Chronic Inflammatory Disorders and Risk of Type 2 Diabetes Mellitus, Coronary Heart Disease, and Stroke
A Population-Based Cohort Study

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Background—This study sought to evaluate whether risks of diabetes mellitus and cardiovascular disease are elevated across a range of organ-specific and multisystem chronic inflammatory disorders.

Methods and Results—A matched cohort study was implemented in the UK Clinical Practice Research Datalink including participants with severe psoriasis (5648), mild psoriasis (85 232), bullous skin diseases (4284), ulcerative colitis (12 203), Crohn’s disease (7628), inflammatory arthritis (27 358), systemic autoimmune disorders (7472), and systemic vasculitis (6283) and in 373 851 matched controls. The main outcome measures were new diagnoses of type 2 diabetes mellitus, stroke, or coronary heart disease. The outcomes were evaluated for each condition in a multiple outcomes model, with adjustment for conventional cardiovascular risk factors. Estimates for different inflammatory conditions were pooled in a random-effects meta-analysis. There were 4695 new diagnoses of type 2 diabetes mellitus, 3266 of coronary heart disease, and 1715 of stroke. The hazard ratio for pooled multiple failure estimate was 1.20 (95% confidence interval [CI], 1.15–1.26). The highest relative hazards were observed in systemic autoimmune disorders (1.32; 95% CI, 1.16–1.50) and systemic vasculitis (1.29; 95% CI, 1.16–1.44). Hazards were increased in organ-specific disorders, including severe psoriasis (1.29; 95% CI, 1.12–1.47) and ulcerative colitis (1.26; 95% CI, 1.14–1.40). Participants in the highest tertile of C-reactive protein had greater risk of multiple outcomes (1.52; 95% CI, 1.37–1.68).

Conclusions—The risk of cardiovascular diseases and type 2 diabetes mellitus is increased across a range of organ-specific and multisystem chronic inflammatory disorders with evidence that risk is associated with severity of inflammation. Clinical management of patients with chronic inflammatory disorders should seek to reduce cardiovascular risk.

(Circulation. 2014;130:837-844.)

Key Words: biomarker ■ coronary disease ■ diabetes mellitus ■ inflammation ■ stroke

Cardiovascular disease (CVD) is the leading cause of death globally. In high-income countries, population distributions for major risk factors for CVD, including smoking, hypertension, and elevated serum cholesterol, are now improving, and age-specific mortality rates are declining. The focus of research has thus shifted to less well-characterized etiologic and antecedent factors. Several studies have suggested that chronic inflammation may be associated with increased risk of atheromatous disease, including coronary heart disease (CHD) and stroke, as well as insulin resistance, leading to the emergence of the metabolic syndrome and type 2 diabetes mellitus (T2DM). These observations may be of considerable importance for the management of patients with chronic inflammatory disorders. These comprise a diverse group of clinical disorders affecting the skin (including psoriasis and bullous skin diseases), gastrointestinal tract (including ulcerative colitis and Crohn’s disease), and joints (inflammatory arthritides), as well as multisystem inflammatory disorders (including systemic autoimmune diseases and systemic vasculitis). Previously reported evidence derives from studies that explored the rates of CVD and T2DM in patients with individual inflammatory diseases, including psoriasis, rheumatoid arthritis, and systemic lupus erythematosus. Studies in individual conditions may be hampered by the limited number of participants with infrequent disorders, leading to inconsistent results and possible false-negative findings from type II statistical error. The great heterogeneity in the design, inflammatory conditions, and outcomes of previous studies prevents general conclusions concerning risks of CVD and T2DM in patients with chronic inflammatory disorders. Such an understanding will be important in understanding the evolution of cardiovascular and metabolic comorbidity and in addressing the prevention of CVD and T2DM.

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Methods

Data
A matched cohort study was implemented with the use of data from the Clinical Practice Research Datalink (CPRD). The CPRD is the world’s largest primary care database comprising anonymized longitudinal electronic patient records from primary care. The CPRD includes extensive clinical, diagnostic, pharmacological, demographic, and hospital information on >12 million UK primary care patients from >650 family practices. Data reaching predefined quality standards are referred to as “up to standard.” The size and geographic distribution of general practices, as well as the age and sex of individuals included in the database, are broadly representative of the UK population. The high quality of CPRD diagnostic and prescription information has been documented in several studies.

Study Population
Chronic inflammatory disorders represented the primary exposure of interest. Cohorts of participants aged >18 years with selected chronic inflammatory disorders recorded between January 1, 2002, and January 31, 2013, and without prior T2DM or prevalent CVD were sampled from the CPRD. To adopt an inclusive approach and avoid bias in the selection of specific diagnostic categories, the study protocol specified the selection of broad categories from the Read code hierarchy (Table I in the online-only Data Supplement). These included organ-specific chronic inflammatory disorders including the following: psoriasis and similar disorders (M16, subsequently excluding pityriasis rosea and related disorders); bullous skin diseases (M14); Crohn’s disease (J40); ulcerative colitis (J41); and inflammatory arthritis (N04). Systemic autoimmune disorders (N00) included systemic lupus erythematosus, scleroderma, and Sjögren syndrome as well as other diffuse connective tissue disorders and systemic vasculitis (G75), including polyarteritis nodosa, Wegener’s granulomatosis, giant cell arteritis, and related conditions. All diagnoses were derived from medical codes recorded in the electronic health record by family physicians. These have been shown previously to have high predictive values across a wide range of clinical diagnoses. Participants were included if the first-ever diagnosis of a chronic inflammatory disease was recorded during the study period (the later of the start of the participant’s record in CPRD or the date of the first outcome code). Participants with a diagnosis of chronic inflammatory disease were matched on age, sex, and family practice with up to 2 controls randomly sampled from all patients in the CPRD who were never diagnosed with a chronic inflammatory disorder. Data were extracted from the CPRD in February 2013.

Outcomes
The study outcomes included new diagnoses of CHD (including myocardial infarction, angina, coronary artery bypass graft, percutaneous coronary transluminal angioplasty), stroke, and T2DM. This cluster of outcomes was selected because chronic inflammation may be associated with vascular and metabolic changes including endothelial dysfunction and insulin resistance, which may precede both CVD and T2DM. Read medical codes used were used to identify incident stroke and CHD events during the study period. T2DM was diagnosed with definitions reported previously with the diagnosis date being the earlier of the first medical code and the first diabetes mellitus prescription. Participants diagnosed with type I diabetes mellitus were excluded from the study. The date of the first outcome code is referred to as the respective outcome index date. Multiple morbidity was defined as the occurrence of ≥2 outcomes in a participant.

Biomarker
Recorded CRP values were analyzed as a biomarker for inflammation severity. The mean of CRP values recorded from 3 months before the study start date to the study end date was included when patients were grouped into tertiles of CRP values, in accord with previous studies. Tertiles were defined separately for patients with chronic inflammation and controls owing to the differing distributions.

Confounders
Several variables known to be associated with CVD and T2DM risk were included as covariates. These included body mass index (<18.5, 18.5–25, >25 to <30, 30 to <35, and ≥35 kg/m²), smoking (never, ex-smoker, current smoker), drinking (never, ex-drinker, current drinker), systolic and diastolic blood pressure (<120/80 mm Hg, normal; 120–139/80–89 mm Hg, prehypertension; ≥140/90 mm Hg, hypertension), total cholesterol (<5.2 mmol/L [desirable], 5.2–6.2 mmol/L [elevated], and ≥6.2 mmol/L [high]), quartiles of creatinine levels (μmol/L), and whether glucocorticoids, statins, and antihypertensive drugs were prescribed. The categories for blood pressure and cholesterol derive from American Heart Association guidelines. For each confounder, the value closest to the study baseline and before chronic inflammation diagnosis was included. The models also included age, age squared (to test for possible nonlinearity association), and sex as confounders.

Statistical Analysis
The analyses were conducted in a time-to-event framework. Participants contributed person-time to the analysis from the study start date (the later of the start of the participant’s record in CPRD or the diagnosis date for a chronic inflammatory condition). Follow-up ended at the earliest of the study outcome index date, date of death, or end of the CPRD record. All participants had at least 12 months of follow-up recorded, and outcomes of interest were only considered after the first 12 months of the follow-up. A Cox proportional hazards model was implemented with the use of a multiple-failure framework for unordered events of different types. The multiple-failure approach permits analysis of data for each of several outcomes in a single model, allowing the most efficient use of each patient’s data and reducing problems of multiple testing. It is assumed that a patient can experience 1 or more of the different outcomes of interest in an unordered fashion. The multiple-failure model evaluates the risk of each outcome in each patient, leading to estimation of the relative hazard for developing any of the study outcomes. This avoids the need to censor records at earlier outcome events or to test hypotheses separately for each outcome. Further methodological details have been reported elsewhere. In a multiple-failure model, all participants are at risk for each study outcome (CHD, stroke, T2DM), but events of each type occurred only once per participant, and when patients experienced an event of one type, they remained at risk of events of other types. In this model, each participant appears 3 times in the data set, once for each outcome event, and survival time is calculated as the time from the study start date to each outcome event. Multiple-event analysis provides greater power to identify overall cardiovascular associations of inflammatory diseases compared with analysis of a single outcome, although investigators cannot adequately account for the series of events. Additional analyses estimated the specific associations between each inflammatory condition and CHD, stroke, T2DM, and multimorbidity in separate Cox regression models. The same estimation models were used for CRP analyses. Sensitivity analyses were also conducted with the use of competing risk analysis to explore the rate of CHD, stroke,
and T2DM when death was considered a competing event. Analyses were adjusted for study covariates, including matched variables and age squared (to test for a possible nonlinearity association). Matching variables were adjusted in the estimation models because in the presence of censoring (eg, loss to follow-up, competing risks), the balance produced by matching may be lost during follow-up, making it necessary to adjust for matching variables in the analysis. In cases in which data for categorical confounders were not available, missing indicator variables were used. No adjustment for multiple comparisons was made, and therefore marginally significant results may be type I errors. However, as the meta-analysis intends a general conclusion as opposed to a specific treatment recommendation, the unadjusted $P$ values seem better suited to an exploratory analysis. The proportionality hazard assumptions were assessed with the use of Schoenfeld residuals and were found not to be violated in most models. In models in which covariates, including age, failed the proportionality assumption, these were modeled as time-varying covariates in sensitivity analyses.

A random-effects meta-analysis was implemented to obtain a pooled estimate of the risk of CVD and T2DM events across all 8 inflammatory conditions. Data were analyzed with the use of STATA version 12.

**Human Studies**

The study was approved by the Independent Scientific Advisory Committee (reference No. 12-078). No patient consent was required.

**Results**

The study cohorts included 5648 participants with severe psoriasis, 85232 with mild psoriasis and related disorders, 4284 with bullous skin disorders, 12203 with ulcerative colitis, 7628 with Crohn’s disease, 27358 with inflammatory arthritis, 7472 with systemic autoimmune diseases, and 6283 with systemic vasculitis (Table 1). Diagnosis of multiple inflammatory disorders was observed in <3% of patients. There were 373851 matched controls without chronic inflammatory conditions matched for age, sex, and family practice. The extent of missing data among cohort patients ranged from 11% (smoking) to 46% (cholesterol) and from 17% (alcohol) to 56% (cholesterol) among controls.

The characteristics of participants at the start of the study are described in Table 1. The mean age at study entry was greater for participants diagnosed with bullous skin diseases or systemic vasculitis (69 years) than for those diagnosed with Crohn’s disease (42 years). A higher proportion of women than men were diagnosed with systemic autoimmune diseases including systemic lupus erythematosus and other connective tissue disorders (83%), as well as inflammatory arthritis (69%) and systemic vasculitis (68%). The crude prevalence of hypertension tended to be greater in those with systemic vasculitis (50%), whereas obesity was more frequent in those with severe psoriasis (23%). Glucocorticoid prescribing ranged from 13% (Crohn’s disease) to 70% (systemic vasculitis).

Table 2 shows the frequency of outcome events by condition for participants with chronic inflammatory disorders and their matched controls. The highest numbers of outcome events were observed in systemic vasculitis (13%), bullous skin disorders (9%), and inflammatory arthritis (9%), whereas the fewest outcomes were observed for Crohn’s disease (4%). In general, a higher proportion of participants with chronic inflammatory disorders experienced outcome events than the control cohort. The absolute risk of outcome events per 1000 patients in the cohort of patients with chronic inflammation was 7.42 for T2DM, 5.12 for CHD, and 2.67 for stroke. The corresponding figures for the control cohort with the same age and sex distribution were 5.32 for T2DM, 4.06 for CHD, and 2.15 for stroke.

Table 3 presents the results of analyses in which each outcome was evaluated separately. Systemic vasculitis was associated with higher relative risk of T2DM, stroke, and CHD. Systemic autoimmune disorders were associated with both stroke and CHD events, and severe psoriasis was associated with T2DM and CHD. Inflammatory arthritis was associated with higher risk of CHD but not stroke or T2DM. With the exception of Crohn’s disease and systemic autoimmune disorders, all inflammatory conditions were associated with increased risk of multimorbidity. Sensitivity analyses in which competing risks analyses were used showed similar patterns with 1 exception: Bullous skin disease was not associated with stroke (hazard ratio, 1.20; 95% confidence interval [CI], 0.98–1.45).

The Figure displays the results from the multiple outcome models, which allowed participants to remain at risk of any of the 3 outcomes. The hazard ratio for pooled estimate for multiple outcomes was 1.20 (95% CI, 1.15–1.26). An estimate of the extent to which the estimates vary between different conditions ($P$) suggested that the estimates were heterogeneous, although

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**Table 1. Characteristics of Participants at Study Start Date (Baseline)**

<table>
<thead>
<tr>
<th>Psoriasis, Severe (5648)</th>
<th>Psoriasis, Mild (85232)</th>
<th>Bullous Skin Diseases (4284)</th>
<th>Crohn’s Disease (27358)</th>
<th>Ulcerative Colitis (12203)</th>
<th>Inflammatory Arthritis (27358)</th>
<th>Autoimmune Diseases (7472)</th>
<th>Systemic Vasculitis (6283)</th>
<th>Controls (373851)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean, (SD), y</td>
<td>47 (16)</td>
<td>46 (18)</td>
<td>68 (20)</td>
<td>42 (18)</td>
<td>47 (18)</td>
<td>57 (16)</td>
<td>52 (17)</td>
<td>69 (14)</td>
</tr>
<tr>
<td>Females, n (%)</td>
<td>2954 (52)</td>
<td>43645 (51)</td>
<td>2457 (57)</td>
<td>4243 (56)</td>
<td>5969 (49)</td>
<td>18747 (69)</td>
<td>6230 (83)</td>
<td>4295 (68)</td>
</tr>
<tr>
<td>Obese* (BMI ≥30 kg/m²)</td>
<td>1288 (23)</td>
<td>16048 (18)</td>
<td>736 (17)</td>
<td>917 (12)</td>
<td>1659 (14)</td>
<td>5712 (21)</td>
<td>1326 (18)</td>
<td>1197 (19)</td>
</tr>
<tr>
<td>Hypertension* &gt;140/90 mmHg</td>
<td>1552 (27)</td>
<td>22410 (26)</td>
<td>1677 (39)</td>
<td>1318 (17)</td>
<td>2860 (23)</td>
<td>9502 (35)</td>
<td>2088 (28)</td>
<td>3124 (50)</td>
</tr>
<tr>
<td>Cholesterol* &gt;6.2 mmol/L</td>
<td>415 (7)</td>
<td>5271 (6)</td>
<td>333 (8)</td>
<td>249 (3)</td>
<td>656 (5)</td>
<td>2286 (8)</td>
<td>562 (8)</td>
<td>828 (13)</td>
</tr>
<tr>
<td>Current smoker</td>
<td>1401 (25)</td>
<td>23405 (27)</td>
<td>588 (14)</td>
<td>1926 (25)</td>
<td>1544 (13)</td>
<td>6108 (22)</td>
<td>1246 (17)</td>
<td>1013 (16)</td>
</tr>
<tr>
<td>Current alcohol use</td>
<td>3250 (22)</td>
<td>51113 (60)</td>
<td>2398 (56)</td>
<td>3959 (52)</td>
<td>7007 (57)</td>
<td>16294 (60)</td>
<td>4281 (57)</td>
<td>3822 (61)</td>
</tr>
<tr>
<td>Glucocorticoids</td>
<td>1250 (22)</td>
<td>10936 (13)</td>
<td>1788 (42)</td>
<td>2153 (28)</td>
<td>3466 (28)</td>
<td>9553 (35)</td>
<td>2197 (29)</td>
<td>4405 (70)</td>
</tr>
<tr>
<td>Elevated creatine</td>
<td>557 (10)</td>
<td>7947 (9)</td>
<td>1053 (25)</td>
<td>789 (10)</td>
<td>1714 (14)</td>
<td>3434 (13)</td>
<td>703 (9)</td>
<td>1435 (23)</td>
</tr>
<tr>
<td>Antihypertensive drugs</td>
<td>1630 (29)</td>
<td>22630 (27)</td>
<td>2393 (56)</td>
<td>1640 (22)</td>
<td>3239 (27)</td>
<td>11075 (40)</td>
<td>3053 (41)</td>
<td>3703 (59)</td>
</tr>
<tr>
<td>Statins prescribed</td>
<td>755 (13)</td>
<td>10487 (12)</td>
<td>1085 (25)</td>
<td>685 (9)</td>
<td>1445 (12)</td>
<td>4959 (18)</td>
<td>1144 (15)</td>
<td>1976 (31)</td>
</tr>
</tbody>
</table>

Data are frequencies (%) except where indicated.  
*For clarity and ease of presentation, only the thresholds identifying at-risk patients are included in the table.
of complete case analysis to validate the findings on the basis of separate Cox regressions, the use of covariates to validate the potential influence of the nonproportionality assumption. The results of these analyses validated the findings from analyses presented. Complete case analysis revealed marginally higher estimates than missing indicator variable analysis, but the significance level and direction of association were similar. No substantive variation in time to event between different inflammatory conditions was observed (median time to event was 4 years for most conditions).

Discussion

This study provides population-level estimates concerning the risk of CVD and T2DM across a wide range of chronic inflammatory disorders. When each outcome was considered separately, an increased risk of T2DM events was observed among 5 of the 8 inflammatory conditions; 3 conditions, including bullous skin diseases, systemic autoimmune diseases, and systemic vasculitis, were associated with increased risk of an incident stroke event; 4 conditions, including severe psoriasis, inflammatory arthritis, ulcerative colitis, and systemic vasculitis, were associated with elevated CHD risk. An increased risk of ≥2 of the outcomes was generally observed except in Crohn’s disease and systemic autoimmune disorders. There was also evidence for a dose-response association because severe psoriasis was associated with higher rates of T2DM and CHD events relative to mild psoriasis. Sensitivity analysis performed in a competing risk framework, with death as a competing risk, confirmed the individual association findings. Notably, a positive dose-response relationship was apparent between CRP and study outcomes. The relationship tended to be steeper in patients with chronic inflammation, possibly suggesting a greater risk of both single and multiple CVD outcomes at higher CRP concentrations in chronic inflammation. This association was consistent across patients with inflammation and controls, supporting the robustness of the relationship. This finding provides some evidence to support the use of CRP to stratify participants according to their risk of CVD because the association was apparent in controls as well as in patients with inflammatory disorders.

The present study presents a novel application of the multiple-outcomes model to estimate the risk that participants diagnosed with diverse inflammatory diseases may experience multiple vascular events in an unordered fashion. For example, in one participant, T2DM may be followed by stroke or by CHD followed by stroke. This analytical framework indicated an increased risk of CVD and T2DM events across most inflammatory conditions. This suggestion received support from the meta-analysis, which pooled findings across diagnostic cohorts, leading to a precise estimate of elevated CVD and T2DM risk across diagnostic categories. The largest effect size was observed among systemic diseases including systemic vasculitis and systemic autoimmune disorders. The risk of multiple CVD and T2DM outcomes also appeared to increase with disease severity in psoriasis. The lack of a dose-response relationship between mean CRP tertiles and stroke risk may be due to several factors, including lower power of the study to detect this association or possibly that this study CRP measure was below a threshold level of exposure beyond which the risk of stroke increases steeply. In addition, stroke

Table 2. Incidence of Study Outcomes by Condition for Participants With Chronic Inflammatory Disorders and Controls

<table>
<thead>
<tr>
<th>Chronic inflammatory conditions cohort</th>
<th>Diabetes Mellitus</th>
<th>Stroke</th>
<th>Coronary Heart Disease</th>
<th>Multimorbidity*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Psoriasis, mild</td>
<td>2388 (3)</td>
<td>709 (1)</td>
<td>1406 (2)</td>
<td>935 (1)</td>
</tr>
<tr>
<td>Psoriasis, severe</td>
<td>235 (4)</td>
<td>49 (1)</td>
<td>134 (3)</td>
<td>80 (2)</td>
</tr>
<tr>
<td>Bullous skin disease</td>
<td>140 (3)</td>
<td>118 (3)</td>
<td>129 (3)</td>
<td>117 (3)</td>
</tr>
<tr>
<td>Crohn’s disease</td>
<td>125 (2)</td>
<td>46 (1)</td>
<td>97 (1)</td>
<td>57 (1)</td>
</tr>
<tr>
<td>Ulcerative colitis</td>
<td>336 (3)</td>
<td>118 (1)</td>
<td>223 (2)</td>
<td>151 (1)</td>
</tr>
<tr>
<td>Inflammatory arthritis</td>
<td>960 (4)</td>
<td>400 (2)</td>
<td>805 (3)</td>
<td>501 (2)</td>
</tr>
<tr>
<td>Systemic autoimmune disorders</td>
<td>187 (3)</td>
<td>89 (1)</td>
<td>180 (3)</td>
<td>90 (1)</td>
</tr>
<tr>
<td>Systemic vasculitis</td>
<td>324 (5)</td>
<td>186 (3)</td>
<td>292 (5)</td>
<td>207 (4)</td>
</tr>
<tr>
<td>Control cohort†</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Psoriasis, mild</td>
<td>3383 (2)</td>
<td>1160 (1)</td>
<td>2398 (1)</td>
<td>1415 (1)</td>
</tr>
<tr>
<td>Psoriasis, severe</td>
<td>253 (2)</td>
<td>73 (1)</td>
<td>159 (2)</td>
<td>77 (1)</td>
</tr>
<tr>
<td>Bullous skin disease</td>
<td>239 (3)</td>
<td>193 (2)</td>
<td>257 (3)</td>
<td>179 (2)</td>
</tr>
<tr>
<td>Crohn’s disease</td>
<td>230 (2)</td>
<td>96 (1)</td>
<td>172 (1)</td>
<td>97 (1)</td>
</tr>
<tr>
<td>Ulcerative colitis</td>
<td>489 (2)</td>
<td>211 (1)</td>
<td>396 (2)</td>
<td>235 (1)</td>
</tr>
<tr>
<td>Inflammatory arthritis</td>
<td>1583 (3)</td>
<td>708 (1)</td>
<td>1256 (2)</td>
<td>780 (2)</td>
</tr>
<tr>
<td>Systemic autoimmune disorders</td>
<td>312 (2)</td>
<td>118 (1)</td>
<td>1023 (7)</td>
<td>134 (1)</td>
</tr>
<tr>
<td>Systemic vasculitis</td>
<td>445 (4)</td>
<td>277 (2)</td>
<td>442 (4)</td>
<td>284 (3)</td>
</tr>
</tbody>
</table>

Data are frequencies (%).

*Participants with ≥2 of the study outcomes.
†Data represent values for controls matched to participants with the respective condition.

The risk of CVD or diabetes mellitus was elevated across a wide range of chronic inflammatory conditions. The highest adjusted hazard ratios were observed in systemic autoimmune disorders (1.32; 95% CI, 1.16–1.50) and systemic vasculitis (1.29; 95% CI, 1.16–1.44). Hazards were also elevated, in comparison with the control cohort, in organ-specific chronic inflammatory disorders including severe psoriasis (1.29; 95% CI, 1.16–1.50), ulcerative colitis (1.26; 95% CI, 1.14–1.40), bullous skin disorders (1.17; 95% CI, 1.03–1.33), mild psoriasis (1.18; 95% CI, 1.13–1.23), and inflammatory arthritis (1.12; 95% CI, 1.05–1.18). There was no evidence for significant between-condition heterogeneity in the risk for multiple outcome events (λ=13.65, df=7).

Table 4 presents the results for CRP analyses. For patients with chronic inflammation, an increasing trend in the risk of CHD, T2DM, and multiple outcomes with greater CRP values was observed. Compared with patients in the bottom tertile of mean CRP values, the hazard ratio for multiple outcomes was 1.27 (95% CI, 1.14–1.41) in the second tertile and 1.52 (95% CI, 1.37–1.68) in the highest tertile. Similar associations, but of lower magnitude, were observed among the control groups. Trend analyses results indicated significant differences across all outcomes.

Sensitivity Analyses

Sensitivity analyses included the use of competing risk analysis to validate the findings from separate Cox regressions, the use of complete case analysis to validate the findings on the basis of missing indicator variables, and the use of time-varying covariates to validate the potential influence of the nonproportionality assumption. The results of these analyses validated the findings from analyses presented. Complete case analysis revealed marginally higher estimates than missing indicator variable analysis, but the significance level and direction of association were similar. No substantive variation in time to event between different inflammatory conditions was observed (median time to event was 4 years for most conditions).
is often preceded by other CVDs and T2DM, and aggressive treatment of these conditions may confound this association. The overall incidence of CVD events was consistent with that in previous studies. The present findings present a more complex picture than previous studies that considered a single outcome measure and a single inflammatory condition. Several studies suggested an increased risk of CHD, stroke, or T2DM events associated with systemic lupus erythemathosus, inflammatory arthritis, and psoriasis. The present findings conducted in a single-outcome/single–inflammatory condition framework indicated, however, that none of the inflammatory conditions (with the exception of systemic vasculitis) considered here were associated with increased risk across all conditions. In a recent meta-analysis, Samarasekera et al noted no association between stroke and severe psoriasis. Our analyses, which included assessment of multimorbidity, multiple-failure analysis, and meta-analysis, suggest that if participants are considered to be at risk of multiple outcomes, psoriasis emerges as being strongly associated with CVD and T2DM events. Fewer data are available for ulcerative colitis and Crohn’s diseases. Yarur et al found higher rates of vascular events in patients diagnosed with combined ulcerative colitis and Crohn’s disease. The present study results imply that ulcerative colitis may be responsible for the observed association. The findings for CRP are in agreement with previous evidence and extend this evidence to mean CRP values and patients with chronic inflammation.

Many experimental models support an association between chronic inflammation and CVD and T2DM. The most attention has been focused on the role of inflammatory cytokines such as interleukins and tumor necrosis factor-α to increase oxidative stress, increase insulin resistance, and oxidize low-density lipoproteins. These actions, which lead to endothelial dysfunction, are all proatherogenic and may contribute to atherosclerotic plaque vulnerable to rupture and initiate a clinical CVD event. The finding that CVD and T2DM events are associated with a wide range of inflammatory conditions strongly supports the hypothesis that any source of chronic inflammation is associated with CVD and T2DM. However, the observational nature of the present study precludes any definitive conclusion regarding causality or mechanism because increased risk does not imply cause and effect. Indeed,
a number of alternative mechanisms are possible, including increased psychosocial stress, reduced physical activity associated with chronic inflammatory disease, and the possible effects of prescribed therapies including anti-inflammatory drugs. It is also important to note that we cannot distinguish between localized vascular inflammation and systemic inflammation as the potential cause of increased risk. However, CRP values in patients with chronic inflammatory disease were higher than those in cohorts of patients with extensive vascular disease (without other chronic inflammatory disease), and this points to a potential role of systemic inflammation in CVD.45

Strengths and Limitations
The present data derive from a primary care database with documented validity of diagnoses for chronic inflammatory conditions, CHD, stroke, and T2DM. The representativeness of the data is well documented, thereby ensuring the generalizability of the findings. Several limitations are worth mentioning. We drew on the Read code classification, used in UK primary care, to provide broad categories of chronic inflammatory disorders for the present analyses. We acknowledge that alternative groupings of conditions might be proposed. However, the etiology of many of these conditions is poorly understood, and classifications based on phenotypic characteristics may sometimes have limited validity. Some diseases (eg, systemic autoimmune disorders and vasculitis) may be located on a spectrum of phenotypic disorders, with disease manifestations varying over time within individuals and varying between different individuals. The present analysis did not take into account disease severity across all inflammatory conditions because there is no agreed definition of severity across different inflammatory conditions. Our findings for increased risk of CHD among severe psoriasis relative to mild psoriasis support similar investigations into other inflammatory conditions. Patients with inflammatory disorders may experience more thorough examination from physicians, leading to increased opportunity to identify T2DM, a silent disease. However, inflammation was associated with increased risk of CHD and stroke, suggesting that surveillance bias is likely to be minimal here. The study did not explore the impact of over-the-counter therapy and nonsteroidal anti-inflammatory drugs on study outcomes, and these could be explored as a potential mechanism in purposefully designed studies. This is an important issue that deserved more explicit attention than was possible within the narrow scope of the present study. However, analyses were adjusted for glucocorticoid46 and statin use. Because <1% of matched controls and only a small percentage (<4%) of patients with inflammation were on other immunosuppressive therapies (eg, methotrexate, azathioprine, cyclosporine) at baseline, with the exception of inflammatory arthritis (21%), we did not adjust for this variable in the estimation models. We cannot exclude the possibility that different associations may be observed for outcome subtypes (eg, between hemorrhagic and ischemic stroke or between different CHD presentations). Sensitivity analyses in which myocardial infarction was used as an outcome indicated results similar to those with the CHD outcome, thereby increasing confidence in the study findings. Our definition of CHD includes angina because this is a common symptom of CHD. We have rerun the analyses excluding angina from CHD codes, and similar patterns were observed with respect to the significance level and direction of the association. In addition, given the objective nature of CHD, stroke, and T2DM diagnoses, the definition of outcomes is unlikely to vary between cases and controls. Selection bias and confounding are also common in observational studies. Because control and case groups were selected from the same sample and information was collected in the same manner, selection and information bias are likely to be minimal.47 In addition, the observed associations were robust to sensitivity analyses, supporting the validity of the findings. In the analysis of clinical data from electronic records, missing values generally present a difficulty. Marston et al48 observed that multiple imputation is not suitable for use in clinical data when observations may be missing not at random. We used the missing indicator variable method, but we acknowledge that all methods have limitations in this context.48 The need to impute may have slightly altered the reported absolute and relative risks. Complete case sensitivity analysis endorsed the present study findings, suggesting that the estimates may be rather conservative. Analyses exploring the potential mediating role of CVD risk factors are possible; however, this may be complicated by the medical surveillance.
of these patients that may lead to treatment of these risk factors. Our estimation models did not stratify for matching, and this might result in slightly conservative estimates. However, additional analyses that accounted for matching by stratification on matched pair gave slightly higher estimates, but the direction of association and significance level were similar in matching adjusted and unadjusted analyses. In the presence of unmeasured confounders, as might be the case in the present data, control of bias may be a greater concern. No adjustment for multiple comparisons was made, and therefore marginally significant results may be type I errors. Finally, approximately a third of patients with inflammation had a CRP value recorded between 90 days before the inflammation diagnosis and study outcome or study end. This limitation is minimalized by the larger number of patients and consistency of findings across different definitions of CRP, outcomes, and groups of people.

Implications for Research and Practice

The risk of CVD and T2DM is increased across a wide range of organ-specific and multisystem chronic inflammatory diseases, with the elevation in risk being associated with CRP as a biomarker of inflammation severity. These observations suggest that similar mechanisms may be responsible for the increased risk of CVD and T2DM events across diverse inflammatory conditions. The nature of these mechanisms merits investigation in prospective studies. Over time, inflammatory disorders may be associated with multiple cardiovascular outcomes, with events occurring in varying sequence. Allowing patients with inflammation to be at risk of different potential combinations of CVD events represents a more realistic model of the clinical evolution of disease than analyzing each type of outcome separately. Prevention of CVD and T2DM merits higher priority in the management of participants with chronic inflammatory disorders. Current management guidelines are generally condition specific. It may be desirable to have a lower threshold for starting preventive medical interventions in most chronic inflammatory conditions. However, the effectiveness of conventional risk factor reduction approaches to CVD and T2DM prevention in chronic inflammatory disorders may require reassessment. CRP values tend to vary over time, and our findings propose that mean CRP values should be preferred to a single baseline value whenever possible. On the basis of these study data, a threshold level of $10 \text{ mg/L}$ could help to identify patients with inflammation at increased risk of CVD and T2DM in primary care. In the absence of chronic inflammation, the threshold may be lower (ie, $>3 \text{ mg/L}$). The consistent evidence for a dose-response relationship between mean CRP and study outcomes appears to support the use of this biomarker to identify patients with inflammation at risk of diabetes mellitus and CVD in clinical practice.

Acknowledgments

This study is based in part on data from the CPRD obtained under license from the UK Medicines and Healthcare Products Regulatory Agency. However, the interpretation and conclusions contained in this report are those of the authors alone.

Sources of Funding

Drs Dregan, Gulliford, and Chowiwenczyk are supported by the National Institute for Health Research Biomedical Research Center at Guy’s and St Thomas’ National Health Service Foundation Trust and King’s College London. The views expressed are those of the author(s) and not necessarily those of the National Health Service, the National Institute of Health Research, or the Department of Health.

Disclosures

None.

References


49. Austin PC. Some methods of propensity-score matching had superior performance to others: results of an empirical in

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**CLINICAL PERSPECTIVE**

Previous research has not evaluated cardiovascular outcomes across a range of chronic inflammatory disorders. This research sought to estimate the risk of type 2 diabetes mellitus and cardiovascular disease across a wide range of organ-specific and multisystem inflammatory disorders. We conducted a prospective cohort study including 156 108 patients with inflammatory disease and 373 851 controls. The study included patients with organ-specific inflammatory disorders affecting the skin (psoriasis and bullous skin diseases), gastrointestinal tract (inflammatory bowel disease), and joints (inflammatory arthritis), as well as multisystem diseases (systemic vasculitis and systemic autoimmune disorders). The study showed a 20% higher risk of type 2 diabetes mellitus, coronary heart disease, and stroke in patients with chronic inflammatory disorders compared with matched controls, even after adjustment for conventional cardiovascular risk factors. There was evidence that the severity of inflammation, with C-reactive protein used as an indicator, is associated with the increase in risk. Future research should seek to identify the common mechanisms underlying these shared associations of different chronic inflammatory disorders. Research should also explore the effects of anti-inflammatory therapies on cardiovascular outcomes in patients with chronic inflammatory disorders. Cardiovascular risk assessment and preventive medical intervention should be an important element in the management of patients with chronic inflammatory disorders. Electronic health records provide a valuable resource for comparative research on cardiovascular outcomes and the impact of therapy for patients with chronic inflammatory disorders.
SUPPLEMENTAL MATERIAL
### Chronic inflammatory disorders included in study.

<table>
<thead>
<tr>
<th>Chronic Inflammatory disorder</th>
<th>Read code</th>
<th>Conditions included</th>
</tr>
</thead>
<tbody>
<tr>
<td>Psoriasis and similar disorders (N=90,880)</td>
<td>M16</td>
<td>Psoriasis and similar disorders: including psoriatic arthropathy; other psoriasis; parapsoriasis; palmoplantar pustular psoriasis; other psoriasis and similar disorders; psoriasis and similar disorders NOS</td>
</tr>
<tr>
<td>Bullous Skin Diseases (N=4,284)</td>
<td>M14</td>
<td>Bullous dermatoses including: dermatitis herpetiformis; subcorneal pustular dermatosis; juvenile dermatitis herpetiformis; impetigo herpetiformis; pemphigus; pemphigoid; benign mucous membrane pemphigoid; erosive pustular dermatosis of the scalp; other specified bullous dematoses; bullous dermatoses NOS.</td>
</tr>
<tr>
<td>Crohn’s Disease (N=7,628)</td>
<td>J40</td>
<td>Regional enteritis – Crohn’s disease - including: regional enteritis of the small bowel; regional enteritis of the large bowel; regional ileocolitis; regional enteritis NOS</td>
</tr>
<tr>
<td>Ulcerative Colitis (N=12,203)</td>
<td>J41</td>
<td>Indiopathic proctocolitis including: ulcerative proctocolitis; ulcerative (chronic) enterocolitis; ulcerative (chronic) ileocolitis; ulcerative pancolitis; other idiopathic proctocolitis; idiopathic proctocolitis NOS</td>
</tr>
<tr>
<td>Inflammatory Arthritis (N=27,358)</td>
<td>N04</td>
<td>Rheumatoid arthritis and other inflammatory polyarthritis including: rheumatoid arthritis; Felty’s syndrome; other rheumatoid arthropathy and visceral/systemic involvement; juvenile rheumatoid arthritis, Still’s disease; chronic post-rheumatic arthropathy; other juvenile arthritis; seropositive erosive rheumatoid arthritis; seropositive rheumatoid arthritis, unspecified; other specified inflammatory polyarthritis; inflammatory polyarthritis NOS.</td>
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<tr>
<td>Systemic Autoimmune Disorders (N=7,472)</td>
<td>N00</td>
<td>Diffuse diseases of connective tissue including: systemic lupus erythematosus; scleroderma; sicca (Sjogren’s syndrome); dermatomyositis; polymyositis; adult Still’s disease; antiphospholipid syndrome; other specified diffuse collagen diseases, collagen diseases NOS.</td>
</tr>
<tr>
<td>Systemic Vasculitis (N=6,283)</td>
<td>G75</td>
<td>Polyarteritis nodosa and allied conditions including: polyarteritis nodosa; acute febrile mucocutaneous lymph node syndrome; hypersensitivity angitis; lethal midline granuloma; Wegener’s granuloma; Giant cell arteritis; thrombotic microangiopathy; Takayasu’s disease; Churg-Strauss vasculitis; Juvenile polyarteritis; microscopic polyangiitis; necrotising vasculopathy unspecified; polyarteritis nodosa and allied conditions NOS</td>
</tr>
</tbody>
</table>