EXTENDED REPORT

Risk of major cardiovascular events in patients with psoriatic arthritis, psoriasis and rheumatoid arthritis: a population-based cohort study

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ABSTRACT

Objectives We aimed to quantify the risk of major adverse cardiovascular events (MACE) among patients with psoriatic arthritis (PsA), rheumatoid arthritis (RA) and psoriasis without known PsA compared with the general population after adjusting for traditional cardiovascular risk factors.

Methods A population-based longitudinal cohort study from 1994 to 2010 was performed in The Health Improvement Network (THIN), a primary care medical record database in the UK. Patients aged 18–89 years of age with PsA, RA or psoriasis were included. Up to 10 unexposed controls matched on practice and index date were selected for each patient with PsA. Outcomes included cardiovascular death, myocardial infarction, cerebrovascular accidents and the composite outcome (MACE). Cox proportional hazards models were used to calculate the HRs for each outcome adjusted for traditional risk factors. A priori, we hypothesised an interaction between disease status and disease-modifying antirheumatic drug (DMARD) use.

Results Patients with PsA (N=8706), RA (N=41 752), psoriasis (N=138 424) and unexposed controls (N=81 573) were identified. After adjustment for traditional risk factors, the risk of MACE was higher in patients with PsA not prescribed a DMARD (HR 1.24, 95% CI 1.03 to 1.49), patients with RA (No DMARD: HR 1.39, 95% CI 1.28 to 1.50, DMARD: HR 1.58, 95% CI 1.46 to 1.70), patients with psoriasis not prescribed a DMARD (HR 1.08, 95% CI 1.02 to 1.15) and patients with severe psoriasis (DMARD users: HR 1.42, 95% CI 1.17 to 1.73).

Conclusions Cardiovascular risk should be addressed with all patients affected by psoriasis, PsA or RA.

INTRODUCTION

Psoriatic arthritis (PsA) is a chronic inflammatory arthritis that occurs in approximately 8%–30% of patients with psoriasis.[1 2] PsA has been linked to an increased prevalence of cardiovascular (CV) comorbidities and CV risk factors.[3] However, the majority of studies performed to date have been cross-sectional. Cohort studies examining the risk of incident CV events in PsA are sparse.[4] Three population-based studies have examined the risk of CV events among patients with psoriasis and have included patients with PsA as a subgroup.[5–7] Existing studies have not examined the risk for incident major adverse cardiovascular events (MACE) including myocardial infarction (MI), cerebrovascular accidents (CVA) and CV death in PsA compared with matched internal controls from a population-based perspective after accounting for the presence of traditional CV risk factors.

Rheumatoid arthritis (RA) and severe psoriasis have been consistently linked to an increased risk for incident MACE.[3 4 8–16] It has been suggested that patients with PsA have a similarly elevated risk for CV disease. However, we recently demonstrated that patients with PsA did not have an increased risk of mortality compared with internal controls, while patients with severe psoriasis (defined as patients with psoriasis prescribed systemic therapy or phototherapy) and RA had substantially elevated mortality (HR 1.75 and 1.54–1.59, respectively).[17] This led us to question whether PsA is associated with incident CV disease from a population-based perspective.

The objective of this study was to examine the risk of incident MACE including MI, CVA and CV death controlling for traditional CV risk factors among patients with PsA, RA or psoriasis compared with unexposed controls using a population-based cohort. We hypothesised similar rates of CV disease among the three groups given known associations with systemic Th1-driven and Th17-driven inflammation.[18 19]

METHODS

Study design and setting

A cohort study was performed using data from The Health Improvement Network (THIN) in the UK between 1994 and 2010. THIN is a large medical record database in which general practitioners (GP) record routine health data about their patients.[20–22] The UK is an ideal setting for examining long-term health outcomes given the gatekeeper model, meaning that GPs are responsible for coordinating all of the patient's care. Additionally, pay-for-performance measures mandate collection of data on CV outcomes and several key CV risk factors including diabetes and smoking.[23]

Study population

All patients with PsA, psoriasis or RA, and between the ages of 18 and 89 years at the index date were included if they had observation time in THIN

after Vision software implementation. Patients were excluded if they had died or were transferred out of the practice prior to the implementation of Vision software. Up to 10 unexposed controls from the general population without PsA, psoriasis, RA, or disease-modifying antirheumatic drugs (DMARD) prescriptions were randomly selected for each patient with PsA and were matched on practice and index date within the practice (defined as latest of registration with the practice and diagnosis date). Unexposed controls were assigned a 'diagnosis date' within 6 months of diagnosis date of the patient with PsA. This algorithm was designed to minimise bias by ensuring that PsA and unexposed controls are followed by similar doctors during similar time periods. For each individual outcome analysis, patients were excluded if they had the outcome of interest prior to the index date.

Exposure definitions

PsA, psoriasis and RA were defined by the presence of at least one READ code consistent with these diseases (READ codes are standard medical diagnosis codes used in the UK general practice system).[24] READ codes for psoriasis (positive predictive value (PPV) 90%),[25] RA (PPV 81% for 'potential cases' defined as single code without DMARD, rheumatoid factor result or rheumatology referral)[26–28] and PsA (PPV 85%)[2 29] have been previously validated within the same or analogous large medical record databases. We have used this definition of PsA in other studies.[2 17 30 31] Patients were classified as PsA if they had a code for PsA, RA if they had a code for RA but not PsA, and psoriasis if they had a code for psoriasis but did not have a code for RA or PsA.

Outcome definitions

Outcomes were defined by READ codes representing the outcome of interest within the study period. The censoring date was the first occurrence of the outcome of interest. Patients were excluded from each analysis if they had the event of interest prior to the index date. MI and stroke were defined by a previously validated set of READ codes with PPV 93%[32] and 77.5%–89.3%, respectively.[33 34] CV death was defined by a set of READ codes chosen based on the UK ICD10 codes classifying a CV death and the Centers for Disease Control ICD9 codes classifying death as heart disease or stroke.[35 36] These codes were extracted within the 60 days before, or earlier than 180 days, following a code signifying the patient's death. Text comments in the database reporting the patient's death as CV were also used to classify CV death. This algorithm has been used previously and is the recommended method for identifying cause of death by THIN. MACE, the composite outcome, was achieved at the first of MI, CVA or CV death.

Person time calculation

The index date (cohort entry) was defined as the latest date of the following events: diagnosis date, 6 months after initial registration with the practice, DMARD initiation (in patients using DMARDs), implementation of Vision software in the patient's practice or a practice-acceptable mortality reporting.[37–40] The index data was similarly calculated in unexposed controls except for 'diagnosis date' was the diagnosis date of the matched patient with disease. Censoring occurred when the event of interest occurred, the patient died, the patient left the practice, the practice stopped participating in THIN, or the study ended in September 2010.

Covariates of interest

All covariates of interest were measured prior to the index date. A priori, we hypothesised a statistical interaction between disease status and both age and DMARD use, as disease severity may be reflected by DMARD use. DMARD exposure was included in the models as a binary variable for exposure at any point up to the index date. Among patients with RA and PsA, DMARDs included methotrexate, sulfasalazine, azathioprine, leflunamide, cyclosporine, mycophenolate, hydroxychloroquine; and biological disease-modifying agents including adalimumab, etanercept and infliximab. In patients with skin psoriasis without a diagnosis of PsA or RA, methotrexate, ciclosporin, biological disease-modifying agents, phototherapy, psoralen plus ultraviolet light therapy (PUVA), retinoids (acitretin and etretinate) and hydroxyurea were considered DMARDs. In the UK, DMARDs can be prescribed by consultants (specialists) but should be captured by GP records with the exception of the biological medications, which are rarely recorded.[20] The following potential confounders were measured: age, sex, smoking, body mass index, blood pressure at baseline, year of cohort entry, Townsend Deprivation Score correlated with socioeconomic

Table 1 Baseline characteristics

	Control	Psoriatic arthritis		Rheumatoid arthritis		Psoriasis	
		No DMARD	DMARD	No DMARD	DMARD	No DMARD	DMARD
	N=81 573	N=4174	N=4532	N=17 912	N=23 840	N=134 095	N=4329
Demographics							
Age (mean (SD))	49.86 (18.25)	51.63 (14.95)	49.80 (13.70)	63.48 (16.15)	59.76 (14.34)	47.56 (17.73)	49.27 (16.52)
Male N (%)	36 806 (45.1)	2121 (50.8)	2329 (51.4)	5185 (28.9)	7129 (29.9)	65 280(48.7)	2201 (50.8)
Disease duration* (Mean years (SD))	N/A	5.75 (7.93)	4.39 (6.92)	8.70 (11.42)	5.98 (8.78)	7.10 (10.51)	12.20 (12.04)
Cohort time (mean (SD))	5.24 (3.92)	5.55 (4.02)	5.02 (3.77)	5.40 (3.99)	5.36 (3.80)	5.41 (3.99)	4.33 (3.40)
Baseline event rates†							
Myocardial infarction N (%)	1925 (2.36)	104 (2.49)	88 (1.94)	818 (4.57)	983 (4.12)	3193 (2.38)	116 (2.68)
Stroke N (%)	1265 (1.55)	59 (1.41)	48 (1.06)	625 (3.49)	531 (2.23)	2015 (1.50)	80 (1.85)
Transient ischaemic attack N (%)	433 (0.53)	20 (0.48)	19 (0.42)	209 (1.17)	165 (0.69)	627 (0.47)	20 (0.46)

Additional baseline characteristics are found in online supplementary table S1.
*Disease duration was calculated from the diagnosis date to start date.
†Note that patients with baseline event rates were excluded from the relevant analyses (eg, patients with a previous MI were excluded from the incident MI analysis and the composite outcome analysis).
DMARD, disease-modifying anti-rheumatic drug; MI, myocardial infarction.

status,[20] urban versus rural living environment, chronic kidney disease, diabetes, hypertension, use of prescription non-steroidal anti-inflammatory drugs (NSAID) and oral corticosteroids prior to index date. The Charlson Comorbidity Score[41] was also calculated, but the typical point for RA was not included in order to better capture differences in other comorbidities among the groups.

Statistical analysis

Covariate distribution among the groups was examined using descriptive statistics. Cox proportional hazards regression models were used to calculate the HR for each group compared with the unexposed group after adjusting for age and sex. Hypothesised effect modifiers, use of DMARDs and age, were tested in the models, and the likelihood ratio test was used to determine significance of the interactions. We then tested the hypothesised confounders in the model using a purposeful selection modelling approach[42] and kept in the model the predetermined confounders (age, sex and traditional CV risk factors) and covariates that changed the main effects by >10% and had a p value<0.1. Log-log survival plots and Schoenfeld residuals were used to assess the assumption of proportionality of hazards. Several sensitivity analyses were performed (more details given in online supplementary figure S1). Statistical analysis was performed using Stata V.13.0 (College Station, Texas, USA).

Sample size determination

Power calculations prior to the start of the study revealed that with 7000 patients with PsA and 35 000 unexposed patients, we would have 90% power to detect an HR as small as 1.28, 1.16 and 1.19 for CV death, MI and stroke, respectively, with an average of 5 years of follow-up per patient in an unadjusted analysis. Baseline event rates were assumed to be 0.16%, 0.49% and 0.35% per year for CV death, MI and stroke, respectively.

Ethics board approval

All data in this study was anonymous to the investigators. This study was approved by the University of Pennsylvania Institutional Review Board and Cegedim's Scientific Review Committee. This manuscript was prepared according to the Strengthening the Reporting of Observational Studies in Epidemiology statement recommendations.[43]

RESULTS

Among 8706 patients with PsA, 41 752 patients with RA, 138 424 patients with psoriasis and 82 258 randomly selected unexposed patients meeting the inclusion criteria, follow-up time in the study period was comparable. Baseline characteristics are found in table 1 (additional patient characteristics are found in online supplementary table S1). Patients with RA were older and more often women. Approximately half the patients with RA and PsA were prescribed a DMARD and 3% of patients with psoriasis had been prescribed a DMARD or received phototherapy. At least 65% of patients with PsA and RA had been prescribed NSAIDs compared with 24% with psoriasis and 47% of controls. Compared with the unexposed population, the prevalence of CV risk factors, MI and stroke in the baseline period were elevated in patients with PsA, RA and psoriasis. Reasons for leaving the cohort (censoring) other than having an outcome of interest were similar among groups (data not shown).

The unadjusted incidence rates of MI, CVA and MACE (composite outcome) are reported in table 2. HRs for MI, stroke, CV death and MACE are presented in table 3. There was a

Table 2 Incidence rate of cardiovascular death, MI, stroke and MACE

	CV death	PY	Incidence rate per 1000 PY	MI	PY	Incidence rate per 1000 PY	Stroke	PY	Incidence rate per 1000 PY	MACE	PY	Incidence rate per 1000 PY
Unexposed	902	427 554	2.1	838	415 547	2.0	1010	419 573	2.4	2055	408 519	5.0
PsA												
All	86	45 889	1.9	123	44 496	2.8	119	45 037	2.6	249	43 710	5.7
No DMARD	57	23 149	2.5	70	22 339	3.1	73	22 643	3.2	148	21 882	6.8
DMARD	29	22 740	1.3	53	22 158	2.4	46	22 394	2.1	101	21 829	4.6
RA												
All	1258	224 336	5.6	1032	212 904	4.8	1094	216 806	5.0	2504	206 264	12.1
No DMARD	672	96 662	7.0	409	91 782	4.5	569	92 952	6.1	1198	88 494	13.5
DMARD	586	127 674	4.6	623	121 122	5.1	525	123 854	4.2	1306	117 770	11.1
Psoriasis												
All	1695	744 257	2.3	1643	721 708	2.3	1810	729 470	2.5	3864	708 554	5.5
No DMARD	1 645	725 493	2.3	1, 603	703 652	2.3	1753	711 187	2.5	3749	690 931	5.4
DMARD	50	18 764	2.7	45	18 056	2.5	57	18 283	3.1	115	17 623	6.5

For comparison, according to UK National Statistics between 2000 and 2009, the incidence of MI for men of all ages was 2.05–3.34/1000 and for women of all ages was 0.84–1.52/1000. The incidence of stroke for men of all ages was 1.78–2.77/1000 and for women of all ages was 1.39–2.08/1000.[44]
DMARD, disease-modifying anti-rheumatic drug; MACE, major adverse cardiovascular events; MI, myocardial infarction; PY, person years; RA, rheumatoid arthritis; PsA, psoriatic arthritis.

Table 3 HRs and 95% CIs for major adverse cardiovascular events

Unexposed	Unadjusted Ref	Age-sex adjusted Ref	Fully adjusted* Ref
Composite outcome			
PsA			
No DMARD	1.34 (1.13 to 1.58)	1.33 (1.13 to 1.58)	1.24 (1.03 to 1.49)
DMARD	0.93 (0.76 to 1.13)	1.17 (.96 to 1.43)	1.17 (.95 to 1.46)
RA			
No DMARD	2.62 (2.44 to 2.81)	1.43 (1.33 to 1.53)	1.39 (1.28 to 1.50)
DMARD	2.17 (2.02 to 2.32)	1.62 (1.51 to 1.74)	1.58 (1.46 to 1.70)
Psoriasis			
No DMARD	1.07 (1.02 to 1.13)	1.16 (1.10 to 1.23)	1.08 (1.02 to 1.15)
DMARD	1.30 (1.08 to 1.57)	1.41 (1.17 to 1.71)	1.42 (1.17 to 1.73)
Myocardial infarction			
PsA			
No DMARD	1.55 (1.21 to 1.98)	1.46 (1.14 to 1.86)	1.36 (1.04 to 1.77)
DMARD	1.19 (0.90 to 1.57)	1.35 (1.03 to 1.79)	1.36 (1.01 to 1.84)
RA			
No DMARD	2.20 (1.96 to 2.48)	1.36 (1.21 to 1.53)	1.33 (1.17 to 1.52)
DMARD	2.55 (2.30 to 2.83)	2.02 (1.82 to 2.24)	1.96 (1.75 to 2.19)
Psoriasis			
No DMARD	1.13 (1.04 to 1.23)	1.19 (1.09 to 1.29)	1.08 (0.98 to 1.18)
DMARD	1.25 (0.92 to 1.68)	1.30 (0.96 to 1.76)	1.26 (0.92 to 1.72)
Stroke			
PsA			
No DMARD	1.34 (1.05 to 1.69)	1.36 (1.08 to 1.73)	1.33 (1.03 to 1.71)
DMARD	0.85 (0.64 to 1.15)	1.12 (0.83 to 1.50)	1.13 (0.83 to 1.55)
RA			
No DMARD	2.54 (2.29 to 2.81)	1.29 (1.16 to 1.43)	1.29 (1.15 to 1.45)
DMARD	1.76 (1.59 to 1.96)	1.27 (1.14 to 1.41)	1.24 (1.10 to 1.39)
Psoriasis			
No DMARD	1.02 (0.95 to 1.11)	1.13 (1.05 to 1.22)	1.08 (.99 to 1.17)
DMARD	1.31 (1.00 to 1.71)	1.45 (1.11 to 1.90)	1.45 (1.10 to 1.92)
Cardiovascular death			
PsA			
No DMARD	1.16 (0.89 to 1.52)	1.30 (0.99 to 1.70)	1.07 (0.79 to 1.44)
DMARD	0.61 (0.42 to 0.88)	0.98 (0.68 to 1.42)	0.96 (0.64 to 1.43)
RA			
No DMARD	3.29 (2.97 to 3.63)	1.55 (1.40 to 1.71)	1.43 (1.28 to 1.59)
DMARD	2.18 (1.96 to 2.42)	1.69 (1.53 to 1.88)	1.66 (1.48 to 1.86)
Psoriasis			
No DMARD	1.07 (0.99 to 1.16)	1.22 (1.13 to 1.34)	1.09 (1.00 to 1.20)
DMARD	1.29 (0.97 to 1.71)	1.49 (1.12 to 1.98)	1.54 (1.15 to 2.05)

*The fully adjusted models include age, sex, hypertension, diabetes, hyperlipidaemia, smoking status (never, past, current) and start year in the cohort.
DMARD, disease-modifying anti-rheumatic drug; RA, rheumatoid arthritis; PsA, psoriatic arthritis.

significant interaction between DMARD status (ever vs never prescribed) and exposure (disease) group ($p<0.001$ for CV death, CVA and MACE, and $p=0.01$ for MI). Therefore, the stratified results are presented. The risk of MACE (composite outcome) was elevated in patients with PsA without a DMARD prescription (HR 1.24, 95% CI 1.03 to 1.49), RA (No DMARD: HR 1.39, 95% CI 1.28 to 1.50 and DMARD user: 1.58, 95% CI 1.46 to 1.70) and severe psoriasis (defined as patients prescribed a DMARD; HR 1.42, 95% CI 1.17 to 1.73).

Patients with PsA had an elevated risk for incident MI (HR 1.36, 95% CI 1.04 to 1.77 and HR 1.36, 95% CI 1.01 to 1.84 for no DMARD and DMARD, respectively). The risk for MI was similarly elevated in patients with RA without a DMARD prescription (HR 1.33, 95% CI 1.17 to 1.51) and patients with severe psoriasis (HR 1.26, 95% CI 0.92 to 1.72), but was substantially higher in patients with RA who had been prescribed a DMARD (HR 1.96, 95% CI 1.75 to 2.19).

The risk of incident stroke was also significantly elevated in patients with PsA without a DMARD prescription (HR 1.33, 95% CI 1.03 to 1.71) which was similar to patients with RA and severe psoriasis. Finally, CV death was only significantly elevated in RA (no DMARD: HR 1.43, 95% CI 1.28 to 1.59 and DMARD: HR 1.66, 95% CI 1.48 to 1.86) and severe psoriasis (HR 1.54, 95% CI 1.15 to 2.05).

A third interaction with age as a continuous variable was tested and found to be significant ($p<0.001$ for all four outcomes). The three-way interactions are presented in figure 1. The relative risk is highest in the younger age groups where the absolute risk is low. Few events occurred in patients younger than 50 years of age (13% of MI, 8% of stroke, 3% of CV death and 10% of composite outcomes).

Our results were robust to several sensitivity analyses (see online supplementary figure S1); varying definitions of the outcomes, restricting to only patients followed regularly, using multiple imputation for smoking and body mass index, and imputing additional DMARD users. However, in examining the role of death as a competing risk factor for CV events, all previously significant associations in PsA were null, whereas, the HR in the other groups remained unchanged. Finally, adjusting for potentially CV-protective medication use (eg, antihypertensives, lipid-lowering medications and antiplatelet agents listed in online supplementary table S1) during the 1 year prior to start date in the cohort and healthcare use in the baseline period (number of GP visits) did not significantly change the results. One such model is illustrated in online supplementary table S2.

DISCUSSION

To our knowledge, this is the first population-based study dedicated to examining MACE in PsA which may be an independent risk factor for major CV events including MI and stroke, although this was only statistically significant for patients who were not prescribed a DMARD. Additionally, this is the first longitudinal population-based study dedicated to the simultaneous examination of the incidence of MACE in PsA, psoriasis and RA after adjusting for traditional CV risk factors. All three diseases had statistically similar risks for the development of incident CV events after adjustment for age, sex, calendar year of cohort entry and traditional CV risk factors.

Strengths of this study include the large cohort of patients, an average of 5 years of follow-up, simultaneous comparison among three disease cohorts in a population-based study and the use of THIN in which the exposures (psoriasis, RA, PsA) and outcomes (MI, CVA) have been validated. The incidences of MI and CVA in our unexposed population are similar to UK National Statistics,[44] lending credence to our algorithms to identify these outcomes and the validity of our unexposed population. These statistics are based on inpatient hospitalisations but support our assumption that we have captured the majority of the outcomes of interest. Furthermore, the increased risk of CV disease in RA and psoriasis are similar to those reported in recent meta-analyses, lending internal validity to our results in PsA.[14 16]

Our study has limitations, including lack of disease activity measures in THIN, generally absent biological medication records, possible missing DMARD prescriptions and the inability to account for over-the-counter NSAID use. THIN does not include data on disease activity in psoriasis or inflammatory arthritis, limiting our ability to examine the effect of disease

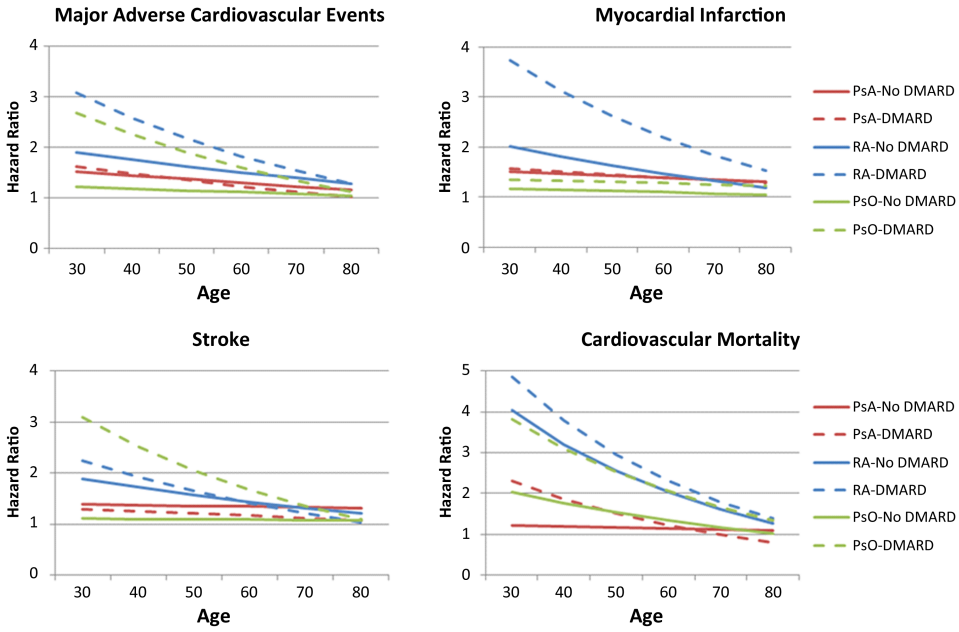

Figure 1 HRs by age. These graphs incorporate the age interaction into the fully adjusted models for major adverse cardiovascular events, cardiovascular mortality, myocardial infarction and stroke. The fully adjusted models include age, sex, hypertension, diabetes, hyperlipidaemia and smoking status (never, past, current).

severity on the incidence of MACE. However, we have shown that simple GP categorisation of body surface area affected by psoriasis is positively correlated with the prevalence of atherosclerotic disease in a prospective study we are conducting nested within the THIN population.[45] Use of a systemic DMARD or phototherapy in patients with psoriasis has previously been used as a proxy for severe psoriasis.[5 10 46] However, DMARDs are less likely to represent a pure marker of disease severity in patients with PsA or RA due to confounding by indication and a potential healthy-user effect in patients with PsA (ie, fewer comorbidities in patients with PsA and psoriasis prescribed a DMARD). By contrast, patients with RA prescribed a DMARD could have had more events because their disease was more severe. However, we are unable to test this hypothesis. In patients with PsA who were prescribed a DMARD, the point estimates were nearly the same as patients without a DMARD prescription, but the CI crossed 1.0. This may be due to a lack of statistical power after stratification by DMARD status. It could also be the result of a healthy-user effect, the anti-inflammatory effect of medications on atherosclerosis or closer follow-up in patients using DMARDs, with more attention to CV risk reduction given more frequent physicians visits.[47 48]

NSAIDs have been associated with the development of CV disease,[49] although this is less clear in patients with RA.[12] Over-the-counter NSAID use may be prevalent among our arthritis cohorts, particularly given that the majority of patients with arthritis have received a prescription NSAID. This should not substantially affect our results, however, as adjustment for prescription NSAID use did not change the main effects (results not shown). Similarly, GPs often do not record the use of biological DMARDs, as these are prescribed directly by rheumatology consultants in the hospital setting.[20] However, according to National Institute for Health and Care Excellence guidelines in the UK, all patients must first fail at least one oral DMARD in order to receive a biological DMARD prescription,[50] so these patients should have been captured in the 'DMARD' group. However, in some cases, the rheumatology consultant will directly prescribe an oral DMARD and the GP may not record this. In a recent validation study, we examined the agreement between GP and medical record report of DMARD use and found that while agreement is overall good, 20 of 53 (38%) patients without a code for a DMARD were reported by the GP to have received a DMARD at some point. In the study, a total of 51 of 87 patients (59%) had either a code for a DMARD or GP report of DMARD use.[29] Therefore, in a sensitivity analysis, we augmented the number of DMARD users by first deriving a propensity score (a treatment prediction model) and then assigning those in the top three quintiles a DMARD prescription; this did not change the results. Finally, there may be patients with PsA in the 'psoriasis-only' cohort who have not yet been diagnosed with inflammatory arthritis or whose diagnosis was not recorded. This concern is not unique to population-based studies but a general issue that makes comparison of cohorts of patients with psoriasis and PsA challenging.[51] The goal of this study was to examine PsA with high specificity and without physical examination or direct questioning of the patients; we did not seek to identify patients with subclinical or undiagnosed PsA.

In conclusion, we report an increased incidence of MACEs in PsA, psoriasis and RA. The HRs for RA and psoriasis were similar to risk estimates in previous studies providing internal validity for the study results in patients with PsA and external validity for the study as a whole. These results suggest the need for improved screening and management of traditional CV risk factors in patients with inflammatory diseases. Future, prospective, randomised, controlled studies are needed to better understand the impact of systemic therapy in decreasing the risk of MACEs in these diseases. Additionally, studies addressing the impact of interventions for traditional CV risk factors on reducing the risk for MACE in patients with inflammatory diseases are needed.

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Supplemental Table 1. Additional Baseline Characteristics

		Control	Psoriatic Arthritis		Rheumatoid arthritis		Psoriasis	
			No DMARD	DMARD	No DMARD	DMARD	No DMARD	DMARD
		N=81,573	N=4,174	N=4,532	N=17,912	N=23,840	N=134,095	N=4,329
Demographics	Socioeconomic Status[1] (Mean(SD))	2.56 (1.48)	2.53 (1.34)	2.51 (1.4)	2.71 (1.4)	2.63 (1.4)	2.64 (1.4)	2.69 (1.4)
	Visits in baseline period (Mean(SD))	36.86 (40.9)	38.73 (43.8)	54.52 (55.3)	43.58 (48.5)	58.64 (60.2)	33.57 (39.8)	52.14 (53.3)
Comorbidities	Diabetes N (%)	4,402 (5.4%)	271 (6.5%)	321 (7.1%)	1,389 (7.8%)	1,842 (7.7%)	6,659 (5.0%)	360 (8.3%)
	Hyperlipidemia N (%)	6,174 (7.6%)	364 (8.7%)	401 (8.9%)	1,747 (9.8%)	2,367 (9.9%)	9,808 (7.3%)	397 (9.2%)
	Hypertension N (%)	15,226 (18.7%)	896 (21.5%)	996 (22.0%)	5,261 (29.4%)	6,551 (27.5%)	22,038(16.4%)	856 (19.8%)
	Heart Failure N (%)	1,227 (1.5%)	51 (1.2%)	34 (0.8%)	810 (4.5%)	653 (2.7%)	1,623 (1.2%)	110 (1.6%)
	Chronic Kidney Disease N (%)	1,498 (1.8%)	60 (1.4%)	99 (2.2%)	569 (3.2%)	824 (3.5%)	1,762 (1.3%)	135 (3.1%)
	Peripheral Vascular Disease N (%)	868 (1.1%)	54 (1.3%)	34 (0.8%)	336 (1.9%)	344 (1.4%)	1,545 (1.2%)	59 (1.4%)
	Atrial Fibrillation N (%)	1,670 (2.1%)	71 (1.7%)	59 (1.3%)	805 (4.5%)	689 (2.9%)	2,210 (1.7%)	87 (2.0%)
	Charlson Index Mean (SD)	0.26 (0.7)	0.27 (0.7)	0.23 (0.6)	0.46 (0.9)	0.37 (0.8)	0.24 (0.7)	0.34 (0.8)
Body Mass Index	Normal N (%)	21,399 (26.2%)	1,086 (26.0%)	1,185 (26.1%)	5,425 (30.3%)	7,932 (33.3%)	43,535 (32.5%)	1,212 (28.0%)
	Overweight N (%)	16,699 (20.5%)	1,183 (28.3%)	1,240 (27.4%)	4,684 (26.2%)	6,701 (28.1%)	35,891 (26.8%)	1,252 (28.9%)
	Obese N (%)	9,706 (11.9%)	844 (20.2%)	1,131 (25%)	2,973 (16.6%)	4,374 (18.4%)	22,159 (16.5%)	1,027 (23.7%)
	Underweight N (%)	1,697 (2.08%)	57 (1.37%)	52 (1.15%)	506 (2.82%)	647 (2.71%)	3,271 (2.44%)	76 (1.76%)
	Missing N (%)	*32,072 (39.3%)*	*1,003 (24%)*	*925 (20.4%)*	*4,324 (24.1%)*	*4,186 (17.6%)*	*29,239 (21.8%)*	*762 (17.6%)*
Smoking Status	Non-Smoker N (%)	37,931 (46.5%)	1,860 (44.6%)	2,134 (47.1%)	8,005 (44.7%)	10,178 (42.7%)	51,286 (38.3%)	1,468 (33.9%)
	Past Smoker N (%)	14,916 (18.3%)	883 (21.2%)	1,109 (24.5%)	3,509 (19.6%)	5,927 (25%)	27,003 (20.1%)	1,075 (24.8%)
	Current Smoker N (%)	17,910 (22%)	950 (22.8%)	905 (20%)	3,731 (20.8%)	5,459 (22.9%)	39,410 (29.4%)	1,418 (32.8%)
	Missing N (%)	*10,816 (13.3%)*	*481 (11.5%)*	*384 (8.47%)*	*2,667 (14.9%)*	*2,246 (9.42%)*	*16,396 (12.2%)*	*368 (8.50%)*
Medications	Prescription NSAID[2]	38,235 (46.9%)	2,838 (68.0%)	3,863 (85.2%)	11,562 (64.6%)	19,982 (83.8%)	31,651 (23.6%)	1,315 (30.4%)

Oral Corticosteroids[3]	7,406 (9.1%)	488 (11.7%)	1,013 (22.4%)	3,926 (21.9%)	10,495 (44.0%)	6,783 (5.06%)	520 (12.0%)
Beta Blocker	7,495 (9.2%)	406 (9.7%)	473 (10.4%)	2,335 (13.0%)	3,097 (13.0%)	10,926 (8.2%)	362 (8.4%)
ARB or ACE inhibitor	8,248 (10.1%)	462 (11.1%)	573 (12.6%)	2,675 (14.9%)	3,652 (15.3%)	11,786 (8.9%)	556 (12.8%)
Any antihypertensive	18,724 (23.0%)	1,079 (25.9%)	1,198 (26.4%)	7,070 (39.5%)	8,867 (37.2%)	27,204 (20.3%)	1,089 (25.2%)
Aspirin	7,462 (9.2%)	381 (9.1%)	335 (7.4%)	2,881 (16.1%)	3, 204 (13.4%)	11,091 (8.3%)	431 (10.0%)
Warfarin	1,226 (1.5%)	52 (1.3%)	57 (1.3%)	513 (2.9%)	635 (2.7%)	1,609 (1.2%)	73 (1.7%)
Clopidogrel	575 (0.7%)	36 (0.9%)	35 (0.8)	226 (1.3%)	299 (1.3%)	848 (0.6%)	51 (1.2%)
Oral anti-diabetic medication	2,439 (3.0%)	144 (3.5%)	179 (4.0%)	768 (4.3%)	907 (3.8%)	3,678 (2.7%)	217 (5.0%)
Insulin	890 (1.1%)	44 (1.1%)	69 (1.5%)	254 (1.4%)	434 (1.8%)	1,418 (1.1%)	89 (2.1%)
Statin	7,374 (9.0%)	392 (9.5%)	497 (11.0%)	2,099 (11.7%)	3,000 (12.6%)	10,652 (7.9%)	521 (12.0%)
Any lipid lowering agent	7,657 (9.4%)	411 (9.9%)	522 (11.5%)	2,205 (12.3%)	3,126 (13.1%)	11,197 (8.4%)	548 (12.7%)

[1]Socioeconomic Status is measured by Townsend Deprivation Score and ranges from 1-5 where 1 is lowest level of deprivation and 5 is the highest level of deprivation.
[2]NSAIDs include tiaprofenic, tenoxicam, sulindac, rofecoxib, piroxicam, naproxen, ketoprofen, indometacin, ibuprofen, flurbiprofen, etodolac, diclofenac, dexibuprofen, celecoxib, parecoxib, lumiracoxib, valdecoxib, benaoxaprofen, fenbufen,flurbiprofen, indoprefen, ketorolac, meloxicam, nabumetone, nimesulide, phenylbutazone, tolmetin, mefanamic acid, diflunisal, etoricoxib
[3]Oral Corticosteroids include betamethasone, beclometasone, dexamethoasone, deflazacort, cortisone acetate, fludrocortisones, hydrocortisone, methylprednisolone, prednisolone, prednisone, triamcinolone

Supplemental Table 2. Hazard Ratios and 95% Confidence Intervals for Major Adverse Cardiovascular Events with Adjustments for Cardioprotective Medications

		Composite	MI	Stroke	CV Death
Unexposed		Ref	Ref	Ref	Ref
PsA	No DMARD	1.22 (1.01-1.46)	1.34 (1.03-1.75)	1.30 (1.01-1.67)	1.04 (0.77-1.40)
	DMARD	1.12 (0.90-1.39)	1.31 (0.97-1.77)	1.07 (0.78-1.47)	0.89 (0.59-1.32)
RA	No DMARD	1.37 (1.26-1.48)	1.32 (1.16-1.50)	1.27 (1.14-1.43)	1.39 (1.24-1.55)
	DMARD	1.51 (1.40-1.63)	1.89 (1.69-2.12)	1.18 (1.05-1.33)	1.55 (1.38-1.74)
Psoriasis	No DMARD	1.07 (1.01-1.14)	1.07 (0.98-1.18)	1.07 (0.98-1.16)	1.08 (0.99-1.18)
	DMARD	1.35 (1.11-1.65)	1.22 (0.89-1.67)	1.38 (1.05-1.83)	1.37 (1.03-1.83)
BB		1.04 (0.97-1.11)	1.26 (1.14-1.40)	1.18 (1.08-1.29)	1.12 (1.03-1.23)
ACE/ARB		1.06 (0.99-1.13)	1.03 (0.92-1.15)	1.14 (1.04-1.26)	1.67 (1.52-1.82)
Statin		0.77 (0.71-0.84)	0.96 (0.84-1.09)	0.96 (0.85-1.09)	1.15 (1.02-1.30)
Visits in baseline period		1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)

The models here represent the fully adjusted models from Table 3 and include age, sex, hypertension, diabetes, hyperlipidemia, smoking status (never, past, current), and start year in the cohort (HR not shown) with the addition of BB, ACE/ARB, statins and visits in the baseline period. Medication use is defined within the one year prior to cohort entrance. Abbreviations: BB = beta-blocker, ACE/ARB = ACE inhibitor or Angiotensin recent blocker

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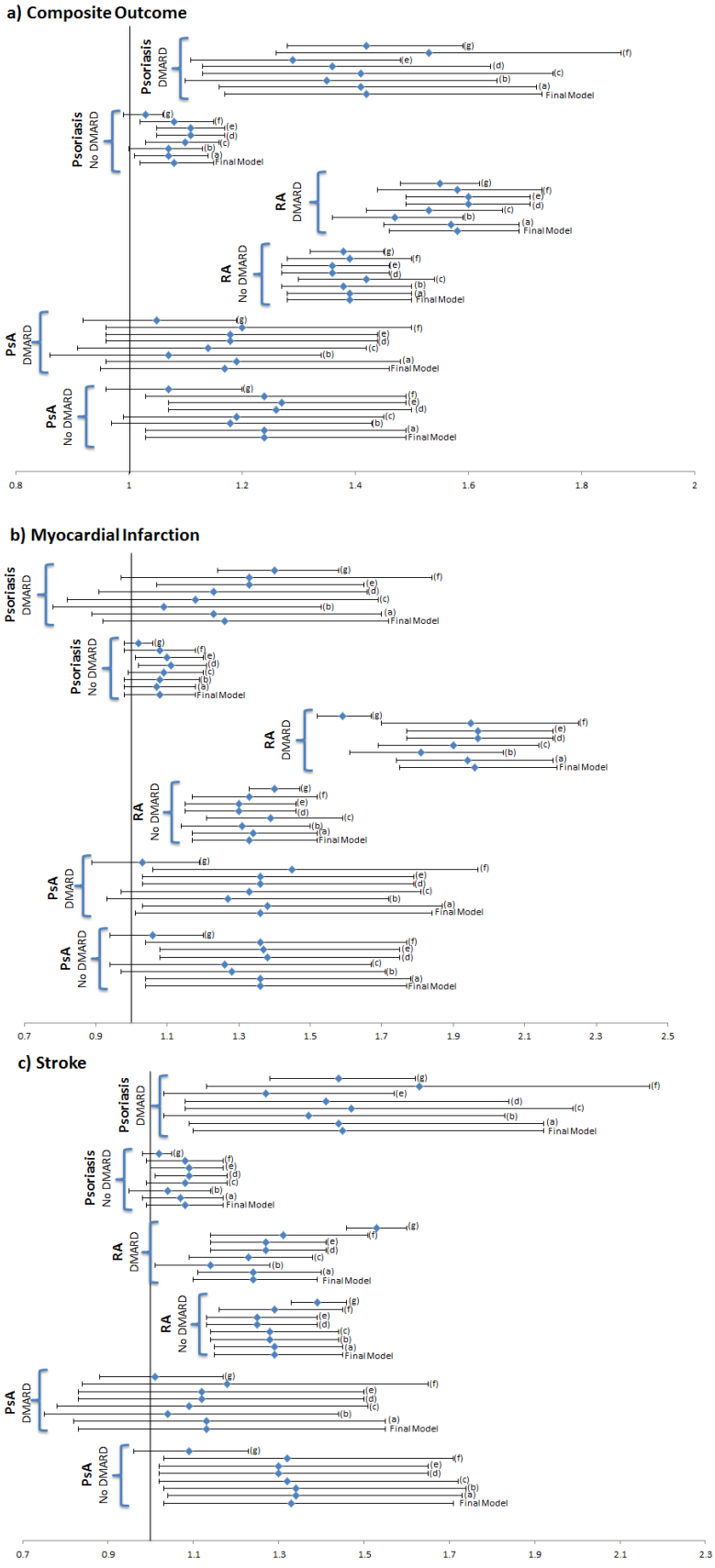
Supplemental Figure 1. Sensitivity Analyses.



Supplemental Figure 1 Legend:

We performed several sensitivity analyses to test the assumptions made in modeling. These are represented in the figure for each outcome stratified by disease-DMARD status and labeled a-g as below. The final model from Table 3 is also included as the lowest line for each disease-dmard category. The following sensitivity analyses were performed: We restricted patients in the cohort to a) only those followed for at least one year prior to index date to ensure capture of comorbidities, b) only those with at least one visit per calendar year during their time in the cohort, c) only those with incident disease defined as patients with at least one year of follow up prior to the first diagnosis code. d) We examined the impact of missing data using multiple imputation (10 iterations) for smoking category and body mass index category. Body mass index was not significant in the full model and therefore not included. The main analysis was then repeated using the imputed smoking values. e) To examine whether missed DMARD prescriptions would have an impact on the results, we predicted DMARD use by first creating a propensity score and then assigned non-DMARD users in the top three quintiles of the propensity score to DMARD use (an increase of approximately 30% in DMARD users). f) A the time varying covariate analysis was designed to test for immortal time bias created by starting follow up time in the DMARD group at first DMARD exposure (included within the start date algorithm noted in the methods). DMARDs were included as a time-varying covariate so that time prior to DMARD initiation was allotted to the "no DMARD" group. This analysis assumed DMARD status as a binary covariate (yes/no) and did not allow for discontinuation (i.e. once exposed to a DMARD, the subject was considered always exposed). We maintained the stratified presentation of the results for easier comparison with the original model. g) We performed a competing risk analysis, including death as a potential outcome. Finally, we utilized alternative definitions for the outcomes including restricting CVA to only ischemic CVA and then only ischemic CVA with a subsequent prescription for anticoagulants or antiplatelet agents (aspirin, cilostazol, clopidogrel, dipyridamole, enoxaparin, heparin, prasugrel, ticlopidine, warfarin). We also broadened the definition of cardiovascular death to include aneurysms and peripheral vascular disease.

The results of these analyses are not shown. The relatively little difference between the point estimates among the final model and the sensitivity analyses suggests results are robust to the assumptions tested.

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Heart risks raised for people with psoriasis, psoriatic arthritis, or RA

A link between psoriasis, psoriatic arthritis, or rheumatoid arthritis and a higher chance of heart attacks, strokes, and other serious heart and circulation problems is confirmed in a detailed new study.

INTRODUCTION

At first glance psoriasis, psoriatic arthritis (arthritis caused by psoriasis), and rheumatoid arthritis (RA) don't seem to have much in common with heart disease. After all, they affect very different parts of the body (the skin and joints as opposed to the heart and blood vessels). However, one thing that may link these illnesses is inflammation.

Inflammation is the body's natural response to injuries (such as cuts, sprains, and broken bones), harmful substances (such as toxins), and germs (such as viruses). Inflammation usually lasts only a short time, helping us to heal or fight off an infection. However, sometimes inflammation lasts much longer and is not helpful, potentially causing damage to our tissues. This is what happens in psoriasis, psoriatic arthritis, and RA.

Many previous studies have suggested that conditions that cause this long-term (chronic) inflammation can also increase the chance of other serious health problems, including heart disease. Nonetheless, there are still gaps in our knowledge about the link between heart disease and these illnesses.

WHAT DID THE RESEARCHERS HOPE TO FIND?

The researchers wanted to explore whether people with RA, psoriasis, or psoriatic arthritis were more likely to have heart attacks and other serious problems related to heart disease than people without these conditions. They were particularly interested in the possible link with psoriatic arthritis, as not much research has explored this.

WHO WAS STUDIED?

Using a UK database of health records the researchers looked at more than 8,700 people with psoriatic arthritis, 41,700 people with RA, and 138,400 people with psoriasis (but not psoriatic arthritis). They also looked at more than 81,500 people who did not have any of these conditions. All of the people were aged 18 to 89.

HOW WAS THE STUDY CONDUCTED?

The researchers followed the people for an average of five years to see whether those with RA, psoriasis, or psoriatic arthritis were more likely to have serious heart and circulation problems than those without these conditions. In particular, the researchers looked at whether people had a heart attack, a stroke, or died of a heart or circulation problem.

They also wanted to explore whether people with more severe RA, psoriasis, or psoriatic arthritis had a higher chance of these problems. To do this they looked at whether people were taking disease-modifying antirheumatic drugs (DMARDs). These medicines are often used by people with more severe cases of these illnesses.

WHAT DOES THE NEW STUDY SAY?

During the study, people who had RA, psoriasis, or psoriatic arthritis were more likely than those without those conditions to have serious heart and circulation problems. The chance of problems varied depending on whether people were taking a DMARD.

- Overall, the increased chance of heart and circulation problems was highest among people with RA. Those not taking a DMARD had nearly a 40 percent higher chance of these problems, while those taking a DMARD had nearly a 60 percent higher chance.
- People with psoriasis had nearly a 10 percent higher chance of these problems if they did not take a DMARD, and around a 40 percent higher chance if they did.
- People with psoriatic arthritis had more than a 20 percent higher chance of these problems if they did not take a DMARD. But those who did take a DMARD did not have an increased chance of these problems.

HOW RELIABLE ARE THE FINDINGS?

This was a very large study that used a reliable database to follow people's health over time. The researchers also took into account many things that can affect a person's chance of serious heart and circulation problems, such as their age, whether they smoked, and whether they had high blood pressure, high cholesterol, or

diabetes. This makes it more likely that the link with RA, psoriasis, and psoriatic arthritis is genuine. It's also worth noting that earlier studies looking at people with RA and psoriasis have had similar findings.

However, the researchers had to make certain assumptions to arrive at their results. Notably, they assumed that people who used DMARDs had more severe illnesses than those who didn't take these medicines. But this may not always have been the case.

WHAT DOES THIS MEAN FOR ME?

If you have RA, psoriasis, or psoriatic arthritis, these findings may sound alarming. But it's important to put them in perspective. If your chance of serious heart and circulation problems is generally low – say, a 2 percent (2 in 100) chance – then a 50 percent increase would raise it to only 3 percent (a 3 in 100 chance).

That's not to say that these findings aren't important, particularly if you already have a raised chance of heart and circulation problems for other reasons. The good news is that you can take steps to lower your risk – for example, by eating a healthy diet, exercising regularly, not smoking, and keeping your blood pressure and cholesterol at healthy levels. You can discuss how best to lower your risk with your doctor.

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From: Ogdie A, Yu Y, Haynes K, *et al*. Risk of major cardiovascular events in patients with psoriatic arthritis, psoriasis and rheumatoid arthritis: a population-based cohort study. *Ann Rheum Dis* 2015;74:326–32. doi:10.1136/annrheumdis-2013-205675LaySummary