

**Full length manuscript**

**Risk of osteoarthritis in an incident cohort of people with psoriatic arthritis: a population-based cohort study**

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## Abstract

**Objective** To determine the risk of a diagnosis of osteoarthritis (OA) in psoriatic arthritis (PsA) patients compared to patients with psoriasis and a general population cohort.

**Methods** Incident PsA patients aged 18-89 years at diagnosis were identified from the UK Clinical Practice Research Datalink between 1998 and 2014. All PsA patients were matched to two cohorts of patients both at a 1:4 ratio. The first cohort included patients with psoriasis (and no PsA) and the second was a general population cohort (with no psoriasis or PsA). The baseline prevalence of OA was calculated for each study cohort. The incidence of OA was calculated and adjusted relative risks ( $RR_{adj}$ ) were calculated using conditional Poisson regression.

**Results** We identified 6,783 incident PsA patients. The baseline prevalence of OA ranged from 22.1% ( $CI_{95}$  21.1-23.1) in the PsA cohort to 12.6% ( $CI_{95}$  12.2-13.0) and 11.0% ( $CI_{95}$  10.6-11.3) in the psoriasis and general population cohorts respectively. The incidence of OA was significantly higher in the PsA cohort compared to the psoriasis and general population cohorts after adjusting for BMI ( $RR_{adj}$  1.68  $CI_{95}$  1.46-1.93 and  $RR_{adj}$  1.86  $CI_{95}$  1.62-2.14 respectively).

**Conclusion** An increased risk of OA was observed in patients with PsA compared to patients with psoriasis alone and those in the general population. Further work is needed to determine whether this reflects a true increase in OA risk or misdiagnosed PsA and the extent to which it can be explained by differences in the opportunity for OA diagnosis between cohorts.

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## Introduction

Psoriatic arthritis (PsA) is a chronic inflammatory arthritis that causes pain, stiffness and swelling around the joints. PsA is well recognised to be progressive, resulting in reduced quality of life and work disability, that can be improved with early diagnosis and effective treatment.<sup>[1,2]</sup> PsA is reported to affect between 10 and 40% of individuals with psoriasis<sup>[3]</sup> and in the majority of patients PsA presents after, or synchronously with, psoriasis onset.<sup>[4]</sup> Osteoarthritis (OA) is a common form of arthritis and typically commences late in the fifth decade.<sup>[5]</sup> OA is a disabling condition which can affect any joint, with the knee, followed by the hand and hip as some of the sites most commonly affected. PsA and OA have long been considered two distinct arthropathies, however they do have some overlapping features and symptoms and in certain circumstances it can be difficult to differentiate between them, particularly in the small joints of the hands or spine.<sup>[5]</sup> It has been demonstrated that obesity is a risk factor for both OA and PsA.<sup>[6,7]</sup> This study aimed to determine the risk of OA in patients with PsA in the United Kingdom (UK), and compare this with the risk in a matched cohort of psoriasis patients without PsA and a matched general population cohort, in order to determine whether there is any evidence of an increased risk of OA in patients with PsA and/or psoriasis and whether there is any evidence of PsA being misdiagnosed as OA.

## Methods

This study used data from the Clinical Practice Research Datalink (CPRD), an electronic healthcare database containing anonymised longitudinal medical records for ~15 million individuals collected within UK primary care, which has been shown to be generally representative of the UK population.<sup>[8]</sup> The protocol was reviewed by the Independent Scientific Advisory Committee for MHRA Database Research (approved protocol 15\_154R).

### *Study population*

A cohort of incident PsA patients was identified in the CPRD who were diagnosed between 1<sup>st</sup> January 1998 and 31<sup>st</sup> December 2014 and aged 18-89 years at diagnosis. Patients were required to have  $\geq 1$  year of data contribution considered to be up to the standard required for research before their PsA diagnosis date (index date). Cases of PsA were matched at a 1:4 ratio to two randomly selected cohorts based on their index date, year of birth, sex and general practice: the first matched cohort (the general population cohort) included patients with no psoriasis, no PsA and no other inflammatory arthritis (which did not include OA) at baseline; the second cohort (the psoriasis cohort) included patients with psoriasis but no diagnosis of PsA or other inflammatory arthritis (which did not include OA) at baseline. The index date of the matched case was assigned to patients in the comparator cohorts and they were required to have  $\geq 1$  year of research standard data contribution prior to the index date. Patients were followed from the index date until the date they were no longer eligible for the cohort or were diagnosed with the outcome of interest. Patients in the general population and psoriasis cohorts who developed psoriasis or PsA after the index date had their person-time contribution to that cohort censored the day before the diagnosis date and then started contributing to the other cohort.

### *Identification of psoriatic arthritis and psoriasis patients*

Patients with PsA were identified based on the presence of a Read code, which previous studies in a similar UK database have found to have a high positive predictive value (85% CI<sub>95</sub> 75.8-91.7%).<sup>[9]</sup> An algorithm was developed to exclude patients where there was evidence to suggest that the PsA diagnosis may have been a misdiagnosis of another condition. This involved identifying patients with other diagnoses (such as rheumatoid arthritis, reactive

arthritis, enteropathic arthritis, gout, fibromyalgia) and looking at the number of codes for each of the different diagnoses, the order in which the different diagnosis codes were recorded and potential supporting evidence, including prescribing, of the alternative diagnosis). The PsA index date was taken as the date of the first PsA Read code. For patients with prescriptions for conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs) before their first PsA code, where there was no evidence of an alternative indication for the prescribing (including methotrexate prescribed on the same date as a psoriasis or dermatology code), the PsA index date was backdated to the date of the first csDMARD prescription; this applied to 17.0% of PsA patients. The index date was also backdated for patients who had received a code for psoriasis and a general non-specific arthritis code on the same date, before their first PsA code.

Patients with psoriasis were identified based on psoriasis Read codes, which have been demonstrated to have a high validity with a questionnaire survey to GPs finding that 90% of psoriasis diagnoses within the study sample (N = 4,634) were confirmed.<sup>[10]</sup> Patients were also identified as having psoriasis if they had received  $\geq 2$  prescriptions for a vitamin D analogue in the absence of a psoriasis code and in the absence of an alternative indication (e.g. vitiligo); this method of identification accounted for approximately 4% of patients identified with psoriasis. The date of psoriasis diagnosis was taken as the date of the first psoriasis Read code. For patients receiving psoriasis specific treatment (e.g. vitamin D analogue, dithranol, coal tar, phototherapy), prior to the date of the first psoriasis Read code, the diagnosis date was backdated to the date of the first psoriasis-specific prescription; this applied to 12.5% of psoriasis patients.

### *Outcome identification*

The primary outcome of interest was a diagnosis of osteoarthritis (OA) of any site, identified based on Read codes. To our knowledge no study has yet validated the recording of general OA of any site within the CPRD. However, one study looking at OA of the hip in the CPRD, in patients aged over 65 years, found a PPV of 88.2% (CI<sub>95</sub> 82.4-94.0%) if clinical or radiographic criteria could be used to confirm the diagnosis.<sup>[11]</sup> As our work formed part of a wider study and these cohorts have been used to study a range of other outcomes reported elsewhere,<sup>[12,13]</sup> initially all cases of OA were identified within the study cohorts, including

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prevalent cases where the OA diagnosis was recorded on or before the date of PsA diagnosis or the corresponding index date. Cases of OA for the incidence analyses were identified from the start of contribution of person-time to the study (i.e. after the date of PsA diagnosis or corresponding index date) following the exclusion of all prevalent cases of OA from the study population. For the secondary analyses, the outcomes of interest were site-specific OA diagnoses of either the hand/wrist, hip/knee and/or spine. For these, the first code for OA of the specific-site of interest was taken as the diagnosis date ignoring any previous general/non site-specific OA codes. As with the primary outcome, incident cases were identified following the exclusion of prevalent cases.

### ***Statistical analyses***

The patient characteristics at baseline for each of the study cohorts were described. The baseline prevalence of OA in each of the cohorts was calculated as a percentage and then those prevalent cases were excluded from the numerators and denominators of the incidence calculations. The incidence of any OA per 10,000 person-years was calculated for each study cohort. Conditional Poisson regression was used to calculate crude and adjusted relative risks (RR) comparing the risk in the PsA cohort with the risk in the general population and psoriasis cohorts. Body-mass-index (BMI), as a continuous variable, based on the closest record within three years of the index date, was adjusted for in the model where available as this is a known risk factor for both OA and PsA. Patients with no BMI record within three years of the index date were excluded from the relative risk calculations. No other variables were considered as potential confounders for adjustment. The same baseline prevalence and incidence analyses were repeated for the three secondary site-specific OA outcomes. The analysis of each site was carried out separately and patients with records of OA of multiple sites were eligible for inclusion in all relevant sites. Two sensitivity analyses were carried out, the first excluded PsA and psoriasis patients who had their index dates backdated based on the presence of a relevant prescription to evaluate the presence of immortal time bias. The second sensitivity analysis aimed to evaluate the impact of diagnostic uncertainty and looked at OA rates starting one year after the index date. Analyses were performed using R 3.3.0 (R Core Team, 2017).

### **Results**

In total, 6,783 eligible incident cases of PsA were identified and matched to 27,132 patients from the general population and 27,132 psoriasis patients. Table one shows the baseline patient characteristics for each cohort. The median age at PsA diagnosis was 49 years (IQR 39-59). The mean duration of follow-up after the index date was approximately 5.5 years in all three cohorts. Data on BMI was missing for around 50% of patients in all cohorts but where available, patients in the PsA cohort had a higher BMI than those in the psoriasis and general population cohorts. The baseline prevalence of OA ranged from 22.1% (CI<sub>95</sub> 21.1-23.1) in the PsA cohort to 12.6% (CI<sub>95</sub> 12.2-13.0) and 11.0% (CI<sub>95</sub> 10.6-11.3) in the psoriasis and general population cohorts respectively. Of the 1,497 PsA patients with a prevalent OA diagnosis, 259 (17.4%) received the OA diagnosis within the 12 months before the PsA diagnosis and 420 (28.1%) within the two years before. Approximately 50% of PsA patients received the OA diagnosis more than five years prior to their PsA diagnosis. The extent of the increased OA prevalence in the PsA cohort, compared to the general population cohort, was greater for those who received their PsA diagnosis before the age of 40 years compared to after the age of 40 (Table 1).

Table two shows the incidence of OA in each of the three cohorts, which ranged from 162.4 per 10,000 person years in the PsA cohort to 117.1 in the psoriasis cohort and 109.2 per 10,000 person years in the general population cohort. The sensitivity analysis to evaluate the impact of backdating the index date found it had little impact, with the revised incidence rates being 158.3, 116.6 and 110.2 per 10,000 person years for the PsA, psoriasis and general population cohorts respectively. The sensitivity analysis looking at OA rates starting one year after the index date reduced the incidence of OA in the PsA population from 162.4 (CI<sub>95</sub> 147.6-177.2) to 140.6 (CI<sub>95</sub> 125.5-155.7) per 10,000 person years but did not substantially change the OA incidence in the psoriasis and general population cohorts (116.9 CI<sub>95</sub> 110.1-123.8 and 111.6 CI<sub>95</sub> 105.5-117.7 per 10,000 person years respectively).

The incidence of OA was significantly higher in the PsA cohort when compared to the general population after adjusting for BMI (RR<sub>adj</sub> 1.86 CI<sub>95</sub> 1.62-2.14) and when compared to the psoriasis cohort (RR<sub>adj</sub> 1.68 CI<sub>95</sub> 1.46-1.93) (Table 3). When looking at OA rates starting one year following the index date these reduced to RR<sub>adj</sub> 1.55 (CI<sub>95</sub> 1.31-1.83) and RR<sub>adj</sub> 1.39 (CI<sub>95</sub> 1.18-1.63) (Table 3).



Table 4 shows the prevalence and incidence of site-specific OA in each of the study cohorts. Only around 50% of OA patients had a code stating the specific site so these will be an underestimate but of those who did it could be seen that patients in the PsA cohort were around three times more likely to have a diagnosis of OA of the hand/wrist before their PsA index date than those in the psoriasis or general population comparator groups were before their matched index date. Increases were seen for hip/knee OA and OA of the spine but to a lesser extent. For site-specific OA diagnosed and recorded after the index date a small increase was observed in OA of the hand/wrist and OA of the spine in the PsA cohort compared with the general population cohort. The prevalence and incidence rates in the general population and psoriasis cohorts were found to be similar for all sites. The sensitivity analysis looking at OA rates starting one year after the index date had the greatest impact on OA of the spine but overall the incidence rates did not substantially change (data not shown).

## Discussion

This large population-based study has demonstrated an 86% and 68% increased risk of an OA diagnosis, after adjusting for BMI, among patients with PsA compared to patients in the general population and patients with psoriasis respectively. Sensitivity analyses found this reduced to a 55% and 39% increased risk when looking at OA diagnoses starting at least one year after the index date. The study also found a higher baseline prevalence of OA diagnoses, particularly of hand/wrist OA, in patients prior to their PsA diagnosis when compared to the matched psoriasis and general population cohorts.

There is considerable variation in the literature in terms of the prevalence and incidence of OA depending on the age group reported and the definition used; whether it is radiographic, symptomatic or self-reported.<sup>[6]</sup> When using electronic healthcare data, variations in the number of OA cases identified can also result from the use of surgical or diagnostic proxies for OA diagnoses.<sup>[14,15]</sup> Our incidence figures for any OA in the general population are, however, in line with those from a UK-based study looking at the consultation incidence of OA using data from the Consultations in Primary Care Archive for a region of England.<sup>[16]</sup> Our prevalence figures in the general population are in line with a recent study using CPRD data by Swain et al., but our incidence figures were higher than those reported in the same paper.<sup>[17]</sup> There are a number of possible explanations for the difference, it could in part be the result of differences in inclusion criteria or definitions and the fact that our study included Read codes for spondylosis within the list of codes for OA. In addition, our study period ran from 2000-2015 whilst the Swain et al. study reported for 2017 and reported a decline in OA incidence between 1997 and 2017, with the earlier years being more in line with our overall incidence.

Only around 50% of patients with an OA diagnosis had a code that specified the actual site. In addition, our identification of site-specific OA did not take into account any prior codes for OA in general that did not specify the site. It is therefore possible that some patients identified based on their first site-specific OA code after their index date may have had a general OA code recorded prior to the index date and have been prevalent rather than incident. Given these limitations it does not seem appropriate to make comparisons between our site-specific

OA figures and those in the literature. The only comparisons that have been made are between the three study cohorts and given that the methods of OA identification were the same for all cohorts the impact should have been similar across cohorts and have a limited impact on the internal comparisons. To our knowledge, no previous study has reported on the incidence of OA in a cohort of patients newly diagnosed with PsA. A study in France has looked at the prevalence of self-reported psoriasis in a cohort of patients with hip OA aged 50-75 years and found the frequency of psoriasis to be almost twice that of the general population.<sup>[18]</sup>

The strengths of our study include its population-based nature, the large number of PsA patients, the inclusion of both a psoriasis and general population comparator and the use of validated codes to identify PsA and psoriasis. To our knowledge, Read codes for OA in general have not been validated and this study did not require any supporting evidence to confirm the diagnosis. It is therefore possible that in some patients OA may have been recorded as a working diagnosis and was later ruled out. One study that aimed to determine the diagnostic accuracy of coding of OA of the hip in the CPRD, in patients aged over 65 years, found a PPV of 88.2% (CI<sub>95</sub> 82.4-94.0%) if clinical or radiographic criteria could be used to confirm the diagnosis.<sup>[11]</sup> PsA and OA have long been considered two distinct arthropathies, however they do have some overlapping features and symptoms and in certain circumstances it can be difficult to differentiate between them, particularly in the small joints of the hands or spine.<sup>[5]</sup> By example the distribution of joints affected can be similar between OA and PsA (both arthropathies can affect the Distal Interphalangeal Joints (DIPJ's of the hands). Clinically and radiologically, the osteoroliferation (bone formation) seen in PsA can be very difficult to distinguish from osteophytes (chunky bone formation) in OA. In addition, not all PsA patients have obvious skin psoriasis at the time of PsA presentation and early joint symptoms.<sup>[19]</sup> The higher baseline prevalence of an OA diagnosis in patients with PsA, and particularly of OA of the hand/wrist, may in part reflect the fact that some patients were initially misdiagnosed as having OA before further investigations led to the PsA diagnosis. This could be supported by the fact that 17.4% and 28.1% of PsA patients with prevalent OA received their OA diagnosis within the one and two years before the PsA diagnosis respectively. The fact that the increase in prevalence prior to PsA diagnosis was greater in those who were diagnosed with PsA before the age of 40 years may also be evidence to support this, as OA in individuals younger than

40 years of age is uncommon.<sup>[20,21]</sup> A recent study from the United States looking at the pathway to PsA diagnosis reported that OA was the second most common misdiagnosis, occurring in 26.6% of the 203 respondents.<sup>[22]</sup> However, in our study, over 50% of PsA patients received their OA diagnosis more than five years before their PsA diagnosis which suggests that misdiagnosed PsA is unlikely to account for all prevalent OA cases, although it is acknowledged that there can be a long delay in the time to PsA diagnosis.

The higher incidence of an OA diagnosis following a PsA diagnosis may suggest an increased risk of OA in patients with PsA compared to those without. This could possibly be secondary to damage from PsA or compounded by obesity. In addition to this, there may be some degree of detection and referral bias as patients undergoing imaging and further investigations for their PsA may be more likely to have their OA identified and diagnosed than those in the general population. This is partly supported by the sensitivity analysis where the increase in OA risk was reduced in the PsA patients when looking more than one year following the index date, suggesting that the increased clinical interaction at and around the time of PsA diagnosis may provide an increased opportunity to diagnose OA. It is therefore possible that the increase in OA incidence in the PsA cohort to some extent reflects a level of undiagnosed OA within the psoriasis and general population cohorts. It is also possible, however, that in some patients the effect of PsA on the joints is actually misdiagnosed as OA.

Within our study cohorts there did appear to be differential levels of missing information on BMI, with 47% missing in the PsA cohort and 56% in the general population cohort. High BMI is known to be associated with an increased risk of both PsA and OA.<sup>[6,23]</sup> If the BMI data are not missing at random it is possible that those with complete data may not be representative of the wider population and also that restricting to those who had a BMI record could have biased the results. In the UK, biologic therapy is almost entirely prescribed in secondary care and is unfortunately not captured within the CPRD. It was therefore not possible to know which patients were exposed to biologic therapy and these exposures could have had an impact on OA incidence within these groups.

This study has demonstrated an increased risk of OA in patients with PsA compared to patients with psoriasis and those in the general population after adjusting for BMI. Further

work is required to determine whether these results reflect a true increase in the risk of symptomatic OA in patients with PsA, or whether it can be explained by differences in the opportunity for OA diagnosis between the different cohorts, an initial misdiagnosis of PsA or a combination of both.

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**Table 1** Baseline characteristics of the psoriatic arthritis, psoriasis and general population cohorts, including prevalence of osteoarthritis codes at index date

	Psoriatic arthritis cohort		Psoriasis cohort		General population cohort	
	N	%	N	%	N	%
<b>N</b>	6,783		27,132		27,132	
<b>Sex (% male)</b>	3,327	49.05	13,308	49.05	13,308	49.05
<b>Median age*, years (IQR)</b>	49	(39-59)	49	(39-59)	49	(39-59)
<b>Mean follow-up post index, years (SD)</b>	5.8	(4.1)	5.5	(4.1)	5.5	(4.1)
<b>Mean duration of psoriasis*, years (SD)</b>	11.3	(10.9)	11.8	(10.6)	---	---
<b>Body mass index<sup>†</sup></b>						
<25.0	869	(12.8)	4,190	(15.4)	4,149	(15.3)
25.0-29.9	1,226	(18.1)	4,511	(16.6)	4,257	(15.7)
30.0-34.9	844	(12.4)	2,602	(9.6)	2,254	(8.3)
≥35.0	641	(9.5)	1,746	(6.4)	1,252	(4.6)
Unknown	3,203	(47.2)	14,083	(51.9)	15,220	(56.1)
<b>Smoking status<sup>†</sup></b>						
Non-smoker	3,059	(45.1)	11,001	(40.6)	13,533	(49.9)
Current smoker	1,605	(23.7)	8,199	(30.2)	6,509	(24.0)
Ex-smoker	2,084	(30.7)	7,480	(27.6)	6,067	(22.4)
Unknown	35	(0.5)	452	(1.7)	1,023	(3.8)
<b>Baseline prevalence of osteoarthritis<sup>‡</sup></b>	1,497	(22.1)	3,408	(12.5)	2,974	(11.0)
<b>Baseline OA prevalence &lt;40 years at index</b>	56	(3.2)	60	(0.9)	49	(0.7)
<b>Baseline OA prevalence ≥40 years at index</b>	1,441	(28.6)	3,348	(16.6)	2,925	(14.5)

IQR = inter-quartile range, SD = standard deviation, \* on the index date, † closest to and within 3 years prior to the index date ‡ ≥1 diagnosis code on or before the index date



**Table 2** Incidence of osteoarthritis in the psoriatic arthritis, psoriasis and general population cohorts

	Cases	Person years	Incidence rate per 10,000 person years CI <sub>95</sub>	
<b>Any osteoarthritis<sup>†</sup></b>				
General population	1374	125,798	109.2	(103.5 - 115.0)
Psoriasis	1432	122,279	117.1	(111.0 - 123.2)
Psoriatic arthritis	464	28,574	162.4	(147.6 - 177.2)

<sup>†</sup>including spondylosis

**Table 3** Risk of incident osteoarthritis in patients with psoriatic arthritis compared with patients in the general population and patients with psoriasis

	Psoriatic arthritis compared with a <u>general population cohort</u>						Psoriatic arthritis compared with a <u>psoriasis cohort</u>					
	Unadjusted			Adjusted <sup>†</sup>			Unadjusted			Adjusted <sup>†</sup>		
	RR	CI <sub>95</sub>	P	RR	CI <sub>95</sub>	P	RR	CI <sub>95</sub>	P	RR	CI <sub>95</sub>	P
<b>Osteoarthritis</b>	1.87	1.67-2.10	<0.0001	1.86	1.62-2.14	<0.0001	1.68	1.50-1.88	<0.0001	1.68	1.46-1.93	<0.0001
<b>Sensitivity analysis<sup>#</sup></b>	1.51	1.33-1.73	<0.0001	1.55	1.31-1.83	<0.0001	1.40	1.23-1.60	<0.0001	1.39	1.18-1.63	<0.0001

<sup>†</sup> adjusted for BMI taken as the closest entry within 3 years of the index date <sup>#</sup> OA diagnoses starting one year after the index date

**Table 4** Risk of site-specific osteoarthritis (OA) in patients with psoriatic arthritis compared with patients in the general population and patients with psoriasis

	Cases before index date (N)	Prevalence (%)	Cases after index date (N)	Person years	Incidence rate per 10,000 person years (CI <sub>95</sub> )	
<b>OA of hand or wrist</b>						
General population	162	0.6	133	146568	9.1	(7.5-10.6)
Psoriasis	184	0.7	143	145353	9.8	(8.2-11.5)
Psoriatic arthritis	132	1.9	53	38506	13.8	(10.1-17.5)
<b>OA of hip or knee</b>						
General population	733	2.7	602	141767	42.5	(39.1-45.9)
Psoriasis	862	3.2	583	140086	41.6	(38.2-45.0)
Psoriatic arthritis	318	4.7	184	37082	49.6	(42.5-56.8)
<b>OA of the spine<sup>†</sup></b>						
General population	1115	4.1	277	140303	19.7	(17.4-22.1)
Psoriasis	1277	4.7	299	138163	21.6	(19.2-24.1)
Psoriatic arthritis	410	6.0	99	36382	27.2	(21.9-32.6)

<sup>†</sup>including spondylosis