Do subjective components of disease activity contribute to heterogeneity in opioid prescriptions in inflammatory rheumatic diseases? Results from ESPOIR and DESIR cohorts

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Abstract

Objective

To determine whether subjective components of disease activity are associated with heterogeneity in opioid prescription in inflammatory rheumatic diseases (IRDs) after accounting for objective inflammatory markers.

Methods

Data from two prospective observational cohorts of early IRDs (ESPOIR for rheumatoid arthritis (RA) and DESIR for spondyloarthritis (SpA)) were included. Opioid prescription duration (converted to monthly binary opioid prescription), disease activity (Disease activity score 28 (DAS28) for RA; Axial spondyloarthritis disease activity score-C-reactive protein (ASDAS-CRP) for SpA) and its components were measured respectively at 13 and 9 occasions spanning 10 and 6 years of follow-up. Group-based trajectory modelling defined opioid-prescription trajectories and mixed-models characterised the evolution of disease activity and its subjective components by opioid-prescription trajectories.

Results

Four distinct opioid-prescription trajectories: no/low (60.5% and 54.3%), declining (14.7% and 15.8%), augmenting (11.9% and 10.7%), and persistent (12.9% and 19.1%) were identified in RA and SpA respectively (60% were prescribed opioids at least once). Those with regular opioid prescriptions (up to 30%) are often older, less educated, have higher BMI and worse disease. No/low trajectory was the reference for examining evolution of disease activity and subjective components (n=810 RA, n=679 SpA). In IRDs, consistently higher disease activity throughout follow-up were seen with persistent (DAS28(β=0.4–0.8); ASDAS-CRP(β=0.4–0.6)), and augmenting (DAS28(β=0.2–0.5); ASDAS-CRP(β=0.3–0.6)) trajectories and until 3- or 4-years of follow-up (DAS28(β=0.3–0.4); ASDAS-CRP(β=0.2–0.3)) with declining trajectory. Likewise, despite accounting for objective inflammation, subjective components had worse scores over follow-up in augmenting and persistent trajectory.

Conclusion

Non-inflammatory pain mechanisms amplify subjective outcomes, thus, worsening composite measures like disease activity.

Key words

opioids, rheumatoid arthritis, spondyloarthritis, trends, heterogeneity

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Introduction

In inflammatory rheumatic diseases (IRDs), apart from inflammatory mechanisms of pain, non-inflammatory mechanisms due to aberrant central pain modulation and pain catastrophising can amplify pain and related patient-reported outcomes (PROs) (1, 2). Thus, despite adequate control of objective markers of inflammation, non-inflammatory pain mechanisms could increase composite measures like disease activity scores due to their impact on subjectively assessed outcomes. In IRDs, short-term opioids may be indicated to circumvent pain due to inflammation until the onset of action of anti-inflammatory and disease-modifying anti-rheumatic agents (DMARDs) (3). Efficacy of long-term opioid use is unknown and is considered detrimental due to rise in safety concerns and addictive potential (4, 5). However, despite universal access to medical care and advances in anti-rheumatic treatment up to 40% of those with IRDs use opioids regularly (3, 6).

Definitions of long-term opioid use in literature are variable ranging from 60 to 180 days of sometimes consecutive, or at times cumulative use of opioids (7-12). Such definitions can arbitrarily designate opioid-use status, but they cannot identify the temporal trends of opioid utilisation (trajectories). There exist sub-groups among those with IRDs in whom unfavourable trajectories of disease activity (13, 14) and PROs (15) have been recorded. Similarly, we hypothesise that, distinct subgroups with common features follow a particular trend of opioid utilisation (favourable to worse) over time in IRDs.

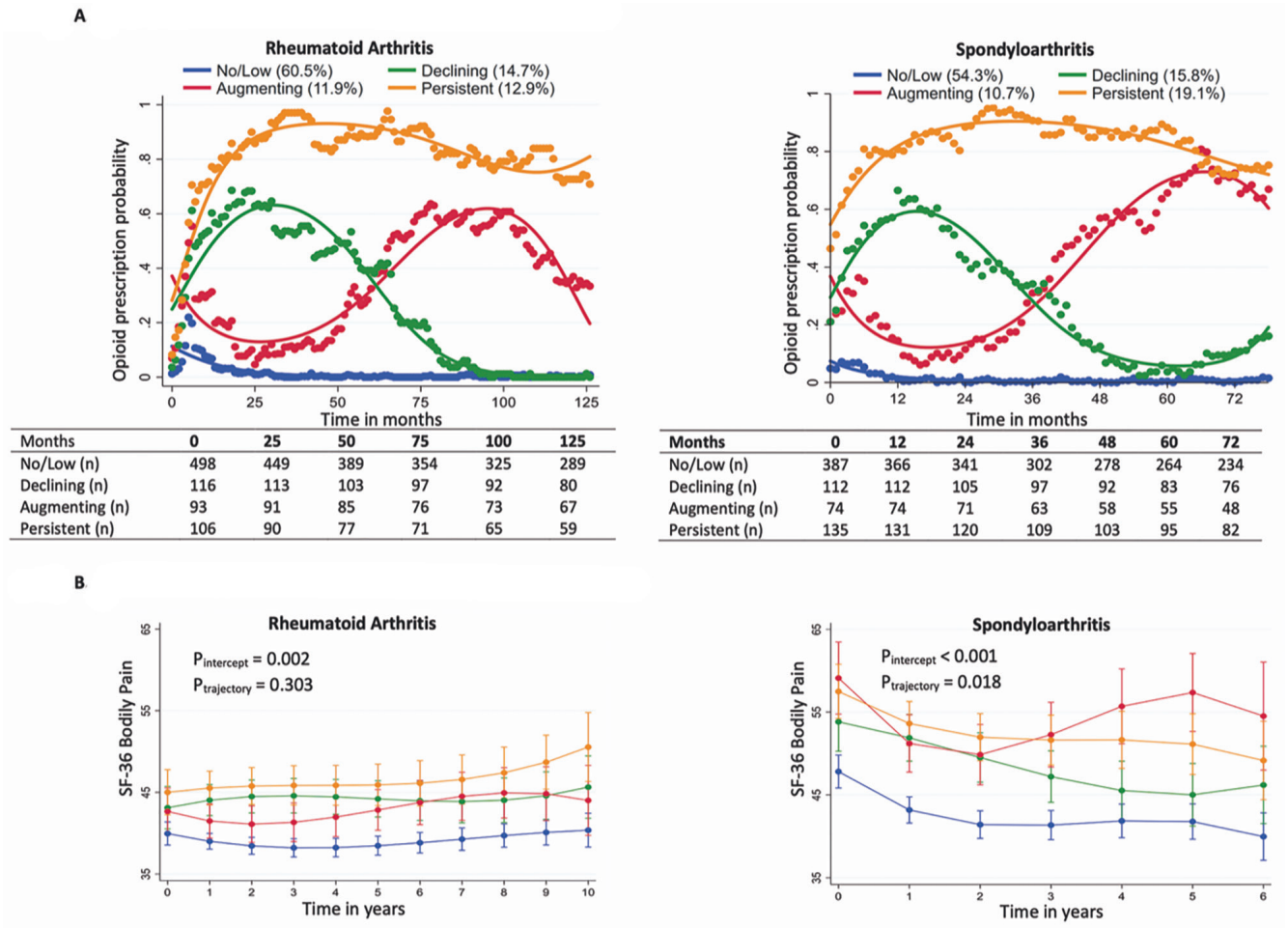
Distinctions between inflammatory and non-inflammatory pain are unclear, thus, the objective and subjective components of disease activity score could respectively be used as their proxies, because, non-inflammatory pain mechanisms might influence the subjectively and not the objectively measured inflammation (16). Past studies have shown that long-term opioid use is associated with high disease activity (7, 11), pain (7), poor functioning (11), and subjective outcomes (7, 11). Inconsistencies prevailed in their association with objectively measured disease activity; few studies reported non-association between chronic opioid-use and objectively measured inflammation (11), while, few others expressed positive associations between anti-rheumatic treatment (glucocorticoid, DMARDs use) – a proxy for inflammatory activity – and chronic opioid use (7). However, anti-rheumatic agents are given at the event of high disease activity, which, being a composite measure, might have had elevated levels due to escalation in subjective components. Therefore, we hypothesise that, long-term opioid use is driven primarily by non-inflammatory pain mechanisms and thus, are dependent on subjectively measured inflammatory activity.

Thus, this longitudinal study with a follow-up of 10- and 6- years amongst those with rheumatoid arthritis (RA) and spondyloarthritis (SpA) respectively, aims: 1) to identify trajectories of opioid prescription over time, and 2) to examine the evolution of disease activity and its subjective components by the opioid-prescription trajectories after accounting for objective markers of inflammation.

Methods

Study design and population

Present study included participants from two ongoing prospective French multicentric cohorts: ESPOIR (Etude et Suivi des Polyarthrites Indifférenciées Récentes) (17) started in 2002 consisting 813 participants with features suggestive of early RA of less than 6 months duration and followed up over 10 years; and DESIR (DEvenir des Spondylarthropathies Indifférenciées Récentes) (18) started in 2007 consisting 708 participants presenting with inflammatory back pain with a highly probable SpA diagnosis, for a duration ranging from 3-months to 3-years and followed up for 6 years (see Supplementary data S1 for inclusion and exclusion criteria). Participants were biologic DMARDs naive at inclusion. Clinical visits were bi-annual for 2 years and annual henceforth, corresponding to 13 and 9 visits, respectively, for ESPOIR and DESIR cohorts, collecting clinical, biological



Months	0	25	50	75	100	125
No/Low (n)	498	449	389	354	325	289
Declining (n)	116	113	103	97	92	80
Augmenting (n)	93	91	85	76	73	67
Persistent (n)	106	90	77	71	65	59

Months	0	12	24	36	48	60	72
No/Low (n)	387	366	341	302	278	264	234
Declining (n)	112	112	105	97	92	83	76
Augmenting (n)	74	74	71	63	58	55	48
Persistent (n)	135	131	120	109	103	95	82

Fig. 1. A: Graphical representation of opioid prescription trajectories. **B**: Evolution of SF-36 Bodily Pain by opioid prescription trajectories.
Models for evolution of SF-36 pain in rheumatoid arthritis are adjusted for sociodemographic, disease-related (symptom duration, erythrocyte sedimentation rate, swollen, and tender joint count, imaging and biological marker), treatment, lifestyle, and health factors.
Models for evolution of SF-36 pain in spondyloarthritis are adjusted for sociodemographic, disease-related (symptom duration, C-reactive protein, arthritis, enthesitis, and synovitis index, imaging and biological marker), treatment, lifestyle, and health factors.
$P_{intercept}$ is *p*-value for difference trajectories at year 0 and $P_{trajectory}$ is *p*-value for interaction of trajectories and time (trajectories*time, trajectories*time^2 and trajectories*time^3)

and imaging information. The study was conducted as per good clinical practice guidelines. Cohort ESPOIR obtained ethical approval from the ethics committee of Montpellier, France (no. 020307), and cohort DESIR obtained ethical approval from Comité de Protection des Personnes Ile de France III. Signed informed consent was given by the participants of both cohorts.

Monthly opioid use

At each visit, the opioid prescription – more frequently mild opioids (*i.e.* codeine, dextropropoxyphene probably until its withdrawal, opium, and tramadol) and less frequently strong opioids (*i.e.* fentanyl often as patches, morphine and oxycodone) – commencement-date and end-date as reported by participants were used to calculate duration of opioid prescription prior to each visit. When the commencement-date was missing, it was imputed by the previous visit-date if opioid prescription of earlier phase lasted until the previous visit-date or otherwise, by a mid-date between previous visit and end-date. Likewise, each missing end-date was imputed with a mid-date between commencement-date and present visit. Opioid prescriptions within six months prior to the first visit were included as reliability on the information collected before start of follow-up tends to diminish with increasing time. Based on the duration of opioid prescription, an opioid prescription variable (yes/no) was calculated for every month for the period six-months prior to first visit and for the period in between two visits.

Pain

The bodily pain subscale of the 36-item short-form questionnaire (SF-36 BP), a valid measure for pain evaluation (19), was assessed at each clinical visit in both cohorts. It is a combination of items that assesses pain intensity and the interference pain causes in the performance of daily activities. Scores were reversed so that higher scores corresponded to higher pain.

Disease activity

Disease activity scores in IRDs are composed of both subjectively and objectively assessed components. Commonly used disease activity scores

Table I. Baseline characteristics of participants by opioid prescription trajectories in rheumatoid arthritis.

Variables	No/Low n=498	Declining n=116	Augmenting n=93	Persistent n=106	*p*-value
Sociodemographic factors					
Male, n (%)	122 (24.5)	19 (16.4)	26 (28.0)	22 (20.7)	0.170
Age, m (SD)	47.1 (13.2)	47.9 (11.8)	50.7 (10.8)	50.3 (10.9)	0.017
Caucasian, n (%)	461 (92.6)	104 (89.7)	86 (92.5)	98 (92.4)	0.767
More than secondary education, n (%)	187 (37.5)	36 (31.0)	16 (17.2)	16 (15.1)	<0.001
Profession*, No job, n (%)	19 (3.8)	6 (5.2)	7 (7.5)	1 (0.9)	0.154
White collar workers, n (%)	89 (17.9)	25 (21.5)	20 (21.5)	26 (24.5)	
Blue collar workers, n (%)	389 (78.3)	85 (73.3)	66 (71.0)	79 (74.5)	
Married*, n (%)	356 (71.6)	87 (75.0)	67 (72.0)	84 (79.2)	0.415
Disease-related factors					
Symptom duration y, m (SD)	0.6 (0.7)	0.6 (0.9)	0.6 (0.6)	0.6 (0.6)	0.631
Disease activity score 28*	5.0 (1.3)	5.1 (1.3)	5.2 (1.2)	5.4 (1.1)	0.027
ESR* in mm/h, m (SD)	28.9 (23.5)	28.8 (27.3)	32.3 (26.0)	30.2 (25.4)	0.638
Swollen joint count (0-28), m (SD)	8.0 (7.0)	8.9 (7.2)	8.8 (7.4)	9.5 (6.6)	0.181
Tender joint count (0-28), m (SD)	7.2 (5.6)	7.1 (4.8)	7.1 (5.3)	7.5 (4.8)	0.952
PGA-VAS* (0-100), m (SD)	57.7 (26.2)	61.9 (25.3)	61.5 (24.6)	66.2 (23.1)	0.011
Radiographic changes as per ACR criteria*, n (%)	70 (14.1)	10 (8.6)	18 (19.3)	12 (11.3)	0.130
Biological markers					
RF positivity*, n (%)	202 (40.6)	52 (44.8)	43 (46.2)	46 (43.4)	0.681
ACPA positivity*, n (%)	189 (38.0)	47 (40.5)	40 (43.0)	39 (36.8)	0.767
Treament					
Non-steroidal anti-inflammatory agents, n (%)	448 (90.0)	103 (88.8)	87 (93.5)	98 (92.4)	0.564
Corticosteroids, n (%)	93 (18.7)	25 (21.5)	17 (18.3)	24 (22.6)	0.735
Disease-modifying anti-rheumatic agents, n (%)	34 (6.8)	8 (6.9)	7 (7.5)	10 (9.4)	0.822
Lifestyle factors					
BMI* in kg/m^2, m (SD)	24.3 (4.2)	26.0 (5.1)	26.5 (5.1)	26.1 (4.4)	<0.001
Smoker, n (%)	230 (46.2)	57 (49.1)	47 (50.5)	54 (50.9)	0.729
Alcohol consumer, n (%)	84 (16.9)	22 (19.0)	14 (15.0)	21 (19.8)	0.781
Health factors					
Rheumatic disease comorbidity index, m (SD)	0.9 (1.2)	0.9 (1.1)	1.3 (1.4)	1.4 (1.6)	<0.001
Pain measures					
SF-36 bodily Pain Scale* (0-100), m (SD)	59.5 (20.6)	63.4 (17.9)	67.3 (18.6)	69.1 (20.7)	<0.001

SD: standard deviation; ESR: erythrocyte sedimentation rate; PGA-VAS: patient assessment of global activity of disease on health-visual analogue scale; ACR: American College of Rheumatology; RF: rheumatoid factor; ACPA: anti-citrullinated protein autoantibodies; BMI: body mass index; SF: short form. *Missing information at baseline: Profession, 1; married, 1; Disease activity score 28, 14; ESR, 11; patient reported global health, 2; radiographic changes, 1; RF positivity, 1; ACPA positivity, 1; BMI, 2; SF-36 bodily pain scale, 4.

for RA and SpA (Suppl. data S2) are Disease activity score 28 (DAS28) and Axial spondyloarthritis disease activity score – C-reactive protein (ASDAS-CRP) respectively. Objective components of DAS28 are erythrocyte sedimentation rate (ESR) measured in mm/h and swollen joint count (SJC) based on 28 joints. For ASDAS-CRP it is CRP (in mg/dl). Subjective components of DAS28 include tender joint count (TJC) based on 0-28 joints and patient assessment of global activity of disease on health using visual analogue scale (PGA-VAS) ranging 0 (no impact) to 100 (worse impact). For ASDAS-CRP it is back pain, joint pain, duration of morning stiffness and PGA-VAS assessed using a visual analogue scale ranging from 0 (no symptoms/impact) to 10 (worst symptoms/impact). Higher score corresponds to higher disease activity.

Covariates

Sociodemographic factors included sex, age (continuous), race (Caucasians or others), education (low or less than or equal to secondary level and high or more than secondary level), marital (couples or single), and professional status (no job, blue, and white collar) as recorded at inclusion. Most covariates described henceforth are assessed repeatedly at clinical visits. Disease-related factors included a distinct set of variables for each cohort. Variables for RA were: clinical and inflammatory markers (symptom duration at baseline, disease activity and its components mentioned above), imaging marker (presence of x-ray changes fulfilling ACR 1987 criteria) (20), and biological markers [Rheumatoid Factor (RF) and ACPA positivity at baseline]. Variables for SpA in DESIR were: clinical and inflammatory markers [symptom duration at baseline, disease activity and its components mentioned above, history of peripheral arthritis (arthritis index), history of peripheral enthesitis (enthesitis index) and number of swollen joints (synovitis index)], imaging marker (presence of sacroiliitis in MRI at baseline) and biological marker (HLA B27 positivity at baseline).

Treatment included current use of NSAIDs, CSs, and DMARDs (conventional and biological). Lifestyle factors included body mass index (BMI), cur-

Table II. Baseline characteristics of participants by opioid prescription trajectories in spondyloarthritis.

Variables	No/Low n=387	Declining n=112	Augmenting n=74	Persistent n=135	*p*-value
Sociodemographic factors					
Male, n (%)	205 (53.0)	41 (36.6)	31 (41.9)	50 (37.0)	0.001
Age*, m (SD)	32.5 (8.3)	34.3 (9.1)	34.5 (8.3)	36.5 (8.6)	<0.001
Caucasian*, n (%)	340 (88.1)	104 (92.9)	68 (91.9)	122 (90.4)	0.433
More than secondary education*, n (%)	244 (63.4)	57 (51.4)	48 (65.7)	69 (51.1)	0.014
Profession*, No profession, n (%)	50 (13.1)	18 (16.1)	10 (13.9)	15 (11.1)	0.184
White collar workers, n (%)	49 (12.8)	24 (21.4)	14 (19.4)	18 (13.3)	
Blue collar workers, n (%)	283 (74.1)	70 (62.5)	48 (66.7)	102 (75.6)	
Married*, n (%)	231 (59.8)	66 (59.5)	57 (79.2)	90 (67.2)	0.010
Disease-related factors					
Symptom duration* y, m (SD)	1.5 (0.9)	1.4 (0.8)	1.3 (0.8)	1.6 (0.8)	0.140
ASDAS-CRP*, m (SD)	2.4 (1.0)	2.8 (0.9)	2.8 (0.8)	3.0 (0.8)	<0.001
CRP* in mg/dl, m (SD)	8.2 (13.6)	9.5 (17.5)	6.9 (12.8)	6.5 (9.5)	0.334
Back pain VAS* (0-10), m (SD)	4.7 (2.5)	5.7 (2.3)	6.2 (2.1)	6.3 (2.0)	<0.001
Joint pain VAS* (0-10), m (SD)	2.3 (2.7)	3.1 (2.7)	3.0 (2.8)	3.5 (2.7)	<0.001
Stiffness duration VAS*(0-10), m (SD)	3.6 (2.7)	4.0 (2.6)	4.1 (2.8)	4.6 (2.4)	0.001
PGA-VAS*(0-10), m (SD)	4.4 (2.5)	5.3 (2.3)	6 (2.3)	6.4 (2.3)	<0.001
Clinical features					
Arthritis index* (0-159), m (SD)	3.0 (7.0)	4.5 (7.8)	2.9 (3.9)	8.5 (12.7)	<0.001
Synovitis index* (0-28), m (SD)	0.2 (1.1)	0.1 (0.4)	0.0 (0.3)	0.1 (0.6)	0.567
Enthesitis index* (0-39), m (SD)	3.0 (4.6)	4.6 (6.4)	4.6 (5.2)	7.3 (7.4)	<0.001
Sacroiliitis features in MRI*, n (%)	136 (36.3)	60 (36.0)	24 (32.9)	35 (26.3)	0.203
Biological marker HLA B27 positivity*, n (%)	245 (63.5)	58 (51.8)	39 (52.7)	68 (50.4)	0.014
Treament					
Non-steroidal anti-inflammatory agents*, n (%)	346 (89.4)	107 (95.5)	71 (97.3)	129 (95.6)	0.013
Corticosteroids, n (%)	52 (13.4)	24 (21.4)	18 (24.3)	37 (27.4)	0.001
Disease-modifying anti-rheumatic agents*, n (%)	47 (12.1)	19 (17.0)	5 (6.8)	24 (17.8)	0.083
Lifestyle factors					
BMI* in kg/m^2, m (SD)	23.5 (3.7)	24.0 (3.8)	23.6 (4.2)	25.0 (4.9)	0.005
Smoker*, n (%)	131 (34.3)	42 (37.8)	30 (41.0)	54 (40.0)	0.521
Alcohol consumer, n (%)	63 (16.3)	15 (13.4)	14 (18.9)	12 (8.9)	0.132
Health factors					
Rheumatic disease comorbidity index, m (SD)	0.3 (0.7)	0.4 (0.7)	0.3 (0.5)	0.5 (0.8)	0.056
Pain measures					
SF-36 bodily Pain Score* (0-100), m (SD)	50.2 (22.3)	58.2 (20.2)	64.8 (19.7)	68.2 (17.9)	<0.001

SD, standard deviation; ASDAS-CRP, Axial spondyloarthritis disease activity score-C-reactive protein; CRP, C-reactive protein; VAS, visual analogue scale; PGA-VAS, patient assessment of global activity of disease on health-visual analogue scale; MRI, magnetic resonance imaging, HLA, human leukocyte antigen; BMI, body mass index; SF short form.
*Missing information at baseline: Age, 1; race, 1; education, 4; profession, 7; married, 5; symptom duration, 2; ASDAS-CRP, 33; CRP, 24, back pain, 4; joint pain, 5; stiffness duration, 4; patient reported global health, 6; arthritis index, 2; enthesitis index, 4; synovitis index, 2, sacroiliitis features in MRI 16, HLA B27 positivity, 1; non-steroidal anti-inflammatory agents, 1; disease-modifying anti-rheumatic agents, 1; BMI, 8; smoker, 7; SF-36 bodily pain scale, 3.

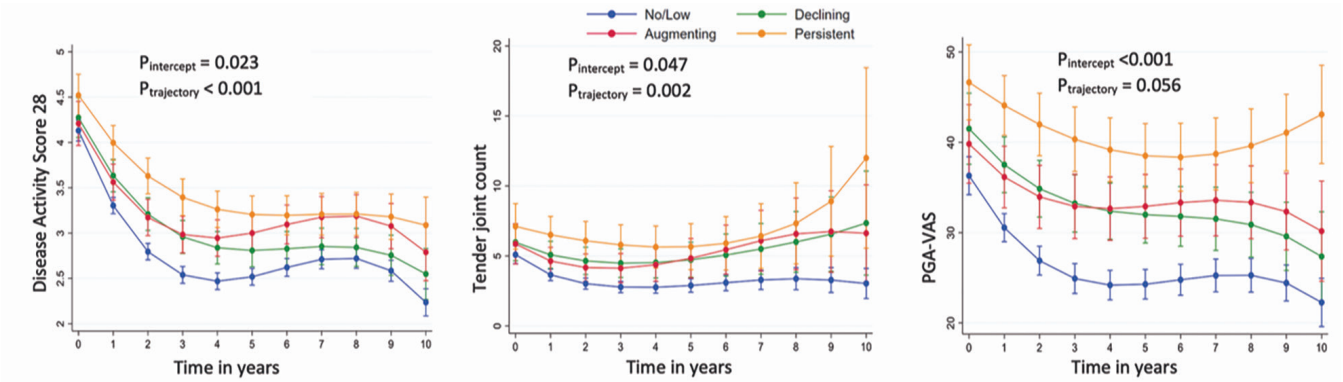
rent smoking, and alcohol consumption. Health factors included the rheumatic disease comorbidity index (RDCI), a validated and weighted comorbidity index for rheumatological outcomes (21) based on self-declared disease status or medication-use history for lung, cardiovascular, fracture, depression (psychological health), diabetes, cancer, and gastrointestinal diseases (Suppl. data S3-RDCI calculation).

Statistical analysis

Both cohorts were analysed separately using Stata v. 15.0 (Stata Corp.). All $p<0.05$ were considered significant.

- *Identification of opioid-prescription trajectories*

Logistic group-based trajectory modelling (GBTM) (22, 23) was used to define the latent polynomial monthly opioid-prescription trajectories. It is a step-wise procedure (24) that clusters individual trajectories that follow a similar trend. For each participant the model calculates posterior probabilities to be in each of the n-groups. Timeline spanned from six-months prior to first visit up to the last documented visit. Models with 2- up to 8-groups with various combinations of polynomial orders up to 3rd order were tested and best fit implied having least negative Bayesian, and Akaike information criteria (BIC, AIC). Model adequacy was determined by the following: each trajectory must contain at least 5% of total participants included, the average of the posterior probability of all individuals assigned to a group must be >0.7, and odds of correct classification (OCC) to a group >5. In addition, graphical representation of trajectories and clinical plausibility determined the best model. Baseline characteristics of individuals belonging to opioid-prescription trajectories were compared descriptively using Pearson's χ^2, Fisher's exact, and



Difference in scores each year over follow-up

Year	Declining vs No/Low	Augmenting vs No/Low	Persistent vs No/Low
0	0.1 (-0.1 ; 0.4)	0.1 (-0.2 ; 0.3)	**0.4 (0.1 ; 0.6)**
1	**0.3 (0.1 ; 0.5)**	**0.2 (0.0 ; 0.5)**	**0.7 (0.5 ; 0.9)**
2	**0.4 (0.2 ; 0.6)**	**0.4 (0.1 ; 0.6)**	**0.8 (0.6 ; 1.0)**
3	**0.4 (0.2 ; 0.6)**	**0.4 (0.2 ; 0.7)**	**0.8 (0.6 ; 1.1)**
4	**0.4 (0.2 ; 0.6)**	**0.5 (0.2 ; 0.7)**	**0.8 (0.6 ; 1.0)**
5	**0.3 (0.1 ; 0.5)**	**0.5 (0.2 ; 0.7)**	**0.7 (0.5 ; 0.9)**
6	0.2 (-0.0 ; 0.4)	**0.5 (0.2 ; 0.7)**	**0.6 (0.3 ; 0.8)**
7	0.1 (-0.1 ; 0.4)	**0.5 (0.2 ; 0.7)**	**0.5 (0.2 ; 0.7)**
8	0.1 (-0.1 ; 0.3)	**0.5 (0.2 ; 0.7)**	**0.5 (0.2 ; 0.7)**
9	0.2 (-0.1 ; 0.4)	**0.5 (0.2 ; 0.8)**	**0.6 (0.3 ; 0.9)**
10	0.3 (-0.0 ; 0.6)	**0.5 (0.2 ; 0.9)**	**0.8 (0.5 ; 1.2)**

Difference in scores each year over follow-up

Declining vs No/Low	Augmenting vs No/Low	Persistent vs No/Low
0.9 (-0.5 ; 2.2)	0.8 (-0.7 ; 2.3)	**2.0 (0.4 ; 3.7)**
1.4 (0.4 ; 2.4)	1.0 (0.0 ; 2.0)	**2.9 (1.5 ; 4.2)**
1.6 (0.6 ; 2.6)	**1.2 (0.2 ; 2.1)**	**3.1 (1.7 ; 4.4)**
1.7 (0.7 ; 2.7)	**1.3 (0.3 ; 2.4)**	**3.0 (1.6 ; 4.4)**
1.8 (0.7 ; 2.8)	**1.6 (0.4 ; 2.8)**	**2.9 (1.4 ; 4.3)**
1.8 (0.6 ; 3.1)	**1.9 (0.5 ; 3.3)**	**2.8 (1.2 ; 4.4)**
2.0 (0.5 ; 3.4)	**2.4 (0.6 ; 4.1)**	**2.8 (0.9 ; 4.7)**
2.2 (0.5 ; 4.0)	**2.8 (0.7 ; 4.9)**	**3.1 (0.9 ; 5.4)**
2.6 (0.6 ; 4.7)	**3.2 (0.7 ; 5.7)**	**4.0 (1.2 ; 6.8)**
3.3 (0.8 ; 5.8)	**3.5 (0.7 ; 6.3)**	**5.6 (1.9 ; 9.4)**
4.3 (0.8 ; 7.8)	**3.6 (0.3 ; 6.9)**	**9.0 (2.8 ; 15.1)**

Difference in scores each year over follow-up

Declining vs No/Low	Augmenting vs No/Low	Persistent vs No/Low
5.2 (0.9 ; 9.5)	3.5 (-1.2 ; 8.2)	**10.3 (5.8 ; 14.8)**
7.0 (3.6 ; 10.4)	**5.6 (1.8 ; 9.4)**	**13.5 (9.9 ; 17.2)**
8.0 (4.4 ; 11.5)	**7.1 (3.2 ; 10.9)**	**15.1 (11.2 ; 18.9)**
8.3 (4.7 ; 11.9)	**8.0 (4.1 ; 11.9)**	**15.4 (11.5 ; 19.4)**
8.2 (4.7 ; 11.7)	**8.5 (4.6 ; 12.3)**	**15.0 (11.1 ; 18.9)**
7.7 (4.2 ; 11.2)	**8.6 (4.7 ; 12.5)**	**14.2 (10.3 ; 18.2)**
7.0 (3.3 ; 10.7)	**8.5 (4.4 ; 12.6)**	**13.6 (9.4 ; 17.7)**
6.3 (2.3 ; 10.2)	**8.3 (4.0 ; 12.7)**	**13.5 (9.1 ; 17.9)**
5.6 (1.6 ; 9.6)	**8.1 (3.6 ; 12.5)**	**14.3 (9.8 ; 18.8)**
5.2 (0.9 ; 9.4)	**7.9 (3.2 ; 12.6)**	**16.6 (12.0 ; 21.3)**
5.1 (-0.5 ; 10.7)	**7.9 (1.8 ; 14.0)**	**20.8 (14.8 ; 26.9)**

Fig. 2. Evolution of disease activity and its subjective components by opioid prescription trajectories in rheumatoid arthritis.
PGA-VAS, patient assessment of global activity of disease on health-visual analogue scale.
The table beneath each graph, shows the evolution of differences in respective outcome (disease activity and subjective components) for each year over the follow-up.
Model for disease activity is adjusted for sociodemographic, disease-related (symptom duration, imaging and biological marker), treatment, lifestyle, and health factors.
Models for subjective outcomes are adjusted for sociodemographic, disease-related (symptom duration, ESR, SJC, imaging and biological marker), treatment, lifestyle, and health factors.
$P_{intercept}$ is *p*-value for difference in trajectories at year 0 and $P_{trajectory}$ is *p*-value for interaction of trajectories and time (trajectories*time, trajectories*time^2 and trajectories*time^3). Those with $p<0.05$ are highlighted.

analysis of variance tests. To validate the identified opioid-prescription trajectories, evolution of SF-36 BP over follow-up by these trajectories were plotted using linear mixed-models (see Suppl. data S4).

- Evolution of disease activity and its subjective components by opioid-prescription trajectories

Analyses were conducted using mixed-models with disease activity and its subjective components as dependent variables and time since inclusion as timescale. All participants with at least a single measure for all co-variates over follow-up are included. Missing observations are assumed to be missing at random. Time, time^2, and time^3 (slope-terms) were incorporated to model non-linear evolution of disease activity variables. Random effects for the intercept and time allowed individual differences in these variables at intercept and took into account their changes over time. While all outcomes had a normal distribution and were assessed using linear mixed-models, TJC (RA) and joint pain (SpA) were assessed using negative binomial mixed-models as their distribution was Poisson with over dispersion. Initial model included time terms, opioid-prescription trajectories and its interaction with time. It was adjusted additionally and sequentially for socio-demographic factors and their interaction with time, disease-related, treatment, lifestyle, and health factors. All of these covariates, except socio-demographic factors, were included as time-dependent variables in the model (except symptom duration, ACPA positivity in RA and symptom duration, imaging and biological marker in SpA were included as baseline variables) to adjust for their value at the time of outcome measurement. Depending on the outcome, adjusting for disease-related factors varied (Suppl. data S4). Differences in the evolution of disease activity and its subjective components as a function of opioid-prescription trajectories were examined by testing interaction of opioid-prescription trajectories with slope terms using the Wald test ($P_{trajectory}$). Interaction of sex, and opioid-prescription, and slope-terms were not significant for all subjective outcomes that assessed pain, hence, both sexes were combined for analysis. Above analysis was also repeated amongst only those fulfilling the ACR 1987 criteria in ESPOIR cohort and the American SpondyloArthritis international Society (ASAS) criteria in DESIR cohort (sensitivity analysis).

Results

Baseline characteristics of both cohorts are described elsewhere (25). In RA and SpA 514/813 and 424/708 participants had been prescribed opioids at least once during follow-up. Amidst those prescribed opioids, 5% in RA and 13.2% in SpA had been prescribed

strong opioids at least once. Only results of completely adjusted models are provided.

Identification of opioid-prescription trajectories

All participants of the respective cohorts (RA, 813 with a mean follow-up of 7.7±3.4 years; SpA, 708 with a mean follow up of 4.8±2 years) were included in the analysis. In both RA and SpA, a 4-group model with a combination of quadratic- and cubic-modelling provided the best fit as per adequacy assessment parameters (Suppl. Table S1). Figure 1a shows the graphical representation of the four opioid-prescription trajectories: no/low (60.5% of RA; 54.3% of SpA), declining (14.7% of RA; 15.8% of SpA), augmenting (11.9% of RA; 10.7% of SpA) and persistent (12.9% of RA; 19.1% of SpA). Comparison of baseline characteristics of participants by opioid-prescription trajectories (Tables I and II) showed that those belonging to augmenting and persistent trajectory had higher mean age ($p \leq 0.017$), low education ($p \leq 0.014$), higher disease activity ($p \leq 0.027$), PGA-VAS ($p \leq 0.011$), pain ($p \leq 0.001$), and BMI ($p \leq 0.005$) (also increased comorbidity ($p < 0.001$) in RA and more often females ($p = 0.001$), augmented NSAIDs, and glucocorticoids use ($p \leq 0.013$) and scores of subjective outcomes ($p \leq 0.001$) in SpA).

Figure 1b shows the evolution of SF-36 BP by opioid-prescription trajectories. The analytic sample constituted all participants of ESPOIR and DESIR that had at least one measure for all variables included in the analysis (ESPOIR, 810; DESIR, 679; Suppl. Fig. S1). In RA, those with declining ($\beta = 3.2$, $p = 0.030$) and persistent ($\beta = 5.0$, $p = 0.001$) trajectory had higher pain at baseline compared to those with no/low trajectory. Through RA course, pain levels were consistently high in persistent trajectory, decreased slightly in declining trajectory and increased in augmenting trajectory, without much difference in their evolution ($P_{trajectory} = 0.303$). In SpA, declining ($\beta = 6.0$, $p = 0.004$), augmenting ($\beta = 11.3$, $p < 0.001$) and persistent ($\beta = 9.7$, $p < 0.001$) trajectories had higher pain than no/low trajectory at baseline. Pain progressively increased in augmenting trajectory and decreased in declining trajectory contributing to significant differences in pain evolution ($P_{trajectory} = 0.018$) by opioid-prescription trajectories.

Evolution of disease activity and its subjective components by opioid-prescription trajectories

Eight hundred and ten out of 813 ESPOIR participants and 679 out of 708 DESIR participants that had at least one measure of all variables constituted the analytic sample (Suppl. Fig. S1).

Results for RA

Figure 2 shows the evolution of DAS28, TJC and PGA-VAS by the opioid-prescription trajectories. In general, the DAS28 and subjective component scores decreased or plateaued over follow-up (except TJC). The table beneath each graph shows the differences in scores (no/low trajectory as reference) for each year over follow-up. At baseline, compared with no/low trajectory: persistent trajectory had higher DAS28 ($\beta = 0.4$, $p = 0.002$), TJC ($\beta = 2.0$, $p = 0.017$), and PGA-VAS ($\beta = 10.3$, $p < 0.001$); declining trajectory had higher PGA-VAS ($\beta = 5.2$, $p = 0.017$). Evolution of DAS28 ($P_{trajectory} < 0.001$), TJC ($P_{trajectory} = 0.002$) among the four opioid-prescription trajectories were not alike. Compared with the no/low trajectory: higher scores for DAS28, TJC and PGA-VAS were evident throughout follow-up for persistent trajectory and from 1st or 2nd year of follow-up for augmenting trajectory; higher TJC from 1 to 10 years of follow-up and PGA-VAS from the beginning to 9 years of follow-up for declining trajectory.

Results for SpA

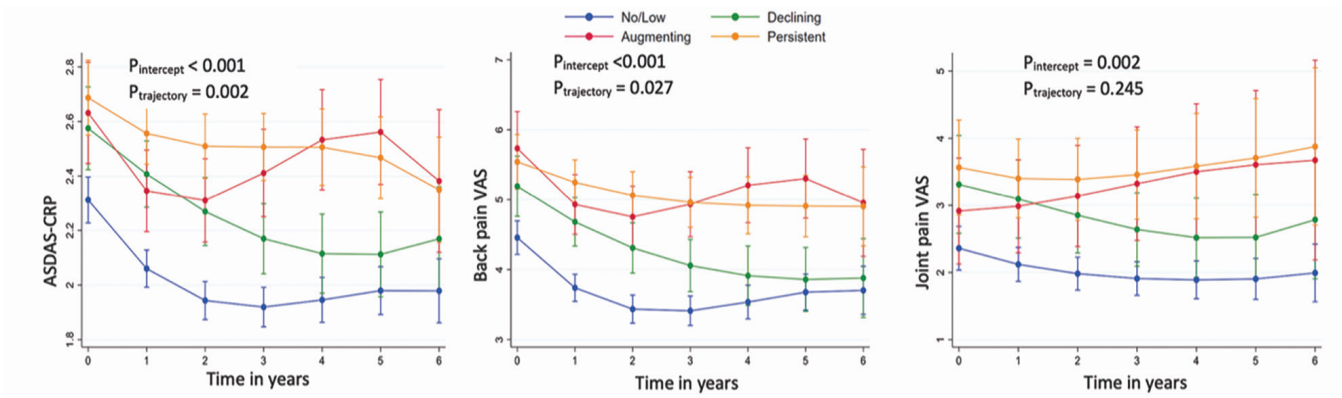
Figure 3 shows the evolution of ASDAS-CRP, back pain, joint pain, stiffness duration and PGA-VAS by the opioid-prescription trajectories. The table beneath each graph shows the differences in scores (no/low group as reference) for each year over follow-up. Overall, scores declined over follow-up for no/low and declining trajectory, remained a plateau for persistent trajectory and often increased for augmenting trajectory. At baseline, compared with no/low trajectory, declining, augmenting, and persistent trajectory had higher scores for ASDAS-CRP ($\beta = 0.3$-0.4, $p \leq 0.003$), back pain ($\beta = 0.7$-1.3, $p \leq 0.003$), and PGA-VAS ($\beta = 0.7$-1.4, $p \leq 0.008$). Likewise, higher joint pain for declining, ($\beta = 0.9$, $p = 0.016$) and persistent trajectory ($\beta = 1.2$, $p = 0.002$) and higher stiffness duration for persistent trajectory ($\beta = 0.8$, $p = 0.001$) were evident. Over follow-up, significant differences in the evolution of ASDAS-CRP ($P_{trajectory} = 0.002$), back pain ($P_{trajectory} = 0.027$) and PGA-VAS ($P_{trajectory} = 0.007$) by opioid-prescription trajectories were seen. Compared with no/low trajectory: persistent and augmenting trajectory had consistently higher scores throughout follow-up for ASDAS-CRP, back pain, joint pain (except at baseline for augmenting trajectory) and PGA-VAS; declining trajectory had higher scores for up to 2- or 3-years of follow-up for all except stiffness duration. For stiffness duration, consistent differences in score were seen only with persistent trajectory.

Sensitivity analysis

Supplementary figures S2 and S3 shows the evolution of disease activity and its subjective components by opioid-prescription trajectories in those fulfilling ACR and ASAS criteria in ESPOIR and DESIR respectively. Results of sensitivity analysis are concordant with the main analysis.

Discussion

This longitudinal study of 10- and 6-year follow-up in those with RA and SpA respectively, suggests the following findings: Firstly, despite advances in the treatment of inflammation in IRDs, up to 30% of them have regular opioid prescriptions from as early as 2 years since disease onset, of which about 13-19% may have been prescribed opioids since IRD onset. Secondly, in comparison with those receiving fewer or no opioid prescriptions, those receiving regular opioid prescriptions had consistently high disease activity scores throughout IRD course, however, dif-



Difference in scores each year over follow-up

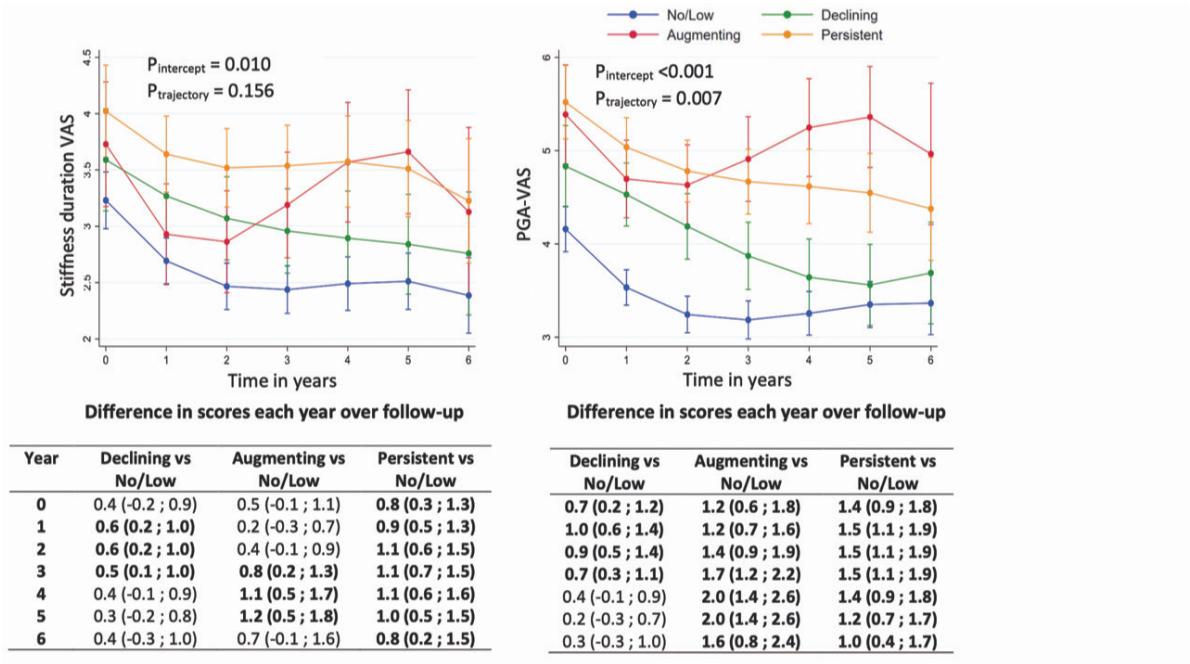
Year	Declining vs No/Low	Augmenting vs No/Low	Persistent vs No/Low
0	**0.3 (0.1 ; 0.4)**	**0.3 (0.1 ; 0.5)**	**0.4 (0.2 ; 0.5)**
1	**0.3 (0.2 ; 0.5)**	**0.3 (0.1 ; 0.5)**	**0.5 (0.4 ; 0.6)**
2	**0.3 (0.2 ; 0.5)**	**0.4 (0.2 ; 0.5)**	**0.6 (0.4 ; 0.7)**
3	**0.3 (0.1 ; 0.4)**	**0.5 (0.3 ; 0.7)**	**0.6 (0.4 ; 0.7)**
4	**0.2 (0.0 ; 0.3)**	**0.6 (0.4 ; 0.8)**	**0.6 (0.4 ; 0.7)**
5	0.1 (0.0 ; 0.3)	**0.6 (0.4 ; 0.8)**	**0.5 (0.3 ; 0.7)**
6	0.2 (0.0 ; 0.4)	**0.4 (0.1 ; 0.7)**	**0.4 (0.1 ; 0.6)**

Difference in scores each year over follow-up

Declining vs No/Low	Augmenting vs No/Low	Persistent vs No/Low
0.7 (0.2 ; 1.2)	**1.3 (0.7 ; 1.9)**	**1.1 (0.6 ; 1.5)**
0.9 (0.5 ; 1.3)	**1.2 (0.7 ; 1.7)**	**1.5 (1.1 ; 1.9)**
0.9 (0.5 ; 1.3)	**1.3 (0.8 ; 1.8)**	**1.6 (1.2 ; 2.0)**
0.6 (0.2 ; 1.1)	**1.5 (1.0 ; 2.0)**	**1.6 (1.1 ; 2.0)**
0.4 (-0.1 ; 0.9)	**1.7 (1.1 ; 2.3)**	**1.4 (0.9 ; 1.9)**
0.2 (-0.3 ; 0.7)	**1.6 (1.0 ; 2.3)**	**1.2 (0.7 ; 1.7)**
0.2 (-0.5 ; 0.8)	**1.3 (0.4 ; 2.1)**	**1.2 (0.5 ; 1.9)**

Difference in scores each year over follow-up

Declining vs No/Low	Augmenting vs No/Low	Persistent vs No/Low
0.9 (0.2 ; 1.7)	0.6 (-0.3 ; 1.4)	**1.2 (0.5 ; 2.0)**
1.0 (0.4 ; 1.6)	**0.9 (0.1 ; 1.6)**	**1.3 (0.7 ; 1.9)**
0.9 (0.3 ; 1.5)	**1.2 (0.4 ; 1.9)**	**1.4 (0.8 ; 2.0)**
0.7 (0.1 ; 1.3)	**1.4 (0.6 ; 2.3)**	**1.5 (0.9 ; 2.2)**
0.6 (0.0 ; 1.3)	**1.6 (0.6 ; 2.6)**	**1.7 (0.9 ; 2.5)**
0.6 (-0.1 ; 1.3)	**1.7 (0.6 ; 2.8)**	**1.8 (0.9 ; 2.7)**
0.8 (-0.1 ; 1.7)	**1.7 (0.2 ; 3.2)**	**1.9 (0.7 ; 3.1)**



Difference in scores each year over follow-up

Year	Declining vs No/Low	Augmenting vs No/Low	Persistent vs No/Low
0	0.4 (-0.2 ; 0.9)	0.5 (-0.1 ; 1.1)	**0.8 (0.3 ; 1.3)**
1	**0.6 (0.2 ; 1.0)**	0.2 (-0.3 ; 0.7)	**0.9 (0.5 ; 1.3)**
2	**0.6 (0.2 ; 1.0)**	0.4 (-0.1 ; 0.9)	**1.1 (0.6 ; 1.5)**
3	**0.5 (0.1 ; 1.0)**	**0.8 (0.2 ; 1.3)**	**1.1 (0.7 ; 1.5)**
4	0.4 (-0.1 ; 0.9)	**1.1 (0.5 ; 1.7)**	**1.1 (0.6 ; 1.6)**
5	0.3 (-0.2 ; 0.8)	**1.2 (0.5 ; 1.8)**	**1.0 (0.5 ; 1.5)**
6	0.4 (-0.3 ; 1.0)	0.7 (-0.1 ; 1.6)	**0.8 (0.2 ; 1.5)**

Difference in scores each year over follow-up

Declining vs No/Low	Augmenting vs No/Low	Persistent vs No/Low
0.7 (0.2 ; 1.2)	**1.2 (0.6 ; 1.8)**	**1.4 (0.9 ; 1.8)**
1.0 (0.6 ; 1.4)	**1.2 (0.7 ; 1.6)**	**1.5 (1.1 ; 1.9)**
0.9 (0.5 ; 1.4)	**1.4 (0.9 ; 1.9)**	**1.5 (1.1 ; 1.9)**
0.7 (0.3 ; 1.1)	**1.7 (1.2 ; 2.2)**	**1.5 (1.1 ; 1.9)**
0.4 (-0.1 ; 0.9)	**2.0 (1.4 ; 2.6)**	**1.4 (0.9 ; 1.8)**
0.2 (-0.3 ; 0.7)	**2.0 (1.4 ; 2.6)**	**1.2 (0.7 ; 1.7)**
0.3 (-0.3 ; 1.0)	**1.6 (0.8 ; 2.4)**	**1.0 (0.4 ; 1.7)**

Fig. 3. Evolution of disease activity and its subjective components by opioid prescription trajectories in spondyloarthritis.
ASDAS-CRP: Axial Spondyloarthritis Disease Activity Score-C-reactive Protein; VAS: visual analogue scale; PGA-VAS: Patient Assessment of Global Activity of Disease on Health-Visual Analogue Scale.
The table beneath each graph, shows the evolution of differences in respective outcome (disease activity and subjective components) for each year over the follow-up.
Model for disease activity is adjusted for sociodemographic, disease-related (symptom duration, synovitis index, imaging and biological marker), treatment, lifestyle, and health factors.
Models for subjective outcomes are adjusted for sociodemographic, disease-related (symptom duration, CRP, synovitis index, imaging and biological marker), treatment, lifestyle, and health factors.
$P_{intercept}$ is *p*-value for difference in trajectories at year 0 and $P_{trajectory}$ is *p*-value for interaction of trajectories and time (trajectories*time, trajectories*time^2 and trajectories*time^3)
Those with $p<0.05$ are highlighted.

ference in scores at each year did not amount to minimal clinically important difference (MCID) reported in the literature (MCID for DAS28=1.2 (26); MCID for ASDAS-CRP=0.9 (27)). Thirdly, elevated subjective outcomes may contribute to high disease activity scores in those with regular opioid prescriptions probably implying the role of non-inflammatory mechanisms of pain or treatment-refractory disease.

Regular opioid use was associated with

increased disease activity and anti-rheumatic treatment (7, 11, 28). Compared with non-users, regular users had significantly high subjectively assessed baseline disease activity, however, differences in objectively assessed inflammatory markers were non-significant (11). Aforementioned studies were done in those with symptom duration ≥5-years and did not account for temporal variations in disease activity, its components, and opioid use, while transitioning from early to longstanding disease. Several factors such as early diagnosis and treatment initiation, adaptation to disease and treatment, disease course by itself, and accessibility to treatment can constantly affect both disease activity and opioid prescription throughout disease course. Therefore, our study, firstly identified the opioid-prescription trajectories – a fixed variable created by using monthly binary opioid prescription data – taking into account the variability in opioid prescription over time. The derived opioid-prescription trajectories were further validated by examining the evolution of pain in each of the trajectories.

Secondly, we examined the evolution of disease activity and its subjective components from early (≤6 months in RA and ≤3years in SpA) to longstanding IRDs by these opioid-prescription trajectories. Differences in disease activity by trajectories (with no/low trajectory as reference) were calculated for each year over follow-up allowing for comparisons at inclusion when participants were biologic DMARD-naive and throughout the disease course after accounting for objective markers of inflammation. Importantly, the availability of repeatedly assessed data from early disease up to a span of 10 and 6 years, respectively, for RA and SpA, allowed us to account for the time-varying nature of disease activity and other covariates. As far as we know, this is the first study that has identified the trajectories of prescription opioids in IRDs and subsequently explored its temporal association with subjective components of inflammation that are influenced by pain sensitisation.

Concordant with past studies (29-31), our study observed an overall declining trend in disease activity and its subjective components (except TJC in RA and joint pain in SpA) in all the opioid-prescription trajectories (except augmenting trajectory of SpA that had a sinusoidal trend with progressive augmentation of all scores from 2 to 5 years). Still, the scores of augmenting and persistent trajectories remained higher than no/low trajectory throughout follow-up. McWilliams *et al*. (15), looked at the evolution of disease activity and its components by heterogenous pain trajectories (low, resolving and unresolving pain) in early RA (symptom duration = 0.8y). In unresolving pain trajectory, DAS28 and subjective components (TJC and PGA-VAS) decreased over follow-up, but always remained significantly higher than the scores of low pain trajectory, while, objective markers (ESR and SJC) declined steadily and approached the values recorded for resolving pain and low pain trajectory. Findings of present study corroborates with them.

Non-inflammatory pain mechanisms via central pain dysregulation (increased excitation and dysfunctional pain modulation) play pivotal role in the augmented pain perception (32) among sub-groups of those with IRDs. McWilliams *et al*. (33) have demonstrated that about 12–40% of those with RA had higher pain and worse PROs while objectively assessed inflammation remained low. Complex neural connectivity of pain affects several regions of brain, thus influencing several PROs and composite scores (16). Pain diminishes the overall well-being of patients and adversely impacts their perception of health and disease. In present study, targeted disease-modifying drugs (*e.g*. biologics) (34) was started when necessary soon after inclusion to the study. These drugs improved both objective inflammation and PROs, however, in an asymmetrical fashion. Improvements seen with objective inflammation did not completely translate to improvement in patient's perception of disease: pain, functioning, impact of disease on patient's health were always higher than the population average. (29-31). Few studies (35-37) recorded only modest diminution of opioid consumption after initiation of DMARDs in IRDs. Present study observed that despite adjusting for DMARDs and objective inflammatory markers over follow-up, disease activity and subjective components levels were always higher in persistent and augmenting opioid-prescription trajectory. Sub-groups with increased perception of disease probably secondary to non-inflammatory pain mechanisms or treatment-refractory disease may consume opioids regularly. Nevertheless, it should also be noted that treatment-refractory disease could also be secondary to augmented central sensitisation.

Limitations are acknowledged here. Opioid-prescription trajectories could not be assessed quantitatively as: 1. the distribution of monthly opioid prescription duration variable did not confirm to analytical norms and also, did not add any further information than the monthly binary variable, and 2. precise information on opioid dose was unavailable. Also, prescriptions may not directly reflect consumption. Sometimes, opioids are prescribed for a long-term, but consumed only when needed. Nevertheless, this study based on binary opioid prescription has brought to fore certain observations that need to be further validated by future studies based on quantitative data on opioid consumption. Strong opioids were prescribed very infrequently, thus, both mild and strong opioids were combined together to arrive at opioid-prescription trajectories.

DAS28 is composed of two objective inflammatory markers (ESR and SJC) out of four components, and ASDAS-CRP, has only one objective marker (CRP) out of five components. To overcome this, we adjusted our analysis for other clinical, and imaging markers of inflammation and anti-inflammatory treatment (DMARDs, corticosteroids, NSAIDs). Disentangling inflammation from sensitisation or *vice versa* using subjective markers is difficult. Past studies explored the assessment of discriminant pain probably secondary to sensitisation by evaluating : DAS28-P index (based on only subjective outcomes) (38), difference between TJC

and SJC >7 (39). Questionnaires evaluating sensitisation component were not available to evaluate this domain further. RDCI, that was used for adjusting for comorbidities, does not include secondary osteoarthritis (OA) or fibromyalgia – contributors of central sensitisation. Data collection for these two diseases were not done systematically. Fibromyalgia may not be a confounder in this context as opioids are not indicated for widespread pain in fibromyalgia. However, OA is implicated in both opioid use and central mechanisms of pain. While analysing RA cohort, we account for it indirectly by adjusting for radiographic changes of joints. SpA cohort is relatively young (mean age 34 years) and thus OA may not be a concern in them.

Overall, despite the current availability of efficacious anti-inflammatory drugs, a proportion of patients with early IRDs receive opioid prescriptions regularly for treating pain of probable non-inflammatory origin. And yet, there is a paucity of studies implicating the role of long-term opioid utilisation in IRDs. Future research should focus on prospective studies that discuss the impact of long-term opioids, and the need to implement multi-disciplinary pain management to manage chronic pain.

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Trial registration number for DESIR: NCT01648907

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