

Original article

Incidence of extra-articular manifestations in ankylosing spondylitis, psoriatic arthritis and undifferentiated spondyloarthritis: results from a national register-based cohort study

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Abstract

Objectives. To estimate the incidence and strength of association of extra-articular manifestations [EAMs, here: anterior uveitis (AU), IBD and psoriasis] in patients with AS, undifferentiated SpA (uSpA) and PsA, compared with controls.

Methods. Three mutually exclusive cohorts of patients aged 18–69 years with AS ($n=8517$), uSpA ($n=10\,245$) and PsA ($n=22\,667$) were identified in the Swedish National Patient Register 2001–2015. Age-, sex- and geography-matched controls were identified from the Swedish Population Register. Follow-up began 1 January 2006, or six months after the first SpA diagnosis, whichever occurred later, and ended at the first date of the EAM under study, death, emigration, 70 years of age, and 31 December 2016. Incidence rates (IRs) and incidence rate ratios were calculated for each EAM, and stratified by sex and age.

Results. Incidence rate ratios for incident AU, IBD and psoriasis were significantly increased in AS (20.2, 6.2, 2.5), uSpA (13.6, 5.7, 3.8) and PsA (2.5, 2.3, n.a) vs controls. Men with AS and uSpA had significantly higher IRs per 1000 person-years at risk for incident AU than women with AS (IR 15.8 vs 11.2) and uSpA (IR 10.1 vs 6.0), whereas no such sex difference was demonstrated in PsA or for the other EAMs.

Conclusions. AU, followed by IBD and psoriasis, is the EAM most strongly associated with AS and uSpA. Among the SpA subtypes, AS and uSpA display a largely similar pattern of EAMs, whereas PsA has a considerably weaker association with AU and IBD.

Key words: Spondyloarthritis, extra-articular manifestations, anterior uveitis, inflammatory bowel disease, psoriasis

Rheumatology key messages

- AS and undifferentiated SpA are strongly associated with future anterior uveitis and IBD.
- A weaker but still significant association with anterior uveitis and IBD was observed in PsA.
- Men with AS and undifferentiated SpA had higher incidence of anterior uveitis than women.

Introduction

SpA is a cluster of rheumatic diseases comprising AS, PsA, arthritis associated with IBD, reactive arthritis and

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undifferentiated SpA (uSpA). These diseases are related through overlapping genetic susceptibility, including MHC class I (mainly HLA-B27) and genes involved in the IL-23 pathway, and shared clinical appearance with possible involvement of the spine and sacroiliac joints, peripheral arthritis and, often, enthesitis [1, 2].

Extra-articular manifestations (EAMs) such as anterior uveitis (AU), IBD and psoriasis are common features and included in the majority of classification criteria for SpA; however, not in the modified New York criteria for AS [3–8]. The occurrence of these EAMs is often reported in studies of AS and the broader concept of SpA, but less frequently in patients with PsA. Meta-analyses and systematic literature reviews have been performed to address how these EAMs vary in prevalence between the SpA subtypes [9–11]. Additionally, some studies have explored the risk of incident EAMs in already established AS or PsA [12–18]. However, to our knowledge, no previous study has estimated the risk of future EAMs in the different SpA subtypes in the same setting.

We, therefore, aimed to assess the incidence and strength of association of AU, IBD and psoriasis in the three major clinical subtypes of SpA (AS, uSpA, PsA) [19], in a large and nationwide cohort study based on register data of patients from clinical practice, and to put these rates in relation to the occurrence in the general population.

Methods

Study setting and register sources

This observational, prospective and nationwide cohort study was based on data from a comprehensive linkage of Swedish health care and population registries. The National Patient Register (NPR) records diagnoses from inpatient care according to the International Classification of Diseases (ICD), and has nationwide coverage since 1987. From 2001, the register also includes diagnoses from all specialized outpatient care, but with some incomplete reporting from private caregivers. NPR was used to identify patients with SpA, and EAMs according to pre-specified ICD codes (Supplementary Table S1, available at *Rheumatology* online).

The Swedish Population Register encompasses demographic data for all Swedish residents and was used to identify matched controls and to ascertain death and emigration for censoring during follow-up.

The Prescribed Drug Register (PDR) was established in July 2005 and holds information on dispensed prescriptions according to the Anatomical Therapeutic Chemical Classification (ATC) system. PDR was used to obtain information on current treatment with DMARDs at start of follow-up. From the Swedish Rheumatology Quality Register, we specifically retrieved data on intravenously administered TNF-inhibitors (infliximab), which are not identified in PDR.

The study was approved by the Regional Ethics Committee, Stockholm, Sweden and has been carried out in compliance with the Helsinki Declaration. Informed consent was not required due to the register-based design.

Cohorts

Patients with AS, uSpA and PsA

Three mutually exclusive cohorts of patients aged 18–69 years with AS ($n = 8517$), uSpA ($n = 10\,245$) and PsA ($n = 22\,667$) were identified from NPR in 2001 through 2015. Eligible patients had at least one physician visit, within rheumatology or internal medicine outpatient care, reporting an ICD version 10 (ICD-10) code corresponding to an AS, PsA or uSpA diagnosis (Supplementary Table S1, available at *Rheumatology* online). ICD codes for uSpA comprise both axial and peripheral SpA [20]. To strengthen the case definition, cases with a physician visit reporting an ICD-10 code for RA or SLE during the same time period (2001–2015) were excluded. Further exclusion criteria were emigration or death before start of follow-up.

Patients with ≥ 2 subtypes of SpA

Patients diagnosed with more than one of the studied subtypes of SpA before start of follow-up ($n = 1798$) were analysed separately as a mixed SpA cohort. Patients who received a different SpA diagnosis during follow-up left their original cohort at that time-point and entered the mixed SpA cohort ($n = 2682$). In total, 4480 patients were included in the mixed SpA cohort: 3014 patients (67%) had a mix of AS and uSpA diagnoses, 998 patients (22%) a mix of uSpA and PsA, 399 patients (9%) a mix of AS and PsA and the remaining 69 patients (2%) a mix of all three subtypes.

Matched controls

For each SpA case, up to five controls were identified from the general population in the Swedish Population Register. The controls were matched for sex, birth-year and county of residence, and were required to be alive and not diagnosed with any of the studied SpA diagnoses at start of follow-up (which was set to the date of start of follow-up for their index patient with SpA).

Follow-up

Follow-up started 1 January 2006, or six months after the first SpA diagnosis in previously undiagnosed cases, whichever occurred later, in order to guarantee at least five years of pre-follow-up data from the specialized outpatient care register and six months data from PDR for each individual. The lag period of six months was used to avoid, as far as possible, inclusion of EAMs already present at the date of SpA diagnosis. Follow-up ended at first occurrence of each respective EAM, death, emigration, 70 years of age or end of study follow-up, 31 December 2016. Patients and their matched controls were censored at

the time of a different SpA diagnosis during follow-up and the patients thereafter contributed with person-years at risk and number of EAMs to the mixed SpA cohort after a lag period of six months. Controls were censored if diagnosed with AS, PsA or uSpA during follow-up and consequently eligible to enter the respective SpA cohort.

Extra-articular manifestations

EAMs under study included AU, IBD with subcategories Crohn's disease (CD) and ulcerative colitis (UC), and psoriasis. AU (flare and chronic) and IBD were identified in NPR according to pre-specified ICD codes. Psoriasis is often managed in primary health care in Sweden and is in those cases not captured by NPR. For that reason, dispensed prescriptions in PDR with an ATC code corresponding to a specific anti-psoriatic drug were also used to identify psoriasis. The pre-specified ICD and ATC codes are described in [Supplementary Table S1](#), available at *Rheumatology* online.

History of EAM at start of follow-up

Patients with a history of EAMs were identified. For AU and IBD, we further demanded a diagnosis within ophthalmology and internal medicine/gastroenterology/surgery care, respectively. We also identified prior chronic AU (ICD-10 H20.1) within five years before start of follow-up, and for those without chronic AU, also the number of flares within the five-year period before start of follow-up. Flares were defined as a physician visit in ophthalmology care listing an AU diagnosis and with a gap of 90 days or longer from the last visit in ophthalmology care with an AU [21].

Incident EAM during follow-up

Patients (together with their matched controls) and controls with a history of AU, IBD and psoriasis at start of follow-up were excluded from the incident AU, IBD and psoriasis analysis, respectively. Each EAM during follow-up was analysed separately and defined as follows:

- i. First occurrence of AU in specialized ophthalmology care.
- ii. First occurrence of IBD, with subcategories CD and UC, in specialized internal medicine, gastroenterology or surgical care.
- iii. First occurrence of either psoriasis in NPR or first dispensed prescription of a specific anti-psoriatic drug.

Flares of AU during follow-up

In a further analysis, we investigated flares of AU during follow-up. As previously described, flares were defined as a physician visit in ophthalmology care listing an AU diagnosis (except chronic AU) and with a gap of 90 days or longer from the last visit in ophthalmology care with an AU. Patients (together with their matched controls), and controls with chronic AU in ophthalmology care within five years before start of follow-up were

excluded from the analysis. Patients and controls were also censored during follow-up if diagnosed with chronic AU.

Statistics

Descriptive statistics are presented as number (percentage) or mean (standard deviation (s.d.)). For each SpA cohort and their corresponding matched controls, the number of incident EAMs and person-years at risk during follow-up were counted. Incidence rates (IRs) with 95% CI assuming a Poisson distribution were calculated and presented as number of events per 1000 person-years at risk, overall and stratified by sex and age intervals. For flares of AU, robust standard errors without assumption of variance was used to calculate the 95% CI for IRs and incidence rate ratios (IRRs).

Cumulative incidence probability curves were plotted for each EAM, stratified by cohort and sex. For the mixed SpA cohort, the cumulative incidence probability curves for AU were further stratified by the presence of psoriasis at start of follow-up.

For the comparison between SpA cases and matched controls, IRRs with 95% CI were calculated as a measure of the strength of association. Statistical analyses were performed by SAS version 9.4 (SAS Institute Inc., Cary, NC, USA).

Results

Characteristics of the AS ($n = 8517$), uSpA ($n = 10\,245$) and PsA ($n = 22\,667$) cohorts and their matched controls are summarized in [Table 1](#) and [Fig. 1](#). A history of AU was registered in 22%, 15% and 2% in the AS, uSpA and PsA cohort, respectively and the majority of diagnoses were made within ophthalmology care. Prior IBD occurred less frequently and was identified in 7%, 6% and 2% of patients with AS, uSpA and PsA. Prior psoriasis was detected in 3% of the patients with AS and in 4% of the patients with uSpA. In the mixed SpA cohort ($n = 4480$, 53% men, mean age 43(12) years), 20%, 7% and 34% had prior AU, IBD and psoriasis, respectively ([Supplementary Table S2](#), available at *Rheumatology* online).

Incident AU

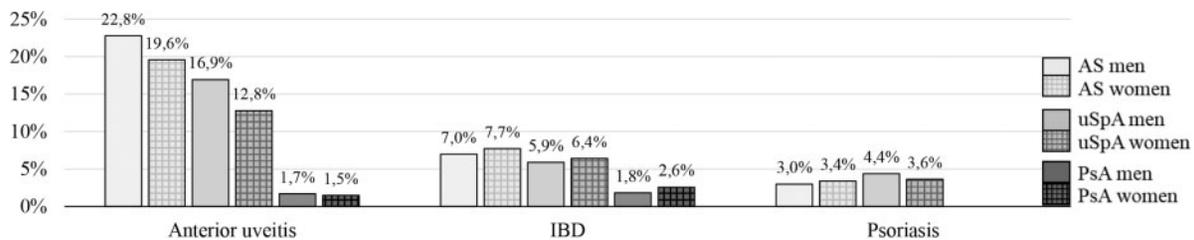
The cumulative incidence plot for first AU is shown in [Fig. 2A](#). The IRs for AU were 14.4, 7.7 and 1.7 events per 1000 person-years at risk in the AS, uSpA and PsA cohort, respectively ([Table 2](#)). Women with AS and uSpA had significantly lower IRs than men with AS (IR 11.2 vs 15.8 per 1000 person-years at risk) and uSpA (IR 6.0 vs 10.1 per 1000 person-years at risk), whereas no significant difference between the sexes was found in PsA. The highest IR point estimates were noted in ages 30–39 years in AS and in ages 18–29 years in uSpA and PsA ([Fig. 3A](#)). In comparison with matched controls, the highest IRR for incident AU was demonstrated in AS (IRR 20.2), followed by uSpA (IRR

TABLE 1 Demographics and disease characteristics at start of follow-up

	AS (n = 8517)	AS controls (n = 39369)	uSpA (n = 10245)	uSpA controls (n = 46903)	PsA (n = 22667)	PsA controls (n = 99254)
Men	5771 (67.8)	26226 (66.6)	4557 (44.5)	20767 (44.3)	10520 (46.4)	45315 (45.7)
Age at start, mean (s.d.)	47 (13)	47 (13)	42 (13)	42 (13)	50 (12)	50 (12)
18–29 years	990 (11.6)	4585 (11.6)	2009 (19.6)	8947 (19.1)	1582 (7.0)	7177 (7.2)
30–39 years	1649 (19.4)	7444 (18.9)	2690 (26.3)	11879 (25.3)	3346 (14.8)	14503 (14.6)
40–49 years	2019 (23.7)	9315 (23.7)	2617 (25.5)	12069 (25.7)	5415 (23.9)	23115 (23.3)
50–59 years	2161 (25.4)	10001 (25.4)	1915 (18.7)	9111 (19.4)	6734 (29.7)	29230 (29.4)
60–69 years	1698 (19.9)	8024 (20.4)	1014 (9.9)	4897 (10.4)	5590 (24.7)	25229 (25.4)
Medication ^a						
DMARDs	2404 (28.2)	267 (0.7)	3224 (31.5)	320 (0.7)	10612 (46.8)	812 (0.8)
csDMARDs	1672 (19.6)	257 (0.7)	2701 (26.4)	300 (0.6)	10084 (44.5)	771 (0.8)
TNFi	1098 (12.9)	29 (0.1)	887 (8.7)	35 (0.1)	1338 (5.9)	82 (0.1)
NSAIDs	5021 (59.0)	3558 (9.0)	5950 (58.1)	3986 (8.5)	11685 (51.6)	10064 (10.1)
Glucocorticoids	1032 (12.1)	865 (2.2)	1760 (17.2)	1014 (2.2)	4027 (17.8)	2732 (2.8)
Prior extra-articular manifestations						
Anterior uveitis (AU) ^b	1852 (21.7)	215 (0.5)	1498 (14.6)	237 (0.5)	356 (1.6)	630 (0.6)
AU, ophthalmology care	1840 (21.6)	210 (0.5)	1491 (14.6)	236 (0.5)	348 (1.5)	615 (0.6)
Chronic AU within 5 years ^b	151 (1.8)	13 (0.0)	154 (1.5)	19 (0.0)	37 (0.2)	50 (0.1)
AU flare within 5 years	1488 (17.5)	131 (0.3)	1205 (11.8)	148 (0.3)	250 (1.1)	411 (0.4)
One flare	701 (8.2)	94 (0.2)	548 (5.3)	99 (0.2)	158 (0.7)	285 (0.3)
Two flares	384 (4.5)	21 (0.1)	322 (3.1)	28 (0.1)	45 (0.2)	63 (0.1)
Three flares	209 (2.5)	10 (0.0)	137 (1.3)	8 (0.0)	21 (0.1)	29 (0.0)
≥ Four flares	206 (2.4)	6 (0.0)	198 (1.9)	13 (0.0)	26 (0.1)	34 (0.0)
IBD ^b	615 (7.2)	411 (1.0)	632 (6.2)	511 (1.1)	504 (2.2)	1166 (1.2)
IBD, internal medicine, gastro- enterology or surgery care	592 (7.0)	391 (1.0)	595 (5.8)	496 (1.1)	466 (2.1)	1134 (1.1)
CD	230 (2.7)	102 (0.3)	212 (2.1)	162 (0.3)	170 (0.7)	358 (0.4)
UC	273 (3.2)	236 (0.6)	277 (2.7)	267 (0.6)	234 (1.0)	657 (0.7)
Overlap CD and UC	89 (1.0)	53 (0.1)	106 (1.0)	67 (0.1)	62 (0.3)	119 (0.1)
Psoriasis ^b	264 (3.1)	589 (1.5)	405 (4.0)	610 (1.3)	n.a.	1740 (1.8)
Psoriasis according to NPR	224 (2.6)	417 (1.1)	340 (3.3)	452 (1.0)		1218 (1.2)
Psoriasis according to PDR	100 (1.2)	322 (0.8)	152 (1.5)	313 (0.7)		1011 (1.0)

Data is presented as number (%) if not stated otherwise. ^aMedication is defined as ≥ 1 dispensed prescription in Prescribed Drug Register within 6 months before start of follow-up. Intravenous TNFi were identified through the Swedish Rheumatology Quality Register. ^bExclusion criteria for the incident AU, AU flares, incident IBD and incident psoriasis analysis, respectively. CD: Crohn's disease; csDMARDs: conventional synthetic DMARDs; n.a.: not applicable; NPR: National Patient Register; PDR: Prescribed Drug Register; TNFi: TNF inhibitors; uSpA: undifferentiated SpA; UC: ulcerative colitis.

FIG. 1 Proportion (%) with a prior anterior uveitis, IBD and psoriasis before start, stratified by sex

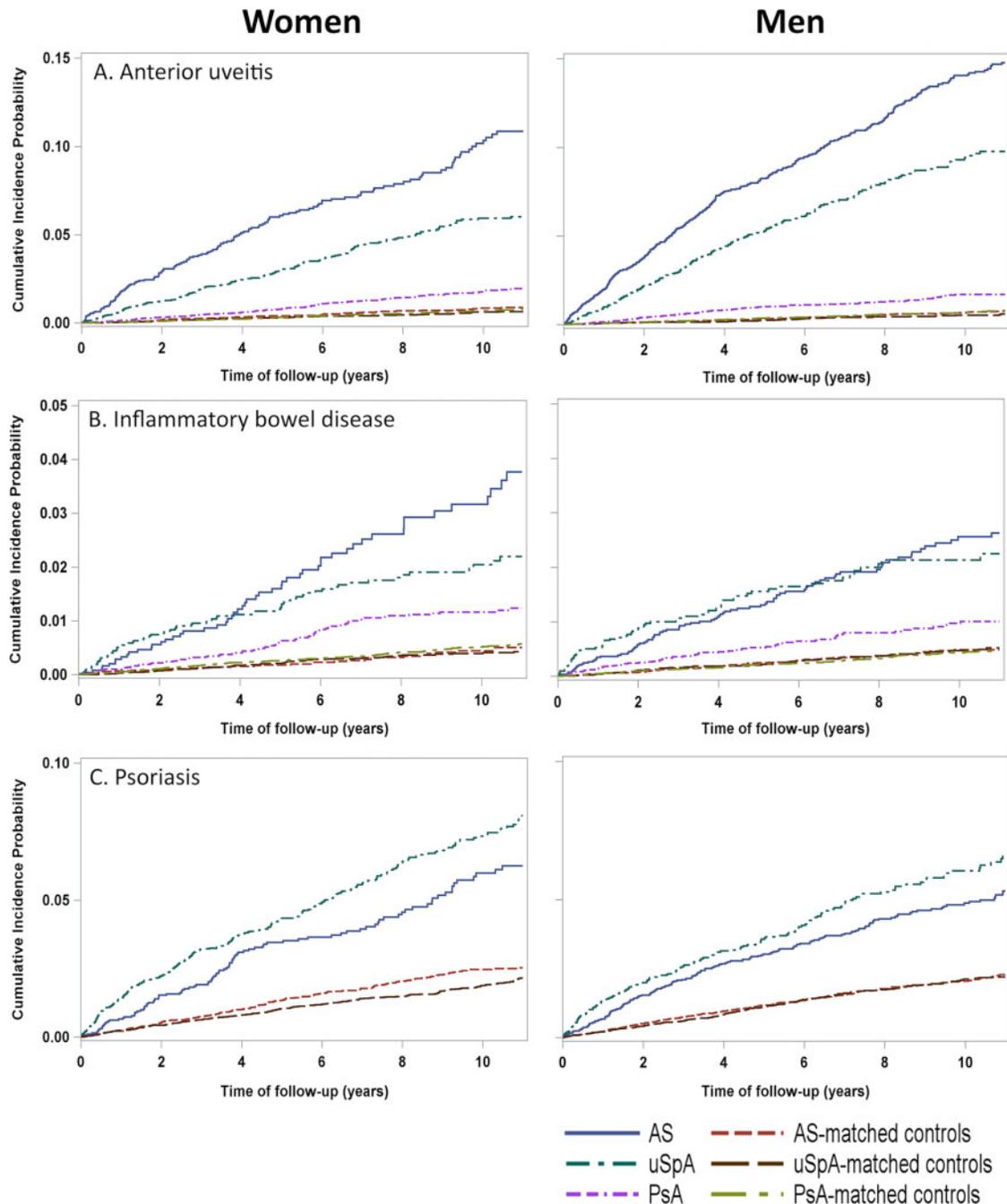


13.6), while the IRR in PsA was considerably lower (IRR 2.5), but yet significantly increased (Table 2, Fig. 4). IRRs were significantly increased in all age intervals with the lowest point estimate for all SpA subtypes in ages 60–69 years (Supplementary Table S3, available at *Rheumatology* online).

Flares of AU during follow-up

During follow-up, 1494 (18%) patients with AS, 1094 (11%) patients with uSpA and 358 (2%) patients with PsA had at least one flare of AU. Of the patients with a flare during follow-up, 58%, 61% and 29% in the AS, uSpA and PsA cohort, respectively, had a prior AU flare

Fig. 2 Cumulative incidence plots of anterior uveitis, IBD and psoriasis in the SpA cohorts and matched controls



Observe that the y-axis scale differs across the extra-articular manifestations.

within five years before start of follow-up. In contrast to incident AU, there was no significant difference in IRs between men and women with AS (Table 2). The highest IR point estimates were noted in ages 40–49 years in AS and uSpA, and in ages 18–29 years in PsA (Fig. 3B). The IRRs for AU flares were 45.1 in AS vs controls, 32.6 in uSpA vs controls, and 3.0 in PsA vs controls (Table 2, Fig. 4).

Incident IBD

The cumulative incidence plot for IBD is shown in Fig. 2B. The IRs were 2.8, 2.5 and 1.1 IBD per 1000 person-years at risk in the AS, uSpA and PsA cohort, respectively (Table 2). There were no significant differences across the sexes in any of the cohorts. The IRRs for incident IBD were similar in AS (IRR 6.2) and uSpA (IRR 5.7), while PsA had a lower association (IRR 2.3). In the

TABLE 2 Incidence rates and IRRs of the extra-articular manifestations in SpA subtypes vs matched controls

	AS			Undifferentiated SpA			PsA		
	Event	IR (95% CI)	IRR (95% CI)	Event	IR (95% CI)	IRR (95% CI)	Event	IR (95% CI)	IRR (95% CI)
Incident AU									
All	581	14.4 (13.2, 15.6)	20.2 (16.8, 24.3)	397	7.7 (7.0, 8.5)	13.6 (11.2, 16.5)	253	1.7 (1.5, 2.0)	2.5 (2.1, 2.9)
Men	435	15.8 (14.4, 17.4)	23.9 (19.0, 30.1)	217	10.1 (8.8, 11.6)	19.1 (14.1, 25.7)	114	1.7 (1.4, 2.0)	2.4 (1.9, 3.0)
Women	146	11.2 (9.6, 13.2)	13.9 (10.1, 19.1)	180	6.0 (5.2, 6.9)	10.1 (7.8, 13.1)	139	1.8 (1.5, 2.1)	2.6 (2.1, 3.2)
AU flares									
All	3714	68.5 (64.3, 72.9)	45.1 (37.0, 54.8)	2625	43.3 (40.2, 46.7)	32.6 (26.8, 39.5)	688	4.6 (4.0, 5.3)	3.0 (2.5, 3.6)
Men	2636	70.3 (65.4, 75.6)	45.6 (35.9, 58.0)	1352	51.6 (46.6, 57.3)	37.2 (27.7, 49.9)	355	5.1 (4.2, 6.3)	3.2 (2.5, 4.1)
Women	1078	64.3 (57.1, 72.4)	43.6 (31.1, 61.2)	1273	37.0 (33.2, 41.3)	28.8 (22.2, 37.2)	333	4.1 (3.4, 5.0)	2.8 (2.2, 3.6)
IBD									
All	143	2.8 (2.4, 3.3)	6.2 (4.8, 8.0)	142	2.5 (2.1, 2.9)	5.7 (4.4, 7.3)	162	1.1 (1.0, 1.3)	2.3 (1.9, 2.8)
Men	90	2.6 (2.1, 3.1)	5.6 (4.1, 7.7)	65	2.6 (2.0, 3.3)	5.5 (3.8, 7.9)	68	1.0 (0.8, 1.3)	2.4 (1.8, 3.2)
Women	53	3.4 (2.6, 4.4)	7.7 (5.0, 11.9)	77	2.4 (1.9, 3.0)	5.8 (4.1, 8.2)	94	1.2 (1.0, 1.5)	2.3 (1.8, 3.0)
CD									
All	73	1.4 (1.1, 1.8)	9.8 (6.5, 14.8)	70	1.2 (1.0, 1.5)	7.0 (4.8, 10.2)	72	0.5 (0.4, 0.6)	2.9 (2.1, 3.9)
Men	44	1.2 (0.9, 1.7)	9.4 (5.6, 15.8)	29	1.2 (0.8, 1.7)	5.7 (3.3, 9.7)	31	0.5 (0.3, 0.6)	3.1 (1.9, 4.9)
Women	29	1.9 (1.3, 2.7)	10.7 (5.6, 20.7)	41	1.3 (0.9, 1.7)	8.4 (5.0, 14.2)	41	0.5 (0.4, 0.7)	2.7 (1.8, 4.0)
UC									
All	70	1.4 (1.1, 1.7)	4.5 (3.2, 6.3)	72	1.2 (1.0, 1.6)	4.8 (3.4, 6.7)	92	0.6 (0.5, 0.8)	2.1 (1.6, 2.6)
Men	46	1.3 (1.0, 1.7)	4.0 (2.7, 6.0)	36	1.4 (1.0, 2.0)	5.4 (3.3, 8.8)	37	0.5 (0.4, 0.8)	2.0 (1.3, 2.9)
Women	24	1.5 (1.0, 2.3)	5.8 (3.2, 10.5)	36	1.1 (0.8, 1.5)	4.3 (2.7, 6.8)	55	0.7 (0.5, 0.9)	2.1 (1.5, 2.9)
Psoriasis									
All	302	5.6 (5.0, 6.3)	2.5 (2.2, 2.9)	458	7.7 (7.0, 8.5)	3.8 (3.3, 4.3)			
Men	200	5.4 (4.7, 6.2)	2.5 (2.1, 3.0)	177	6.9 (6.0, 8.1)	3.3 (2.7, 4.0)			
Women	102	6.1 (5.0, 7.5)	2.5 (2.0, 3.1)	281	8.3 (7.4, 9.4)	4.2 (3.6, 4.9)			

IRs are presented as number of events per 1000 person-years at risk with 95% CI. IRRs with estimated 95% CI are the ratios between the IRs in the AS, uSpA and PsA cohorts and their respective matched controls. AU: anterior uveitis; CD: Crohn's disease; IR: incidence rate; IRR: incidence rate ratios; UC: ulcerative colitis.

sub-analyses of CD and UC, patients with AS had a significantly stronger association with CD than UC (IRR 9.8 vs IRR 4.5).

Incident psoriasis

The cumulative incidence plot for psoriasis is shown in Fig. 2C. The IRs were 5.6 and 7.7 psoriasis per 1000 person-years at risk in the AS and uSpA cohort, respectively (Table 2). Patients with uSpA had a slightly stronger association with psoriasis (IRR 3.8) than patients with AS (IRR 2.5).

Results for the mixed SpA cohort

The IRs and IRRs for the studied EAMs in the mixed SpA cohort vs matched controls are summarized in Supplementary Table S4, available at *Rheumatology* online. Overall, the IRRs were 18.6, 38.4, 5.0 and 4.4 for incident AU, flares of AU, incident IBD and psoriasis. Patients with psoriasis at baseline had significantly lower IRR for incident AU vs matched controls than patients without psoriasis at baseline (IRR 6.8 vs 27.4) (Supplementary Fig. S1, available at *Rheumatology* online).

Sensitivity analyses

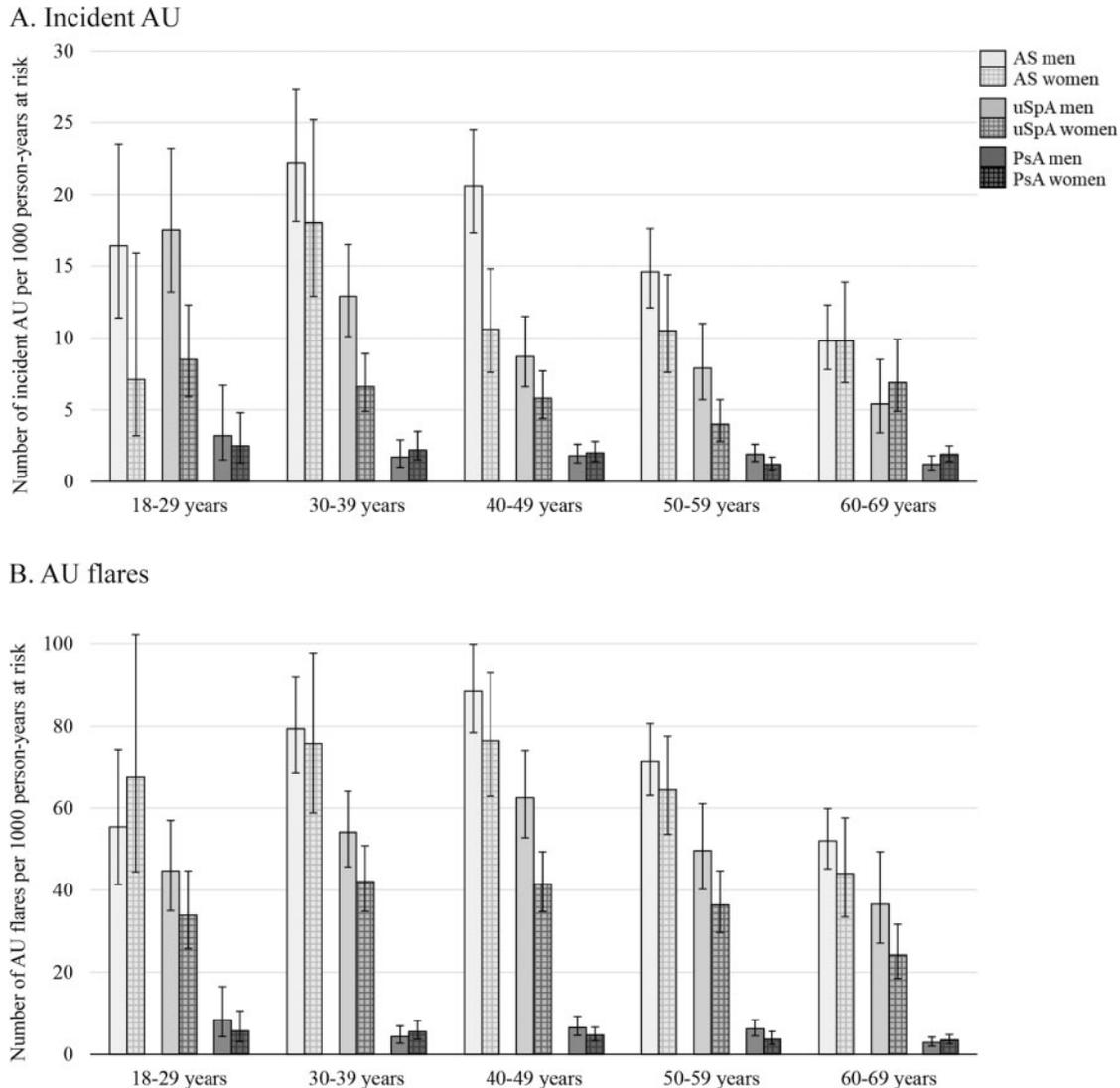
In a sensitivity analysis, the patients with mixed SpA were not excluded from their original cohorts and baseline characteristics regarding prior EAMs were recalculated. This resulted in a higher prevalence of psoriasis at baseline for AS [6.5%, difference between sensitivity and main analyses (Δ) 3.4%] and uSpA (9.4%, Δ 5.4%), whereas the prevalence of AU in ophthalmology care (AS 22.0%, Δ 0.4%; uSpA 15.6%, Δ 1.0%) and IBD in internal medicine/gastroenterology/surgery care (AS 6.9%, Δ -0.1%; uSpA 6.1%, Δ 0.3%) were similar. For PsA, the prevalence of AU (2.0%, Δ 0.5%) and IBD (2.3%, Δ 0.2%) were slightly changed.

Supplementary materials not described elsewhere

For all studied EAMs, the number of events, person-years at risk, IRs and IRRs (per age intervals) are presented in Supplementary Tables S3, S5 and S6, available at *Rheumatology* online.

Discussion

In this register-based cohort study investigating the incidence and strength of association of different EAMs in the SpA subtypes, we demonstrate a similarly increased

Fig. 3 Incidence rates for (A) incident AU and (B) AU flares, stratified sex and age interval

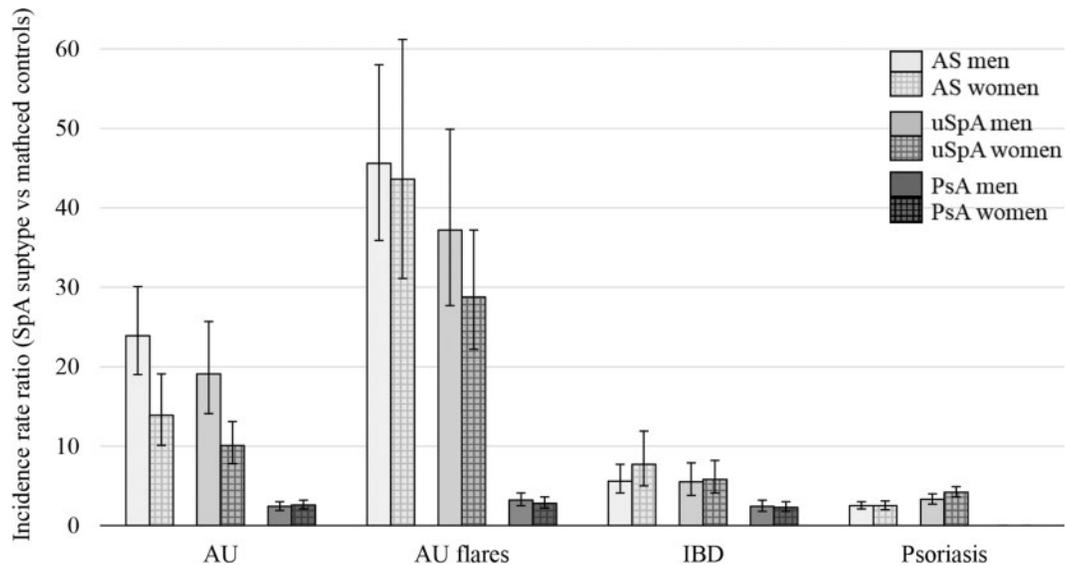
anterior uveitis

association of AU, IBD and psoriasis in patients with AS and uSpA but a clear difference compared with PsA, where the associations of AU and IBD were much weaker, yet still significantly increased compared with the general population.

A few previous studies have reported the incidence of EAMs in established AS and PsA vs controls from the general population. However, none of the studies have analysed AS and PsA in the same setting, and for uSpA, data is lacking. Reassuringly, the relative risks found in the present study for incident AU, IBD and psoriasis in AS vs controls and for incident AU in PsA are in the same range as previously demonstrated for AS and PsA separately [12–14, 16]. Furthermore, a Danish register-based study observed an increased risk of incident CD and UC in PsA compared with the general population, also with risk levels in accordance

with the present study [15]. Two other studies, though, described a significantly increased risk of CD but not of UC in patients with PsA [12, 17]. However, the results in these studies may have been hampered by a low number of incident IBD in the PsA cohort. Nevertheless, in the AS cohort (vs matched controls) we also observed a significantly stronger association with CD than with UC.

With regard to the prevalence of EAMs in SpA, prior meta-analyses of patients with AS and non-radiographic axial SpA (nr-axSpA) have reported prevalence of AU and IBD in accordance with our baseline results in AS and uSpA, respectively [9, 11]. The prevalence of psoriasis was higher in the meta-analyses than the detected prevalence of psoriasis in AS and uSpA in our study. This is probably in part explained by the exclusion of patients with mixed diagnoses, because the sensitivity

Fig. 4 Incidence rate ratios (SpA subtype vs matched controls) with 95% CI for each extra-articular manifestation

analyses demonstrated increased prevalence of psoriasis in both AS and uSpA when the patients with mixed SpA were kept in their original cohorts. Also, the register-based design has most likely resulted in some underestimation of the prevalence of psoriasis. In contrast to our results, a systematic literature review of uveitis in SpA reported a history of uveitis in 25.1% of patients with PsA, whereas a register-based study reported (similarly with our results) prior uveitis in only 1.5% of the patients with PsA [10, 12]. However, the prevalence reported by the systematic literature review was based on 1341 patients in total, which may have been highly selected and not representative of the whole heterogeneous PsA spectrum. Our estimates in AS and uSpA are consistent with other studies that further support the reliability of our results for PsA.

The uSpA cohort comprises nr-axSpA as well as peripheral SpA and the associations of EAMs should preferably have been related to these clinical phenotypes, but cannot be discriminated by the ICD codes. In a Swedish validation study of uSpA, 44% fulfilled the ASAS criteria for axial SpA and, additionally, 29% the ASAS criteria for peripheral SpA [20]. Due to their similar clinical appearance, nr-axSpA and AS are often grouped together into one entity and it is well recognized that nr-axSpA can evolve into AS over time [22, 23]. In accordance with this, the greatest overlap of diagnoses in the present study was between AS and uSpA. Thus, the similarities of the associations of EAMs in AS and uSpA are not unexpected.

Despite the overall similar pattern of EAMs in AS and uSpA, patients with AS had a stronger association with AU than patients with uSpA (IRR 20.2 vs 13.6). In the present study, the AS cohort had a higher mean age and probably a longer symptom duration than the uSpA

cohort. Symptom duration has been positively associated with AU and could at least partly account for the higher prevalence of prior AU in AS compared with uSpA [9, 24, 25]. A presumably higher proportion of HLA-B27 in AS than in uSpA could further explain the difference found [20, 26]. The typical HLA-B27-associated AU has an acute onset, is unilateral, often reoccurs and, in line with our results in AS and uSpA, has a male preponderance [27]. We also demonstrated a stronger association of AU flares (vs incident AU) in patients with AS and uSpA, which likely mirrors the higher tendency for reoccurrence in these two subtypes both in comparison to the general population and PsA. Interestingly, the difference between men and women with AS was less pronounced for AU flares than for incident AU. One possible hypothesis, which needs to be further explored, is that women with AS have a lower risk than men of incident AU but a more similar risk of reoccurrence.

Some limitations with the study need to be recognized. First, due to the register-based study design, we cannot exclude misclassifications. Previous studies have validated the ICD codes in NPR for the SpA subtypes, psoriasis and IBD. For patients with available imaging and/or HLA-B27, the positive predictive values (PPVs) for fulfilling the modified New York criteria and any set of SpA criteria were 80% and 97%, respectively, in AS and corresponding PPVs in uSpA were 26% and 89%, respectively [20]. Importantly, the ICD codes for uSpA cannot discriminate between axial and peripheral SpA. Another Swedish validation study, also including primary care, demonstrated PPVs within the range of 81% to 100% for psoriasis and 63% to 92% for PsA [28]. At least one registered diagnosis with IBD in NPR corresponded to a PPV of 88% for any IBD, whereas lower

PPVs were noted for each of CD and UC [29]. Second, despite the separate analyses for patients with more than one SpA subtype, some remaining overlap between the diagnoses are unavoidable. Third, patients and EAMs managed in primary care are not captured by the NPR. Thus, patients with a probable milder SpA might be missed out and may limit the generalizability of the present results. Regarding the outcomes, psoriasis especially may be underestimated due to possible management exclusively in primary care. Moreover, the ATC codes used, in addition to ICD codes, to identify psoriasis were not available before July 2005 and do not capture non-specific treatment such as topical steroids. Fourth, outcomes managed in outpatient specialized care before 2001 are not identified, which might have underestimated (in all cohorts) the proportion with a prior outcome, particularly for non-chronic conditions such as AU flares. Consequently, some truly prevalent outcomes might have been identified as incident. Fifth, there is a risk of detection bias due to the well-known association of EAMs in SpA, which could underestimate the prevalence and incidence of in particular psoriasis in the matched controls. However, the prevalence of psoriasis in controls (1.3–1.8%) was only somewhat lower than the expected prevalence, around 2%, for the total population [30]. Last, we lack HLA-B27, which had been of interest especially in relation to AU, and clinical data of axial and peripheral involvement, which precludes exploration of the results in relation to clinical phenotype.

The major strength of the study is the large sample of patients with different SpA diagnoses derived from everyday clinical practice and analysed in the same setting. In addition, by using data from a comprehensive register-linkage, the loss of follow-up is minimized.

Conclusion

AU, followed by IBD and psoriasis, is the EAM most strongly associated with AS and uSpA. Among the SpA subtypes, AS and uSpA display a largely similar pattern of EAMs, whereas PsA is considerably less associated with AU and IBD. Men with AS and uSpA had higher incidence of AU than women with AS and uSpA, whereas no such sex difference was demonstrated in PsA or for the other EAMs.

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Data availability statement

The data sets generated and analysed during the present study are not publicly available due to the General Data Protection Regulation. For data access requests, please contact the corresponding author. All data relevant to the study are included in the article.

Supplementary data

Supplementary data are available at *Rheumatology* online.

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