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C-reactive protein concentration and risk of coronary heart disease, stroke, and mortality: an individual participant meta-analysis

The Emerging Risk Factors Collaboration*

Summary
Background Associations of C-reactive protein (CRP) concentration with risk of major diseases can best be assessed by long-term prospective follow-up of large numbers of people. We assessed the associations of CRP concentration with risk of vascular and non-vascular outcomes under different circumstances.

Methods We meta-analysed individual records of 160 309 people without a history of vascular disease (ie, 1·31 million person-years at risk, 27 769 fatal or non-fatal disease outcomes) from 54 long-term prospective studies. Within-study regression analyses were adjusted for within-person variation in risk factor levels.

Results Log, CRP concentration was linearly associated with several conventional risk factors and inflammatory markers, and nearly log-linearly with the risk of ischaemic vascular disease and non-vascular mortality. Risk ratios (RRs) for coronary heart disease per 1-SD higher log e CRP concentration (three-fold higher) were 1·63 (95% CI 1·51–1·76) when initially adjusted for age and sex only, and 1·37 (1·27–1·48) when adjusted further for conventional risk factors; 1·44 (1·32–1·57) and 1·27 (1·15–1·40) for ischaemic stroke; 1·71 (1·53–1·91) and 1·55 (1·37–1·76) for vascular mortality; and 1·55 (1·41–1·69) and 1·54 (1·40–1·68) for non-vascular mortality. RRs were largely unchanged after exclusion of smokers or initial follow-up. After further adjustment for fibrinogen, the corresponding RRs were 1·23 (1·07–1·42) for coronary heart disease; 1·32 (1·18–1·49) for ischaemic stroke; 1·34 (1·18–1·52) for vascular mortality; and 1·34 (1·20–1·50) for non-vascular mortality.

Interpretation CRP concentration has continuous associations with the risk of coronary heart disease, ischaemic stroke, vascular mortality, and death from several cancers and lung disease that are each of broadly similar size. The relevance of CRP to such a range of disorders is unclear. Associations with ischaemic vascular disease depend considerably on conventional risk factors and other markers of inflammation.

Introduction C-reactive protein (CRP), a plasma protein synthesised by the liver, is a sensitive and dynamic systemic marker of inflammation.1 Its concentration in the circulation can increase by up to 10 000-fold during acute responses to serious infection or major tissue damage.2 In the absence of such spikes, however, the year-to-year within person variations in CRP concentration are similar to those in total cholesterol concentration and systolic blood pressure.3 The stability of this protein during long-term frozen blood storage and availability of standardised assays have assisted studies of CRP.4,4 Aside from whether measurement of CRP is useful in assessment of vascular risk,5,6 studies are needed to help find out if CRP is a mediator of vascular disease.7,8 CRP binds to LDL9,10 and is present in atherosclerotic plaques,9 so it has been proposed that CRP may have a causal role in coronary heart disease. In a literature-based meta-analysis11 of 22 prospective studies, the relative risk for coronary heart disease was 1·6 (95% CI 1·5–1·7) in a comparison of people in the top third (mean 2·4 mg/L) and bottom third (1·0 mg/L) of the CRP distribution.

To help judge the likelihood of causality, information is needed about the extent to which disease associations with CRP concentrations are independent of conventional risk factors.7 Previous studies were not adequately powered to assess whether CRP concentration is associated with different stroke subtypes,12–17 and whether concentration is associated exclusively with vascular disease or also with non-vascular diseases.9 The shape of the dose-response association between CRP concentration and the risk of vascular and non-vascular diseases has not been well characterised. Furthermore, powerful analyses are needed to find out whether the strength of association of CRP concentration and risk of disease varies by age, sex, or other clinically relevant subgroups.18 We therefore assessed the independence, specificity, magnitude, and shape of associations of CRP concentration with vascular and non-vascular outcomes under different circumstances.

Methods Study design Details of study selection, and data collation and harmonisation in the Emerging Risk Factors Collaboration have been described previously.19 Investigators from 116 prospective studies of cardiovascular risk factors, with a total of 1·2 million participants, shared individual
records. In these studies, participants were not selected on the basis of having previously had cardiovascular disease; vascular morbidity and cause-specific mortality were recorded on the basis of clearly defined criteria; and accrued follow-up was more than 1 year. Analyses were restricted to participants without any known history of cardiovascular disease (ie, myocardial infarction, angina, or stroke defined according to study criteria). Information about CRP concentration, age, sex, and other conventional vascular risk factors was available in 54 studies, with a total of 160 309 participants with 27 769 first-ever non-fatal or fatal vascular and non-vascular disease outcomes (webappendix p 2 and p 15). Baseline information was not available for non-vascular diseases. Complete information was available for CRP concentration, age, sex, systolic blood pressure, smoking habits, history of diabetes mellitus (type 1 or 2, though usually not specified), body-mass index, and concentrations of triglycerides and total cholesterol in 109 742 participants from 37 studies. High-sensitivity CRP assays were used in 52 of 54 studies. The CRP standards used were identified in 43 studies (webappendix p 4). International Classification of Diseases codings (to at least three numbers) were used to register fatal diseases, which were ascertained from information provided on death certificates (webappendix p 6). Medical records, autopsy findings, and other supplementary sources were used to help classify deaths in 41 of 54 studies. Standard definitions of myocardial infarction based on Monitoring Trends and Determinants in Cardiovascular Disease (MONICA) or WHO criteria were reported in 49 studies. Diagnosis of stroke on the basis of typical clinical features and characteristic changes on brain imaging was reported in 40 studies, enabling attribution of stroke types (eg, cerebral ischaemia, cerebral haemorrhage, or subarachnoid haemorrhage).

The study was approved by an ethics review committee in Cambridgeshire, UK.

**Statistical analyses**

Details of the statistical methods have been previously provided. Normal distributions were obtained with natural logarithm (log_e) transformation of positively skewed variables, including CRP concentration. The pooled SD for baseline log_e CRP concentration was 1.11.

![Figure 1: Geometric mean C-reactive protein (CRP) concentration in men and women according to cohort and assay source (A) and within 5-year bands adjusted for cohort (B)](image-url)

Data from the third National Health and Nutrition Examination Survey (NHANESIII) and Population Study of Women in Göteborg (GOTOW) are not represented in the graph because they did not use high sensitivity CRP assays. NS=not stated. Error bars represent the 95% CIs.
which corresponds to a three-fold difference (ie, e^{1.11}) in mg/L on the original scale of CRP measurement. Sex-specific associations of CRP with various risk factors were assessed, using a linear mixed model adjusted for age.22 The primary outcome was coronary heart disease (ie, first-ever myocardial infarction or fatal coronary heart disease), with subsidiary analyses of stroke by subtype, death from vascular disease, and aggregate of non-vascular death (with subdivisions modelled on the approach of a previous study23). Only first non-fatal vascular outcomes or deaths recorded at age 40 years or older were included in the primary analysis (ie, deaths preceded by non-fatal coronary heart disease or stroke were not included in the analyses). We did a subsidiary analysis for fatal outcomes without censoring for previous non-fatal outcomes. Analyses involved a two-stage approach with estimates of association calculated separately within each study before data from different studies were pooled by use of random-effects meta-analysis. We used fixed-effect models for parallel analyses. For the 42 studies analysed as prospective cohorts, hazard ratios were calculated with Cox proportional hazards regression stratified by sex (and, when appropriate, by trial group). The assumptions for the proportionality of hazards were met. For the 12 case-control studies nested within prospective cohorts, odds ratios were calculated with conditional or unconditional logistic regression models, as appropriate. Hazard ratios and odds ratios were assumed to represent nearly the same relative risk and are collectively described as risk ratios (RRs). As directly measured concentrations of LDL-cholesterol were available for 48 475 participants, the concentration of non-HDL cholesterol was used as the main marker of cholesterol content in proatherogenic lipoproteins rather than that of LDL-cholesterol estimated with the Friedewald formula.24,25

Study-specific RRs were calculated within overall quantiles of baseline concentrations of CRP, and were combined on the log scale by use of multivariate random-effects meta-analysis, and plotted against pooled mean usual concentrations within each quantile. 95% CIs were estimated from variances attributed to the groups to reflect the amount of information within each group (including the reference group). When associations were nearly log-linear, regression coefficients were calculated to estimate the RR associated with a 1-SD higher concentration). RRs were adjusted progressively for age, sex, and several other conventional risk factors, with the evidence of association indicated by the Wald χ² statistic.23 The sequence of introduction of variables into the model followed the example of a previous report.23 To help distinguish whether CRP concentration or inflammatory processes in general might be relevant to disease risk, we also adjusted for other circulating markers of inflammation (such as fibrinogen). P statistic was used as a measure of consistency across studies—ie, the percentage of variance in estimated log RR that was attributable to between study variation as opposed to sampling variation. Values of P close to 0 correspond to lack of heterogeneity. We investigated diversity at the study level by grouping studies according to recorded characteristics and meta-regression.

We corrected concurrently for regression dilution in CRP concentration and in potential confounding factors.26,27 Regression dilution ratios for each characteristic were calculated with regression of serial measurements on baseline concentrations, adjusted for conventional risk factors plus baseline log, CRP concentration and duration of follow-up.28,29 Correction for within-person variation in CRP concentration and potential confounders was achieved.

Figure 2: Cross-sectional associations between geometric mean C-reactive protein (CRP) concentration and some conventional risk factors and other characteristics.

Mean CRP concentration was adjusted to age 50 years. Error bars represent the 95% CIs. BP=blood pressure.

r=Pearson's correlation coefficient (95% CI) for association between the risk marker and loge CRP concentration in men and women combined.

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by use of conditional expectations of long-term average (usual) concentrations of CRP and confounders predicted from regression calibration models, and used in assessments of associations with disease risk. For analyses we used Stata (version 10.0).

Role of the funding source
SK and JD had full access to all data in the study and had final responsibility to submit the report for publication. The study was conducted and analysed independently from its funders.

Results
Mean age of participants at entry into the study was 60 years (SD 8); 76 171 (48%) were women; and 78 619 (49%) were European and 75 919 (47%) were North American. During 1·31 million person-years at risk (median 5·8 years to first outcome, IQR 2·5–9·5), there were 10 451 coronary heart disease outcomes (7381 non-fatal myocardial infarctions and 3070 deaths from coronary diseases), 2846 ischaemic strokes, 469 haemorrhagic strokes, 1180 unclassified strokes, and 1659 deaths from other vascular diseases, 10 236 from non-vascular diseases, and 860 from unknown causes. Mean loge CRP concentration varied between studies and increased with age (figure 1), but SDs were generally similar between studies (webappendix p 2). The overall median for baseline CRP concentration was 1·72 mg/L (5th percentile 0·25, 95th percentile 12·4).

CRP concentration was positively correlated with concentrations of non-HDL cholesterol, log e triglycerides, fibrinogen, and interleukin 6, systolic blood pressure, body-mass index, and log, leucocyte count; and inversely with concentrations of HDL cholesterol and albumin (figure 2). CRP concentration was higher in women than in men, in smokers than in non-smokers, and in people with diabetes than in those without, and was lower in alcohol drinkers than in non-drinkers and in physically active people than in those not physically active (figure 2; webappendix p 8). More than one CRP measurement was available in 22 124 participants with 24 222 serial measurements (mean interval 5·1 years, SD 2·4; webappendix p 16). The regression-dilution ratio of loge CRP concentration, adjusted for age and sex, was 0·58 (95% CI 0·52–0·63), indicating a year-to-year consistency that was generally similar to that for systolic blood pressure (0·54, 0·51–0·58), and concentrations of total cholesterol (0·59, 0·54–0·64), HDL cholesterol (0·74, 0·70–0·78), and fibrinogen (0·51, 0·46–0·56) in the same individuals.

In analyses adjusted for age and sex only, associations of log, CRP concentration with the risk of coronary heart disease and ischaemic stroke were nearly log-linear, with no obvious risk thresholds (figure 3A). The corresponding associations of CRP concentration with all vascular mortality and with all non-vascular mortality seemed curvilinear. RR for coronary heart disease, adjusted for age and sex only, per 1-SD higher usual log, CRP concentration (ie, three-fold higher CRP concentration) was 1·68 (95% CI 1·59–1·78), with the RR possibly higher for fatal (1·84, 1·59–2·14) than for non-fatal myocardial infarction (1·59, 1·45–1·75; p=0·04; 38 studies, 8360 cases 23 studies, 2611 cases 20 studies, 2022 cases 19 studies, 1767 cases 18 studies, 1467 cases 17 studies, 1481 cases 16 studies, 1439 cases 15 studies, 1425 cases 14 studies, 1406 cases 13 studies, 1320 cases 12 studies, 1242 cases 11 studies, 1214 cases 10 studies, 1184 cases 9 studies, 1135 cases 8 studies, 1171 cases 7 studies, 1129 cases 6 studies, 1075 cases 5 studies, 1023 cases 4 studies, 930 cases 3 studies, 832 cases 2 studies, 786 cases 1 study, 461 cases

Figure 3: Risk ratios for major vascular and non-vascular outcomes by quantiles of C-reactive protein (CRP) concentration, with different degree of adjustment for potential confounders
Adjusted study-specific log, risk ratios were combined by use of multivariate random-effects meta-analysis. The adjustments were age, sex, and study only (A); age, sex, study, systolic blood pressure, smoking, history of diabetes, body-mass index, concentrations of log, triglycerides, non-HDL cholesterol, and HDL cholesterol, and alcohol consumption (B); and (A) plus (B) plus fibrinogen (C). Studies with fewer than ten cases of any outcome were excluded from the analysis of that outcome. Error bars represent the 95% CIs, calculated using floating absolute risk technique. The sizes of the boxes are proportional to the inverse of the variance of the risk ratios.
were excluded from the analysis of that outcome. The risk ratios are presented per 1·11 higher loge CRP (ie, 1-SD), corresponding to a three-fold higher CRP concentration. Horizontal lines represent the

### Figure 3C and Table 2 show RRs for coronary heart disease per 1-SD higher levels of each risk factor were 1·37 (95% CI 1·27–1·48) with CRP concentration, 1·28 (1·16–1·40) with non-HDL-cholesterol concentration, and 1·35 (1·25–1·45) with systolic blood pressure (webappendix p 19). The RRs with CRP were 1·55 (1·37–1·76) for vascular mortality and 1·54 (1·40–1·68) for non-vascular mortality after adjustment of conventional risk factors (webappendix p 10).

Figure 3C and table 2 show RRs for coronary heart disease associated with CRP after adjustment for conventional risk factors was reduced from 1·36 (95% CI 1·22–1·52) to 1·23 (1·07–1·42) after further adjustment for fibrinogen (Wald χ² was reduced from 29 to 8; table 2). By comparison, the corresponding adjusted RR for coronary heart disease was 1·21 (1·08–1·35) per 1-SD higher usual fibrinogen concentration. RR for ischaemic stroke associated with CRP after adjustment for conventional risk factors did not differ after further adjustment for fibrinogen (table 2). RR for non-vascular death was 1·52 (1·37–1·69) with CRP concentration after adjustment for conventional risk factors, and 1·34 (1·20–1·50; webappendix p 11) after further adjustment for fibrinogen. When fibrinogen was replaced with another marker of inflammation (eg, leucocyte count) in the model, reduction in the RR was smaller (albeit based on fewer data). Since only about 10% of individuals had concomitant data for CRP concentration, conventional risk factors, fibrinogen concentration, and at least one other inflammatory marker, more detailed adjustment for inflammation was not possible.

There may have been heterogeneity between studies in RRs for coronary heart disease (I²=26%, 95% CI 0–53). Apart from possibly higher RRs in men than in women (p=0·015). RRs for coronary heart disease did not vary in clinically relevant subgroups—such as people with diabetes, increased concentrations of lipids, and obesity, or in smokers—or with other participant or study characteristics (webappendix pp 20–21), or in exploratory analyses of individuals with morbid obesity or very high concentrations of lipids (webappendix p 20). Likewise, evidence of heterogeneity between studies in RRs for ischaemic stroke was not clear (I²=0, 0–54). Qualitatively similar results to those reported here were noted in analyses that did not correct for regression dilution; adjusted for smoking amount (webappendix p 12); used
**Discussion**

The current study has shown that CRP concentration is as consistent within individuals during several years as are total cholesterol concentration and systolic blood pressure. In individuals without initial vascular disease, associations of CRP concentration with subsequent risk of coronary heart disease, ischaemic stroke, and deaths from vascular and non-vascular diseases (including several cancers and respiratory diseases) were generally log-linear in shape. These associations persisted in analyses in which smokers and the initial years of follow-up were excluded.

Associations of CRP with vascular and non-vascular outcomes were each of broadly similar size. These findings resemble results previously reported with other downstream markers of inflammation, notably fibrinogen concentration,27 leucocyte count,28 albumin concentration,29 or erythrocyte sedimentation rate.30 Like CRP, each of these factors is modulated by mediators of inflammatory cascades (eg, interleukin 6), and our data confirm that such inflammatory markers are associated with CRP. Although persistent low-grade inflammation is proposed to be relevant to vascular and malignant diseases,31 the mechanisms are not known. The associations that we noted between CRP concentration and death from external causes (eg, injury) might be attributed, at least in part, to confounding by comorbidity at baseline.

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chronic disorders, most of the association with ischaemic vascular disease depends on conventional risk factors and fibrinogen concentration.\textsuperscript{23–26} If fibrinogen mediates the association between CRP concentration and risk of coronary heart disease, then correction for fibrinogen could be an overadjustment.

In studies in which CRP-related genotypes are proxies for life-long CRP concentration (ie, Mendelian randomisation analyses), such difficulties in interpretation should be avoided, provided the genotypes are not correlated with fibrinogen. In previous analyses, including a study of 28 000 patients with coronary heart disease and 100 000 controls,\textsuperscript{27} null associations were reported between CRP-related genotypes and fibrinogen concentration,\textsuperscript{28} conventional risk factors,\textsuperscript{29} and risk of coronary heart disease.\textsuperscript{30–32} Hence, our findings—taken with available genetic data—reduce the likelihood of causality for CRP in coronary heart disease. Results from randomised trials have shown that statins reduce concentrations of CRP in healthy individuals and in those with stable vascular disease.\textsuperscript{33} Rosuvastatin reduced the risk of first-ever vascular disease in individuals who had lower-than-average LDL-cholesterol concentration and higher-than-average CRP concentration.\textsuperscript{34} But, since statins potentely affect LDL-cholesterol concentration (an established causative risk factor in coronary disease), studies of these drugs cannot provide specific causal inferences about CRP concentration. Immunosuppressant or anti-inflammatory drugs, or vaccination, have not yet been adequately studied as prophylactic interventions to test the inflammation hypothesis.\textsuperscript{35}

This meta-analysis differs from previous reports in several important ways. First, it was larger and more comprehensive. Second, use of individual participant data enabled a consistent approach to adjustment for potential confounders and exploration of subgroups. Third, associations were corrected for measurement error and within-person variation (ie, regression dilution\textsuperscript{36–39}), using information from 22 124 participants with serial measurements. Fourth, individuals with a history of coronary heart disease or stroke were excluded, reducing any effects of clinically evident disease on CRP concentration. Although there was heterogeneity in the findings in relation to coronary heart disease (no greater in extent to that seen with non-HDL-cholesterol concentration in the same studies\textsuperscript{40}), little of it could be attributed to the recorded characteristics. Since most disease outcomes were recorded among white participants, the findings do not necessarily apply to non-white individuals. Our results confirm that CRP concentration can differ substantially in different ethnic groups (eg, concentrations were 26% higher in black individuals and 16% lower in east Asian individuals than in white people).\textsuperscript{41}

Large studies are needed that concurrently assess several proximal (eg, interleukin 6) and distal (eg, CRP, fibrinogen) markers of inflammation, and markers of rupture-prone plaque (eg, lipoprotein-associated phospholipase A\textsubscript{2}^\textsuperscript{42}), as well as their genetic and lifestyle determinants. Further work is also needed to assess whether evidence of low-grade inflammation mainly indicates external triggers (eg, socioeconomic position or infection), insulin resistance, hereditary predisposition, or some combination of such factors.\textsuperscript{43–45}

In subsequent analyses from this collaboration, we will assess CRP concentration for the prediction of vascular disease—a separate issue requiring analytical approaches that are different from those used in this meta-analysis.\textsuperscript{46–48}

<table>
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<th>Studies</th>
<th>Outcomes</th>
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<td>Plus conventional risk factors\textsuperscript{†}</td>
<td>7</td>
<td>1547</td>
<td>1.42 (1.15–1.74)</td>
</tr>
<tr>
<td>Plus log, interleukin 6</td>
<td>7</td>
<td>1547</td>
<td>1.19 (1.01–1.41)</td>
</tr>
</tbody>
</table>

| **Ischaemic stroke** | | | |
| Adjusted for age, sex, and study (n=47 353) | 11 | 1481 | 1.49 (1.34–1.67) | 49 | 16% (0–57) |
| Plus conventional risk factors\textsuperscript{†} | 11 | 1481 | 1.32 (1.18–1.47) | 24 | 0% (0–60) |
| Plus fibrinogen | 11 | 1481 | 1.22 (1.18–1.43) | 22 | 0% (0–60) |
| Adjusted for age, sex, and study (n=19 382) | 6 | 890 | 1.37 (1.23–1.52) | 35 | 0% (0–75) |
| Plus conventional risk factors\textsuperscript{†} | 6 | 890 | 1.28 (1.14–1.44) | 16 | 0% (0–75) |
| Plus albumin | 6 | 890 | 1.21 (1.07–1.35) | 10 | 0% (0–75) |
| Adjusted for age, sex, and study (n=14 076) | 7 | 1252 | 1.40 (1.26–1.55) | 42 | 0% (0–71) |
| Plus conventional risk factors\textsuperscript{†} | 7 | 1252 | 1.25 (1.11–1.41) | 13 | 0% (0–71) |
| Plus log, leucocyte count | 7 | 1252 | 1.15 (1.02–1.29) | 5 | 0% (0–71) |
| Adjusted for age, sex, and study (n=9918) | 3 | 480 | 1.63 (1.47–2.29) | 8 | 63% (0–89) |
| Plus conventional risk factors\textsuperscript{†} | 3 | 480 | 1.47 (1.09–1.98) | 6 | 42% (0–83) |
| Plus log, interleukin 6 | 3 | 480 | 1.18 (0.98–1.41) | 3 | 0% (0–90) |

Analyses were restricted to participants with complete information about sex, trial group, and all the conventional risk factors plus each inflammatory marker. Studies with fewer than ten cases were excluded from the analysis of each outcome. Data are number, unless otherwise indicated. *Per 1·11 higher log CRP (ie, 1–SD), corresponding to a three-fold higher CRP concentration, progressively adjusted and stratified (when appropriate) by sex and trial group. \textsuperscript{1}Age, sex, systolic blood pressure, smoking, history of diabetes, body-mass index, concentrations of log triglycerides, non-HDL cholesterol, and HDL cholesterol, and alcohol consumption.