EXTENDED REPORT

The epidemiology of extra-articular manifestations in ankylosing spondylitis: a population-based matched cohort study

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ABSTRACT

Objective To assess the incidence and risks of common extra-articular manifestations (EAMs), that is, acute anterior uveitis (AAU), psoriasis and inflammatory bowel disease (IBD), in patients with ankylosing spondylitis (AS) compared with population-based controls.

Methods All incident patients with AS (n=4101) from the UK Clinical Practice Research Datalink (1987–2012) were matched with up to seven control subjects without AS by year of birth, sex and practice (n=28 591). Incidence rates, cumulative incidence rates and adjusted (adj) HRs for the development of EAMs were calculated, with time-dependent adjustments for age, sex, comorbidity and medication use.

Results At diagnosis of AS, the proportion of patients with an EAM was 11.4% for AAU, 4.4% for psoriasis and 3.7% for IBD. Incidence rates of EAMs were 8.9/1000 person-years for AAU, 3.4/1000 person-years for psoriasis and 2.4 /1000 person-years for IBD in AS. The 20-year cumulative incidence was 24.5%, 10.1% and 7.5%, respectively. Risks of EAMs were 1.5-fold to 16-fold increased versus controls, with an adj HR of 15.5 (95% CI 11.6 to 20.7) for AAU, adj HR of 1.5 (95% CI 1.1 to 1.9) for psoriasis and adj HR of 3.3 (95% CI 2.3 to 4.8) for IBD. For psoriasis and IBD, the highest risks were found in the 1st years after diagnosis, while developing AAU continued to be increased also 10 years after diagnosis of AS.

Conclusions The risk of, in particular AAU, but also of psoriasis and IBD, is significantly increased in patients with AS compared with controls. Hazard patterns are different for each of the EAMs.

INTRODUCTION

Ankylosing spondylitis (AS) is a chronic, inflammatory rheumatic disease with an estimated incidence of three to seven per 100 000 person-years and an estimated prevalence up to 0.6% in Western populations.[1–4] AS is the prototype of a group of rheumatic diseases referred to as spondyloarthritis (SpA), which share genetic, clinical and radiographic features. Although AS is characterised by axial and peripheral joint manifestations, multiple other organ systems can be involved during the disease course.[5] Already during the 1960s, Moll and Wright observed the striking association between AS and several other disorders, such as psoriasis and inflammatory bowel disease (IBD).[6] Nowadays, acute anterior uveitis (AAU), psoriasis and IBD are considered as the three common extra-articular manifestations (EAMs) of AS, which are related to the concept of SpA.[5 7]

EAMs are of growing interest because of their role in the diagnosis of SpA and their impact on a patient's health-related quality of life, as well as on treatment choices. The presence of one of the three concept-related EAMs, in particular AAU, increases the probability of axial or peripheral SpA in patients presenting with chronic back pain or peripheral arthritis.[8 9] This is underlined by the inclusion of the EAMs in different criteria sets which aim to classify the whole spectrum of SpA, such as the Amor criteria and the European Spondyloarthropathy Study Group criteria.[10 11] The EAMs are also inherently part of the recently developed Assessment of SpondyloArthritis international Society classification criteria for axial and peripheral SpA.[12 13] Further, EAMs can add complexity to patient care, since their presence influences treatment decisions and may require collaboration with other specialists.[14] Moreover, EAMs can affect the prognosis and outcome of AS, especially health-related quality of life, work participation and healthcare costs, at any moment, and their presence should therefore be taken into account when studying health outcomes. EAMs are rather frequent in patients with AS and may present before or after the diagnosis of AS.[7] It has been estimated that AAU occurs in 20–30% of patients with AS, psoriasis in 10–15% and IBD in 5–10% of patients.[7 15 16] However, these estimations are only based on cross-sectional data in selected populations.

Given the high prevalence of EAMs in patients with AS and their impact on diagnosis, treatment, prognosis and outcomes, it is relevant to gain insight in the epidemiology of the EAMs. To our knowledge, no longitudinal data on the relation between AS and the development of EAMs have been published. Moreover, studies comparing the frequency of occurrence of EAMs between patients with AS and population-based controls are scarce, and did not statistically adjust for a wide range of potential confounders.[17] The aims of the present study were (1) to determine the incidence rates and relative risks of AAU, psoriasis and IBD in patients with AS as compared with population-based controls, thereby taking into account potential confounders including comorbidities and drug use, and (2) to describe the timing of onset and hazard patterns of EAMs along the course of AS.

METHODS

Data source

A retrospective cohort study was conducted using data from the Clinical Practice Research Datalink (CPRD), formerly known as the General Practice Research Database. The CPRD comprises prospectively collected computerised medical records for over 10 million patients under care of general practitioners (GPs) from 1987 with ongoing data collection. Patients enrolled in CPRD are representative of the total UK population. The data recorded in the CPRD include patient demographics, lifestyle parameters, medical history, laboratory test results, referrals to consultants, hospitalisations and prescriptions. The accuracy and completeness of a wide range of diseases has been well validated and documented.[18]

Study population

The study population (1987–2012) consisted of all patients aged 16 years or older with a first ever recording of AS during their period of valid data collection. The start of valid data collection of each practice was defined as the date at which the practice was included into CPRD, the GP's dataset was approved as 'up-to-standard' and the practice was computerised. Each patient with AS was matched by year of birth, sex, calendar time and practice to up to seven control subjects without a diagnosis of AS at any time. The date of the first AS diagnosis after valid data collection defined the index date. Control patients were assigned the same index date as their matched patient with AS. In three subcohorts for each EAM, every patient was followed from his index date (start of follow-up) until either the first occurrence of the EAM-outcome of interest or until the end of CPRD follow-up (ie, the end of valid data collection, the date of the patient's transfer out of the practice or the patient's death).

Study outcomes and confounding

Outcomes of interest included the first ever event of AAU, psoriasis or IBD (Crohn's disease or ulcerative colitis) after start of follow-up. Diagnoses of EAMs were identified by Read codes (operational definitions are available upon request). Follow-up time was divided into 30-day intervals. Only incident outcomes of interest were evaluated, which means the three subcohorts only included patients and controls who did not have a history of the EAM-outcome of interest before index date.

The presence of potential confounders was assessed by reviewing the computerised medical records for any evidence of confounders before the start of an interval. Potential confounders that were determined for all EAMs included sex, body mass index, smoking status and alcohol use (all at index date), age, prescriptions for non-steroidal anti-inflammatory drugs in the 6 months before the start of an interval and the number of GP visits in the year before the start of an interval.

For each EAM, specific potential confounders were selected based on literature of potential risk factors for the development of the EAMs, including a history of (chronic) diseases, infections in the 6 months before the start of an interval and medication use in the 6 months before the start of an interval. Detailed information on the potential confounders for each EAM is shown in online supplementary file A.

Statistical analysis

Differences in baseline characteristics between patients with AS and controls in dichotomous data were compared using χ^2 testing. Incidence rates (and 95% CI) for each EAM were estimated as the number of patients, respectively controls, with the respective EAM per 1000 person-years. Analyses were stratified for sex and age categories (16–29 years, 30–39 years, 40–49 years, 50–59 years and ≥60 years). Incidence rate ratios (IRRs) (and 95% CI) were calculated by dividing the incidence rate for patients by the incidence rate for controls. Non-parametric Kaplan-Meier methods were used to estimate the cumulative incidences (and 95% CI) of the EAMs, which included the presence of EAMs at index date and after index date.

Time-dependent Cox proportional hazards models were used to estimate HRs for the risk of developing a new EAM after the index date in patients with AS versus controls. Analyses were stratified for sex, age at index date and duration of disease (defined as the time since index date). Statistical time-dependent adjustments were made for all potential confounders that resulted in a change of the β-coefficient >1% in age/sex adjusted (adj) analyses.

In our study, the date of diagnosis of AS was defined as the first ever recorded diagnosis of AS after valid data collection. However, information about the actual diagnosis may have been lacking. In order to increase the likelihood of capturing true incident patients with AS, two sensitivity analyses were performed. First, we included only patients with AS whose first ever diagnosis had occurred at least 1 year after start of valid data collection. In the second sensitivity analysis, we stratified patients by their age at index date (<50 years vs ≥50 years), because usually AS is diagnosed before the age of 50 years.[19] Therefore, patients aged ≥50 years at index date are less likely true incident patients.

All statistical analyses were conducted using SAS V.9.1 software.

RESULTS

Baseline

Baseline characteristics of the patients with AS (n=4101) and matched controls (n=28 591; 98% of patients having 7 controls) are presented in table 1. The mean age at index date was 43.7 years for patients with AS and 43.6 years for controls, and 70.6% of the patients were male. The median duration of follow-up was 5.4 years for patients and controls. Patients with AS were five times more likely to have recently been prescribed non-steroidal anti-inflammatory drugs compared with controls. Baseline characteristics of the three subcohorts including patients and controls who did not have a diagnosis of AAU, psoriasis or IBD before index date, are shown in online supplementary file B.

Incidence rate, IRR and cumulative incidence of EAMs

Table 2 shows incidence rates as well as IRRs of the EAMs. Incidence rates of EAMs were 2-fold to 20-fold increased with AS versus controls: IRR 21.1 (95% CI 16.3 to 27.3) for AAU, 1.9 (95% CI 1.5 to 2.4) for psoriasis and 5.3 (95% CI 3.8 to 7.4) for IBD. All IRRs were higher in men as compared with women. They decreased with older age for AAU and IBD, and remained stable with age for psoriasis (figure 1). Figure 2 shows that a substantial proportion of the EAMs occurred before the index date. For AAU, the cumulative incidence was 11.9% (95% CI 10.9% to 12.9%) in AS at index date, compared with 0.5% (95% CI 0.4% to 0.6%) in controls, and increased in patients to 24.5% (95% CI 20.6% to 28.5%) after 20 years, which was significantly faster than in controls. The cumulative incidence of psoriasis was 4.7% (95% CI 4.1% to 5.4%) in patients compared with 2.6% (95% CI 2.4% to 2.8%) in controls at the

Table 1 Characteristics of patients with AS and matched controls at index date

Characteristic	Patients with AS (%) N=4101	Controls (%) N=28 591
Male	2897 (70.6)	20 173 (70.6)
Age at index date (years)		
16–29	773 (18.8)	5407 (18.9)
30–39	1115 (27.2)	7781 (27.2)
40–49	887 (21.6)	6203 (21.7)
50–59	618 (15.1)	4314 (15.1)
60+	708 (17.3)	4886 (17.1)
Smoking		
Current	1489 (36.3)	9022 (31.6)*
Ex	616 (15.0)	3966 (13.9)*
Never	1825 (44.5)	13 081 (45.5)
Unknown	171 (4.2)	2522 (8.8)*
Alcohol		
Yes	2817 (68.7)	19 118 (66.9)*
No	647 (15.8)	3588 (12.5)*
Unknown	637 (15.5)	5885 (20.6)*
BMI		
<20	220 (5.4)	1386 (4.8)
20–25	1123 (27.4)	7612 (26.6)
25–30	939 (22.9)	6664 (23.3)
>30	500 (12.2)	3409 (11.9)
Unknown	1319 (32.2)	9520 (33.3)
Medication 6 months before index date		
NSAID	1923 (46.9)	2460 (8.6)*
History of EAM before index date		
AAU	466 (11.4)	143 (0.5)*
Psoriasis	182 (4.4)	749 (2.6)*
IBD	151 (3.7)	176 (0.6)*

*Statistically significant difference ($p<0.05$) between patients with AS and controls, based on χ^2 test.
AAU, acute anterior uveitis; AS, ankylosing spondylitis; BMI, body mass index; EAM, extra-articular manifestation; IBD, inflammatory bowel disease; NSAID, non-steroidal anti-inflammatory drug.

index date and increased, thereafter, gradually to 10.1% (95% CI 8.4% to 11.9%) in patients after 20 years with a slope comparable with controls. The cumulative incidence of IBD in patients with AS showed a comparable pattern as psoriasis and increased from 4.0% (95% CI 3.4% to 4.6%) at index date (vs 0.6%, 95% CI 0.5% to 0.7% in controls) to 7.5% (95% CI 6.0% to 0.3%) after 20 years.

Table 2 Incidence rate of AAU, psoriasis and IBD in patients with AS and controls

	Patients with AS		Controls		
	EAM, n	Incidence rate†	EAM, n	Incidence rate†	Incidence rate ratio* (95% CI)
AAU	203	8.91	80	0.42	21.1 (16.3 to 27.3)
Psoriasis	90	3.36	341	1.81	1.9 (1.5 to 2.4)
IBD	62	2.36	84	0.44	5.3 (3.8 to 7.4)

*The incidence rate ratio is calculated as the incidence rate for patients divided by the incidence rate for controls.
†Number of patients or controls with EAM/1000 person-years.
AAU, acute anterior uveitis; AS, ankylosing spondylitis; EAM, extra-articular manifestation; IBD, inflammatory bowel disease.

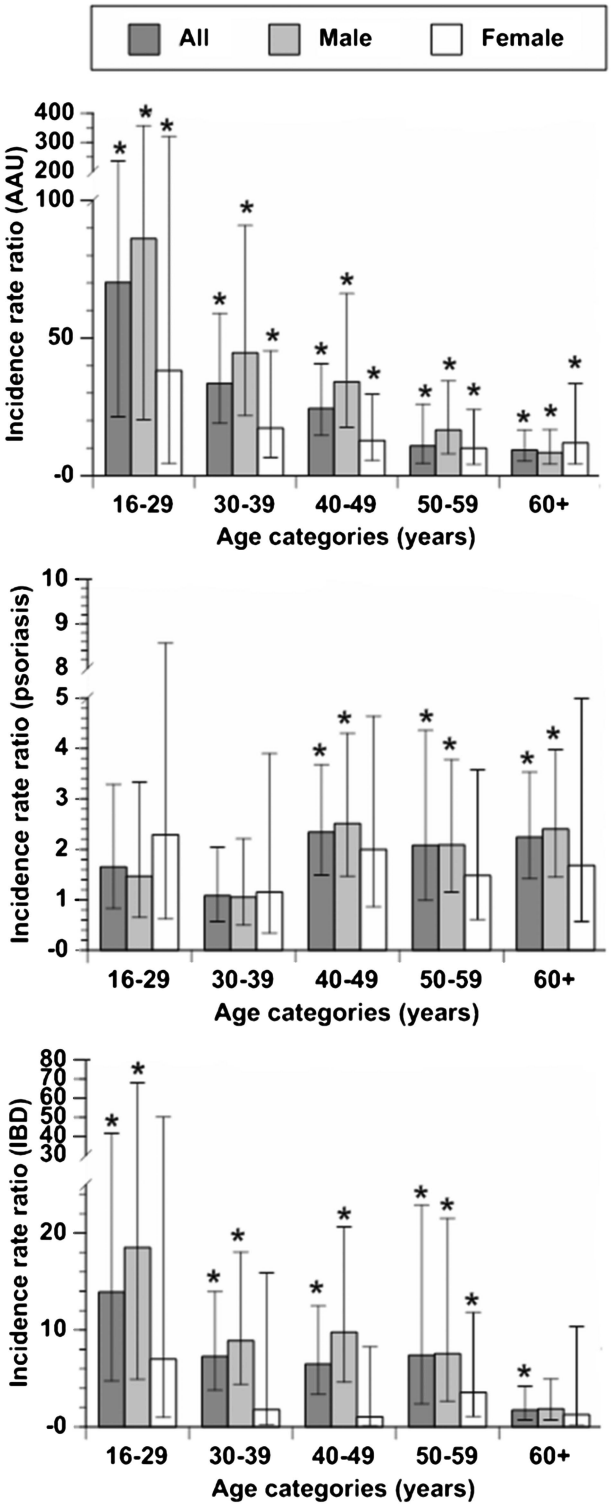

Figure 1 Incidence rate ratios between patients with AS and controls for AAU, psoriasis and IBD according to different age categories and sex categories. * Statistically significant. AS, ankylosing spondylitis; AAU, acute anterior uveitis; IBD, inflammatory bowel disease.

Risk of EAMs with AS

Table 3 shows that patients with AS had a 16-fold (adj HR 15.5, 95% CI 11.6 to 20.7) increased risk of a first episode of AAU as compared with controls. The risk of psoriasis was 1.5-fold (adj HR 1.5, 95% CI 1.1 to 1.9) and the risk of IBD was 3-fold (adj

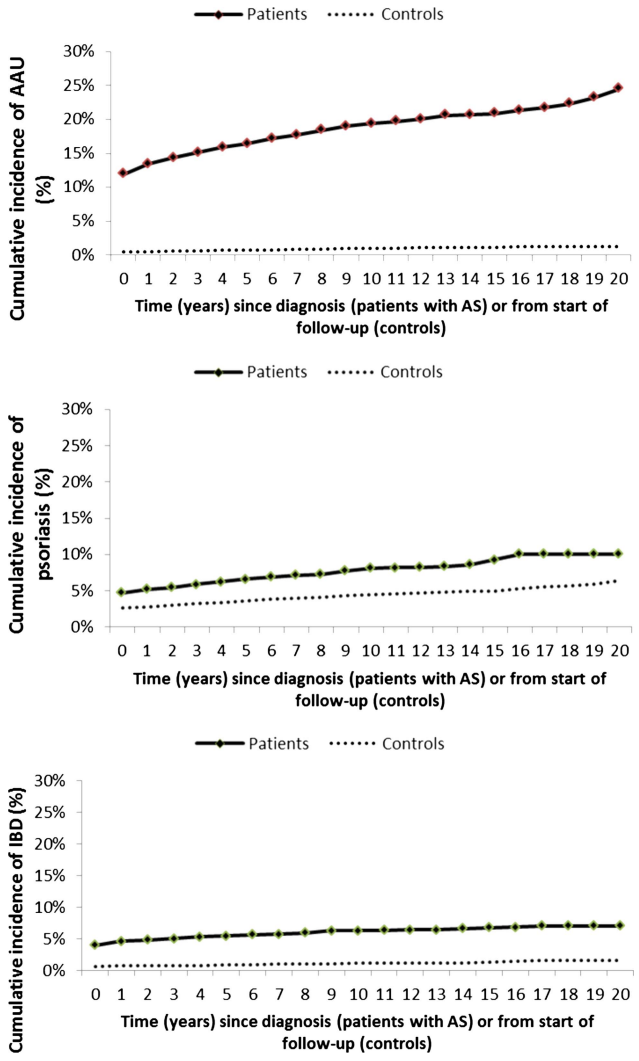

Figure 2 Cumulative incidence of AAU, psoriasis and IBD among patients with AS and matched controls starting from the index date. AS, ankylosing spondylitis; AAU, acute anterior uveitis; IBD, inflammatory bowel disease.

HR 3.3, 95% CI 2.3 to 4.8) increased. Risks of EAMs were higher in men than in women. The risk of all EAMs was highest in the 1st year after diagnosis. While the risk of AAU was still ninefold increased 10 years after index date, the risk had dropped to baseline levels after 5 years for psoriasis and after 10 years for IBD.

Sensitivity analyses

The results of the sensitivity analysis with a lead-in time of 1 year were comparable with the main analysis for AAU, psoriasis and IBD. The adj HRs for AAU, psoriasis and IBD were 13.7 (95% CI 10.1 to 18.7), 1.3 (95% CI 1.0 to 1.8) and 3.1 (95% CI 2.1 to 4.6), respectively.

The risk of AAU was found to be higher in younger (diagnosis of AS at <50 years of age) patients (adj HR 20.8, 95% CI 14.5 to 29.9) versus older (diagnosis at ≥50 years of age) patients (adj HR 8.5, 95% CI 5.2 to 13.9). This was also found for IBD (adj HR 4.3, 95% CI 2.7 to 6.8 (diagnosis at <50 years of age) vs 1.8, 95% CI 0.9 to 3.7 (diagnosis at ≥50 years of age)). The risk for psoriasis was not different with age of diagnosis (adj HR 1.3, 95% CI 0.9 to 1.8 (diagnosis at <50 years of age) vs 1.8, 95% CI 1.2 to 2.7 (diagnosis at ≥50 years of age)).

DISCUSSION

This study showed a 16-fold increased risk for AAU, a 1.5-fold increased risk for psoriasis and a 3.3-fold increased risk for IBD in patients with AS as compared with controls without AS. The risk for AAU remained increased during the course of the disease, whereas the excessive risks for psoriasis and IBD were mainly present in the 1st years after the index date. EAMs were often already present before the diagnosis of AS: 12% of patients had a diagnosis of AAU, whereas 5% had a diagnosis of psoriasis and 4% a diagnosis of IBD at the index date. Twenty years after the index date, these percentages were roughly doubled to 25%, 10% and 7.5%, respectively.

Our results are slightly different from a retrospective cohort study from Sweden.[17] In that study, Bremander *et al* reported age-adjusted and sex-adjusted standardised morbidity rates for AAU (34.4), psoriasis (2.9) and IBD (9.3), which were higher than the HRs found in the present study. However, the Swedish study did not correct for potential confounders and included prevalent and incident cases, for diagnosis of AS and of EAMs. This may have hampered the interpretation and comparison with our results. Of note, the incidences of the different EAMs in the controls found in our study are in line with reported incidences of these conditions in general populations.[20–23]

One of the objectives of our study was to gain more insight in the time of onset of EAMs in relation to the diagnosis of AS. Until now, it was assumed that the prevalence of AAU was positively associated with disease duration, although evidence was only based on cross-sectional data.[15 16] The present study confirms this association and shows that the cumulative incidence of a first episode of AAU continued to increase more than 15 years after the index date. The association with a longer duration of the disease and development of either psoriasis or IBD is less clear. In a meta-regression analysis performed by our group, we were unable to show an association between disease duration and the prevalence of psoriasis and IBD, although studies with short disease durations were under-represented in this analysis.[15] In the present study, we confirmed that the majority of the patients were either diagnosed with psoriasis or IBD before the index date or developed the condition early in the disease course.

The relatively high prevalence of EAMs at the index date found in the present study emphasises their potential role in the diagnostic process of patients with chronic (inflammatory) back pain. In particular, AAU should raise the suspicion of SpA, since this condition is relatively rare in the general population and rather frequent in patients with SpA. Moreover, it has been shown that AAU has a high positive likelihood ratio (LR 13.9) for the diagnosis of axial SpA in patients with chronic low back pain.[9] The presence of psoriasis and IBD may also contribute to the diagnosis of SpA, although positive LRs were much lower (LR 3.8 and 4.3, respectively).[9] On this line, it is interesting to learn that the findings in the present study confirm those of early SpA cohorts, which also showed high prevalences of EAMs early in the disease. In a German inception cohort including 462 patients with axial SpA, the prevalences of AAU, psoriasis and IBD were 20.9%, 10.2% and 2.6%, respectively, in the subgroup of AS (mean symptom duration 5.2 years).[24] Another inflammatory back pain cohort from France found in the subgroup of 181 newly diagnosed patients with AS (mean

Table 3 Risks of AAU, psoriasis and IBD in patients with AS, compared with controls

	AAU (n=3611)*			Psoriasis (n=3907)†			IBD (n=3938)‡		
	n	Age-sex adj HR (95% CI)	Full-adj HR§ (95% CI)	n	Age-sex adj HR (95% CI)	Full-adj HR¶ (95% CI)	n	Age-sex adj HR (95% CI)	Full-adj HR** (95% CI)
No AS	80	1.0	1.0	341	1.0	1.0	83	1.0	1.0
AS	203	20.9 (16.2 to 27.1)	15.5 (11.6 to 20.7)	90	1.9 (1.5 to 2.4)	1.5 (1.1 to 1.9)	62	5.5 (3.9 to 7.6)	3.3 (2.3 to 4.8)
Sex									
Female	52	13.5 (8.6 to 21.0)	10.7 (6.6 to 17.5)	23	1.7 (1.1 to 2.6)	1.5 (0.9 to 2.5)	9	2.4 (1.1 to 5.1)	1.2 (0.5 to 2.8)
Male	151	25.7 (18.6 to 35.4)	18.4 (12.9 to 26.4)	67	1.9 (1.5 to 2.5)	1.4 (1.1 to 2.0)	53	7.0 (4.8 to 10.1)	4.6 (3.0 to 7.1)
Age at index date (years)									
16–29	40	34.9 (16.9 to 71.9)	21.1 (9.3 to 47.7)	11	1.2 (0.6 to 2.2)	0.7 (0.3 to 1.4)	16	10.3 (4.8 to 22.2)	5.7 (2.2 to 14.5)
30–39	73	43.0 (24.3 to 76.1)	37.3 (20.3 to 68.7)	20	1.5 (0.9 to 2.5)	1.1 (0.6 to 1.9)	19	6.3 (3.4 to 11.6)	5.0 (2.4 to 10.2)
40–49	46	16.8 (10.2 to 27.5)	11.3 (6.4 to 19.9)	25	2.6 (1.7 to 4.1)	2.2 (1.3 to 3.7)	16	6.6 (3.4 to 13.0)	3.3 (1.5 to 7.2)
50–59	34	17.9 (9.9 to 32.4)	15.1 (7.9 to 28.8)	21	2.3 (1.4 to 3.7)	2.2 (1.3 to 3.7)	5	2.1 (0.8 to 5.6)	1.2 (0.4 to 3.5)
≥ 60	10	4.6 (2.1 to 10.0)	3.6 (1.6 to 8.1)	13	1.8 (1.0 to 3.2)	1.5 (0.8 to 2.8)	6	3.1 (1.2 to 8.1)	2.8 (1.0 to 7.5)
Duration since index date (years)									
<1	53	33.5 (23.5 to 47.9)	23.5 (15.9 to 36.6)	18	2.6 (1.6 to 4.1)	1.9 (1.2 to 3.1)	22	14.0 (8.6 to 22.5)	7.4 (4.4 to 12.6)
1–5	88	21.3 (15.7 to 28.9)	16.1 (11.6 to 22.5)	38	1.9 (1.4 to 2.7)	1.5 (1.1 to 2.1)	23	5.0 (3.1 to 7.9)	3.0 (1.8 to 5.0)
5–10	46	18.0 (12.5 to 25.9)	14.1 (9.7 to 20.7)	24	1.8 (1.2 to 2.7)	1.4 (0.9 to 2.2)	13	3.9 (2.2 to 7.7)	2.7 (1.5 to 4.9)
>10	16	11.4 (6.6 to 19.6)	9.2 (5.7 to 16.0)	10	1.3 (0.7 to 2.4)	1.1 (0.6 to 2.1)	4	2.1 (0.8 to 5.9)	1.5 (0.5 to 4.1)

*Only patients without diagnosis of AAU before or at index date.
†Only patients without diagnosis of psoriasis before or at index date.
‡Only patients without diagnosis of IBD before or at index date.
§Adjusted for: age, sex, the use of NSAIDs in the previous 6 months, number of GP visits in the previous 6 months.
¶Adjusted for: age, sex, smoking status at index date, alcohol use at index date, the use of antidepressants, antimycotics, coronary vasodilators and antihypertensives in previous 6 months, history of hypertension, atopic or contact dermatitis and skin infection in previous 6 months, and the number of GP visits in the previous 6 months.
**Adjusted for: age, sex, smoking status at index date, alcohol use at index date, the use of NSAIDs, antidepressants and anxiolytics/hypnotics in the previous 6 months, number of GP visits in the previous 6 months.
AAU, acute anterior uveitis; adj, adjusted; AS, ankylosing spondylitis; GP, general practitioners; IBD, inflammatory bowel disease; NSAID, non-steroidal anti-inflammatory drug.

symptom duration 1.6 years) prevalences of 11.1% for AAU, 14.4% for psoriasis and 7.2% for IBD.[25]

The present study has some limitations. First, we cannot exclude misclassification of the diagnosis in a proportion of the patients with AS, which was also shown in a study from Wales among GPs. In that study, 12% of patients with a diagnosis of AS within the GP dataset had a different diagnosis in the rheumatology dataset and 24% of patients with an AS code in the rheumatology dataset were not recorded as having AS using GP records.[26] In our study, the result is probably a non-differential misclassification which may have underestimated the reported risk of EAMs. Also, misclassification of the EAMs is possible. Different studies, however, confirmed the validity of the diagnoses in the CPRD database. For example, it has been shown that the diagnosis of IBD was highly probable or probable in 92% (95% CI 86% to 96%) of the cases.[27] Second, a proportion of our patients with AS that we considered as 'incident', may have suffered from AS for a longer period of time, either because of a delay in diagnosis or because the first diagnostic code for AS in CPRD did not correlate with the actual diagnostic date of AS. This can be reflected by the relatively high mean age at diagnosis which was 43.7 years. AS is typically diagnosed at an age between 30 years and 35 years.[19 24 25] Therefore, sensitivity analyses were performed, which showed higher HRs for AAU and IBD in the patient group with an index date before the age of 50 years. This is in line with our expectations and could be explained by either misclassification of exposure or by the higher risk for a first episode of AAU and IBD at a younger age. Misclassifying prevalent patients as 'incident' may therefore underestimate the risk of EAMs after the diagnosis of AS. Third, we cannot fully exclude diagnostic bias. The relation between AS and the three common EAMs is widely recognised. Therefore, EAMs may be more easily diagnosed in patients with AS as compared with patients without AS, which may have overestimated the risk. Fourth, we did not have information on specific patient and disease characteristics, such as disease activity and human leucocyte antigen B27 (HLA-B27) status, which may possibly have influenced the risk of EAMs and would have facilitated identification of patients at risk for an EAM. Moreover, prescriptions of biologicals were not included in the CPRD, which may possibly also have influenced the risk of EAMs.[28 29]

Strengths of this study are that it has a large sample size, and that it is the first study that estimates the relative risks of AAU, psoriasis and IBD in patients with AS compared with population-based controls, while controlling for possible confounding factors including smoking status and body mass index, for which detailed information was available. Further, this study is the first showing longitudinal data on the association of EAMs in relation to the disease course in patients with AS.

In conclusion, this study shows that among patients presenting with AS a significantly increased risk of AAU, psoriasis and IBD is observed compared with controls, although hazard patterns are different for each of the EAMs. The occurrence of EAMs before the diagnosis of AS confirms their contributory role in the diagnostic process. Given the high risk of all EAMs, awareness of clinicians on EAMs is important in view of treatment choices and impact on quality of life in patients with AS.

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