Original article

Socio-demographic determinants in the evolution of pain in inflammatory rheumatic diseases: results from ESPOIR and DESIR cohorts

Sushmithadev Kumaradev [1,2], Christian Roux[1,3], Jérémie Sellam[4], Serge Perrot[5], Thao Pham[6], Aline Dugravot[2,*] and Anna Molto[1,3,*]

Abstract

Objective. To determine whether socio-demographic factors are associated with heterogeneity in pain evolution in inflammatory rheumatic diseases (IRDs) after accounting for disease-specific characteristics in a system with universal health care.

Methods. This analysis included the data from two prospective observational cohorts of early IRDs (ESPOIR for early RA and DESIR for early SpA). Data on pain was measured, respectively, on 13 and 9 occasions spanning 10 and 6 years of follow-up using the Short-Form 36 bodily pain score for 810 participants of ESPOIR, and 679 participants of DESIR. Linear mixed models were used to characterize differences in pain evolution as a function of age (tertiles), sex, ethnicity, education, marital, and professional status, after accounting for disease-related, treatment, lifestyle, and health factors.

Results. While transitioning from early (disease duration $\leq$6 months for RA and $\leq$3 years for SpA) to long-standing disease, differences in pain evolution emerged as a function of age ($P < 0.001$), sex ($P = 0.050$), and ethnicity ($P = 0.001$) in RA, and as a function of age ($P = 0.048$) in SpA; younger age, males, and Caucasians exhibited lower pain in the latter phases of both diseases. Highly educated participants (RA, $\beta = -3.8$, $P = 0.007$; SpA, $\beta = -6.0$, $P < 0.001$) for both diseases, and Caucasians ($\beta = -5.6$, $P = 0.021$) for SpA presented with low pain early in the disease, with no changes throughout disease course.

Conclusion. Being older, female, non-Caucasian and having lower education was found to be associated with worse pain in early and/or long-standing IRDs, despite universally accessible health-care. Early identification of at-risk populations and implementation of multidisciplinary strategies may reduce patient-reported health outcome disparities.

Trial registration registrations. ESPOIR: ClinicalTrials.gov, www.clinicaltrials.gov, NCT03666091. DESIR: ClinicalTrials.gov, www.clinicaltrials.gov, NCT01648907.

Key words: pain evolution, rheumatoid arthritis, spondyloarthritis, socio-demographic factors, pain outcome

Rheumatology key messages

- Socio-demographic characteristics were associated with interindividual heterogeneity in experience of pain in both early and long-standing inflammatory rheumatic diseases.
- Low education impacted pain at or before disease onset; demographic traits impacted pain temporally after the onset of disease and throughout its course.
- Multidisciplinary treatment of pain should start early in disease, targeting those with worse pain outcomes.

[1]Clinical Epidemiology Applied to Rheumatic and Musculoskeletal Diseases, [2]Epidemiology of Ageing and Neurodegenerative Diseases, Inserm 1153, Université de Paris, [3]Department of Rheumatology, APHP-Centre, Cochin Hospital, [4]Department of Rheumatology, APHP-Centre, Saint-Antoine Hospital, [5]Pain Clinic, APHP-Centre, INSERM U897, Cochin Hospital, Paris and [6]Department of Rheumatology, APHM, Sainte-Marguerite Hospital, Aix-Marseille Univ, Marseille, France

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Correspondence to: Sushmithadev Kumaradev, Université de Paris, Inserm U1153 EpiAgeing, 10 Avenue de Verdun, 75010 Paris, France. E-mail: sushmithadev.kumaradev@inserm.fr

*Aline Dugravot and Anna Molto contributed equally to this study.

Introduction

Pain mechanisms in inflammatory rheumatic diseases (IRDs) are multifactorial and are broadly classified as inflammatory (related to disease pathophysiology) and non-inflammatory (attributed to dysregulation of peripheral and central pain-conducting pathways) [1, 2]. The pattern of pain evolution in IRDs is characterized by prominently decreasing pain in the early phases, probably due to early diagnosis and treatment, followed by pain plateauing in the ensuing years [3, 4] at a level higher than the population average [5, 6]. Emerging findings suggest that pain course is not uniform to all; unresolving pain probably linked to non-inflammatory mechanisms was observed among subgroups of those with IRDs, despite optimally controlled inflammation and universally accessible health-care advances [7]. In addition to disease severity [8, 9], the treatment initiated [10] and individuals' lifestyle and psychological health, it has been found that socio-demographic characteristics potentially contribute about 5–11% of the observed pain heterogeneity in IRDs [11, 12]; older age [13, 14], female sex [15–18], non-Caucasian ethnicity [19] and low socio-economic status [20] are associated with increased pain in IRDs; however, the consistency of this association throughout the disease course is unknown.Previous studies reporting associations between socio-demographic characteristics and pain in IRDs were based on cross-sectional [21, 22] or longitudinal design that either did not account for non-linear evolution of pain in IRDs [11], were not based on repeatedly assessed pain measures [23], or were limited to patients with early [18] or long-standing disease [13, 14]. The aforesaid studies may have missed relevant information about temporal changes in pain associated with the transition from early to long-standing IRDs. Fluctuations in disease-specific characteristics, response to treatment, health, and pain coping behaviours accompanying disease-phase transitioning, could modify the effect of socio-demographic characteristics on pain evolution. For instance, prospective studies on early RA found that sex differences in pain were often apparent during the course of the disease [24, 25] and not before 6 months since symptom onset [18, 26], highlighting the importance of assessing temporal trends in pain. Thus, exploring the impact of socio-demographic characteristics on pain while transitioning from early to long-standing IRDs can help the understanding of pain behaviour among vulnerable groups, and the implementation of appropriate treatment strategies quite early in disease course. Accordingly, this study aimed to assess the evolution of pain in IRDs as a function of socio-demographic characteristics, after accounting for disease-specific, current treatment, lifestyle, and psychological and health factors using repeated measures since disease onset for up to 6 years or longer.

Methods

Study design and participants

The participants of this study belong to the two ongoing prospective French multicentric cohorts in a setting of universally accessible health-care: ESPOIR (Etude et Suivi des Polyarthrites Indifférenciées Récentes) [27] started in 2002/2005 and DESIR (DEvenir des Spondylarthropathies Indifférenciées Récentes) [28] started in 2007/2010. ESPOIR comprises 813 participants aged 18–70 years with features suggestive of early RA of $<$6 months duration followed up over 10 years. DESIR comprises 708 participants aged 18–50 years, presenting with inflammatory back pain with a highly probable SpA diagnosis, for a duration ranging from 3 months to 3 years followed up for 6 years. Participants were biologic DMARDs naïve at inclusion. Clinical visits were conducted biannually in the initial 2 years of follow-up and annually henceforth, corresponding to 13 and 9 visits, respectively, for ESPOIR and DESIR cohorts, collecting clinical, biological and radiographic 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.

Pain

The bodily pain subscale of the 36-item short-form questionnaire (SF-36 BP) was used as a valid measure for pain evaluation [29, 30]. In both the cohorts, the SF-36 BP comprises two questions evaluating pain intensity and interference "over last 8 days". (Refer to the Supplementary Data S1, available at *Rheumatology* online, regarding the SF-36 BP component questions and scoring pattern.) Both pain intensity and interference scores were averaged to obtain SF-36 BP. To ease interpretation, the scores were reversed so that higher scores corresponded to higher pain. Apart from SF-36 BP, a visual analogue scale [30, 31] measure ranging from 0 (no pain) to 100 (worst imaginable pain), measuring joint pain intensity when mobilized (joint mobilization pain) and when at rest (resting joint pain) for ESPOIR, and a numerical rating scale [31] ranging from 0 (no pain) to 10 (worst imaginable pain) measuring back pain intensity during the day (back pain) and at night (night pain) for DESIR were also considered. Numerical rating scale scores were multiplied by 10 to assure uniformity in the range of pain measures (0–100) across the different scales. Pain variables were assessed at each clinical visit.

Socio-demographic factors

Demographic factors included sex, age at inclusion (continuous, tertiles) and ethnicity (participants self-identified themselves as Caucasians or Others—those

belonging to African, Asian, Maghrebian, or other origin). Social factors included education, and marital and professional status as recorded at inclusion. The highest attained education was categorized as low education (less than or equal to secondary level) or high education (more than secondary level). Marital status was categorized as couples (married or cohabiting) or single (unmarried, divorced and widowed). Professional status was classified as no job (those without a job or retired), or blue-collar (labourers, farmers or artisans), and white-collar (intermediate and executive professional) workers.

Covariates

Disease-related factors included symptom duration and a distinct set of variables for each cohort. Variables for ESPOIR were: inflammatory marker (ESR in mm/h), clinical markers (tender, and swollen joint count based on 28 joints), imaging marker (presence of X-ray changes fulfilling ACR 1987 criteria) [32], and biological markers (RF and ACPA positivity). Variables for DESIR were: inflammatory marker (CRP in mg/dl), clinical markers [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) and biological marker (HLA B27 positivity). The rationale behind the choice of disease-related factors is given in the supplement (Supplementary Data S2, available at *Rheumatology* online). Treatment included current use of NSAIDs, CSs, DMARDS and analgesics. Lifestyle factors included BMI, current smoking, and alcohol consumption status. Health factors included the rheumatic disease comorbidity index (RDCI), a validated and weighted comorbidity index for rheumatological outcomes [33] based on self-declared disease status or medication use history for lung, cardiovascular, fracture, depression (as a measure of psychological health), diabetes, cancer, and gastrointestinal diseases. (Refer to Supplementary Data S3, available at *Rheumatology* online, for RDCI calculation.) All covariates were assessed repeatedly at clinical visits and analysed as time-dependent variables whenever feasible.

Statistical analysis

Descriptive statistics comparing population characteristics by tertiles of each pain score were determined using Pearson's χ^2, Fischer's exact and analysis of variance (ANOVA) tests. Both cohorts were analysed separately, using linear mixed models with continuous pain variables as dependent variables and time since inclusion (t_0) as timescale. Based on cubic spline regression, time, time^2, and time^3 (slope terms) were incorporated to model non-linear evolution of pain. Random effects for the intercept and time allowed individual differences in pain score at intercept and changes in pain over time. Five multivariate models were examined. Model 1 was adjusted for socio-demographic characteristics and their interaction with time (slope terms). Thereafter, model 1 was additionally and sequentially adjusted for disease-related (model 2), treatment (model 3), lifestyle (model 4), and health (model 5) factors. Differences in the evolution of pain as a function of socio-demographic factors were tested by examining whether interaction of socio-demographic factors with slope terms ($P_{trajectory}$) improved model fit using the Wald test. Additionally, the above analysis was repeated restricting the analytic sample to those fulfilling the ACR 1987 criteria in the ESPOIR cohort and the American SpondyloArthritis international Society (ASAS) criteria in the DESIR cohort as a part of sensitivity analysis. All analysis was performed using Stata version 15.0 (Stata Corp.). All $P < 0.05$ were considered significant.

Results

Eight hundred and ten of 813 ESPOIR participants and 679 of 708 DESIR participants having at least one measure for all variables constituted the analytic sample (Supplementary Fig. S1, available at *Rheumatology* online). The retention rates of the participants at the end of 5 years of follow-up were 61.7% and 58.2%, and at the end of follow-up were 53.5% and 43.4%, respectively, for ESPOIR and DESIR; 74.9% of ESPOIR and 58.2% of DESIR participants had data collected in at least 7 visits/waves for all variables considered for analysis.Table 1 shows the baseline characteristics of the analytic sample of both cohorts. ESPOIR participants were more likely older (ESPOIR *vs* DESIR mean age 48.1 *vs* 33.6 years, $P < 0.001$), predominantly female (76.8% *vs* 54.8%, $P < 0.001$), less educated (68.4% *vs* 39.9%, $P < 0.001$) and had higher pain scores (mean SF-36 BP 62.2 *vs* 56.7, $P < 0.001$) than DESIR participants. Interaction terms assessing the role of disease-related factors (inflammatory and clinical markers) in the evolution of pain (SF-36 BP) within socio-demographic groups (sex, ethnicity, and education) were not significant ($P_{interaction} > 0.07$).

Supplementary Tables S1 (ESPOIR) and S4 (DESIR), available at *Rheumatology* online, compare the baseline characteristics of participants by the tertiles of SF-36 BP at inclusion. In ESPOIR, participants with higher SF-36 BP had lower education, used analgesics more frequently and had higher ESR, tender and swollen joint counts, BMI, and RDCI. In DESIR, across SF-36 BP tertiles an increasing percentage of non-Caucasians, low education, CS and analgesic use, and increasing CRP, peripheral arthritis, and enthesitis were seen. The results for joint mobilization, and resting joint pain of ESPOIR (Supplementary Tables S2 and S3, available at *Rheumatology* online) and back and night pain of DESIR (Supplementary Tables S5 and S6, all available at *Rheumatology* online) are provided in the Supplementary Data.

Table 1 Baseline characteristics of RA (ESPOIR) and SpA (DESIR) cohorts

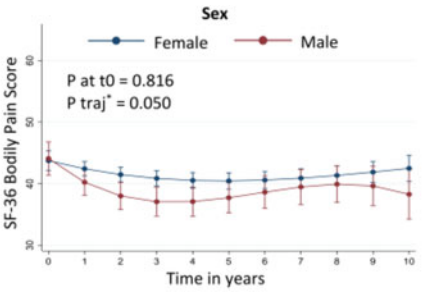
Variables	RA (ESPOIR, *N* = 794)	SpA (DESIR, *N* = 642)
Socio-demographic factors		
Male, *n* (%)	184 (23.2)	290 (45.2)
Age, *m* (S.D.), years	48.1 (12.6)	33.6 (8.6)
Caucasian, *n* (%)	733 (92.3)	577 (89.9)
More than secondary education, *n* (%)	251 (31.6)	386 (60.1)
Profession, no job, *n* (%)	32 (4.0)	89 (13.9)
White-collar workers, *n* (%)	158 (19.9)	90 (14.0)
Blue-collar workers, *n* (%)	604 (76.1)	463 (72.1)
Married, *n* (%)	579 (72.9)	418 (65.1)
Disease-related factors		
Symptom duration, *m* (S.D.), years	0.6 (0.7)	1.5 (0.9)
Inflammatory markers		
ESR, *m* (S.D.)	29.4 (24.7)	
CRP, *m* (S.D.)		7.5 (13.0)
Clinical markers		
Tender joint count (0–28), *m* (S.D.)	8.4 (7.0)	
Swollen joint count (0–28), *m* (S.D.)	7.2 (5.4)	
Arthritis index (0–159), *m* (S.D.)		4.2 (8.2)
Synovitis index (0–28), *m* (S.D.)		0.1 (0.8)
Enthesitis index (0–39), *m* (S.D.)		4.2 (5.8)
Imaging markers, *n* (%)		
Radiographic changes as per ACR criteria	108 (13.6)	218 (34.0)
Sacroiliitis features in MRI		
Biological markers		
RF positivity, *n* (%)	334 (42.1)	
ACPA positivity, *n* (%)	306 (38.5)	
HLA B27 positivity, *n* (%)		380 (59.2)
Treatment		
NSAIDs, *n* (%)	722 (90.9)	597 (93.0)
CSs, *n* (%)	156 (19.7)	116 (18.1)
DMARDs, *n* (%)	55 (6.9)	87 (13.6)
Analgesics, *n* (%)	538 (67.8)	406 (63.2)
Lifestyle factors		
BMI, *m* (S.D.), kg/m^2	25.0 (4.5)	23.9 (3.9)
Smoker, *n* (%)	377 (47.5)	234 (36.5)
Alcohol consumer, *n* (%)	138 (17.4)	97 (15.1)
Health factors		
Rheumatic disease comorbidity index, *m* (S.D.)	1.1 (1.3)	0.4 (0.7)
Pain measures		
SF-36 bodily pain scale (0–100), *m* (S.D.)	62.2 (20.4)	56.7 (22.0)
Joint mobilization pain[a] (0–100), *m* (S.D.)	54.9 (25.8)	
Resting joint pain[a] (0–100), *m* (S.D.)	37.0 (27.5)	
Back pain[b] (0–100), *m* (S.D.)		49.8 (27.1)
Night pain[b] (0–100), *m* (S.D.)		46.8 (30.3)

Only characteristics of participants with measures for all variables at baseline are described. In 16 out of the 810 ESPOIR analytic samples and in 37 out of the 679 DESIR analytic samples, there were one or more missing variables at baseline. [a]Joint mobilization and resting joint pain are measured using a visual analogue scale in the ESPOIR cohort. [b]Back and night pain are measured using a numerical rating scale in the DESIR cohort. *m*: mean, SF-36: 36-item short-form survey.

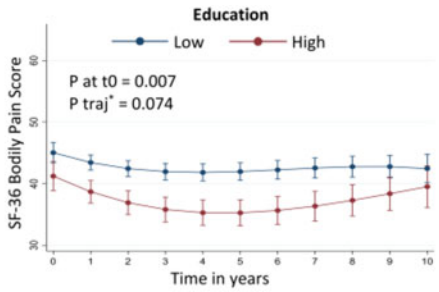
Results for RA (ESPOIR)

Univariate and all five multivariate models showing the association between covariates and pain variables (namely, SF-36 BP, joint mobilization, and resting joint pain) assessed at inclusion are provided in the supplement (Supplementary Tables S7, S8 and S9, available at *Rheumatology* online). Fig. 1 represents the 10-year evolution of SF-36 BP (Supplementary Fig. S2 for joint mobilization pain and Supplementary Fig. S3 for resting joint pain, available at *Rheumatology* online) by socio-demographic groups in the fully adjusted model. Correspondingly, evolution of differences in pain score for each year of follow-up are shown in green in Fig. 2 and Supplementary Table S13, available at *Rheumatology*

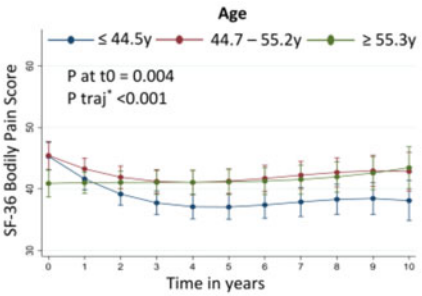
Fig. 1 Evolution of SF-36 bodily pain by socio-demographic subgroups from inclusion to up to 10 years in RA (ESPOIR cohort)



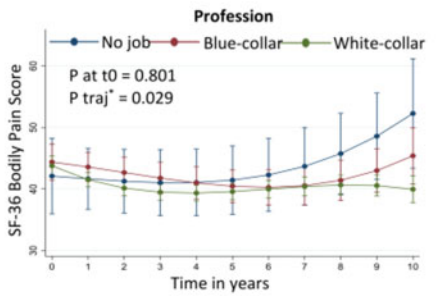
Years	0-2	>2-4	>4-6	>6-8	>8-10
Females	622	505	447	421	388
Males	188	154	137	117	109



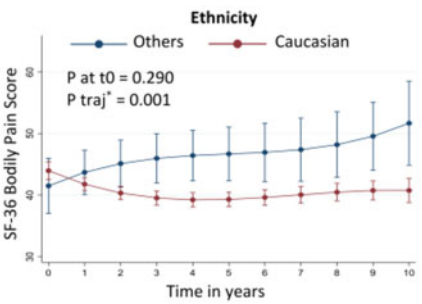
Years	0-2	>2-4	>4-6	>6-8	>8-10
Low	555	442	402	372	338
High	255	217	182	166	159



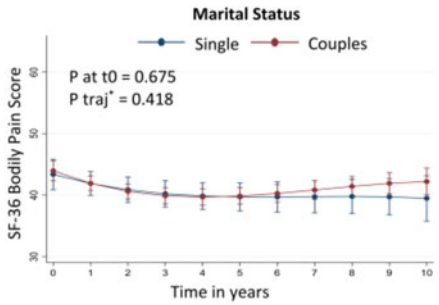
Years	0-2	>2-4	>4-6	>6-8	>8-10
≤44.5 y	289	229	187	169	164
44.7 – 55.2 y	253	212	203	189	173
≥55.3 y	268	218	194	180	160



Years	0-2	>2-4	>4-6	>6-8	>8-10
No job	32	29	24	25	23
Blue	160	127	115	105	88
White	618	503	445	408	386



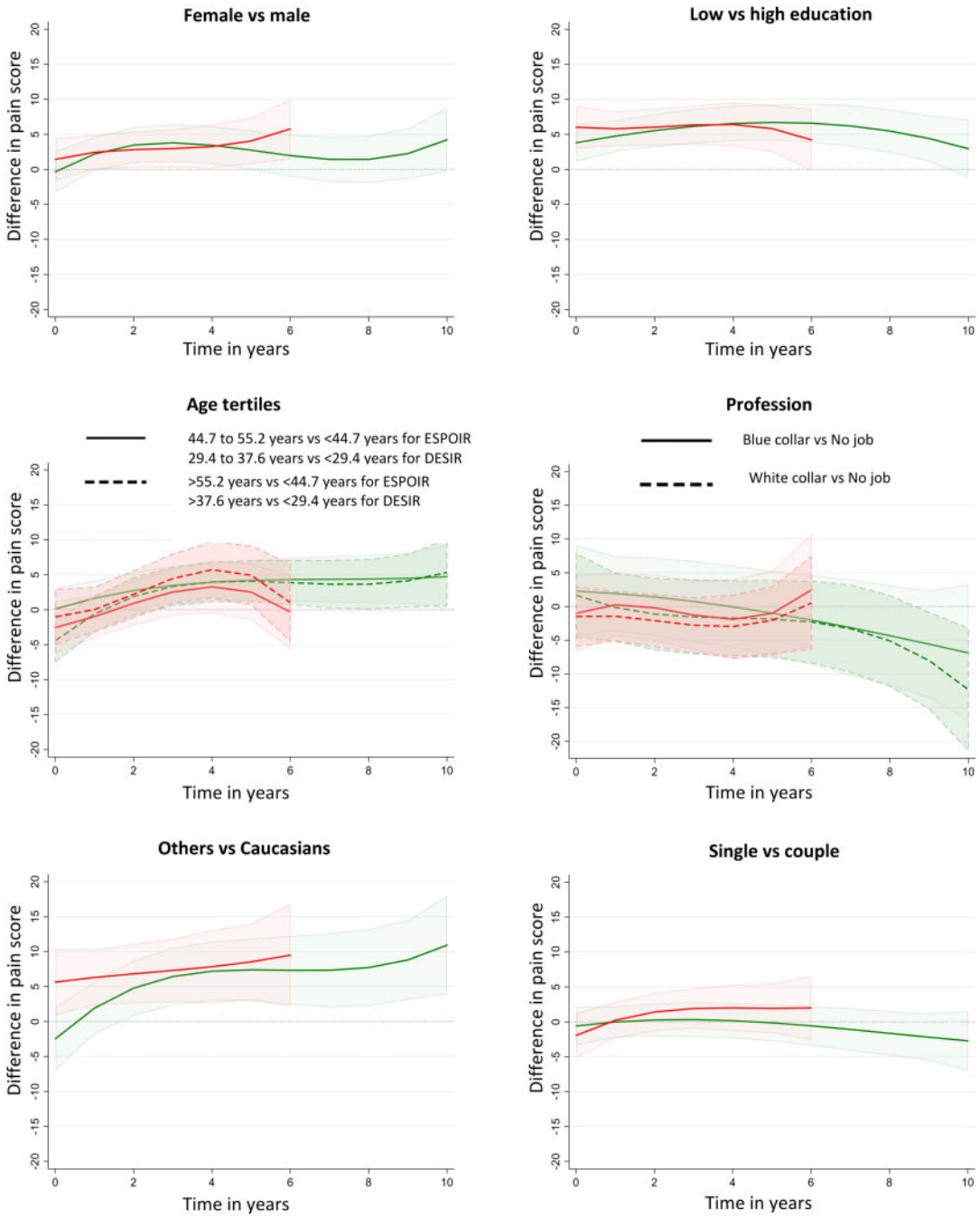
Years	0-2	>2-4	>4-6	>6-8	>8-10
Others	62	48	35	30	34
Caucasian	748	611	549	508	463



Years	0-2	>2-4	>4-6	>6-8	>8-10
Single	217	168	144	138	124
Couples	593	491	440	400	373

**P* for difference in pain trajectories/evolution (drawn from testing the interactions between socio-demographic factor and slope terms using the Wald test). Analysis adjusted for socio-demographic factors (sex, age, ethnicity, education, professional and marital status assessed at inclusion) and their interaction with slope terms (time, time^2 and time^3), and disease-related (symptom duration, ESR, tender and swollen joint count, presence of radiographic structural lesions, RF positivity, ACPA positivity), treatment (anti-inflammatory and analgesic agents), lifestyle-related (BMI, smoking, and alcohol consumption status) and health factors (rheumatic disease comorbidity index). Disease-related, treatment, lifestyle-related and health factors were time-dependent, with some exceptions (symptom duration and ACPA positivity at baseline and their interactions with slope terms) were used in analysis. The tables beneath the figures indicate the total number of participants by socio-demographic subgroups contributing at least once to the analysis for every 2 years from year 0 to 10. Estimates came from Margins command in STATA. SF-36, short-form 36.

Fig. 2 Evolution of differences in SF-36 bodily pain by socio-demographic subgroups in RA and SpA



Analysis adjusted for socio-demographic factors (sex, age, ethnicity, education, professional and marital status assessed at inclusion) and their interaction with slope terms (time, time^2 and time^3), and disease-related, treatment, lifestyle-related, and health factors. The green line represents the ESPOIR cohort and the red line the DESIR cohort. SF-36, short-form 36

online (Table 2 for joint mobilization and resting joint pain). Pain did not differ by sex at inclusion ($P_{t0} \geq 0.38$ for 3 pain scores). Though differential pain evolution by sex was not evident [P for interaction between sex and slope terms ($P_{trajectory} \geq 0.05$)], from 2 up to 4 years after inclusion males, had lower pain scores than females. Pain evolution differed across age; although the youngest tertile had higher pain at inclusion ($\beta = 4.4$, $P = 0.005$ for SF-36 BP), they showed a significant decrease in both SF-36 BP and joint mobilization pain ($P_{trajectory} < 0.001$ for both) over

Table 2 Differences in visual analogue scale pain scores by socio-demographic factors over follow-up in RA

	Sex		Age				Ethnicity		Education		Profession				Marital status	
	Female *vs* male		Tertile 2 *vs* tertile 1		Tertile 3 *vs* tertile 1		Others *vs* Caucasians		Low *vs* high		Blue-collar *vs* no job		White-collar *vs* no job		Single *vs* couples	
Year	β	(95% CI)	β	(95% CI)	β	(95% CI)	β	(95% CI)	β	(95% CI)	β	(95% CI)	β	(95% CI)	β	(95% CI)
Joint mobilization pain																
0	−1.5	(−5.0, 1.9)	**−5.0**	**(−8.5, −1.4)**	**−9.0**	**(−12.6, −5.4)**	−4.4	(−9.8, 1.0)	**4.2**	**(1.0, 7.4)**	−5.4	(−13.4, 2.5)	−4.6	(−11.8, 2.7)	1.8	(−1.5, 5.0)
1	1.3	(−1.5, 4.0)	−1.6	(−4.4, 1.2)	**−3.1**	**(−5.9, −0.2)**	−0.8	(−5.0, 3.4)	**5.8**	**(3.2, 8.3)**	−4.4	(−10.7, 1.9)	−3.6	(−9.3, 2.1)	2.5	(−0.1, 5.0)
2	**2.9**	**(0.0, 5.7)**	0.5	(−2.4, 3.4)	0.4	(−2.5, 3.3)	1.3	(−3.1, 5.7)	**6.6**	**(4.0, 9.3)**	−3.8	(−10.2, 2.7)	−3.0	(−8.9, 2.9)	2.4	(−0.2, 5.1)
3	**3.6**	**(0.7, 6.5)**	1.5	(−1.4, 4.5)	1.9	(−1.1, 4.9)	2.1	(−2.4, 6.6)	**6.9**	**(4.2, 9.6)**	−3.4	(−9.9, 3.1)	−2.7	(−8.7, 3.2)	1.9	(−0.8, 4.6)
4	**3.6**	**(0.8, 6.4)**	1.8	(−1.1, 4.7)	2.0	(−0.9, 5.0)	2.1	(−2.4, 6.6)	**6.7**	**(4.1, 9.4)**	−3.1	(−9.5, 3.2)	−2.6	(−8.4, 3.2)	1.1	(−1.6, 3.7)
5	**3.2**	**(0.3, 6.0)**	1.5	(−1.4, 4.4)	1.2	(−1.8, 4.2)	1.5	(−3.1, 6.1)	**6.3**	**(3.6, 8.9)**	−2.9	(−9.2, 3.5)	−2.6	(−8.4, 3.1)	0.2	(−2.5, 2.8)
6	2.6	(−0.4, 5.6)	0.9	(−2.1, 4.0)	0.1	(−3.1, 3.2)	0.7	(−4.3, 5.6)	**5.6**	**(2.9, 8.4)**	−2.5	(−9.2, 4.2)	−2.7	(−8.7, 3.3)	−0.6	(−3.4, 2.2)
7	2.1	(−1.1, 5.3)	0.3	(−2.9, 3.6)	−0.9	(−4.3, 2.4)	−0.1	(−5.4, 5.3)	**5.0**	**(2.1, 7.9)**	−1.9	(−8.9, 5.1)	−2.7	(−9.0, 3.7)	−1.0	(−4.0, 2.1)
8	1.9	(−1.4, 5.2)	0.0	(−3.4, 3.3)	−1.2	(−4.7, 2.2)	−0.4	(−5.8, 5.0)	**4.5**	**(1.5, 7.5)**	−0.9	(−8.0, 6.3)	−2.5	(−9.0, 3.9)	−0.7	(−3.8, 2.4)
9	2.3	(−1.2, 5.8)	0.1	(−3.4, 3.6)	−0.3	(−3.9, 3.3)	0.0	(−5.4, 5.5)	**4.3**	**(1.1, 7.4)**	0.6	(−7.0, 8.2)	−2.1	(−9.0, 4.7)	0.3	(−2.9, 3.6)
10	3.5	(−1.2, 8.2)	1.0	(−3.7, 5.6)	2.4	(−2.4, 7.2)	1.6	(−5.6, 8.7)	**4.5**	**(0.2, 8.7)**	2.7	(−7.7, 13.0)	−1.4	(−10.7, 7.8)	2.4	(−1.9, 6.8)
P_{traj}*	0.052		**<0.001**				0.169		0.301		0.654				0.153	
Resting joint pain																
0	1.2	(−2.0, 4.5)	−0.9	(−4.3, 2.4)	**−3.3**	**(−6.7, 0.0)**	−3.0	(−8.0, 2.1)	**9.0**	**(6.0, 12.0)**	−4.5	(−12.0, 3.0)	**−7.2**	**(−14.0, −0.3)**	1.7	(−1.4, 4.7)
1	**2.7**	**(0.1, 5.3)**	0.7	(−1.9, 3.4)	−1.8	(−4.5, 0.8)	1.5	(−2.5, 5.5)	**7.4**	**(5.0, 9.9)**	−2.6	(−8.6, 3.4)	−5.2	(−10.7, 0.2)	0.3	(−2.1, 2.7)
2	**3.4**	**(0.7, 6.0)**	1.6	(−1.1, 4.4)	−0.8	(−3.6, 1.9)	4.0	(−0.1, 8.1)	**6.5**	**(4.0, 8.9)**	−1.5	(−7.5, 4.6)	−3.9	(−9.5, 1.6)	−0.7	(−3.2, 1.8)
3	**3.3**	**(0.6, 6.0)**	1.9	(−0.8, 4.7)	−0.2	(−3.0, 2.6)	**5.0**	**(0.8, 9.2)**	**5.9**	**(3.4, 8.4)**	−0.9	(−7.0, 5.2)	−3.1	(−8.6, 2.4)	−1.5	(−4.0, 1.1)
4	**2.8**	**(0.2, 5.4)**	1.7	(−0.9, 4.4)	0.1	(−2.7, 2.8)	**4.9**	**(0.8, 9.0)**	**5.8**	**(3.3, 8.2)**	−0.7	(−6.5, 5.2)	−2.6	(−7.9, 2.8)	−1.9	(−4.4, 0.5)
5	2.0	(−0.6, 4.6)	1.3	(−1.4, 3.9)	0.1	(−2.7, 2.8)	4.0	(−0.1, 8.2)	**5.8**	**(3.4, 8.2)**	−0.6	(−6.4, 5.2)	−2.2	(−7.5, 3.1)	−2.1	(−4.6, 0.3)
6	1.1	(−1.6, 3.9)	0.6	(−2.2, 3.4)	−0.1	(−3.0, 2.7)	2.9	(−1.6, 7.4)	**6.0**	**(3.5, 8.5)**	−0.4	(−6.4, 5.6)	−1.9	(−7.3, 3.6)	−2.2	(−4.7, 0.4)
7	0.4	(−2.5, 3.2)	0.0	(−3.0, 2.9)	−0.4	(−3.4, 2.6)	1.9	(−2.8, 6.6)	**6.3**	**(3.6, 8.9)**	0.1	(−6.1, 6.4)	−1.4	(−7.1, 4.2)	−2.0	(−4.7, 0.7)
8	−0.1	(−3.0, 2.8)	−0.5	(−3.5, 2.4)	−0.8	(−3.8, 2.3)	1.4	(−3.3, 6.2)	**6.4**	**(3.8, 9.1)**	1.2	(−5.2, 7.5)	−0.7	(−6.4, 5.0)	−1.7	(−4.4, 1.0)
9	0.0	(−3.0, 3.0)	−0.7	(−3.8, 2.3)	−1.1	(−4.2, 2.1)	1.9	(−2.9, 6.7)	**6.3**	**(3.6, 9.1)**	2.9	(−3.7, 9.6)	0.4	(−5.6, 6.4)	−1.3	(−4.2, 1.5)
10	0.8	(−3.4, 4.9)	−0.5	(−4.6, 3.6)	−1.3	(−5.6, 3.0)	3.7	(−2.6, 10.0)	**6.0**	**(2.2, 9.7)**	5.7	(−3.4, 14.9)	2.1	(−6.1, 10.2)	−0.9	(−4.7, 2.9)
P_{traj}*	0.185		0.330				**0.029**		0.215		0.518				0.104	

In the RA/ESPOIR cohort: tertile 1 = ≤44.5 years, tertile 2 = 44.7–55.2 years and tertile 3 = ≥55.3 years. Highlighted values correspond to a *P*-value < 0.05. **P* for difference in pain trajectories/evolution (drawn from testing the interactions between socio-demographic factor and slope terms using the Wald test). Analysis adjusted for socio-demographic factors (sex, age, ethnicity, education, professional and marital status assessed at inclusion) and their interaction with slope terms (time, time^2 and time^3), and time-dependent disease-related, treatment, lifestyle, and health factors.

follow-up compared with the oldest tertile. No ethnic differences in pain were observed at inclusion ($P_{t0} \geq 0.11$), but, compared with Caucasians, other ethnic groups showed increased SF-36 BP ($P_{trajectory} = 0.001$) and resting joint pain ($P_{trajectory} = 0.029$) over follow-up. Education-based differences in pain were present since inclusion (low *vs* high education $\beta = 3.8$, $P = 0.007$ for SF-36 BP, $\beta = 4.2$, $P = 0.011$ for joint mobilization pain, $\beta = 9.0$, $P < 0.001$ for resting joint pain) without evolutionary changes (Ptrajectory ≥ 0.074). Profession-related differences in pain evolution were not consistent; compared with white-collar workers, those with no job had higher resting joint pain at inclusion ($\beta = 4.5$ for no job and $\beta = -2.7$ for white-collar workers, $P = 0.048$), and increased SF-36 BP ($P_{trajectory} = 0.029$) in the later years of follow-up.

Results for SpA (DESIR)

Univariate and all five multivariate models showing the association between covariates and pain at inclusion for SF-36 BP, back, and night pain are provided in the supplement (Supplementary Tables S10, S11 and S12, available at *Rheumatology* online). Fig. 3 represents the 6-year evolution of SF-36 BP (Supplementary Fig. S4 for back pain and Supplementary Fig. S5 for night pain, available at *Rheumatology* online) by socio-demographic groups in the fully adjusted model. Correspondingly, evolution of differences in pain score for each year over follow-up are shown in red in Fig. 2 and Supplementary Table S13, available at *Rheumatology* online (Table 3 for back and night pain). Sex differences in pain assessed at inclusion and pain evolution were not significant ($P_{t0} \geq 0.09$ and $P_{trajectory} \geq 0.32$); however, from 1 up to at least 4 years of follow-up, males had more decrease in pain scores than females. The youngest tertile experienced a larger decrease in pain over follow-up than the oldest tertile ($P_{trajectory} = 0.048$ for SF-36 BP, $P_{trajectory} = 0.015$ for back pain). Compared with Caucasians, other ethnic groups had higher pain scores at inclusion ($\beta = 5.6$, $P = 0.021$ for SF-36 BP) that persisted without evolutionary changes ($P_{trajectory} \geq 0.29$) except for back pain ($P_{trajectory} = 0.009$). Higher pain since inclusion persisted constantly through follow-up in those with low education ($\beta = 6.0$, $P < 0.001$ for SF-36 BP, $\beta = 6.3$, $P = 0.001$ for back pain and $\beta = 8.0$, $P < 0.001$ for night pain at inclusion; all $P_{trajectory} \geq 0.167$) compared with those with high education. Compared with singles, couples had higher back ($\beta = 4.7$, $P = 0.019$) and night pain scores ($\beta = 7.1$, $P = 0.001$) at inclusion; nevertheless, they showed reduced pain over follow-up ($P_{trajectory} \leq 0.004$ for both numerical rating scales). Despite non-significant pain evolution by professional categories ($P_{trajectory} \geq 0.15$), inconsistently, those with no job had higher back and night pain compared with white-collar workers.

Sensitivity analysis

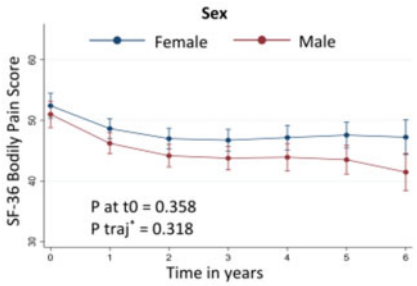
Supplementary Figs S6 and S7, available at *Rheumatology* online, show the 10- and 6-year evolution of SF-36 bodily pain score by socio-demographic groups in the fully adjusted model, respectively, for those fulfilling the ACR 1987 criteria in the ESPOIR cohort ($N = 686$) and the ASAS criteria in the DESIR cohort ($N = 470$). Supplementary Fig. S8, available at *Rheumatology* online, correspondingly shows the evolution of differences in pain scores in both cohorts. The pattern of evolution of all pain scores by socio-demographic factors were in concordance with the main analysis (results shown only for SF-36), except that, due to lack of sufficient power, differences in pain as a function of sex and age over follow-up were not evident.

Discussion

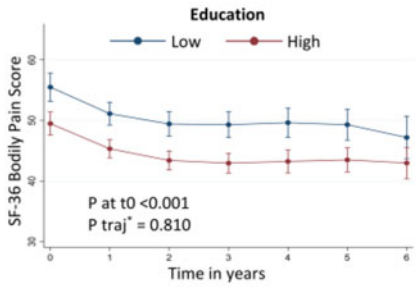
This longitudinal study based on two cohorts of patients with early RA (ESPOIR) and early SpA (DESIR) with repeatedly assessed pain over, respectively, 10 and 6 years presented three salient findings. First, socio-demographic disparities based on sex, age, ethnicity and education were important contributors to pain in early (disease duration $\leq$6 months for RA and $\leq$3 years for SpA) and long-standing IRDs. Of these, disparities in ethnicity and education were associated with clinically meaningful differences in pain scores over follow-up in a consistent manner when compared with the minimal clinically important difference in SF-36 BP score in RA corresponding to 4.9 [34]. Second, differences in pain evolution as a function of demographic factors emerged while transitioning from early to long-standing disease; those who were older at the early disease phase, females, and non-Caucasians, although having similar pain levels to their counterparts during early phases of disease, reported higher pain during the disease course. Third, the impact of social factors on pain occurs much earlier to disease-phase transitioning. Educational disparities did not catalyse changes in pain level through the disease course; the higher pain in those with low education was present from the early phases of disease. Associations between marital status and pain, and between professional status and pain were not consistent.

The present study, compared pain among socio-demographic groups at inclusion when participants were biologic DMARD-naïve and throughout the disease course, after accounting for disease-specific, treatment, lifestyle and health characteristics. 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 pain and other covariates, thus, giving an insight into the variations in the association between socio-demographic factors and pain in both early and long-standing disease. As far as we know, this is the first study that has examined pain evolution in IRDs among socio-economically disparate groups. By considering the evolution of three pain scores for each disease, an overall view (limiting biases related to pain assessment instruments) was obtained. Sensitivity analysis done by restricting the analysis to those who

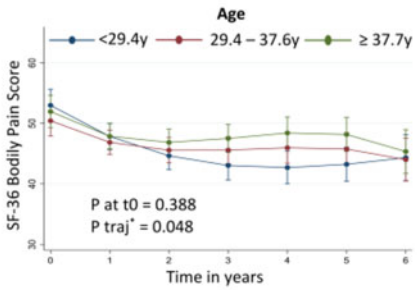
Fig. 3 Evolution of SF-36 bodily pain by socio-demographic subgroups from inclusion to up to 6 years in SpA (DESIR cohort)



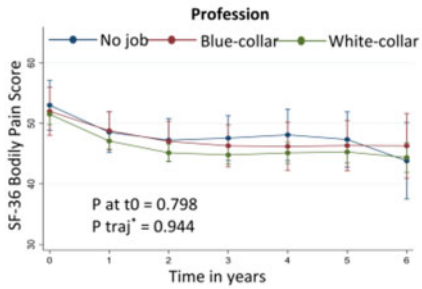
Years	0-1	>1-2	>2-3	>3-4	>4-5	>5-6
Females	365	314	224	200	200	193
Males	311	265	207	179	164	164



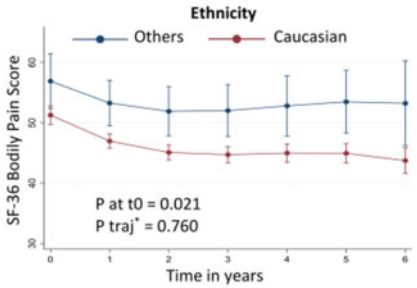
Years	0-1	>1-2	>2-3	>3-4	>4-5	>5-6
Low	270	218	159	144	139	126
High	406	361	272	235	225	231



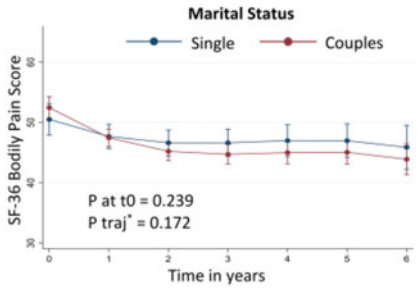
Years	0-1	>1-2	>2-3	>3-4	>4-5	>5-6
<29.4 y	234	194	144	133	122	116
29.4 – 37.6 y	226	193	143	123	114	119
≥37.7 y	216	192	144	123	128	122



Years	0-1	>1-2	>2-3	>3-4	>4-5	>5-6
No job	91	72	55	49	51	40
Blue	98	88	68	58	52	55
White	487	419	308	272	261	262



Years	0-1	>1-2	>2-3	>3-4	>4-5	>5-6
Others	69	51	27	35	30	28
Caucasian	607	528	404	344	334	329



Years	0-1	>1-2	>2-3	>3-4	>4-5	>5-6
Single	244	208	145	132	123	108
Couples	432	371	286	247	241	249

* *P* for difference in pain trajectories/evolution (drawn from testing the interactions between socio-demographic factor and slope terms using Wald test). Analysis adjusted for socio-demographic factors (sex, age, ethnicity, education, professional and marital status assessed at inclusion) and their interaction with slope terms (time, time^2, and time3), and disease-related (symptom duration, CRP, arthritis, synovitis, and enthesitis indices, presence of sacroiliitis, human leukocyte antigen B27 positivity), treatment (anti-inflammatory and analgesic agents), lifestyle-related (BMI, smoking, and alcohol consumption status), and health factors (rheumatic disease comorbidity index). Disease-related, treatment, lifestyle-related and health factors were time-dependant with some exceptions (symptom duration, presence of sacroiliitis and human leukocyte antigen B 27 positivity at baseline and their interaction with slope terms) were used in analysis. The tables beneath the figures indicate the total number of participants by socio-demographic sub-groups contributing at least once to the analysis by every year from year 0 to 6. Estimates came from Margins command in STATA.

Table 3 Differences in numerical rating scale pain scores by socio-demographic factors over follow-up in SpA

	Sex		Age				Ethnicity		Education		Profession				Marital status	
	Female *vs* male		Tertile 2 *vs* tertile 1		Tertile 3 *vs* tertile 1		Others *vs* Caucasians		Low *vs* high		Blue-collar *vs* no job		White-collar *vs* no job		Single *vs* couples	
Year	β	(95% CI)	β	(95% CI)	β	(95% CI)	β	(95% CI)	β	(95% CI)	β	(95% CI)	β	(95% CI)	β	(95% CI)
Back pain																
0	3.2	(−0.5, 6.9)	−3.0	(−7.5, 1.5)	−2.6	(−7.4, 2.1)	**13.2**	**(7.5, 19.0)**	**6.3**	**(2.6, 10.0)**	2.9	(−4.1, 9.8)	1.9	(−3.5, 7.3)	**−4.7**	**(−8.6, −0.8)**
1	**3.4**	**(0.4, 6.4)**	0.8	(−2.9, 4.5)	−0.7	(−4.5, 3.2)	**4.7**	**(−0.1, 9.5)**	**6.1**	**(3.0, 9.1)**	−0.8	(−6.5, 4.8)	−1.1	(−5.5, 3.4)	−0.7	(−3.8, 2.5)
2	**3.7**	**(0.6, 6.8)**	2.7	(−1.1, 6.5)	1.9	(−2.1, 5.9)	3.4	(−1.7, 8.5)	**6.6**	**(3.5, 9.7)**	−3.0	(−8.9, 2.8)	−3.6	(−8.2, 1.1)	1.5	(−1.7, 4.8)
3	**4.1**	**(0.9, 7.3)**	3.3	(−0.6, 7.2)	**4.4**	**(0.3, 8.6)**	**6.1**	**(0.8, 11.4)**	**7.4**	**(4.2, 10.7)**	−4.0	(−10.1, 2.1)	**−5.0**	**(−9.8, −0.3)**	2.4	(−1.0, 5.8)
4	**4.4**	**(0.7, 8.1)**	3.1	(−1.3, 7.6)	**6.1**	**(1.5, 10.8)**	**9.5**	**(3.4, 15.6)**	**8.1**	**(4.4, 11.8)**	−4.0	(−10.9, 2.9)	−5.0	(−10.4, 0.5)	2.7	(−1.2, 6.6)
5	**4.6**	**(0.7, 8.4)**	2.8	(−1.9, 7.5)	**6.2**	**(1.3, 11.1)**	**10.6**	**(4.2, 17.0)**	**8.2**	**(4.3, 12.1)**	−3.4	(−10.7, 4.0)	−2.8	(−8.6, 3.0)	2.9	(−1.2, 7.0)
6	4.4	(−0.6, 9.4)	2.9	(−3.3, 9.1)	4.0	(−2.5, 10.4)	6.1	(−2.5, 14.7)	**7.2**	**(2.0, 12.3)**	−2.4	(−12.1, 7.3)	2.0	(−6.0, 10.0)	3.7	(−1.7, 9.0)
P_{traj}*		0.924		**0.015**				**0.009**		0.733				0.151		**0.004**
Night pain																
0	2.5	(−1.6, 6.6)	0.2	(−4.8, 5.3)	−1.6	(−6.8, 3.7)	**10.7**	**(4.2, 17.1)**	**8.0**	**(3.9, 12.1)**	2.6	(−5.2, 10.4)	0.9	(−5.1, 6.9)	**−7.1**	**(−11.5, −2.8)**
1	**3.6**	**(0.2, 7.0)**	−1.4	(−5.5, 2.8)	−0.1	(−4.4, 4.3)	**6.2**	**(0.8, 11.7)**	**5.5**	**(2.1, 8.9)**	0.5	(−5.9, 6.9)	−1.9	(−6.9, 3.1)	−1.4	(−4.9, 2.2)
2	**4.4**	**(1.0, 7.9)**	−1.0	(−5.3, 3.2)	1.2	(−3.3, 5.6)	**6.4**	**(0.8, 12.0)**	**5.4**	**(2.0, 8.9)**	−1.4	(−8.0, 5.1)	−4.4	(−9.5, 0.7)	1.0	(−2.6, 4.7)
3	**4.8**	**(1.3, 8.4)**	0.3	(−4.0, 4.7)	2.4	(−2.2, 6.9)	**8.9**	**(3.0, 14.7)**	**6.8**	**(3.2, 10.4)**	−3.2	(−9.9, 3.6)	**−6.3**	**(−11.5, −1.0)**	1.4	(−2.4, 5.1)
4	**4.7**	**(0.7, 8.7)**	1.8	(−3.0, 6.7)	3.5	(−1.6, 8.6)	**11.3**	**(4.7, 18.0)**	**8.6**	**(4.6, 12.7)**	−4.4	(−12.0, 3.1)	**−7.1**	**(−13.0, −1.1)**	1.0	(−3.3, 5.3)
5	3.8	(−0.4, 8.0)	2.5	(−2.6, 7.6)	4.8	(−0.6, 10.2)	**11.4**	**(4.5, 18.4)**	**9.9**	**(5.6, 14.1)**	−5.0	(−13.0, 3.0)	**−6.4**	**(−12.7, −0.1)**	1.2	(−3.3, 5.7)
6	2.1	(−3.3, 7.5)	1.4	(−5.3, 8.1)	6.3	(−0.7, 13.2)	6.9	(−2.4, 16.2)	**9.5**	**(3.9, 15.1)**	−4.8	(−15.3, 5.7)	−3.8	(−12.4, 4.9)	3.4	(−2.4, 9.2)
P_{traj}*		0.608		0.269				0.294		0.167				0.298		**0.001**

In the SpA/DESIR cohort: tertile 1 = <29.4 years, tertile 2 = 29.4–37.6 years, tertile 3 = ≥37.7 years. Highlighted values correspond to a *P*-value < 0.05. **P* for difference in pain trajectories/evolution (drawn from testing the interactions between socio-demographic factor and slope terms using the Wald test). Analysis adjusted for socio-demographic factors (sex, age, ethnicity, education, professional and marital status assessed at inclusion) and their interaction with slope terms (time, time^2 and time^3), and time-dependent disease-related, treatment, lifestyle, and health factors.

fulfilled diagnostic criteria was also in concordance with the above findings.

Sex-attributed differences in pain [16, 24], disease activity [35], treatment response [36], and quality of life [37] are known in IRDs. In accordance with past findings [15, 38], women in this study with SpA reported higher crude pain scores compared with men (Supplementary Tables S10–S12, available at *Rheumatology* online). However, adjustment for disease-specific characteristics (inflammatory and clinical markers) attenuated the observed sex differences in pain in early IRD. With ongoing disease and treatment, a lesser improvement in pain was seen for a short while in women with RA before their pain scores decreased further to plateau with those of men. Confirming our findings, no sex differences in pain were reported in early IRD studies [18, 26], whereas improvement in pain was better among men in long-standing IRDs [15, 25].

The impact of age on pain was variable in early and long-standing IRDs. In early RA, our study findings—higher pain in younger persons—were in disaccord with past studies reporting no association between pain and age [17, 26]. Discrepancies might be due to differences in adjustment for covariates, as even in our study, association between age and pain was revealed only after adjustment for disease-related factors, lifestyle factors, and comorbidities (Supplementary Tables S7–S9, available at *Rheumatology* online). In long-standing disease, our study findings were congruent with those of past research [13, 14]—increasing pain with ageing. With disease continuum and appropriate treatment initiation, younger persons experienced more decrease in pain than older persons, thereby, establishing an age-based pain gap.

Ethnic minorities reported worse levels for most rheumatological outcomes [11, 19, 39]. In this study, compared with Caucasians, all measures except joint mobilization pain were higher among other ethnic groups. Predominantly, the disease-specific inflammation–mediated heightened pain sensitivity of affected joints mediated joint mobilization pain more than the more general non-inflammatory central pain mechanisms [40], and thus did not differ across ethnic groups. Factors yet revealed may increase the susceptibility of ethnic minorities to non-inflammatory central pain mechanisms.

Across the spectrum of IRDs, low levels of socio-economic indicators like education, occupation, income or home ownership were often associated with increased pain [20]. In this study, education-based pain differences were present even in the early disease phase and persisted throughout. This is in accordance with antecedent studies that demonstrated higher pain in those with low education in both early [41] and long-standing disease [11, 21, 22, 42]. Some showed a gradient in the association between years of education and pain [11]. This study failed to demonstrate consistent association between pain and profession, unlike the antecedent studies [43]. Discrepancies might have risen due to differences in the classification of professional categories and the use of socio-economic indicators between the studies. Family resources like income and house ownership predicted pain better than occupational status [21, 44].

Social environment, both quantitatively (in terms of the extent of the social network) and qualitatively (in terms of the emotional and necessary support provided by the extended family and friends [42] or marital life quality [12, 45]), play important roles in the long-term pain outcome in IRDs. In our study, lack of association between pain and marital status in RA could have stemmed from the fact that assessment of marital status is not synonymous to marital quality, a better predictor of pain. In early SpA, couples reported more back pain, eventually coping as well as those single, widowed or separated; given a fairly younger age onset in SpA, family commitments may have increased the pain susceptibility in early disease.

Complex and interacting multiple mechanisms underlie the socio-demographic differences in pain. First, biological mechanisms can result in altered pain sensitivity and pain modulation; hormonal differences between sexes [46], various ethnic origins [47], age-related degenerative changes in the nervous system [48], and associated comorbidities [48] can contribute to neurobiological alterations affecting pain perception. Second, psychological mechanisms (by affecting mood, anxiety and depression, comprehension, acceptance and adherence to health-promoting behaviours) and the utilization of coping strategies can influence pain responsivity [46, 47, 49]. Women [46], ethnic minorities [47], those at socio-economic disadvantage [50] and with poor marital quality [49] often rely on passive coping strategies and indulge in maladaptive pain behaviour and pain catastrophizing [8, 9]. Third, socio-cultural mechanisms such as pain-, religion-, and health-related beliefs [46, 47] and sex, age, and ethnic differences in societal expected roles and accepted behaviours can affect pain [51].

Limitations included non-availability of information regarding the characteristics, location, and mechanisms of pain. Pain variables were collected based on the self-report of pain over a short time span (past 8 days) that may not exactly reflect past pain experiences. However, pain levels reported over short time spans are more reliable with regards to the accuracy of reporting rather than compared with pain reported over the long term. Also, the data is collected in the same manner for all participants at all time points over follow-up, and any inaccuracy in measure will be random. Overall, this could be assumed to be a good representation of the pain of these participants over the years. Pain coping strategies and behaviours, and the quality and quantity of social support, which can influence pain outcomes, were unavailable. Non-pharmacological pain interventions were not assessed. Due to lack of details regarding monetary resources per person, the impact of socio-economic disadvantage on pain evolution has been insufficiently explored. Finally,

comorbidities and medication use were self-reported and are subject to recall bias.

Persistent pain in IRDs despite adequate access to advanced treatment leads to patient dissatisfaction and secondarily augments the health burden. Understanding the evolution of pain in IRDs and its associated factors seems important for identifying those with poor pain prognosis and imparting effective multimodal treatment. Sex, age, ethnic origin, and education play important roles in the pain experienced in early and long-standing IRDs.

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Data availability statement

The datasets generated and/or analysed during the current study are not publicly available due to consent restrictions. Programming codes used for statistical analysis during the current study are available from the corresponding author upon reasonable request.

Supplementary data

Supplementary data are available at *Rheumatology* online.

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