



Swansea University
Prifysgol Abertawe



Cronfa - Swansea University Open Access Repository

This is an author produced version of a paper published in:
Seminars in Arthritis and Rheumatism

Cronfa URL for this paper:
<http://cronfa.swan.ac.uk/Record/cronfa39111>

Paper:

Cooksey, R., Brophy, S., Kennedy, J., Gutierrez, F., Pickles, T., Davies, R., Piguet, V. & Choy, E. (2018). Cardiovascular risk factors predicting cardiac events are different in patients with rheumatoid arthritis, psoriatic arthritis and psoriasis. *Seminars in Arthritis and Rheumatism*
<http://dx.doi.org/10.1016/j.semarthrit.2018.03.005>

This item is brought to you by Swansea University. Any person downloading material is agreeing to abide by the terms of the repository licence. Copies of full text items may be used or reproduced in any format or medium, without prior permission for personal research or study, educational or non-commercial purposes only. The copyright for any work remains with the original author unless otherwise specified. The full-text must not be sold in any format or medium without the formal permission of the copyright holder.

Permission for multiple reproductions should be obtained from the original author.

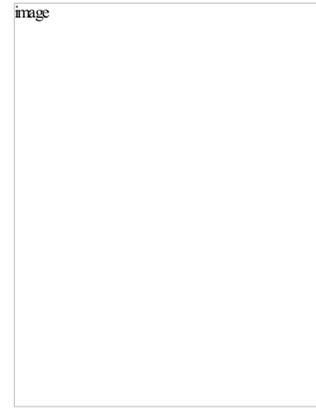
Authors are personally responsible for adhering to copyright and publisher restrictions when uploading content to the repository.

<http://www.swansea.ac.uk/library/researchsupport/ris-support/>

Author's Accepted Manuscript

Cardiovascular risk factors predicting cardiac events are different in patients with rheumatoid arthritis, psoriatic arthritis and psoriasis

Roxanne Cooksey, Sinead Brophy, Jonathan Kennedy, Fabiola Fernandez Gutierrez, Tim Pickles, Ruth Davies, Vincent Piguet, Ernest Choy



www.elsevier.com/locate/bios

PII: S0049-0172(17)30621-2
DOI: <https://doi.org/10.1016/j.semarthrit.2018.03.005>
Reference: YSARH51325

To appear in: *Seminars in Arthritis and Rheumatism*

Cite this article as: Roxanne Cooksey, Sinead Brophy, Jonathan Kennedy, Fabiola Fernandez Gutierrez, Tim Pickles, Ruth Davies, Vincent Piguet and Ernest Choy, Cardiovascular risk factors predicting cardiac events are different in patients with rheumatoid arthritis, psoriatic arthritis and psoriasis, *Seminars in Arthritis and Rheumatism*, doi:10.1016/j.semarthrit.2018.03.005

This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting galley proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

**Cardiovascular risk factors predicting cardiac events are different in patients with
rheumatoid arthritis, psoriatic arthritis and psoriasis**

Roxanne Cooksey*¹, PhD, Prof Sinead Brophy¹, PhD, Jonathan Kennedy¹, PhD, Fabiola Fernandez Gutierrez¹, PhD, Tim Pickles², BSc, Ruth Davies², PhD, Prof Vincent Piguet², MD, Prof Ernest Choy², MD.

1. Swansea University, Data Science Building (Second Floor), Swansea University Medical School, Singleton Park, Swansea, SA2 8PP

2. Division of Infection and Immunity, Cardiff University School of Medicine, Heath Park, Cardiff CF14 4XN

*Corresponding author Roxanne Cooksey, Swansea University, Data Science Building (Second Floor), Swansea University Medical School, Singleton Park, Swansea, SA2 8PP. Email: r.cooksey@swansea.ac.uk, Telephone: +44 1792 602221.

Key words

Psoriasis, psoriatic arthritis, rheumatoid arthritis, cardiovascular, epidemiology, risk factor.

Abstract

Objectives: Increased cardiovascular risk in rheumatoid arthritis (RA) is well established. Examining traditional cardiovascular risk factors alone underestimates cardiovascular risk in RA. Systemic inflammation, measured by erythrocyte sedimentation rate or C-reactive protein is also a major risk factor. However, the contribution of traditional cardiovascular risk factors (such as obesity and hyperlipidaemia) compared to inflammation is uncertain in psoriatic arthritis (PsA) and RA. We examine the incidence of Major Adverse Cardiac Events

(MACE) among patients with RA, PsA, psoriasis and controls adjusting for risk factors, inflammation and Disease Modifying Anti-Rheumatic Drug treatment, to better define cardiovascular risk.

Methods: Using the Secure Anonymised Information Linkage databank, comprising routinely collected Welsh health data from 1999 to 2013, the incidence and first occurrence of a MACE in individuals with RA (n=8650), PsA (n=2128) and psoriasis (n=24630) compared to controls (n=1187706) was investigated.

Results: Traditional cardiovascular risk factors are higher in RA, PsA and psoriasis than controls. After adjusting for these factors, additional cardiovascular risk was only significantly increased in female RA patients (HR: 1.3, 95% CI: 1.0-1.7, p=0.047) and psoriasis (HR: 1.2, 95% CI: 1.0-1.4, p=0.022) but not statistically significant for PsA (HR: 1.5, 95% CI: 0.9-2.5, p=0.126). ESR and CRP were increased in patients with RA but not in patients with psoriasis.

Conclusion: Additional increased cardiovascular risk was observed in female RA and psoriasis but not PsA. Systemic inflammation is higher in RA but not psoriasis, indicating that there are varying mediators of cardiovascular risk across these conditions.

Introduction

Patients with inflammatory arthritis such as rheumatoid Arthritis (RA), have a higher incidence of cardiovascular events.(1, 2) Importantly, cardiovascular risk in RA cannot be explained by traditional cardiovascular risk factors alone (3) and systemic inflammation is independently associated with increased cardiovascular risk.(4) Consequently, cardiovascular risk scores used routinely in the general population, such as the Framingham

risk score underestimate risk in patients with RA.(5) The QRISK2 score includes RA as an independent risk factor and inflates 10-year cardiovascular risk estimates for those with RA by 1.38 times in males and 1.5 times in females. This is comparable to those recommended by European League Against Rheumatism (EULAR) in patients with RA, which recommends a multiplication factor of 1.5 to the algorithms calculating cardiovascular risk factor for the general population.(6) In RA, systematic review and meta-analysis suggested treatment with tumour necrosis factor inhibitors and methotrexate could reduce cardiovascular events, however, data on the effect of DMARDs and biologic treatment on cardiovascular risk in psoriasis and Psoriatic Arthritis (PsA) were limited.(7) PsA is another common chronic inflammatory arthritis occurring in a third of patients with psoriasis. A meta-analysis concluded that ischemic heart disease, peripheral vascular disease and atherosclerosis are increased in patients with psoriasis and traditional cardiovascular risk factors such as diabetes, hypertension, dyslipidaemia, high body mass index, and metabolic syndrome were also more common in these patients.(8) (9, 10) Moreover, comorbidities were associated with more severe psoriasis.

Whether increased cardiovascular risk in psoriasis and PsA is due to more prevalent traditional cardiovascular risk factors remains unclear. Studies demonstrating an increased risk of cardiovascular disease, when controlling for traditional cardiovascular risk factors have tended to be retrospective, population-based studies (11, 12) (13) (14). Limitations of these studies include missing data on family history of ischaemic heart disease, use of NSAIDs and systemic inflammation. Furthermore, case-control approaches frequently adopted by such studies may not be as strong as cohort studies.

A systematic review of cardiovascular comorbidities in PsA reviewed 28 eligible studies.(15) Data from these studies were conflicting with only one study reporting increased cardiovascular mortality. Four studies (4810 PsA patients in total) found increased cardiovascular comorbidity, however, only one of these was a prospective study with 453 patients.(16)

A meta-analysis was carried out by Alamanos et al. and found a wide variation in the annual incidence of PsA, ranging from 0.1 to 23.1 cases per 100,000 (median 6.4/100,000) inhabitants with large differences between countries. The mean age at diagnosis varied between 40.7 and 52 years (median 47.7 years). Prevalence rates also varied between 1 case per 100,000 (Japan) to 420 per 100,000 (Italy) inhabitants.(17) Depending on the definitions used (e.g. diagnostic codes, patient self-reporting, rheumatologist diagnosis and classification criteria) prevalence and incidence rates of PsA in psoriasis patients range from 6% to 41%.

More recently, a systematic review and meta-analysis found PsA to be an independent risk factor for cardiovascular disease. However, this study did not take into account traditional cardiovascular risk factors.(18) Other studies using surrogate markers, such as flow-mediated occlusion and carotid intima-media thickness, found increased prevalence of atherosclerosis. However, many studies have also found that traditional cardiovascular risk factors: hypertension, diabetes and dyslipidaemia were also more common in patients with PsA.(19-22) A single-centre study, based on hospital data, found cardiovascular comorbidities and traditional cardiovascular risk factors were more common in PsA compared to psoriasis patients.(23) In a prospective cohort study of 158 PsA patients followed-up from time of diagnosis, the 10-year cumulative cardiovascular events increased

by 17%.(24) Similar to RA, Framingham risk score significantly underestimated risk in these patients.

Two inception cohorts using the Clinical Practice Research Datalink have provided opposing results; Parisi et al(25)., found no increased risk of major cardiovascular events while Degran et al(26)., reported an increased risk for severe psoriasis patients.

Recently, a large prospective, UK-based study on data from The Health Improvement Network dataset found that cardiovascular events by 40-50% in patients with RA and severe psoriasis (severity defined by DMARD usage).(27) In patients with PsA, cardiovascular risk increased by 20%, which was significantly lower than patients with RA or severe psoriasis. In contrast to patients with psoriasis taking DMARDs, patients with PsA taking DMARDs have lower risk of cardiovascular events. However, it is not clear if this suggests an effect of DMARDs on cardiovascular risk or on disease severity. Similar to previous studies, family history of cardiovascular diseases was not available. In addition, data on ESR or CRP were not available, so the impact of systemic inflammation and DMARDs could not be assessed.(2) Recently, a German study investigating RA has demonstrated that ESR and CRP are significantly elevated in the 6 months prior to an MI compared to controls. There was also a strong association between higher CRP and MI. Furthermore, treatment with prednisone, biologic or other DMARDs was not associated with risk of MI. (28)

Here we examine the cardiovascular events in patients with RA, PsA and psoriasis using the Secure Anonymised Information Linked (SAIL) Databank in Wales, which includes nationwide health data from primary and secondary care, including family history of cardiovascular disease and ESR as linking health data provides a more robust, multi-source perspective which enhances analysis compared to using isolated datasets. (29)

Methods

Study design and patients

The SAIL databank,(30) is a data repository which allows person-based data linkage across datasets. This databank includes Welsh GP data, hospital in- and out-patient records, as well as mortality data collected by the Office of National Statistics (ONS). SAIL holds over a billion anonymised records. It uses a split-file approach to ensure anonymisation and overcome issues of confidentiality and disclosure in health-related data warehousing. Demographic data is sent to a partner organization, NHS Wales Informatics Service, where identifiable information is removed; clinical data are sent directly to the SAIL Databank and an individual is assigned an encrypted Anonymised Linking Field (ALF). The ALF is used to link anonymised individuals across datasets, facilitating longitudinal analysis of an individual's journey through multiple health, education and social datasets.(31) Data collected by GPs is captured via Read Codes (5-digit codes related to diagnosis, medication and process of care codes).(32) Hospital inpatient and outpatient data are collected in the Patient Episode Database for Wales, which contains clinical information regarding patients' hospital admissions, discharges, diagnoses and operations, using the International Classification of Diseases (ICD-10) clinical coding system. The ONS Mortality dataset contains demographic data, place of death and underlying cause of death (also ICD-10).

Patients were identified from GP records from the SAIL databank. Individuals who had at least one READ Code consistent with RA, PsA or psoriasis (Supplementary Table 1) in their GP records were assigned to their respective condition groups. Only those who were over the age of 18 at first mention, which was considered as the diagnosis date, were included.

Data was linked at the person-level to hospital admissions, and ONS mortality data to explore cardiovascular events.

The PsA group comprised individuals positive for PsA codes within their GP record but could additionally have psoriasis codes in their medical history. The psoriasis group had codes for psoriasis only. The RA group may present with a skin disorder initially and so individuals who had RA codes were assigned to the RA group (whether or not they also had psoriasis and PsA codes present). The control population comprised of individuals who did not present with RA, PsA or psoriasis codes. A random date was generated for the control population that could be used as a substitute for a 'diagnosis date.' Data was included from January 1999 to December 2013 for optimum data coverage purposes.

Ethical approval

Data held in the SAIL databank are anonymised and therefore, no ethical approval is required. All data contained in SAIL has the permission from the relevant Caldicott Guardian or Data Protection Officer. SAIL-related projects are required to obtain Information Governance Review Panel (IGRP) approval.

Major adverse cardiac events (MACEs)

Primary outcome measures were MACEs, namely, myocardial infarction (MI), cerebrovascular accident (CVA) and associated deaths identified from the GP, hospital admissions and ONS datasets (Supplementary Table 2 & 3 for coding definitions).

Covariates of interest and confounding factors

Traditional cardiovascular risk factors included age at diagnosis, age at study start, gender, BMI, smoking status, hypertension, hyperlipidaemia, diabetes, previous cardiovascular disease and family history of cardiovascular disease were collected from the GP records where relevant READ Codes were present or calculated from available data (e.g. height and weight for BMI). Measure of inflammation was based on ESR. Potential confounders, such as medications (Non-Steroidal Anti-Inflammatory Drugs (NSAIDs), DMARDs, oral corticosteroids, and topical steroids) statistical analyses. All covariates and confounders were identified from the GP records and the codes used are available in Supplementary Tables 4 - 15.

Statistical analysis

Descriptive statistics were used to examine age, sex and covariate distribution for RA, PsA, psoriasis and the control population. A Cox proportional model was employed to calculate hazard ratios for each group. Censoring occurred when a patient died, lost to follow-up (moving out of Wales, so that health records were incomplete) or reaching the end of the study.

Univariate analyses were performed to determine significance and candidate variables to be included in the Cox proportional hazard model. Significant covariates (p -value of 0.25 or less) were incorporated into the model (Supplementary Tables 16, 17 & 18).

A subgroup analysis was performed which involved individuals who had no MACE events prior to diagnosis of RA, PsA or psoriasis.

Likelihood ratio tests were used to determine the significance of interactions. Missing data was treated as missing.

Results

The population consisted of 8,650 RA, 2,128 PsA and 24,630 psoriasis patients identified from GP records. The control population comprised 1,187,706 individuals present in the GP without codes for RA, PsA, or psoriasis. The mean age of the study population was approximately 50 years. The characteristics of patients and the control group at baseline are reported in Table 1.

The prevalence of co-morbidities and medications taken by the group are presented in Table 2. Individuals with RA tended to take more medication, with 68.2% and 54.3% having ever taken DMARDs and oral steroids, respectively. Hypertension, diabetes and hyperlipidaemia tended to be more prevalent in the RA, PsA and psoriasis patients. At the time of diagnosis, smoking was more prevalent in patients with RA and psoriasis but a similar rate of smoking was observed among patients with PsA and the control population. Interestingly, individuals who ever smoked were lower in patients with PsA than control, RA or psoriasis. Previous ischemic heart disease was more prevalent in RA and psoriasis but lower in patients with PsA. Family history of ischemic heart disease is more common in RA, psoriasis and PsA and use of NSAIDs, DMARDs and steroids were also higher in these patients compared to controls.

In the control population, the incidence rate of MI was 1.9 per 1000 person-years follow-up and 3.0 per 1000 person-years for stroke. Incidence rates of MI, Stroke, and MACE were higher in patients with RA and psoriasis but not in PsA (Table 3).

After controlling for the traditional cardiovascular risk factors MACEs were statistically significantly increased for individuals with psoriasis (HR: 1.2, 95% CI: 1.0-1.4, $p=0.022$) but there was no evidence of an increase for RA and PsA patients (Table 4) when compared to controls. However, when incorporating gender interactions by condition, RA was associated with increased MACEs in females (HR: 1.3, 95% CI: 1.0 to 1.7, $p=0.047$). The greatest predictor of MACE was a previous MACE event (Supplementary Table 19 & 20).

Subgroup analysis, which removed individuals who had MACE events prior to diagnosis, demonstrated that RA (HR: 1.2, 95% CI: 1.0-1.3, $p=0.038$) and psoriasis patients (HR: 1.1, 95% CI: 1.0-1.3, $p=0.025$) had an increased risk of MACE in comparison to controls (Supplementary Table 21) but not for patients with PsA compared to controls. Furthermore, MACE remained significantly increased in patients with RA and psoriasis after the addition of NSAIDs, DMARDs, topical steroids and oral steroids into the statistical model. Likelihood odds ratio tests found no statistical significant interaction between DMARDs and MACEs by condition, meaning that DMARDs did not have significantly different effects within individuals with RA, PsA or psoriasis compared to controls (data not shown). When controlling for age, gender, and BMI there was a significant increase in the mean level of ESR in individuals with RA (regression coefficient: 4.9, 95% CI: 2.7 to 7.0, $p<0.001$) but not psoriasis or psoriatic arthritis compared to controls.

Sensitivity analysis included all individuals aged 50 years or below which demonstrated no increased risk of MACE for individuals with RA and PsA, however, the risk of MACE was significantly increased for individuals with psoriasis (HR: 1.3, 95% CI: 1.1 to 1.6, $p= 0.015$).

Discussion

To our knowledge, this is the first study to demonstrate that patients with psoriasis, similar to patients with RA, have increased MACEs even after controlling for traditional cardiovascular risk factors including family history of ischaemic heart disease. This suggests additional factors contribute to the development of cardiovascular events in these conditions. MACEs were highest in patients with RA and these patients also had higher levels of inflammation, as indicated by increased ESR. In PsA, ESR levels were not significantly increased which may be explained in part by the individuals with RA being a more homogenous group of older females. Indeed, research has shown that elevated ESR is a significant predictor of cardiovascular risk in women with PsA (33) and so suggests a gender effect. Furthermore, psoriatic arthritis is a heterogeneous disease with differential effects on inflammatory markers; one of the limitations of the study is lack of data on the type of PsA which may explain the lack of statistical significant difference in ESR between PsA and controls. However, our findings replicate those reported by Paramarta et al, who demonstrated that ESR and CRP were normal in a PsA cohort (34). In RA, inflammation levels may explain the higher MACE events. However, inflammation was not higher for those with psoriasis when compared with controls and so may not explain the higher levels of MACE in the psoriasis population. These findings are consistent with previous data in RA but are novel for psoriasis.

Our data showed that MACE was not higher in those with PsA after controlling for traditional cardiovascular risk factors. Previous findings from cross-sectional studies,(9, 10, 35) and more recently, two population-based longitudinal studies have found increased

cardiovascular events in patients with PsA. One population study using data from the UK reported a 20% increased risk of MACEs in PsA although this study did not include family history of ischaemic heart disease as a risk factor.(27) Another study from Norway(36) found increased prevalence of self-reported angina pectoris, hypertension and history of percutaneous coronary intervention but not for MI or CVA in patients with PsA, although cardiovascular risk factors were higher in these patients (higher prevalence of hypertension, tobacco smoking and increased BMI). This is in agreement with our findings which shows that traditional cardiovascular risk factors such as hypertension, diabetes, increased BMI and family history of ischaemic heart disease are more prevalent in patients with psoriasis and PsA as well as RA. In our study, traditional cardiovascular risk factors fully account for MACE in PsA, suggesting adjustment in cardiovascular risk score is unnecessary for patients with PsA.

Potential explanations for the discrepancies in findings surrounding cardiovascular risk may be associated with the differing methodologies employed. For instance, cross-sectional, case-control and cohort studies have investigated cardiovascular risk and the approach used may explain different results.

Case definitions may also vary from study to study, for instance, previous studies using electronic health records have stratified patients using phototherapy and differing DMARDs as surrogate markers for disease severity which may not accurately classify the level of disease activity (25-27). Patients must assess the benefits and risks to starting treatments, in particular, systemic and biologic therapies which may cause adverse effects. Patient centred care and education means that an individual with psoriasis is informed to make a personal decision regarding their treatment and an absence of DMARD therapies in their patient

record may reflect this choice, rather than a proxy for disease severity. In fact, a great dissatisfaction has been reported with current psoriasis treatment options (37-39), which may cause resistance to agreeing to these medications.

Previous studies have recruited patients attending secondary care while we studied patients in primary care, so we may have also included more patients with both milder and more severe disease, potentially representing individuals with the condition more appropriately. Cross-sectional studies conducted with patients recruited from secondary care, are more likely to include patients with increased comorbidities and severe diseases than patients considered in our study. This may be particularly important for PsA which is a heterogeneous condition. Disease varies from spondyloarthropathy, mono/oligo-arthritis or polyarthritis.

The Swedish Early Psoriatic Arthritis Register found that ESR and CRP were higher in RA than PsA(40), which we have also found. Patients with polyarticular disease have higher ESR and CRP compared to patients with axial disease; whilst patients with mono-/oligo-arthritis have intermediate values. However, in psoriasis the ESR and CRP are usually normal and so not routinely assessed. In our study we also found no difference between controls and psoriasis.

The fact that PsA patients had lower cardiovascular risk than patients with psoriasis is surprising given most patients with PsA suffer from psoriasis. This may be explained by higher usage of DMARDs, particularly methotrexate which can lower cardiovascular risk. However, in this study we found no interaction between DMARDs and PsA in terms of predicting cardiovascular risk. This differs from the study by Ogdie et al (27), who found an association between DMARD usage and higher cardiovascular risk in patients with psoriasis or PsA. Ogdie et al used DMARD as a surrogate for disease severity. However, this is not

ideal as different DMARDs may have different impact on cardiovascular risk. For instance, Methotrexate is associated with reduced cardiovascular risk in patients with RA, while Acitretin is associated with hyperlipidaemia. Thus, difference in specific DMARDs used in psoriasis and PsA may contribute to why are results are not in agreement with Ogdie et al.

Strength and Limitations

Strengths

A considerable strength of the study is the linkage between the GP and hospital admissions datasets, allowing the robust and reliable clinical picture of the population. This study also includes data on family history of ischaemic heart disease and ESR. MACE-related hospital admissions and associated deaths were identified using ICD-10 codes from hospital admissions, not relying on algorithms or text comments from health records and as such, MACEs are confirmed in the datasets. Utilising routine data we include a nation-wide, large-scale population that does not result in a small, potentially unrepresentative sample (11, 24, 41, 42) , restrict the sample to a single gender, nor rely on self-reported diagnoses (43); linking routine health data means that a representative cohort can be created with conditions and events confirmed in one or all of the datasets. The routine data also allows more patients to be assessed, when compared to studies that use individuals who fulfil certain disease specific criteria, which may change or be updated in the future. Diagnostic criteria parameters for psoriatic arthritis and rheumatoid arthritis (44, 45) (there is no specific criteria for psoriasis, at present) may not be reliably available in routine data. Strictly adhering to criteria may cause early disease or less severe cases to be missed, even though the disease in these individuals could progress to meet all aspects of a given criteria over time. This would result in a limited and biased sample that is likely to have more severe

disease and therefore increased risk of comorbidities, including cardiac events, thereby over-inflating cardiac risk estimations. To utilise routine data to its full potential, it makes sense in this instance to allow clinical coding of conditions to define the populations, especially since primary care and secondary care physicians are qualified in identifying conditions, as our prevalence rates confirm; our 0.71% rate of RA is comparable to the 1% cited elsewhere,(46) while our 0.2% rate of PsA is in line with general population estimates of 0.3% to 1%,(47) and finally, our 2.0% rate of psoriasis was similar to UK findings of 1.9%.(48)

Furthermore, the incidence rate of MI observed in our study was 1.9 per 1000 person (Table 2) which is comparable to the rate of 1.5 reported for men and 0.6 reported for women living in England in 2010 (49) but our rate of stroke was 3.0 per 1000 person years, which is somewhat higher than the rates for men (1.8) and women (1.4) in England during 2007.(49)

Limitations

It is possible that there is some fluidity between the classified groups; as psoriasis and psoriatic arthritis frequently coexist, individuals who are assigned to the psoriasis group based on psoriasis Read Codes could actually have PsA which has not yet been detected. In addition, identifying individuals with arthropathy from GP records means that their condition may or may not be confirmed by a rheumatologist. It is worthy to note that our classification of PsA patients differs from those used previously. In this study, patients assigned to the PsA group could also have codes for psoriasis. The reason for this is that PsA and psoriasis frequently coexist and excluding individuals who present with both PsA and psoriasis codes from analysis could potentially omit 30% of the PsA population(50). Furthermore, another study has demonstrated that over a half of psoriasis patients who

received systemic or biologic therapies at study start had an inflammatory arthritis diagnosis by the end of follow-up (25).

We can also expect a degree of missing data when using routine data for research purposes.

We did not have a true marker for disease severity within the data and could not assess its role in cardiovascular risk in this study. However, as per previous studies we explored the role of DMARDs as a surrogate marker for severity and found no interaction between DMARDs and cardiovascular risk.

There was limited data on the usage of biologic therapies however findings suggest that biologic usage is not associated with risk of MI in RA. Further work to explore the role of the biologics will be useful to understand the true risk of cardiovascular disease in inflammatory arthritis and psoriasis.

Conclusions

Cardiovascular events were increased in female RA patients and in individuals with psoriasis after adjusting for traditional cardiovascular risk factors. The increased risk of cardiovascular events in RA may be attributed to inflammation. In psoriasis there are other additional unidentified risk factors for cardiovascular events and this needs more investigation. In PsA, risk of MACE appears to be attributed to increased prevalence of traditional cardiovascular risk factors. Cardiovascular risk score adjustment, such as recommended by EULAR for RA may not be applicable for PsA. Distinct factors are responsible for cardiovascular events in different chronic inflammatory diseases and as such cardiovascular risk reduction strategies need to be disease specific and not standard across these conditions.

Key messages

- There is an increased cardiovascular risk in women with RA and men and women with psoriasis but not for PsA.
- There are additional, unidentified risk factors of MACE in psoriasis.
- Cardiovascular risk strategies need to be disease specific for inflammatory arthritis conditions and psoriasis.

Acknowledgements

We would like to thank our funding source, Pfizer for supporting this investigation. This work uses data provided by patients and collected by the National Health Service as part of their care and support. This study utilises anonymised data held in the Secure Anonymised Information Linkage (SAIL) system which is part of the national e-health records research infrastructure for Wales. We would like to acknowledge all the data providers who make anonymised data available for research. For further information on the SAIL databank and enquiries in how to access the data, please visit the SAIL website (<http://www.saildatabank.com>). This work was also conducted as part of the Welsh Arthritis Research Network and the National Centre for Population Health and Well-being Research.

Conflict of interest statement

Pfizer provided the funding for this study following an ICRP grant application however, the funders had no involvement in the study and as such, the authors declare no competing interests. EC has received consultancy and speaker fee from Pfizer.

Funding statement

This work was supported by Pfizer ICRP grant to EC, RC, SB, TP, RD and VP.

References

1. Meune C, Touze E, Trinquart L, Allanore Y. Trends in cardiovascular mortality in patients with rheumatoid arthritis over 50 years: a systematic review and meta-analysis of cohort studies. *Rheumatology (Oxford)*. 2009;48(10):1309-13.
2. Kristensen SL, McInnes IB, Sattar N. Psoriasis, psoriatic arthritis and cardiovascular risk: are we closer to a clinical recommendation? *Ann Rheum Dis*. 2015;74(2):321-2.
3. Dessein PH, Joffe BI, Veller MG, Stevens BA, Tobias M, Reddi K, et al. Traditional and nontraditional cardiovascular risk factors are associated with atherosclerosis in rheumatoid arthritis. *J Rheumatol*. 2005;32(3):435-42.
4. Graf J, Scherzer R, Grunfeld C, Imboden J. Levels of C-reactive protein associated with high and very high cardiovascular risk are prevalent in patients with rheumatoid arthritis. *PLoS One*. 2009;4(7):e6242.
5. Arts EE, Popa C, Den Broeder AA, Semb AG, Toms T, Kitas GD, et al. Performance of four current risk algorithms in predicting cardiovascular events in patients with early rheumatoid arthritis. *Ann Rheum Dis*. 2015;74(4):668-74.
6. Agca R, Heslinga SC, Rollefstad S, Heslinga M, McInnes IB, Peters MJ, et al. EULAR recommendations for cardiovascular disease risk management in patients with rheumatoid arthritis and other forms of inflammatory joint disorders: 2015/2016 update. *Ann Rheum Dis*. 2016.
7. Roubille C, Richer V, Starnino T, McCourt C, McFarlane A, Fleming P, et al. The effects of tumour necrosis factor inhibitors, methotrexate, non-steroidal anti-inflammatory drugs and corticosteroids on cardiovascular events in rheumatoid arthritis, psoriasis and psoriatic arthritis: a systematic review and meta-analysis. *Ann Rheum Dis*. 2015;74(3):480-9.

8. Miller IM, Ellervik C, Yazdanyar S, Jemec GB. Meta-analysis of psoriasis, cardiovascular disease, and associated risk factors. *J Am Acad Dermatol*. 2013;69(6):1014-24.
9. Belinchon I, Vanaclocha F, de la Cueva-Dobao P, Coto-Segura P, Labandeira J, Herranz P, et al. Metabolic syndrome in Spanish patients with psoriasis needing systemic therapy: Prevalence and association with cardiovascular disease in PSO-RISK, a cross-sectional study. *J Dermatolog Treat*. 2015;26(4):318-25.
10. Edson-Heredia E, Zhu B, Lefevre C, Wang M, Barrett A, Bushe CJ, et al. Prevalence and incidence rates of cardiovascular, autoimmune, and other diseases in patients with psoriatic or psoriatic arthritis: a retrospective study using Clinical Practice Research Datalink. *J Eur Acad Dermatol Venereol*. 2015;29(5):955-63.
11. Calamita AB, Calamita Z, Braga JC. Risk factors for cardiovascular disease in psoriasis: relation to inflammation assessed by the severity and duration of illness. *Inflamm Allergy Drug Targets*. 2013;12(6):385-90.
12. Torres T, Sales R, Vasconcelos C, Martins da Silva B, Selores M. Framingham Risk Score underestimates cardiovascular disease risk in severe psoriatic patients: implications in cardiovascular risk factors management and primary prevention of cardiovascular disease. *J Dermatol*. 2013;40(11):923-6.
13. Gelfand JM, Neimann AL, Shin DB, Wang X, Margolis DJ, Troxel AB. Risk of myocardial infarction in patients with psoriasis. *JAMA*. 2006;296(14):1735-41.
14. Gelfand JM, Dommasch ED, Shin DB, Azfar RS, Kurd SK, Wang X, et al. The risk of stroke in patients with psoriasis. *J Invest Dermatol*. 2009;129(10):2411-8.
15. Jamnitski A, Symmons D, Peters MJ, Sattar N, McInnes I, Nurmohamed MT. Cardiovascular comorbidities in patients with psoriatic arthritis: a systematic review. *Ann Rheum Dis*. 2013;72(2):211-6.
16. Buckley C, Cavill C, Taylor G, Kay H, Waldron N, Korendowych E, et al. Mortality in psoriatic arthritis - a single-center study from the UK. *J Rheumatol*. 2010;37(10):2141-4.
17. Alamanos Y, Voulgari PV, Drosos AA. Incidence and prevalence of psoriatic arthritis: a systematic review. *J Rheumatol*. 2008;35(7):1354-8.
18. Polachek A, Touma Z, Anderson M, Eder L. Risk of cardiovascular morbidity in patients with psoriatic arthritis: A meta-analysis of observational studies. *Arthritis Care Res (Hoboken)*. 2016.
19. Popescu C, Pintilie AM, Bojinca V, Balanescu A, Ionescu R. Cardiovascular risk in psoriatic arthritis - a cross-sectional study. *Maedica (Buchar)*. 2014;9(1):19-24.
20. Mok CC, Ko GT, Ho LY, Yu KL, Chan PT, To CH. Prevalence of atherosclerotic risk factors and the metabolic syndrome in patients with chronic inflammatory arthritis. *Arthritis Care Res (Hoboken)*. 2011;63(2):195-202.
21. Tam LS, Tomlinson B, Chu TT, Li M, Leung YY, Kwok LW, et al. Cardiovascular risk profile of patients with psoriatic arthritis compared to controls--the role of inflammation. *Rheumatology (Oxford)*. 2008;47(5):718-23.
22. Lin YC, Dalal D, Churton S, Brennan DM, Korman NJ, Kim ES, et al. Relationship between metabolic syndrome and carotid intima-media thickness: cross-sectional comparison between psoriasis and psoriatic arthritis. *Arthritis Care Res (Hoboken)*. 2014;66(1):97-103.
23. Husted JA, Thavaneswaran A, Chandran V, Eder L, Rosen CF, Cook RJ, et al. Cardiovascular and other comorbidities in patients with psoriatic arthritis: a comparison with patients with psoriasis. *Arthritis Care Res (Hoboken)*. 2011;63(12):1729-35.
24. Ernste FC, Sanchez-Menendez M, Wilton KM, Crowson CS, Matteson EL, Maradit Kremers H. Cardiovascular risk profile at the onset of psoriatic arthritis: a population-based cohort study. *Arthritis Care Res (Hoboken)*. 2015;67(7):1015-21.
25. Parisi R, Rutter MK, Lunt M, Young HS, Symmons DPM, Griffiths CEM, et al. Psoriasis and the Risk of Major Cardiovascular Events: Cohort Study Using the Clinical Practice Research Datalink. *J Invest Dermatol*. 2015;135(9):2189-97.

26. Dregan A, Charlton J, Chowienczyk P, Gulliford MC. Chronic inflammatory disorders and risk of type 2 diabetes mellitus, coronary heart disease, and stroke: a population-based cohort study. *Circulation*. 2014;130(10):837-44.
27. Ogdie A, Yu Y, Haynes K, Love TJ, Maliha S, Jiang Y, 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(2):326-32.
28. Meissner Y, Zink A, Kekow J, Rockwitz K, Liebhaber A, Zinke S, et al. Impact of disease activity and treatment of comorbidities on the risk of myocardial infarction in rheumatoid arthritis. *Arthritis Res Ther*. 2016;18(1):183.
29. Husain MJ, Brophy S, Macey S, Pinder LM, Atkinson MD, Cooksey R, et al. HERALD (health economics using routine anonymised linked data). *BMC Med Inform Decis Mak*. 2012;12:24.
30. Ford DV, Jones KH, Verplancke JP, Lyons RA, John G, Brown G, et al. The SAIL Databank: building a national architecture for e-health research and evaluation. *BMC Health Serv Res*. 2009;9:157.
31. Lyons R, Ford D, Jones K. The Secure Anonymised Information Linkage (SAIL) system in Wales has privacy protection at its heart. *BMJ*. 2014;348:g2384.
32. Chisholm J. The Read clinical classification. *BMJ*. 1990;300(6732):1092.
33. Eder L, Wu Y, Chandran V, Cook R, Gladman DD. Incidence and predictors for cardiovascular events in patients with psoriatic arthritis. *Ann Rheum Dis*. 2016;75(9):1680-6.
34. Paramarta JE, De Rycke L, Ambarus CA, Tak PP, Baeten D. Undifferentiated spondyloarthritis vs ankylosing spondylitis and psoriatic arthritis: a real-life prospective cohort study of clinical presentation and response to treatment. *Rheumatology (Oxford)*. 2013;52(10):1873-8.
35. Lin HW, Wang KH, Lin HC, Lin HC. Increased risk of acute myocardial infarction in patients with psoriasis: a 5-year population-based study in Taiwan. *J Am Acad Dermatol*. 2011;64(3):495-501.
36. Gulati AM, Semb AG, Rollefstad S, Romundstad PR, Kavanaugh A, Gulati S, et al. On the HUNT for cardiovascular risk factors and disease in patients with psoriatic arthritis: population-based data from the Nord-Trøndelag Health Study. *Ann Rheum Dis*. 2016;75(5):819-24.
37. Lebwohl MG, Bachelez H, Barker J, Girolomoni G, Kavanaugh A, Langley RG, et al. Patient perspectives in the management of psoriasis: results from the population-based Multinational Assessment of Psoriasis and Psoriatic Arthritis Survey. *J Am Acad Dermatol*. 2014;70(5):871-81 e1-30.
38. Stern RS, Nijsten T, Feldman SR, Margolis DJ, Rolstad T. Psoriasis is common, carries a substantial burden even when not extensive, and is associated with widespread treatment dissatisfaction. *J Investig Dermatol Symp Proc*. 2004;9(2):136-9.
39. Eliasson L, Bewley AP, Mughal F, Johnston KM, Kuznik A, Patel C, et al. Evaluation of psoriasis patients' attitudes toward benefit-risk and therapeutic trade-offs in their choice of treatments. *Patient Prefer Adherence*. 2017;11:353-62.
40. Lindqvist UR, Alenius GM, Husmark T, Theander E, Holmstrom G, Larsson PT, et al. The Swedish early psoriatic arthritis register-- 2-year followup: a comparison with early rheumatoid arthritis. *J Rheumatol*. 2008;35(4):668-73.
41. Rosales Alexander JL, Cantero-Hinojosa J, Salvatierra J, Magro Checa C, Gonzalez-Gay MA, Raya Alvarez E. Cardiovascular risk assessment according to a national calibrated score risk index in psoriatic arthritis patients without clinically evident cardiovascular disease or classic atherosclerosis risk factors. *Joint Bone Spine*. 2014;81(2):164-8.
42. Pehlevan S, Yetkin DO, Bahadir C, Goktay F, Pehlevan Y, Kayatas K, et al. Increased prevalence of metabolic syndrome in patients with psoriatic arthritis. *Metab Syndr Relat Disord*. 2014;12(1):43-8.
43. Li WQ, Han JL, Manson JE, Rimm EB, Rexrode KM, Curhan GC, et al. Psoriasis and risk of nonfatal cardiovascular disease in U.S. women: a cohort study. *Br J Dermatol*. 2012;166(4):811-8.

44. Taylor W, Gladman D, Helliwell P, Marchesoni A, Mease P, Mielants H, et al. Classification criteria for psoriatic arthritis: development of new criteria from a large international study. *Arthritis Rheum.* 2006;54(8):2665-73.
45. Aletaha D, Neogi T, Silman AJ, Funovits J, Felson DT, Bingham CO, 3rd, et al. 2010 Rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. *Arthritis Rheum.* 2010;62(9):2569-81.
46. Symmons D, Turner G, Webb R, Asten P, Barrett E, Lunt M, et al. The prevalence of rheumatoid arthritis in the United Kingdom: new estimates for a new century. *Rheumatology (Oxford).* 2002;41(7):793-800.
47. Gladman DD, Antoni C, Mease P, Clegg DO, Nash P. Psoriatic arthritis: epidemiology, clinical features, course, and outcome. *Ann Rheum Dis.* 2005;64 Suppl 2:ii14-7.
48. Seminara NM, Abuabara K, Shin DB, Langan SM, Kimmel SE, Margolis D, et al. Validity of The Health Improvement Network (THIN) for the study of psoriasis. *Br J Dermatol.* 2011;164(3):602-9.
49. Townsend N, Wickramasinghe K, Bhatnagar P, Smolina K, Nichols M, Leal J, Luengo-Fernandez R, Rayner M (2012). *Coronary heart disease statistics 2012 edition.* British Heart Foundation: London.
50. Zachariae H. Prevalence of joint disease in patients with psoriasis: implications for therapy. *Am J Clin Dermatol.* 2003;4(7):441-7.

Accepted manuscript

Table 1: Baseline Characteristics

	Control (n=1187706)	RA (n=8650)	PsA (n=2128)	Psoriasis (n=24630)
Age at study start (Confidence Intervals)	39.0 (16.3) (39 to 39)	48.1 (15.0) (47.8 to 48.4)	38.5 (13.2) (37.9 to 39.1)	40.2 (15.4) (40 to 40.4)
Mean Age at diagnosis/ Random date (SD)	50 (17.2) (50 to 50)	59.6 (14.6) (59.3 to 59.9)	50.3 (13.1) (49.7 to 50.9)	51.4 (16.2) (51.2 to 51.6)
Male	49% (585049/1187422) (49.2 to 49.4)	32% (2780/8650) (31.1 to 33.1)	47% (998/2127) (44.8 to 49.1)	49% (12037/24627) (48.3 to 50.0)
Baseline BMI	25.5 (5.1) (25.5 to 25.5)	26.8 (5.5) (26.7 to 26.9)	27.8 (5.9) (27.5 to 28.1)	26.5 (5.4) (26.4 to 26.6)
Smoker	21.2% (251423/1187706) (21.1 to 21.2)	24.6% (2129/8650) (23.7 to 25.5)	21.9% (467/2128) (20.2 to 23.8)	27.9% (6877/24630) (27.4 to 28.5)
Statin use	0.8 % (9275/1187706) (0.8 to 0.8)	1.6% (137/8650) (1.3 to 1.9)	0.9% (19/2128) (0.6 to 1.4)	1.1% (278/24630) (1.0 to 1.3)
ESR (SD)	8.5 (12.8) (8.5 to 8.5)	11.0 (17.1) (10.6 to 11.4)	12.1 (15.4) (11.4 to 12.8)	8.9 (14.1) (8.7 to 9.1)

ESR and Statin use were not included in the statistical model due to being on the MACE pathway.

Table 2: Smoking, comorbidity and medication history throughout patient record

	Control (n=1187706)	RA (n=8650)	PsA (n=2128)	Psoriasis (n=24630)
Ever smoked	50.9 % (604705/1187706)	50.1% (4410/8650)	46.7% (994/2128)	50% (12391/24630)
(Confidence Intervals)	(50.8 to 51.0)	(50.2 to 52.0)	(44.6 to 48.8)	(49.7 to 50.9)
Hyperlipidemia	7.3% (86258/1187706)	13.9% (1202/8650)	12.6% (268/2128)	11.4% (2796/24630)
	(7.2 to 7.3)	(13.2 to 14.6)	(11.3 to 14.1)	(11.0 to 11.8)
Diabetes	7.8% (92345/1187706)	14.1% (1220/8650)	13.1% (278/2128)	11.9% (2936/24630)
	(7.7 to 7.8)	(13.4 to 14.9)	(11.7 to 14.6)	(11.5 to 12.3)
Hypertension	21.6% (256665/1187706)	39.7% (3434/8650)	33.3% (709/2128)	29.9% (7368/24630)
	(21.5 to 21.7)	(38.7 to 40.7)	(31.4 to 35.4)	(29.4 to 30.5)
Ischaemic heart disease	6.7% (79811/1187706)	14.5% (1258/8650)	7.8% (166/2128)	9.6% (2371/24630)
	(6.7 to 6.8)	(13.8 to 15.3)	(6.7 to 9.0)	(9.3 to 10.0)
Family history of ischaemic heart disease	14.1% (167577/1187706)	18.5% (1604/8650)	22.3% (474/2128)	18.5% (4562/24630)
	(14.1 to 14.2)	(17.7 to 19.4)	(20.6 to 24.1)	(18.0 to 19.0)
NSAIDs	61.5% (730476/1187706)	92.9% (8034/8650)	92.6% (1970/2128)	79.9% (19680/24630)
	(61.4 to 61.6)	(92.3 to 93.4)	(91.4 to 93.6)	(79.4 to 80.4)
DMARDs	1.2% (13735/1187706)	68.2% (5896/8650)	57.1% (1214/2128)	7.5% (1847/24630)
	(1.1 to 1.2)	(67.9 to 69.9)	(54.9 to 59.1)	(7.2 to 7.8)
Oral steroids	13.5% (159918/1187706)	54.3% (4699/8650)	33.8% (720/2128)	22.6% (5566/24630)
	(13.4 to 13.5)	(53.3 to 55.4)	(31.9 to 35.9)	(22.1 to 23.1)
Topical steroids	33.1% (393324/1187706)	53.8% (4656/8650)	80.3% (1708/2128)	84.4% (20778/24630)
	(33.0 to 33.2)	(52.8 to 54.9)	(78.5 to 81.9)	(83.9 to 84.8)

Table 3: Incidence of MI, Stroke and MACE (excluding individuals who have had events pre-diagnosis)

	MI Cases	Person Years Follow-up	Incidence rate per 1000 PY (95% CI)	Stroke Cases	Person Years Follow-up	Incidence rate per 1000 PY (95% CI)	MACE Cases	Person Years Follow-up	Incidence rate per 1000 PY (95% CI)
Control	13708	7367124	1.9 (1.8 to 1.9)	21936	7371519	3.0 (2.9 to 3.0)	33456	7367124	4.5 (4.5 to 4.6)
RA	241	57005	4.2 (3.7 to 4.8)	340	57093	5.4 (5.4 to 6.6)	548	57005	9.6 (8.8 to 10.5)
PsA	24	14801	1.6 (1.1 to 2.4)	19	14801	1.3 (0.8 to 2.0)	43	14801	2.9 (2.2 to 3.9)
Psoriasis	373	165063	2.3 (2.0 to 2.5)	569	165200	3.4 (3.2 to 3.7)	879	165063	5.3 (5.0 to 5.7)

Table 4: Hazard ratio of developing a major adverse cardiac event (MACE) by condition compared to control population with gender as an interaction term

	Hazard Ratio	95% CI
RA	1.0	0.8 to 1.3
PsA	1.5	0.9 to 2.5
Psoriasis*	1.2	1.0 to 1.4
<i>Interaction:</i>	1.3	1.0 to 1.7
RA x Female*		
PsA x Female	0.5	0.2 to 1.1
Psoriasis x Female	0.9	0.7 to 1.1
<i>Adjusted for:</i>		
Female	0.7	0.6 to 0.7**
Age at diagnosis	1.2	1.1 to 1.2**
Age at study start	0.9	0.9 to 0.9**
DMARD	1.1	1.0 to 1.3*
NSAIDS	2.1	1.9 to 2.2**
Topical steroids	0.9	0.9 to 0.9**
Oral steroids	1.1	1.1 to 1.2**
BMI	1.0	1.0 to 1.0
Smoker	1.2	1.2 to 1.2**
Hyperlipidemia	1.2	1.2 to 1.3**
Diabetes	1.4	1.3 to 1.4**
Hypertension	1.3	1.2 to 1.3**
Ischaemic heart disease in family	1.1	1.1 to 1.1**

*p<0.05; **p<0.01

Table 5: Hazard ratio of developing a major adverse cardiac event (MACE) by condition compared to control population in individuals of 50 years old or younger

	Hazard Ratio	95% CI
RA	1.0	0.7 to 1.5
PsA	1.2	0.6 to 2.3
Psoriasis*	1.3	1.1 to 1.6
<i>Adjusted for:</i>		
Female	0.5	0.5 to 0.5**
Age at diagnosis	1.1	1.1 to 1.1**
Age at study start	1.0	1.0 to 1.0*
DMARD	1.2	1.0 to 1.6
NSAIDS	2.1	1.9 to 2.5**
Topical steroids	0.9	0.8 to 1.0*
Oral steroids	1.2	1.1 to 1.3**
BMI	1.0	1.0 to 1.0
Smoker	1.5	1.3 to 1.6**
Hyperlipidemia	1.3	1.1 to 1.4**
Diabetes	1.6	1.4 to 1.8**
Hypertension	1.4	1.3 to 1.6**
Ischaemic heart disease in family	1.1	1.0 to 1.2*

*p<0.05; **p<0.01

Conflict of interest statement

Pfizer provided the funding for this study following an ICRP grant application however, the funders had no involvement in the study and as such, the authors declare no competing interests. Professor Ernest Choy has received consultancy and speaker fees from Pfizer.

Accepted manuscript