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C-reactive protein: relation to total mortality, cardiovascular mortality and cardiovascular risk factors in men

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Background There is much interest in reported associations between serum C-reactive protein and incident ischaemic heart disease. It is uncertain what this association represents. We aimed to assess the effect of confounding from a number of different sources in the Caerphilly Prospective Heart Disease Study and in particular whether the low grade inflammation indicated by C-reactive protein may be the mechanism whereby non-circulating risk factors may influence pathogenesis of ischaemic heart disease.

Methods Plasma specimens collected during 1979–83 from 1395 men with sufficient sample remaining were assayed for serum C-reactive protein by ELISA. Subsequent mortality and incident ischaemic heart disease events were ascertained from death certificates, hospital records and electrocardiographic changes at 5-yearly follow-up examinations.

Results There was a positive association between C-reactive protein and incident ischaemic heart disease ($P<0{\cdot}005$) mainly with fatal disease ($P<0{\cdot}002$). There was also a positive association with all-cause mortality ($P<0{\cdot}0001$). C-reactive protein was significantly associated with a number of non-circulating risk factors including body mass index ($P<0{\cdot}0001$), smoking ($P<0{\cdot}0001$), low forced expiratory volume in 1 s ($P<0{\cdot}0001$), height ($P=0{\cdot}025$), low childhood social class ($P=0{\cdot}014$) and age ($P=0{\cdot}036$). C-reactive protein was also associated positively with circulating risk factors including viscosity, leukocyte count, fibrinogen (all $P<0{\cdot}0001$) and insulin ($P=0{\cdot}0058$). After adjustment for non-circulating risk factors the association with all-incident ischaemic heart disease and ischaemic heart disease death became non-significant, but the association with all-cause mortality remained ($P=0{\cdot}033$). Further adjustment for fibrinogen however removed any hint of an increasing trend in odds for all three outcomes.

Conclusion C-reactive protein levels are raised in association with a variety of established cardiovascular risk factors. Neither C-reactive protein nor the systemic inflammation it represents appears to play a direct role in the development of ischaemic heart disease.
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Key Words: C-reactive protein, inflammation, ischaemic heart disease, all-cause mortality.

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Introduction

There has recently been much interest in the relationship between systemic inflammation and cardiovascular events[1,2]. C-reactive protein is the major human acute phase protein and is a sensitive indicator of inflammation occurring in the body. Its synthesis by the liver is regulated to a large extent by the pro-inflammatory cytokine IL-6 and also by TNFα[3]. Strong associations have been shown in prospective studies between serum C-reactive protein and cardiovascular events in subjects with stable and unstable angina[4–6] and in asymptomatic subjects[7–11].

Elevated serum C-reactive protein is associated with many non-circulating cardiovascular risk factors including smoking, obesity, low social class and other types of chronic infection[12]. Elevated serum C-reactive protein levels are also associated with many circulating risk factors including elevated serum fibrinogen and clotting

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factors, insulin resistance, elevated triglycerides and blood glucose, and depressed high-density lipoprotein cholesterol[12].

It is not clear however what these associations represent. There are three possibilities which are not mutually exclusive. First, elevations in C-reactive protein may be a non-specific response to any environmental stimulus, and may not be related directly or indirectly with the pathogenesis of ischaemic heart disease. Second, elevated C-reactive protein may be a response to inflammation which is primarily occurring in the vessel wall at the site of the atherosclerotic lesion. This inflammation may be producing an elevation in conventional cardiovascular risk factors as an epiphenomenon, with or without a primary role in pathogenesis. Third, the inflammatory mechanisms of which C-reactive protein is an indicator, may be acting at a distance to the blood vessel wall to produce elevations in conventional cardiovascular risk factors or in other inflammatory mediators, such as TNFα, which play a role in pathogenesis. C-reactive protein may thus be an indicator of intermediate mechanisms linking non-circulating risk factors to the causation of ischaemic heart disease.

If the first possibility is important, then C-reactive protein would not be expected to be a specific marker of coronary death, and its association with coronary disease should be greatly attenuated by controlling for non-circulating risk factors. If the second possibility is important, then the association of C-reactive protein with incident ischaemic heart disease would be expected to be greatly attenuated by controlling for prevalent ischaemic heart disease at baseline. If the third possibility is important, then the association of non-circulating risk factors with ischaemic heart disease would be expected to attenuate by controlling for C-reactive protein. The extent to which inflammation in the second and third possibilities is acting through conventional biological cardiovascular risk factors or through novel inflammatory mediators can be assessed by adjusting their association with incident ischaemic heart disease for C-reactive protein or vice versa.

We aimed to explore these possibilities in a prospective study of middle-aged men in whom a wide range of conventional and novel cardiovascular risk factors have been related to incident ischaemic heart disease.

Methods

The Caerphilly Prospective Heart Disease Study[13] recruited 2512 men aged 45–59 years in the Caerphilly area of South Wales during 1979-83. Symptoms and electrocardiographic (ECG) abnormalities suggestive of past or current ischaemic heart disease were ascertained and a range of cardiovascular risk factors were measured, including smoking history, standing height, body weight, blood pressure, forced expiratory volume in 1 s (FEV1), total cholesterol, high-density lipoprotein and low-density lipoprotein cholesterol[14], fibrinogen, plasma viscosity and leucocyte count[15]. Socio-economic status was classified according to the Registrar General's social class of current occupation and father's occupation during childhood[16]. Subjects were followed up at 5-year intervals. Follow-up to phase IV was completed during 1994–97, an average of 13·7 years after entry.

Deaths were classified according to the ninth revision of the International Classification of Diseases (ICD9) as due to ischaemic heart disease (ICD9 410–414); circulatory (ICD9 390–459) or non-circulatory causes. Incident ischaemic heart disease was ascertained from death certificates, review of hospital notes and ECG changes using the same conventions as in previous prospective analyses of this cohort[13,17]. Three groups were thus included as incident cases of ischaemic heart disease: fatal ischaemic heart disease (death coded as ICD9 410–414); clinical myocardial infarction (hospitalized episodes meeting WHO criteria of combinations of serial ECG changes, cardiac enzyme abnormalities and acute symptoms); and development of new Q or QS waves (Minnesota codes 1-1-1 through 1-2-5, or 1-2-7) on follow-up ECG in the absence of Q or QS waves on the ECG recorded at entry.

Frozen plasma specimens banked at the entry (phase I) had been stored at -20 °C since collection in 1979–83, with one thaw cycle. About a quarter of the specimens were missing due to depletion of material during previous sero-epidemiological studies involving about one-quarter of the cohort. Resources available for the present study were sufficient for assay of 1395 consecutively retrieved specimens.

C-reactive protein was assayed as described earlier using an in-house ELISA method[11]. Each sample of stored sera was analysed for C-reactive protein on one of 30 different plates. The inter-assay coefficient of variation for the $2{\cdot}4\ \mathrm{mg}\,.\,l^{-1}$ and $8{\cdot}7\ \mathrm{mg}\,.\,l^{-1}$ standard specimens included in most batches were 16% and 5% respectively. Intra-assay variation was 5%. Specimens with values of less than $1\ \mathrm{mg}\,.\,l^{-1}$ and more than $10\ \mathrm{mg}\,.\,l^{-1}$ were re-assayed at the appropriate dilution to yield a value between $1\ \mathrm{mg}\,.\,l^{-1}$ and $10\ \mathrm{mg}\,.\,l^{-1}$, and the assay result then corrected for dilution. The proportion of men with incident disease varied widely from plate to plate and there was some evidence of laboratory drift. Adjustment for plate was made throughout the statistical analysis.

Statistical methods

Potential risk factors for incident ischaemic heart disease were divided into two groups for the purposes of analysis i.e. circulating and non-circulating variables. Non-circulating variables included social class, father's social class, height, body mass index, age, smoking history, alcohol consumption (yes/no) and mean forced expiratory volume in 1 s and were investigated as predictors of C-reactive protein using multiple regression techniques

Table 1 Odds ratios and 95% confidence intervals for incident ischaemic heart disease (both fatal and non-fatal) by quintiles of C-reactive protein

Quintiles of C-reactive protein*	All men				Men with prevalent disease				Men without prevalent disease			
	Yes	No	OR†	95% CI†	Yes	No	OR†	95% CI†	Yes	No	OR†	95% CI†
Lowest	26	253	1·00	base	8	39	1·00	base	18	214	1·00	base
2nd	42	239	1·70	0·96, 3·03	17	46	2·16	0·68, 6·89	25	193	1·46	0·72, 2·96
3rd	37	240	1·40	0·78, 2·51	15	54	1·26	0·42, 3·81	22	186	1·25	0·61, 2·56
4th	66	213	2·20	1·26, 3·84	28	48	2·66	0·90, 7·85	38	165	1·79	0·90, 3·54
Highest	78	201	2·11	1·23, 3·62	33	53	1·74	0·60, 4·99	45	148	1·85	0·97, 3·55
Test for trend‡			$P=0·0048$				$P=0·4414$				$P=0·0364$	

OR = odds ratio; CI = confidence interval.
*Quintiles: 0·05–0·82, 0·83–1·42, 1·43–2·33, 2·34–3·87, 3·88–27·06 mg . l^{-1}.
†Adjusted for plate; n = 1370.
‡Test for linear trend with logarithm C-reactive protein, having adjusted for plate using logistic regression.

in STATA[18]. Similarly C-reactive protein was investigated as a possible predictor of various circulating variables including total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, triglyceride, insulin, glucose, systolic blood pressure, fibrinogen, viscosity, platelets and white blood cell count.

C-reactive protein, total triglyceride, glucose and insulin had distributions with a marked positive skew and were logarithm-transformed throughout. Other circulating variables were only logarithm-transformed when modelled as dependent variables.

The associations between incident ischaemic heart disease, mortality and C-reactive protein were investigated using logistic regression in STATA[18]. By including additional variables in the logistic models, associations were adjusted for the confounding effects of selected coronary risk factors and ELISA plate. The significance of associations was assessed using the likelihood ratio test. The extent to which C-reactive protein might explain associations between other risk factors and incident ischaemic heart disease was investigated by comparing model coefficients before and after the inclusion of C-reactive protein.

Associations between fatal ischaemic heart disease, all-cause mortality and C-reactive protein were further investigated by fitting Cox regression models, in STATA[18]. These models allowed us to make additional adjustments for time of death and competing causes of death. C-reactive protein was analysed both as a categorical variable (quintiles) and as a continuous variable but all significance tests were based on the latter.

Results

C-reactive protein at baseline was measured on the stored sera of 1395 Caerphilly men; 56% (1395/2512) of the full cohort. Approximately 18% (249/1395) of this group experienced new incident events between phases I and IV, including 9% (129/1395) that died from ischaemic heart disease. Total mortality from all causes was approximately 20% (275/1395). The corresponding figures among men whose specimens were not analysed for C-reactive protein were 15% (162/1117), 8% (89/1117) and 20% (224/1117).

Before adjustment for other factors there was a significant and positive association between C-reactive protein and incident ischaemic heart disease ($P<0·005$). The odds ratio for the highest quintile of C-reactive protein versus the lowest was 2·11 (95% confidence interval 1·23 to 3·62). The association did not differ significantly between those with or without a previous history of ischaemia (test for statistical interaction: chi-squared = 0·80, df = 1, $P=0·37$) although evidence for an increasing trend with increasing level of C-reactive protein was stronger among the latter (Table 1). There was a strong positive association with fatal ischaemic heart disease ($P=0·0019$), but little evidence of an association with non-fatal disease ($P=0·65$). Among incident cases the association between C-reactive protein and ischaemic heart disease death failed to reach statistical significance (chi-squared = 3·1, df = 1, $P=0·08$).

There was a strong and positive association between C-reactive protein and all-cause mortality ($P<0·000l$) with an odds ratio of 2·32 (confidence interval 1·47 to 3·67) for the highest versus the lowest quintile (Table 2). C-reactive protein was significantly and positively associated with mortality from both circulatory disease ($P=0·0009$) and non-circulatory disease ($P=0·0067$) although the trend with the latter was less graded, being clearly defined only in the upper part of the C-reactive protein distribution.

Having adjusted for other non-circulating variables, C-reactive protein was positively and significantly associated with body mass index ($P<0·0001$), age ($P=0·036$), lower social class in childhood ($P=0·0140$), smoking ($P<0·000l$) and height ($P=0·025$) and negatively associated with mean forced expiratory volume in 1 s ($P<0·000l$) (Table 3). Also after adjustment for non-circulating variables, C-reactive protein was positively associated with viscosity ($P<0·000l$), leukocyte count ($P<0·000l$), platelet count ($P=0·030$), insulin ($P=0·0058$) and fibrinogen ($P<0·0001$) (Table 4).

Table 2 Odds ratios and 95% confidence intervals for deaths from all causes (both circulatory and non-circulatory) by quintiles of C-reactive protein

Quintiles of C-reactive protein*	Mortality											
	Total				Circulatory				Non-circulatory			
	Yes	No	OR†	95% CI†	Yes	No	OR†	95% CI†	Yes	No	OR†	95% CI†
Lowest	43	236	1·00	base	17	262	1·00	base	26	253	1·00	base
2nd	40	241	0·96	0·59, 1·57	22	259	1·33	0·66, 2·65	18	263	0·72	0·37, 1·39
3rd	43	234	1·12	0·69, 1·83	22	255	1·36	0·68, 2·71	21	256	0·94	0·50, 1·78
4th	66	213	1·97	1·23, 3·15	41	238	2·39	1·26, 4·54	25	254	1·42	0·76, 2·67
Highest	83	196	2·32	1·47, 3·67	50	229	2·35	1·26, 4·40	33	246	2·04	1·10, 3·77
Test for trend‡			$P<0·0001$				$P=0·0009$				$P=0·0067$	

OR = odds ratio; CI = confidence interval.
*Quintiles: 0·05–0·82, 0·83–1·42, 1·43–2·33, 2·34–3·87, 3·88–27·06 mg . l^{-1}.
†Adjusted for plate.
‡Test for linear trend with logarithm C-reactive protein, having adjusted for plate using logistic regression.

Table 3 Relative change in C-reactive protein associated with change in non-circulating variables

Explanatory variable	Relative change in C-reactive protein*	95% Confidence interval	*P* value
Age (per 5 years)	1·065	1·004, 1·129	0·0356
Body mass index (25th to 75th centile)	1·287	1·210, 1·369	<0·0001
Smoking history			
Ex-smoker (vs never)	1·060	0·909, 1·237	<0·0001
Cigar/pipe smoker (vs never)	1·228	1·010, 1·492	
1–14 cigarettes per day (vs never)	1·189	0·984, 1·437	
15–24 cigarettes per day (vs never)	1·517	1·271, 1·810	
⩾25 cigarettes per day (vs never)	1·434	1·184, 1·737	
Social class			
II (vs I)	0·828	0·635, 1·079	0·4536
IIInm (vs I)	0·833	0·629, 1·103	
IIIm (vs I)	0·932	0·724, 1·201	
IV (vs I)	0·950	0·710, 1·273	
V (vs I)	0·849	0·601, 1·199	
Missing (vs I)	1·174	0·766, 1·799	
Father's social class			
IIInm (vs I/II)	0·988	0·727, 1·343	0·0140
IIIm (vs I/II)	1·339	1·098, 1·634	
IV (vs I/II)	1·325	1·037, 1·692	
V (vs I/II)	1·243	0·898, 1·719	
Missing (vs I)	1·358	1·053, 1·751	
Height (25th to 75th centile)	1·085	1·010, 1·165	0·0248
Mean FEV1 (25th to 75th centile)	0·825	0·764, 0·890	<0·0001
Alcohol (any vs none)	0·994	0·815, 1·212	0·9534

*Adjusted for plate and all other non-circulating variables listed.

Odds ratios for C-reactive protein by incident ischaemic heart disease, fatal ischaemic heart disease and all-cause mortality decreased in magnitude (becoming closer to 1) after adjustment for non-circulating variables (Table 5). Only the association with all-cause mortality remained statistically significant ($P=0·033$). Additional adjustment for systolic blood pressure and total cholesterol lowered odds ratios only slightly but further adjustment for fibrinogen removed any hint of an increasing trend in odds with increasing level of C-reactive protein for all three outcomes. When the associations between C-reactive protein, all-cause mortality and ischaemic heart disease death were re-analysed using Cox regression, similar results were obtained (data not shown).

Further investigation using logistic regression models (data not shown) suggested that the association between C-reactive protein and incident ischaemic

Table 4 Relative change in circulating variables associated with an increase in C-reactive protein from the 25th to the 75th centile

Dependent variable	Relative change in dependent variable associated with an increase in C-reactive protein from the 25th to the 75th centile*	95% Confidence interval	*P* value
Systolic blood pressure	1·007	0·997, 1·016	0·1766
Total cholesterol	1·001	0·986, 1·016	0·9229
High-density lipoprotein cholesterol	0·983	0·962, 1·004	0·1127
Total triglyceride	1·011	0·971, 1·053	0·5916
Viscosity	1·024	1·020, 1·028	<0·0001
Platelets	1·022	1·002, 1·042	0·0302
Leukocytes	1·090	1·069, 1·111	<0·0001
Glucose	1·003	0·990, 1·016	0·6340
Insulin	1·083	1·024, 1·146	0·0058
Fibrinogen	1·116	1·100, 1·132	<0·0001
Low-density lipoprotein cholesterol	1·004	0·983, 1·026	0·7069

*Relative change in the dependent variable, adjusted for the effects of non-circulating variables and plate to plate variations in C-reactive protein, by multiple regression models.

Table 5 Odds ratios and 95% confidence intervals for incident ischaemic heart disease and mortality by quintiles of C-reactive protein, both before and after adjustment for non-circulating and circulating variables

Risk factors adjusted for	Quintiles of C-reactive protein	All incident ischaemic heart disease (n=1239)		Fatal ischaemic heart disease (n=1158)		Total mortality (n=1268)	
		Odds ratio	95% CI	Odds ratio	95% CI	Odds ratio	95% CI
Plate	2nd vs lowest	1·47	0·80, 2·71	1·01	0·44, 2·34	0·80	0·47, 1·35
	3rd vs lowest	1·32	0·71, 2·44	1·37	0·61, 3·07	1·13	0·68, 1·87
	4th vs lowest	1·86	1·03, 3·36	2·16	1·01, 4·61	1·89	1·16, 3·10
	Highest vs lowest	2·01	1·14, 3·56	2·04	0·98, 4·27	2·11	1·30, 3·43
	χ^2 test for trend	*P*=0·0148		*P*=0·0134		*P*=0·0001	
Plate, age, body mass index, height, FEV1, alcohol, smoking, current and father's social class	2nd vs lowest	1·28	0·68, 2·41	0·85	0·36, 2·04	0·72	0·41, 1·25
	3rd vs lowest	1·10	0·59, 2·07	1·12	0·48, 2·57	0·92	0·54, 1·58
	4th vs lowest	1·59	0·86, 2·95	1·70	0·77, 3·77	1·54	0·90, 2·61
	Highest vs lowest	1·53	0·83, 2·82	1·30	0·59, 2·86	1·43	0·84, 2·42
	χ^2 test for trend	*P*=0·1337		*P*=0·2208		*P*=0·0331	
Model 2 plus systolic blood pressure, total cholesterol and fibrinogen	2nd vs lowest	1·11	0·58, 2·10	0·72	0·29, 1·76	0·65	0·37, 1·15
	3rd vs lowest	0·92	0·48, 1·75	0·93	0·39, 2·19	0·84	0·49, 1·45
	4th vs lowest	1·14	0·60, 2·15	1·20	0·53, 2·75	1·27	0·74, 2·19
	Highest vs lowest	0·96	0·50, 1·86	0·79	0·34, 1·84	1·08	0·61, 1·91
	χ^2 test for trend	*P*=0·8308		*P*=0·8430		*P*=0·3393	

FEV1=forced expiratory volume in 1 s.

heart disease could be explained by the combined effects of three conventional risk factors: smoking, body mass index and fibrinogen. By contrast, adjustment for C-reactive protein had little effect on the association of smoking or body mass index with incident ischaemic heart disease and explained none of the association between incident ischaemic heart disease and fibrinogen (Table 6).

Discussion

We have been able to confirm previously reported associations between serum C-reactive protein and future cardiac events[4–11] and, for the first time, with all-cause mortality. We were also able to confirm previously reported associations with both non-circulating and circulating risk factors including age, smoking, father's low social class, obesity, elevated fibrinogen, platelets, plasma viscosity, white blood cell count, insulin resistance[11,19] and, for the first time, with reduced forced expiratory volume in 1 s.

C-reactive protein was associated with future cardiac events and, if anything, this was slightly stronger in subjects without evidence of ischaemic heart disease at baseline, suggesting that C-reactive protein is not merely an indicator of inflammation occurring within the atherosclerotic lesion. Furthermore, the association with

Table 6 Associations between incident ischaemic heart disease and potential risk factors before and after adjustment for logarithm of C-reactive protein

Risk factor	Unadjusted for log C-reactive protein		Adjusted for log C-reactive protein	
	OR†	95% CI	OR†	95% CI
Age (per 5 years)	1·19	0·97, 1·45	1·18	0·97, 1·44
Body mass index (75th vs 25th centile)	1·27	1·04, 1·55	1·23	1·01, 1·51
Height (75th vs 25th centile)	1·06	0·83, 1·35	1·04	0·82, 1·33
Mean FEV1 (75th vs 25th centile)	1·05	0·81, 1·35	1·08	0·83, 1·40
Current smoker (vs never smoked)	2·16	1·26, 3·70	2·07	1·20, 3·56
Ex-smoker (vs never smoked)	1·24	0·69, 2·21	1·22	0·68, 2·18
Manual workers (vs non-manual workers)	0·86	0·58, 1·28	0·86	0·58, 1·28
Father manual worker (vs father non-manual worker)	1·05	0·59, 1·84	1·00	0·56, 1·76
Alcohol (any vs none)	0·68	0·36, 1·31	0·68	0·36, 1·31
Systolic blood pressure (75th vs 25th centile)	1·46	1·17, 1·82	1·46	1·17, 1·82
Total cholesterol (75th vs 25th centile)	1·43	1·17, 1·74	1·42	1·17, 1·73
Fibrinogen (75th vs 25th centile)	1·66	1·34, 2·04	1·68	1·34, 2·11
Viscosity (75th vs 25th centile)	1·53	1·25, 1·88	1·52	1·22, 1·89
Platelets (75th vs 25th centile)	1·09	0·88, 1·36	1·08	0·87, 1·34
Leukocytes (75th vs 25th centile)	1·39	1·11, 1·75	1·36	1·08, 1·72
Total triglyceride* (75th vs 25th centile)	1·43	1·13, 1·80	1·43	1·13, 1·80
Glucose* (75th vs 25th centile)	1·18	1·03, 1·35	1·17	1·03, 1·34
Insulin* (75th vs 25th centile)	1·32	1·03, 1·70	1·30	1·01, 1·67

n=1239.
OR=odds ratio; FEV1=forced expiratory volume in 1 s.
*Not all 1239 men have data on total triglyceride, glucose and insulin. Correct totals are 1187, 1195 and 1042 respectively.
†Adjusted for plate and all/other non-circulating variables.

both circulatory and non-circulatory mortality suggests that the low grade inflammation, as indicated by serum C-reactive protein, is not specifically a predictor of coronary events.

The association of C-reactive protein with incident ischaemic heart disease was attenuated and became non-significant by controlling for non-circulating risk factors, particularly smoking and to a lesser extent obesity. Some earlier studies have not suggested any confounding of the association by smoking or body mass index[5,7]. Others have either shown some confounding by smoking that was insufficient to remove the effect of C-reactive protein, although control for smoking was not as rigorous as in this study[11], or have found the effect to be restricted to smokers[10], which in itself could be interpreted as confounding by smoking. Our failure to detect an independent effect may be due to a lack of statistical power. However, adjusting the effect of non-circulating risk factors for C-reactive protein did not diminish the magnitude of their associations with ischaemic heart disease, suggesting that these risk factors are acting through mechanisms other than low grade inflammation of which C-reactive protein is taken to be an indicator.

The associations of C-reactive protein with incident ischaemic heart disease and total mortality were completely abolished by controlling for fibrinogen. This power of fibrinogen to explain the association of C-reactive protein with incident ischaemic heart disease has been observed in some[20], but not other studies[7]. This inconsistency may be due to chance, or to differences in the precision of assays for both fibrinogen and C-reactive protein. Controlling the effect of fibrinogen for C-reactive protein did not diminish the relationship, suggesting that fibrinogen in this study population is the more specific and proximal risk factor of ischaemic heart disease.

It is possible that systemic inflammation may still be important in the pathogenesis of ischaemic heart disease, but that C-reactive protein is not the best measure. To investigate this further, a second acute phase marker (serum amyloid A) was measured in a subsample of the cohort: 180 men with incident ischaemic heart disease and 189 controls. The pattern of results was similar though less clear-cut than those seen for C-reactive protein in analyses of the main cohort, with significant associations among the controls for serum amyloid A with fibrinogen, viscosity and leukocyte count (all $P<0·03$), but no independent relationship between serum amyloid A and incident ischaemic heart disease after adjustment for these and other cardiovascular risk factors ($P=0·75$).

Rigorous control of confounding revealed that C-reactive protein was not an independent risk factor for incident chronic heart disease, in contrast to earlier studies which, with one exception[7] have not controlled for confounding factors to the same degree. Our study suggests that the explanation for the association of C-reactive protein with ischaemic heart disease is that C-reactive protein levels are raised non-specifically by a variety of exposures that are themselves implicated in the pathogenesis of ischaemic heart disease. We found no support for the notion that C-reactive protein itself, or the systemic inflammation it represents, plays a role in the pathogenesis of ischaemic heart disease, other than through association with circulating fibrinogen.

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