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C-reactive protein, cardiovascular risk factors and the association with myocardial infarction in men

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Abstract. Doggen CJM, Berckmans RJ, Sturk A, Manger Cats V, Rosendaal FR (Leiden University Medical Center, the Netherlands). C-reactive protein, cardiovascular risk factors and the association with myocardial infarction in men. *J Intern Med* 2000; 248: 406–414.

Objectives. This study had three objectives: first, to investigate the association of C-reactive protein levels and myocardial infarction amongst men; secondly, to study the associations of C-reactive protein levels with cardiovascular risk factors; and thirdly, to adjust the risk of myocardial infarction for such factors.

Design and subjects. A case–control study including 560 patients with a first myocardial infarction who had survived at least 6 months, plus 646 control subjects.

Results. Patients had significantly higher levels of C-reactive protein (mean 2.2 mg L^{-1}) than control subjects (mean 1.7 mg L^{-1} ; $P < 0.001$). Persons in the highest quintile of C-reactive protein had an

unadjusted 1.9-fold increased risk of myocardial infarction compared with persons in the lowest quintile (odds ratio 1.9, 95% CI: 1.3–2.7). C-reactive protein was, in addition to smoking, associated with several cardiovascular risk factors: age, obesity, diabetes, blood pressure, triglycerides and inversely associated to HDL cholesterol. Adjustment for these variables, especially for total cholesterol, HDL cholesterol and triglycerides, substantially decreased the risk of myocardial infarction for persons in the highest quintile of C-reactive protein, compared to those in the lowest quintile, to 1.3 (95% CI: 0.9–1.9).

Conclusions. Our findings confirm previous reports that C-reactive protein predicts the risk of myocardial infarction. However, this association does not appear to be causal, since the increase in risk can to a large extent be explained by the presence of other cardiovascular risk factors.

Keywords: C-reactive protein, inflammation marker, myocardial infarction, risk factors.

Introduction

The chronic process of atherosclerosis and the acute process of thrombosis are both involved in the development of a myocardial infarction [1]. Atherosclerosis is increasingly thought to be an inflammatory disease and inflammatory cells may account for the local weakening of the atherosclerotic plaque that results in its rupture, with the consequential formation of a thrombus and occlusion of the artery [2, 3]. It is possible that inflammation not only contributes to the progression of atherosclerosis but might also play a role in the activation of clotting factors. C-reactive protein, a sensitive marker of

inflammatory activity, induces monocytes to express tissue factor, the initiator of the extrinsic pathway of coagulation [4]. Thus, inflammation may influence the chronic as well as the acute process [1, 5].

C-reactive protein is an acute phase protein and its production by the liver is stimulated by cytokines, such as interleukin-6. Its plasma level is increased up to several hundred-fold during acute inflammation [6]. It has been suggested that this protein is a risk factor for recurrent events in patients with angina pectoris and in patients with unstable coronary artery disease [7–10]. The risk of elevated C-reactive protein levels for a first myocardial infarction has been investigated in several nested

case-control studies with conflicting results [11–13]. C-reactive protein is an acute-phase reactant that may rise in response to many stimuli. Therefore, associations with cardiovascular risk factors or subclinical disease are likely explanations for the observed associations of C-reactive protein and risk. In the 'Study of Myocardial Infarctions Leiden (SMILE)', we investigated C-reactive protein levels in 560 men with a nonfatal myocardial infarction and 646 control subjects from the Netherlands, and calculated risks of myocardial infarction with increasing quintile of C-reactive protein level. We extensively assessed the relationship of C-reactive protein levels with other markers of risk and adjusted the risk of myocardial infarction for cardiovascular risk factors that were found to be associated with C-reactive protein levels.

Materials and methods

Details of the 'Study of Myocardial Infarctions Leiden' have been described elsewhere [14]. Briefly, patients were men below the age of 70 years, with a first myocardial infarction that had occurred between January 1990 and January 1996. The control group also consisted of men, frequency matched on age to the patients, who had undergone an orthopaedic intervention between January 1990 and May 1996 and had received prophylactic anticoagulants for a short period after the intervention. Both patients and control subjects were born in the Netherlands. They completed a questionnaire on smoking habits, alcohol use and the presence of diabetes. Smoking was defined as never, former or current. Blood pressure was measured after a rest of at least 10 min with the person sitting in an upright position. The body mass index was derived by dividing weight (kilograms) by squared height (metres), and obesity was defined at an index of 30 kg m^{-2} or above.

Fasting blood samples were drawn from the antecubital vein in Sarstedt Monovette tubes and obtained between July 1994 and February 1997. Blood in the first tube was allowed to clot and the serum was used for measuring total cholesterol, HDL cholesterol and triglyceride levels. Blood taken in 0.109 mol L^{-1} trisodium citrate was centrifuged for 10 min at $3000 g$ at room temperature. The citrated plasma was aliquoted in multiple tubes

and immediately stored at -80°C . Total cholesterol and triglyceride concentrations were measured using enzymatic assays adapted to a Hitachi 747 (Boehringer Mannheim). High density lipoprotein (HDL) cholesterol concentration was measured on a Hitachi 911 (Boehringer Mannheim). C-reactive protein levels were measured using an enzyme linked immunosorbent assay (CRP EIA HS assay; Kordia, the Netherlands). The within-day, between microplate coefficient of variation was 5.2% at 0.82 mg L^{-1} and 6.8% at 8.9 mg L^{-1} ($n = 16$). The between-day coefficient of variation was 5.3% and 5.1% at the same respective concentrations ($n = 10$).

The mean age of patients and control subjects at the time of blood sampling was 59.1 (SE 0.4) and 57.3 (SE 0.4) years, respectively. The median time between myocardial infarction, orthopaedic intervention and blood collection was, respectively, 2.6 years and 2.9 years, with a minimum of 6 months. The closer the proximity of the event to the time of blood collection, the higher the C-reactive protein levels in the Cardiovascular Health Study [12]. To evaluate whether C-reactive protein levels decreased after myocardial infarction in our study, we stratified the elapsed time since myocardial infarction into 1-year categories. The elapsed time since myocardial infarction did not relate to C-reactive protein levels (Table 1).

As C-reactive protein levels were skewed, $\log_{10}$ -transformation was applied. These log-transformed values were used in the analyses and differences between the log-transformed values were tested by means of analysis of variance (ANOVA). However, all values presented are converted back to geometric means with the appropriate 95% confidence interval (CI). *P*-values were considered significant at a value < 0.05 . Quintiles of C-reactive protein were defined on the basis of the distribution of C-reactive protein levels amongst control subjects. The lowest quintile was used as a reference category for calculating odds ratios (OR). Logistic regression was used to adjust for age, smoking and other cardiovascular risk factors. Confidence intervals of 95% (95% CI) for odds ratios were calculated by the method of Woolf [15] or based on the standard errors from the logistic model. A linear test for trend [16] was used to assess any relationship between increasing quintiles of C-reactive protein levels and the risk of myocardial infarction. Quintiles of total cholesterol, HDL cho-

lesterol and triglyceride levels were defined on the basis of the distribution amongst control subjects. However, in the logistic regression model the three lipid factors were included as continuous variables, as were systolic and diastolic blood pressure.

Results

C-reactive protein level in patients with myocardial infarction and control subjects

The mean C-reactive protein level amongst patients with a myocardial infarction was 2.2 mg L^{-1} (CI: 2.0–2.4) and varied between 0.1 mg L^{-1} and 46.8 mg L^{-1} . For control subjects the mean level was 1.7 mg L^{-1} (CI: 1.6–1.9), with a range between 0.03 mg L^{-1} and 115.1 mg L^{-1} . Levels in patients were significantly higher compared with control subjects ($P < 0.001$). The difference was also evident in the absence of alcohol use, obesity or diabetes, but not in the absence of smoking (Table 2). C-reactive protein levels above 10 mg L^{-1} , indicating the presence of organic disease [6], e.g. rheumatoid arthritis or colitis ulcerosa, were found in 38 patients and 55 control subjects. Exclusion of these persons reduced the mean C-reactive protein levels to 1.9 mg L^{-1} (CI: 1.8–2.1) for patients and to 1.4 mg L^{-1} (CI: 1.3–1.5) for control subjects ($P < 0.001$).

Association between C-reactive protein level and cardiovascular risk factors

As can be seen in Fig. 1, overall C-reactive protein levels increase gradually with age, with levels at 70–75 years being almost twice those at 30–40 years. At all ages, except amongst the very oldest, C-reactive protein levels in patients were between 0.3 and 0.5 mg L^{-1} higher than in controls.

Smokers had higher C-reactive protein levels than never smokers, with former smokers having intermediate levels, in patients as well as in control subjects (both $P < 0.001$; Table 2). Alcohol use was associated with C-reactive protein levels in patients, with never users having higher levels compared with regular users. However, no difference in levels was found amongst control subjects. Obese persons had higher levels of C-reactive protein compared to

men without this risk factor (all $P < 0.05$; Table 3). Men with diabetes had higher levels compared to those without diabetes, although this was only significantly in patients.

Systolic and diastolic blood pressure were significantly associated with increased C-reactive protein levels in control subjects, but not in patients. The mean C-reactive protein level for 104 control subjects with a systolic blood pressure of 165 mm Hg or above was 2.8 mg L^{-1} (CI: 2.3–3.5), compared with 1.6 mg L^{-1} (CI: 1.4–1.7) for those with lower levels of systolic blood pressure ($P < 0.001$). The mean C-reactive protein level of 179 control subjects with diastolic blood pressure of 95 mm Hg or above was 2.0 mg L^{-1} (CI: 1.7–2.4) vs. 1.6 mg L^{-1} (CI: 1.4–1.8) for those with lower blood pressure ($P < 0.05$).

The C-reactive protein level was not associated with total cholesterol levels in patients, nor in control subjects (Table 3). However, low C-reactive protein levels were found in control subjects and patients in the highest quintile of HDL cholesterol. In contrast, high levels of C-reactive protein were found in control subjects in the highest quintile of triglyceride levels. In patients, no consistent trend was found in C-reactive protein levels in association with triglyceride quintiles.

C-reactive protein level and risk of myocardial infarction, adjusted for cardiovascular risk factors

The distribution of patients and control subjects by quintiles of C-reactive protein levels is shown in Table 4. The risk of myocardial infarction increased with increasing quintiles ($P < 0.001$ for trend). The unadjusted risk of myocardial infarction for men in the highest quintile, compared with those in the lowest quintile was 1.9-fold increased (OR 1.9, 95% CI: 1.3–2.7). A similar trend was found for men under the age of 50 years. Adjustment for age and smoking led to similar patterns in the risk of myocardial infarction; the highest risk was found for men in the highest quintile. Adjustment for age, total cholesterol, HDL cholesterol and triglycerides lowered the estimated odds ratios; the unadjusted odds ratio of 1.9 for the highest vs. the lowest quintile of C-reactive protein, decreased to 1.3 (OR 1.3, 95% CI: 0.9–1.9). Further adjustment for smoking, alcohol use, obesity, diabetes and blood

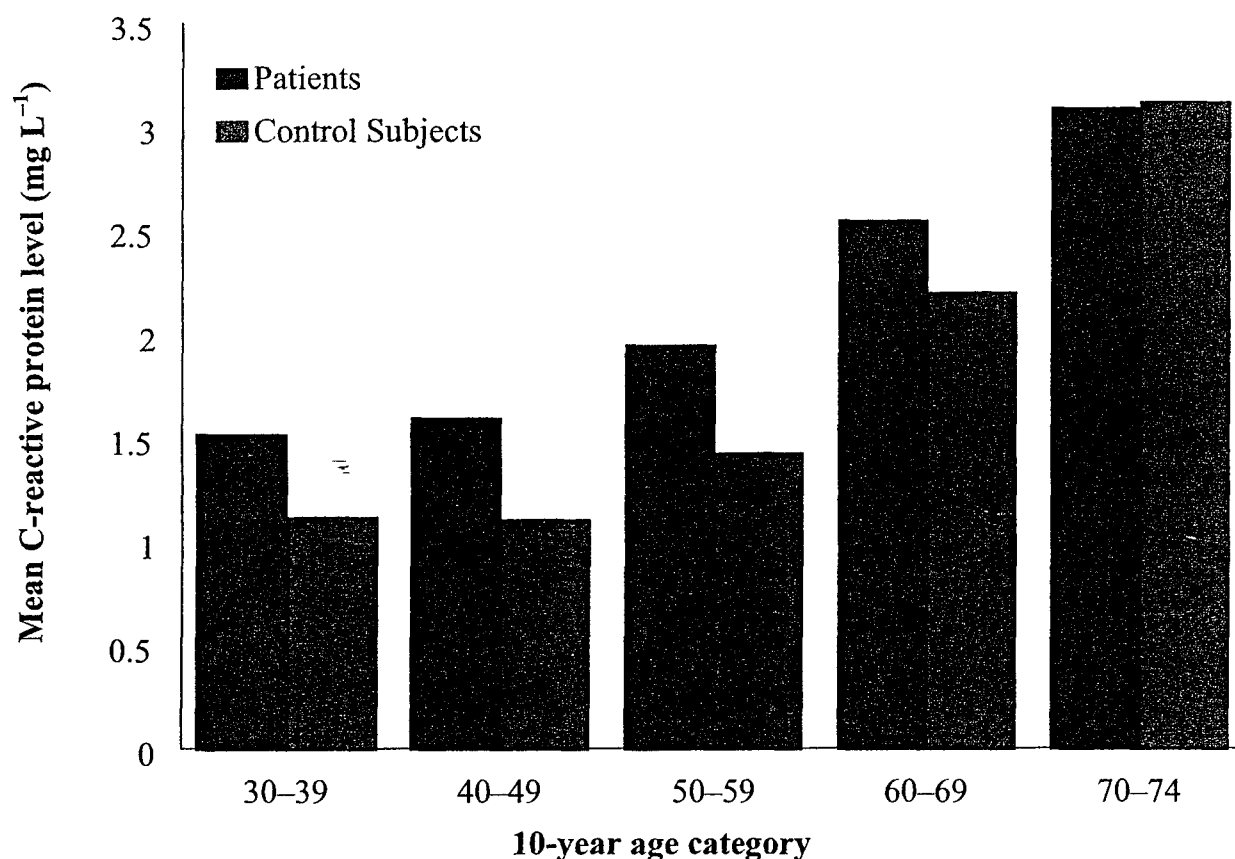


Fig. 1 C-reactive protein levels amongst patients with myocardial infarction and control subjects, by 10-year age categories.

		10-year age categories				
C-reactive protein level (mg L ⁻¹)		30-39	40-49	50-59	60-69	70-74
Patients	N	10	99	161	221	69
	Mean (CI)	1.5 (0.8-3.0)	1.6 (1.3-2.0)	2.0 (1.7-2.3)	2.6 (2.2-3.0)	3.1 (2.5-3.9)
Control subjects	N	46	104	181	248	57
	Mean (CI)	1.1 (0.7-1.7)	1.1 (0.9-1.4)	1.4 (1.2-1.7)	2.2 (1.9-2.6)	3.1 (2.3-4.3)
P-value		0.53	0.02	0.01	0.16	0.97
ANOVA						

Table 1 Elapsed time since myocardial infarction and C-reactive protein levels

Number of years since myocardial infarction	Number of patients	C-reactive protein level (mg L ⁻¹) mean (CI)
0.5-1	33	1.6 (1.2-2.3)
1-2	157	2.2 (1.8-2.6)
2-3	121	2.2 (1.8-2.7)
3-4	116	2.5 (2.0-3.1)
4-5	113	2.2 (1.8-2.6)
5-6	20	2.6 (1.7-4.0)

P-value ANOVA = 0.46

pressure, several of the cardiovascular risk factors identified as being associated with C-reactive protein levels, did not alter these odds ratios.

To rule out the effect of outlying values we repeated these analyses for persons who had a C-reactive protein level lower than 10 mg L⁻¹. This gave an unadjusted risk of myocardial infarction for men in the highest quintile compared to those in the lowest quintile of 2.2 (OR 2.2, 95% CI: 1.5-3.2). Adjustments for age, total cholesterol, HDL cholesterol and triglycerides decreased this risk to 1.4 (OR 1.4, 95% CI: 1.0-2.1), without any increased risk

Table 2 Difference in C-reactive protein levels between patients with myocardial infarction and control subjects and the association between C-reactive protein levels and cardiovascular risk factors in both groups

	C-reactive protein (mg L ⁻¹)				P-value of difference patients and control subjects
Cardiovascular risk factor	Patients		Control subjects		
	Number	Mean (CI)*†	Number	Mean (CI)*†	
Overall	560	2.2 (2.0–2.4)	646	1.7 (1.6 –1.9)	< 0.001
Smoking					
Never	44	1.3 (0.9–1.8)	117	1.1 (1.0–1.5)	0.71
Former	362	2.1 (1.8–2.3)	314	1.7 (1.5–1.9)	0.02
Current	154	3.0 (2.6–3.5)	215	2.1 (1.8–2.5)	< 0.01
		< 0.001		< 0.001	
Alcohol					
Never	103	2.9 (2.3–3.6)	64	1.7 (1.2–2.4)	< 0.01
Occasionally	32	2.0 (1.4–3.1)	21	1.7 (1.0–2.9)	0.61
Regularly	425	2.1 (1.9–2.3)	561	1.7 (1.6–1.9)	< 0.01
		0.03		1.0	
Obesity ‡					
Absent	463	2.1 (1.9–2.3)	539	1.5 (1.4–1.7)	< 0.001
Present	96	3.0 (2.4–3.7)	106	2.8 (2.3–3.4)	0.72
		< 0.01		< 0.001	
Diabetes					
Absent	526	2.2 (2.0–2.4)	624	1.7 (1.5–1.9)	< 0.001
Present	34	3.6 (2.5–5.1)	22	2.3 (1.3–4.1)	0.15
		< 0.01		0.23	

*P-values mentioned in this column are those of ANOVA comparing, e.g. never, former and current smokers.

†Median values of C-reactive protein level showed the same trend.

‡For two persons length and weight were not available.

for the second, third or fourth quintile compared to the first quintile.

Discussion

This study amongst 560 men with a first myocardial infarction and 646 control subjects shows that C-reactive protein levels are associated with myocardial infarction, with a nearly 2-fold increased risk for persons in the highest quintile of C-reactive protein levels, compared with those in the lowest quintile. Many major cardiovascular risk factors such as age, smoking, obesity and diabetes were associated with high C-reactive protein levels. Systolic blood pressure and triglyceride levels were positively associated with C-reactive protein levels, and HDL cholesterol was negatively associated with C-reactive protein levels. This implies that the relationship of C-reactive protein levels with myocardial infarction is confounded by these factors. Adjustment for cardiovascular risk factors, in particular, adjustment for total cholesterol, HDL cholesterol and triglycerides, substantially decreased the risk of myocardial

infarction for men in the highest quintile to 1.3 (95% CI: 0.9–1.9) compared to men in the lowest quintile. Thus, the association of C-reactive protein levels with myocardial infarction can, to a large extent, be explained by the presence of cardiovascular risk factors.

C-reactive protein levels amongst patients were higher compared with control subjects, which corresponds to the results of the Physicians' Health Study (PHS) [11]. Both that study and this one show C-reactive protein as a predictor of myocardial infarction. In our study, most of the risk associated with C-reactive protein disappeared after adjustment for other risk factors. This is corroborated by the Dutch Hoorn study, a 5-year follow-up study, in which the relative risk between C-reactive protein and cardiovascular mortality also substantially decreased after adjustment for several risk factors [17]. It is also corroborated by a Danish nested case-control study, in which C-reactive protein was not an independent predictor of coronary heart disease [18]. The most likely, though not only, explanation is that C-reactive protein level predicts risk because

Table 3 C-reactive protein levels by quintile of total cholesterol, HDL cholesterol and triglycerides amongst patients with myocardial infarction and control subjects

		C-reactive protein (mg L ⁻¹)				P-value of difference patients and control subjects
Quintile	Range	Patients		Control subjects		
		Number‡	Mean (CI)*†	Number‡	Mean (CI)*†	
Total cholesterol (mmol L ⁻¹)						
1	< 5.02	85	2.3 (1.7–3.0)	128	1.8 (1.4–2.3)	0.20
2	5.02–5.57	112	2.2 (1.8–2.7)	129	1.5 (1.2–1.8)	< 0.01
3	5.58–6.08	104	2.1 (1.7–2.6)	129	1.6 (1.3–2.0)	0.06
4	6.09–6.79	129	2.1 (1.7–2.5)	128	1.8 (1.5–2.2)	0.34
5	≥ 6.80	126	2.4 (2.0–2.9)	131	2.0 (1.6–2.4)	0.11
			0.84		0.26	
HDL cholesterol (mmol L ⁻¹)						
1	< 1.06	197	2.8 (2.4–3.2)	128	2.4 (2.0–3.0)	0.30
2	1.06–1.22	133	2.3 (1.9–2.9)	128	2.1 (1.7–2.6)	0.49
3	1.23–1.38	109	2.1 (1.6–2.6)	130	1.5 (1.3–1.9)	0.05
4	1.39–1.61	83	1.8 (1.4–2.2)	129	1.3 (1.1–1.6)	0.06
5	≥ 1.62	32	1.1 (0.8–1.5)	128	1.4 (1.1–1.7)	0.26
			< 0.001		< 0.001	
Triglycerides (mmol L ⁻¹)						
1	< 0.83	42	2.1 (1.4–3.2)	125	1.4 (1.1–1.7)	0.07
2	0.83–1.09	60	2.0 (1.5–2.8)	131	1.5 (1.2–1.9)	0.15
3	1.10–1.41	103	2.2 (1.8–2.8)	131	1.7 (1.4–2.1)	0.11
4	1.42–2.03	154	2.4 (2.0–2.9)	128	1.9 (1.6–2.3)	0.08
5	≥ 2.04	198	2.2 (1.9–2.5)	130	2.1 (1.8–2.5)	0.93
			0.75		0.02	

*P-values mentioned in this column are those of ANOVA, comparing, e.g. C-reactive protein levels by quintiles of total cholesterol within patients.

†Median values of C-reactive protein level showed the same trend.

‡Cholesterol levels were missing for three patients and one control subject. HDL cholesterol levels for six patients and three control subjects and triglyceride levels for three patients and one control subject.

it is a marker for these other risk factors. In the MONICA Augsburg Cohort study, the relationship between C-reactive protein levels and the incidence of coronary heart disease events also decreased after

adjustments were made [19]. However, the effect in the PHS, after adjustment for several identical risk factors, remained [11]. In the analysis in which patients were matched with control subjects on the

Table 4 Risk of myocardial infarction with increasing quintile of C-reactive protein levels after adjustment for cardiovascular risk factors (odds ratios with 95% confidence interval)

Variable adjusted for		Quintile of C-reactive protein level (mg L ⁻¹)				
		< 0.65	0.65–1.18	1.19–2.07	2.08–4.23	≥ 4.24
–	1	0.9 (0.6–1.3)	1.1 (0.7–1.6)	1.7 (1.2–2.4)	1.9 (1.3–2.7)	
Age	1	0.8 (0.6–1.2)	1.0 (0.7–1.5)	1.6 (1.1–2.2)	1.8 (1.2–2.6)	
Age, smoking [‡]	1	0.8 (0.6–1.2)	1.0 (0.7–1.5)	1.6 (1.1–2.3)	1.8 (1.2–2.6)	
Age, smoking, diabetes, alcohol, obesity, systolic and diastolic blood pressure	1	0.8 (0.5–1.2)	1.1 (0.7–1.6)	1.7 (1.1–2.5)	1.8 (1.2–2.7)	
Age, total cholesterol, HDL cholesterol and triglycerides	1	0.8 (0.5–1.2)	0.8 (0.6–1.3)	1.2 (0.8–1.8)	1.3 (0.9–1.9)	
Age, smoking, diabetes, alcohol, obesity, systolic and diastolic blood pressure, total cholesterol, HDL cholesterol and triglycerides	1	0.8 (0.5–1.2)	0.9 (0.6–1.4)	1.4 (1.0–2.2)	1.4 (0.9–2.1)	

presence or absence of subclinical disease, the Cardiovascular Health Study found a nonsignificant 1.8-fold increased risk of myocardial infarction for men in the highest quartile [12]. This is in contrast with the Multiple Risk Factor Intervention Trial. This latter study included only high risk men, which probably accounts for the similar baseline levels of C-reactive protein in patients with a myocardial infarction and control subjects [13].

The levels of C-reactive protein differ between studies, which is likely to be the result of different prevalences of cardiovascular risk factors, such as smoking, obesity, diabetes and hypertension, which are associated with high C-reactive protein levels. It has been suggested that C-reactive protein might causally affect atherosclerosis or thrombosis, and thereby increase the risk of myocardial infarction [1, 5]. Reversely, cardiovascular risk factors promote atherosclerosis and the increase in C-reactive protein levels in patients with myocardial infarction could reflect the intrinsic inflammation and tissue damage within the arterial lesions. Another possibility in this respect might be prior infection with *Helicobacter Pylori* and *Chlamydia Pneumoniae*, which in some studies, but not all, are associated with coronary heart disease and various cardiovascular risk factors, and with increased production of C-reactive protein levels [20–23]. We must also retain that C-reactive protein levels might be a surrogate for cytokines. Recently, it has been suggested that C-reactive protein might activate the complement system, thereby promoting inflammation and thrombosis [24]. C-reactive protein could also act as an intermediate factor in the association of cardiovascular risk factors and myocardial infarction. After adjustment for several cardiovascular risk factors, the risk of myocardial infarction for men in the highest quintile decreased to a nonsignificant 1.4-fold increased risk, supporting this option. Residual confounding, i.e. the presence of unknown confounders, could well explain the remaining 40% increased risk.

We found that increasing age was associated with increasing C-reactive protein levels. These results are in agreement with a study amongst 303 men aged 50–69 years from London, in which increased levels were found with increasing age [21]. This is to be expected, as cardiovascular risk factors are likely to accumulate in the elderly. As C-reactive protein levels are elevated in the presence of these risk

factors, higher levels are found in older people. This could also explain why the difference in C-reactive protein levels between patients and control subjects diminishes with increasing age; control subjects probably catch up with patients with regard to the presence of cardiovascular risk factors. In the Cardiovascular Health Study amongst adults aged 65 years and older, no association between age and levels of C-reactive protein was found [25]. Another explanation for the increase in C-reactive protein levels with increasing age, is the increase in prevalence of inflammatory disorders in the elderly.

Amongst patients and healthy control subjects, a clear association existed between smoking and C-reactive protein levels, with smokers having the highest level, which confirms the results of other studies [8, 11, 17–19, 26]. This agrees with the concept that smoking causes bronchial inflammation, as C-reactive protein is a marker of inflammation and thus an elevation in levels was to be expected. We found a strong association between obesity and C-reactive protein levels, which confirms the results of other studies [17–19, 21, 25–27]. It is hypothesized that adipose tissue may play a role in the regulation of serum C-reactive protein levels via interleukin-6 production [27]. A positive and negative association with, respectively, triglycerides and HDL cholesterol, without any association of C-reactive protein levels with total cholesterol in control subjects, has also been reported before [21, 25].

Several points need to be made with regard to our 'Study of Myocardial Infarctions Leiden'. Our results only apply to men, as we did not include women. In several studies in which women were included the results were more pronounced than amongst men [12, 28]. However, amongst women the risk of cardiovascular events also decreased substantially after adjustment for several risk factors, as in our study [29]. C-reactive protein was no longer an independent predictor of coronary heart disease in a follow-up study including both men and women [18]. As C-reactive protein levels are measured at least 6 months after the myocardial infarction, and for most patients several years later, we cannot be certain that they reflect the pre-myocardial infarction levels. Levels could have become elevated as a consequence of myocardial infarction. Moreover, our study only included individuals who had survived a myocardial infarction. A study amongst

188 patients with a myocardial infarction described that patients dying within 6 months had a high rise in C-reactive protein measured several hours after the onset of symptoms [30]. Since we saw no effect of time since the event, at least 6 months later, neither is likely to have affected our results. If there were a persistent effect as a result of the event, it would increase the difference between patients and controls and could not explain the absence of a significant effect in the adjusted analysis. As a control group, we invited persons who had undergone an orthopaedic intervention more than 6 months ago, the majority of whom had the intervention more than 2 years previously. It is very unlikely that an intervention so long ago influenced C-reactive protein levels, especially since most interventions were connected with a passing injury. Both control subjects and patients were living in the same area, and so we believe that our control group is a good representation of the general population from where the patients arose.

In conclusion, C-reactive protein levels are higher amongst patients with a previous myocardial infarction compared with controls, and an increased risk of myocardial infarction seems apparent with increasing quintile of C-reactive protein. As the level of C-reactive protein is associated with several cardiovascular risk factors, the risk of myocardial infarction diminished after adjustment for these risk factors and resulted in a nonsignificant 1.4-fold increased risk for men in the highest quintile, compared to men in the lowest quintile. Adjustment for lipids in particular, decreased the risk to 1.3-fold. Therefore, the association of C-reactive protein levels with risk of myocardial infarction is largely explained by other risk factors, and the remaining unconfounded association, if it exists, is small.

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References

- 1 Ross R. The pathogenesis of atherosclerosis: a perspective for the 1990s. *Nature* 1993; 362: 801–9.
- 2 Munro JM, Cotran RS. The pathogenesis of atherosclerosis: atherogenesis and inflammation. *Lab Invest* 1988; 58: 249–61.
- 3 Alexander RW. Inflammation and coronary artery disease. *N Engl J Med* 1994; 331: 468–9.
- 4 Cermak J, Key NS, Bach RR, Balla J, Jacob HS, Vercellotti GM. C-reactive protein induces human peripheral blood monocytes to synthesize tissue factor. *Blood* 1993; 82: 513–20.
- 5 Nieminen MS, Mattila K, Valtonen V. Infection and inflammation as risk factors for myocardial infarction. *Eur Heart J* 1993; 14 (Suppl. K): 12–6.
- 6 Pepys MB, Weatherall DJ, Ledingham JGG, Warrell DA, eds. The acute phase response and C-reactive protein. In: *Oxford Textbook of Medicine* 3. Oxford: Oxford University Press, 1996: 1527–33.
- 7 Berk BC, Weintraub WS, Alexander RW. Elevation of C-reactive protein in 'active' coronary artery disease. *Am J Cardiol* 1990; 65: 168–72.
- 8 Haverkate F, Thompson SG, Pyke SDM, Gallimore JR, Pepys MB. Production of C-reactive protein and risk of coronary events in stable and unstable angina. *Lancet* 1997; 349: 462–6.
- 9 Toss H, Lindahl B, Siegbahn A, Wallentin L. Prognostic influence of increased fibrinogen and C-reactive protein levels in unstable coronary artery disease. *Circulation* 1997; 96: 4204–10.
- 10 Biasucci LM, Liuzzo G, Grillo RL, Caligiuri G, Rebuzzi AG, Buffon A *et al.* Elevated levels of C-reactive protein at discharge in patients with unstable angina predict recurrent instability. *Circulation* 1999; 99: 855–60.
- 11 Ridker PM, Cushman M, Stampfer MJ, Tracy RP, Hennekens CH. Inflammation, aspirin, and the risk of cardiovascular disease in apparently healthy men. *N Engl J Med* 1997; 336: 973–9.
- 12 Tracy RP, Lemaitre RN, Psaty BM, Ives DG, Evans RW, Cushman M *et al.* Relationship of C-reactive protein to risk of cardiovascular disease in the elderly. Results from the Cardiovascular Health Study and the Rural Health Promotion Project. *Arterioscler Thromb Vasc Biol* 1997; 17: 1121–7.
- 13 Kuller LH, Tracy RP, Shaten J, Meilahn EN. Relation of C-reactive protein and coronary heart disease in the MRFT nested case-control study. *Am J Epidemiol* 1996; 144: 537–47.
- 14 Doggen CJM, Manger Cats V, Bertina RM, Rosendaal FR. Interaction of coagulation defects and cardiovascular risk factors: increased risk of myocardial infarction associated with factor V Leiden or prothrombin 20210A. *Circulation*

- 1998; 97: 1037–41.
- 15 Woolf B. On estimating the relation between blood group and disease. *Ann Hum Genet* 1955; 19: 251–3.
- 16 Schlesselman JJ, Schlesselman JJ, eds. Basic methods of analysis. In: *Case-Control Studies*. New York, Oxford: Oxford University Press, 1982: 203–6.
- 17 Jager A, Hinsbergh VWM, Kostense PJ, Emeis JJ, Yudkin JS, Nijpels G *et al.* Von Willebrand factor, C-reactive protein, and 5-year mortality in diabetic and nondiabetic subjects. The Hoorn Study. *Arterioscler Thromb Vasc Biol* 1999; 19: 3071–8.
- 18 Gram J, Bladbjerg EM, Møller L, Sjol A, Jespersen J. Tissue-type plasminogen activator and C-reactive protein in acute coronary heart disease. A nested case-control study. *J Intern Med* 2000; 247: 205–12.
- 19 Koenig W, Sund M, Fröhlich M, Fischer H, Löwel H, Döring A *et al.* C-reactive protein, a sensitive marker of inflammation, predicts future risk of coronary heart disease in initially healthy middle-aged men. Results from the MONICA (Monitoring Trends and Determinants in Cardiovascular Disease) Augsburg Cohort Study, 1984–92. *Circulation* 1999; 99: 237–42.
- 20 Patel P, Mendall MA, Carrington D, Strachan DP, Leatham E, Molineaux N *et al.* Association of *Helicobacter pylori* and *Chlamydia pneumoniae* infections with coronary heart disease and cardiovascular risk factors. *Br Med J* 1995; 311: 711–4.
- 21 Mendall MA, Patel P, Ballam L, Strachan D, Northfield TC. C reactive protein and its relation to cardiovascular risk factors: a population based cross sectional study. *Br Med J* 1996; 312: 1061–5.
- 22 Ridker PM, Kudsins RB, Stampfer MJ, Poulin S, Hennekens CH. Prospective study of *Chlamydia pneumoniae* IgG seropositivity and risks of future myocardial infarction. *Circulation* 1999; 99: 1161–4.
- 23 Parente F, Imbesi V, Cucino C, Maconi G, Russo U, Duca PG, Bianchi Porro G. *Helicobacter pylori* CagA seropositivity does not influence inflammatory parameters, lipid concentrations and haemostatic factors in healthy individuals. *J Intern Med* 2000; 247: 213–7.
- 24 Lagrand WK, Visser CA, Hermens WT, Niessen HWM, Verheugt FWA, Wolbink G, Hack E. C-reactive protein as a cardiovascular risk factor. More than an epiphenomenon? *Circulation* 1999; 100: 96–102.
- 25 Tracy RP, Psaty BM, Macy E, Bovill EG, Cushman M, Cornell ES, Kuller LH. Lifetime smoking exposure affects the association of C-reactive protein with cardiovascular disease risk factors and subclinical disease in healthy elderly subjects. *Arterioscler Thromb Vasc Biol* 1997; 17: 2167–76.
- 26 Danesh J, Muir J, Wong Y, Ward M, Gallimore JR, Pepys MB. Risk factors for coronary heart disease and acute-phase proteins. *Eur Heart J* 1999; 20: 954–9.
- 27 Yudkin JS, Stehouwer CD, Emeis JJ, Coppock SW. C-reactive protein in healthy subjects: associations with obesity, insulin resistance, and endothelial dysfunction: a potential role for cytokines originating from adipose tissue? *Arterioscler Thromb Vasc Biol* 1999; 19: 972–8.
- 28 Ridker PM, Buring J, Shih J, Matias M, Hennekens CH. Prospective study of C-reactive protein and the risk of future cardiovascular events among apparently healthy women. *Circulation* 1998; 98: 731–3.
- 29 Ridker PM, Hennekens CH, Buring JE, Rifai N. C-reactive protein and other markers of inflammation in the prediction of cardiovascular disease in women. *N Engl J Med* 2000; 342: 836–43.
- 30 Pietilä KO, Harmoinen AP, Jokiniitty J, Pasternack AI. Serum C-reactive protein concentration in acute myocardial infarction and its relationship to mortality during 24 months of follow-up in patients under thrombolytic treatment. *Eur Heart J* 1996; 17: 1345–9.

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