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C-reactive protein: associations with haematological variables, cardiovascular risk factors and prevalent cardiovascular disease

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Summary. C-reactive protein (CRP) has been proposed as a risk factor for cardiovascular disease; however, this association is confounded by mutual relationships with both classical and haematological cardiovascular risk factors. We, therefore, measured CRP with a high-sensitivity assay in stored plasma samples from 414 men and 515 women in the north Glasgow MONICA (MONItoring trends in CArdiovascular diseases) survey, to study its correlation with haematological variables, classical risk factors and prevalent cardiovascular disease. CRP correlated with age, oral contraceptive use, menopause and most classical cardiovascular risk factors (except blood pressure). CRP also correlated with plasma levels of the pro-inflammatory cytokine interleukin 6, and haematocrit, viscosity, red cell aggregation, white cell count, and coagulation factors [fibrinogen, factor (F) VII in women, FVIII, FIX] and inhibitors (antithrombin and protein C in women; protein S) but not coagulation activation markers. CRP was significantly associated with prevalent cardiovascular disease in both men ($P = 0{\cdot}03$) and women ($P = 0{\cdot}009$), however, the association became non-significant after adjustment for firstly classical risk factors, then fibrinogen. We conclude that correlations with classical and haematological risk factors account for a substantial component of the association of CRP with prevalent cardiovascular disease, but there is evidence of a residual, independent effect among women.

Keywords: C-reactive protein, thrombosis, cardiovascular disease, fibrinogen, inflammation.

There is increasing interest in the plasma or serum level of C-reactive protein (CRP), a commonly assayed marker of the reactant plasma protein component of the inflammatory response, as a predictor of cardiovascular disease (CVD), including coronary heart disease (CHD) (Danesh *et al,* 2000a), stroke (Ford & Giles, 2000; Gussekloo *et al,* 2000), peripheral arterial disease (Ridker *et al,* 1998) and venous thromboembolism (Lowe *et al,* 2000). While it has been suggested that CRP is an 'independent' risk factor for CHD and may play a causal role in CHD (Lagrand *et al,* 1999), the association of CRP with CVD may partly reflect mutual associations with established CVD risk factors (Danesh *et al,* 2000a). CRP is also associated with haematological risk predictors of CVD, including fibrinogen, plasma viscosity and white cell count, which (like CRP) are associated with acute-phase reactions mediated by cytokines such as interleukin 6 (IL-6) (Woodward *et al,* 1999; Danesh *et al,* 2000b; Mendall *et al,* 2000; Lowe *et al,* 2001).

We, therefore, assayed plasma CRP levels using a high-sensitivity automated immunonephelometric assay (Lowe *et al,* 2001), and related them to established CVD risk factors, haematological CVD risk factors, plasma IL-6 and prevalent CVD in a random UK population sample: the third North Glasgow MONICA (MONItoring trends in CArdiovascular diseases) survey (Lowe *et al,* 1997, 1999; Woodward *et al,* 1997, 1999).

SUBJECTS AND METHODS

Between January and August 1992, 1958 men and women, aged 25–74 years, were randomly sampled from the area of Glasgow which lies north of the River Clyde, as the third in a series of samples from this population contributing to the international MONICA Project (World Health Organization Principal Investigators, 1988). Subjects were

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sent, by post, a questionnaire to bring with them for checking at a screening clinic. Included in this questionnaire were the Rose chest pain and Edinburgh claudication questionnaires, and questions on socio-demographic status, past medical history, smoking and alcohol consumption, and female contraceptive and hormone replacement therapy use, menopause and pregnancy. At the clinic, height, weight, blood pressure, a 12-lead electrocardiogram and carbon monoxide (CO) in expired air were recorded, and a non-fasting blood sample was taken by trained nurses, centrifuged, and plasma and serum aliquots stored at −70°C. Clinic sessions took place between 09.00 hours and 16.00 hours (Lowe *et al*, 1997; Woodward *et al*, 1997).

From the blood samples, total and high-density lipoprotein (HDL) cholesterol, triglycerides, thiocyanate and cotinine were measured in serum, and vitamin C was measured in plasma (Woodward *et al*, 1997). Details of statistical sampling procedures (Crombie *et al*, 1989), assays of lipids (Smith *et al*, 1989), objective measures of tobacco smoke inhalation [carbon monoxide in expired air (CO), thiocyanate (SCN) and cotinine] (Woodward *et al*, 1991), and vitamin C levels (Vuilleumier & Keck, 1989) have been reported previously. Haematological variables measured included coagulation factors, inhibitors and markers: fibrinogen, factor (F)VII, FVIII, FIX, antithrombin, protein C, protein S, prothrombin fragment 1 + 2 (*F*1 + 2), and thrombin–antithrombin (TAT) complexes (Lowe *et al*, 1997); whole blood viscosity, haematocrit, plasma viscosity, relative blood viscosity, red cell aggregation, white cell count and IL-6 (Woodward *et al*, 1999); and activated protein C (APC) ratio and activated partial thromboplastin time (APTT) (Lowe *et al*, 1999). CRP was measured in residual plasma samples using a high-sensitivity immunonephelometric assay (Dade Behring, Marburg, Germany; Lowe *et al,* 2001).

Statistical methods. Subjects were classified as having prevalent CVD if: they self-reported a prior doctor diagnosis of angina, myocardial infarction or stroke; they reported the correct sequence of answers to either the Rose or Edinburgh claudication questionnaires; or they exhibited Q/QS or ST or T wave changes on their electrocardiogram, as previously described (Woodward *et al*, 1997).

As the distribution of CRP was highly skewed, it was summarized using percentiles: the three quartiles and the 5th–95th percentile range. For the same reason, Spearman's rank correlation coefficients were used to summarize associations. A log transformation was used to improve the approximation of a normal probability distribution before any statistical tests were carried out or confidence limits calculated.

CRP was compared with thrombotic variables, commonly accepted cardiovascular risk factors (including smoking and drinking) and social class. Cigarette status was classified according to self-report as never/ex/current, and CO, SCN and cotinine were all used as objective biochemical measures of smoking to assess current smoking dose. Alcohol was recorded as consumption in the past, and in the week prior to completing the questionnaire. The data were categorized into never/zero (no consumption in the past week)/low/medium/high, where the class limits for the last three groups are the sex-specific tertiles of last week's consumption. Social class was classified as manual/non-manual according to occupation (Office of Population Censuses and Surveys, 1990), with married women coded according to their husband's occupation.

Odds ratios (OR) for prevalent CVD, by equal quarters of CRP, were estimated from logistic regression models. Tests for log linearity were carried out using the rank of each quarter as a continuous measure in the logistic regression model. Correlations and OR were adjusted for age, as age is a fundamental determinant of most of the variables considered. OR for CRP were also calculated after further adjustment for a range of cardiovascular risk factors that might be considered potential confounders.

RESULTS

CRP was measured in 414 men and 550 women, this being 49% of the entire study population. There was insufficient remaining plasma to measure CRP in the remaining 51%.

Table I shows CRP levels, in men and women, by 10-year age groups. CRP rose with age ($P < 0{\cdot}0001$) in each sex group, but was not significantly different between the sexes ($P = 0{\cdot}47$). Note that the lower limit of 0·18 mg/l in many age/sex groups was the lowest level that the assay could measure. Current oral contraceptive use was significantly ($P = 0{\cdot}02$) associated with a higher level of CRP in non-pregnant, premenopausal women aged 25–34 years. Median (fifth percentile, first quartile, third quartile, 95%

Table I. Age and sex-specific distributions for CRP (mg/l).

		Age (years)				
	n	25–34	35–44	45–54	55–64	65–74
Men	414	0·47 (0·19, 1·08) 0·18–2·53	0·86 (0·33, 1·71) 0·18–8·73	1·12 (0·51, 1·86) 0·19–7·28	2·13 (0·91, 4·40) 0·30–10·00	1·42 (0·70, 3·04) 0·34–8·93
Women	550	0·68 (0·26, 2·10) 0·18–6·85	0·67 (0·34, 1·42) 0·18–6·16	1·08 (0·48, 2·18) 0·18–6·63	1·15 (0·65, 2·38) 0·18–9·47	1·46 (0·70, 4·45) 0·19–12·90

Summary statistics shown are median (first, third quartile) and 5th percentile to 95th percentile.

percentile) values were 1·11 (0·18, 0·41, 3·65, 7·05) for those who used oral contraceptives ($n = 36$) and 0·46 (0·18, 0·26, 1·47, 3·81) for those who did not ($n = 53$). Among the non-pregnant 45–54-year-old women not taking hormone replacement therapy, postmenopausal women had significantly ($P = 0·05$) higher values of CRP than premenopausal women. Medians (and values as above) were 1·32 (0·18, 0·62, 2·44, 7·27) for postmenopausal women ($n = 45$) and 0·63 (0·18, 0·29, 1·23, 2·83) for premenopausal women ($n = 42$). Among all non-pregnant women aged 45–54 years, those taking hormone replacement therapy ($n = 26$) had higher CRP levels than other postmenopausal women. This difference was not significantly different ($P = 0·55$), but the lack of significance could be as a result of the small numbers involved: the median (and values as above) CRP for hormone replacement therapy users was 2·15 (0·25, 0·71, 2·93, 8·97).

CRP was significantly related to most of the haematological variables assayed, as well as IL-6 (Table II). Even taking an extreme significance level (to protect against multiple significance testing) of 0·1%, CRP was significantly linearly associated with: fibrinogen, FIX, protein S, plasma viscosity and white cell count in both sexes; FVIII and IL-6 in men; and FVII, antithrombin, protein C, corrected blood viscosity, red cell aggregation and whole blood viscosity in women. Indeed, the only variables in Table II for which there was definitely no indication ($P > 0·05$) of a linear association with CRP were *F*1 + 2 (both assays), TAT and relative blood viscosity. All the relationships with CRP were in the positive direction except for APTT (men) and APC ratio (women). In most cases, the associations with CRP were similar in each sex group: exceptions were FVII, antithrombin and protein C, which were much stronger in women.

Table III shows relationships between CRP and continuous cardiovascular risk factors. Taking the 0·1% level of significance once more, CRP was significantly positively monotonically associated with: body mass index [weight/(height squared)] in both sexes; serum thiocyanate and cotinine in men; and serum total cholesterol and triglycerides in women. It was significantly negatively associated with serum HDL cholesterol in women. As in Table II, it is easier to list the variables for which there is definitely no evidence of association: here only blood pressure showed no such evidence ($P > 0·05$). The apparent sex difference in the association of CRP with total cholesterol (only of importance in women) is of note.

Categorical risk factors are the subject of Table IV. In agreement with the results for CO, SCN and cotinine in Table III, current smoking appeared to elevate CRP. However, there was no evidence that ex-smokers had different CRP levels to those who had never smoked, nor of any effects of alcohol on CRP. Women of relatively high social class had a significantly ($P = 0·0008$) higher CRP than other women, but social class appeared to have no such role for men ($P = 0·60$).

Of the men, 123 (30%) had prevalent CVD; of the women, 174 (32%) had prevalent CVD. Of those with CVD,

Table II. Age-adjusted Spearman's rank correlations between CRP and coagulation factor activities, inhibitor activities, activation markers and rheological variables.

	Men		Women	
	r	*P*-value*	*r*	*P*-value*
Fibrinogen	0·36	0·0001	0·39	0·0001
FVII	0·07	0·19	0·25	0·0001
FVIII	0·17	0·0005	0·12	0·005
FIX	0·23	0·0001	0·40	0·0001
Antithrombin	−0·006	0·91	0·19	0·0001
Protein C	0·01	0·81	0·14	0·001
Protein S	0·19	0·0004	0·18	0·0002
*F*1 + 2 (London)	−0·02	0·76	0·07	0·29
*F*1 + 2	−0·03	0·59	0·03	0·52
TAT	0·08	0·14	−0·05	0·28
APTT	−0·13	0·04	−0·06	0·29
APC ratio	0·03	0·61	−0·11	0·04
Whole blood viscosity	0·17	0·002	0·22	0·0001
Haematocrit	0·13	0·02	0·11	0·02
Corrected blood viscosity	0·16	0·005	0·22	0·0001
Plasma viscosity	0·38	0·0001	0·28	0·0001
Relative blood viscosity	−0·007	0·91	0·04	0·43
Red cell aggregation	0·17	0·003	0·28	0·0001
White cell count	0·30	0·0001	0·22	0·0001
IL-6	0·28	0·001	0·22	0·003

*P-value of 0·0001 means $P \leq 0·0001$.

Table III. Age-adjusted Spearman's rank correlations between CRP and cardiovascular risk factors that are continuous variables.

	Men		Women	
	r	*P*-value*	*r*	*P*-value*
Total cholesterol	0·06	0·20	0·17	0·0001
HDL cholesterol	−0·14	0·007	−0·21	0·0001
Triglycerides	0·11	0·02	0·34	0·0001
Diastolic blood pressure	0·07	0·16	0·07	0·12
Systolic blood pressure	0·03	0·57	0·05	0·21
Body mass index	0·19	0·0001	0·31	0·0001
Plasma vitamin C	−0·11	0·03	0·14	0·002
Carbon monoxide	0·11	0·03	0·10	0·02
Thiocyanate	0·17	0·0007	0·12	0·004
Cotinine	0·16	0·001	0·12	0·005

*P-value of 0·0001 means $P \leq 0{\cdot}0001$.

Table IV. Age-adjusted mean CRP (mg/l) by drinking habit, smoking habit and social class.

	Men		Women	
	Mean (95% CI)	*P*-value	Mean (95% CI)	*P*-value
Alcohol intake		0·56		0·46
Never	0·86 (0·54–1·32)		0·88 (0·66–1·18)	
Zero*	1·25 (0·98–1·61)		1·18 (0·98–1·41)	
Low	1·07 (0·86–1·35)		1·03 (0·80–1·33)	
Medium	1·01 (0·81–1·26)		0·96 (0·76–1·22)	
High	1·03 (0·84–1·26)		1·09 (0·86–1·39)	
Cigarette smoker				
Never	0·93 (0·73–1·19)	0·04	0·86 (0·73–1·02)	0·003
Ex	1·02 (0·83–1·25)		1·13 (0·91–1·41)	
Current	1·26 (1·08–1·46)	0·57	1·24 (1·05–1·45)	0·05
Social class		0·60		0·0008
Non-manual	1·17 (0·93–1·48)		0·85 (0·72–1·00)	
Manual	1·09 (0·97–1·24)		1·22 (1·07–1·39)	

*Zero in past week, but currently a drinker.
95% CI, 95% confidence interval.

the vast majority (93%) had CHD; the remainder had cerebrovascular or peripheral vascular disease. CRP was significantly linearly related to prevalent CVD, such that the odds of having the disease generally increased ($P < 0{\cdot}05$) with increasing CRP across its quarters (Table V), for both men and women, after adjustment for age. After further adjustment for major cardiovascular risk factors, the OR decreased appreciably. The trend was then no longer statistically significant, although there was still a clear indication of a rise in odds with increasing CRP (Table V). Even after the multiple adjustment, women in the highest quarter (2·38 mg/l or greater) had significantly higher odds of prevalent CVD than those in the lowest quarter (below 0·41 mg/l), the estimated OR being 1·87. Further adjustment for fibrinogen abolished any trend for association of CRP with CVD in men, but had no effect on this association in women (Table V).

DISCUSSION

While there is current interest in the potential role of CRP as a predictor of CVD, there is controversy as to its direct role. A causal role for CRP has been postulated (Lagrand *et al*, 1999). While CRP appears to be an 'independent' risk factor for CHD in meta-analyses of prospective studies, this association is substantially reduced on adjustment for established CHD risk factors, which correlate with CRP levels (Danesh *et al*, 1999). CRP is also associated with several acute-phase reactant haematological CHD risk factors, including fibrinogen, white cell count and plasma

Table V. OR for prevalent CVD by quarters of CRP (first quarter = 1), including a test for linear trend in the log OR.

Quarter	No. (%) of subjects with CHD	Adjusted for age			Multiple adjusted*			Fully adjusted†		
		OR	(95% CI)	*P*-value	OR	(95% CI)	*P*-value	OR	(95% CI)	*P*-value
Men										
1	20 (19·6%)	1		0·03	1		0·12	1		0·44
2	26 (24·8%)	1·00	(0·50–1·99)		0·89	(0·42–1·87)		0·76	(0·33–1·66)	
3	33 (32·0%)	1·31	(0·67–2·58)		1·21	(0·59–2·49)		1·02	(0·47–2·22)	
4	44 (42·3%)	1·88	(0·97–3·64)		1·56	(0·77–3·15)		1·16	(0·53–2·54)	
Women										
1	28 (20·7%)	1		0·009	1		0·07	1		0·09
2	39 (28·1%)	1·39	(0·79–2·44)		1·38	(0·74–2·60)		1·12	(0·56–2·27)	
3	49 (35·5%)	1·86	(1·07–3·22)		1·34	(0·72–2·51)		1·27	(0·64–2·52)	
4	58 (42·0%)	2·39	(1·38–4·13		1·87	(1·00–3·49)		1·87	(0·90–3·88)	

*Adjusted for age, total cholesterol, triglycerides, diastolic blood pressure, plasma vitamin C, smoking status (never/ex/current) and cotinine (plus menopause/HRT status and contraceptive pill status for women).
†Adjusted as above, plus fibrinogen.
OR, odds ratio; 95% CI, 95% confidence interval.

viscosity (Danesh *et al,* 2000a,b; Mendall *et al,* 2000). In the Caerphilly Prospective Heart Disease Study in men, Mendall *et al* (2000) observed that the association of CRP with incident CHD was abolished after adjustment for established CHD risk factors and fibrinogen.

There are few published studies on the associations of CRP with established cardiovascular risk factors in healthy persons (Danesh *et al*, 1999; Hak *et al*, 1999; Yudkin *et al*, 1999; Mendall *et al,* 2000). Only one of these studies also included haematological predictors of CHD (Mendall *et al,* 2000), which were limited to fibrinogen, white cell and platelet counts, and plasma viscosity. Also, this study was restricted to men. In the third north Glasgow MONICA survey, which had approximately equal numbers of men and women, we have performed an extensive profile of established and haematological cardiovascular risk factors (including coagulation times, factors, inhibitors and activation markers) rheological variables, white cell count and the pro-inflammatory cytokine IL-6 (Lowe *et al*, 1997, 1999; Woodward *et al*, 1997, 1999). This has enabled us to perform a detailed analysis of the relationships of CRP with all these risk factors, as well as to prevalent CVD.

We confirmed a recent report of an increase in CRP with age (Hutchison *et al,* 2000). While we observed no significant difference in CRP levels between men and women, we confirmed previous reports that current usage of oral contraceptives (Fröhlich *et al*, 1999) or of oral hormone replacement therapy (Cushman *et al*, 1999; Ridker *et al*, 1999; Lowe *et al,* 2000) was associated with elevated CRP levels. The distribution of CRP in Glasgow is similar to that in representative populations of Germany and France (Imhof *et al*, 2003).

CRP levels correlated significantly with levels of the pro-inflammatory cytokine IL-6, in accordance with the report of Yudkin *et al* (1999). CRP levels also correlated significantly with other haematological measures of the acute-phase response, including fibrinogen, white cell count and plasma viscosity. These findings are similar to those of Mendall *et al* (2000) in men, and confirm similar associations in women. Furthermore, we observed significant correlations of CRP with other rheological measures (blood viscosity, haematocrit, red cell aggregation) and coagulation factors (factors VII, VIII and IX, especially in women) that are associated with cardiovascular risk. However, we observed no association of CRP with coagulation activation markers, possibly because CRP was also associated with coagulation inhibitors, especially in women (Table II).

We confirmed that CRP correlated with most established cardiovascular risk factors, except blood pressure (Tables III and IV). These findings are generally consistent with those of other recent reports (Danesh *et al*, 1999; Hak *et al*, 1999; Yudkin *et al*, 1999; Mendall *et al,* 2000). Two of these reports highlighted the association of CRP with measures of insulin resistance, including tissue plasminogen activator antigen (Hak *et al*, 1999; Yudkin *et al*, 1999). We observed no association of CRP with alcohol consumption, and an inverse association with social class only in women.

We observed an association of CRP with prevalent CVD on univariate analysis in both men and women, which was

reduced to non-statistical significance by adjustment for established cardiovascular risk factors (Table V). Further adjustment for fibrinogen abolished any trend for association of CRP with CVD in men, as observed by Mendall *et al* (2000) in the prospective Caerphilly study, but had no effect on this association in women. The reason for this sex difference is unclear and requires gender comparisons in large prospective studies.

In conclusion, we have confirmed: (a) that CRP is significantly associated with most established, and haematological, cardiovascular risk factors for CVD in a large random sample of the general population; and (b) that the association of CRP with prevalent CVD in this sample is greatly reduced by adjustment for these risk factors. These findings are consistent with those of Mendall *et al* (2000), and with their suggestion that CRP may not play a role in the pathogenesis of CHD, other than through its association with haematological variables such as fibrinogen. To date, there are few data to support the hypothesis that reduction in circulating CRP levels reduces the risk of CVD. In contrast, there is increasing evidence that reducing plasma fibrinogen (e.g. by ancrod; Lowe, 2001) or plasma viscosity (e.g. by pravastatin; Lowe *et al,* 2000) reduces cardiovascular risk.

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