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

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Abstract

Objective: To determine whether sociodemographic 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 rheumatoid arthritis (RA) and DESIR for early spondyloarthritis (SpA)). Data on pain was measured respectively at 13 and 9 occasions spanning 10 and 6 years of follow-up using Short-Form 36 bodily pain amongst 810 participants of ESPOIR, and 679 participants of DESIR. Linear mixed models were used to characterise 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 ≤6 months for RA and ≤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 (RA, $\beta=-3.8$, $p=0.007$; SpA, $\beta=-6.0$, $p<0.001$) in both diseases, and Caucasians ($\beta=-5.6$, $p=0.021$) in SpA presented with low pain early in the disease, with no changes throughout disease course.

Conclusion: Those older, females, non-Caucasians and lowly educated have worse pain in early and/or long-standing IRDs despite universally accessible health-care. Early identification of at-risk population and implementation of multi-disciplinary 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, sociodemographic factors, pain outcome

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Key messages

- Sociodemographic characteristics attributed to interindividual heterogeneity in either early or long-standing inflammatory rheumatic diseases.
- Low education impact pain at/before disease onset; demographic traits impact pain temporally through disease course.
- Multi-disciplinary treatment of pain should start early in disease targeting those with worse pain outcomes.

INTRODUCTION

Pain mechanisms in inflammatory rheumatic diseases (IRDs) are multifactorial, broadly classified as inflammatory, related to disease pathophysiology and non-inflammatory, attributed to dysregulation of peripheral and central pain conducting pathways.(1, 2) Pattern of pain evolution in IRDs is characterised by prominently decreasing pain in early phases, probably due to early diagnosis and treatment, followed by pain plateauing in the ensuing years(3, 4) at a level higher than population average.(5, 6) Emerging findings suggest that pain course is not uniform to all; unresolving pain linked probably to non-inflammatory mechanisms was observed among sub-groups of those with IRDs despite optimally controlled inflammation and universally accessible health-care advances.(7) Besides disease severity(8, 9), treatment initiated(10) and individuals' lifestyle and psychological health, sociodemographic characteristics potentially contribute to about 5 – 11% of 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, consistency of this association throughout disease course remains unanswered.

Previous studies reporting associations between sociodemographic characteristics and pain in IRDs were based on cross-sectional(21, 22) or longitudinal design that either did not account for nonlinear evolution of pain in IRDs,(11) or was not based on repeatedly assessed pain measures,(23) or was limited to those with early (18) or long-standing disease.(13, 14) Aforesaid studies may have missed relevant information on 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 sociodemographic characteristics on pain evolution. For instance, prospective studies on early rheumatoid arthritis (RA) found that sex differences in pain were often apparent with disease continuum(24, 25) and not before

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six months since symptom onset(18, 26) highlighting the importance of assessing temporal trends in pain. Thus, exploring the impact of sociodemographic characteristics on pain while transitioning from early to long-standing IRDs can help understand pain behaviour among vulnerable groups and implement appropriate treatment strategies quite early in disease course. Accordingly, this study aimed to assess the evolution of pain in IRDs as a function of sociodemographic characteristics, after accounting for disease-specific, current treatment, lifestyle, and psychological and health factors using repeated measures since disease onset up to 6 years or greater.

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 2002/05 and DESIR (DEvenir des Spondylarthropathies Indifférenciées Récentes)(28) started in 2007/10. ESPOIR comprises 813 participants aged 18 – 70 years with features suggestive of early RA of less than 6 months duration followed up over 10 years. DESIR comprises 708 participants aged 18 – 50 years, presenting with inflammatory back pain highly probable of spondyloarthritis (SpA) diagnosis, for a duration ranging 3 months to 3 years followed up for six years. Participants were biological Disease Modifying Anti-Rheumatic Drugs (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 had obtained ethical approval from ethics committee of Montpellier, France (no. 020307), and cohort DESIR had obtained ethical approval from Comitte de Protection des Personnes Ile de France III. Signed informed consent was given by participants of both cohorts.

Pain

The bodily pain sub-scale of Short Form 36 (SF-36 BP) questionnaire is used as a valid measure for pain evaluation.(29, 30) In both the cohorts, SF-36 BP comprises two questions evaluating pain intensity and interference “over last 8 days”. Refer to supplement (supplementary data S1, available at *Rheumatology* online) regarding SF-36 BP component questions and scoring pattern. Both pain intensity and interference scores were averaged to obtain SF-36 BP. To ease interpretation, scores were reversed such that, higher scores correspond to higher pain. Apart from SF-36 BP, a visual analogue scale (VAS)(30, 31)

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measure ranging from 0 (no pain) to 100 (worst imaginable pain), measuring joint pain intensity when mobilized (joint mobilisation pain) and when at rest (resting joint pain) for ESPOIR, and a numerical rating scale (NRS)(31) ranging from 0 (no pain) to 10 (worst imaginable pain) measuring back pain intensity during day (back pain) and at night (night pain) for DESIR were also considered. NRS scores were multiplied by ten to assure uniformity in the range of pain measures (0 – 100) across the different scales. Pain variables were assessed at each clinical visit.

Sociodemographic 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, marital, and professional status recorded at inclusion. Highest attained education was categorised as low education (less than or equal to secondary level) and high education (more than secondary level). Marital status was grouped as couples (married or cohabiting) and single (unmarried, divorced and widowed). Professional status was classified as no job (those without job or retired), blue-collar (laborers, farmers or artisans), and white-collar (intermediate and executive professionals) workers.

Covariates

Disease-related factors included symptom duration and a distinct set of variables for each cohort. Variables for ESPOIR are: inflammatory marker (erythrocyte sedimentation rate (ESR) in mm/hr), clinical markers (tender, and swollen joint count based on 28 joints), imaging marker (presence of x-ray changes fulfilling American College of Rheumatology (ACR) 1987 criteria),(32) biological markers (rheumatoid factor, and anti-cyclic citrullinated peptide antibodies (ACPA) positivity). Variables for DESIR are: inflammatory marker (C-Reactive Protein (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 magnetic resonance imaging), and biological marker (human leukocyte antigen (HLA) B27 positivity). 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 non-steroidal anti-inflammatory drugs (NSAIDs), corticosteroids, DMARDS, and analgesics. Lifestyle factors included body mass index (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

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use history for lung, cardiovascular, fracture, depression (as a measure of psychological health), diabetes, cancer, and gastrointestinal diseases. Refer to supplement (supplementary data S3, available at *Rheumatology* online) for RDCI calculation. All covariates were assessed repeatedly at clinical visits and analysed as time-dependant variables whenever feasible.

Statistical Analysis

Descriptive statistics comparing population characteristics by tertiles of each pain score were done using Pearson's Chi square, 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 (t0) as timescale. Based on cubic spline regression, time, time^2, and time^3 (slope terms) were incorporated to model nonlinear 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 sociodemographic 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 sociodemographic factors were tested by examining if interaction of sociodemographic factors with slope terms ($p_{trajectory}$) improved model fit using the Wald test. Additionally, above analysis was repeated restricting the analytic sample to those fulfilling ACR 1987 criteria in ESPOIR cohort and American spondyloarthritis international society (ASAS) criteria in DESIR cohort as a part of sensitivity analysis. All analysis was done 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 figure S1, available at *Rheumatology* online). The retention rate 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 have at least 7 measures of all variables considered for analysis. **Table 1** shows 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

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assessing the role of disease-related factors (inflammatory and clinical markers) in the evolution of pain (SF-36 BP) among sociodemographic groups (sex, ethnicity, and education) were not significant ($P_{interaction}$>0.07).

Supplementary tables S1 (ESPOIR) and S4 (DESIR), available at *Rheumatology* online, compared baseline characteristics of participants by 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 count, BMI, and RDCI. In DESIR, across SF-36 BP tertiles an increasing percentage of non-Caucasians, low education, corticosteroid, and analgesic use and increasing CRP, peripheral arthritis, and enthesitis were seen. Results for joint mobilisation, and resting joint pain of ESPOIR (supplementary table S2 and S3) and back, and night pain of DESIR (supplementary table S5 and S6, all available at *Rheumatology* online) are provided in the supplement.

Results for rheumatoid arthritis (ESPOIR)

Univariate and all five multivariate models showing the association between covariates and pain variables namely, SF-36 BP, joint mobilisation, and resting joint pain, assessed at inclusion are provided in the supplement (supplementary table S7, S8, S9, available at *Rheumatology* online). **Figure 1** represents the 10-year evolution of SF-36 BP (supplementary figure S2 for joint mobilization pain and supplementary figure S3 for resting joint pain, available at *Rheumatology* online) by sociodemographic groups in the fully adjusted model. Correspondingly, evolution of differences in pain score for each year of follow-up are shown in green in **Figure 2** and supplementary table S13, available at *Rheumatology* online (**Table 2** for joint mobilization and resting joint pain). Pain did not differ by sex at inclusion (p_{t0}≥0.38 for 3 pain scores). Though differential pain evolution by sex was not evident (p for interaction between sex and slope terms ($p_{trajectory}$≥0.05), from 2 up to 4 years after inclusion males had lower pain scores than females. Pain evolution differed across age; although youngest tertile had higher pain at inclusion (β=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 follow-up compared to oldest tertile. No ethnic differences in pain were observed at inclusion (p_{t0}≥0.11), but, compared to Caucasians, others ethnic group 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 β=3.8, p=0.007 for SF-36 BP, β=4.2, p=0.011 for joint mobilization pain, β=9.0, p<0.001 for resting joint pain) without evolutionary changes (ptrajectory≥0.074). Profession-related differences in pain evolution were not

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consistent; compared with white-collar workers those with no job had higher resting joint pain at inclusion (β=4.5 for no job and β=- 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 spondyloarthritis (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 table S10, S11, S12, available at *Rheumatology* online). **Figure 3** represents the 6-year evolution of SF-36 BP (supplementary figure S4 for back pain and supplementary figure S5 for night pain, available at *Rheumatology* online) by sociodemographic groups in the fully adjusted model. Correspondingly, evolution of differences in pain score for each year over follow-up are shown in **red in Figure 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 was not significant (p_{t0}≥0.09 and $p_{trajectory}$≥0.32); though from 1 up to at least 4 years of follow-up, males had more decrease in pain scores than females. Youngest tertile experienced a larger decrease in pain over follow-up than oldest tertile ($p_{trajectory}$=0.048 for SF-36 BP, $p_{trajectory}$=0.015 for back pain). Compared to Caucasians, other ethnic group had higher pain scores at inclusion (β=5.6, p=0.021 for SF-36 BP) that persisted without evolutionary changes ($P_{trajectory}$≥0.29) except for back pain ($P_{trajectory}$=0.009). Higher pain since inclusion persisted constantly through follow-up in those with low education (β=6.0, p<0.001 for SF-36 BP, β=6.3, p=0.001 for back pain and β=8.0, p<0.001 for night pain at inclusion; all $p_{trajectory}$≥0.167) compared with highly educated. Compared to singles, couples had higher back (β=4.7, p=0.019) and night pain (β=7.1, p=0.001) at inclusion; nevertheless, they showed improvement in pain over follow-up ($p_{trajectory}$≤0.004 for both NRS). Despite non-significant pain evolution by professional categories (ptrajectory≥0.15), inconsistently, those with no job had higher back and night pain compared to white-collar workers.

Sensitivity analysis

Supplementary figure S6 and S7, available at *Rheumatology* online, show the 10- and 6-year evolution of SF-36 bodily pain score by sociodemographic groups in the fully adjusted model respectively for those fulfilling ACR 1987 criteria in ESPOIR cohort (N=686) and ASAS criteria in DESIR cohort (N=470). Supplementary figure S8, available at *Rheumatology* online, correspondingly shows the evolution of differences in pain score in both cohorts. The pattern of evolution of all pain scores by sociodemographic

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factors were in concordance with 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 on early RA (ESPOIR) and early SPA (DESIR) with repeatedly assessed pain over respectively 10 and 6 years presented three salient findings. Firstly, sociodemographic disparities based on sex, age, ethnicity and education were important contributors of pain in early (disease duration ≤6 months for RA and ≤3 years for SpA) or long-standing IRDs. Of which ethnic, and educational disparities had 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) Secondly, differences in pain evolution as a function of demographic factors emerged while transitioning from early to long-standing disease; those older at early disease phase, females, and non-Caucasians—having similar pain levels as their counterparts at early phases of disease—reported higher pain during disease course. Thirdly, impact of social factors on pain is much earlier to disease-phase transitioning. Educational disparities did not catalyst changes of pain through disease course; higher pain in those with low education was present since early phases of disease. Associations between marital, and professional status and pain were not consistent.

Present study, compared pain among sociodemographic groups at inclusion when participants were biological DMARDs naïve and through the disease course, after accounting for disease-specific, treatment, lifestyle and health characteristics. Importantly, availability of repeatedly assessed data since early disease up to a span of ten and six years respectively for RA and SpA, allowed to account for time-varying nature of pain and other covariates, thus, giving an insight into the variations in the association between sociodemographic factors and pain in both early and long-standing disease. As far as we know, this is the first study that examined pain evolution in IRDs among socio-economically disparate groups. By considering evolution of three pain scores for each disease, an overall view limiting biases related to pain assessment instruments were obtained. Sensitivity analysis done by restricting to those who 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. Underpinning past findings,(15, 38) women of this study (SpA) reported higher crude pain scores compared with men (supplementary table S10 – S12, available at *Rheumatology*

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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 was reported in early IRD studies,(18, 26) whilst, improvement in pain was better among men in long-standing IRDs.(15, 25)

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, lifestyle factors, and comorbidities (supplementary table S7 – S9, available at *Rheumatology* online). In long-standing disease, our study findings were congruent to that of past(13, 14)—increased pain with ageing. With disease continuum and appropriate treatment initiation, younger persons experienced decreasing pain than those older, 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 except joint mobilisation pain were higher among other ethnic groups. Predominantly, disease-specific inflammation-mediated heightened pain sensitivity of affected joints mediated joint mobilisation pain than the more general non-inflammatory central pain mechanisms(40), and thus, did not differ across ethnic groups. Factors yet unravelled, may increase susceptibility of ethnic minorities to non-inflammatory central pain mechanisms.

Across the spectrum of IRDs, low levels of socioeconomic indicators like education, occupation, income or homeownership were often associated with increased pain.(20) In this study, education-based pain differences were present even at early disease phase and persisted throughout. Confirmingly, antecedent studies 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 antecedent studies.(43) Discrepancies might have risen due to differences in the classification of professional categories, and use of socio-economic indicators between studies. Family resources like income and house ownership predicted pain better than occupational status.(21) (44)

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Social environment both quantitatively in terms of extent of social network and qualitatively in terms of the emotional and necessary support from entourage(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.

Complexly interacting multiple mechanisms underlie the sociodemographic differences in pain. Firstly, biological mechanisms can result in altered pain sensitivity and pain modulation; hormonal differences between sex,(46) and various ethnic origins,(47) age-related degenerative changes of nervous system,(48) and associated comorbidities(48) can contribute to neuro-biological alterations affecting pain perception. Secondly, psychological mechanisms by affecting mood, anxiety and depression, comprehension, acceptance and adherence to health-promoting behaviours, and the utilisation of coping strategies can influence pain responsivity.(46, 47, 49) Women,(46) ethnic minorities,(47) those at socioeconomic disadvantage(50) and with poor marital quality(49) often rely on passive coping strategies and indulge in maladaptive pain behaviour and pain catastrophising.(8, 9) Thirdly, socio-cultural mechanisms such as pain, religion-, and health-related beliefs (46, 47) and sex, age, and ethnic differences in the societal expected role 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 their past pain experiences. However, pain levels reported over short time spans are more reliable with regards to the accuracy of reporting rather than compared to pain reported over 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 at random. Overall, this could be assumed as a good representation of pain of these participants over the years. Pain coping strategies and behaviours, quality and quantity of social support that can influence pain outcomes were unavailable. Non-pharmacological pain interventions were not assessed. Due to lack of details regarding monetary resources per person, impact of socioeconomic disadvantage on pain evolution is insufficiently explored. Finally, comorbidities and medication use were self-reported and are subject to recall bias.

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

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Authors' contributions: SK, CR, AD & AM developed the hypothesis and study design. SK & AD performed statistical analysis. SK & AD wrote the first and successive drafts of the manuscript. All authors contributed to review of manuscript and approved the final version to be published. SK, AD, AM had full access to the data and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Table 1. Baseline characteristics of rheumatoid arthritis (ESPOIR) and spondyloarthritis (DESIR) cohorts

Variables	Rheumatoid arthritis (ESPOIR, N=794)	Spondyloarthritis (DESIR, N=642)
Sociodemographic factors		
Male, n (%)	184 (23.2)	290 (45.2)
Age, m (SD)	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 y, m (SD)	0.6 (0.7)	1.5 (0.9)
Inflammatory markers		
Erythrocyte sedimentation rate, m (SD)	29.4 (24.7)	
C-reactive protein, m (SD)		7.5 (13.0)
Clinical markers		
Tender joint count (0-28), m(SD)	8.4 (7.0)	
Swollen joint count (0-28), m(SD)	7.2 (5.4)	
Arthritis index (0-159), m (SD)		4.2 (8.2)
Synovitis index (0-28), m (SD)		0.1 (0.8)
Enthesitis index (0-39), m (SD)		4.2 (5.8)
Imaging markers, n (%)		
Radiographic changes as per ACR criteria	108 (13.6)	
Sacroiliitis features in MRI		218 (34.0)
Biological markers		
RF positivity, n (%)	334 (42.1)	
ACPA positivity, n (%)	306 (38.5)	
HLA B27positivity, n (%)		380 (59.2)
Treament		
Non steroidal anti-inflammatory agents, n (%)	722 (90.9)	597 (93.0)
Corticosteroids, n (%)	156 (19.7)	116 (18.1)
Disease modifying anti rheumatic agents, n (%)	55 (6.9)	87 (13.6)
Analgesics, n (%)	538 (67.8)	406 (63.2)
Lifestyle Factors		
BMI in Kg/m^2, m (SD)	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 (SD)	1.1 (1.3)	0.4 (0.7)
Pain Measures		
SF-36 Bodily Pain Scale (0-100), m (SD)	62.2 (20.4)	56.7 (22.0)
Joint mobilisation pain[1] (0-100), m (SD)	54.9 (25.8)	
Resting joint pain[1] (0-100), m (SD)	37.0 (27.5)	
Back pain[2] (0-100), m (SD)		49.8 (27.1)
Night pain[2] (0-100), m (SD)		46.8 (30.3)

ACR, American college of rheumatology; MRI, magnetic resonance imaging; RF, rheumatoid factor; ACPA, anti-cyclic citrullinated peptide antibody; HLA, human leukocyte antigen; BMI, body mass index; SF-36, short form-36

1 Joint mobilisation and resting joint pain are measured using visual analogue scale in ESPOIR cohort

2 Back and night pain are measured using numerical rating scale in DESIR cohort

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Only characteristics of participants with measures for all variables at baseline are described. 16 out of 810 ESPOIR analytic sample and 37 out of 679 DESIR analytic sample had one or more missing variables at baseline

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Table 2. Differences in visual analogue scale pain scores by sociodemographic factors over follow-up in rheumatoid arthritis

	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)	B	(95% CI)	β	(95% CI)	β	(95% CI)	β	(95% CI)	β	(95% CI)	β	(95% CI)
Joint mobilisation 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*	

CI, confidence interval. In rheumatoid arthritis/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 sociodemographic factor and slope terms using Wald test).

Analysis adjusted for sociodemographic factors (sex, age, ethnicity, education, professional and marital status assessed at inclusion) and their interaction with slope terms (time, time², and time3), and time-dependant disease-related, treatment, lifestyle, and health factors

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Table 3. Differences in numerical rating scale pain scores by sociodemographic factors over follow-up in spondyloarthritis

	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)	B	(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***	

CI, confidence interval.

In spondyloarthritis/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 sociodemographic factor and slope terms using Wald test).

Analysis adjusted for sociodemographic factors (sex, age, ethnicity, education, professional and marital status assessed at inclusion) and their interaction with slope terms (time, time², and time3), and time-dependant disease-related, treatment, lifestyle, and health factors.

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Figure 1. Evolution of SF-36 bodily pain by sociodemographic sub-groups from inclusion up to 10 years in rheumatoid arthritis (ESPOIR cohort).

* P for difference in pain trajectories/evolution (drawn from testing the interactions between sociodemographic factor and slope terms using Wald test). Analysis adjusted for sociodemographic factors (sex, age, ethnicity, education, professional and marital status assessed at inclusion) and their interaction with slope terms (time, time², and time3), and disease-related (symptom duration, erythrocyte sedimentation rate, tender and swollen joint count, presence of radiographic structural lesions, rheumatoid factor positivity, anti-cyclic citrullinated peptide antibody positivity), treatment (anti-inflammatory and analgesic agents), lifestyle-related (body mass index, 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 and anti-cyclic citrullinated antibody 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 sociodemographic sub-groups contributing at least once to the analysis by every 2 years from year 0 to 10. Estimates came from Margins command in STATA.

Figure 2. Evolution of differences in SF-36 bodily pain by sociodemographic sub-groups in rheumatoid arthritis and spondyloarthritis. Analysis adjusted for sociodemographic factors (sex, age, ethnicity, education, professional and marital status assessed at inclusion) and their interaction with slope terms (time, time², and time3), and disease-related, treatment, lifestyle-related, and health factors. The green line represents the ESPOIR cohort and the red line the DESIR cohort.

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Figure 3. Evolution of SF-36 bodily pain by sociodemographic sub-groups from inclusion up to 6 years in spondyloarthritis (DESIR cohort).

* P for difference in pain trajectories/evolution (drawn from testing the interactions between sociodemographic factor and slope terms using Wald test). Analysis adjusted for sociodemographic factors (sex, age, ethnicity, education, professional and marital status assessed at inclusion) and their interaction with slope terms (time, time², and time3), and disease-related (symptom duration, C-reactive protein, arthritis, synovitis, and enthesitis indices, presence of sacroilitis, human leukocyte antigen B27 positivity), treatment (anti-inflammatory and analgesic agents), lifestyle-related (body mass index, 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 sacroilitis 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 sociodemographic sub-groups contributing at least once to the analysis by every year from year 0 to 6. Estimates came from Margins command in STATA.

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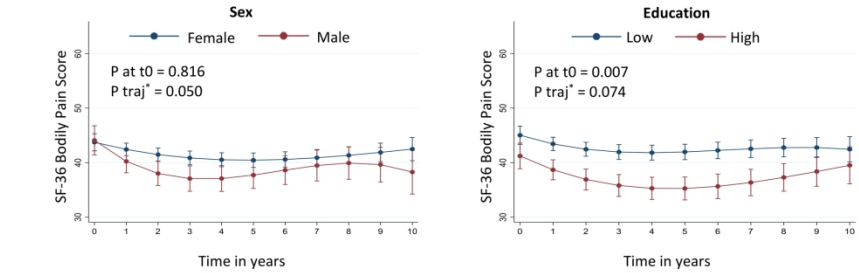
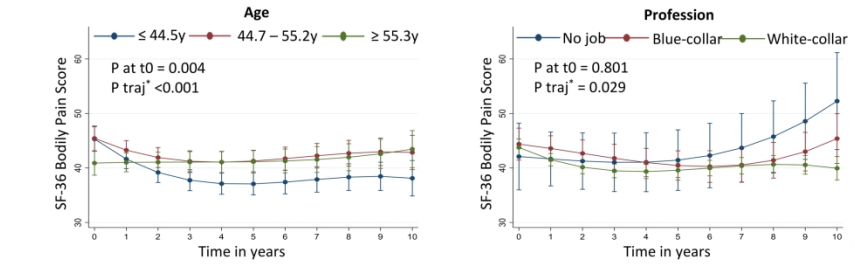


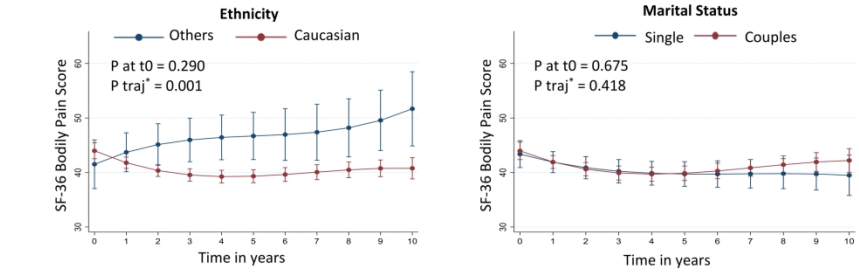
Years	0-2	2-4	4-6	6-8	8-10
Females	622	505	447	421	388
Males	188	154	137	117	109

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 y	289	229	187	169	164
44 – 55 y	253	212	203	189	173
>55 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

189x261mm (300 x 300 DPI)

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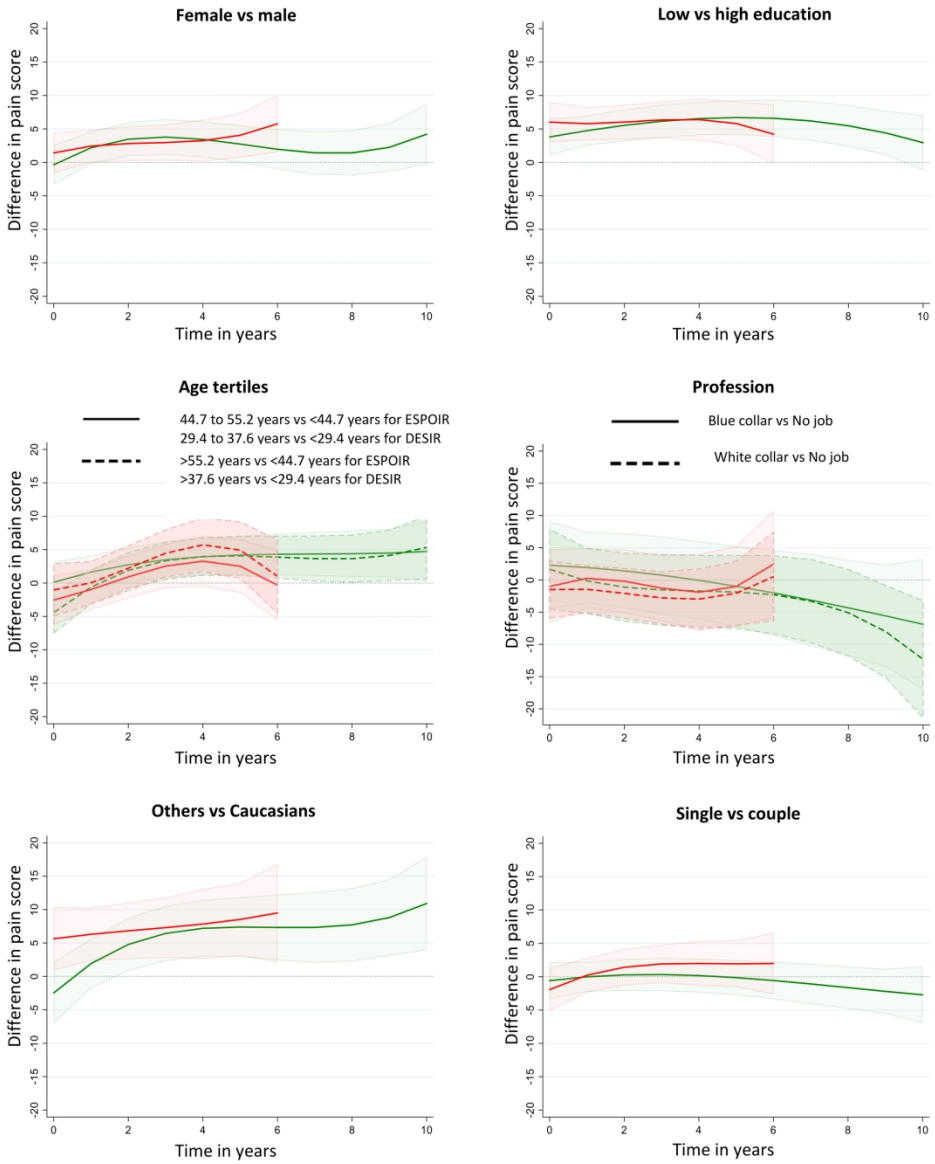

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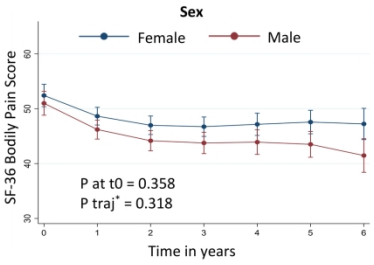
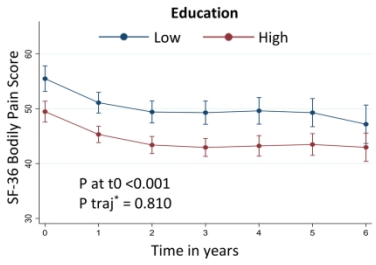
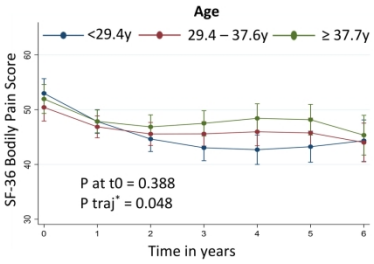


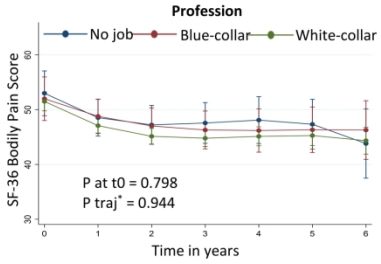
Years	0-1	1-2	2-3	3-4	4-5	5-6
Females	365	314	224	200	200	193
Males	311	265	207	179	164	164



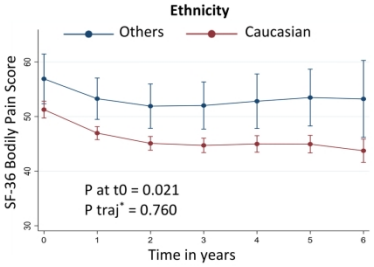
Years	0-1	1-2	2-3	3-4	4-5	5-6
Low	270	218	159	144	139	126
High	406	361	272	235	225	231



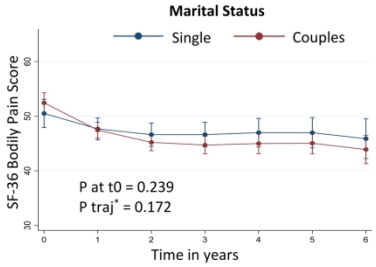
Years	0-1	1-2	2-3	3-4	4-5	5-6
≤29 y	234	194	144	133	122	116
29 – 37 y	226	193	143	123	114	119
>37 y	216	192	144	123	128	122



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

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