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EXTENDED REPORT

Incidence and predictors for cardiovascular events in patients with psoriatic arthritis

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ABSTRACT

Objective To assess the incidence and risk factors of cardiovascular events in patients with psoriatic arthritis (PsA).

Methods A cohort analysis was conducted involving patients recruited and followed over the period from 1978 to 2013 in a large PsA clinic. The participants were assessed at 6 to 12-month intervals according to a standard protocol. The collected information included demographics, lifestyle habits, medical history, medications use and PsA-related outcomes. The primary outcome was a composite major cardiovascular end point comprising myocardial infarction, ischaemic stroke, revascularisation or cardiovascular death. The association between the features of disease activity and the occurrence of cardiovascular events was assessed using Cox proportional hazard models.

Results A total of 1091 patients with PsA were analysed. During the follow-up period, 104 cardiovascular events occurred. A considerable proportion of patients developed a cardiovascular event (19.8% of the patients by the age of 70 years and 30.1% of patient by the age of 80 years). No trend in the risk of developing cardiovascular events was observed over the decades from 1978 to 2013 (p=0.73). In multivariate analysis, the following variables were independent predictors of major cardiovascular events: hypertension (relative risk (RR) 1.81, p=0.015), diabetes (RR 2.72, p<0.001) and the number of dactylitic digits (RR 1.20, p<0.001). Sedimentation rate was a significant predictor only among women (RR 1.83, p=0.02).

Conclusion A significant proportion of patients with PsA develop cardiovascular events during the course of their disease. Increased cardiovascular risk is associated with a combination of traditional cardiovascular risk factors and disease activity.

INTRODUCTION

Psoriasis is an immune-mediated skin disease affecting 2%–3% of the population.[1] Psoriatic arthritis (PsA) is an inflammatory arthritis that affects 14%–30% of people with psoriasis, and can lead to significant joint damage and disability.[2 3] Recent literature highlighted the increased cardiovascular risk in patients with psoriatic disease.[4–6]

A recent meta-analysis found that patients with psoriasis have 40% increased risk of developing cardiovascular diseases.[7] Although the information about cardiovascular risk in PsA is limited compared with that in psoriasis, several studies showed a similar trend.[8 9] Ogdie *et al*[10] reported that the risk of developing major cardiovascular events, myocardial infarction (MI) and stroke was higher in patients with PsA who were not using disease-modifying antirheumatic drugs (DMARDs) and was similar to that in patients with psoriasis and rheumatoid arthritis (RA).

The increased cardiovascular morbidity in psoriatic disease may be partially attributed to the high prevalence of obesity-related metabolic abnormalities, such as impaired glucose tolerance and atherogenic lipid profile,[6 11] in addition to unhealthy lifestyle habits (eg, smoking, physical inactivity) that are common in these patients. Moreover, the effect of certain medications used for psoriasis and arthritis, including non-steroidal anti-inflammatory drugs (NSAIDs) and acitretin, may also have a deleterious effect on the vasculature system. These factors may act synergistically with systemic inflammation to promote atherogenesis.

While the independent effect of disease-related inflammation on cardiovascular risk is established in RA, few studies have thus far attempted to elucidate the link between metabolic abnormalities and PsA-related factors to determine the independent effect of psoriatic disease activity on cardiovascular morbidity. Several studies found an association between the extent of inflammation and surrogate end points of cardiovascular outcomes. This association was independent of traditional cardiovascular risk, supporting the notion that PsA is a risk factor for cardiovascular morbidity.[12–14]

In this cohort study we aimed (1) to estimate the cumulative incidence of cardiovascular events in patients with PsA and (2) to identify independent predictors for developing cardiovascular events in these patients.

METHODS

Patients and setting

A cohort analysis was conducted in patients followed from 1978 to 2013 at the University of Toronto PsA clinic. Patients attending the clinic are enrolled in an ongoing prospective study aimed at assessing prognostic factors in PsA. Each patient is assessed at 6–12-month intervals according to a standard protocol.[15] Information collected and stored in a database includes demographics, lifestyle habits, medical history, medication use, disease-related outcomes and laboratory findings. The majority (98%) of the patients in the clinic met the ClASsification of Psoriatic ARthritis (CASPAR) criteria for classification of PsA.[16] Patients who developed a cardiovascular event prior to the diagnosis of PsA were excluded from the study. All subjects' written consent was obtained according to the Declaration of Helsinki.

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The study has been approved by the University Health Network Ethics Board.

Data collection and definitions

The clinic database was searched to identify patients who developed cardiovascular events. Each identified event was then evaluated by reviewing data from hospital admissions, death certificates and medical records from relevant specialists. Two physicians (LE, DDG) discussed equivocal events and reached a consensus designation regarding the diagnosis. The primary composite end point occurred at the time of the first major cardiovascular event with components including MI, ischaemic stroke, revascularisation or cardiovascular death. MI was defined as one of the following: definite electrocardiographic abnormalities; typical symptoms with probable electrocardiographic abnormalities and abnormal enzymes; typical symptoms and abnormal enzymes. Revascularisation was defined as any of the following procedures: coronary bypass surgery, coronary angioplasty with or without stent insertion and carotid endarterectomy. A secondary composite end point was the first cardiovascular event, including major cardiovascular events as defined above, angina, transient ischaemic accident (TIA) and congestive heart failure (CHF). Angina pectoris was defined as chest discomfort that was aggravated by physical activity and relieved by rest or by the use of nitroglycerine and confirmed by a cardiologist or abnormal findings on myocardial perfusion study or angiography. CHF was defined based on typical symptoms and signs on physical examination, abnormal chest X-ray or abnormal finding on echocardiogram. Ischaemic stroke was defined as sudden onset of focal neurological deficit lasting more than 24 h and attributable to a focal vascular cause. The definition of TIA was the same as stroke but the neurological deficit resolved within 24 h.

Predictors of cardiovascular events

Both traditional cardiovascular risk factors and PsA-related variables were assessed as predictors of cardiovascular events. Traditional cardiovascular risk factors were defined based on the use of medications or findings on physical examination or laboratory tests. The following traditional cardiovascular risk factors were assessed: diabetes mellitus, hypertension, elevated triglycerides (>3.2 mmol/L), elevated cholesterol (total cholesterol >5.2 mmol/L) and ever-smoking (current or past history of daily smoking for at least 1 year). The following PsA-related variables were assessed: duration of psoriasis and PsA, tender and swollen joint count, number of dactylitic digits, enthesitis count, clinically damaged joint count (defined as the presence of limitation of range of movement of >20% of the range not related to the presence of joint effusion, presence of joint deformity, subluxation, loosening or ankylosis), psoriasis area and severity index (PASI), erythrocyte sedimentation rate (ESR), leucocyte count, health assessment questionnaire (HAQ), Short form Health Survery-36 (SF-36) physical component score (PCS) and use of the following medications: NSAIDs, oral corticosteroids, DMARDs and tumour necrosis factor-α blockers.

Statistical analysis

Baseline descriptive statistics were computed with continuous variables summarised by their means and SDs and categorical variables summarised by proportions. The time from the date of birth to the date of the first cardiovascular event was the response of interest; individuals who were event-free at the date they were last known to be alive were censored at this time. A two-parameter Weibull model for this time was used to assess whether there was a trend with age in the risk of cardiovascular events, treating non-cardiovascular death as a competing risk. Non-parametric estimates of the cumulative incidence function for the composite cardiovascular event were obtained, again treating non-cardiovascular death as a competing risk and the age at study entry as a left-truncation time since events were only modelled after study entry.

Multivariate Cox proportional hazard models were fitted for the age at the occurrence of the primary and secondary composite cardiovascular event with time-dependent explanatory variables. The dates that cardiovascular risk factors changed were obtained from patient records when available; if laboratory measurements were not available at a particular visit, the last

Table 1 Characteristics of the study population at clinic entry

Age	43.8±12.8
Sex: male (%)	612 (56.1)
Duration of psoriasis (years)	15.17±12.38
Duration of PsA (years)	5.65±7.95
Hypertension (%)	220 (20.2)
High triglycerides (%)	197 (22)
High cholesterol (%)	365 (40.6)
Diabetes (%)	59 (5.5)
Smoking-ever (%)	408 (44)
PASI	
<10 (%)	619 (83.5)
10–19 (%)	77 (10.4)
>19 (%)	45 (6.1)
Tender joint count	
0 (%)	205 (18.8)
1–7 (%)	512 (46.9)
>7 (%)	374 (34.3)
Swollen joint count	
0 (%)	328 (30.1)
1–7 (%)	477 (43.7)
>7 (%)	286 (26.2)
Damaged joint count	
0 (%)	704 (64.6)
1–9 (%)	280 (25.7)
10–19 (%)	60 (5.5)
≥20 (%)	45 (4.1)
Dactylitic digits	0.66±1.50
HAQ	
0 (%)	105 (18.9)
0.1–0.5 (%)	150 (27)
>0.5 (%)	300 (54.1)
SF-36 PCS	
<30 (%)	162 (30.5)
31–45 (%)	219 (41.2)
>45 (%)	151 (28.4)
Current use of MTX	168 (15.8)
Current use of other DMARDs	88 (8.3)
Current use of anti-TNF agents	25 (2.3)
Current use of corticosteroids	30 (2.8)
Current use of NSAIDs	608 (55.8)

DMARD, disease-modifying antirheumatic drug; HAQ, health assessment questionnaire; MTX, methotrexate; NSAIDs, non-steroidal anti-inflammatory drugs; PASI, psoriasis area and severity index; PsA, psoriatic arthritis; TNF, tumour necrosis factor.

Table 2 The estimated cumulative probability of developing primary cardiovascular events in psoriatic arthritis*

By age (years)	Overall	Men	Women
50	3.3	3.5	2.9
60	8.5	11.3	4.9
70	19.8	25.5	13.4
80	30.1	40.3	21.4

*Non-cardiovascular death was considered as a competing event.

recorded test measurements were used. Since information about triglycerides, cholesterol, PASI, smoking, HAQ and SF-36 was not collected routinely during the first years of the cohort, a distinct missing code was assigned to these variables when they were unavailable in order to minimise the exclusion of patients from the multivariate analysis. Again the age at study entry was the left-truncation time. To assess whether there was a trend in risk of cardiovascular events according to calendar time (ie, a cohort effect) another Cox regression model was fitted including decade (1978–1989, 1990–1999, 2000–2013) of study entry as a stratification factor and a test was carried out to assess whether risk was different over these decades. As a screening phase, each of the above-mentioned predictors was included in a separate regression model adjusting for duration of PsA and sex, with date of birth as time of origin. All variables that achieved significance at the 10% level were then included in a more comprehensive multivariate model that adjusted for the duration of PsA and sex and cardiovascular risk factors. Backward elimination was used to eliminate non-significant covariates from the multivariate regression model.

RESULTS

A total of 1091 patients who had more than one visit and were followed from 1 January 1978 to 20 November 2013 were included in the study. Nine subjects were excluded since they developed cardiovascular event prior to the first visit in the clinic. This cohort had a total of 19 649 person-years of follow-up, with a mean of 9.84±8.61 years per person from clinic entry to the last assessment or any cardiovascular event. The characteristics of the study population at baseline are summarised in table 1.

The cumulative incidence of cardiovascular events in PsA

During the follow-up period, a total of 104 cardiovascular events occurred (57 MI, 9 stroke, 19 revascularisation, two cardiovascular death, 10 angina, one TIA and six CHF). As expected, the risk of developing cardiovascular events increased with age ($p<0.0001$ for a test of trend with the Weibull model). The analysis showed that a considerable proportion of patients developed a cardiovascular event. An estimated 19.8% of the patients experience the composite cardiovascular event by age 70, and 30.1% of patients experience it by the age 80. The rise in cardiovascular risk in women lagged by a decade compared with men (seventh decade in women vs sixth decade in men). The analysis which stratified on the decade of study entry did not suggest evidence of a cohort effect ($p=0.73$). The complete results are presented in table 2 and figure 1.

Factors associated with cardiovascular events

In the univariate analysis traditional cardiovascular risk factors, including hypertension, diabetes mellitus and hypertriglyceridaemia predicted major and all cardiovascular events (tables 3 and 4). In addition, elevated ESR in women, tender joint count, the number of dactylitic digits, leucocyte and neutrophil counts, the level of disability, as measured by SF-36-PCS, and methotrexate use predicted primary and/or all cardiovascular events. After adjusting for traditional cardiovascular risk factors, the number of dactylitic digits (major and all cardiovascular events), tender joint count (major and all cardiovascular events), methotrexate use (all cardiovascular events), low SF-36-PCS (all cardiovascular events) and elevated ESR in women (major and all cardiovascular events) remained independent predictors.

Multivariate analysis

In multivariate analysis the following variables were independent predictors of major cardiovascular events: hypertension (relative risk (RR) 1.81, 95% CI 1.11 to 2.92), diabetes (RR

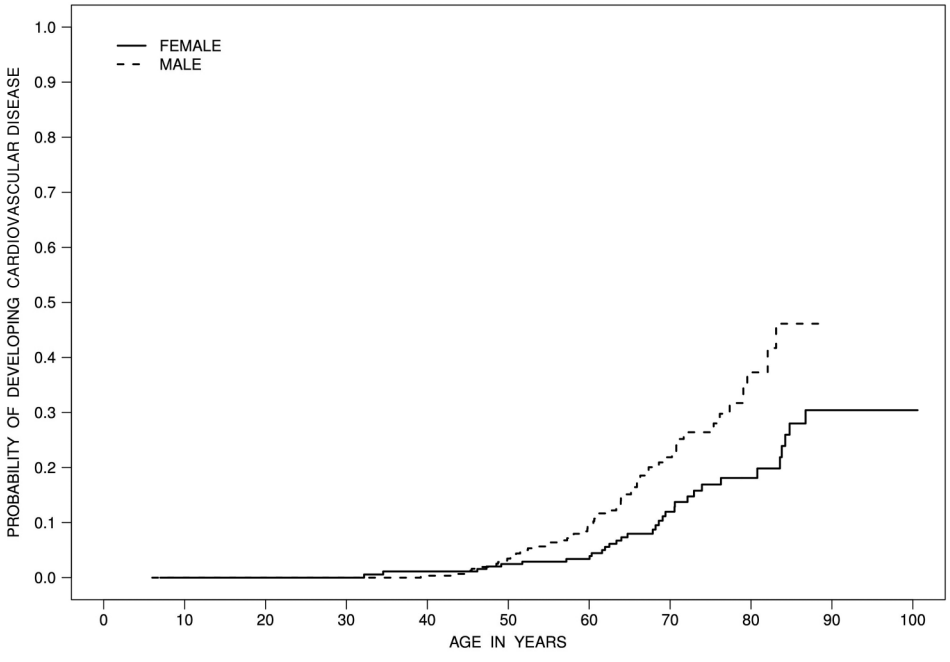

Figure 1 Non-parametric estimates of the cumulative incidence functions for experiencing the composite cardiovascular event by gender in patients with psoriatic arthritis, treating non-cardiovascular death as a competing risk.[17]

Table 3 Predictors for major cardiovascular events—Cox regression analysis with age as time scale (n=1090, 85 events)

	Model 1*		Model 2†		Multivariate reduced‡	
Variable	**RR (95% CI)**	**p Value**	**RR (95% CI)**	**p Value**	**RR (95% CI)**	**p Value**
Smoker: ever	1.54 (0.93 to 2.56)	0.09			1.60 (0.96 to 2.67)	0.09
Hypertension	**1.85 (1.18 to 2.90)**	**0.007**			**1.81 (1.12 to 2.92)**	**0.015**
Diabetes	**3.00 (1.79 to 5.02)**	**<0.0001**			**2.72 (1.60 to 4.62)**	**0.0002**
High cholesterol	1.39 (0.87 to 2.19)	0.16				
High triglyceride	**1.76 (1.10 to 2.81)**	**0.02**			1.42 (0.87 to 2.32)	0.16
Duration of psoriasis	1.00 (0.99 to 1.02)	0.60	1.00 (0.99 to 1.02)	0.69		
Tender joint count						
1–7 vs 0	**1.96 (1.17 to 3.26)**	**0.01**	**1.94 (1.15 to 3.27)**	**0.01**		
>7 vs 0	**2.14 (1.17 to 3.89)**	**0.01**	1.76 (0.95 to 3.26)	0.07		
Swollen joint count						
1–7 vs 0	1.28 (0.79 to 2.06)	0.31	1.17 (0.72 to 1.90)	0.53		
>7	1.69 (0.89 to 3.20)	0.11	1.48 (0.77 to 2.86)	0.24		
Enthesitis count	1.22 (0.94 to 1.61)	0.14	1.25 (0.94 to 1.65)	0.12		
Dactylitis count	**1.23 (1.11 to 1.36)**	**<0.0001**	**1.21 (1.10 to 1.35)**	**0.0002**	**1.20 (1.08 to 1.34)**	**0.0008**
Damaged joint count						
1–9 vs 0	1.44 (0.82 to 2.50)	0.20	1.54 (0.86 to 2.75)	0.14		
10–19 vs 0	1.23 (0.60 to 2.52)	0.57	1.26 (0.60 to 2.66)	0.54		
≥20 vs 0	1.30 (0.63 to 2.66)	0.47	1.53 (0.74 to 3.17)	0.25		
PASI						
10–19 vs <10	0.99 (0.39 to 2.47)	0.98	0.83 (0.33 to 2.09)	0.68		
>19 vs <10	0.92 (0.22 to 3.78)	0.91	0.92 (0.22 to 3.81)	0.91		
Urate (log μmol/L)	1.67 (0.79 to 3.52)	0.18	1.41 (0.69 to 2.88)	0.34		
ESR		**0.008**		**0.01**		**0.02**
Men	**1.13 (0.87 to 1.47)**		**1.09 (0.83 to 1.43)**		**1.04 (0.79 to 1.37)**	
Women	**1.91 (1.19 to 3.07)**		**1.87 (1.15 to 3.05)**		**1.83 (1.12 to 2.99)**	
Leucocytes (log $\times 10^9$/L)	**1.90 (1.00 to 3.61)**	**0.049**	1.73 (0.87 to 3.43)	0.11		
Neutrophils (log $\times 10^9$/L)	**1.75 (1.04 to 2.96)**	**0.04**	1.68 (0.92 to 3.06)	0.09		
HAQ						
0.1–0.5 vs 0	1.28 (0.69 to 2.36)	0.43	1.10 (0.57 to 2.11)	0.77		
>0.5 vs 0	1.20 (0.61 to 2.38)	0.59	0.90 (0.45 to 1.80)	0.76		
SF-36 PCS						
31–45 vs <30	1.07 (0.65 to 1.76)	0.78	1.13 (0.66 to 1.91)	0.65		
>45 vs <30	**0.43 (0.22 to 0.84)**	**0.01**	0.52 (0.26 to 1.03)	0.06		
Medication use						
Anti TNF vs none	0.99 (0.48 to 2.01)	0.98	0.99 (0.47 to 2.04)	0.97		
MTX vs none	1.64 (0.64 to 4.14)	0.29	1.62 (0.62 to 4.21)	0.33		
Other DMARDs vs none	0.82 (0.45 to 1.50)	0.52	0.96 (0.52 to 1.79)	0.91		
Oral corticosteroids	1.84 (0.67 to 5.09)	0.23	1.58 (0.56 to 4.44)	0.39		
Use of NSAIDs	0.91 (0.58 to 1.41)	0.67	0.91 (0.58 to 1.42)	0.68		

Bolded items are statistically significant in multivariate analysis.
*Each model included a single predictor, sex and PsA duration.
†Each model included the predictor on the respective row with sex, PsA duration, hypertension, diabetes, smoking and high triglyceride.
‡The full model included sex, PsA duration, diabetes, smoking and high triglyceride.
DMARD, disease-modifying antirheumatic drug; ESR, erythrocyte sedimentation rate; HAQ, health assessment questionnaire; MTX, methotrexate; NSAIDs, non-steroidal anti-inflammatory drugs; PASI, psoriasis area and severity index; PsA, psoriatic arthritis; RR, relative risk; TNF, tumour necrosis factor.

2.72, 95% CI 1.60 to 4.62) and the number of dactylitic digits (RR 1.20 95% CI 1.08 to 1.34). The interaction between ESR and gender was statistically significant showing a differential effect of ESR on cardiovascular risk across the genders. ESR was a significant predictor only among women (RR 1.83, 95% CI 1.12 to 2.99).

Similar results were found in the multivariate model that assessed predictors for any cardiovascular event: hypertension (RR 1.71, 95% CI 1.11 to 2.64), diabetes (RR 2.53, 95% CI 1.54 to 4.16), dactylitic digits (RR 1.18 95% CI 1.06 to 1.32) and ESR in women (RR 1.70, 95% CI 1.10 to 2.62).

DISCUSSION

Recent literature highlighted the increased cardiovascular risk in patients with PsA. In this study we investigated the incidence and predictors of clinical cardiovascular events in a large well-phenotyped cohort over a period of more than 35 years. We found that a considerable proportion of the patients develop cardiovascular events. The risk of developing cardiovascular events was explained in part by traditional cardiovascular risk factors; however, the level of disease activity and the extent of systemic inflammation were independent predictors of cardiovascular events.

Table 4 Predictors for any cardiovascular event—Cox regression analysis with age as time scale (n=1091, 100 events)

	Model 1*		Model 2†		Multivariate model‡	
Variable	**RR (95% CI)**	**p Value**	**RR (95% CI)**	**p Value**	**RR (95% CI)**	**p Value**
Smoker: ever	1.16 (0.74 to 1.83)	0.52			1.12 (1.71 to 1.78)	0.62
Hypertension	**1.75 (1.16 to 2.63)**	**0.008**			**1.71 (1.11 to 2.64)**	**0.02**
Diabetes	**2.83 (1.74 to 4.58)**	**<0.0001**			**2.53 (1.54 to 4.16)**	**0.0002**
High cholesterol	1.13 (0.74 to 1.71)	0.58				
High triglyceride	**1.64 (1.06 to 2.52)**	**0.03**			1.32 (0.84 to 2.07)	0.23
Duration of psoriasis	1.01 (0.99 to 1.02)	0.45	1.00 (0.99 to 1.02)	0.67		
Tender joint count						
1–7 vs 0	**1.73 (1.08 to 2.76)**	**0.02**	**1.69 (1.05 to 2.73)**	**0.03**		
>7 vs 0	**2.27 (1.33 to 3.88)**	**0.003**	**1.88 (1.08 to 3.27)**	**0.03**		
Swollen joint count						
1–7 vs 0	1.26 (0.82 to 1.95)	0.29	1.16 (0.74 to 1.80)	0.52		
>7	1.71 (0.95 to 3.08)	0.08	1.50 (0.82 to 2.74)	0.19		
Enthesitis count	1.18 (0.90 to 1.54)	0.23	1.18 (0.90 to 1.55)	0.23		
Dactylitis count	**1.21 (1.09 to 1.33)**	**0.0003**	**1.19 (1.07 to 1.32)**	**0.001**	**1.18 (1.06 to 1.32)**	**0.003**
Damaged joint count						
1–9 vs 0	1.56 (0.93 to 2.63)	0.09	1.55 (0.90 to 2.66)	0.11		
10–19 vs 0	1.42 (0.74 to 2.71)	0.29	1.37 (0.70 to 2.66)	0.34		
≥20 vs 0	1.20 (0.61 to 2.37)	0.60	1.36 (0.67 to 2.72)	0.39		
PASI						
10–19 vs <10	1.24 (0.56 to 2.74)	0.59	1.09 (0.48 to 2.43)	0.83		
>19 vs <10	1.28 (0.39 to 4.13)	0.68	1.22 (0.38 to 3.96)	0.84		
Urate (log μmol/L)	1.27 (0.72 to 2.26)	0.41	1.11 (0.65 to 1.87)	0.71		
ESR		**0.006**		**0.01**		**0.03**
Men	**1.06 (0.82 to 1.35)**		**1.03 (0.79 to 1.32)**		**0.98 (0.76 to 1.26)**	
Women	**1.83 (1.19 to 2.82)**		**1.73 (1.12 to 2.67)**		**1.70 (1.10 to 2.62)**	
Leucocytes (log $\times 10^9$/L)	1.43 (0.69 to 2.95)	0.34	1.30 (0.61 to 2.78)	0.50		
Neutrophils (log $\times 10^9$/L)	1.21 (0.75 to 1.95)	0.43	1.18 (0.73 to 1.91)	0.49		
HAQ						
0.1–0.5 vs 0	0.89 (0.41 to 1.91)	0.76	0.83 (0.38 to 1.78)	0.63		
>0.5 vs 0	1.43 (0.76 to 2.71)	0.27	1.13 (0.59 to 2.16)	0.71		
SF-36 PCS						
31–45 vs <30	0.91 (0.51 to 1.62)	0.74	1.07 (0.69 to 1.93)	0.82		
>45 vs <30	**0.35 (0.17 to 0.72)**	**0.004**	**0.45 (0.22 to 0.95)**	**0.035**		
Medication use						
Anti TNF vs none	1.07 (0.56 to 2.03)	0.84	1.08 (0.55 to 2.09)	0.82		
MTX vs none	**2.64 (1.19 to 5.85)**	**0.02**	**2.64 (1.16 to 6.04)**	**0.02**		
Other DMARDs vs none	0.90 (0.52 to 1.56)	0.71	1.04 (0.59 to 1.83)	0.89		
Oral corticosteroids	1.92 (0.77 to 4.77)	0.16	1.68 (0.66 to 4.23)	0.27		
Use of NSAIDs	0.95 (0.64 to 1.44)	0.82	0.93 (0.62 to 1.41)	0.74		

Bolded items are statistically significant.
*Each model included a single predictor, sex and PsA duration.
†Each model included the predictor on the respective row with sex, PsA duration, hypertension, diabetes, smoking and high triglyceride.
‡The full model included sex, PsA duration, hypertension, diabetes, smoking and high triglyceride.
DMARD, disease-modifying antirheumatic drug; ESR, erythrocyte sedimentation rate; HAQ, health assessment questionnaire; MTX, methotrexate; NSAIDs, non-steroidal anti-inflammatory drugs; PASI, psoriasis area and severity index; PsA, psoriatic arthritis; RR, Relative Risk; TNF, tumour necrosis factor.

Several recent population-based studies showed that the risk of developing cardiovascular events in patients with PsA is higher than in the general population and may be higher than in people with psoriasis alone.[10 18] Psoriatic disease is strongly linked with obesity and its related metabolic abnormalities, including dyslipidaemia, glucose intolerance and hypertension that predispose to clinical cardiovascular events.[6 11] This raises the question whether the entire cardiovascular risk is explained by the high prevalence of metabolic abnormalities in these patients and whether the extent of inflammatory burden has an independent effect on cardiovascular risk. In the present study we found that although traditional cardiovascular risk factors are strong predictors of cardiovascular events, the burden of inflammation and disease activity independently affected cardiovascular risk. These findings are in line with studies that reported an association between the extent of inflammation and vascular abnormalities representing different stages of atherogenesis, including vascular inflammation,[19] endothelial dysfunction[14] and atherosclerotic plaques.[20]

Biomarkers of systemic inflammation predict the development of cardiovascular events in the general population and in patients with RA.[21–23] Patients with PsA tend to have lower levels of

inflammatory markers compared with patients with RA; however, in our study higher levels of ESR among women, independently predicted the development of cardiovascular events. Elevated tender joint counts and dactylitic digits count also predicted the occurrence of cardiovascular events independently of traditional cardiovascular events. These factors reflect the extent of clinical disease activity and have been associated with worse long-term outcomes including radiographical damage progression and poor function.[24] Interestingly the severity of psoriasis, a previously reported predictor of cardiovascular events,[25 26] was not associated with this outcome in our study, possibly due to the lower prevalence of patients with severe psoriasis compared with series from dermatology clinics. These findings are in line with our previous observation that showed an association between the levels of ESR and disease activity over time and severity of atherosclerotic plaques in the carotid artery.[20] Other studies found an association between polymorphisms within genes of the immune system and cardiovascular risk.[27 28]

Current guidelines from rheumatology and dermatology societies recognise the high cardiovascular risk in patients with psoriasis and PsA and the need for screening for cardiovascular risk factors and stratification of patients according to their cardiovascular risk based on accepted risk scores.[29 30] However, since clinical risk prediction algorithms, such as the Framingham risk score, do not factor in the effect of systemic inflammation secondary to psoriatic disease in the risk assessment, they may underestimate the actual risk.[31 32] Similar findings were reported in RA.[33] It has been suggested that vascular imaging modalities may improve risk stratification of patients with PsA.[32] Unlike in RA, where EUropean League Against Rheumatism (EULAR) suggested adaptation of the risk score using a 1.5 multiplication factor to patients with more severe disease phenotype,[30] no attempt has been made to account for severity of psoriatic disease in any of the guidelines.

Our study had several potential limitations. The long follow-up period could have resulted in trend in the risk related to changes in screening and treatment of cardiovascular risk factors. However, in our analysis we did not find any significant trend in the risk of developing cardiovascular events over the past three decades. Another limitation is lack of information about potential predictors of cardiovascular events such as physical activity, family history of cardiovascular events and body mass index. In addition, information about current versus past smoking, use of lipid lowering and antihypertensive medications as well as high-density cholesterol and low-density cholesterol were not collected routinely during the first two decades; therefore, these variables were not included as covariates in the regression models. However, part of the effect of these factors is likely reflected by other traditional risk factors that were measured. Last, we could not account for disease activity prior to the first visit to the clinic; however, 42.7% of the patients were seen in the clinic within the first 2 years since the diagnosis. The strengths of the study are the relatively large sample of patients that have been followed for several decades and the comprehensive and accurate phenotyping of the patients that allowed an estimation of the inflammatory burden of the disease over time.

In summary, we have found that a significant proportion of patients with PsA develop cardiovascular events at some point in the course of their disease. Increased cardiovascular risk is associated with a combination of traditional cardiovascular risk factors and elevated levels of disease activity. These results highlight the importance of screening and controlling all traditional cardiovascular risk factors as well as targeting for minimal disease activity that can potentially reduce cardiovascular risk.

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