Discrete trajectories of resolving and persistent pain in people with rheumatoid arthritis despite undergoing treatment for inflammation: Results from three UK cohorts

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- Pain progression is heterogeneous in people with rheumatoid arthritis
- Persistent pain is predicted by high disability
- Even when inflammation resolves, the commonest trajectory is Persistent Pain
- Additional pain management might help people with rheumatoid arthritis

Discrete trajectories of resolving and persistent pain in people with rheumatoid arthritis despite undergoing treatment for inflammation: Results from three UK cohorts.

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Abbreviations: SF36-Short Form-36 questionnaire, RA – rheumatoid arthritis, HAQ – health assessment questionnaire, BSRBR – British Society for Rheumatology Biologics Register, ERAN-Early Rheumatoid Arthritis Network, BMI-body mass index, RF-rheumatoid factor, ESR-erythrocyte sedimentation rate, TJC-tender joint count, SJC-swollen joint count, VAS-visual analogue scale, DAS28-28 joint disease activity score, GMM – Growth Mixture Modelling, AIC – Akaike Information Criteria, BIC – Bayesian Information Criteria, ssBIC-sample-size adjusted BIC LMR-LRT -Lo-Mendell-Rubin likelihood ratio test , BLRT- bootstrap likelihood ratio test. VAS-GH-visual analogue scale-general health, DMARD-disease-modifying anti-rheumatic drug, SD-standard deviation, CI-confidence interval, ACR-American College of Rheumatology.

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Abstract

Rheumatoid arthritis (RA) is an example of human chronic inflammatory pain. Modern treatments suppress inflammation, yet pain remains a major problem for many people with RA. We hypothesised that discrete RA subgroups might display favourable or unfavourable pain trajectories when receiving treatment, and that baseline characteristics will predict trajectory allocation.

Growth Mixture Modelling was used to identify discrete trajectories of SF36-Bodily Pain scores during 3 years in 3 RA cohorts (Early RA Network (ERAN); n=683, British Society for Rheumatology Biologics Register Biologics (n=7090) and Non-Biologics (n=1720) cohorts. Logistic regression compared baseline predictor variables between trajectories. The role of inflammation was examined in a subgroup analysis of people with normal levels of inflammatory markers after 3 years.

Mean SF36-Bodily Pain scores in each cohort improved but remained throughout 3y follow up >1 SD worse than the UK general population average. Discrete Persistent Pain (59% to 79% of cohort participants) and Resolving Pain (19% to 27%) trajectories were identified in each cohort. In ERAN, a third trajectory displaying persistently Low Pain (23%) was also identified. In people with normal levels of inflammatory markers after 3 years, 65% of them were found to follow a Persistent Pain trajectory. When trajectories were compared, greater disability (aORs 2.3-2.5 per unit baseline Health Assessment Questionnaire score) and smoking history (aORs 1.6-1.8) were risk factors for Persistent Pain trajectories in each cohort.

In conclusion, distinct trajectories indicate patient subgroups with very different pain prognosis during RA treatment. Inflammation does not fully explain the pain trajectories, and non-inflammatory factors as well as acute phase response predict which trajectory an individual will follow. Targeted treatments additional to those which suppress inflammation might reduce the long term burden of arthritis pain.

Perspective

Immunosuppression reduces inflammation in RA, but pain outcomes are less favourable. Discrete Persistent and Resolving Pain trajectories were identified following treatment, both in early and established RA. Smoking and higher disability at baseline predicted persistent pain. Identifying patient subgroups with poor pain prognosis could enable adjunctive treatment to improve outcome.

Introduction

Arthritis is a common cause of chronic musculoskeletal pain and disability; especially across ageing populations. Arthritis has traditionally been classified as either inflammatory (e.g. rheumatoid arthritis; RA) or non-inflammatory (e.g. osteoarthritis; OA, the commonest reason for joint replacement surgery). RA is a systemic, autoimmune condition with a predilection for synovial joints of the hands and feet. Synovitis (inflammation of the joint lining) contributes to pain, and also leads to joint damage. Important contributions of inflammation to OA pain are now well recognised [33], although RA remains the prototypical form of inflammatory arthritis. Pain is cited by patients as the most important symptom of RA. Early intensive immunosuppressive treatment in people with RA aims to prevent long term pain and disability [34]. Disease modifying anti-rheumatic drugs (DMARDs) and glucocorticoids can reduce inflammation for many people with RA, and can also reduce pain. Those who do not respond adequately to conventional synthetic (cs)DMARDs might yet benefit from biologic (b)DMARDs such as tumour necrosis factor (TNF)α inhibitors.

While clinical experience confirms that many people benefit greatly from current treatments [34], chronic pain remains the most difficult problem for many people with RA [30]. At a population level, average pain incompletely improves after DMARDs are commenced or changed [1, 30], and mean pain scores for RA populations remain worse than UK population mean values even 12 months after baseline [30, 31]. Pain can remain problematic even when inflammatory disease is in remission [26], suggesting important pain mechanisms additional to ongoing inflammation. Central sensitisation might contribute to RA pain [22, 51], whereas joint damage might now be less important following introduction of effective DMARDs [7]. Subgroups of people with RA have been identified for whom non-inflammatory mechanisms might contribute to ongoing pain and high clinical scores for disease activity [28, 51], and interest exists about whether they represent distinct phenotypes of RA.

Reporting of mean effects might conceal subgroups of people with quite different outcomes, as people with RA display heterogeneous prognosis and response to treatment. One year after commencing bDMARDs, more than 50% of people with RA reported pain at problematic levels [30]. Other studies have reported heterogeneity between individuals in the progression of other aspects of RA, such as trajectories of disease activity, functional limitations, fatigue and mental distress [11, 12, 36, 37, 45]. Previous study of disease trajectories has focused on single study groups. However, pain trajectories might either be generic or specific to particular patient or treatment groups [20]. Comparing different patient groups allows us to identify generic factors that might be amenable to interventions aiming to improve patient outcomes.

We hypothesised that patient subgroups exist that display different pain trajectories, and that these trajectories are shared across people with early or established RA receiving csDMARDs or bDMARDs. The aim of this study was to identify discrete pain trajectories in people with RA and then to examine factors that might explain which trajectory individuals will follow. We analysed data from 3 well-described hospital-based cohorts, which varied in disease duration and treatment regimens. The Early RA Network (ERAN) is an inception cohort which recruited people at physician diagnosis of RA. The 2 British Society for Rheumatology Biologics Registry (BSRBR) cohorts studied here recruited participants with established and active RA either on commencing TNFα inhibitors (BSRBR Biologics cohort) or not initiating bDMARD treatment (BSRBR Non-Biologics cohort). We explore whether sub-groups with different disease progression vary as a function of treatment (BSRBR Biologics cohort vs BSRBR Non-Biologics cohort) or disease stage (BSRBR cohorts vs ERAN). In order to explore whether factors other than inflammation might determine pain progression we also examined pain trajectories in the sub-group of participants with normalisation of acute phase response and swollen joint count.

Methods

Patients and Recruitment

The Early Rheumatoid Arthritis Network (ERAN) inception cohort collected data from outpatient clinics in the UK and Eire [16, 24]. Patients were recruited when they were diagnosed with RA by a consultant rheumatologist. The British Society for Rheumatology Biologic Register (BSRBR) cohorts collected data from outpatient clinics in the UK [46]. The BSRBR-Biologics cohort recruited people who were starting biologics as part of their routine care, having failed to respond adequately to other DMARDs. The BSRBR-Non-Biologics cohort recruited people with RA who were using non-biologic DMARDs. Both BSRBR cohorts were observational studies of people predominantly with active RA [18]. Data used for this study were provided for baseline, and up to 3 years follow up, between 2002 and 2013. The data from BSRBR were collected, stored and managed at the University of Manchester, UK.

UK National Health Service ethical approvals were in place for ERAN (Trent Research Ethics Committee reference 01/4/047) and the 2 BSRBR cohorts (North West Multicentre Research Ethics Committee reference 00/8/53). All participants gave signed informed consent in line with the Declaration of Helsinki.

Patients and Data

Data collection for all cohorts was from multiple centres and included physical examinations, interviews and reference to medical notes. Data collected that were common to all 3 cohorts included age, sex, smoking, 28-joint disease activity score (DAS28 [48], which is a composite score derived from erythrocyte sedimentation rate (ESR) in mm per hour, 100mm visual analogue scale-general health (VAS-GH), tender joint count for 28 joints (TJC) and swollen joint count for the same 28 joints (SJC)), body mass index (BMI), serology (seropositive [25] was defined as testing positive for either Rheumatoid Factor (RF) or citrullinated proteins according to each study centre's normal ranges), 1987 American College of Rheumatology (ACR) diagnostic criteria (5/7 clinical features) [3], health assessment questionnaire (HAQ) for disability [6], and Short Form-36 (SF36) [50]. SF-36 subscale data were used to estimate pain (Bodily Pain), disability (Physical Function), fatigue (Vitality) and psychological health (Mental Health). SF-36-Bodily Pain assesses the severity of pain and its impact upon daily activities [50]. Pain data from people providing baseline and at least 50% of follow up data points were included in analyses. SF-36 data were norm transformed to the expected UK population estimates following standard methodology [21, 50]. Briefly, this z-transformation normalises the SF36 data from this study to the measured mean of 50 and standard deviation (sd) of 10 from the UK population, taking age and gender structure into account. Therefore a normed SF36 score of 50 is the expected average for the UK general population. In the BSRBR-Non-Biologics cohort, the DAS28 components were only available at baseline. Co-morbidities were classified as present or absent. Further to the data collected, rearrangements were derived of the DAS28 formula, designed to act as surrogate indices of central sensitisation and/or non-inflammatory pain; DAS28-P (the proportion of DAS28 derived from patient-reported variables, TJC and VAS-GH)[22, 31] and Tender-Swollen Difference (TSD; TJC minus SJC)[40].

Statistical Analysis

Trajectories of pain

The norm-transformed SF36-Bodily Pain data were examined for trajectories of progression from baseline to 3 years. Each cohort was examined separately using the descriptive technique of linear growth mixture modelling (GMM) to allow the separation of latent subgroups of people based upon similarities between their pain trajectories. GMM is related to structural equation modelling, and will statistically select groups of people with similar trajectories. We performed GMM to produce models with increasing numbers of trajectories, starting with 1 trajectory, and then examined model selection criteria to inform the optimal model choice and the addition of another trajectory (see below). Additional trajectories were selected until the criteria suggested that no more should be selected, and there was no predetermined numbers of trajectories for each cohort.

Model selection criteria

The Akaike Information Criteria (AIC), Bayesian Information Criteria (BIC), sample-size adjusted BIC (ssBIC) were used to estimate the amount of information lost within models, and higher values indicated worse performance. Entropy described the overall probability of the cases being assigned to the correct trajectory. The Lo-Mendell-Rubin likelihood ratio test (LMR-LRT) and bootstrap likelihood ratio test (BLRT) were significance tests comparing the fit for the model with k trajectories to the model with k-1 trajectories (statistical significance indicated an improved fit compared to the k-1 model). Trajectory membership numbers consisting of <5% of the sample were automatically rejected. Trajectories were named to describe their pain prognosis. The findings were confirmed by repeating the analyses of optimal trajectories while accounting for the distribution and frequency of missing data by using pattern mixture analysis [27, 32]. This adjusted for missing data by examining pain at timepoint *t* and its association with missing pain data at timepoint *t+1.*

Analysis of inflammation and pain

Additional analysis was performed to assess the pain trajectories in participants with very low inflammation at follow up. These people were selected if they had both a 0/28 swollen joint count and ESR reading of ≤22 (men) or ≤29 (women) at the 3 year study visit. The GMM and pattern mixture models for pain trajectories were also performed in this subgroup of the BSRBR-Biologics cohort.

Comparisons across trajectories

Baseline differences between people allocated to each trajectory were examined using ANOVAs with a Bonferroni correction and Pearson Chi-square. Multinomial or binary logistic regression was performed to find variables that predicted membership of pain trajectories. The conditional probabilities of trajectory membership were used to derive probability weights, which were used to confirm that the logistic regression analyses were not unduly influenced by cases where trajectory was less certain.

Progression of important clinical measures

The mean longitudinal progression of DAS28 (the disease activity index and its composite variables) and HAQ-disability were plotted for the membership of each pain trajectory.

Software

GMM, pattern mixture models were performed using Mplus (Muthen and Muthen, Los Angeles, USA) and all other statistics and data management was performed using SPSS v22 (IBM, Chicago, USA).

Results

Study demographics

Baseline demographics were similar between the 3 cohorts, except that ERAN participants had shorter symptom duration and were more likely to smoke, and the BSRBR-Biologics participants had overall more severe disease activity and disability (Table 1). Mean SF36-Bodily Pain scores improved between baseline and first follow up ($p<0.001$ for each cohort), but remained throughout the 3 year follow up >1 SD (10 points) worse than values normalised to the expected UK population average (Figure 1a).

Description of trajectories

The trajectory modelling process is summarised in Table 2. For ERAN, a 3 trajectory model was optimal, by reference to the AIC, BIC, ssBIC, LMR-LRT and BLRT. In the BSRBR-Biologics and Non-Biologics cohorts, 2 trajectory models were selected. Three trajectory models were rejected for the BSRBR cohorts due to the small membership numbers (<4% of participants) in one trajectory within each 3 trajectory model (Table 2). The mean SF36-Bodily Pain scores over time for each trajectory are shown in Figure 1b-d. The GMMs provided probabilities for each person of being allocated to the correct trajectory. These are the entropy scores (Table 2).

In ERAN, the most populous of the 3 trajectories (59% of participants) showed a consistently high mean pain level across the 3 years (Persistent Pain trajectory). A second trajectory (23%) showed a consistently low mean pain level across the 3 years, approximating closely to the expected UK population average for Bodily Pain scores of 50 (Low Pain trajectory). The third trajectory (19%) showed an initially high mean pain level at baseline that improved approaching the expected UK population average across the three years (Resolving Pain trajectory; Figure 1b).

In the BSRBR-Biologics cohort, each of the 2 trajectories showed improvement from baseline to 6 months (Figure 1c). In the most populous trajectory (79% of participants), mean Bodily Pain scores remained worse, by a clinically important extent, than expected UK population means during the 3 year follow up (Persistent Pain trajectory). In the second trajectory (21%), Bodily Pain scores improved to approach the expected UK population mean (Resolving Pain trajectory).

In the BSRBR-Non-Biologics cohort, 2 trajectories were again identified (Figure 1d). The most populous trajectory (73% of participants) showed persistent high mean pain levels (Persistent Pain trajectory), whereas in the other trajectory (27%) Bodily Pain scores improved to approach the expected UK population mean (Resolving Pain trajectory).

Pain trajectories in people attaining very low inflammation

Analysis was performed in the subgroup of people from the BSRBR-Biologics cohort with very low inflammation at the 3 year study visit (SJC = 0/28 and ESR ≤22 in men and ≤29 in women; n=1199, with n=570 giving complete SF36-Bodily Pain across all time points). This was performed to investigate whether those people with inflammation that returned to normal levels formed a single (Resolving Pain) trajectory. As in the host cohorts, in this subgroup the 2 trajectories of Persistent Pain (n=777, 65%) and Resolving Pain (n=422, 35%) were also found (see Figure 2).

Baseline characteristics compared between people in discrete trajectories

Baseline demographics, clinical measures and self-reported questionnaire scores were compared between trajectories. In univariate analyses (Table 3), baseline variables that were heterogeneous between different trajectories within each of the 3 cohorts were BMI, DAS28, Tender Joint Count, Tender-Swollen Difference, DAS28-P, HAQ disability scores, co-morbidities, SF36-Physical Function, -Vitality and -Mental Health scores, and smoking status. In ERAN, additional pairwise analyses were performed examining the differences at baseline between the Persistent Pain and the Resolving Pain trajectories. Mean baseline DAS28 was similar between these 2 trajectories, but the Persistent Pain trajectory had significantly higher baseline BMI (p=0.019), Tender-Swollen Difference (p<0.001), DAS28-P (p=0.001), HAQ disability scores (p=0.008), more comorbidities (p=0.012), less Vitality (p=0.023), and fewer people that had never smoked (p=0.042) (Table 3). Baseline SF36-Bodily Pain scores were similar between Persistent and Resolving Pain trajectories in ERAN.

Variables associated with heterogeneity were examined as independent predictors of allocation to each trajectory, and adjusted odds ratios were generated using multinomial and binary logistic regression (Table 4). The baseline variables that showed significant independent associations with Persistent rather than Resolving Pain trajectories in all cohorts were higher HAQ disability score and smoking (either current or ex-smokers; Table 4). In ERAN, baseline variables showing significant and independent associations with Low rather than Persistent Pain trajectory were lower Bodily Pain, lower HAQ disability and never smoking (Table 4). The significant findings from the logistic regression analyses in each of the 3 cohorts were retained when probability weightings were used to adjust for the likelihood of trajectory membership.

Secondary analyses of all cohorts (and all eligible cases) replaced DAS28 with either its 4 components or derived variables in order to explore possibly divergent associations of pain trajectory with baseline inflammatory or non-inflammatory factors contributing to disease activity scores. When all 4 DAS28 component variables were included in the model lower ESR was associated with the Resolving Pain trajectories in ERAN (aOR; 0.99, 95% CI 0.98 to 1.00) and in the BSRBR-Biologics (aOR: 1.00, 95% CI 0.99 to 1.00) cohorts, but not significantly so in the BSRBR-Non-Biologics cohort. Associations between other baseline DAS28 components or derived variables and pain trajectory did not replicate between cohorts.

Progression of other important outcomes

The longitudinal progression of other key clinical outcomes (DAS28 and HAQ disability) generally followed the progression observed in Bodily Pain scores in each pain trajectory in each cohort (Supplement Figure 1). People allocated to Persistent Pain trajectories displayed persistently high or increasing HAQ disability, and mean DAS28 scores that might initially improve, but remained higher than other trajectories in all cohorts. HAQ disability and DAS28 scores in the Resolving Pain trajectories converged with the low levels of disability and disease activity observed in ERAN throughout the Low Pain trajectory. Longitudinal progression of DAS28 components also followed pain progression in BSRBR cohort Pain trajectories (Supplement Figure 2). However, in ERAN, although VAS and Tender Joint Count remained increased in the Persistent Pain group, ESR and Swollen Joint Counts decreased by 3 years to levels that were similar in all 3 pain trajectory groups (Supplement Figure 2).

Discussion

RA is an example of chronic inflammatory pain. Mean Bodily Pain scores of people with RA improved during treatment of inflammation, but remained worse than the expected UK general population average throughout 3 years follow up. However, this average conceals discrete subgroups of patients who experience very different favourable or unfavourable pain progressions. Baseline inflammation predicted good poor pain trajectories, but suppression of inflammation did not invariably lead to a good pain prognosis. Non-inflammatory factors such as smoking status and disability predicted allocated to the Persistent Pain trajectory. Targeted treatments additional to those which suppress inflammation might improve prognosis in those otherwise destined to suffer chronic pain.

Pain prognosis in RA

Many people with RA do very well on modern DMARD therapies by many measures of success. However, we show that a substantial majority (65%) of people achieving low inflammatory disease suffers from persistent pain. We previously showed that people presenting with active RA continued to report worse pain scores than the population average one year later [30, 31], and now show that pain persists over a 3 year follow up. Improvements in mean Bodily Pain scores following the introduction of TNF-alpha blocking agents appear less than might be expected from improvements in inflammatory disease activity, as measured by DAS28. Seventeen percent of people might report DAS28 remission 12 months after bDMARD initiation [19], but we show that improvements occur in DAS28 during follow up even people with persistent pain.

Discrete pain trajectories in RA

We found that people with clinically-determined active RA can be stratified into discrete groups with good or poor pain prognosis. Although pain scores in one group decreased to the UK general population mean, a much larger group (up to 79% of cohort participants) continued to report persistent and substantial pain. The Persistent Pain trajectory was observed even in those whose inflammatory disease responded well to treatment. Thus, for this subgroup pain remains a consistent clinical problem despite effective treatment of inflammation.

Persisting and Resolving Pain trajectories were replicated across different cohorts, including patients with differing disease duration (early or established RA) or on different treatments (cDMARD or bDMARD). Discrete persistent and improving pain trajectories might also be observed in juvenile idiopathic arthritis [43], but have not previously been elucidated in adult RA. Discrete persistent and improving trajectories have been found in RA for disease activity scores [5, 10], psychological distress [37] or disability [36]. Persistently high psychological distress or high disability trajectories also displayed higher baseline pain scores, and less improvement in pain over 3 year follow up [36, 37]. However, our findings on RA pain differ in some important ways from these other patient outcomes. The Persistent Pain trajectories in our cohorts were more populous (59%-79%) than unfavourable trajectories for other outcomes of disease activity (2.6 to 10.7%), psychological distress (12%) [37] or disability (15 to 20%) [36]. We showed that many people with good suppression of disease activity have persistent pain, and these data indicate that many people with favourable trajectories of distress or disability also continue to experience pain.

Predictors of pain trajectory allocation and therapeutic implications

Persistent Pain trajectory allocation was associated with lower inflammatory (ESR) and worse non-inflammatory (disability, smoking) characteristics at baseline. Our observations that seropositivity was not significantly associated with pain trajectory, and that *lower* ESR at baseline predicted Persistent Pain trajectory allocation, contrasts with predictors of poor inflammatory disease prognosis. This might indicate a lesser contribution of DMARD-modifiable inflammation to persistent pain in our patient groups. Treatments that suppress inflammatory disease, both csDMARDs and bDMARDs as used by patients in these cohorts, might be most effective at reducing pain in those with objective evidence of inflammation, for example raised ESR. Persistent inflammation might be expected to lead to persistent pain, but our findings show that Persistent Pain trajectories can be identified in people with little evidence of persistent inflammation.

We found that greater disability and smoking status at baseline indicated patients destined to follow a Persistent Pain trajectory across the 3 cohorts. Disability and smoking predicted pain trajectory allocation independent on inflammation measures [38], and baseline disability and smoking similarly predicted pain prognosis in conditions not usually associated with joint inflammation [442].

Identifying people destined to have persistent pain might help target additional pain management strategies that might be employed in parallel to DMARD treatment. Such evidence-based treatments might include cognitive behavioural therapies [41], although integration of medical and psychological approaches can prove challenging.

Further research might also explore whether predictive factors (disability and smoking status) identified in the current study indicate non-inflammatory pain mechanisms that are amenable to specific interventions. Increasing physical activity can reduce musculoskeletal pain [13, 49]. Supervised exercise in RA can reduce both pain and disability [4], suggesting a direct link between maintaining activity and improved pain prognosis. Smoking might alter pain processing [42], inflammatory disease activity [8], or response to treatment. Possible effects of smoking cessation interventions on RA pain deserve further study.

Beyond baseline variables measured in the current study, other factors might be important in driving persistent pain in RA, including alterations in pain processing such as central sensitisation. Central sensitisation can also inflate DAS28 [22, 35, 39, 40, 47] and non-inflammatory mechanisms might explain our finding that DAS28 itself predicted pain prognosis during DMARD therapy less well than did the objective measure of inflammation, ESR. A high proportion of DAS28 derived from patient reported components (high DAS28-P) at baseline [22], or a higher Tender-Swollen Joint Count difference [40] in those allocated to the Persistent Pain trajectory might suggest greater central sensitisation [29]. Tender-Swollen Difference

predicted pain trajectory in people with early RA in the current study, but these derived measures did not significantly predict pain trajectory in established disease. Similarly, others have not found derived measures to predict other outcomes in established RA [9, 23]. Further research would be needed to determine whether improved measures of central sensitisation, for example using quantitative sensory testing, might predict pain prognosis better than DAS28 derived measures.

Study limitations

Our study is subject to a number of limitations. Each cohort was analysed separately and in parallel, and the baseline variables were not matched between cohorts. This limits comparisons between cohorts, but our consistent findings between cohorts suggest generalisability. Scales focussing on other aspects of pain, or with different sensitivities, might have produced different results to the SF36-Bodily Pain subscale. Different patient experiences after baseline assessment might alter psychological processes that moderate their interpretation and experience of pain [14, 15], in addition to any effects of inflammatory disease. Effects of psychosocial risk factors on the different pain trajectories in people with RA deserve further attention in order to identify modifiable risks that might be targets for specific intervention. It is possible that different pain trajectories would be detected in other treatment contexts, such as clinical trials or in people already undergoing stable treatment. Furthermore we would be optimistic that different treatment regimens might increase patient allocation to Resolving Pain trajectories, which only accounted for approximately one quarter of our study populations. The Low Pain trajectory identified in ERAN, characterised by low pain at baseline, was not replicated in the BSRBR cohorts. This is likely due to eligibility criteria for inclusion in BSRBR requiring high disease activity and recruitment taking place at a time when new medications were being prescribed. People commencing biologics in the UK usually have DAS28 > 5.1[34]) and are highly symptomatic. Conversely, ERAN participants were not recruited based upon any thresholds of disease activity measurements (beyond those required to achieve diagnosis). Another reason for this different trajectory in ERAN might be that pain in early RA might be more amenable to successful DMARD treatment. Current practice is guided by evidence that intensive early treatment of RA improves long term outcomes [17, 34].

Conclusions

Persistent pain remains a major clinical challenge in RA, despite modern treatment of inflammation. Our data indicate that discrete groups of people with RA are destined to experience persistent or resolving pain. Persistent Pain trajectories cannot be adequately explained by persistent inflammatory disease activity, and this might reflect life style factors

or central sensitization, both of which might be amenable to intervention. Inflammation might also contribute to pain in other forms of arthritis, including OA [33]. However, if suppressing inflammation alone does not prevent persistent pain in RA, then anti-inflammatory approaches are unlikely to provide a complete solution for chronic pain in these other conditions. Further work might investigate the aetiology of pain in joints with no evidence of inflammation. RA provides an important human model of pain in which inflammation and non-inflammatory factors interact. Identifying subgroups destined to display different pain trajectories should help improve clinical trial design, treatment allocation and, ultimately, pain outcomes for people with RA.

Declarations

Ethics approval and consent to participate:

UK National Health Service ethical approvals were in place for ERAN (Trent Research Ethics Committee reference 01/4/047) and the 2 BSRBR cohorts (North West Multicentre Research Ethics Committee reference 00/8/53). All participants gave signed informed consent in line with the Declaration of Helsinki.

Consent for publication:

No further consent for publication of materials were required.

Availability of data and material:

Data from BSRBR are available from Drs Alan Roach and Chris Hiley (British Society for Rheumatology, London). Data were prepared and provided by Prof Kimme Hyrich, Drs Kath Watson and Katie McGrother (University of Manchester).

The ERAN study database is currently held at the University Of Nottingham (please direct requests for data to DAW).

Competing interests:

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Author contributions:

Study design: DFM, DAW, EF, OD, PDK, AY

Data collection: DAW, PDK, AY

Analysis: OD, DFM, EF, DAW

Critical appraisal of analysis: DFM, DAW, EF, OD, PDK, AY

Writing and editing manuscript: DFM, DAW, EF, OD, PDK, AY

Approval of final version of manuscript: DFM, DAW, EF, OD, PDK, AY

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Table 1: Baseline demographics and clinical data of participants

Table 1: Sample sizes, means (standard deviations) and percentages are shown for baseline demographics. Complete cases; the subgroup of Data Set for whom SF36-Bodily Pain data are available for all time points. BMI= body mass index; DAS28= Disease Activity Score in 28 joints; HAQ=health assessment questionnaire for disability; CRP= C-reactive protein.

Table 2: Summary of the model selection process

Table 2: Indices and statistics for GMMs using complete cases are shown for models with different numbers of trajectories. ERAN=Early RA Network; BSRBR=British Society for Rheumatology Biologics Register; AIC= Akaike's information criterion; BIC= Bayesian information criterion; ssBIC= sample size-adjusted BIC; LRT= Lo-Mendell-Rubin likelihood ratio test p value; BLRT= Bootstrapped likelihood ratio test P value. The selected model for each cohort study is shown in **bold**.

Table 3: Comparison of baseline variables between trajectories

Table 3: Mean (standard deviation) or percentages are shown for each latent trajectory at baseline. P values for heterogeneity between trajectories are shown. In the ERAN data set, significance in pairwise comparisons between Persistent Pain and Resolving Pain trajectories are indicated (* $p<0.05$ with Bonferonni correction). Higher scores in the SF36 subscales reflect better quality of life. BMI= body mass index; DAS28= Disease Activity Score in 28 joints; VAS-GH=visual analogue scale; TJC= tender joint count; SJC= swollen joint count; HAQ=health assessment questionnaire for disability; ESR= erythrocyte sedimentation rate; CRP= C-reactive protein; Seropositive= positive for Rheumatoid factor or citrullinated proteins.

Table 4: Multinomial logistic regression for Persistent Pain trajectory in each cohort

Table 4: In ERAN the adjusted odds ratios (aOR) for Persistent Pain are displayed, compared to each of the other trajectories. Persistent Pain was used as the reference category, and the aOR and CI's were then inverted. Multinomial logistic regression was performed; and each aOR indicates the change in risk per unit increase (per year of age, unit of BMI, year of duration, unit of DAS28, unit of HAQ, per point of SF36 subscale). Higher scores in the SF36 subscales reflect better quality of life. Categorical variables aORs showed risks for comorbidities (Yes) and current smoker or ex-smoker compared to never smoked. Statistically significant findings are presented in **bold**.

Figure 1: Changes over time in reported bodily pain in RA cohorts

Figure 1.

A: Mean SF36-Bodily Pain normed values at each time point are given for (A) each cohort and at each time point from the trajectories yielded by the GMM analysis (B, C, D). B. ERAN cohort. “Low Pain” (23%), “Persistent Pain” (59%) and “Resolving Pain” (19%). C. BSRBR-Biologics cohort. “Persistent Pain” (78%) and “Resolving Pain” (22%). D. BSRBR-Non-Biologics cohort. “Persistent Pain” (78%) and “Resolving Pain” (22%). A normed SF36 Bodily Pain score of 50 represents the UK population mean. Higher scores in the SF36 subscales reflect better quality of life.

Figure 2: Trajectories of bodily pain in people with RA with low inflammation measures after 3 years of follow up

Figure 2

Mean values of SF36-Bodily Pain for each trajectory in our sensitivity analysis of people in the BSRBR Biologics cohort who showed a 0/28 swollen joint count and ESR reading of ≤22 (men) or ≤29 (women) at the 3 year study visit (n=1199, with n=570 providing complete pain data). The average pain score for the UK general population is shown as 50. Numbers were not sufficient for analysis in the ERAN cohort (n=180, with n=64 providing complete pain data). Follow up data for these variables were unavailable for BSRBR-Non-Biologics cohort. A normed SF36 Bodily Pain score of 50 represents the UK population mean. Higher scores in the SF36 subscales reflect better quality of life.

Figure 1: Changes over time in reported bodily pain in RA cohorts

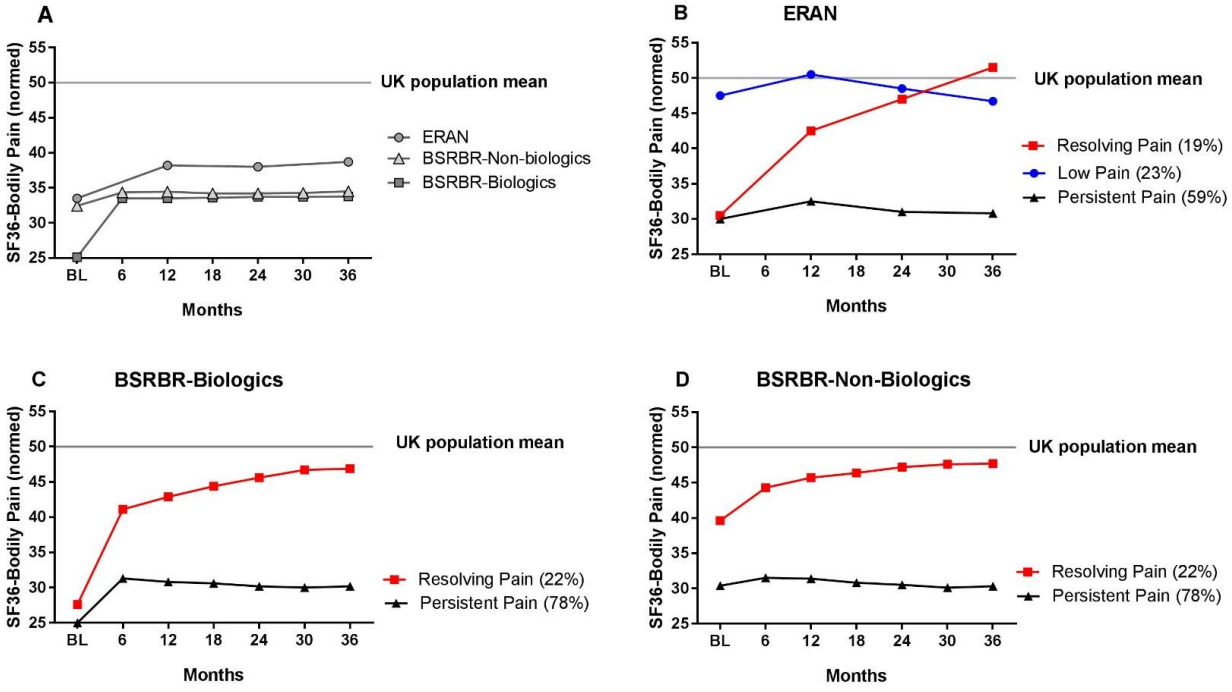

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Figure 2

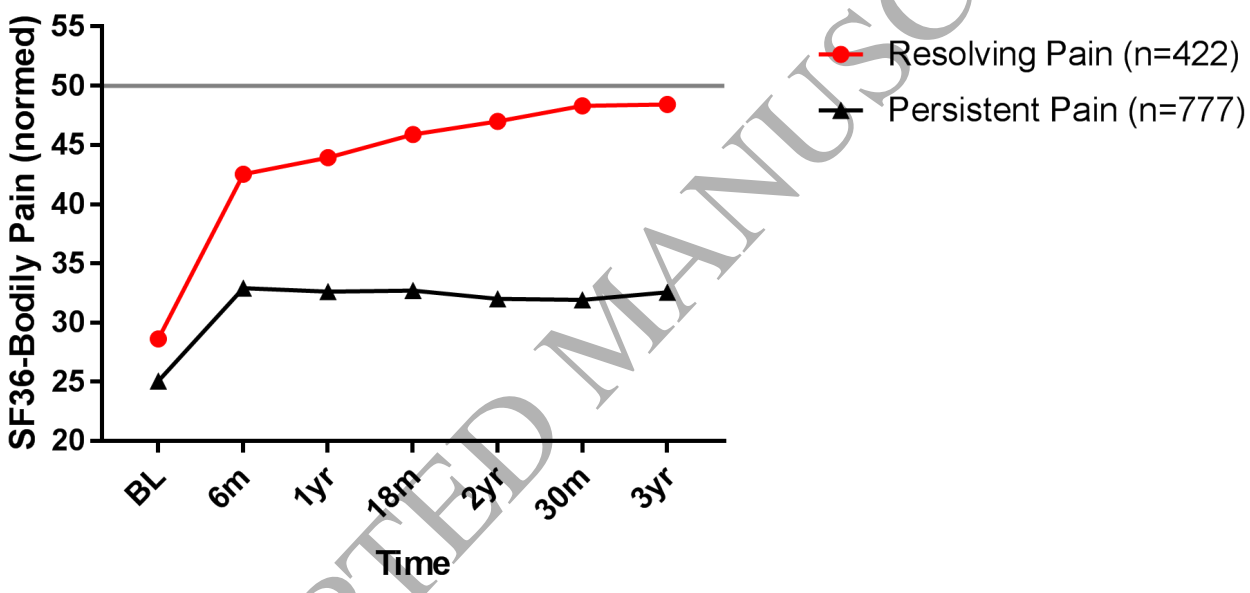

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Table 1: Baseline demographics and clinical data of participants

	ERAN		BSRBR-Biologics		BSRBR-Non-Biologics	
	All cases	Complete cases	All cases	Complete cases	All cases	Complete Cases
Sample size	683	264	7090	3138	1720	605
Age	57 (13)	56 (14)	57 (11)	57 (11)	61 (12)	62 (12)
Female %	66%	71%	77%	77%	75%	75%
BMI	28 (5)	28 (5)	27 (7)	27 (6)	27 (6)	26 (6)
Smoker %	35%	30%	19%	17%	19%	16%
Duration (years)	0.8 (1.3)	0.8 (1.4)	13 (10)	13 (10)	10 (11)	11 (11)

Disability (HAQ)	1.1 (0.8)	1.0 (0.7)	2.0 (0.6)	2.0 (0.6)	1.4 (0.8)	1.3 (0.8)
DAS28	4.6 (1.6)	4.7 (1.5)	6.6 (1.0)	6.6 (1.0)	5.0 (1.3)	4.8 (1.3)
CRP	23 (32)	24 (31)	47 (44)	48 (44)	29 (31)	29 (34)
Seropositive %	63%	61%	65%	65%	58%	60%

Table 1: Sample sizes, means (standard deviations) and percentages are shown for baseline demographics. Complete cases; the subgroup of Data Set for whom SF36-Bodily Pain data are available for all time points. BMI= body mass index; DAS28= Disease Activity Score in 28 joints; HAQ=health assessment questionnaire for disability; CRP= C-reactive protein.

Table 2: Summary of the model selection process

	Number of latent trajectories in GMM			
	1 trajectory	2 trajectories	3 trajectories	4 trajectories
ERAN				
AIC	7723	7687	**7682**	7685
BIC	7748	7723	**7729**	7742
ssBIC	7726	7691	**7688**	7692
Entropy		0.709	**0.665**	0.63
LMR-LRT		<0.001	**0.030**	0.636
BLRT		<0.001	**0.013**	0.654
Largest trajectory (%)	264 (100%)	147 (56%)	**155 (59%)**	106 (40%)
Second largest trajectory (%)		117 (44%)	**60 (23%)**	71 (27%)
Third largest trajectory (%)			**49 (19%)**	52 (20%)
Fourth largest trajectory (%)				35 (13%)
BSRBR-Biologics				
AIC	152407	**152299**	152237	Not done
BIC	152480	**152390**	152346	
ssBIC	152442	**152342**	152289	
Entropy		**0.595**	0.714	
LMR-LRT		**0.0491**	0.0002	
BLRT		**<0.0001**	<0.0001	
Largest trajectory (%)	3138 (100%)	**2483 (79%)**	2430 (77%)	
Second largest trajectory		**655 (21%)**	654 (21%)	

(%)				
Third largest trajectory (%)			54 (2%)	
BSRBR-Non-Biologics				
AIC	28623	**28586**	28563	Not done
BIC	28676	**28652**	28642	
ssBIC	28638	**28605**	28585	
Entropy		**0.677**	0.758	
LMR-LRT		**<0.0001**	0.004	
BLRT		**<0.0001**	<0.0001	
Largest trajectory (%)	605 (100%)	**441(73%)**	445 (74%)	
Second largest trajectory (%)		**164 (27%)**	139 (23%)	
Third largest trajectory (%)			21 (3%)	

Table 2: Indices and statistics for GMMs using complete cases are shown for models with different numbers of trajectories. ERAN=Early RA Network; BSRBR=British Society for Rheumatology Biologics Register; AIC= Akaike's information criterion; BIC= Bayesian information criterion; ssBIC= sample size-adjusted BIC; LRT= Lo-Mendell-Rubin likelihood ratio test p value; BLRT= Bootstrapped likelihood ratio test P value. The selected model for each cohort study is shown in **bold**.

Table 3: Comparison of baseline variables between trajectories

	ERAN				BSRBR-Biologics			BSRBR-Non-Biologics		
	Low pain	Persistent pain	Resolving pain	Heterogeneity p value	Resolving pain	Persistent pain	Heterogeneity p value	Resolving pain	Persistent pain	Heterogeneity p value
Age	55 (15)	57 (13)	55 (16)	0.451	54 (12)	58 (11)	<0.001	59 (12)	62 (11)	<0.001
Female	70%	74%	63%	0.329	76%	77%	0.659	73%	75%	0.382
BMI	25.8 (3.7)	28.7 (5.7)	26.6 (4.5)	<0.001	25.7 (5.6)	27.1 (6.8)	<0.001	25.9 (4.9)	27.3 (5.8)	<0.001
Current smoker	30%	33%	29%	0.819	15%	20%	<0.001	16%	20%	<0.001
Duration	10 (17)	9 (11)	11 (14)	0.554	12 (9)	14 (10)	<0.001	7 (9)	11 (11)	<0.001
Seropositive	55%	62%	68%	0.459	63%	65%	0.134	57%	58%	0.678
DAS28	3.4 (1.2)	5.0 (1.4)	5.0 (1.4)	<0.001	6.4 (1.0)	6.6 (1.0)	<0.001	4.5 (1.3)	5.1 (1.3)	<0.001
VAS-GH	21 (16)	51 (23)	46 (25)	<0.001	70 (20)	73 (19)	0.442	42 (25)	55 (23)	<0.001
TJC	3 (4)	9 (7)	7 (7)	<0.001	14 (7)	16 (7)	<0.001	6 (6)	8 (7)	<0.001
SJC	4 (5)	7 (6)	7 (6)	0.002	11 (6)	11 (6)	0.214	5 (5)	6 (5)	0.431
ESR	26 (22)	33 (26)	43 (32)	0.017	45 (28)	47 (29)	0.030	31 (24)	34 (23)	0.094

CRP	11 (23)	27 (30)	31 (39)	0.022	46 (41)	48 (45)	0.414	26 (32)	29 (31)	0.259
DAS28-P	0.33 (0.12)	0.45 (0.10)	0.41 (0.09)	<0.001	0.47 (0.08)	0.48 (0.07)	0.001	0.40 (0.11)	0.44 (0.10)	<0.001
Tender-Swollen Difference	-0.60 (4.40)	2.74 (6.41)	0.11 (5.77)	<0.001	3.22 (7.06)	4.45 (7.18)	<0.001	0.75 (5.02)	2.70 (5.79)	<0.001
Comorbidities	48%	70%	57%	0.029	48%	64%	<0.001	50%	67%	<0.001
Disability (HAQ)	0.38 (0.41)	1.31 (0.72)*	1.03 (0.62)*	<0.001	1.7 (0.6)	2.1 (0.5)	<0.001	0.8 (0.6)	1.6 (0.7)	<0.001
SF36 (normed)										
Bodily Pain	48 (6)	30 (9)	30 (8)	<0.001	40 (9)	30 (7)	<0.001	28 (8)	24 (7)	<0.001
Physical function	44 (9)	25 (14)	30 (12)	<0.001	20 (12)	14 (10)	<0.001	37 (12)	22 (12)	<0.001
Vitality	54 (8)	39 (10)	43 (10)	<0.001	35 (10)	32 (10)	<0.001	46 (10)	38 (10)	<0.001
Mental health	55 (8)	45 (11)	49 (9)	<0.001	44 (11)	40 (11)	<0.001	52 (9)	45 (11)	<0.001

Table 3: Mean (standard deviation) or percentages are shown for each latent trajectory at baseline. P values for heterogeneity between trajectories are shown. In the ERAN data set, significance in pairwise comparisons between Persistent Pain and Resolving Pain trajectories are indicated (* $p<0.05$ with Bonferonni correction). Higher scores in the SF36 subscales reflect better quality of life. BMI= body mass index; DAS28= Disease Activity Score in 28 joints; VAS-GH=visual analogue scale; TJC= tender joint count; SJC= swollen joint count; HAQ=health assessment questionnaire for disability; ESR= erythrocyte sedimentation rate; CRP= C-reactive protein; Seropositive= positive for Rheumatoid factor or citrullinated proteins.

Table 4: Multinomial logistic regression for Persistent Pain trajectory in each cohort

	ERAN Persistent Pain (vs Low Pain)		ERAN Persistent Pain (vs Resolving Pain)		BSRBR-Biologics		BSRBR-Non-Biologics	
	aOR (95% CI)	p	aOR (95% CI)	p	aOR (95% CI)	p	aOR (95% CI)	p
Age	1.01 (0.99 - 1.04)	0.340	0.99 (0.98 - 1.01)	0.550	**1.02 (1.01 - 1.03)**	**<0.001**	1.01 (0.99 - 1.02)	0.314
BMI	1.02 (0.95 - 1.10)	0.553	1.00 (0.96 - 1.05)	0.947	**1.03 (1.02 - 1.05)**	**<0.001**	**1.03 (1.00 - 1.06)**	**0.029**
Duration	1.02 (0.97 - 1.06)	0.457	0.99 (0.98 - 1.00)	0.123	**1.02 (1.01 - 1.02)**	**<0.001**	**1.03 (1.01 - 1.05)**	**<0.001**
Current smoker	1.16 (0.52 - 2.56)	0.717	**1.83 (1.05 - 3.18)**	**0.032**	**1.72 (1.41 - 2.11)**	**<0.001**	1.34 (0.89 - 2.02)	0.156
Ex-smoker	**4.65 (1.73 - 12.50)**	**0.002**	1.52 (0.86 - 2.67)	0.146	**1.17 (1.00 - 1.37)**	**0.045**	**1.64 (1.18 - 2.28)**	**0.003**
DAS28	0.91 (0.67 - 1.24)	0.542	0.54 (0.69 - 1.02)	0.073	**0.91 (0.84 - 0.99)**	**0.019**	0.97 (0.86 - 1.10)	0.629
Disability (HAQ)	**5.43 (2.44 - 12.05)**	**<0.001**	**2.31 (1.51 - 3.56)**	**<0.001**	**2.36 (2.05 - 2.73)**	**<0.001**	**2.52 (1.91 - 3.32)**	**<0.001**
CoMorbidity	1.18 (0.57 - 2.48)	0.655	1.28 (0.78 - 2.09)	0.332	**1.39 (1.20 - 1.60)**	**<0.001**	1.21 (0.89 - 1.65)	0.215
Bodily Pain	**0.76 (0.70 - 0.81)**	**<0.001**	1.02 (0.99 - 1.06)	0.224	**0.98 (0.97 - 0.99)**	**<0.001**	**0.93 (0.91 - 0.95)**	**<0.001**
Vitality	0.99 (0.95 - 1.03)	0.579	**0.97 (0.94 - 1.00)**	**0.028**	1.00 (0.99 - 1.01)	0.704	0.99 (0.98 - 1.01)	0.561
Mental Health	1.02 (0.98 - 1.07)	0.318	0.99 (0.96 - 1.02)	0.425	**0.98 (0.97 - 0.99)**	**<0.001**	**0.97 (0.95 - 0.99)**	**0.001**

Table 4: In ERAN the adjusted odds ratios (aOR) for Persistent Pain are displayed, compared to both of the other trajectories. Persistent Pain was used as the reference category, and the aOR and CI's were then inverted. Multinomial logistic regression was performed; and each aOR indicates the change in risk per unit increase (per year of

age, unit of BMI, year of duration, unit of DAS28, unit of HAQ, per point of SF36 subscale). Higher scores in the SF36 subscales reflect better quality of life. Categorical variables aOR's showed risk directly compared to a reference category (No comorbidities and Never smoked). Statistically significant findings are presented in **bold**.