearity of the associations, and to compare the shape and magnitude of the associations, CRP, fibrinogen, leukocyte count, BMI, systolic blood pressure, and cholesterol were categorized into quintiles of the baseline distribution. CRP was, in separate analysis, divided into 6 clinical relevant categories using cut-points 0.5, 1, 2, 3, and 10 mg/l.

C-reactive protein, fibrinogen, and leukocyte count had a skewed distribution and for continuous analyses were log-transformed to obtain a normal distribution. Hazard ratios were calculated per 1-standard deviation (SD) increment in log-transformed variables adjusted and unadjusted for the effect of one another. HR of mortality per 1-SD higher $\log_e$-CRP (SD = 1.08) is equivalent to that for a threefold higher CRP on the original (mg/l) scale.

Missing values for categorical covariates were coded as such and not excluded from analyses. Effect modification in the association of CRP categories and mortality by sex, BMI, smoking and physical activity were tested by a likelihood ratio test. We did not correct our results for regression dilution. All analyses were performed using Stata 11.0 (StataCorp. 2009. Stata Statistical Software: Release 11. College Station, TX: StataCorp LP).

Results

Among 18,586 study participants with available CRP data, 1,736 were excluded due to a history of cancer (N = 959), myocardial infarction (N = 602) and stroke (N = 260) at baseline. Of the 16,850 participants entered in the present analysis, 2,603 deaths (1,452 in men and 1,151 in women) were registered after 230,958 person years of follow up [median 14.3, mean (SD) 13.7 (2.7) years]. The average age of participants at baseline was about 60 years and 45 % were men (Table 1, Supplement Table 1). There were no significant differences in baseline characteristics between the subgroups in whom CRP were and were not measured (data not shown). Men and women with lower levels of CRP tended to be younger and leaner than those with higher serum CRP levels, were more physically active, less likely to smoke or be on HRT, had lower concentrations of cholesterol, lower blood pressure, and a lower prevalence of diabetes at baseline (Supplement Table 1).

Baseline serum CRP was positively associated with risk of all-cause mortality in both sexes (Fig. 1). Hazard ratio [95 % confidence interval (CI)] of all-cause mortality in participants with CRP levels ranging 3–10 and >10 mg/l compared to those <0.5 mg/l were 1.56 (1.26–1.93) and 1.87 (1.43–2.43) respectively in men and 1.34 (1.07–1.68) and 1.98 (1.50–2.63) in women.

Cancer (N = 1,035) and CVD (N = 823) accounted for about 40 and 30 % of all deaths recorded in this study respectively. Baseline CRP was positively associated with risk of cardiovascular mortality and mortality from "other causes", but was not significantly related to risk of cancer mortality in categorical analysis (Fig. 2). However, the test for linear trend for the association of CRP and cancer mortality was statistically significant in both sexes ($P < 0.03$). The multivariate adjusted hazard ratios (95 % CI) of death comparing CRP levels 3–10 mg/l with <0.5 mg/l in men and women were 2.12 (1.40–3.22) and 1.43 (0.92–2.23) for CVD mortality respectively, 1.17 (0.85–1.60) and 1.37 (0.96–1.96) for cancer mortality, and 1.60 (1.06–2.41) and 1.14 (0.76–1.71) for mortality from "other causes". For mortality from all different causes, the trend of the association in women was less graded than that in men with the increased risk being significant only at the higher thresholds of the CRP distribution (Figs. 1, 2).

Table 1 Baseline characteristics in EPIC-Norfolk participants with available baseline measurement of CRP

	Men (N = 8,334)	Women (N = 10,252)
Age	59.1 (9.1)	58.4 (9.2)
C-reactive protein (mg/l)[a]	1.56 (0.3, 9.7)	1.64 (0.3, 9.9)
Fibrinogen (g/l)[a]	2.78 (1.80, 4.26)	2.89 (1.84, 4.30)
Leukocyte count (1,000/μl)[a]	6.43 (4.30, 9.80)	6.22 (4.10, 9.50)
Body mass index (kg/m^2)	26.5 (3.2)	26.1 (4.2)
Smoking (current)	984 (11.9 %)	1,105 (10.9 %)
Alcohol intake (U/week)	10.2 (11.6)	4.4 (5.5)
Systolic blood pressure (mmHg)	137.1 (17.5)	133.5 (18.7)
Total cholesterol (mmol/l)	6.04 (1.10)	6.29 (1.20)
Physical activity		
Inactive	2,519 (30.2 %)	3,071 (30.0 %)
Moderately inactive	2,061 (24.7 %)	3,278 (32.0 %)
Moderately active	1,908 (22.9 %)	2,302 (22.5 %)
Active	1,846 (22.2 %)	1,601 (15.6 %)
Social class		
[I] Professionals	630 (7.7 %)	627 (6.3 %)
[II] Manager	3,140 (38.2 %)	3,543 (35.4 %)
[III NM] Skilled non-manual worker	1,019 (12.4 %)	2,009 (20.0 %)
[III M] Skilled manual worker	2,086 (25.4 %)	2,104 (20.1 %)
[IV] Semi-skilled worker	1,084 (13.2 %)	1,322 (13.2 %)
[V] Non-skilled worker	231 (2.8 %)	384 (3.8 %)
Education level		
Degree	1,282 (15.4 %)	1,106 (10.8 %)
A-level	3,794 (45.6 %)	3,652 (35.6 %)
O-level	735 (8.8 %)	1,170 (11.4 %)
No qualification	2,517 (30.2 %)	4,319 (42.2 %)
Prevalent disease		
Cancer	303 (3.6 %)	656 (6.4 %)
Diabetes	258 (3.1 %)	147 (1.4 %)
Myocardial infarction	476 (5.7 %)	126 (1.2 %)
Stroke	154 (1.9 %)	106 (1.0 %)
Hormone replacement therapy		
Current		2,138 (20.9 %)
Former		1,164 (11.4 %)
Never		6,942 (67.8 %)
Postmenopausal (vs. premenopausal)		7,996 (78.0 %)

Values are mean (SD) or number (%) unless otherwise stated

[a] Geometric mean (5th, 95th percentile)

Adequate information was available for 16,463 participants for analysis regarding leukocyte count, 20,149 participants for analysis regarding fibrinogen, and 11,703

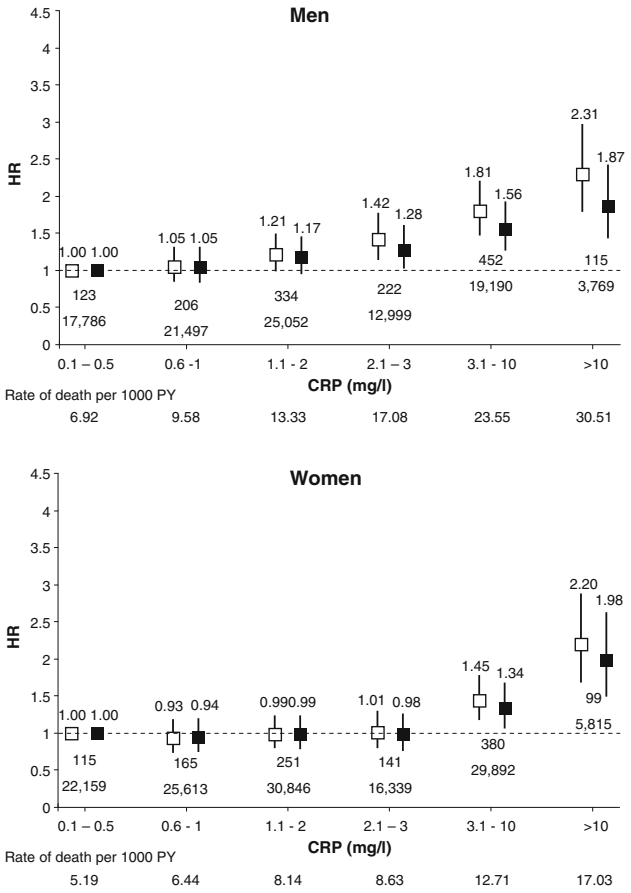

Fig. 1 Hazard ratio for all-cause mortality in increasing high-sensitivity CRP categories. *White boxes* are age-adjusted hazard ratios. *Black boxes* are hazard ratios adjusted for age, smoking, BMI, physical activity, alcohol intake, systolic blood pressure, total cholesterol, social class, history of diabetes, and in women menopausal status and HRT at baseline. Number above each box is the hazard ratio and the numbers below each box are the number of deaths and person-years of follow up in each category of baseline CRP

participants for analysis regarding all three markers after excluding those with prevalent disease at baseline. The median (inter-quartile range) for fibrinogen was 2.9 (2.4, 3.4) and for leukocyte count was 6.3 (5.4, 7.4). The Pearson partial correlation coefficient (adjusted for age and sex) showed weak partial correlations between CRP, Fibrinogen and leukocyte count [partial correlation coefficient was $R = 0.29$ for CRP-Fibrinogen, $R = 0.19$ for CRP-WBC and $R = 0.20$ for fibrinogen-WBC (all P values <0.001)]. Serum fibrinogen in men and leukocyte count in men and women were positively associated with risk of all-cause mortality (Fig. 3) and mortality from CVD and "other causes" (Supplement Figures 1-2). Multivariate adjusted hazard ratio (95 % CI) of all-cause mortality comparing the highest to lowest quintiles was 1.34 (1.15–1.56) in men and 1.09 (0.90–1.31) in women for fibrinogen and 1.34 (1.11–1.62) in men and 1.33 (1.09–1.62) in women for leukocyte count. However, among the 11,703 participants with available information on all three inflammation markers after entering logarithmic transformed CRP, fibrinogen, and leukocyte count in the same model, only CRP remained significantly associated with risk of all cause and cause specific mortality (Supplement Table 2).

In continuous analysis, assuming a log-linear association, a standard deviation increment in $\log_e$-CRP (corresponding to threefold higher baseline CRP) was associated with about a 20 % higher risk of all-cause and CVD mortality and mortality from "other causes". The multivariate adjusted HRs (95 % CI) in men and women were 1.21 (1.15–1.28) and 1.22 (1.15–1.31) for all-cause mortality respectively, 1.22 (1.11–1.35) and 1.22 (1.08–1.38) for CVD mortality, and 1.27 (1.14–1.43) and 1.20 (1.05–1.38) for mortality from "other causes" (Fig. 4, Supplement Figure 3). The magnitude of the association was weaker for cancer mortality and statistically significant in women and borderline significant in men (HR 1.06 (95 % CI 0.97–1.17) in men and 1.15 (1.04, 1.28) in women). Relative risk of death per threefold higher baseline CRP (1-SD higher $\log_e$-CRP) was similar in men and women and in analyses including and excluding participants with a history of cancer, myocardial infarction, and stroke at baseline. The HRs were slightly attenuated but remained significant after excluding deaths that occurred in the first 5 years of follow up. The hazard ratios per threefold higher baseline CRP did not vary considerably by baseline levels of smoking, BMI, physical activity or HRT use. The association of CRP and mortality was relatively stronger in the younger compared to older participants and the interaction was significant among men but not women.

There was not a significant interaction by sex in the association of CRP and mortality. However, significantly elevated HR of mortality in men was observed at notably lower clinical threshold categories of baseline CRP than that of mortality in women (Figs. 1, 2). This pattern persisted in analyses restricted to non-smokers and HRT non-users (Supplement Figures 4-5), was more evident when CRP was divided in a larger number of categories (Supplement Figure 6), and was most notable for CVD mortality (Fig. 2). A less graded trend in women than in men was also notable in the association of baseline fibrinogen and leukocyte count with risk of all-cause mortality (Fig. 3).

The association of inflammation markers, especially CRP, with risk of all-cause and cause-specific mortality was relatively strong compared to known lifestyle and cardiovascular risk factors (Supplement Tables 3–5).

There was not a notable change in the results in analyses that excluded participants with CRP > 10 mg/l, fibrinogen > 6 mg/l, or leukocyte count > 11,000, in analyses excluding participants with a history of diabetes (N = 462)

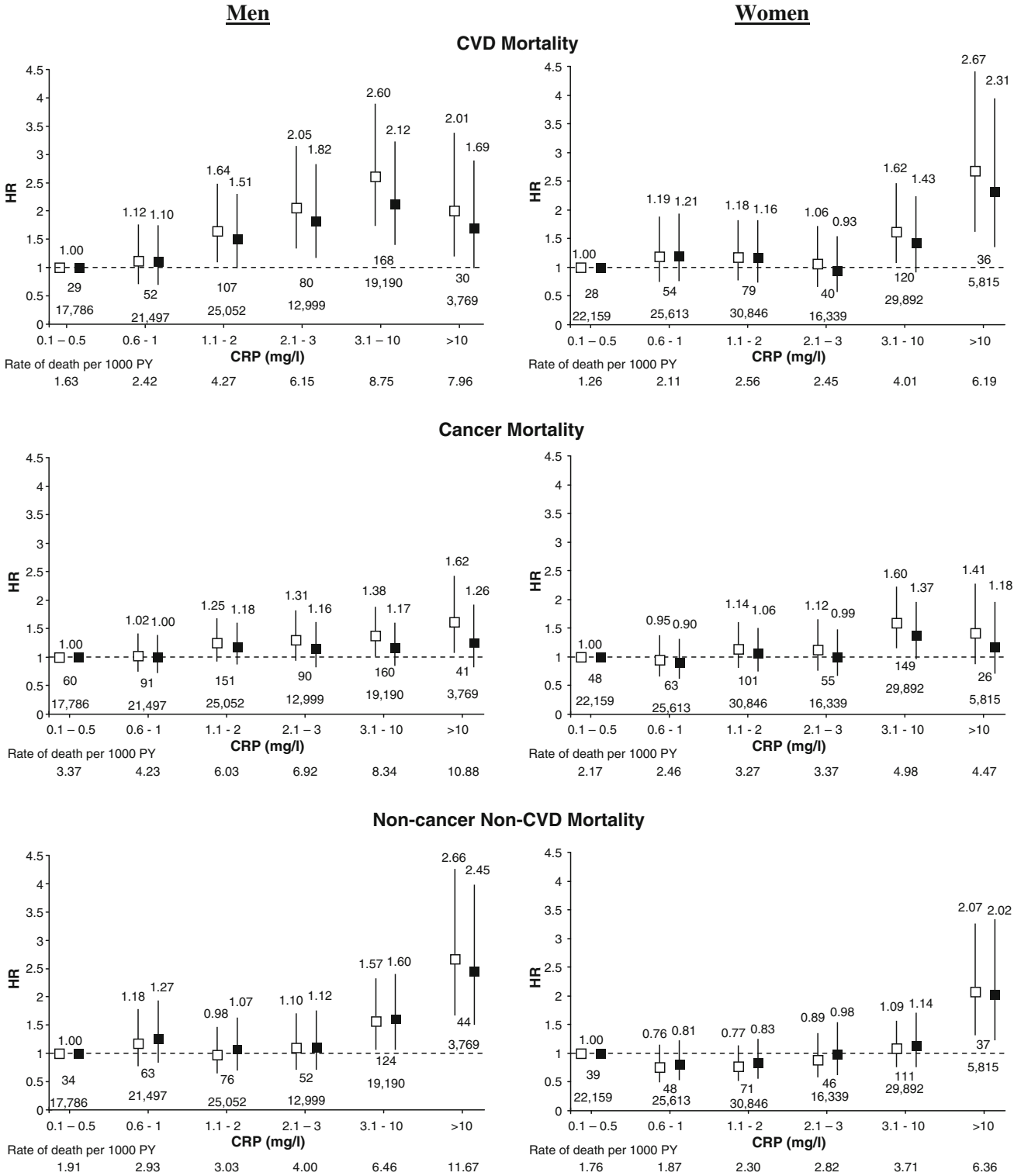

Fig. 2 Hazard ratios for Cardiovascular and cancer mortality and mortality from other causes in increasing high-sensitivity CRP categories. *White boxes* are age-adjusted hazard ratios. *Black boxes* are hazard ratios adjusted for age, smoking, BMI, physical activity, alcohol intake, systolic blood pressure, total cholesterol, social class, history of diabetes, and in women menopausal status and HRT at baseline. Number above each box is the hazard ratio and the numbers below each box are the number of deaths and person-years of follow up in each category of baseline CRP

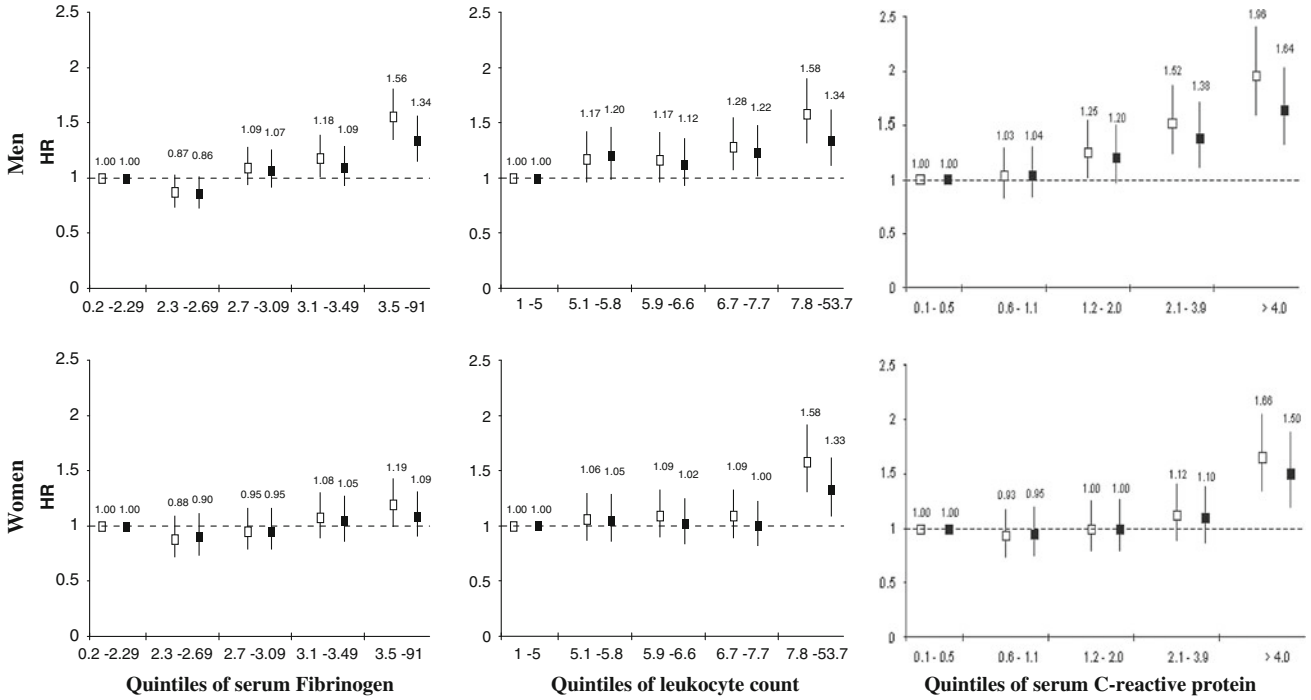

Fig. 3 Hazard ratio for all-cause mortality in increasing serum fibrinogen, leukocyte count, and serum CRP quintiles. *White boxes* are age-adjusted hazard ratios. *Black boxes* are hazard ratios adjusted for age, smoking, BMI, Physical activity, alcohol intake, systolic blood pressure, total cholesterol, social class, history of diabetes, menopausal status and HRT (only in women) at baseline. Among 9,163 men and 10,968 women with available serum fibrinogen measurement, there were 1,853 and 1,429 deaths from all causes after 122,163 and 151,521 person years of follow up in men and women respectively. Among 7,406 men and 9,057 women with available serum leukocyte count measurement, there were 1,360 and 1,050 deaths from all causes after 95,178 and 120,416 person years of follow up in men and women respectively. Among 7,452 men and 9,397 women with available serum CRP, there were 1,452 and 1,151 deaths from all causes after 100,294 and 130,664 person years of follow up in men and women respectively

at baseline, in analyses that further adjusted for LDL-cholesterol and HDL-cholesterol, in analyses that excluded participants with missing data on any of the covariates or when covariates were entered in the model as continuous variables (data not shown).

Discussion

The results of the present study indicate that serum CRP strongly predicts long-term risk of death from cardiovascular and non-cardiovascular causes occurring on average 14 years later. The magnitude of increased risk of mortality was comparable to other established risk factors such as smoking, history of diabetes, BMI, cholesterol levels and blood pressure. A positive but weaker association with risk of mortality was also observed for fibrinogen and leukocyte count which attenuated after adjustment for CRP. The shapes of the associations appeared somewhat different in men and women. The associations of CRP with mortality sub-types did not differ substantially by baseline levels of BMI, smoking, and physical activity. The association of CRP and mortality appeared somewhat stronger among the younger age groups especially among men. The dose–response association observed for CRP with all-cause and CVD mortality that persisted after adjusting for known lifestyle and cardiovascular risk factors provides strong evidence for the association of CRP and mortality. There was a positive linear association between markers of inflammation and cancer mortality in this study. Lack of statistical significance in categorical analysis could be due to lack of statistical power or heterogeneity of different cancers and we had limited statistical power to examine specific cancer sites.

Our results confirm findings from previous studies which have also shown a positive association between CRP and risk of all-cause and cardiovascular mortality [4, 28–31]. The role of CRP and inflammation in atherosclerosis and cardiovascular disease and mortality has been extensively discussed [4, 34, 35]. However, this study and the Emerging Risk Factors Collaboration (ERFC) [4] observed that CRP is also linked to non-cardiovascular mortality. The mechanisms are not well known. One possible explanation is by a theory known as "inflamm-aging" [1, 2, 36]. This theory suggests that progressive filling of the immune system by activated lymphocytes and macrophages in

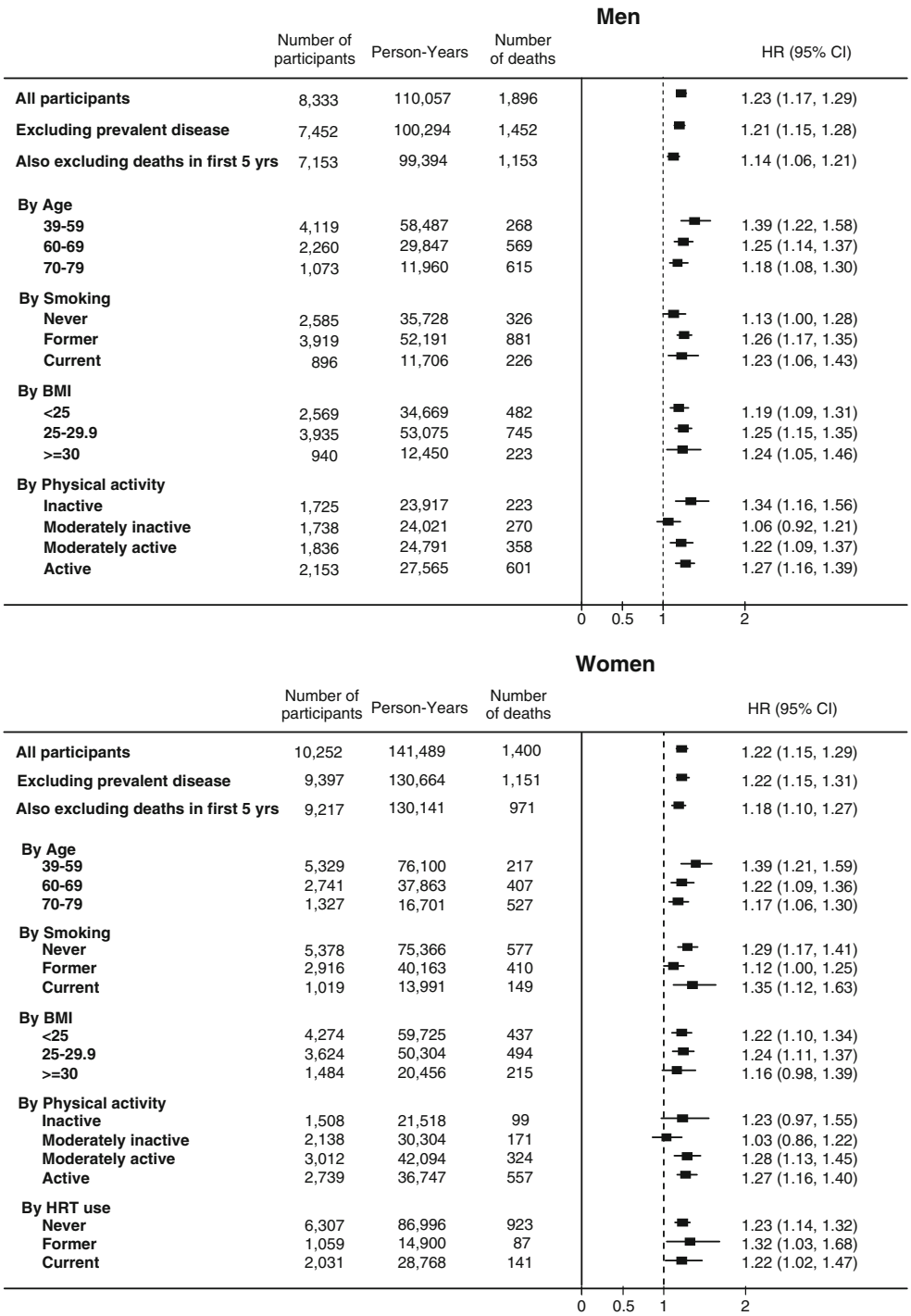

Fig. 4 Hazard ratio for all-cause mortality per threefold higher baseline CRP. Explanation of terms: Prevalent disease: baseline history of cancer, myocardial infarction and stroke. BMI: body mass index. HRT: post menopausal HRT. *Black boxes* are hazard ratios adjusted for (where appropriate) age, smoking, BMI, Physical activity, alcohol intake, systolic blood pressure, total cholesterol, social class, history of diabetes, menopausal status and HRT (only in women) at baseline. Lines represent 95 % CIs

response to long-term exposure to a variety of antigens (infection, food, etc.), results in a reduced capacity to respond to infectious and stress factors later in life. It additionally leads to a pro-inflammatory state resulting from increased activated immune cells and pro-inflammatory cytokines. The pro-inflammatory state is suggested to cause long-term tissue damage and an increased susceptibility to non-infectious diseases, such as atherosclerosis, and diabetes, where immunity and inflammation play a role [1, 2, 36, 37]. Consequently, the process of inflamm-aging is

detrimental for longevity. The association of CRP with a wide-range of age-related diseases (CVD [4–6], cancer [7–9], diabetes [10] and dementia [38]) and also shorter survival in patients with higher CRP levels in a variety of conditions such as CVD [39], stroke [40], cancer [41], and COPD [42], underpins this theory. Although causal links between CRP and diseases such as CVD and cancer are not supported by mendelian randomization studies using CRP related genes [8, 43, 44], the magnitude of the differences in CRP by genotype limit the power of these studies to exclude a causal role since the identified genes only account for 1.5–5 % of the variation in CRP levels [43, 44]. They also do not preclude a causal role for systemic inflammation, of which CRP is an indicator, in the pathogenesis of diseases.

Other markers of inflammation such as leukocyte count, and to a lesser degree fibrinogen, were also associated with the risk of mortality in this study, which also supports the inflamm-aging hypothesis. However, after adjustment for one another only CRP remained a significant predictor of mortality. Our finding was consistent with previous studies [4, 29] in which the association of CRP and mortality persisted after adjustment for Fibrinogen.

The association of CRP and mortality may be due to inflammation and higher CRP levels in participants with pre-existing clinical and subclinical diseases. We excluded participants with a known diagnosis of myocardial infarction, cancer and stroke from the analysis and also repeated the analysis excluding deaths occurring in the first 5 years of follow up to minimize the possibility that CRP concentrations might be elevated as a consequence of pre-existing known or preclinical disease. Although CRP had a stronger association with deaths occurring in the first 5 years of follow up, it was a relatively strong predictor of deaths occurring thereafter.

The distribution of CRP in our population was comparable between men and women who are not taking HRT, regardless of menopausal status (unpublished data). However, although there was not a statistically significant interaction by sex, the shape of the association between CRP and subtypes of mortality in women displayed a somewhat threshold effect while it was more positively graded in men. The reasons are not well known. One potential explanation might be the effect of sex hormones. Previous in vivo and in vitro studies have shown that sex-hormones play a role in the immune and inflammation processes and exert both pro- and anti-inflammatory effects [45–47]. The protective effects of estrogen in conditions where inflammation has a key role in the pathogenesis, such as neurodegeneration [46] and atherosclerosis [45, 47] are in line with our findings and suggest that perhaps estrogen or progesterone might to some extend repress the detrimental effects of chronic inflammation on tissue damage. Although not specifically mentioned, a sex difference similar to our study was observed in the shape of association of CRP and mortality [31] and the association of CRP and incident CVD [6, 48] in previous studies.

It is widely believed that CRP levels above 10 mg/l reflect acute phase reactions and are therefore excluded from analysis regarding risk of disease in many studies. However, our results show that CRP $>$ 10 mg/l is a strong and significant predictor of risk of deaths from cardiovascular and non-cardiovascular causes occurring more than 5 years, and up to 17 years, later and thus does not merely reflect acute events. Less than 10 % of deaths in individuals with baseline CRP $>$ 10 mg/l occurred in first 5 years of follow-up. Highest fifths of fibrinogen and leukocyte count were similarly predictive of long-term risk of mortality.

Cigarette smoking is one of the strongest determinants of serum CRP [13, 19] and one of the most important risk factors of mortality. However, the association of CRP and mortality, although slightly stronger in current smokers, was apparent in never smokers. Obesity [13–15] and HRT use [49] are also known to be associated with a pro-inflammatory state. However, the association of CRP and mortality was not modified by BMI or HRT use.

Although analyses were adjusted for potential confounding factors such as BMI, smoking and other cardiovascular risk factors, the possibility of residual confounding by unmeasured or imperfectly measured confounders exists. Nevertheless, there was strong evidence of association between inflammation markers, especially CRP, and mortality independent of known risk factors, which favours the hypothesis that inflammation, is a primary and powerful mechanism in the pathogenesis of disease, rather than a by-product of smoking and metabolic abnormalities, and may play an important role in determining survival.

A third of the individuals randomly selected were recruited in the study. Although the participation rate might affect the generalizability of the descriptive statistics, it is unlikely to affect the magnitude or direction of the exposure-outcome associations especially as the age–sex structure of the EPIC-Norfolk study participants were approximately similar to the UK population. Moreover, although CRP data was not available for all participants, there was no notable difference in the baseline characteristics between those who did and did not have CRP data. Thus selection bias should not be a considerable problem in this study.

Potential strengths of our study is the long duration of follow-up, and the large size of the study population with large age range, ability to compare directly men and women, and to stratify analysis based on smoking status and BMI. A potential limitation of this study was that CRP and fibrinogen were measured in serum that was stored

frozen for 10–15 years. However, previous studies have shown that CRP [50] and fibrinogen [51] are relatively stable in frozen plasma.

The results of this study showed a higher risk of mortality from cardiovascular and non-cardiovascular causes associated with higher levels of inflammatory markers which suggest that inflammation may have a role in developing adverse health outcomes.

Acknowledgments We thank all study participants, general practitioners and the EPIC-Norfolk study team for their contribution. The EPIC-Norfolk study is supported by funding from the Medical Research Council and Cancer Research UK with additional support from the Stroke Association, British Heart Foundation, Research into Ageing, and the Academy of Medical Science. S.A. is supported by the Gates Cambridge scholarship. Funding sources did not have a role in the design and conduct of the study, the collection, management, analysis, and interpretation of the data or the preparation, review, approval, or decision to submit the manuscript. S.A. analysed the data and wrote the manuscript with co-authors. R.L. performed all data management and record linkage. KTK and NJW are principal investigators in the EPIC-Norfolk population study. All authors provided detailed comments on the manuscript, reviewed and edited the manuscript and contributed to the discussion.

Conflict of interest The authors declare that there is no conflict of interest associated with this manuscript.

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