EPIDEMIOLOGICAL SCIENCE

Mortality in patients with psoriatic arthritis in Sweden: a nationwide, population-based cohort study

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ABSTRACT

Objectives To compare all-cause mortality and causes of death between patients with psoriatic arthritis (PsA) and the general population in Sweden.

Methods Adults with at least one main PsA diagnosis (International Classification of Diseases-10: L40.5/M07.0–M07.3) from outpatient rheumatology/internal medicine departments 2001–2017 were identified from the National Patient Register. Each case was matched to five population comparator-subjects on sex/county/age at the case's first arthritis diagnosis. Follow-up ran from 1 January 2007, or from first PsA diagnosis thereafter, until death, emigration or 31 December 2018. Mortality was assessed overall, and stratified by sex and duration since diagnosis (diagnosis before/after 1 January 2007), using matched Cox proportional hazard regression (excluding/including adjustments for comorbidity) or Breslow test, as appropriate. Incidence rate ratios (IRR) of death, overall and stratified by sex/duration since diagnosis/age, as well as causes of death in PsA cases and comparator-subjects were also described.

Results All-cause mortality was elevated in PsA (HR: 1.11 (95% CI: 1.07 to 1.16); IRR: 1.18 (95% CI: 1.13 to 1.22)), mainly driven by increased risks in women (HR: 1.23 (95% CI: 1.16 to 1.30)) and cases with longer time since diagnosis (HR: 1.18 (95% CI: 1.12 to 1.25)). IRR of death were significantly increased for all ages except below 40 years, with the numerically highest point-estimates for ages 40–59 years. When adjusted for comorbidity, however, the elevated mortality risk in PsA disappeared. Causes of death were similar among PsA cases/comparator-subjects, with cardiovascular disease and malignancy as the leading causes.

Conclusions Mortality risk in PsA in Sweden was about 10% higher than in the general population, driven by excess comorbidity and with increased risks mainly in women and patients with longer disease duration.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Psoriatic arthritis, as other chronic inflammatory diseases, such as rheumatoid arthritis, ankylosing spondylitis and psoriasis, is associated with elevated risks for a number of different comorbidities, including cardiovascular disease. However, in contrast to the increased mortality reported in the other conditions, prior mortality estimates in psoriatic arthritis have been inconsistent.

WHAT THIS STUDY ADDS

⇒ In this nationwide Swedish study, the largest assessment to date anywhere regarding mortality in psoriatic arthritis (assessing more than 33 000 patients for up to 12 years), the all-cause mortality was elevated by around 10% as compared with the general population, mainly driven by increased risks among women and patients with longer duration since diagnosis, and emanating from an excess comorbidity burden. The distributions of causes of death were, however, similar between patients and population comparator-subjects.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Considering the advances in the diagnosis and treatment of psoriatic arthritis, contemporary, nationwide mortality estimates, as well as identification of predictors and leading causes of death, are important to enable prevention of premature mortality.

INTRODUCTION

Psoriatic arthritis (PsA) is an inflammatory arthritic disease, associated with psoriasis (PsO). Similar to several other chronic inflammatory diseases, such as rheumatoid arthritis (RA) and ankylosing spondylitis (AS),[1–5] PsO and PsA are both associated with an elevated burden of traditional cardiovascular disease (CVD) risk factors, increased subclinical atherosclerosis and a higher prevalence of manifest CVD.[4 6–12] Beyond this, several other conditions, including infections and depression, as well as the extra-musculoskeletal manifestations uveitis and inflammatory bowel disease (IBD), are also more common in PsA than in the general population.[13 14]

Although RA and AS are both associated with increased all-cause mortality,[15–20] in PsA the available data regarding mortality are conflicting.[21–35] Many of these, at least seemingly contradictive, prior estimates are derived from hospital-based, single centre cohorts or smaller population-based assessments, but even when focusing on larger, population-based studies (including around 5000–20 000 PsA cases), some report an increased all-cause mortality in PsA,[29 30 33] while others do not.[18 27 35 36] In a recent meta-analysis, all-cause mortality in the overall PsA population was not found to be elevated (risk ratio: 1.12 (95% CI: 0.96 to 1.30)).[19] A sex difference

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was observed, however, with a significantly increased mortality risk among female patients (risk ratio: 1.19 (95% CI: 1.04 to 1.36)).[19] Meanwhile, PsO has been more consistently associated with an elevated mortality risk, which also appears to increase with more severe skin involvement.[27 36 37]

In light of these conflicting data, the current nationwide, population-based study aimed to compare all-cause mortality between patients with PsA and matched general population comparator-subjects in Sweden, overall as well as stratified by sex and duration since diagnosis. Secondary objectives were to describe the cause of death distributions among patients with PsA and comparator-subjects, and to investigate socioeconomic and disease-related mortality predictors.

METHODS

Study setting and data sources

This is a nationwide, population-based cohort study of all-cause mortality in patients with PsA and matched general population comparator-subjects, using linked (via the personal identification number, unique to every permanent resident in Sweden), prospectively collected data from high-quality, nationwide, Swedish administrative and healthcare registers. In Sweden, PsA is typically diagnosed and treated in specialised outpatient care, normally at rheumatology or internal medicine departments.[38] However, milder cases without need of disease-modifying anti-rheumatic drug (DMARD) therapy may be referred back to primary care after the initial diagnosis.

Administrative data, including International Classification of Diseases (ICD) diagnostic codes and dates, from inpatient and specialised (non-primary) outpatient care are recorded in the Swedish National Patient Register (NPR).[39] Inpatient care data are available since 1964, with complete national coverage from 1987. The outpatient part of the NPR was started in 2001. Its coverage is now nearly complete, although missing information from some private caregivers.[40] From each healthcare episode/visit, one main and, optionally, secondary diagnostic codes are recorded (using the Swedish versions of ICD-7: 1964–1968; ICD-8: 1968–1986; ICD-9: 1987–1996; ICD-10: 1997-present), as are any procedural-codes for surgery, etc. For the present study, ICD-codes from the NPR were used to identify PsA cases, and ICD-codes and procedural-codes to assess comorbidities (online supplemental tables S1 and S2).

Prescription drugs dispensed by Swedish pharmacies are since 2005 registered in the Prescribed Drug Register (PDR), with a near 100% coverage.[41 42] For the current study, PDR data were used to describe anti-rheumatic drug use, and as a complement to the NPR for identification of certain comorbidities (online supplemental table S3). Data on intravenous DMARDs administered in-hospital, which are not captured in the PDR, were retrieved by combining information from the PDR and the Swedish Rheumatology Quality Register.[43]

General population comparator-subjects were identified from the Total Population Register at Statistics Sweden, which was also the source of information on descent, immigration, emigration, residency and level of formal education.[44]

The primary outcome, all-cause mortality, as well as causes of death, were assessed using data from the Cause of Death Register, containing information on date and cause of death (according to ICD-codes; online supplemental table S1) for all deceased residents in Sweden since 1961.[45]

Study population and follow-up

All individuals in Sweden, having received at least one main diagnosis of PsA (ICD-10: L40.5/M07.0/M07.1/M07.2/M07.3) from outpatient visits to rheumatology or internal medicine departments at age 18 years or more (PsA index case definition) during 2001–2017, were identified from the NPR. Subjects who had received ICD-codes for PsA exclusively from inpatient care were not included, as PsA in Sweden is typically diagnosed and managed in specialised outpatient care, and a prior study also showed a high validity of our case definition, with 86% fulfilling established PsA classification criteria.[46] For each PsA case, five general population comparator-subjects were randomly identified, matched on sex, county and age at first registered arthritis diagnosis for the index case. Matching at first arthritis, rather than PsA, diagnosis was chosen as some cases were expected to first receive another arthritis diagnosis, before characterisation as PsA.

The date each PsA case fulfilled the index case definition (see above) served as their index date. PsA cases were followed from 1 January 2007, if their index date was prior to this, or from the index date if later, until death, emigration or end of the study on 31 December 2018. Comparator-subjects' assessment period started simultaneously with their index case. PsA cases that died or emigrated before the start of the study period on 1 January 2007 were excluded together with their matched comparator-subjects. Comparator-subjects who died, emigrated or were themselves diagnosed with PsA before the start of their individual assessment periods were also excluded, but their respective index cases retained, as long as at least one of their five comparator-subjects could be included. Comparator-subjects diagnosed with PsA during follow-up served as comparator-subjects until receiving their first ever ICD-code for PsA (main/secondary diagnosis from any department), and thereafter (if meeting the PsA index case definition) as PsA cases with their own matched comparator-subjects. Figure 1 describes the study inclusion (final study population: 33 026 PsA cases and 161 094 comparator-subjects).

Outcomes

The primary outcome was all-cause mortality among the PsA cases in relation to comparator-subjects. Matched comparisons were conducted overall, as well as stratified for sex and duration since PsA diagnosis (as a surrogate marker for disease duration; index date prior to 1 January 2007 ('longer duration since diagnosis'/prevalent cases) vs index date 2007–2017 ('newly diagnosed cases')). Furthermore, crude mortality rates (MR) and incidence rate ratios (IRR) of death between PsA cases and comparator-subjects were calculated overall and stratified for sex, age-intervals and duration since PsA diagnosis. Since PsA is associated with increased risks for various other diseases,[4 9 10 13 14] and since patients will not die from the arthritis itself, in our main analyses we did not adjust the mortality estimates for comorbidity status, arguing that analyses without such adjustments will better capture the full impact of PsA on mortality. However, in order to explore the influence of measurable comorbidities, potentially related to PsO/PsA, on mortality, we also conducted an additional analysis including such adjustments (for the overall comparison between PsA cases and comparator-subjects).

As a secondary outcome, cause of death frequencies in PsA cases and comparator-subjects, based on the underlying cause of death registered in the Cause of Death Register, were described, divided into eight categories. Finally, potential socioeconomic and health-related predictors (extra-musculoskeletal manifestations, general comorbidities, surgery, present/diagnosed prior to start of follow-up) of increased mortality within the PsA group

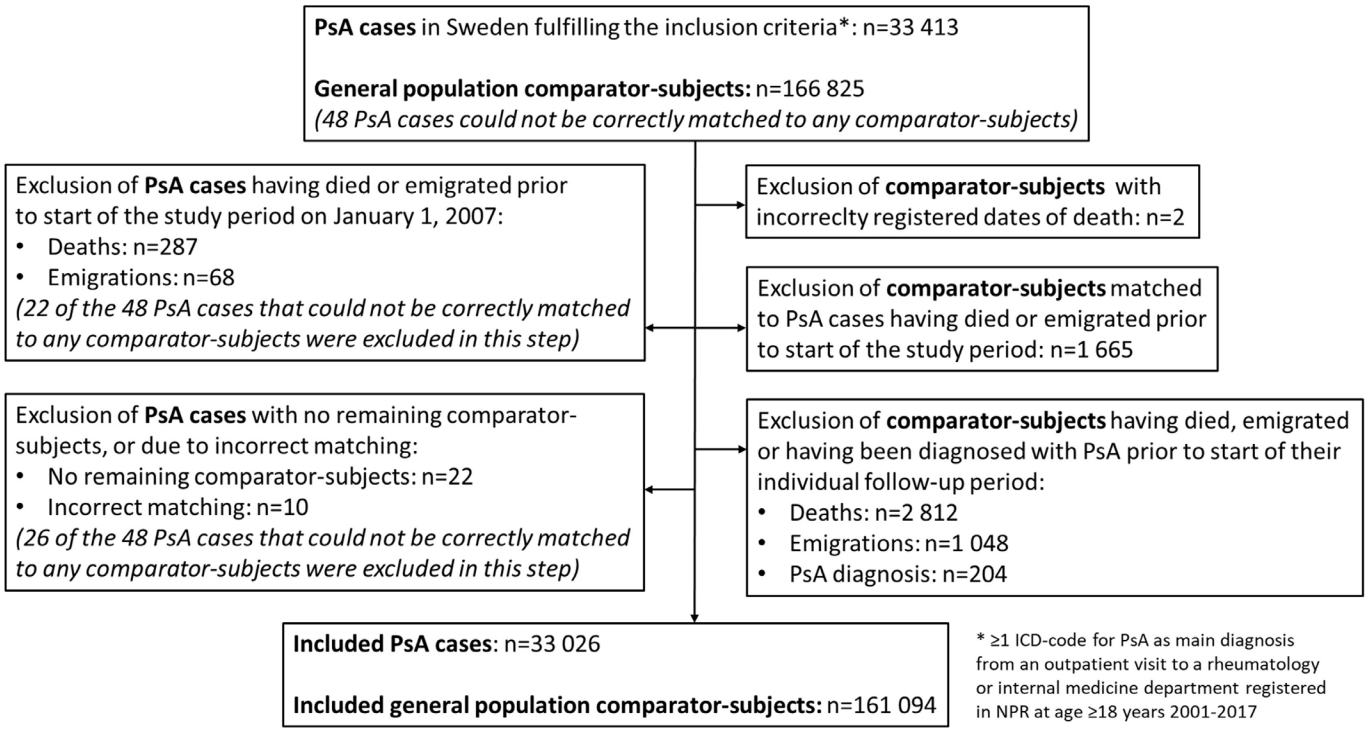

Figure 1 Inclusion flow chart. ICD, International Classification of Diseases; NPR, National Patient Register; PsA, psoriatic arthritis.

were investigated and related to the corresponding estimates among the comparator-subjects.

Statistics

All-cause mortality was visualised by Kaplan-Meier curves and compared by Cox proportional hazard regression analyses, accounting for the matched design. In case the Cox proportionality assumptions did not hold (as evaluated graphically in Kaplan-Meier curves and by log-minus-log plots), matched Breslow test was used instead. Estimated time to 10% mortality was described for all analyses to enhance comparability. While our main analyses were unadjusted for comorbidity status, in an additional analysis adjustments for education (>12 vs ≤12 years) and the presence of general comorbidities prior to start of follow-up (CVD, diabetes mellitus, infection (any; see table 1), chronic pulmonary disease, chronic kidney disease, malignancy, anxiety and depression; all yes/no, assessed as described in table 1) were added to the matched Cox proportional hazard regression, comparing all-cause mortality between PsA cases and comparator-subjects.

Crude total, age-interval-specific, sex-specific and duration from diagnosis-specific MR for PsA cases and comparator-subjects were expressed as the number of deaths per 1000 person-years (PY) at risk, and the respective IRR with 95% CI (Byar method).

Mortality predictors at start of follow-up among the PsA cases were assessed by separate Cox proportional hazard regression models, adjusted for sex and age (or in case of violation of the Cox proportionality assumptions matched Breslow test). For comparability, the same analyses were also conducted separately among comparator-subjects. In the entire material (ie, including both PsA and comparator-subjects) we moreover assessed whether the interaction terms between the PsA case/comparator-subject status and the assessed predictors were significant, indicating a difference of the predictive ability in the two groups. Variables that were significantly associated with mortality in PsA in these analyses were then further examined in multivariate Cox proportional hazard regression analyses in PsA and comparator-subjects, respectively, again including an assessment of interaction terms in the entire material.

Sensitivity analyses

In relation to the primary outcome assessment, a number of sensitivity analyses were performed to account for: (1) potential misclassification of PsA diagnoses among the cases; (2) that an increased mortality may be expected during the first months after diagnosis of a disease; (3) potential survivorship bias due to the possible time-lag between the matching of comparator-subjects to PsA cases and the start of the individual assessment period (see Study population and follow-up above). The sensitivity analyses are described in greater detail in the online supplement.

Patient and public involvement

A patient research partner (see Acknowledgements) was involved in the research group and took part in discussions of the current results.

RESULTS

Study population characteristics

The study population consisted of 33 026 PsA cases and 161 094 comparator-subjects (figure 1). For 90% of PsA cases, all five matched comparator-subjects could be included, while only 1.8% entered the analyses with three or fewer comparator-subjects. At the start of their individual follow-up, the PsA cases had a mean (SD) age of 52 (14) years and 45% were men (table 1). Regarding duration since PsA diagnosis, 12 568 (38%) cases had been diagnosed prior to the start of the study period at 1 January 2007 (thus constituting the longer duration since PsA diagnosis subset/prevalent cases). All assessed comorbidities were numerically more frequent among PsA cases than comparator-subjects at the start of follow-up (table 1). Anti-rheumatic therapy at

Table 1 Demographics and disease characteristics of the psoriatic arthritis and comparator-subject cohorts at start of follow-up

	PsA cases (n=33 026)	Population comparator-subjects (n=161 094)
Demographics		
Male sex, n (%)	15 004 (45)	73 060 (45)
Age at inclusion criteria fulfilment*, years, mean (SD)	51 (14)	NA
Age at the start of follow-up, years, mean (SD)	52 (14)	52 (14)
Duration between inclusion criteria fulfilment* and the start of follow-up, years, mean (SD)	1.2 (2.0)	NA
Foreign origin, n (%)	3201 (9.7)	25 772 (16)
Level of education >12 years, n (%)	9071 (28)	51 807 (33)
Longer duration since PsA diagnosis†, n (%)	12 568 (38)	NA
General comorbidities		
Cardiovascular disease‡	13 499 (41)	49 375 (31)
Hypertension§	4818 (15)	14 276 (8.9)
Ischaemic heart disease§	2043 (6.2)	7283 (4.5)
Congestive heart disease§	775 (2.3)	2545 (1.6)
Thromboembolic venous disease§	898 (2.7)	2770 (1.7)
Cerebrovascular disease§	1162 (3.5)	4949 (3.1)
Other atherosclerotic disease§	622 (1.9)	2088 (1.3)
Cardiovascular medication¶	12 922 (39)	47 139 (29)
Diabetes mellitus‡	2836 (8.6)	9451 (5.9)
Diabetes mellitus§	2191 (6.6)	6821 (4.2)
Diabetes medication¶	2422 (7.3)	8352 (5.2)
Infection, any§	15 675 (48)	53 935 (34)
Infection requiring inpatient care**	9785 (30)	32 936 (20)
Chronic pulmonary disease§	2248 (6.8)	6467 (4.0)
Chronic kidney disease§	264 (0.8)	706 (0.4)
Malignancy§	2427 (7.3)	10 573 (6.6)
Anxiety and depression‡	9593 (29)	34 704 (22)
Anxiety or depression§	3535 (11)	13 525 (8.4)
Anxiety or depression medication excluding benzodiazepines¶	7489 (23)	25 743 (16)
Benzodiazepine medication¶	3449 (10)	12 795 (7.9)
PsA-related extra-musculoskeletal manifestations		
Anterior uveitis§	716 (2.2)	1129 (0.7)
Posterior uveitis§	40 (0.1)	118 (0.1)
Inflammatory bowel disease§	750 (2.3)	1832 (1.1)
Joint surgery		
Hip replacement surgery††	899 (2.7)	2537 (1.6)
Knee replacement surgery††	813 (2.5)	1540 (1.0)
Other joint surgery††	2065 (6.3)	3287 (2.0)
Number of prior hospitalisations‡‡, median (IQR)	3 (1–7)	2 (1–5)
Pharmacological treatment§§		
NSAIDs	20 244 (61)	26 444 (16)
Oral glucocorticosteroids	6418 (19)	3607 (2.2)
csDMARDs	10 651 (32)	1252 (0.8)
tsDMARDs or bDMARDs	2183 (6.6)	73 (<0.1)
Anti-IL-12/23 therapy	40 (0.1)	0 (0)
Anti-IL-17 therapy	26 (0.1)	0 (0)
Anti-phosphodiesterase 4 therapy	49 (0.1)	1 (<0.1)
Anti-TNF therapy	2082 (6.3)	71 (<0.1)
JAK inhibition therapy	0 (0)	0 (0)
T-cell modulation therapy	17 (0.1)	2 (<0.1)

Continued

Table 1 Continued

	PsA cases (n=33 026)	Population comparator-subjects (n=161 094)

N (%) if not otherwise stated.
Missing data, n PsA cases/comparator-subjects: Foreign origin 1/6; education level 362/2939.
*Having received ≥1 ICD-code for PsA as main diagnosis from an outpatient visit to a rheumatology or internal medicine department registered in NPR at age ≥18 years 2001–2017.
†Patients with a first ICD diagnosis of PsA (as main diagnosis from an outpatient department of rheumatology or internal medicine at age ≥18 years) registered prior to the start of the study assessment period on 1 January 2007.
‡Based on ≥1 ICD code for such diagnoses or ≥1 drug dispensations suggesting such comorbidity prior to the individual's start of follow-up.
§Frequencies of individual comorbidities and extra-musculoskeletal manifestations are based on ≥1 ICD code from either an outpatient visit to a physician or an inpatient care episode in NPR (as main or secondary diagnosis and from any department) prior to start of the individual's follow-up (ICD codes from inpatient care available since 1968 and from outpatient care since 2001).
¶Based on ≥1 dispensation of pharmacological agents suggesting such comorbidity in the PDR prior to the individual's start of follow-up (available since 2005).
**Based on ≥1 ICD code for infection as main diagnosis from an inpatient care episode in NPR prior to the individual's start of follow-up.
††Based on procedure codes in NPR prior to the start of the individual's follow-up.
‡‡Based on inpatient care episodes registered in NPR prior to the individual's start of follow-up.
§§Based on ≥1 dispensation in the PDR during 1-year prior to the individual's start of follow-up (of for intravenously administered infliximab and abatacept ongoing treatment at the individual's start of follow-up as registered in the SRQ).
bDMARD, biologic disease-modifying anti-rheumatic drug; csDMARD, conventional synthetic disease-modifying anti-rheumatic drug (including azathioprine, auranofin, chloroquine, cyclosporine, hydroxychloroquine, leflunomide, methotrexate, sodium aurothiomalate, sulfasalazine); ICD, International Classification of Diseases; IL, interleukin; JAK, Janus kinase; NA, not applicable; NPR, National Patient Register; NSAID, non-steroidal anti-inflammatory drug; PDR, Prescribed Drugs Register; PsA, psoriatic arthritis; SRQ, Swedish Rheumatology Quality Register; TNF, tumour necrosis factor; tsDMARD, targeted synthetic disease-modifying anti-rheumatic drug.

start of and during follow-up is described in table 1 and online supplemental table S5, respectively, while online supplemental table S4 displays characteristics of the PsA cases and comparator-subjects stratified for sex.

All-cause mortality

During the 12-year study period (2007–2018), PsA cases and comparator-subjects were followed for a median (IQR) 8.8 (7.1) and 8.8 (7.2) years, respectively, contributing a total of 268 383 and 1 302 152 PY at risk. Over this period, 3121 deaths (9.4%) occurred among the PsA cases and 12 883 deaths (8.0%) among the comparator-subjects, while 312/2858 PsA cases/comparator-subjects were censored due to emigration and 525 comparator-subjects due to themselves being diagnosed with PsA.

In the main analysis, this resulted in a significantly increased all-cause mortality among the PsA cases in relation to comparator-subjects (HR: 1.11 (95% CI: 1.07 to 1.16), figure 2; crude IRR: 1.18 (95% CI: 1.13 to 1.22), table 2). All sensitivity analyses also gave results in line with this (online supplemental file 1). After adjustment for comorbidities, however, PsA was no longer associated with an increased all-cause mortality (HR: 0.96 (95% CI: 0.92 to 1.01)), indicating that it is the excess comorbidity burden in the patients with PsA that drives the elevated mortality risk.

On stratification, the increased mortality in our main analysis was seen to mainly emanate from female PsA cases and PsA cases with longer duration since diagnosis, respectively (figure 3; table 2). Overall, as well as for female PsA cases, the crude IRRs of death were significantly increased during all age-intervals except below 40 years, with the numerically highest point-estimates at ages 40–49 and 50–59 years

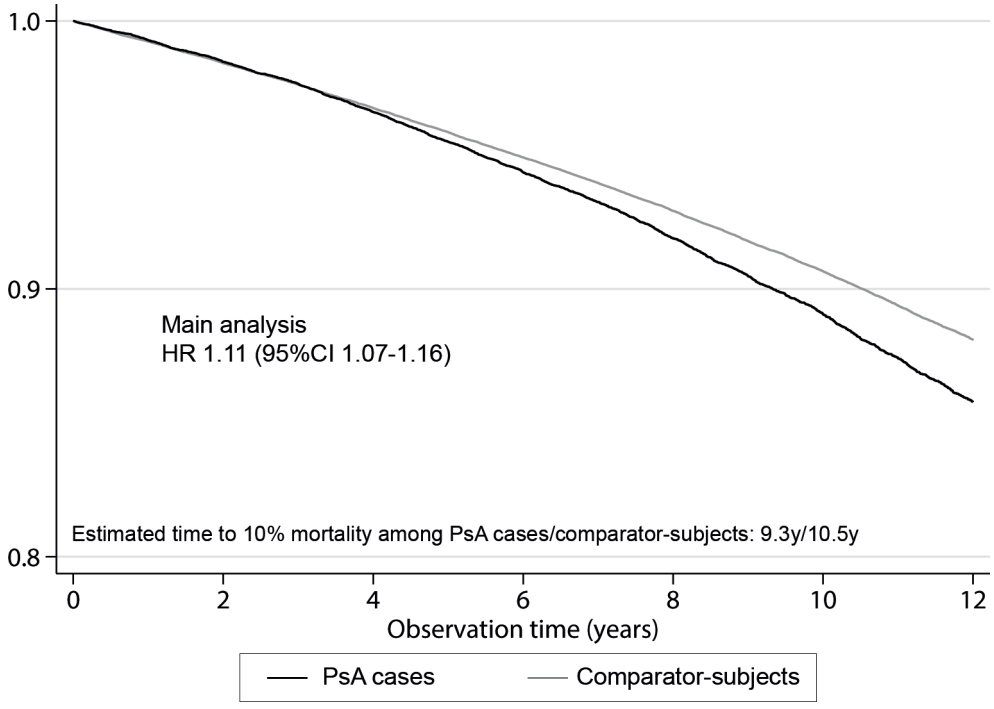

Figure 2 Comparison of all-cause mortality between patients with psoriatic arthritis in Sweden and matched general population comparator-subjects. Kaplan-Meier survival curves and matched Cox proportional HR, comparing all-cause mortality among PsA cases (n=33 026) to that of general population comparator-subjects, matched for sex, age and county (n=161 094), in Sweden 2007–2018. PsA, psoriatic arthritis; y, years.

Table 2 Mortality rates and incidence rate ratios of death between the psoriatic arthritis cases and comparator-subjects in total and by sex, age and disease duration

	PsA cases (n=33 026)			Population comparator-subjects (n=161 094)			Incidence rate ratio (95% CI)
	Number of deaths	Person-years at risk	Mortality rate*	Number of deaths	Person-years at risk	Mortality rate*	
Males							
Age (y)†							
<40	12	14 859	0.8	69	72 523	1.0	0.85 (0.46 to 1.57)
40–49	50	24 559	2.0	209	119 714	1.7	1.17 (0.86 to 1.59)
50–59	151	30 780	4.9	646	149 270	4.3	1.13 (0.95 to 1.35)
60–69	348	30 555	11.4	1657	147 452	11.2	1.01 (0.90 to 1.14)
70–79	468	15 650	29.9	2177	73 989	29.4	1.02 (0.92 to 1.12)
≥80	430	4100	104.9	1709	17 268	99.0	1.06 (0.95 to 1.18)
Total	1459	120 503	12.1	6467	580 216	11.1	1.09 (1.03 to 1.15)
Females							
Age (y)†							
<40	6	18 703	0.3	29	90 727	0.3	1.00 (0.42 to 2.42)
40–49	40	25 993	1.5	113	127 240	0.9	1.73 (1.21 to 2.49)
50–59	129	35 034	3.7	485	172 431	2.8	1.31 (1.08 to 1.59)
60–69	375	39 667	9.5	1475	194 126	7.6	1.24 (1.11 to 1.39)
70–79	492	21 577	22.8	1982	104 890	18.9	1.21 (1.09 to 1.33)
≥80	620	6907	89.8	2332	32 523	71.7	1.25 (1.15 to 1.37)
Total	1662	147 880	11.2	6416	721 936	8.9	1.27 (1.20 to 1.34)
Total							
Age (y)†							
<40	18	33 562	0.5	98	163 249	0.6	0.89 (0.54 to 1.48)
40–49	90	50 552	1.8	322	246 955	1.3	1.37 (1.08 to 1.73)
50–59	280	65 814	4.3	1131	321 701	3.5	1.21 (1.06 to 1.38)
60–69	723	70 221	10.3	3132	341 578	9.2	1.12 (1.04 to 1.22)
70–79	960	37 227	25.8	4159	178 879	23.3	1.11 (1.03 to 1.19)
≥80	1050	11 007	95.4	4041	49 791	81.2	1.18 (1.10 to 1.26)
Total	3121	268 383	11.6	12 883	1 302 152	9.9	1.18 (1.13 to 1.22)
Duration since PsA diagnosis							
Longer duration‡	1943	139 379	13.9	7459	670 174	11.1	1.25 (1.19 to 1.32)
Newly diagnosed§	1178	129 004	9.1	5424	631 979	8.6	1.06 (1.00 to 1.13)

*Per 1000 person-years.
†For example a PsA case born on 1 January 1967, diagnosed with PsA prior to 1 January 2007, and not dying or emigrating during the 12-year study assessment period, would contribute 10 person-years at risk to the 40–49 age-interval and two person-years at risk to the 50–59 age-interval.
‡Patients with a first ICD diagnosis of PsA (as main diagnosis from an outpatient department of rheumatology or internal medicine at age ≥18 years) registered prior to the start of the study assessment period on 1 January 2007.
§Patients with a first ICD diagnosis of PsA (as main diagnosis from an outpatient department of rheumatology or internal medicine at age ≥18 years) registered during the study period 2007–2017.
ICD, International Classification of Diseases; PsA, psoriatic arthritis.; y, years.

(table 2). There were similar, but weaker and non-significant age-trends among men.

Causes of death

Causes of death were overall similarly distributed between PsA cases and comparator-subjects, with CVD and malignancies being the leading causes in both cohorts. Numerically a slightly higher percentage of PsA cases than comparator-subjects died from causes other than malignancies (71% vs 66%; table 3).

Predictors of mortality

Lower socioeconomic status (using education level as proxy), prior joint surgery (which in PsA may reflect more severe disease, at least in prevalent cases) and presence of all assessed general comorbidities at the start of follow-up were significant predictors of mortality among both PsA cases and comparator-subjects in the sex- and age-adjusted analyses (table 4). Extra-musculoskeletal manifestations, that is, uveitis and IBD, did not predict mortality in PsA (estimated time to 10% mortality among PsA cases with/without prior anterior/posterior uveitis was 9.3/9.3 years, p=0.568 by Breslow test and for PsA cases with/without IBD 8.3/9.3 years, p=0.277 by Breslow test), while IBD, but not uveitis, was associated with increased mortality among the comparator-subjects (adjusted HR: 1.25 (95% CI: 1.07 to 1.45) for IBD; 0.98 (95% CI: 0.82 to 1.17) for uveitis).

Apart from the differing results regarding IBD, differences in the predictive abilities between the PsA and comparator-subject cohorts, as demonstrated by significant interactions, were only observed for prior hip and/or knee replacement surgery, which was a stronger mortality predictor in PsA, and for comorbid malignancy or anxiety/depression, both stronger mortality predictors in comparator-subjects (table 4). The multivariate predictor analyses rendered similar results, although without a between-group difference in the predictive ability of comorbid malignancy (online supplemental table S6).

DISCUSSION

Main findings

In this large, nationwide, population-based, 12-year, cohort study (PsA cases, n=33 026), the all-cause mortality risk in patients with PsA diagnosed in specialised rheumatology/

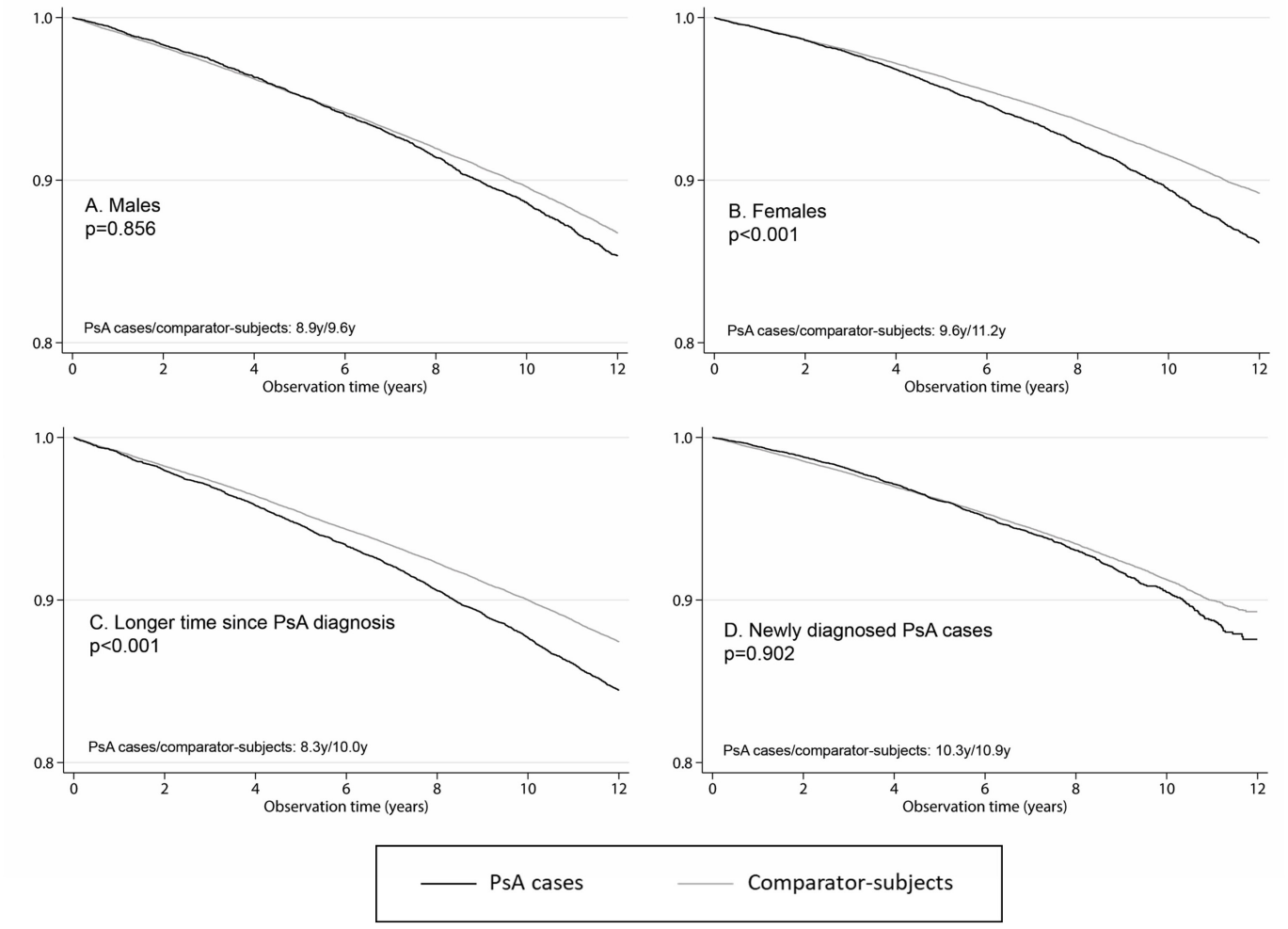

Figure 3 Comparison of all-cause mortality between patients with psoriatic arthritis in Sweden and matched general population comparator-subjects, stratified for sex and duration since PsA diagnosis. Kaplan-Meier survival curves, comparing all-cause mortality between PsA cases and general population comparator-subjects, matched for sex, age and county, in Sweden 2007–2018, stratified for sex and duration since PsA diagnosis. Estimated time to 10% mortality displayed below the curves. (A) 15 004 male PsA cases versus 73 060 male comparator-subjects; p=0.856 for the between-group comparison by matched Breslow test. (B) 18 022 female PsA cases versus 88 034 female comparator-subjects; HR: 1.23 (95% CI: 1.16 to 1.30) for the between-group comparison by matched Cox proportional hazard regression. (C) 12 568 prevalent PsA cases diagnosed prior to start of the study period on 1 January 2007 versus their 60 190 comparator-subjects; HR: 1.18 (95% CI: 1.12 to 1.25) by matched Cox proportional hazard regression. (D) 20 458 newly diagnosed PsA cases (ie, diagnosed 2007–2017) versus their 100 904 comparator-subjects; p=0.902 for the between-group comparison by matched Breslow test. PsA, psoriatic arthritis; y, years.

internal medicine care in Sweden was significantly increased, although only by around 10%, compared with the general population, mainly driven by increased risks in women and patients with longer duration since PsA diagnosis. When adjusting for comorbidity status, the increased mortality risk disappeared, indicating that the excess comorbidity burden in PsA (whether causally related to PsO/PsA or not) is the driving force behind the elevated mortality. The cause of death distributions were similar between PsA cases and comparator-subjects, with CVD and malignancy being the leading causes of death in both groups. Predictors of mortality were also generally similar in both cohorts (lower socioeconomic status, general comorbidities, prior joint surgery), although IBD did not predict mortality in PsA and hip/knee replacement surgery was a stronger mortality predictor in PsA than in the general population.

Previous research

Many of the contradictive, prior mortality estimates in PsA derive from hospital-based, single centre cohorts or smaller population-based studies (with fewer than 1000 PsA cases; online supplemental table S7). Considering that hospital-based studies are likely to capture patients with more severe disease compared with population-based cohorts, mortality estimates from such assessments may be expected to be inflated. However, even the results of these studies are inconsistent in observing an elevated mortality risk in PsA or not (online supplemental table S7). Turning to larger population-based assessments, two studies from Taiwan (9572 patients, 2001–2012, and 8795 patients, 2000–2012) demonstrated a standardised mortality ratio (SMR) of 1.47 (95% CI: 1.36 to 1.58) and HR of 1.52 (95% CI: 1.39 to 1.66), respectively.[29 30] Furthermore, the SMR was also increased at 1.34 (95% CI: 1.16 to 1.52) in a Canadian study (15 430 patients, 1996–2016).[33] On the other hand, large population-based studies from the UK (8706 patients, 1994–2010),[27] Denmark (9817 patients, 1998–2014),[36] Israel (5275 patients, 2003–2018)[35] and Norway (18 700 patients, 2010–2017),[18] did not demonstrate an increased mortality risk in PsA, with reported HR of 1.02 (95% CI: 0.92 to 1.12), stratified HR

Table 3 Causes of death* in the psoriatic arthritis and comparator-subject cohorts, in total and stratified for sex

	Males		Females		Total	
	PsA cases	Population comparator-subjects	PsA cases	Population compartor-subjects	PsA cases	Population compartor-subjects
Total number of deaths	n=1459	n=6467	n=1662	n=6416	n=3121	n=12 883
Cardiovascular disease	446 (31)	1888 (29)	446 (27)	1547 (24)	892 (29)	3435 (27)
Diabetes mellitus	38 (2.6)	173 (2.7)	29 (1.7)	143 (2.2)	67 (2.1)	316 (2.5)
Infections	96 (6.6)	359 (5.6)	116 (7.0)	336 (5.2)	212 (6.8)	695 (5.4)
Chronic pulmonary disease	64 (4.4)	208 (3.2)	96 (5.8)	317 (4.9)	160 (5.1)	525 (4.1)
Chronic kidney disease	7 (0.5)	24 (0.4)	6 (0.4)	17 (0.3)	13 (0.4)	41 (0.3)
Malignancy	387 (27)	2077 (32)	503 (30)	2315 (36)	890 (29)	4392 (34)
Suicide	45 (3.1)	156 (2.4)	27 (1.6)	100 (1.6)	72 (2.3)	256 (2.0)
Other	389 (27)	1626 (25)	459 (28)	1712 (27)	848 (27)	3338 (26)

N (%) if not otherwise stated.
*Causes of death were identified from the Cause of Death Register, using the International Classification of Diseases code for the underlying cause of death. Cause of death missing for one male and one female comparator-subject. Deaths due to acute exacerbation of chronic obstructive pulmonary disease (n=13/20 among male/female PsA cases; n=45/72 among male/female comparator-subjects) were counted as both infection and chronic pulmonary disease.
PsA, psoriatic arthritis.

of 1.06 (no CI reported) and adjusted HR of 1.02 (95% CI: 0.90 to 1.15) and 1.06 (95% CI: 0.99 to 1.13), respectively. This diversity of results was also highlighted in a recent meta-analysis, wherein no increased all-cause mortality in the overall PsA population was found (relative risk 1.12 (95% CI: 0.96 to 1.30)), although the point estimate was very similar to that found in the present study (and an increased risk was indeed observed among female patients with PsA, see below).[19] In the aforementioned Israeli cohort, the final, non-increased mortality estimate was adjusted for comorbidities, whereas their crude assessment did show an elevated HR in line with ours at 1.16 (95% CI: 1.04 to 1.29).[35] Aiming to quantify the total impact of PsA and its associated comorbidities on mortality, in our main analyses we did not adjust our morality estimates for comorbidities, as we consider this to better illustrate the real burden of PsA. As expected, however, when including such adjustments in an additional analysis, the elevated mortality risk associated with PsA disappeared.

In women with PsA, we found the all-cause mortality risk relative to their sex-matched comparator-subjects to be higher than in male patients, although with lower absolute MR. This observation is in line with the above mentioned meta-analysis,[19] as well as the recently published Norwegian study,[18] both of which (similar to us) found a significantly increased mortality risk among female, but not male, patients with PsA. To establish the reasons behind this sex difference was beyond the scope of the current study. A higher impact of PsA-related comorbidities on mortality among women compared with men could, however, be hypothesised, and also receives some support from the observation that the percental differences in deaths due to CVD and infections between patients and comparator-subjects were marginally higher for women than men (table 3). The finding that the mortality risk in relation to age-matched and sex-matched comparator-subjects increases with longer duration since diagnosis is compatible with negative effects of long-term systemic inflammation, and may also reflect the accumulation of PsA-related comorbidities over time.

Of note, while we do observe an increased all-cause mortality in the overall PsA population, the risk-increase of around 10% is lower than that previously reported for RA (estimated excess risk

Table 4 Predictors at start of follow-up of mortality among PsA cases and comparator-subjects

	Proportion at start of follow-up, PsA cases/comparator-subjects	PsA cases HR (95% CI)*	Population comparator-subjects HR (95% CI)*
Higher education (>12 y vs ≤12 y)	28/32%	0.66 (0.60 to 0.73)	0.65 (0.62 to 0.68)
General comorbidities			
Cardiovascular disease†	41/31%	1.79 (1.64 to 1.95)	1.67 (1.61 to 1.74)
Diabetes mellitus†	8.6/5.9%	1.82 (1.66 to 1.98)	1.91 (1.82 to 2.00)
Infection‡	48/34%	1.60 (1.49 to 1.71)	1.65 (1.59 to 1.71)
Chronic pulmonary disease‡	6.8/4.0%	2.03 (1.84 to 2.24)	2.21 (2.08 to 2.34)
Chronic kidney disease‡	0.8/0.4%	4.61 (3.85 to 5.51)	3.90 (3.48 to 4.38)
Malignancy‡	7.3/6.6%	1.63 (1.49 to 1.78)§	1.76 (1.69 to 1.84)
Anxiety/depression†	29/22%	1.58 (1.47 to 1.71)§	1.89 (1.82 to 1.96)
Joint surgery			
Hip and/or knee replacement surgery‡	4.7/2.4%	1.37 (1.24 to 1.52)§	1.15 (1.07 to 1.23)
Other joint surgery (small or large joints)‡	6.3/2.0%	1.27 (1.13 to 1.42)	1.15 (1.04 to 1.28)

*Separate sex-/age-adjusted models.
†≥1 relevant ICD-code in the NPR and/or ≥1 relevant drug dispensation in the PDR prior to start of follow-up.
‡≥1 relevant ICD/procedure-code in NPR prior to start of follow-up.
§In the entire material, the interaction terms between the PsA case/comparator-subject status and these predictors were significant (malignancy p=0.014; anxiety/depression p<0.001; hip/knee replacement surgery p=0.024), indicating a difference of the predictive ability in the two groups.
ICD, International Classification of Diseases; NPR, National Patient Register; PDR, Prescribed Drugs Register; PsA, psoriatic arthritis; y, years.

24–126%) or AS (38–64%).[15–20] This may also partly explain the conflicting results of prior PsA studies, some of which may have been underpowered to detect a risk-increase of this size. Interestingly, prior studies have found a more clearly elevated mortality risk in PsO than in PsA.[27 36] While this could be due to different effects of skin and joint inflammation, it may also be hypothesised that one mechanism underlying such results could be that patients with mild PsO more often than PsA may not seek medical care at all, or are managed exclusively in primary care, rendering them not to be included in mortality assessments. Anyhow, in a recent meta-analysis, the all-cause mortality in PsO (of any severity) was increased in the same general range as that observed for PsA in the present study (pooled relative risk 1.21 (95% CI: 1.14 to 1.28)), whereas it was higher in severe PsO.[37]

To estimate cause-specific mortality was beyond the aims of the present study. However, apart from the minor sex-differences alluded to above, the cause of death distributions were overall similar between PsA cases and comparator-subjects. In accordance with a number of previous publications,[18 29 33 35 36] deaths due to CVD and malignancy were the leading causes in both groups.

Within our PsA population, disease severity, as reflected by previous joint surgery, was a significant predictor of all-cause mortality. Of particular interest, prior hip and/or knee replacement surgery was a stronger mortality predictor in PsA than in comparator-subjects. Prior studies regarding the predictive roles of disease activity and severity on mortality in PsA are limited. In two earlier studies, higher disease activity and elevated acute phase reactants were, however, associated with an increased risk of death in PsA.[28 32] General comorbidities were strong predictors of mortality in both PsA and comparator-subjects, whereas extra-musculoskeletal manifestations (ie, IBD, uveitis) did not predict increased mortality in PsA, despite IBD being related to mortality in the population. Our results also indicate that the relative contribution of some conditions, in particular anxiety/depression, to mortality may be greater in the general population than in patients with PsA, where disease-specific factors also play a role. Finally, lower socioeconomic status, approximated by shorter education, was a significant non-differential predictor of mortality among PsA cases and comparator-subjects, in accordance with prior assessments in both PsA and the general population.[32 35 47]

Strengths and limitations

The large size (the largest to date on this topic) and population-based approach of our study, including patients with PsA with variable disease severity, is expected to provide estimates close to the true MR. The register-based methodology allowed nationwide identification of PsA cases and comparator-subjects from the general population in a uniform and systematic manner. This enabled direct comparisons with internal comparator-subjects, which has previously been shown to yield better mortality approximations than external comparisons (SMRs).[48]

PsA cases managed exclusively in primary care, as well as a minority subset of cases managed only by private caregivers, are not captured by the NPR and thus not included in the current study. The proportion of individuals with only primary care health contacts for PsA has been estimated at 8.5% and 26.7%, respectively, in two assessments from southern Sweden prior to 2010.[38 49] In the first of these studies, however, only 18–24% of the PsA cases with a diagnosis deriving exclusively from primary care were found to fulfil established PsA classification criteria.[38] The proportion of PsA cases exclusively followed in private specialised care units that do not report to the NPR (which most nowadays do) is expected to differ regionally, depending on the availability of private caregivers. Patients followed at such units might, however, occasionally also consult public rheumatology departments. Considering that both of these groups of patients may have a milder disease than those included in our study, the observed mortality risk could be somewhat overestimated, although the exact size of such overestimation is unknown.

Furthermore, the validity of the PsA diagnoses in the NPR may be a potential limitation. However, the PsA case definition used for the present assessment has shown high validity, with a positive predictive value for the fulfilment of established PsA classification criteria of 86%.[46] Misclassification of PsA diagnoses in the NPR is thus unlikely to have had a substantial impact on our mortality estimates, which is further supported by the similar results in the sensitivity analysis in which 20% of the PsA cases were randomly replaced by one of their own matched comparator-subjects. Misclassification of the main outcome is not a major concern because of virtually complete ascertainment, but misclassification of the cause of death is likely to be present despite the reliable data deriving from the Cause of Death Register. However, this misclassification is possibly non-differential for the PsA cases and comparator-subjects and unlikely to have significantly flawed our results.

Finally, the nationwide register sources used for the current study unfortunately do not provide sufficient coverage regarding lifestyle factors, disease characteristics and clinical variables that would allow for adjustment or stratification for important variables such as smoking, other risk factors for CVD not captured by ICD-codes, disease severity or PsA phenotype. Nor do we know the time of symptom onset, and thus used time since PsA diagnosis as surrogate marker for disease duration. In light of the clear risks of confounding by indication in relation to comorbidities, as well as difficulties to distinguish impact of treatments from that of disease activity, attempting to assess potential relationships between anti-rheumatic treatment exposures (non-steroidal anti-inflammatory drugs, glucocorticosteroids, DMARDs) and mortality in PsA would require a dedicated study in its own right, and was thus beyond the scope of the present manuscript.

Conclusions

In conclusion, in this large, population-based study from Sweden, the mortality risk in PsA was estimated at about 10% higher than in the general population, with increased risks mainly in women and patients with longer disease duration (time since PsA diagnosis), and emanating from an excess comorbidity burden. The cause of death distribution in PsA was similar to that in the general population. However, further studies are warranted to disentangle the effects of disease activity and medication on mortality risk.

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Supplementary file

Mortality in patients with psoriatic arthritis in Sweden – a nationwide, population-based cohort study

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Supplementary Table S1. ICD-codes used to define arthritic diseases, comorbidities and causes of death

	ICD-8 1968-1986	ICD-9 1987-1996	ICD-10 1997-2018
Arthritic diseases			
Psoriatic arthritis	696.00	696A	L40.5; M07.0; M07.1; M07.2; M07.3
Juvenile arthritis	712.00	714D	M08.0; M08.1; M08.2; M08.3; M08.4; M08.8; M08.9; M09.0; M09.1; M09.2; M09.8
Ankylosing spondylitis	712.40	720A	M45.9
Spondyloarthritis	713.10; 713.11; 713.12; 713.19; 726.99	720B; 720C; 720W; 720X	M46.0; M46.1; M46.8; M46.9
Inflammatory bowel disease related arthritis	Not applicable	713B	M07.4; M07.5; M07.6
Reactive arthritis	136.03; 714.90	099D; 711B; 711D; 711X	M02.1; M02.3; M02.8; M02.9; M03.2; M03.6
Rheumatoid arthritis	712.10; 712.20; 712.38; 712.39	714A; 714B; 714C; 714W; 719D	M05.0; M05.1; M05.2; M05.3; M05.8; M05.9; M06.0; M06.2; M06.3; M06.8; M06.9; M12.3
Undifferentiated arthritis	711.00; 711.01; 711.02; 711.03; 711.04; 711.05; 711.06; 711.07; 711.08; 711.09; 714.93; 714.98; 715.99	714X; 716F; 716G; 716W; 716X	M06.4; M13.0; M13.1; M13.8; M13.9
General comorbidities			
Hypertension[a]	400-404	401-405	I10-I15
Ischaemic heart disease[a]	410-414	410-414	I20-I25
Congestive heart disease[a]	425; 427,00; 427,10; 428,99	425; 428	I11.0; I13.0; I13.2; I42; I43; I50
Thromboembolic venous disease[a]	321; 450,01; 450,03; 451,00; 451,98; 451,99; 452,99; 453,09; 671,01; 671,02; 671,08; 671,09; 673,98; 673,99	325; 415B; 437G; 451B; 451C; 451W; 451X; 452; 453A; 453C; 453D; 453W; 453X; 527B; 671D; 671E; 671F; 673C	G08; I26; I63.6; I67.6; I80.1-I80.9; I81; I82.0; I82.2-I82.9; K75.1; O22.3; O22.5; O87.1; O87.3; O88.2
Cerebrovascular disease[a]	430; 431; 433-438	430-432; 434-438	G45; G46; I60-I64; I66-I69
Other atherosclerotic disease[a]	432; 440-442; 443,10; 443,90; 443,99; 444; 445,00	433; 440-442; 443B; 443X; 444; 447B; 557	I65; I70-I72; I73.1; I73.9; I74; K55.0-K55.1
Diabetes mellitus	250	250; 648A	E10-E14; O24
Infections	000-134; 136,01; 136,02; 136,04; 136,08; 136,09; 245,01; 289,40; 320,00; 320,10; 320,80; 320,99; 322; 324; 360,00; 360,08; 360,09; 362; 363,98; 363,99; 366,00;	001-134; 136A; 136C; 136D; 136E; 136F; 136W; 136X; 137-139; 245A; 254B; 320; 321; 323D; 323E; 323G; 324; 326; 360A; 370B; 370D; 370E; 370F; 372A;	A00-B99; D73.3; D76.2; E06.0; E32.1; G00; G04.1; G04.2; G06; H00.0; H44.0; H60.0; H60.1; H60.2; H60.3; H65.0; H66; H70; I30.1; I33.0; I40.0; J00; J01;

	367,00; 368,00; 368,03; 369,00; 369,01; 380,00; 380,01; 381; 382; 383; 420; 421,00; 460,99; 461; 462; 463; 464; 465,99; 466,99; 470; 471; 472; 473; 474; 480,99; 481,99; 482; 483,99; 484,99; 485,02; 485,09; 486; 490,99; 501,99; 503; 508,00; 508,01; 508,02; 508,03; 510; 511,10; 513,99; 522,50; 527,30; 528,30; 562,02; 562,11; 566; 567,00; 567,01; 567,02; 569,00; 572,99; 590; 592,04; 592,05; 595,00; 595,01; 597,00; 597,01; 597,08; 599,02; 601,00; 604,00; 604,01; 607,30; 607,40; 607,50; 611,00; 611,01; 612; 614,99; 616,00; 616,01; 616,02; 616,03; 620; 622,00; 622,08; 622,09; 622,10; 622,11; 622,18; 622,19; 629,40; 630; 635; 645,90; 645,91; 670; 678,00; 678,01; 678,02; 680; 681; 682; 683; 684,08; 684,09; 686,00; 686,90; 686,91; 686,98; 710; 720; 732,99; 910,10; 911,10; 912,10; 913,10; 914,10; 915,10; 916,10; 917,10; 918,10; 918,11; 998,50; 999,20; 999,30	373B; 380B; 381A; 382; 383A; 383B; 420; 421A; 460; 461; 462; 463; 464; 465; 466; 473; 475; 480; 481; 482; 483; 484; 485; 486; 487; 490; 496; 510; 511B; 513; 522E; 522F; 522H; 527D; 528D; 562A; 562B; 566; 567B; 567C; 569F; 572A; 572B; 590A; 590B; 590C; 590D; 590W; 590X; 595A; 597A; 597W; 598A; 599A; 601A; 601C; 601D; 603B; 604A; 604X; 607B; 607C; 608A; 608E; 611A; 614A; 614C; 614D; 614E; 614X; 615A; 615X; 616A; 616B; 616D; 616E; 616X; 634A; 635A; 636A; 637A; 638A; 639A; 646G; 658E; 659D; 670; 675A; 675B; 675C; 675W; 675X; 680; 681; 682; 683; 684; 685; 686A; 686W; 686X; 711A; 711E; 711F; 711G; 711H; 711W; 711X; 728A; 730; 790H; 790W; 958D; 996G; 998F; 999D	J02; J03; J04; J05; J06; J09; J10; J11; J12; J13; J14; J15; J16; J18; J20; J21; J22; J32; J34.0; J36; J39.0; J39.1; J44.0; J85; J86; J98.7; K04.4; K04.6; K04.7; K11.3; K12.2; K57.0; K57.2; K57.4; K57.8; K61; K63.0; K75.0; L00; L01; L02; L03; L04; L05; L08; L30.3; M00; M46.2; M46.3; M46.4; M46.5; M60.0; M65.0; M65.1; M71.0; M71.1; M72.6; M86; N10; N11.0; N11.1; N13.6; N15.1; N15.9; N30.0; N30.8; N34.0; N39.0; N41.0; N41.2; N41.3; N43.1; N45.0; N45.9; N48.2; N49.9; N61; N70.0; N71.0; N72; N73.0; N73.1; N73.2; N75.1; N76.4; N98.0; O03.0; O03.5; O04.0; O04.5; O05.0; O05.5 O06.0; O06.5; O07.0; O07.5; O08.0; O23; O41.1; O75.3; O85; O86; O91; R57.2; R65.0; R65.1; T79.3; T80.2; T81.4; T82.6; T82.7; T83.5; T83.6; T84.5; T84.6; T84.7; T85.7; T87.4; T88.0; Y95; U04 **Or any of the following with an auxiliary code from A00-B99:** F02.4; G01; G02; G05.0; G05.1; G05.2; G07; G53.1; G63.0; G73.4; G94.0; H03; H06.1; H13.0; H13.1; H19.1; H19.2; H22.0; H32.0; H45.1; H62.0; H62.1; H62.2; H62.3; H67.0; H67.1; H75.0; H94.0; I32.0; I32.1; I41.0; I41.1; I41.2; I43.0; I52.0; I52.1; I68.1; I79.0 I79.1; I98.0;

			I98.1; J17.0; J17.1; J17.2; J17.3; K23.0; K23.1; K67; K77.0; K87.1; K93.0; K93.1; L99.8; M01.0; M01.1; M01.2; M01.3; M01.4; M01.5; M01.6; M01.8; M03.0; M03.1; M49.0; M49.1; M49.2; M49.3; M63.0; M63.1; M63.2; M68.0; M73.0; M73.1; M90.0; M90.1; M90.2; N08.0; N08.8; N16.0; N22.0; N29.0; N29.1; N33.0; N33.8; N37.0; N51; N74.0; N74.1; N74.2; N74.3; N74.4; N77.0; N77.1
Chronic pulmonary disease	491-493; 517; 518,99	491-494; 496; 515; 516D; 516W; 516X; 517	J41-J44; J45-J47; J84.1; J84.8; J84.9; J99
Chronic kidney disease	582,00; 582,09	585	N18
Malignancy	140-201; 202,00; 202,19; 202,28; 202,98; 203-207	140-208	C00-C97
Anxiety or depression	296,00; 296,20; 298,00; 300,00; 300,20; 300,30; 300,40; 300,88; 300,99; 790,20	296B; 296D; 298A; 300A; 300C; 300D; 300E; 300W; 300X; 308; 309; 311	F31.3-F31.5; F32-F34; F40-F43; F53.0
Suicide[b]	Not relevant	Not relevant	X60-X84; Y10-Y34
PsA related extra-musculoskeletal manifestations			
Anterior uveitis	364,00; 364,02; 364,09	364A; 364B; 364C; 364D	H20; H22.1
Posterior uveitis	365,00; 365,01; 365,02; 365,03; 365,04; 365,08; 365,09	363A; 363B; 363C	H30; H32.8
Inflammatory bowel disease	563,00; 563,10; 563,98; 563,99; 569,02	555-556	K50-K51

[a] Combined for the assessment of cardiovascular disease. [b] Only used for the cause of death assessment. ICD, international classification of diseases.

Supplementary Table S2. Procedure-codes used to define comorbidities

	1964-1996	1997-2017
Hip replacement surgery	8410; 8413; 8414; 8415; 8419	NFB; NFC
Knee replacement surgery	8423; 8424; 8425; 8426; 8427; 8428	NGB; NGC
Other joint surgery	8390; 8392; 8393; 8399; 8420; 8421; 8422; 8429; 8430; 8431; 8432; 8433; 8434; 8436; 8437; 8438; 8450; 8642	NBB; NBC; NCB; NCC; NDB; NDC; NDE; NDF; NDG; NHB; NHC; NHE; NHF; NHG

Supplementary Table S3. ATC-codes for anti-rheumatic treatments and used to define comorbidities

	ATC codes
Anti-rheumatic treatments	
NSAIDs	M01AA01-M01AX04
Oral glucocorticosteroids	H02AB06
csDMARDs	L01BA01; L04AX03; A07EC01; L04AA13; L04AD01; L04AX01; M01CB01; M01CB03; P01BA01; P01BA02
Anti-IL12/23 therapy	L04AC05
Anti-IL17 therapy	L04AC10; L04AC13
Anti-Phosphodiesterase 4 therapy	L04AA32
Anti-TNF therapy	L04AB01; L04AB02; L04AB4; L04AB05; L04AB06
JAK inhibition therapy	L04AA29
T-cell modulation therapy	L04AA24
General comorbidities	
Cardiovascular disease	B01AA; B01AB; B01AC02-B01AC07; B01AC13-B01AC18; B01AC22-B01AC26; B01AC30-B01AC56; B01AE; B01AF; B01AX05; C01A; C01D; C01EB17; C01EB18; C02AC05; C02C; C02DB; C02LC05; C02LE; C02LF; C02LG02; C03A-C03E; C07AA01-C07AA06; C07AA12-C07AA14; C07AA16-C07AA27; C07AB02-C07AB08; C07AB10-C07AB13; C07AB52; C07AG; C07B-C07F; C08; C09; C10
Diabetes mellitus	A10
Anxiety or depression medications excluding benzodiazepines	N06A
Benzodiazepines	N05BA

ATC, anatomical therapeutic chemical classification; csDMARD, conventional, synthetic, disease-modifying, anti-rheumatic drug; IL, interleukin; JAK, Janus kinase; NSAID, non-steroidal anti-inflammatory drug; TNF, tumor necrosis factor.

Supplementary Table S4. Demographics and disease characteristics of the psoriatic arthritis and comparator-subject cohorts at start of follow-up, stratified for sex

	Males		Females	
	PsA cases (n=15 004)	**Population comparator-subjects (n=73 060)**	**PsA cases (n=18 022)**	**Population comparator-subjects (n=88 034)**
Demographics				
Age at inclusion criteria fulfillment[a], yrs, mean (SD)	51 (14)	NA	52 (15)	NA
Age at the start of follow-up, yrs, mean (SD)	52 (14)	52 (14)	53 (15)	53 (15)
Duration between inclusion criteria fulfillment[a] and the start of follow-up, yrs, mean (SD)	1.2 (1.9)	NA	1.3 (2.0)	NA
Foreign origin, n (%)	1 391 (9.3%)	11 273 (15%)	1 810 (10%)	14 499 (17%)
Level of education >12 years, n (%)	3 806 (26%)	21 239 (30%)	5 265 (30%)	30 478 (35%)
Longer duration since PsA diagnosis[b], n (%)	5 592 (37%)	NA	6 976 (39%)	NA
General comorbidities				
Cardiovascular disease[f]	5 759 (38%)	21 587 (30%)	7 740 (43%)	27 788 (32%)
Hypertension[c]	2 256 (15%)	6 838 (9.4%)	2 562 (14%)	7 438 (8.4%)
Ischaemic heart disease[c]	1 180 (7.9%)	4 426 (6.1%)	863 (4.8%)	2 857 (3.2%)
Congestive heart disease[c]	439 (2.9%)	1 454 (2.0%)	336 (1.9%)	1 091 (1.2%)
Thromboembolic venous disease[c]	348 (2.3%)	1 225 (1.7%)	550 (3.1%)	1 545 (1.8%)
Cerebrovascular disease[c]	563 (3.8%)	2 548 (3.5%)	599 (3.3%)	2 401 (2.7%)
Other atherosclerotic disease[c]	314 (2.1%)	1 140 (1.6%)	308 (1.7%)	948 (1.1%)
Cardiovascular medication[e]	5 499 (37%)	20 551 (28%)	7 423 (41%)	26 588 (30%)
Diabetes mellitus[f]	1 326 (8.8%)	4 940 (6.8%)	1 510 (8.4%)	4 511 (5.1%)
Diabetes mellitus[c]	1 008 (6.7%)	3 532 (4.8%)	1 183 (6.6%)	3 289 (3.7%)
Diabetes medication[e]	1 166 (7.8%)	4 532 (6.2%)	1 256 (7.0%)	3 820 (4.3%)
Infection, any[c]	6 284 (42%)	21 717 (30%)	9 391 (52%)	32 218 (37%)
Infection requiring inpatient care[d]	3 914 (26%)	13 717 (19%)	5 871 (33%)	19 219 (22%)
Chronic pulmonary disease[c]	772 (5.1%)	2 527 (3.5%)	1 476 (8.2%)	3 940 (4.5%)
Chronic kidney disease[c]	153 (1.0%)	404 (0.6%)	111 (0.6%)	302 (0.3%)
Malignancy[c]	964 (6.4%)	4 090 (5.6%)	1 463 (8.1%)	6 483 (7.4%)
Anxiety and depression[f]	3 078 (21%)	11 725 (16%)	6 515 (36%)	22 979 (26%)
Anxiety or depression[c]	1 159 (7.7%)	4 959 (6.8%)	2 376 (13%)	8 566 (9.7%)
Anxiety or depression medication excluding benzodiazepines[e]	2 276 (15%)	8 239 (11%)	5 213 (29%)	17 504 (20%)
Benzodiazepine medication[e]	1 099 (7.3%)	4 248 (5.8%)	2 350 (13%)	8 547 (9.7%)
PsA related extra-musculoskeletal manifestations				
Anterior uveitis[c]	362 (2.4%)	543 (0.7%)	354 (2.0%)	586 (0.7%)
Posterior uveitis[c]	17 (0.1%)	54 (0.1%)	23 (0.1%)	64 (0.1%)
Inflammatory bowel disease[c]	267 (1.8%)	834 (1.1%)	483 (2.7%)	998 (1.1%)
Joint surgery				
Hip replacement surgery[g]	376 (2.5%)	1 004 (1.4%)	523 (2.9%)	1 533 (1.7%)
Knee replacement surgery[g]	291 (1.9%)	558 (0.8%)	522 (2.9%)	982 (1.1%)
Other joint surgery[g]	832 (5.5%)	1 417 (1.9%)	1 233 (6.8%)	1 870 (2.1%)
Number of prior hospitalisations[h], median (IQR)	2 (1-5)	1 (0-3)	5 (2-8)	3 (1-5)
Pharmacological treatment[i]				
NSAIDs	9 267 (62%)	10 375 (14%)	10 977 (61%)	16 069 (18%)
Oral glucocorticosteroids	2 685 (18%)	1 346 (1.8%)	3 733 (21%)	2 261 (2.6%)
csDMARDs	4 845 (32%)	487 (0.7%)	5 806 (32%)	765 (0.9%)
tsDMARDs or bDMARDs	1 025 (6.8%)	25 (<0.1%)	1 158 (6.4%)	48 (0.1%)
Anti-IL12/23 therapy	19 (0.1%)	0 (0%)	21 (0.1%)	0 (0%)
Anti-IL17 therapy	18 (0.1%)	0 (0%)	8 (<0.1%)	0 (0%)

Anti-Phosphodiesterase 4 therapy	23 (0.2%)	1 (<0.1%)	26 (0.1%)	0 (0%)
Anti-TNF therapy	977 (6.5%)	23 (<0.1%)	1 105 (6.1%)	48 (0.1%)
JAK inhibition therapy	0 (0%)	0 (0%)	0 (0%)	0 (0%)
T-cell modulation therapy	4 (<0.1%)	2 (<0.1%)	13 (0.1%)	0 (0%)

N (%) if not otherwise stated. [a] Having received ≥1 ICD-code for PsA as main diagnosis from an outpatient visit to a rheumatology or internal medicine department registered in NPR at age ≥18 years 2001-2017. [b] Patients with a first ICD diagnosis of PsA (as main diagnosis from an outpatient department of rheumatology or internal medicine at age ≥18 years) registered prior to start of the study assessment period on January 1, 2007. [c] Frequencies of individual comorbidities and extra-musculoskeletal manifestations are based on ≥1 ICD code from either an outpatient visit to a physician or an inpatient care episode in NPR (as main or secondary diagnosis and from any department) prior to start of the individual´s follow-up (ICD codes from inpatient care available since 1968 and from outpatient care since 2001). [d] Based on ≥1 ICD code for infection as main diagnosis from an inpatient care episode in NPR prior to the individual´s start of follow-up. [e] Based on ≥1 dispensation of pharmacological agents suggesting such comorbidity in the PDR prior to the individual´s start of follow-up (available since 2005). [f] Based on ≥1 ICD code for such diagnoses or ≥1 drug dispensations suggesting such comorbidity prior to the individual´s start of follow-up. [g] Based on procedure codes in NPR prior to the start of the individual´s follow-up. [h] Based on inpatient care episodes registered in NPR prior to the individual's start of follow-up. [i] Based on ≥1 dispensation in the PDR during one year prior to the individual´s start of follow-up (of for intravenously administered infliximab and abatacept ongoing treatment at the individual´s start of follow-up as registered in the SRQ). bDMARD, biologic disease-modifying anti-rheumatic drug; csDMARD, conventional synthetic disease-modifying anti-rheumatic drug (including azathioprine, auranofin, chloroquine, cyclosporine, hydroxychloroquine, leflunomide, methotrexate, sodium aurothiomalate, sulfasalazine); IL, interleukin; IQR, inter-quartile range; JAK, Janus kinase; NA, not applicable; NPR, National Patient Register; NSAID, non-steroidal anti-inflammatory drug; PDR, Prescribed Drugs Register; PsA, psoriatic arthritis; SD, standard deviation; SRQ, Swedish Rheumatology Quality Register; TNF, tumor necrosis factor; tsDMARD, targeted synthetic disease-modifying anti-rheumatic drug. Missing data, n male PsA cases/male comparator-subjects/female PsA cases/female comparator-subjects: Foreign origin 0/5/1/1; Education level 175/1 476/187/1 463.

Supplementary Table S5. Anti-rheumatic treatment during follow-up for the psoriatic arthritis and comparator-subject cohorts

Pharmacological treatment during follow-up[a]	PsA cases (n=33 026)	Population comparator-subjects (n=161 094)
NSAIDs	27 139 (82%)	79 348 (49%)
Oral glucocorticosteroids	16 035 (49%)	20 000 (12%)
csDMARDs	21 776 (66%)	3 762 (2.3%)
tsDMARDs or bDMARDs	9 362 (28%)	675 (0.4%)
Anti-IL12/23 therapy	569 (1.7%)	19 (<0.1%)
Anti-IL17 therapy	1 071 (3.2%)	24 (<0.1%)
Anti-Phosphodiesterase 4 therapy	1 050 (3.2%)	39 (<0.1%)
Anti-TNF therapy	8 700 (26%)	623 (0.4%)
JAK inhibition therapy	96 (0.3%)	5 (<0.1%)
T-cell modulation therapy	321 (1.0%)	43 (<0.1%)

Figures presented are n (%). [a] Based on ≥1 dispensation in the PDR from the individual´s start of follow-up until Dec 31, 2018, death or censoring (of for intravenously administered infliximab and abatacept treatment during this period as registered in the SRQ). bDMARD, biologic disease-modifying anti-rheumatic drug; csDMARD, conventional synthetic disease-modifying anti-rheumatic drug (including azathioprine, auranofin, chloroquine, cyclosporine, hydroxychloroquine, leflunomide, methotrexate, sodium aurothiomalate, sulfasalazine); IL, interleukin; JAK, Janus kinase; NSAID, non-steroidal anti-inflammatory drug; PDR, Prescribed Drugs Register; SRQ, Swedish Rheumatology Quality Register; TNF, tumor necrosis factor; tsDMARD, targeted synthetic disease-modifying anti-rheumatic drug.

Supplementary Table S6. Predictors at start of follow-up of mortality among PsA cases and comparator-subjects, respectively, according to multivariate Cox proportional hazard regression models

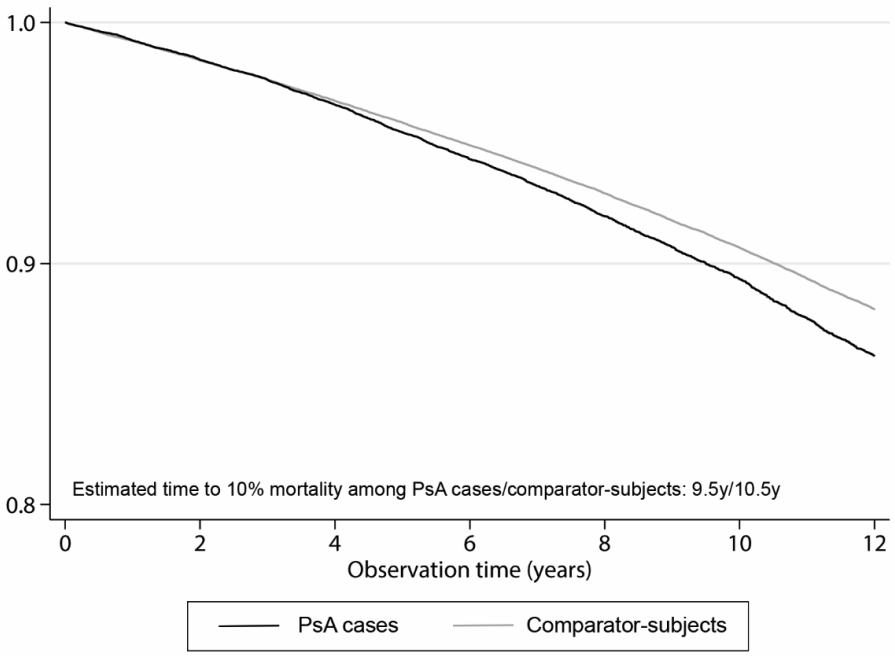
	Proportion at start of follow-up, PsA cases /comparator-subjects	PsA cases HR (95%CI)[a]	Population comparator-subjects HR (95%CI)[a]
Male sex	45/45%	1.36 (1.26-1.47)*	1.59 (1.54-1.65)
Higher age (per year)	NA	1.10 (1.09-1.10)*	1.10 (1.10-1.11)
Higher education (>12y vs ≤12y)	28/32%	0.68 (0.61-0.75)	0.67 (0.64-0.71)
Cardiovascular disease[b]	41/31%	1.44 (1.31-1.58)	1.33 (1.28-1.39)
Diabetes[b]	8.6/5.9%	1.48 (1.35-1.63)	1.56 (1.48-1.64)
Infection[c]	48/34%	1.28 (1.19-1.38)	1.33 (1.28-1.38)
Chronic pulmonary disease[c]	6.8/4.0%	1.68 (1.51-1.87)	1.68 (1.58-1.79)
Chronic kidney disease[c]	0.8/0.4%	3.42 (2.82-4.15)	2.64 (2.33-2.99)
Malignancy[c]	7.3/6.6%	1.48 (1.34-1.62)	1.55 (1.48-1.63)
Anxiety/depression[b]	29/22%	1.38 (1.27-1.49)*	1.59 (1.53-1.66)
Hip and/or knee replacement surgery[c]	4.7/2.4%	1.23 (1.10-1.37)*	1.02 (0.95-1.10)
Other joint surgery (small or large joints)[c]	6.3/2.0%	1.17 (1.03-1.31)	1.03 (0.93-1.15)

[a] Multivariate models in PsA cases and population comparator-subjects, respectively. [b] ≥1 relevant ICD-code in the NPR and/or ≥1 relevant drug dispensation in the PDR prior to start of follow-up. [b] ≥1 relevant ICD/procedure-code in NPR prior to start of follow-up. * In the entire material, the interaction terms between the PsA case/comparator-subject status and these predictors were significant (sex p<0.001; age p=0.010; anxiety/depression p<0.001; hip/knee replacement surgery p=0.006), indicating a difference of the predictive ability in the two groups. NA, not applicable; NPR, National Patient Register; PDR, Prescribed Drugs Register; PsA, psoriatic arthritis; y, years.

Sensitivity analyses for the primary outcome (i.e. all-cause mortality) assessment

For the primary outcome (comparison of all-cause mortality between psoriatic arthritis [PsA] cases and comparator-subjects) a number of different sensitivity analyses were conducted.

A. To account for potential misclassification of PsA diagnoses among the cases:
In a prior validation of our ICD-code based PsA case definition, 86% of 400 assessed cases were found to fulfil established PsA classification criteria.[1] Thus, to account for potential misclassification of PsA diagnoses among cases in the current all-cause mortality assessment, a sensitivity analysis was performed by randomly replacing 20% (i.e. slightly more than the 14% found to be misclassified in the validation study) of the PsA cases with one of their own comparator-subjects. Both the 20% of PsA cases to be replaced and which of their individual comparator-subjects to use for the replacement were chosen at random. Results of this sensitivity analysis (**Supplementary Figure S1)** remained similar to those of the main analysis.

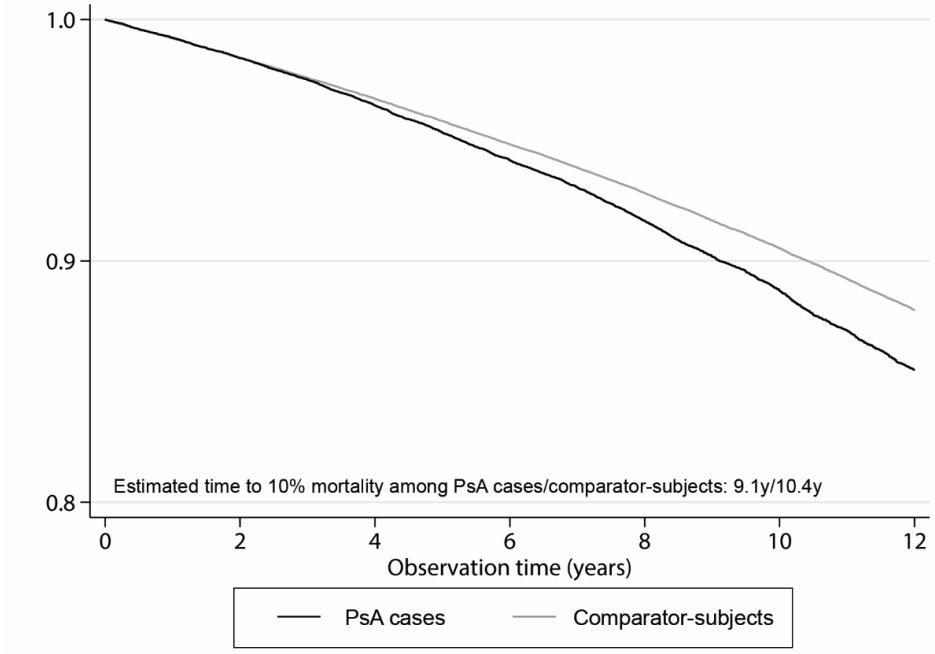


Supplementary Figure S1. Sensitivity analysis to account for potential misclassification of psoriatic arthritis diagnoses among the cases. Kaplan-Meier survival curves, comparing all-cause mortality between PsA cases (n=33 026) and general population comparator-subjects, matched for sex, age and county (n=161 094), in Sweden 2007-2018, after random replacement of 20% of the PsA cases (n=6 605) with one of their own matched comparator-subjects. HR:1.09 (95%CI:1.05-1.14) by matched Cox proportional hazard regression. CI, confidence interval; HR, hazard ratio; PsA, psoriatic arthritis; y, years.

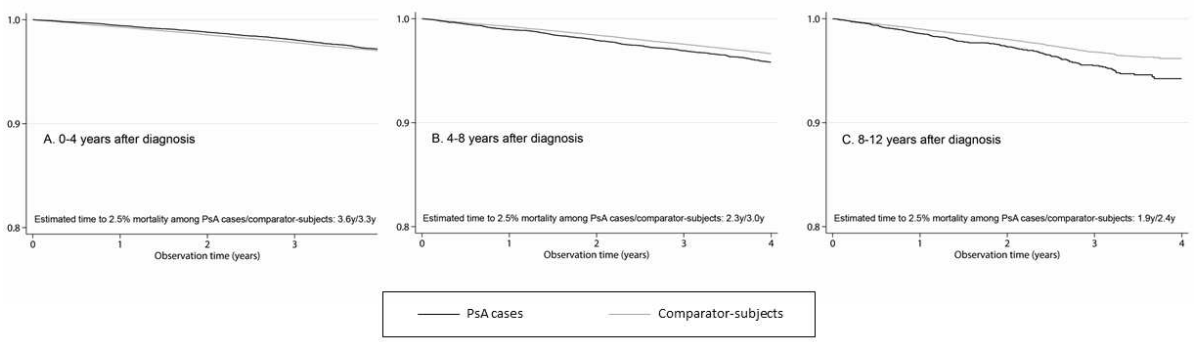
B. To account for the fact that an increase in mortality may be expected during the first months after diagnosis of a disease (since diagnoses are sometimes made during diagnostic work-up for symptoms driven by other and potentially more acutely dangerous conditions):

To assess whether the excess deaths in the PsA cohort of our main analysis was driven by an increase in mortality during the time-period just subsequent to the PsA diagnoses being made, in a sensitivity analysis we applied a delayed start of the follow-up until 6 months after the first diagnostic event for PsA cases diagnosed between July 1, 2006, and December 31, 2017 (and with corresponding delay also for their respective comparator-subjects). Furthermore, for PsA cases diagnosed during the study period (2007-2017 [i.e. the "newly diagnosed cases" subset]; and their respective matched comparator-subjects), we also performed analyses splitting the follow-up time (per case/comparator-subject) into three consecutive 4-year periods.

Delaying the start of the follow-up until 6 months after a diagnostic event did not change the results of our analysis (**Supplementary Figure S2**). When splitting the follow-up time for newly diagnosed cases into three consecutive periods, the mortality among PsA cases was actually seen to be decreased during the first 4 years after diagnosis, but becoming significantly increased during the subsequent periods 4-8 and 8-12 years after diagnosis (**Supplementary Figure S3**) – results thus well in line with our finding of an increased mortality mainly among PsA patients with longer duration since PsA diagnosis (**Figure 3** of the main Manuscript).



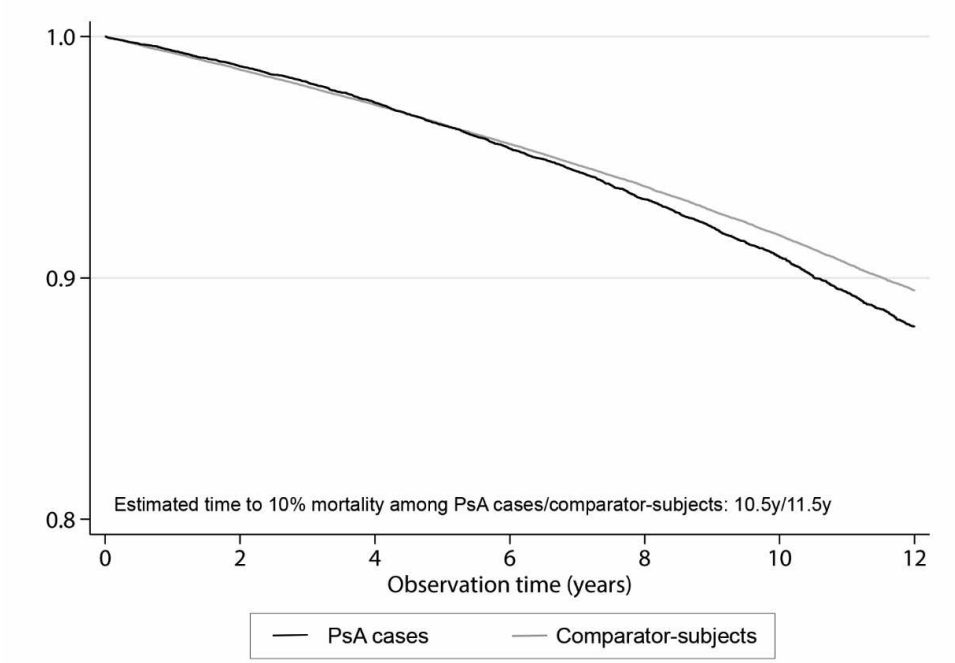
Supplementary Figure S2. Sensitivity analysis to account for a potential increase in mortality during the first months after diagnosis. Kaplan-Meier survival curves, comparing all-cause mortality between PsA cases (n=32 953) and general population comparator-subjects, matched for sex, age and county (n=160 138), in Sweden 2007-2018, after delay of the start of follow-up by 6 months for PsA cases diagnosed from July 1, 2006, onwards (and for their respective comparator-subjects). HR:1.12 (95%CI:1.08-1.17) by matched Cox proportional hazard regression. CI, confidence interval; HR, hazard ratio; PsA, psoriatic arthritis; y, years.



Supplementary Figure S3. Sensitivity analysis, splitting the follow-up time into three consecutive 4-year periods for newly diagnosed psoriatic arthritis cases. Kaplan-Meier survival curves, comparing all-cause mortality between PsA cases diagnosed 2007-2017 ("newly diagnosed cases") and general population comparator-subjects, matched for sex, age and county, in Sweden 2007-2018, with the follow-up time split into: **A.** 0-4 years after diagnosis (PsA cases n=20 458; comparator-subjects n=100 904); p=0.006 for the between-group comparison by matched Breslow test. **B.** 4-8 years after diagnosis (remaining PsA cases n=14 612; comparator-subjects n=69 154); HR 1.12 (95%CI 1.01-1.25) by matched Cox proportional hazard regession. **C.** 8-12 years after diagnosis (remaining PsA cases n=6 667; comparator-subjects n=30 473); HR:1.21 (95%CI:1.02-1.42) by matched Cox proportional hazard regression. CI, confidence interval; HR, hazard ratio; PsA, psoriatic arthritis; y, years.

C. To account for potential survivorship bias:

As described in the Study population and follow-up section of Methods, the matching of comparator-subjects to PsA cases was done at the time of the first registered arthritis diagnosis in outpatient care for the index case. Thus, mainly for prevalent PsA cases diagnosed prior to the start of our study period on January 1, 2007, there is a time-lag between the matching and the individual start of follow-up, with a potential for survivorship bias since only comparator-subjects still alive at the start of follow-up will be included in the analysis. To account for this, we performed a sensitivity analysis limited to PsA cases for whom all 5 matched comparator-subjects were included in the assessment, which did not change the conclusion from our main analysis (**Supplementary Figure S4**).



Supplementary Figure S4. Sensitivity analysis to account for potential survivorship bias. Kaplan-Meier survival curves, comparing all-cause mortality between PsA cases (n=29 703) and general population comparator-subjects, matched for sex, age and county (n=148 515), in Sweden 2007-2018, when limiting the analysis to PsA cases for whom all 5 matched comparator-subjects could be included in the assessment. p<0.001 for the between-group comparison by matched Breslow test. PsA, psoriatic arthritis; y, years.

Supplementary Table S7. Prior hospital-based and smaller population-based mortality studies in psoriatic arthritis

Period	Country	N of PsA cases	Type of study	All-cause mortality SMR (95% CI)
1978-1993 [2]	Canada	428	Hospital-based	1.62 (1.21-2.12)
1978-2004 [3]	Canada	680	Hospital-based	1.36 (1.12-1.64)
1978-2017 [4]	Canada	1490	Hospital-based	0.92 (0.80-1.05)
1985-2007 [5]	UK	453	Hospital-based	0.82 (0.58-1.13)
1995-2011 [6]	Sweden	464	Hospital-based	1.22 (0.89-1.63)
1970-2017 [7]	USA	164	Population-based	0.85 (0.61-1.15)
1997-2006 [8]	Denmark	607	Population-based	1.74 (1.32-2.30)[a]
1999-2008 [9]	Hong-Kong	778	Population-based	1.59 (1.16-2.03)

a. Not SMR (95%CI), but rate ratio (95%CI) of all-cause mortality in relation to the general population. SMR, standardized mortality ratio.

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