Association of C-Reactive Protein With Cardiovascular Disease Mortality According to Diabetes Status

Pooled analyses of 25,979 participants from four U.K. prospective cohort studies

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OBJECTIVE—C-reactive protein (CRP) is associated with the risk of cardiovascular disease (CVD), whether the effects are modified by diabetes status is still unclear. This study investigated these issues and assessed the added value of CRP to predictions.

RESEARCH DESIGN AND METHODS—Participants were drawn from representative samples of adults living in England and Scotland. Cox proportional hazards regression models were used to relate baseline plasma CRP with all-cause and CVD mortality during follow-up in men and women with and without diabetes. The added value of CRP to the predictions was assessed through c-statistic comparison and relative integrated discrimination improvement.

RESULTS—A total of 25,979 participants (4.9% with diabetes) were followed for a median of 93 months, during which period there were 2,767 deaths (957 from CVD). CRP (per SD loge) was associated with a 53% (95% CI 43–66) and 43% (38–49) higher risk of cardiovascular and all-cause mortality, respectively. These associations were log linear and did not differ according to diabetes status (both P ≥ 0.08 for interaction), sex, and other risk factors. Adding CRP to conventional risk factors improved predictions overall and separately by diabetes status but not for CVD mortality, although such improvements only were marginal based on several discrimination statistics.

CONCLUSIONS—The association between CRP and CVD was similar across diabetes status, and the effects are broadly similar across levels of other conventional risk factors.

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With classic risk factors failing to fully explain the variance in cardiovascular disease (CVD), investigators have sought to identify new risk indices (1–3). This effort has implicated several biomarkers, potentially reflecting different metabolic pathways, in the etiology of CVD (3). C-reactive protein (CRP), an inflammatory biomarker, is one of the most well-documented emerging CVD risk factors (4,5). Concentrations of CRP in the upper part of the distribution within the normal range and above are associated with the long-term risk of CVD and all-cause mortality in different populations (6,7).

There is a suggestion that the association of CRP with CVD is modified by diabetes status (8); however, few such studies exist. In the present population-based cohort studies among individuals with and without diabetes, we investigated the associations of baseline plasma CRP levels with cardiovascular and all-cause mortality. In doing so, we also took the opportunity to investigate whether these associations were modified by sex and other conventional cardiovascular risk factors. In addition, we examined whether the knowledge of CRP can improve CVD risk prediction beyond conventional risk factors alone.
and calcium blockers). During the second visit, conducted within a few days of the first, nurses gathered clinical data. In the seated position, systolic and diastolic blood pressures were measured on three occasions using an Omron HEM-907, with a 5-min rest between each reading; an average of the second and third readings was used in the present analyses.

Biochemical measures
Peripheral blood samples were collected in serum tubes and centrifuged at room temperature. All serum samples were frozen at $-70^\circ$C until assay. CRP concentrations were analyzed from serum using the N Latex high-sensitivity CRP (hsCRP) mono immunoassay on the Behring Nephelometer II analyzer. The limit of detection was 0.17 mg/L, and the coefficient of variation was $<6\%$ for this assay. The analysis of HbA$_1c$ levels from plasma was performed using the Tosoh G7 analyzer (Tosoh Bioscience, Worcestershire, U.K.), with a coefficient of variation $<2.5\%$.

Ascertained of disease-specific mortality
Consenting study members were linked to the National Health Service mortality records, from which a death certificate was located. Classification of the underlying cause of death was based on information on the death certificate together with any additional observations made by the certifying physician. Diagnoses for primary cause of death were made using the ICD-9 and ICD-10, 390–459, denoting CVD deaths.

Statistical methods
Normal distribution was obtained with the natural logarithm (log$_e$) of the positively skewed CRP. Cox proportional hazards regression models were used to compute the hazard ratio and accompanying 95% CI for a 1-SD increase in log$_e$ CRP in relation to all-cause and CVD mortality. The proportional hazards assumption was tested with the use of the cumulative sums of Martingale-based residuals methods (12) and found not to be violated. Cox models were also used to compare participants across quintiles of CRP and across three subgroups defined by CRP $<$1, 1–3, and $>$3 mg/L (13), with 95% CIs in both analyses derived from the floating absolute-risk methods (14). The log linearity of the association was assessed by fitting a continuous predictor across quintiles of CRP. Interaction between diabetes and CRP was assessed by adding an interaction term to models that included the main effect of diabetes and log$_e$ CRP. The heterogeneity of the association also was assessed within sex and other subgroups of participants defined by the level of classical risk factors (above vs. below the median for continuous variables). Heterogeneity across subgroups was assessed through three-way interaction tests.

The predictive utility of the models was assessed overall and separately for participants with and without diabetes by computing the area under the receiver operating characteristic curve (AUC). AUC comparisons used nonparametric methods (15). The relative integrated discrimination improvement (RIDI%), which measures the percentage improvement in discrimination when an extra variable is added to a prediction model (16), was computed. The 95% CIs for the RIDI% were derived with the use of the nonparametric bootstrap percentiles CI method, based on 1,000 replications. We also calculated 1) the likelihood ratio $\chi^2$, which compares the adequacy of a model with covariates fitted to a set of data to that of the null model (without covariates) fitted to the same dataset; and 2) the Akaike information criterion (AIC), which allows for comparisons between models (nested or not): the smaller the value of the statistic, the better the model fits the data (17). Finally, we assessed the closeness between predicted and observed outcome rates using the Hosmer and Lemeshow calibration test (18). The basic model included age, sex, smoking, systolic blood pressure, BMI, waist circumference, physical activity, and total cholesterol. Additional models were constructed by adding CRP to the basic model as well as interaction terms of CRP with diabetes status and sex. The incremental value of CRP was further assessed by refitting the Framingham Anderson general equation for the prediction of cardiovascular mortality (without electrocardiographic left ventricular hypertrophy, a missing predictor in our sample) data with and without CRP (19). Comparisons were extended with the computation of the net reclassification improvement (16) based on four categories of 5-year predicted probability (i.e., 0 to $<$2.5, 2.5 to $<$5, 5 to $<$7.5, and $\geq$7.5%).

The main analyses included all participants with valid data. Sensitivity analyses also were conducted to account for the possible effects of infections and other factors on baseline levels of CRP, because these could distort the association of CRP with outcomes. This was performed by restricting the analyses to those participants with baseline levels of CRP $\leq$10 mg/L. All data analysis used SAS/STAT version 9.1 for Windows (SAS Institute, Cary, NC).

RESULTS—Of 25,979 participants included, 1,283 (4.9%) had diabetes. Participants mainly were white (97.7%), with ethnic minorities (2.4%) comprising three distinct groups (black: 144 [0.6%], Asians: 321 [1.2%], and others: 126 [0.5%]). The median CRP was 1.8 mg/L (interquartile range 0.8–4.1) overall; 1.7 mg/L (0.8–3.6) in men and 2 mg/L (0.8–4.5) in women (Wilcoxon test, $P < 0.0001$); and 3.2 mg/L (1.5–6.2) and 1.8 mg/L (0.8–4.0), respectively, in participants with and without diabetes ($P < 0.0001$). The relationships between quintiles of CRP and study covariates are depicted in Table 1 and Supplementary Table 1 based on three subgroups of CRP (i.e., $<1,1–3,$ and $>3$ mg/L). The least favorable levels of conventional risk factors were apparent in the higher CRP groups. Most of these relationships were stepwise across the CRP quintiles.

Fatal outcomes
A median follow-up of 93 months (25th to 75th percentiles 56–118) gave rise to 2,767 deaths (cumulative incidence 10.6%) recorded (including 1,466 [53%] deaths in men and 1,301 [47%] in women), of which 957 (cumulative incidence 3.7%) were of cardiovascular origin (including 535 [56%] cardiovascular deaths in men and 422 [44%] in women). During this period, 305 (23.8%) deaths, including 134 cardiovascular deaths (cumulative frequency 10.4%), were recorded in participants with diabetes. The equivalent in those without diabetes was 2,462 (10%) all-cause deaths and 823 (3.3%) cardiovascular deaths.

CRP and outcomes overall and by diabetes status
CRP was positively and continuously associated with CVD and all-cause and cardiovascular mortality, with an SD higher log$_e$ CRP conferring a 53% (95% CI 43–64) higher risk of cardiovascular death and a 43% (38–49) higher risk of death from any cause. In people with and without diabetes, an SD higher log$_e$ CRP was associated with 54% (28–85) and 52% (41–63), respectively, greater risk of cardiovascular death and 53% (35–72) and 41% (35–47), respectively, greater risk of all-cause death.
Table 1—Baseline characteristics across quintiles of CRP according to diabetes status

|                      | No diabetes | Diabetes | P trend | P trend | P trend |
|----------------------|-------------|----------|---------|---------|---------|
| Quintile 1 | Quintile 2 | Quintile 3 | Quintile 4 | Quintile 5 | NA | Quintile 1 | Quintile 2 | Quintile 3 | Quintile 4 | Quintile 5 | NA |
| n                   | 5,186       | 4,435    | 5,339   | 4,807   | 4,929   | 255    | 255      | 265       | 252       | 256      | NA           |
| Median CRP (mg/L)   | (minimum to maximum) | 0.4 (0.1–0.6) | 0.9 (0.7–1.2) | 1.8 (1.3–2.4) | 3.3 (2.5–4.8) | 8.1 (4.9–115.0) | NA       | 0.7 (0.1–1.2) | 1.7 (1.3–2.3) | 3.2 (2.4–4.0) | 5.3 (4.1–7.5) | 12.5 (7.6–93.3) | NA |
| Age (years)         |             | 50.1 (11.9) | 53.6 (12.9) | 56.0 (12.9) | 57.6 (13) | 59.0 (13.2) | <0.0001 | 62.7 (12.5) | 63.0 (12.3) | 65.2 (11.1) | 62.9 (12.0) | 62.4 (12.4) | <0.0001 |
| Women (%)           |             | 55.9      | 49.9     | 50.6     | 55.6     | 60.1     | <0.0001 | 37.6      | 37.2      | 42.3      | 52.0      | 62.9      | <0.0001 |
| Current smoker (%)  |             | 19.0      | 20.7     | 24.9     | 26.9     | 31.5     | <0.0001 | 15.0      | 20.6      | 17.0      | 22.6      | 26.2      | 0.002    |
| Systolic blood pressure (mmHg) | 127.6 (17.2) | 132.7 (18.7) | 135.3 (19.4) | 138.3 (20.6) | 138.6 (20.5) | <0.0001 | 142.6 (21) | 141.9 (19.9) | 142.4 (22.1) | 142.5 (23.2) | 142.8 (22.6) | 0.84 |
| Resting heart rate (bpm) | 68 (10)    | 69 (11)   | 70 (11)  | 71 (11)  | 73 (12)  | <0.0001 | 71 (12)  | 70 (11)  | 71 (13)  | 74 (13)  | 78 (12)  | <0.0001 |
| BMI (kg/m²)         |             | 24.7 (3.3) | 26.3 (3.7) | 27.4 (4.2) | 28.6 (4.7) | 29.4 (5.7) | <0.0001 | 27.1 (3.6) | 29.1 (4.7) | 30.2 (4.8) | 31.8 (6.4) | 33.0 (6.2) | <0.0001 |
| Waist circumference (cm) | 83.8 (11.0) | 89.1 (11.8) | 91.9 (12.3) | 94.4 (12.8) | 96.1 (13.5) | <0.0001 | 93.8 (11.9) | 99.4 (13.5) | 103.4 (12.9) | 105.3 (14.3) | 106 (14.5) | <0.0001 |
| Waist-to-hip ratio  |             | 0.84 (0.08) | 0.87 (0.08) | 0.88 (0.08) | 0.89 (0.09) | 0.89 (0.12) | <0.0001 | 0.91 (0.08) | 0.93 (0.08) | 0.95 (0.08) | 0.94 (0.08) | 0.93 (0.08) | 0.002 |
| Total cholesterol (mmol/L) | 5.5 (1.0)   | 5.8 (1.1)  | 6.0 (1.2) | 6.0 (1.2) | 5.9 (1.2) | <0.0001 | 5.3 (1.0) | 5.6 (1.1) | 5.7 (1.0) | 5.7 (1.2) | 5.7 (1.1) | 0.002 |
| HbA1c (%)           |             | 5.2 (0.3)  | 5.2 (0.4) | 5.3 (0.4) | 5.3 (0.4) | 5.4 (0.4) | <0.0001 | 7.1 (1.3) | 7.3 (1.2) | 7.6 (1.7) | 7.6 (1.4) | 7.9 (1.8) | <0.0001 |
| Ethnicity, white (%)|             | 97.4      | 97.8     | 97.8     | 98.1     | 98.1     | 0.006    | 91.4      | 95.3      | 95.6      | 96.4      | 96.9      | 0.005    |

P trend, P for linear trend; P value, P for the difference between participants with diabetes and those without. NA, not applicable.
to diabetes status is summarized in Supplementary Table 3. Within subgroups, the association of CRP with cardiovascular mortality was similar in participants with and without diabetes (all P value ≥0.17 for interaction). Associations also were broadly similar within subgroups for all-cause mortality but with two exceptions. For this outcome, significant heterogeneity was apparent in those below the median of BMI (P = 0.01 for interaction) and physical activity frequency (P = 0.04), largely driven by the small number of participants with diabetes within those subgroups. Across complementary subgroups, associations of CRP with cardiovascular mortality by diabetes status always were similar (all P ≥ 0.09 for the three-way interaction tests).

**Added value of CRP to CVD risk prediction**

Measures of model performance are summarized in Table 2 for the total cohort and participants with and without diabetes separately. The basic model (without CRP) had acceptable to good discriminatory power in predicting cardiovascular and all-cause mortality, with an AUC ranging from 0.748, for cardiovascular mortality in people with diabetes, to 0.859 for the same outcome in participants without diabetes. Adding CRP to the basic model improved both the model goodness of fit and its discriminatory power. In participants with diabetes, however, there was no evidence for improvements in the AUC for the prediction of cardiovascular death (P = 0.31 for the difference in AUC). Despite some attenuation in the effect sizes, CRP always was positively associated with the outcomes in all multivariable models. Fit statistics for models with continuous log, CRP were better than those for the equivalent models with three categories of CRP (i.e., <1, 1–3, and ≥3 mg/L). For instance, at the total cohort level, the AIC and Δlikelihood ratio χ² (main vs. basic models) for CVD mortality were 9.732 and 46, respectively, for models with log, CRP and 9.746 and 31, respectively, for models with three categories for CRP (Table 2). Adding the interaction terms of sex × CRP or diabetes × CRP (applicable only to the total cohort) did not improve the performance of the model (Table 2).

Based on RIDI% estimates, adding CRP to the basic model conferred similar levels of improvement for cardiovascular mortality prediction in the total cohort and in participants with and without diabetes taken separately (Table 3). For the prediction of all-cause mortality, the magnitude of the improvement was greater for participants with diabetes (RIDI% 17.52 [95% CI 4.87–38.13]), although the CI was large and always overlapped with other estimates. For the prediction of CVD mortality in diabetic participants, RIDI% was not significant when CRP was added to the basic model (RIDI% 3.03 [−0.26 to 18.14]).

In multivariable Cox models that incorporated components of the Framingham Anderson CVD mortality risk score, CRP was significantly associated with CVD mortality during follow-up (hazard ratio per SD log, 1.36 [95% CI 1.24–1.48]). Change in likelihood ratio χ² with the
### CONCLUSIONS

Findings from this study confirm that CRP with cardiovascular death was similarly among participants with diabetes and those without. The hazard ratios with cardiovascular death, similarly among participants with diabetes, were 1.44 (95% CI 1.32–1.58) and 1.26 (0.89–1.75) for diabetes (P = 0.09 for interaction) and 1.21 (1.05–1.39) and 1.18 (1.02–1.35) for all-cause mortality (P = 0.03 for interaction). The association of CRP with cardiovascular death was not seen to vary markedly by diabetes status, sex, and other conventional risk factors. The association of CRP with CVD and all-cause mortality did not seem to vary markedly by diabetes status, sex, and other conventional risk factors. The association of CRP with CVD and all-cause mortality did not seem to vary markedly by diabetes status, sex, and other conventional risk factors.

### Table 2—AUCs (95% CIs), AIC, likelihood ratio \( \chi^2 \), and calibration \( \chi^2 \) for the prediction of all-cause and CVD mortality in participants with and without diabetes

| Model*                  | All-cause mortality | Cardiovascular mortality |
|-------------------------|---------------------|--------------------------|
|                         | AIC                  | Calibration \( \chi^2 \) (P value) | AUC | AIC                  | Calibration \( \chi^2 \) (P value) | AUC |
| Total cohort            |                     |                          |     |                     |                          |     |
| Basic model             | 30,658               | 3,355                    | 28.7 | 0.842 (0.833–0.851) | <0.0001 | 9,771 | 1,426 | 33.7 | 0.858 (0.845–0.871) | 0.01 |
| Basic model + CRP       | 30,567               | 3,450                    | 20.4 | 0.846 (0.837–0.854) | 0.57   | 9,746 | 1,457 | 22.3 | 0.860 (0.848–0.874) | 0.21 |
| Basic model + loge CRP  | 30,537               | 3,479                    | 18.1 | 0.846 (0.837–0.855) | 0.67   | 9,733 | 1,469 | 23.3 | 0.861 (0.848–0.874) | 0.99 |
| Main model + sex        | 30,529               | 3,488                    | 16.0 | 0.846 (0.837–0.855) | 0.79   | 9,734 | 1,469 | 23.4 | 0.861 (0.848–0.874) | 0.62 |
| Participants without diabetes |           |                          |     |                     |                          |     |
| Basic model             | 27,721               | 3,086                    | 19.7 | 0.842 (0.832–0.851) | <0.0001 | 8,557 | 1,250 | 27.0 | 0.859 (0.845–0.873) | 0.02 |
| Basic model + CRP       | 27,641               | 3,170                    | 17.7 | 0.845 (0.836–0.855) | 0.80   | 8,530 | 1,281 | 17.2 | 0.861 (0.847–0.876) | 0.62 |
| Basic model + loge CRP  | 27,628               | 3,183                    | 16.3 | 0.846 (0.836–0.855) | 0.97   | 8,525 | 1,286 | 21.5 | 0.862 (0.848–0.876) | 0.71 |
| Main model + sex        | 27,628               | 3,183                    | 16.3 | 0.846 (0.836–0.855) | 0.97   | 8,525 | 1,286 | 21.5 | 0.862 (0.848–0.876) | 0.71 |
| Participants with diabetes |             |                          |     |                     |                          |     |
| Basic model             | 1,722                | 142                      | 18.3 | 0.752 (0.713–0.791) | 0.02   | 729   | 93    | 5.6  | 0.748 (0.696–0.800) | 0.31 |
| Basic model + CRP       | 1,713                | 155                      | 11.6 | 0.764 (0.726–0.802) | 0.10   | 731   | 94    | 7.5  | 0.750 (0.699–0.802) | 0.39 |
| Basic model + loge CRP  | 1,686                | 180                      | 7.3  | 0.776 (0.737–0.814) | NA     | 724   | 99    | 3.0  | 0.756 (0.705–0.806) | NA  |
| Main model + sex        | 1,688                | 180                      | 6.8  | 0.776 (0.737–0.814) | 0.65   | 723   | 102   | 11.0 | 0.760 (0.710–0.811) | 0.37 |

*Basic model included the following variables: age, sex, smoking, systolic blood pressure, BMI, waist circumference, total cholesterol, and physical activity (and diabetes status for the total cohort). Calibration refers to the Hosmer and Lemeshow calibration based on 10 subgroups and 8 df; \( P \) difference, \( P \) for the difference in AUC between the model of interest and the main model. NA, not applicable.
Mechanisms of effect

Several mechanistic pathways have been suggested to explain the accelerated atherothrombosis process in people with diabetes. Those related to chronic hyperglycemia include oxidative stress, advanced glycation end products, endothelial dysfunction, acute-phase response, and procoagulant states. Based on these mechanisms, differences in the effects of CRP on CVD risk could be hypothetically observed in people with and without diabetes (with a less favorable risk for the former) as the result of differences in the pathological processes responsible for increased CRP in people with and without diabetes. The absence of any significant heterogeneity in our study and the large ERFC overview (7) argues against such a hypothesis. Some have instead suggested that other cardiovascular risk factors that frequently displayed less favorable levels in people with diabetes compared with those without can mask the association between CRP and CVD and make it a less stronger determinant in people with diabetes (24). However, our data, and other adequately powered studies (7), have shown that despite attenuation in effect estimates after adjustment for multiple cardiovascular risk factors, the association of CRP with CVD does not differ by diabetes status.

Sex differentials

In the ERFC overview (7), there was a significant heterogeneity between men and women in the association of CRP with coronary heart disease, with the magnitude of the association being less important in women. Others instead have found significant interactions in both people with and without diabetes, with greater effect estimates always recorded in women (8). We found that CRP affected the risk of mortality in similar ways in men and women regardless of their diabetes status. Some apparent differences by sex in the effect estimates were a reflection of the low statistical power in some subgroups, as indicated by wider CI about estimates and the lack of an significant interaction by diabetes status within and across sex subgroups.

Incremental predictive utility of CRP

The incremental value of CRP to CVD prediction has been largely assessed in the general population (25, 26) but less in people with diabetes (27). Results in the general population have been inconsistent, with some showing marginal to sizable improvement and others no added value at all (25, 26). However, methods for assessing improvement in model performance in many of those studies have been largely criticized (25, 26). One study in people with diabetes found that adding CRP to established risk factors had meaningless effects on the performance of models in predicting cardiovascular mortality (27). This is consistent with our findings of nonsignificant improvement in the goodness-of-fit statistics and discriminatory power subsequent to adding CRP in people with diabetes. However, such improvement was more apparent in people with diabetes for the prediction of all-cause mortality and among participants without diabetes and the total cohort for both outcomes. However, the clinical and public health relevance of the range of improvement found has to be questioned.

Study limitations and strengths

The current analyses were based on a single measurement of CRP, and there was no possibility to adjust for regression dilution bias (7). Our results, however, are similar to those from studies that have performed such adjustment (7). In addition, it has been demonstrated that CRP was stable to those from studies that have performed such adjustment (7). In addition, it has been demonstrated that CRP was stable measurement of CRP, and there was no possibility to adjust for regression dilution bias (7). Our results, however, are similar to those from studies that have performed such adjustment (7). In addition, it has been demonstrated that CRP was stable measurement of CRP, and there was no possibility to adjust for regression dilution bias (7). Our results, however, are similar to those from studies that have performed such adjustment (7). In addition, it has been demonstrated that CRP was stable
size and number of deaths recorded, our ability to directly compare the effects of CRP on mortality risk in people with and without diabetes, and our ability to assess the possible effects of sex and other cardiovascular risk factors on the observed relationships.

Based on available evidence (4,28,29), a causal role for CRP in CVD is less certain. Therefore, CRP may not be a target for CVD prevention (2,30). It is expected that trials of specific CRP antagonists and low-dose methotrexate will clarify this in the future (31). The JUPITER (Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin) has shown that CRP was useful for targeting statin therapy in healthy individuals with normal-range LDL cholesterol (32). Other studies have suggested inconsistent effects of CRP on CVD risk prediction beyond traditional predictors (25,26). Our study suggests that CRP levels convey prediction information on the risk of CVD that is complementary to that provided by conventional cardiovascular risk factors and that improvement in the predictions is likely similar in people with diabetes and those without but is not affected by sex. Such improvements, however, remain modest and do not lend strong support to any recommendation of routinely measuring CRP for the purpose of enhancing the prediction of future risk of major outcomes. Our study also extends previous reports that traditional risk factors were similar determinants of the risk of CVD regardless of diabetes status (33–35).

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A.P.K. conceived of the design of the study, analyzed and interpreted data, drafted the manuscript, and performed critical revision of the manuscript for important intellectual content. G.D.B. and S.C. conceived of the manuscript, and performed critical revision of the manuscript for important intellectual content. E.S. performed critical revision of the manuscript. M.H. performed critical revision of the manuscript for important intellectual content. E.S. acquired data, analyzed and interpreted data, performed critical revision of the manuscript for important intellectual content, and is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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