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C-reactive protein in the prediction of cardiovascular and overall mortality in middle-aged men: a population-based cohort study

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Aims Cut-offs for C-reactive protein concentrations have been recommended for risk stratification, but little is known about how these cut-offs predict cardiovascular risk in population-based cohorts. We therefore assessed the association of C-reactive protein levels with cardiovascular mortality in a population-based cohort of 2321 middle-aged men stratified by the presence of cardiovascular disease (CVD) at baseline.

Methods and results C-reactive protein concentrations were categorized according to current recommendations (1 and 3 mg/L). During the 15 year follow-up, 77 men without CVD and 121 men with CVD at baseline died of CVD. In men without CVD at baseline ($n = 1476$), age-adjusted cardiovascular mortality was 4.1-fold higher (95% CI 2.1–8.2) for C-reactive protein levels between 3.0 and 9.9 mg/L at baseline than for C-reactive protein levels <1.0 mg/L. In men with CVD at baseline ($n = 845$), the corresponding age-adjusted cardiovascular mortality was 3.3-fold higher (95% CI 2.0–5.3). Adjustment for conventional CVD risk factors attenuated the risk somewhat. Further adjustment for dietary and lifestyle factors and factors related to insulin resistance did not affect the association. Classification of C-reactive protein by tertiles gave qualitatively similar results, but identified twice as many men at high risk. C-reactive protein levels also predicted overall mortality.

Conclusion Currently, recommended cut-offs for C-reactive protein levels identify men at risk for cardiovascular and overall death independently of conventional and other risk factors in a population-based sample of middle-aged men with and without CVD at baseline. Lower cut-offs may better identify men at high risk for cardiovascular death, but improvement of current recommendations will require standardization of C-reactive protein assays.

Introduction

Numerous epidemiological, experimental, histological, and *in vitro* studies have firmly implicated inflammation in the pathogenesis of cardiovascular disease (CVD).[1–3] Several markers of inflammation, including white blood cell count and concentrations of interleukin-6 and albumin, have predicted cardiovascular risk, but C-reactive protein has most consistently identified persons at risk for major cardiovascular events.[4,5] C-reactive protein levels have been associated with a wide variety of cardiovascular endpoints, including myocardial infarction, coronary heart disease (CHD) mortality, stroke, and CVD mortality, in men and women with and without CVD[2,6–11] in numerous cohort and clinical studies. Furthermore, C-reactive protein predicts CVD risk beyond other CVD risk factors.[1,10,12,13] In a meta-analysis including 14 epidemiological studies published before the year 2000, C-reactive protein concentrations in the upper third conferred a two-fold higher risk of a CVD event than concentrations in the lower third in both men and women and in persons with and without known CVD at baseline.[5] In a very recent updated meta-analysis of 22 epidemiological studies, however, C-reactive protein concentrations in the upper third increased risk of a CHD event by only 1.6-fold.[2] This has provoked debate as to the usefulness of C-reactive protein for cardiovascular risk stratification.[2,14]

Although C-reactive protein is an acute-phase reactant and as such non-specific, C-reactive protein levels are stable, have a long half-life, and show little diurnal variation.[15,16] The biological variability over a 12 year period was similar to that for blood pressure and cholesterol.[2] There are still problems with standardization between kits, but interassay measurement of

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C-reactive protein has a coefficient of variation <10% for the most widely used kits. Based on the evidence, the American Heart Association (AHA) and the Center for Disease Control (CDC) have recommended that C-reactive protein be used as an adjunct for risk stratification in the prevention of CVD in persons at intermediate risk for a CHD event.[16] In these recommendations, cut-offs of 1.0 and 3.0 g/dL were recommended for categorization into low-, intermediate-, and high-risk groups.[16]

Since the publication of these recommendations, only a few studies have been published that apply these cut-offs in the prediction of CVD endpoints.[12,13,17] We therefore sought to assess the risk associated with C-reactive protein in the prediction of CVD mortality and overall mortality in 2321 middle-aged men stratified by the presence of CVD at baseline. We categorized C-reactive protein concentrations using cut-offs of 1.0 and 3.0 g/dL as recommended by the AHA/CDC and compared these cut-offs with tertiles based on the distribution of C-reactive protein levels in the 2321 men.

Methods

Study population

The Kuopio Ischaemic Heart Disease Risk Factor Study (KIHD) is a prospective population-based study.[18] The study population comprised a random age-stratified sample living in eastern Finland who were 42, 48, 54, or 60 years old at baseline between 1984 and 1989. Of the 3235 eligible men, 2682 (83%) participated in the study. The University of Kuopio Research Ethics Committee approved the study. All participants gave their written informed consent. The study complies with the Declaration of Helsinki.

For the present study, men with a history of diabetes or cancer at baseline ($n = 228$) were excluded. Men with missing data for C-reactive protein ($n = 52$) or with C-reactive protein levels ≥10 mg/L ($n = 81$) were also excluded, leaving 2321 men for the analyses.

Measurement of high-sensitive C-reactive protein

Serum C-reactive protein was measured with an immunometric assay (Immulite High Sensitivity C-reactive protein Assay, DPC, Los Angeles, CA, USA).[19] This C-reactive protein assay has been standardized against the WHO International Reference Standard for C-reactive protein Immunoassay 85/506. At the level of 3.2 mg/L, the within-run CV is 2.8% and the total CV is 3.1%. We used C-reactive protein cut-offs of 1.0 and 3.0 mg/L as recommended by the AHA/CDC.[16] To limit confounding with acute infection or diseases associated with hypersedimentation, we excluded men with C-reactive protein concentrations ≥10.0 mg/L.

Other biochemical measurements

Blood glucose was measured using a glucose dehydrogenase method after precipitation of proteins by trichloroacetic acid. Serum insulin was determined with a Novo Biolabs radioimmunoassay kit (Novo Nordisk, Bagsvaerd, Denmark). LDL and HDL fractions were separated from fresh serum by combined ultracentrifugation and precipitation. Lipoprotein fraction cholesterol and triacylglycerol levels were measured enzymatically.

Other assessments

Dietary intake of saturated (SAFA), monounsaturated (MUFA), and polyunsaturated (PUFA) fat, fruits and vegetables, and fibre were calculated in grams/day from 4 day food records adjusted by total energy intake before further analysis (residual method).[20] Assessment of medical history and medications, family history of diseases, smoking, alcohol consumption, adult socioeconomic status, and moderate-to-vigorous leisure-time physical activity has been described previously.[21–23] Body mass index (BMI) was computed as weight divided by the square of height. Waist girth was recorded as the average of two measurements taken after inspiration and expiration at the midpoint between the lowest rib and the iliac crest. Blood pressure was measured with a random-zero mercury sphygmomanometer.

Ascertainment of all-cause and cardiovascular deaths

Deaths were ascertained by computer linkage to the national death registry using the Finnish social security number. There were no losses to follow-up. All deaths that occurred between study entry (from March 1984 to December 1989) and December 2001 were included. Deaths coded with the Ninth International Classification of Diseases codes 390–459 were considered CVD deaths. Deaths coded as CHD (410–414) or stroke (430–436) were all validated according to the international criteria adopted by the WHO MONICA (MONItoring of Trends and Determinants of CArdiovascular Disease) Project.[24,25] The province of Kuopio participated in the multinational MONICA project between 1982 and 1992,[25] during which time the FINMONICA coronary registry group classified CHD deaths.[25] Thereafter, information was collected from hospitals and classified using identical criteria.

Statistical analysis

To assess the association of C-reactive protein levels with cardiovascular mortality, C-reactive protein concentrations were classified into <1.0, 1.0–2.9 mg/L, and 3.0–9.9 mg/L as recommended by the AHA/CDC.[16] The difference in cardiovascular, metabolic, dietary, and lifestyle risk factors among the C-reactive protein categories at baseline were assessed using one-way ANOVA or χ^2 test as indicated. The associations of the C-reactive protein categories with cardiovascular mortality were assessed with Cox proportional hazards models. Unless otherwise noted, men were stratified by the presence of CVD at baseline. We also classified C-reactive protein levels into thirds (tertiles were derived from the combined groups of men with and without CVD at baseline) for comparison. Adjustment was made for model 1: age and year of examination; model 2: variables in model 1 and conventional cardiovascular risk factors at baseline (LDL cholesterol, systolic blood pressure, use of blood pressure medication, and cigarette smoking); and model 3: variables in model 2 and factors related to diet (energy intake, energy-adjusted intake of SAFA, MUFA, and PUFA; fibre; and fruits and vegetables), insulin resistance (fasting concentrations of insulin, glucose and HDL cholesterol, and BMI), and lifestyle (minutes/week of moderate-to-vigorous physical activity, alcohol intake, and socioeconomic status). Tests of the linear trend across a categorical variable were conducted by entering the categorical variable as a continuous variable into the Cox proportional hazards models. For analyses with continuous variables, the natural logarithm (serum insulin, C-reactive protein, triacylglycerol levels, and dietary PUFA intake) or square root (dietary fruit and vegetable intake) was used for continuous variables with a skewed distribution. Data were missing for biochemical factors ($n = 5$–35), dietary factors ($n = 24$), lifestyle ($n = 0$–34), blood pressure ($n = 13$), and BMI ($n = 9$), in which cases the missing values were replaced with the mean or median. Measurements of waist circumference were missing from 469 men, for which reason BMI was used in Cox proportional hazards analyses. Significance was considered to be $P < 0.05$. All statistical analyses were performed with SPSS 11.0 for Windows (SPSS Inc., Chicago, IL, USA).

Results

The median follow-up for the 2321 men was 14.6 years (range 0.02–17.8 years). During this time, 77 men without

CVD at baseline and 121 men with CVD at baseline died of CVD. In the entire cohort, most cardiovascular, metabolic, dietary, and lifestyle risk factors were more pronounced in men with C-reactive protein levels between 3.0 and 9.9 mg/L than in men with lower levels (*Table 1*).

C-reactive protein concentrations and cardiovascular mortality

High C-reactive protein levels categorized using the 1.0 and 3.0 mg/L cut-offs recommended by the CDC and AHA were associated with a higher cardiovascular mortality during follow-up in both men with and without CVD even after extensive adjustment for confounding or mediating factors (*Figure 1*). In men without CVD at baseline, C-reactive protein levels between 3.0 and 9.9 mg/L at baseline were associated with a four-fold higher cardiovascular mortality than C-reactive protein levels <1.0 mg/L after adjustment for age and year of examination (*Table 2*). Adjustment for conventional cardiovascular risk factors attenuated the risk somewhat, which was mainly due to adjustment for smoking and, to a lesser extent, systolic blood pressure. Further adjustment for dietary factors and factors related to insulin resistance did not affect the association. Overall, a graded risk over the 1.0 and 3.0 mg/L cut-offs was present, but the greatest increase in risk seemed to come with an increase in C-reactive protein levels between 1.0 and 3.0 mg/L. Other variables in model 3 that significantly predicted CVD mortality included age [relative risk (RR) = 1.08, $P = 0.004$], smoking (20 or more cigarettes/day vs. none; RR = 3.5, $P < 0.001$), systolic blood pressure (RR = 1.03, $P < 0.001$), logarithm of energy-adjusted PUFA intake (RR = 0.20, $P = 0.014$), and the square root of energy-adjusted fruit and vegetable intake (RR = 0.90, $P = 0.003$). For the overall fit of model 3, the −2 log likelihood was 911, $\chi^2 = 111.8$, and $P < 0.001$. Adding C-reactive protein to the model improved the fit of the model ($\chi^2 = 10.3$, $P = 0.001$).

Statistical power was limited for examining mortality due to CHD and stroke in men without CVD at baseline. Men with high C-reactive protein levels were, however, also more likely to die of CHD (48 deaths, C-reactive protein levels 3.0–9.9 vs. <1.0 mg/L, model 1: RR = 3.51, 95% CI 1.55–7.97) and stroke (13 deaths, model 1: RR = 7.60, 95% CI 1.39–42) during the follow-up in models adjusting for age and year of examination.

In men with CVD at baseline, those with C-reactive protein levels between 3.0 and 9.9 mg/L at baseline were associated with a 3.3-fold higher cardiovascular mortality than those with C-reactive protein levels <1.0 mg/L after adjustment for age and year of examination (*Table 2*). Adjustment for conventional cardiovascular risk factors attenuated the risk somewhat, which was mainly due to adjustment for smoking and, to a lesser extent, use of blood pressure medication. Further adjustment for dietary factors and factors related to insulin resistance did not affect the association. Overall, the greatest increase in risk seemed to occur in men with C-reactive protein levels ≥3.0 mg/L. Other variables in model 3 that significantly predicted CVD mortality included smoking (20 or more cigarettes/day vs. none: RR = 2.6, $P < 0.001$), history of ischaemic heart disease (RR = 1.5, $P = 0.048$), LDL cholesterol levels (RR = 1.3, $P = 0.003$), use of blood pressure medication (RR = 2.0, $P < 0.001$), systolic blood pressure (RR = 1.01, $P = 0.003$), and dietary energy intake (RR = 0.99, $P = 0.030$). For the overall fit of model 3, the −2 log likelihood was 1474, $\chi^2 = 108.6$, and $P < 0.001$. Adding C-reactive protein to the model improved the fit of the model ($\chi^2 = 7.5$, $P = 0.023$).

Statistical power was also limited for examining mortality due to CHD and stroke in men with CVD at baseline. In age- and examination-year-adjusted analyses, men with CVD at baseline who had high C-reactive protein levels were also more likely to die of CHD (91 deaths, C-reactive protein levels 3.0–9.9 vs. <1.0 mg/L, model 1: RR = 2.50, 95% CI 1.44–4.34) and stroke (13 deaths, model 1: RR = 2.40, 95% CI 0.64–9.02) during the follow-up.

The 1.0 and 3.0 mg/L cut-offs for C-reactive protein concentrations corresponded to the 42nd and 84th percentiles, respectively. We repeated the analyses of the association of C-reactive protein levels with CVD mortality at baseline using tertile cut-offs (0.84 and 1.83 mg/L) for the combined population of men with and without CVD at baseline. The overall findings were similar, but the association with mortality using tertile cut-offs seemed to be slightly stronger in men without CVD at baseline, but slightly weaker in men with CVD at baseline.

C-reactive protein concentrations and overall mortality

In all, 204 men without CVD at baseline and 214 men with CVD at baseline died of any cause during the follow-up. The highest overall mortality was in men with CVD at baseline who had high C-reactive protein levels and the lowest mortality was in men without CVD who had low C-reactive protein levels (*Figure 1B*). Overall, the general trends seen for CVD mortality were reflected in all-cause mortality for both men with and without CVD at baseline (*Table 3*). In model 3, the variables mainly responsible for the attenuation of the association of C-reactive protein with mortality were alcohol intake, socioeconomic status, and BMI.

Discussion

C-reactive protein concentrations categorized according to the AHA/CDC guidelines were a powerful predictor of CVD mortality independently of conventional and non-conventional cardiovascular risk factors in men with and without CVD at baseline. Moreover, C-reactive protein levels predicted overall mortality. Although the overall risk ratios for CVD mortality were similar for the AHD/CDC cut-offs and cut-offs based on tertiles for this population-based sample, the AHD/CDC cut-offs identified that less than half of the men at high risk had the AHA/CDC cut-offs corresponded to tertiles.

Our findings suggest that C-reactive protein concentrations are useful for cardiovascular risk stratification in middle-aged men with and without CVD. Men with C-reactive protein levels >3.0 mg/L or in the upper third were 4.1–5.0 times more likely to die of CVD than men with low C-reactive protein levels during the follow-up. Adjustment for conventional CVD risk factors attenuated the association somewhat, mainly due to smoking, but the risk was still 2.9–3.5-fold higher. Findings for men with

Table 1 Baseline characteristics of the middle-aged men after stratification by serum C-reactive protein concentrations at baseline

	C-reactive protein			*P*-value
	0.10–0.99 mg/L	1.00–2.99 mg/L	3.00–9.99 mg/L	
n	974	976	371	
Age (year)	52.5 (5.3)	53.2 (5.1)	53.5 (5.0)	0.001
CVD (%)	31	37	49	<0.001
Smokers (%)	22	33	50	<0.001
Family history of CHD (%)	50	50	50	0.96
Alcohol consumption (g/week)	26 (5, 73)	32 (5, 99)	43 (9, 119)	<0.001
Socioeconomic status, 0–1.0, low to high	0.57 (0.24)	0.52 (0.23)	0.49 (0.23)	<0.001
Systolic blood pressure (mmHg)	131 (16)	135 (15)	136 (18)	<0.001
Diastolic blood pressure (mmHg)	87 (10)	90 (10)	89 (11)	<0.001
Blood pressure medication (%)	15	22	30	<0.001
BMI (kg/m^2)	25.6 (2.9)	27.3 (3.3)	28.1 (4.0)	<0.001
Waist girth (cm)	87 (9)	92 (9)	95 (11)	<0.001
Serum LDL cholesterol (mmol/L)	4.0 (1.0)	4.1 (1.0)	4.2 (1.0)	<0.001
Serum HDL cholesterol (mmol/L)	1.4 (0.3)	1.3 (0.4)	1.2 (0.3)	<0.001
Serum triacylglycerol (mmol/L)	1.0 (0.8, 1.4)	1.2 (0.8, 1.6)	1.3 (0.9, 1.8)	<0.001
Fasting blood glucose (mmol/L)	4.5 (0.5)	4.6 (0.5)	4.6 (0.5)	0.001
Fasting serum insulin (mU/L)	8.7 (6.7, 11.3)	10.4 (7.9, 13.8)	9.4 (7.2, 12.5)	<0.001
Moderate-to-vigorous LTPA (min/week)	130 (51, 247)	106 (31, 215)	108 (28, 236)	0.001
Dietary fibre (g/day, energy adjusted)	26.2 (7.4)	25.5 (6.7)	26.0 (7.9)	<0.001
Dietary energy (kJ/day)	10 952 (2,632)	10 697 (2,710)	10 294 (2,670)	<0.001
Dietary fruit and vegetables (g/day, energy adjusted)	401 (301, 523)	377 (277, 497)	374 (279, 473)	0.022
Dietary fat (g/day, energy adjusted)	101 (15)	103 (16)	104 (16)	<0.001
SAFA (g/day, energy adjusted)	54 (12)	56 (11)	56 (12)	<0.001
MUFA (g/day, energy adjusted)	34 (6)	35 (6)	35 (6)	0.028
PUFA (g/day, energy adjusted)	12 (10, 15)	12 (10, 15)	11 (9, 15)	0.76
C-reactive protein (mg/L)	0.6 (0.4, 0.8)	1.6 (1.3, 2.1)	4.6 (3.7, 5.8)	

Values are mean (SD), proportions, or medians (interquartile ranges); LTPA, leisure-time physical activity; *P*-values are for the difference among groups (one-way ANOVA or χ^2-test). Data on waist circumference was available for only 1862 men.

CVD already at baseline were similar, except that the RR associated with elevated C-reactive protein levels was somewhat weaker. Interestingly, further adjustment for factors related to insulin resistance and obesity or dietary factors did not attenuate the risk, even though C-reactive protein levels and other markers of inflammation are associated with especially abdominal obesity and insulin resistance. Most studies have adjusted for conventional cardiovascular risk factors, but more extensive adjustment for factors related to insulin resistance, including obesity, BMI and insulin levels, or for detailed dietary factors, has much less often been done.[2,5]

A very recent analysis of 22 epidemiological studies, including the recent Reykjavik study, found a modest 1.6-fold increase in coronary risk.[2] The authors attributed the stronger two-fold association of C-reactive protein with coronary risk in 14 studies published before the year 2000[5] to publication bias. The publication has also sparked a debate as to the utility of C-reactive protein for cardiovascular risk stratification. Our findings agree better with the earlier meta-analysis of studies before the year 2000,[5] and suggest that C-reactive protein would be clinically useful for risk stratification even after taking into account a large number of conventional and non-conventional cardiovascular risk factors. The discrepancies in results among studies do not seem to be due simply to assays, endpoints, or study design,[2] but they may reflect population differences.

Overall mortality was also increased in men with high C-reactive protein levels. Although in large part a reflection of the increased cardiovascular mortality, inflammation and the immune system contribute to the pathogenesis of many cancers.[26] Subclinical inflammation may also be a marker for occult cancer.

The relatively small per cent (16%) of men in this study with C-reactive protein levels $\geq$3.0 mg/L could be due to either population differences in the distribution of C-reactive protein levels or differences among assays used in different studies. The distribution of C-reactive protein levels between men and women and among the Japanese, Europeans, and Americans of European, African, and Mexican ethnic background has been similar in some studies.[27–30] The current cut-offs of 1 and 3 mg/L proposed by the AHA/CDC were said to correspond to the average tertile cut-offs of more than 15 populations representing more than 40 000 people.[31] In a meta-analysis of 14 studies comprising 2557 incident cases of CHD, however, the corresponding cut-offs for tertiles were 1.0 and 2.4 mg/L,[5] and were even lower in the Reykjavik study.[2] These cut-offs are closer to the tertile cut-offs of 0.84 and 1.83 mg/L found in our cohort. In the debate about the comparatively low predictive value of C-reactive protein in the Reykjavik study, it was suggested that one reason for the low risk may be because of the relatively low levels of C-reactive protein in that cohort, which is clearly not an

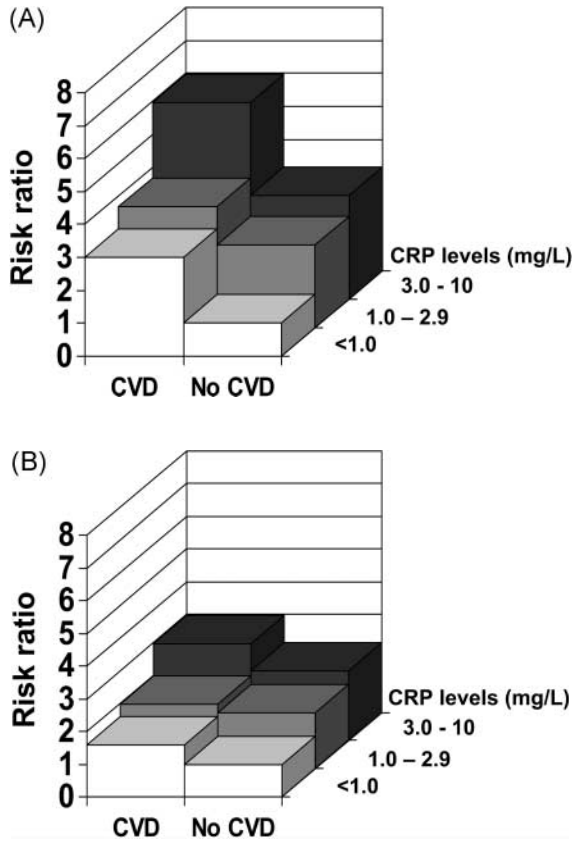

Figure 1 (*A*) Cardiovascular and (*B*) overall mortality by C-reactive protein levels categorized using 1.0 and 3.0 mg/L as cut-offs and presence of CVD at baseline after adjustment for age and year of examination, conventional cardiovascular risk factors at baseline (LDL cholesterol, systolic blood pressure, use of blood pressure medication, and cigarette smoking), factors related to diet (energy intake, energy-adjusted intake of SAFA, MUFA, and PUFA; fibre; and fruits and vegetables), factors related to insulin resistance (fasting concentrations of insulin, glucose and HDL cholesterol, and BMI), and lifestyle factors (minutes/week of moderate to vigorous physical activity, alcohol intake, and socioeconomic status). The reference category is men without CVD at baseline and C-reactive protein levels <1.0 mg/L. The highest mortality was in men with CVD and high C-reactive protein levels.

explanation in our study. The lack of standardization among assays nonetheless makes firm conclusions about the relative distributions of C-reactive protein concentrations among different cohorts difficult, because low median values may be a reflection of the assay rather than the population.

In a comparison of the United States Federal Drug Administration-approved Immulite high-sensitivity C-reactive protein assay that was used in this study with three other commonly used commercial assays, the assays differed substantially from each other in the absolute C-reactive protein values and their distribution.[32] The current lack of standardization among high-sensitivity C-reactive protein assays means that there will be discrepancies in the risk stratification of individuals among kits when using fixed cut-offs by the AHA/CDC. In these men, the AHA/CDC cut-offs detected less than half of the men without CVD who would have otherwise been classified as high risk, had the AHA/CDC cut-offs corresponded to the tertile cut-offs of this population-based cohort. Efforts to standardize the C-reactive protein assays are currently underway.[16]

Table 2 RR (95% CI) of cardiovascular death according to C-reactive protein categories during the 14.9 year follow-up in 2321 middle-aged men without diabetes or cancer at baseline

C-reactive protein levels (mg/L)	*n*	Model 1	Model 2	Model 3	C-reactive protein tertiles (mg/L)	*n*	Model 1	Model 2	Model 3
No CVD at baseline ($n/N = 77/1476$)									
0.10–0.99	675	1	1	1	0.10–0.83	563	1	1	1
1.00–2.99	612	2.73 (1.53–4.89)	2.26 (1.26–4.06)	2.39 (1.29–4.44)	0.84–1.82	490	3.95 (1.88–8.29)	3.33 (1.58–7.03)	3.65 (1.65–8.05)
3.00–9.99	189	4.11 (2.08–8.16)	2.94 (1.46–5.91)	2.90 (1.36–6.19)	1.83–9.99	423	4.98 (2.38–10.4)	3.57 (1.68–7.57)	3.88 (1.72–8.73)
P-value for the trend		<0.001	0.001	0.004			<0.001	0.001	0.002
CVD at baseline ($n/N = 121/845$)									
0.10–0.99	299	1	1	1	0.10–0.83	237	1	1	1
1.00–2.99	364	1.59 (0.99–2.56)	1.20 (0.75–1.98)	1.15 (0.69–1.93)	0.84–1.82	288	1.58 (0.91–2.76)	1.27 (0.73–2.23)	1.23 (0.69–2.20)
3.00–9.99	182	3.27 (2.02–5.30)	2.02 (1.21–3.36)	1.91 (1.12–3.27)	1.83–9.99	320	2.70 (1.62–4.51)	1.75 (1.03–2.99)	1.73 (0.99–3.04)
P-value for the trend		<0.001	0.005	0.010			<0.001	0.025	0.032

Cox proportional hazards, with adjustment as follows: model 1, adjusted for age and year of examination; model 2, adjusted for variables in model 1 and conventional cardiovascular risk factors at baseline (LDL cholesterol, systolic blood pressure, use of blood pressure medication, and cigarette smoking (none, 1–19 cigarettes/day or 20 or more cigarettes/day); model 3, adjusted for variables in model 2 and factors related to diet (energy intake, energy-adjusted intake of SAFA, MUFA, and PUFA; fibre; and fruits and vegetables), insulin resistance (fasting concentrations of insulin, glucose and HDL cholesterol, and BMI), and lifestyle (minutes/week of moderate to vigorous physical activity, alcohol intake, and socioeconomic status).

Table 3 RR (95% CI) of any death according to C-reactive protein categories during the 13.6 year follow-up in 2321 middle-aged men without diabetes or cancer at baseline

C-reactive protein levels (mg/L)	*n*	Model 1	Model 2	Model 3	C-reactive protein tertiles (mg/L)	*n*	Model 1	Model 2	Model 3
No CVD at baseline ($n/N = 204/1476$)									
0.10–0.99	675	1	1	1	0.10–0.83	563	1	1	1
1.00–2.99	612	1.99 (1.44–1.74)	1.67 (1.20–2.31)	1.60 (1.14–2.24)	0.84–1.82	490	1.83 (1.27–2.65)	1.60 (1.11–2.32)	1.52 (1.04–2.22)
3.00–9.99	189	2.92 (1.97–4.33)	2.04 (1.36–3.07)	1.95 (1.27–3.01)	1.83–9.99	423	2.55 (1.78–3.65)	1.80 (1.24–2.60)	1.71 (1.16–2.54)
P-value for the trend		<0.001	<0.001	0.001			<0.001	0.002	0.003
CVD at baseline ($n/N = 214/845$)									
0.10–0.99	299	1	1	1	0.10–0.83	237	1	1	1
1.00–2.99	364	1.56 (1.10–2.20)	1.28 (0.90–1.83)	1.27 (0.88–1.84)	0.84–1.82	288	1.23 (0.91–1.84)	1.03 (0.73–2.23)	1.04 (0.68–1.58)
3.00–9.99	182	2.89 (2.01–4.15)	1.95 (1.33–2.86)	1.95 (1.31–2.92)	1.83–9.99	320	2.28 (1.59–3.27)	1.62 (1.11–2.36)	1.68 (1.13–2.50)
P-value for the trend		<0.001	<0.001	0.001			<0.001	0.003	0.002

Cox proportional hazards, with adjustment as follows: model 1, adjusted for age and year of examination; model 2, adjusted for variables in model 1 and conventional cardiovascular risk factors at baseline (LDL cholesterol, systolic blood pressure, use of blood pressure medication, and cigarette smoking (none, 1–19 cigarettes/day or 20 or more cigarettes/day); model 3, adjusted for variables in model 2 and factors related to diet (energy intake, energy-adjusted intake of SAFA, MUFA, and PUFA; fibre; and fruits and vegetables), factors related to insulin resistance (fasting concentrations of insulin, glucose and HDL cholesterol, and waist girth), and lifestyle factors (minutes/week of moderate to vigorous physical activity, alcohol intake, and socioeconomic status).

The cut-offs for C-reactive protein levels recommended by the AHA/CDC predict cardiovascular and overall mortality independently of conventional and other risk factors in a population-based sample of middle-aged men with and without CVD at baseline. Our findings suggest that lower cut-offs may better identify men at high risk for cardiovascular mortality, but improvement of the AHA/CDC recommendations will require standardization of the C-reactive protein assays commonly in use and study in other populations.

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