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

Running title: Dregan et al.; Inflammation and cardiovascular risk

Alex Dregan, PhD1; Judith Charlton, MSc2; Phil Chowienczyk, MD3; Martin C Gulliford, FFPH1

1King’s College London, Dept of Primary Care and Public Health Sciences, London, and NIHR Biomedical Research Centre at Guy’s and St Thomas’ NHS Foundation Trust, London; 2King’s College London, Dept of Primary Care and Public Health Sciences, London; 3King’s College London, British Heart Foundation Centre, London, United Kingdom

Address for Correspondence:
Alex Dregan, PhD
King’s College London
Department of Primary Care and Public Health, 6th Floor
Capital House, 42 Weston Street
London, SE1 3QD, United Kingdom
Tel: 0044 207 8486639
Fax: 0044 207 8486620
E-mail: alexandru.dregan@kcl.ac.uk

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Abstract

**Background**—The study aimed to evaluate whether risks of diabetes and cardiovascular disease (CVD) are elevated across a range of organ-specific and multi-system chronic inflammatory disorders.

**Methods and Results**—A matched cohort study was implemented in the UK Clinical Practice Research Datalink (CPRD) including participants with severe psoriasis (5,648), mild psoriasis (85,232), bullous skin diseases (4,284), ulcerative colitis (12,203), Crohn’s disease (7,628), inflammatory arthritis (27,358), systemic autoimmune disorders (7,472), systemic vasculitis (6,283) and 373,851 matched controls. The main outcome measures were new diagnoses of type 2 diabetes mellitus (T2DM), stroke, or coronary heart disease (CHD). The outcomes were evaluated for each condition in a multiple outcomes model, adjusting for conventional cardiovascular risk factors. Estimates for different inflammatory conditions were pooled in a random effects meta-analysis. There were 4,695 new diagnoses of T2DM, 3,266 for CHD and 1,715 for stroke. The hazards 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, CI: 1.16-1.44) and systemic vasculitis (1.29, CI: 1.16-1.44). Hazards were increased in organ-specific disorders, including severe psoriasis (1.29, CI: 1.12-1.47) and ulcerative colitis (1.26, CI: 1.14-1.40). Participants in the highest tertile of CRP had greater risk of multiple outcomes (1.52, CI: 1.37-1.68).

**Conclusions**—The risk of cardiovascular diseases and T2DM is increased across a range of organ-specific and multi-system chronic inflammatory disorders with evidence that risk is associated with severity of inflammation. Clinical management of patients with chronic inflammatory disorders should aim to reduce cardiovascular risk.

**Key words:** biomarker, inflammation, coronary heart disease, diabetes mellitus, stroke, CRP
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-characterised aetiological 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 (T2DM).<sup>1,2</sup> 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), the gastrointestinal tract (including ulcerative colitis and Crohn’s disease), joints (inflammatory arthritides), as well as multi-system 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,<sup>3,4</sup> rheumatoid arthritis,<sup>5,6</sup> and systemic lupus erythematosus (SLE).<sup>7</sup> 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, as well as in addressing the prevention of CVD and T2DM, in these patients. The present research employed a prospective cohort design using the electronic health records of a large primary care database to evaluate the hypothesis that risks of CHD, stroke, and T2DM are
consistently elevated across a range of chronic inflammatory diseases affecting either single systems or multi-system inflammatory disorders. C-reactive protein (CRP) was analysed as an index of inflammation severity.

Methods

Data

A matched cohort study was implemented using data from the Clinical Practice Research Datalink (CPRD). The CPRD is the world’s largest primary care database comprising anonymised longitudinal electronic patient records from primary care. The CPRD includes extensive clinical, diagnostic, pharmacological, demographic, and hospital information on over 12 million UK primary care patients from over 650 family practices. Data reaching predefined quality standards are referred to as ‘up-to-standard’. The size and geographical 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 1st of January 2002 and 31st of January 2013, and without prior T2DM or prevalent CVD were sampled from the CPRD. In order 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 (Supplemental Table). These included organ-specific chronic inflammatory disorders including: psoriasis and similar disorders (M16, subsequently excluding

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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 Sjogren 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 into the electronic health record by family physicians. These have been shown previously to have high predictive values, across a wide range of clinical diagnoses.9, 10 Participants were included if the first ever diagnosis of a chronic inflammatory disorder was recorded during the study period (the later of the start of the participant’s record or 01/01/2002 to the earliest of the death date, end of record, or 31/01/2013). Data on systemic therapy (including methotrexate, azathioprine, cyclosporine, hydroxyurea) and phototherapy (PUVA) treatment were used to further differentiate psoriasis participants into those with ‘mild’ or ‘severe’ psoriasis as reported previously.3 Psoriasis was broken down into severe and mild because previous research suggested that the burden of comorbidity increases with disease severity, inclusion of mild cases, as well as severe, allowed evaluation of this possibility.3, 11, 12 Participants with a diagnosis of chronic inflammatory disease were matched on age, gender, and family practice with up to two controls randomly sampled from all patients in the CPRD 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 were used to identify incident stroke and CHD events during the study period. T2DM was diagnosed using definitions reported previously with the diagnosis date being the earlier of the first medical code and the first diabetes prescription. Participants diagnosed with type I diabetes 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 two or more outcomes in a participant.

Biomarker

Recorded CRP values were analysed as biomarker for inflammation severity. The mean of CRP values recorded from 3 months prior to study start date to the study end date was included grouping patients into tertiles of CRP values, in line with previous studies. Tertiles were defined separately for CI patients 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 (BMI; <18.5, 18.5 to 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 (BP) (<120/80 mmHg normal, 120-139/80-89 mmHg prehypertension, ≥140/90 mmHg hypertension), total cholesterol (<5.2 mmol/L (desirable), 5.2 to 6.2 mmol/L (elevated), and >6.29 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 non-linearity association), and gender 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 chronic inflammatory condition). Follow-up ended at the earliest of the study outcome index date, date of death, or the end of the CPRD record. All participants had at least 12 months of follow-up record and outcomes of interest were only considered after the first 12 months of the follow-up. Cox proportional hazards model was implemented using 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 most efficient use of each patient’s data and reducing problems of multiple testing. It is assumed that a patient can experience one or more of the different outcomes of interest in an unordered fashion. The single multiple failure model evaluates the risk of the 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 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, when patients experience an event of one type they remained at risk of events of other types. In this model each participant appears three times in the dataset, 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 to analysis of single outcome, although cannot adequately account for the series of events. Additional
analyses estimated the specific associations between each inflammatory condition and CHD, stroke, T2DM, and multi-morbidity in separate Cox regression models. The same estimation models were used for CRP analyses. Sensitivity analyses were also conducted using competing risk analysis\(^25\) 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 possible non-linearity association). Matching variable were adjusted in the estimation models because in the presence of censoring (e.g. 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.\(^26\) Where data for categorical confounders was not available missing indicator variables were used. No adjustment for multiple comparisons was made so that 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 using Schoenfeld residuals and found not to be violated in most models. In models where covariates, including age, failed the proportionality assumption, these were modelled as time-varying covariates in sensitivity analyses. A random effects meta-analysis \(^27\) was implemented to obtain a pooled estimate of the risk of CVD and T2DM events across all eight inflammatory conditions. Data were analysed using STATA version 12.

**Human studies**

The study was approved by the Independent Scientific Advisory Committee (ISAC; Ref: 12-078). No patient consent required.
Results

The study cohorts included 5,648 participants with severe psoriasis, 85,232 with mild psoriasis and related disorders, and 4,284 with bullous skin disorders, 12,203 with ulcerative colitis, 7,628 with Crohn’s disease, 27,358 with inflammatory arthritis, 7,472 with systemic autoimmune diseases, and 6,283 with systemic vasculitis (Table 1). Diagnosis of multiple inflammatory disorders was observed in fewer than three percent of patients. There were 373,851 matched controls without chronic inflammatory conditions matched for age, gender 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) compared to those diagnosed with Crohn’s disease (42 years). A higher proportion of women than men were diagnosed with systemic autoimmune diseases including SLE 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 systemic vasculitis (50%), while obesity was more frequent in 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%), while 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 1,000 patients in
the cohort of chronic inflammation patients 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, while 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 multi-morbidity. Sensitivity analyses using competing risks analyses showed similar patterns with one exception: bullous skin disease was not associated with stroke (HR, 1.20 [95% CI, 0.98-1.45]).

Figure 1 displays the results from the multiple outcome models, which allowed participants to remain at risk of any of the three outcomes. The hazard ratio for pooled estimate for multiple outcomes was 1.20 (CI: 1.15-1.26). An estimate of the extent to which the estimates vary between different conditions ($I^2$) suggested that the estimates were heterogeneous, although the risk of CVD or diabetes was elevated across a wide range of chronic inflammatory conditions. The highest adjusted hazard ratios were observed in systemic autoimmune disorders (1.32, CI: 1.16-1.50) and systemic vasculitis (1.29, 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, CI: 1.12-1.47), ulcerative colitis (1.26, CI: 1.14-1.40), bullous skin disorders (1.17, CI: 1.03-1.33), mild psoriasis (1.18, CI: 1.14-1.22), and inflammatory arthritis (1.12, CI: 1.05-1.18). There was no evidence for significant between-condition heterogeneity in the risk for multiple outcome events ($\lambda=13.65$, df=7).
Table 4 presents the results for CRP analyses. For chronic inflammation patients, an increasing trend in the risk of CHD, T2DM, and multiple outcomes with greater CRP values was observed. Comparing to patients in the bottom tertile of mean CRP values, the hazard ratio for multiple outcomes was 1.27 (CI: 1.14-1.41) in the second tertile and 1.52 (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, use of complete case analysis to validate the findings based on missing indicator variable, and the use of time-varying covariates to validate the potential influence of non-proportionality 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. Considering each outcomes separately, an increased risk T2DM events was observed among five of the eight inflammatory conditions; three conditions, including bullous skin diseases, systemic autoimmune diseases, and systemic vasculitis, were associated with increased risk of an incident stroke event; four conditions including severe psoriasis, inflammatory arthritis, ulcerative colitis, and systemic vasculitis, were
associated with elevated CHD risk. An increased risk of two or more of the outcomes was generally observed except in Crohn’s disease and systemic autoimmune disorders. There was also evidence for a dose-response association since 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 chronic inflammation patients possibly suggesting a greater risk of both single and multiple CVD outcomes at higher CRP concentrations in chronic inflammation. This association was consistent across inflammation patients 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 as 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 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-relationship between mean CRP tertiles and stroke risk may be due to several factors, including study lower power 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. Also, stroke 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 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 SLE, inflammatory arthritis, and psoriasis. The current 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 multi-morbidity, 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 combined ulcerative colitis and Crohn’s disease diagnosed patients. Present study results imply that ulcerative colitis may be responsible for the observed association. The findings for CRP are in line with previous evidence and extend this evidence to mean CRP values and chronic inflammation patients.

Many experimental models support an association between chronic inflammation with CVD and T2DM. Most attention has focusing on the role of inflammatory cytokines such as interleukins and tumour necrosis factor-alpha to increase oxidative stress, increase insulin resistance and oxidise low-density lipoproteins. These actions which lead to endothelial
dysfunction are all pro-atherogenic and may contribute to atherosclerotic plaque vulnerable to rupture and initiate a clinical CVD event.\textsuperscript{44} The finding that CVD and T2DM events were 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 localised vascular inflammation and systemic inflammation as the potential cause of increased risk. However, it is notable that values of CRP 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.\textsuperscript{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 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 aetiology of many of these conditions is poorly understood and classifications based on phenotypic characteristics may sometimes have limited validity. Some diseases (e.g. 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 as 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. Inflammatory disorder patients 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 non-steroidal anti-inflammatory drugs (NSAIDs) 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 possible within the narrow scope of the present study. However, analyses adjusted for glucocorticoid and statins use. Because fewer than 1% of matched controls and only a very small % (<4%) of inflammation patients were on other immunosuppressive therapies (e.g. 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 sub-types as for example between haemorrhagic and ischemic stroke or between different CHD presentations. Sensitivity analyses using MI as an outcome indicated similar results to the CHD outcome increasing confidence in the study findings. Our definition of CHD includes angina as this is a common symptom of coronary heart disease. We have re-run the analyses excluding angina from CHD codes and similar patterns were observed with respect to the significance level and direction of
the association. Also, 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. As 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 here.32 Also, 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 al.47 observed that
multiple imputation is not suitable for use in clinical data when observations may be missing not
at random. We employed the missing indicator variable method but we acknowledge 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 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.49 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.26
No adjustment for multiple comparisons was made so that marginally significant results may be
type I errors. Finally, about a third of inflammation patients had a CRP value recorded between
90 days pre-inflammation diagnosis and study outcome or study end. This limitation is
minimalized by the larger number of patients and findings consistency across different
Implications for research and practice

The risk of CVD and T2DM is increased across a wide range of organ-specific and multi-system chronic inflammatory diseases, with the elevation in risk being associated with CRP as 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 inflammation patients to be at risk of different potential combinations of CVD events represents a more realistic model of the clinical evolution of disease than analysing 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 single baseline whenever possible. Based on thus study data a threshold level of around 10 mg/L could help identify inflammation patients at increased risk of CVD and T2DM in primary care. In the absence of chronic inflammation the threshold may be lower (i.e. >5 mg/L). The consistent evidence for a dose-relationship between mean CRP and study outcomes appear to support the use of this biomarker to identify inflammation patients at risk of diabetes and CVD in clinical practice.
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Conflict of Interest Disclosures: None.

References:


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Table 1. Characteristics of participants at study start date (baseline). Figures are frequencies (column percent) except where indicated.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Psoriasis, Severe (5,648)</th>
<th>Psoriasis, Mild (85,232)</th>
<th>Bullous Skin Diseases (4,284)</th>
<th>Crohn’s Disease (7,628)</th>
<th>Ulcerative Colitis (12,203)</th>
<th>Inflammatory Arthritis (27,358)</th>
<th>Autoimmune Diseases (7,472)</th>
<th>Systemic Vasculitis (6,283)</th>
<th>Controls (373,851)</th>
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<tr>
<td>Age (Years, mean, SD)</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>
<td>47 (19)</td>
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<tr>
<td>Females - %</td>
<td>2,954 (52)</td>
<td>43,645 (51)</td>
<td>2,457 (57)</td>
<td>4,243 (56)</td>
<td>5,969 (49)</td>
<td>18,747 (69)</td>
<td>6,230 (83)</td>
<td>4,295 (68)</td>
<td>21,3972 (57)</td>
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<td>Obese a (BMI ≥ 30 Kg/m2)</td>
<td>1,288 (23)</td>
<td>16,048 (18)</td>
<td>736 (17)</td>
<td>917 (12)</td>
<td>1,659 (14)</td>
<td>5,712 (21)</td>
<td>1,326 (18)</td>
<td>1,197 (19)</td>
<td>57,661 (15)</td>
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<td>Hypertension &gt;140/90mmHg</td>
<td>1,552 (27)</td>
<td>22,410 (26)</td>
<td>1,677 (39)</td>
<td>1,318 (17)</td>
<td>2,860 (23)</td>
<td>9,502 (35)</td>
<td>2,088 (28)</td>
<td>3,124 (50)</td>
<td>97,032 (26)</td>
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<td>Cholesterol &gt;6.2 mmol/L</td>
<td>415 (7)</td>
<td>5,271 (6)</td>
<td>333 (8)</td>
<td>249 (3)</td>
<td>656 (5)</td>
<td>2,286 (8)</td>
<td>562 (8)</td>
<td>828 (13)</td>
<td>21,814 (6)</td>
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<td>Current smoker</td>
<td>1,401 (25)</td>
<td>23,405 (27)</td>
<td>1,926 (25)</td>
<td>1,544 (13)</td>
<td>6,108 (22)</td>
<td>1,246 (17)</td>
<td>1,013 (16)</td>
<td>82,880 (22)</td>
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<tr>
<td>Current alcohol</td>
<td>3,250 (58)</td>
<td>51,113 (60)</td>
<td>2,398 (56)</td>
<td>3,959 (52)</td>
<td>7,007 (57)</td>
<td>16,294 (60)</td>
<td>4,281 (57)</td>
<td>3,822 (61)</td>
<td>227,644 (61)</td>
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<td>Glucocorticoids</td>
<td>1,250 (22)</td>
<td>10,936 (13)</td>
<td>1,788 (42)</td>
<td>2,153 (28)</td>
<td>3,466 (28)</td>
<td>9,553 (35)</td>
<td>2,197 (29)</td>
<td>4,405 (70)</td>
<td>43,689 (12)</td>
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<td>Elevated creatinine</td>
<td>557 (10)</td>
<td>7,947 (9)</td>
<td>1,053 (25)</td>
<td>789 (10)</td>
<td>1,714 (14)</td>
<td>3,434 (13)</td>
<td>703 (9)</td>
<td>1,435 (23)</td>
<td>26,368 (7)</td>
</tr>
<tr>
<td>Antihypertensive drugs</td>
<td>1,630 (29)</td>
<td>22,630 (27)</td>
<td>2,393 (56)</td>
<td>1,640 (22)</td>
<td>3,239 (27)</td>
<td>11,075 (40)</td>
<td>3,053 (41)</td>
<td>3,703 (59)</td>
<td>101,157 (27)</td>
</tr>
<tr>
<td>Statins prescribed</td>
<td>755 (13)</td>
<td>10,487 (12)</td>
<td>1,085 (25)</td>
<td>685 (9)</td>
<td>1,445 (12)</td>
<td>4,959 (18)</td>
<td>1,144 (15)</td>
<td>1,976 (31)</td>
<td>45,785 (12)</td>
</tr>
</tbody>
</table>

a For clarity and ease of presentation reasons only the thresholds identifying at risk patients are included in the table.
**Table 2.** Incidence of study outcomes by condition for chronic inflammatory disorders participants and controls. Figures are frequencies (%).

<table>
<thead>
<tr>
<th>Chronic inflammatory conditions cohort</th>
<th>Diabetes</th>
<th>Stroke</th>
<th>CHD</th>
<th>Multi-morbidity*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Psoriasis, Mild</td>
<td>2,388 (3)</td>
<td>709 (1)</td>
<td>1,406 (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>152 (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>
</tbody>
</table>

*participants with two or more of the study outcomes

†data represent values for controls matched to participants with the respective condition
Table 3. Adjusted* hazard ratios (95% Confidence Interval) of diabetes mellitus, stroke, CHD and multi-morbidity (two or more outcomes) in different chronic inflammatory disorders compared to matched controls.

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Diabetes HR (95%CI)</th>
<th>P</th>
<th>Stroke HR (95%CI)</th>
<th>P</th>
<th>Coronary heart disease HR (95%CI)</th>
<th>P</th>
<th>Multi-morbidity HR (95%CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Psoriasis, Mild</td>
<td>1.17 (1.11-1.24)</td>
<td>0.001</td>
<td>1.08 (0.98-1.18)</td>
<td>0.133</td>
<td>1.03 (0.97-1.11)</td>
<td>0.323</td>
<td>1.15 (1.05-1.25)</td>
<td>0.002</td>
</tr>
<tr>
<td>Psoriasis, Severe</td>
<td>1.30 (1.08-1.56)</td>
<td>0.006</td>
<td>0.93 (0.64-1.36)</td>
<td>0.724</td>
<td>1.29 (1.01-1.64)</td>
<td>0.042</td>
<td>1.48 (1.07-2.05)</td>
<td>0.017</td>
</tr>
<tr>
<td>Bullous Skin Disease</td>
<td>1.20 (0.97-1.48)</td>
<td>0.099</td>
<td>1.35 (1.05-1.73)</td>
<td>0.019</td>
<td>1.12 (0.89-1.41)</td>
<td>0.326</td>
<td>1.57 (1.24-2.00)</td>
<td>0.001</td>
</tr>
<tr>
<td>Crohn’s Disease</td>
<td>0.96 (0.76-1.21)</td>
<td>0.725</td>
<td>0.74 (0.51-1.07)</td>
<td>0.112</td>
<td>1.10 (0.84-1.45)</td>
<td>0.495</td>
<td>1.16 (0.82-1.65)</td>
<td>0.392</td>
</tr>
<tr>
<td>Ulcerative Colitis</td>
<td>1.29 (1.11-1.49)</td>
<td>0.001</td>
<td>1.14 (0.90-1.44)</td>
<td>0.294</td>
<td>1.13 (0.95-1.35)</td>
<td>0.174</td>
<td>1.37 (1.11-1.70)</td>
<td>0.004</td>
</tr>
<tr>
<td>Inflammatory Arthritis</td>
<td>1.03 (0.94-1.12)</td>
<td>0.529</td>
<td>1.06 (0.93-1.20)</td>
<td>0.407</td>
<td>1.13 (1.03-1.24)</td>
<td>0.013</td>
<td>1.23 (1.10-1.38)</td>
<td>0.001</td>
</tr>
<tr>
<td>Systemic autoimmune disorders</td>
<td>1.10 (0.91-1.33)</td>
<td>0.331</td>
<td>1.54 (1.15-2.06)</td>
<td>0.003</td>
<td>1.49 (1.21-1.84)</td>
<td>0.001</td>
<td>1.28 (0.96-1.7)</td>
<td>0.094</td>
</tr>
<tr>
<td>Systemic Vasculitis</td>
<td>1.33 (1.13-1.58)</td>
<td>0.001</td>
<td>1.31 (1.05-1.64)</td>
<td>0.018</td>
<td>1.23 (1.02-1.48)</td>
<td>0.030</td>
<td>1.51 (1.21-1.81)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

* adjusted for age, age squared, gender, blood pressure, cholesterol, BMI, smoking, alcohol, serum creatinine levels, glucocorticoids, antihypertensives and statins. Controls were matched for year of birth, gender, and practice. HR=hazard ratios; CI=confidence intervals.
Table 4. Dose-response relationship between tertiles of mean CRP levels and study outcome.

<table>
<thead>
<tr>
<th></th>
<th>Multiple outcomes</th>
<th>CHD</th>
<th>Stroke</th>
<th>Diabetes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CI cases</td>
<td>Controls</td>
<td>CI cases</td>
<td>Controls</td>
</tr>
<tr>
<td>N(%)</td>
<td>46,108 (27)</td>
<td>40,644 (13)</td>
<td>47,549 (33)</td>
<td>44,116 (15)</td>
</tr>
<tr>
<td>Median(IQR)</td>
<td>6 (3.14)</td>
<td>4 (2.8)</td>
<td>6 (3.14)</td>
<td>4 (2.8)</td>
</tr>
<tr>
<td>CRP tertiles – HR^† (95%CI)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lowest</td>
<td>Reference</td>
<td>Reference</td>
<td>Reference</td>
<td>Reference</td>
</tr>
<tr>
<td></td>
<td>1.27</td>
<td>1.20</td>
<td>1.23</td>
<td>1.17</td>
</tr>
<tr>
<td></td>
<td>(1.14-1.41)</td>
<td>(1.07-1.36)</td>
<td>(1.05-1.45)</td>
<td>(0.97-1.40)</td>
</tr>
<tr>
<td>Second</td>
<td>1.52</td>
<td>1.44</td>
<td>1.33</td>
<td>1.18</td>
</tr>
<tr>
<td></td>
<td>(1.37-1.68)</td>
<td>(1.30-1.60)</td>
<td>(1.14-1.56)</td>
<td>(1.00-1.30)</td>
</tr>
<tr>
<td>Highest</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>0.023</td>
</tr>
</tbody>
</table>

^Controls: Mean values, First tertile: 0-3 mg/L; Second tertile: 3.01-6 mg/L; Third tertile: >6.02 mg/L. Patients: Mean values, First tertile: 0-4 mg/L; Second tertile: 4.00-10 mg/L; Third tertile: >10.01 mg/L. ^Chronic inflammation. ^HR=Hazard ratios; CI=Confidence Intervals.
Figure Legend:

**Figure 1.** Forest plot displaying random effect meta-analysis of the influence of diverse chronic inflammatory conditions on multiple cardiovascular and type II diabetes outcomes. HR=Hazard ratios; CI=Confidence intervals.
<table>
<thead>
<tr>
<th>Chronic Inflammatory Disease</th>
<th>HR (95% CI)</th>
<th>% Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systemic Autoimmune Disorders</td>
<td>1.32 (1.16, 1.50)</td>
<td>8.96</td>
</tr>
<tr>
<td>Systemic Vasculitis</td>
<td>1.29 (1.16, 1.44)</td>
<td>11.24</td>
</tr>
<tr>
<td>Psoriasis, Severe</td>
<td>1.29 (1.16, 1.50)</td>
<td>8.96</td>
</tr>
<tr>
<td>Ulcerative Colitis</td>
<td>1.26 (1.14, 1.40)</td>
<td>11.95</td>
</tr>
<tr>
<td>Psoriasis, Mild</td>
<td>1.18 (1.13, 1.23)</td>
<td>23.47</td>
</tr>
<tr>
<td>Bullous Skin Diseases</td>
<td>1.17 (1.03, 1.33)</td>
<td>9.03</td>
</tr>
<tr>
<td>Inflammatory Arthritis</td>
<td>1.12 (1.05, 1.18)</td>
<td>19.94</td>
</tr>
<tr>
<td>Crohn's Disease</td>
<td>1.06 (0.90, 1.24)</td>
<td>6.47</td>
</tr>
<tr>
<td>Overall (I-squared = 48.7%, p = 0.058)</td>
<td>1.20 (1.15, 1.26)</td>
<td>100.00</td>
</tr>
</tbody>
</table>
Chronic Inflammatory Disorders and Risk of Type 2 Diabetes Mellitus, Coronary Heart Disease, and Stroke: A Population-Based Cohort Study
Alex Dregan, Judith Charlton, Phil Chowienczyk and Martin C. Gulliford

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### 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 polyarthropathy 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 polyarthropathy; inflammatory polyarthropathy NOS.</td>
</tr>
<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 angiitis; 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>