RMD Open
Rheumatic & Musculoskeletal Diseases

ORIGINAL RESEARCH

Trajectories of self-reported pain-related health outcomes and longitudinal effects on medication use in rheumatoid arthritis: a prospective cohort analysis using the Australian Rheumatology Association Database (ARAD)

Huai Leng Pisaniello ,[1,2] Susan Lester,[2,3] Oscar Russell,[1,2,3] Rachel Black,[2,3] Joanna Tieu,[2,3] Bethan Richards,[4,5,6] Claire Barrett,[7,8] Marissa Lassere,[9,10] Lyn March,[11,12] Rachelle Buchbinder ,[13] Samuel L Whittle,[2,3,13] Catherine L Hill[2,3]

To cite: Pisaniello HL, Lester S, Russell O, *et al*. Trajectories of self-reported pain-related health outcomes and longitudinal effects on medication use in rheumatoid arthritis: a prospective cohort analysis using the Australian Rheumatology Association Database (ARAD). *RMD Open* 2023;**9**:e002962. doi:10.1136/rmdopen-2022-002962

► Additional supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/rmdopen-2022-002962).

Received 23 December 2022
Accepted 7 July 2023

For numbered affiliations see end of article.

Correspondence to
Dr Huai Leng Pisaniello; huaileng.pisaniello@adelaide.edu.au

ABSTRACT

Objective To determine distinct trajectories of self-reported pain-related health status in rheumatoid arthritis (RA), their relationship with sociodemographic factors and medication use.

Methods 988 Australian Rheumatology Association Database participants with RA (71% female, mean age 54 years, mean disease duration 2.3 years) were included. Distinct multi-trajectories over 15-year follow-up for five different self-reported pain-related health outcome measures (Health Assessment Questionnaire Disability Index, visual analogue scores for pain, arthritis, global health and the Assessment of Quality of Life utility index) were identified using latent variable discrete mixture modelling. Random effects models were used to determine associations with medication use and biologic therapy modification during follow-up.

Results Four, approximately equally sized, pain/health status groups were identified, ranging from 'better' to 'poorer', within which changes over time were relatively small. Important determinants of those with poorer pain/health status included female gender, obesity, smoking, socioeconomic indicators and comorbidities. While biologic therapy use was similar between groups during follow-up, biologic therapy modifications ($p_{linear}<0.001$) and greater tendency of non-tumour necrosis factor inhibitor use ($p_{linear}<0.001$) were observed in those with poorer pain/health status. Similarly, greater use of opioids, prednisolone and non-steroidal anti-inflammatory drugs was seen in those with poorer pain/health status.

Conclusion In the absence of disease activity information, distinct trajectories of varying pain/health status were seen from the outset and throughout the disease course in this RA cohort. More biologic therapy modifications and greater use in anti-inflammatories, opioids and prednisolone were seen in those with poorer pain/health status, reflecting undesirable lived experience of persistent pain in RA.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Despite treatment advances in rheumatoid arthritis (RA), persistent pain and suboptimal health status may remain significant in some patients, even in those with adequately controlled disease or in disease remission.

WHAT THIS STUDY ADDS

⇒ We performed multi-trajectory analysis, using five different self-reported pain-related health outcome measures, with patients with RA classified into four distinct pain-related health status subgroups, which were associated with sociodemographic and lifestyle factors.

⇒ Differences in the pain-related health status between subgroups were evident at baseline and were relatively stable over time. Greater use of opioids, anti-inflammatories and prednisolone and changes in biologic therapy were seen in those with poorer pain-related health status.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This study highlights the importance of evaluating the overall well-being and pain experience of those living with RA from the outset, with a view to the development of appropriate management strategies in addition to suppression of disease inflammation.

INTRODUCTION

Over the last two decades, significant improvements in disease-related outcomes in rheumatoid arthritis (RA) are evident.[1–3] Patients presenting with inflammatory arthritis suspicious of RA are diagnosed earlier and treated intensively, alongside the major advances in targeted therapy using biologic/targeted synthetic disease modifying anti-rheumatic drugs (b/tsDMARDs).[1 2 4–6] However, mismatch between low disease activity or disease remission and patient-reported outcomes such as pain, fatigue and global disease activity remains. This is an ongoing treatment conundrum in the context of a treat-to-target approach in RA, especially in those with persistent pain despite remission in disease inflammation.[7 8]

Conventionally, the 28-Joint Disease Activity Score (DAS28), a universal composite scoring tool, is commonly used by treating physicians and in clinical trials to assess disease activity and treatment response in RA.[9 10] However, careful interpretation of the DAS28 scoring is crucial when it comes to determining disease remission objectively. For instance, discordance between the objective clinical assessment of joint inflammation and patient global disease activity (PGA) in the DAS28 scoring was observed in one-third of a multi-ethnic adult RA study cohort on treatment.[11] Patients with RA who have achieved a state of DAS28 remission may still experience clinically significant pain.[7] Similarly, McWilliams and colleagues identified 58% and 27% of their study cohort had partial improvement in pain and worsening pain after 12 months respectively, as assessed by the change of the DAS28-P index (defined as 'the proportion of DAS28 contributed by the patient-reported components') over time.[12] We recently showed that persistently high DAS28-P index scores predicted poor treatment response in an Australian early RA cohort, reflecting risks of underdiagnosed non-inflammatory pain and unnecessary escalation of RA treatment.[13] Such phenomenon is also observed in those with RA disease remission assessed using other index-based criteria endorsed by the American College of Rheumatology (ACR) and the European Alliance of Associations for Rheumatology (EULAR).[14] As highlighted by Studenic and his colleagues, two-thirds of their RA outpatient cohort achieved 'near-remission' based on fulfilling three of four of the Boolean-based criteria, with PGA being the primary limiting variable in defining disease remission.[15] Additionally, a cross-sectional study in Portugal demonstrated lack of ultrasonographic disease inflammation in RA patients with high levels of PGA reporting who were otherwise in remission.[16] More importantly, in a recent meta-analysis, despite using the ACR/EULAR Boolean-based remission criteria, patients in near-remission scored similarly in their PGA levels compared with those in non-remission, potentially with unintended risks of unnecessary treatment escalation.[17] These findings highlight the nuances behind the role of the PGA beyond the objective measure of disease remission in real-world clinical practice and the importance of dissecting the intention of treatment in RA, especially in those with persistent pain despite objective evidence of disease control.

Health status is regarded as the overall perception of the state of physical health, mental health and social well-being, and is an ever-changing metric in one's life course, ranging from a state of wellness to illness onset and its trajectory, if present.[18–20] In patients with RA, persistent pain may have an impact on their overall health status, as pain is regarded as the highest outcome priority for improvement.[2 21–23] Persistent pain in RA is multifaceted, largely driven not only by the complex dynamics between peripheral joint inflammation and nociplastic central pain processing, but it is also by the totality of the overall lived experience of the individual's health over time.[24 25] For example, higher levels of pain experienced in RA were significantly correlated with poor quality of life, defined by reduced overall health perception, lack of independence and decline in biopsychosocial functioning.[11 26–30] Therefore, looking into the intertwined relationship between the complex dynamics of pain in RA and the negative corollary health outcomes that followed has the potential to provide further insights into the overall impression of the well-being of the person living with RA. To date, little is known of the temporal relationship between pain and health status of patients living with RA, and more importantly, how pain-related health status trajectories translate into the patterns of medication use.

In this longitudinal study of a national cohort of patients with established RA, we first aimed to identify distinct subgroups of trajectories of self-reported pain-related health status, measured by different pain-related health outcome measures. Second, we aimed to examine the baseline sociodemographic and comorbidities within each of these identified trajectories. Finally, we aimed to use these identified trajectories as predictors of the time-varying effects on medication use.

METHODS

Study database

The Australian Rheumatology Association Database (ARAD) is a voluntary national registry founded in 2001 that aims to collect longitudinal data on long-term safety and effectiveness of b/tsDMARDs and health outcomes in patients with inflammatory arthritis. Information on the ARAD establishment, methodology and governance has been discussed in detail previously.[31 32]

In brief, ARAD participants with inflammatory arthritis completed self-reported questionnaires biannually (options of paper or online format from August 2009) until January 2014. Since then, questionnaires have been completed once every year after the initial 2 years of biannual follow-up. These self-reported questionnaires consist of sociodemographic information, current arthritis-related medication use, comorbidities (ie, comorbid medical illnesses), symptoms related to arthritis, and measures of health outcomes and quality of life.

All ARAD participants provided written permission to be contacted by ARAD investigators and written informed consent for study participation and for anonymous data analyses and associated data linkages. Ethics approval for ARAD has been granted by 18 committees snd organisations across all Australian states and territories.

Eligibility criteria

Study participants were selected from an ARAD snapshot from August 2021. Inclusion criteria were participants with rheumatologist-diagnosed RA and aged between 25 and 75 years old at diagnosis. We included ARAD participants who entered ARAD within 5 years of diagnosis and with at least 3 years of follow-up, therefore the study comprised participants with their RA diagnosis date between 1998 and 2018. Baseline data on age, gender, smoking and alcohol history, body mass index (BMI), education, employment, disability and comorbidities were extracted from the self-reported responses provided at ARAD entry.

Study outcomes

In this study, for included ARAD participants, five different self-reported pain-related health outcome measures derived from the ARAD questionnaires were used in the analysis, encompassing the overall pain experience and health status over time. These were (1) arthritis-related disability measured by the Health Assessment Questionnaire Disability Index, HAQ-DI (0–3 scale, higher score indicates higher level of disability), (2) pain level over the past week, measured on a 0–100 mm visual analogue score, VAS scale (higher score indicates greater pain), (3) participant-reported arthritis 'condition' (disease impact) measured on a 0–100 mm scale (higher score indicates worse arthritis), (4) participant-reported global health item measured on a 0–100 mm scale (higher score indicates better global health) and (5) the utility composite score of the Assessment of Quality of Life, AQoL, which ranges from 1.00 (indicating full health), to 0.00 (indicating death-equivalent), and to −0.04 (indicating a state worse than death).[33–36]

Socioeconomic status

In addition to education level and disability support reported in ARAD, socioeconomic status (SES) was also measured by the Index of Socioeconomic Advantage and Disadvantage (IRSAD), and Socio-Economic Indexes for Areas (SEIFA) developed by the Australian Bureau of Statistics.[37] The IRSAD quintile, according to 2016 Australian population census data, was assigned using SA1 areas, which are the smallest SEIFA, and correspond to an average of 400 people.

Comorbidity index

A modification of the Rheumatic Disease Comorbidity Index (RDCI) was used as a measure of comorbidity (range 0–9), with osteoporosis substituted for fracture.[38] Additional comorbidities in relation to medical illnesses that contribute to the index were lung disease, cardiovascular disease, hypertension, depression, cancer, gastrointestinal ulcer or stomach problems.

Medications

Current use of opioids, non-steroidal anti-inflammatory drugs (NSAIDs), oral glucocorticoids, oral and subcutaneous methotrexate, and b/tsDMARDs were obtained from each completed questionnaire, however, dosage information was not available.

Statistical analysis

All analyses were performed in Stata V.16.1 (StataCorp LLC, TS, USA).

Trajectories of self-reported pain-related health outcome measures

Group-based multi-trajectory modelling, using all five self-reported pain-related health outcome measures, was performed to identify distinct groups of participants followed from ARAD baseline to a maximum of 15 years. Analysis was performed using the Stata ado 'traj', which uses a discrete mixture modelling approach, a form of group-based trajectory modelling (GBTM), to stratify latent subgroups of participants based on homogeneity of between-individual trajectories for which follow-up time was modelled as a continuous variable, with both linear and quadratic terms.[39–41] The optimal number of trajectory groups was established based on the model selection criteria using the Akaike information criteria (AIC), Bayesian information criteria (BIC), entropy (which determines the overall probability of the individuals being accurately assigned to a homogenous trajectory) and the log-likelihood.[39–42] The reporting of this trajectory analysis was prepared in accordance with the Guidelines for Reporting on Latent Trajectory Studies Checklist.[43]

Baseline comparisons between the identified trajectory groups for sociodemographic, medication use and other relevant variables were performed using the Jonckheere-Terpstra test for ordinal data.

Medication use

Trajectory subgroups were considered as the predictors in a random intercept, longitudinal panel regression analysis of NSAIDs, glucocorticoids, opioids, methotrexate and b/tsDMARDs use over follow-up, using both binomial and multinomial (for b/tsDMARD use only) models. The results were interpreted as predicted marginal probabilities (with 95% CI) and orthogonal polynomial linear contrasts were used to assess ordinal trends between trajectory groups. The results were also presented as (subject-specific) ORs and the corresponding 95% CI, with all p values of <0.05 being considered statistically significant.

Modification of b/tsDMARD was also examined by time-to-event analysis in which failure times were defined at the initiation of, or change in, b/tsDMARD treatment. Multiple failures (modifications of b/tsDMARD) were possible for each individual, and therefore these data

Table 1 Baseline data on general demographics, socioeconomic demographics, medication use and comorbidities for participants stratified by pain-related health status trajectory groups

Baseline	All	Group 1 (better)	Group 2	Group 3	Group 4 (poorer)	p_{trend}
Number of participants, N	988	169	285	316	218	
Age at diagnosis: mean (SD)	53 (11)	50 (12)	52 (11)	54 (11)	54 (11)	0.005
Age at ARAD entry: mean (SD)	54 (11)	52 (12)	54 (11)	56 (11)	54 (11)	0.003
Disease duration (years): mean (SD)	2.3 (1.4)	2.3 (1.4)	2.2 (1.4)	2.4 (1.3)	2.4 (1.4)	0.17
Follow-up years: mean (SD)	6.7 (4.1)	6.9 (4.3)	7.2 (4.3)	6.7 (4.3)	5.9 (4.1)	0.004
Females: n (%)	703 (71%)	94 (56%)	200 (70%)	241 (76%)	168 (77%)	<0.001
BMI (WHO category): n (%)						<0.001
Normal	156/643 (24%)	40/121 (33%)	62/206 (30%)	40/194 (21%)	14/122 (11%)	
Overweight	228/643 (35%)	60/121 (50%)	74/206 (36%)	62/194 (32%)	32/122 (26%)	
Obese	259/643 (40%)	21/121 (17%)	70/206 (34%)	92/194 (47%)	76/122 (62%)	
Current smoker: n (%)	160/987 (16%)	18 (11%)	40 (14%)	61 (19%)	41 (19%)	0.009
Disability support: n (%)	111 (11%)	0	14 (5%)	33 (10%)	64 (29%)	<0.001
Education: n (%)						<0.001
Did not complete high school	245/987 (25%)	35 (21%)	62 (22%)	86 (27%)	62 (28%)	
Completed high school	337/987 (34%)	60 (36%)	77 (27%)	114 (36%)	86 (39%)	
Post high school	405/987 (41%)	74 (44%)	146 (51%)	115 (37%)	70 (32%)	
SES quintile**: n (%)						<0.001
Q1 (lowest)	163/831 (20%)	15/141 (11%)	40/229 (17%)	63/271 (23%)	45/90 (24%)	
Q2	173/831 (21%)	36/141 (25%)	38/229 (17%)	51/271 (19%)	48/90 (25%)	
Q3	178/831 (21%)	29/141 (21%)	41/229 (18%)	67/271 (25%)	41/90 (22%)	
Q4	160/831 (19%)	22/141 (16%)	56/229 (24%)	53/271 (20%)	29/90 (15%)	
Q5 (highest)	157/831 (19%)	39/141 (28%)	54/229 (24%)	37/271 (14%)	27/90 (14%)	
Comorbidity index: mean (SD)	1.0 (1.3)	0.6 (0.9)	0.8 (1.1)	1.1 (1.3)	1.8 (1.6)	<0.001
Trajectory analysis outcomes						
HAQ-DI: mean (SD)	1.0 (0.7)	0.4 (0.5)	0.7 (0.6)	1.2 (0.5)	1.7 (0.7)	<0.001
Pain VAS: mean (SD)	46 (26)	26 (24)	40 (23)	51 (23)	61 (21)	<0.001
Arthritis condition VAS: mean (SD)	46 (26)	27 (26)	40 (25)	53 (22)	61 (21)	<0.001
Global health VAS: mean (SD)	63 (20)	76 (19)	69 (17)	60 (17)	48 (19)	<0.001
AQoL utility index: mean (SD)	0.52 (0.25)	0.74 (0.21)	0.63 (0.18)	0.48 (0.19)	0.26 (0.17)	<0.001
Medications: n (%)						
Opioids	330 (33%)	25 (15%)	70 (25%)	121 (38%)	114 (52%)	<0.001
Prednisolone	471 (48%)	66 (39%)	141 (49%)	146 (46%)	118 (54%)	0.022
NSAIDs	444 (45%)	72 (43%)	138 (48%)	147 (47%)	87 (40%)	0.37
Methotrexate	723 (73%)	141 (83%)	219 (77%)	210 (66%)	153 (70%)	<0.001
Other csDMARD	20 (2%)	1 (0.6%)	4 (1.4%)	9 (29%)	6 (2%)	
b/tsDMARD	537 (54%)	91 (54%)	148 (52%)	167 (53%)	131 (60%)	0.17

Trend tests (p_{trend}) were performed using the Jonckheere-Terpstra test.
*SES was measured by the Index of Relative Socioeconomic Advantage and Disadvantage (IRSAD).
AQoL, Assessment of Quality of Life; ARAD, Australian Rheumatology Association Database; BMI, body mass index; b/tsDMARDs, biologic/targeted synthetic disease modifying anti-rheumatic drugs; csDMARDs, conventional synthetic disease modifying anti-rheumatic drugs; HAQ-DI, Health Assessment Questionnaire Disability Index; NSAIDs, non-steroidal anti-inflammatory drugs; SES, socioeconomic status; VAS, visual analogue score.

Table 2 Model fit selection criteria for choosing the optimal number of trajectory latent classes (groups), and the number of participants assigned to each class

N_classes	AIC	BIC	LL	Entropy	Class 1 (%)	Class 2 (%)	Class 3 (%)	Class 4 (%)	Class 5 (%)
1	146 116	146 165	146 096		100	–	–	–	–
2	135 720	135 808	135 684	0.95	49	51	–	–	–
3	132 739	132 866	132 687	0.92	35	37	28	–	–
4	131 391	131 558	131 323	0.88	17	29	32	22	–
5	Inestimable (singular variance-covariance matrix)			–	–	–	–	–	–

Lower values of the Akaike information criterion (AIC), the Bayesian information criterion (BIC) and the log-likelihood (LL) indicate better model fit. Entropy is the average posterior probability of class membership, with values closer to one indicating greater precision, and values >0.7 indicating satisfactory discrimination between classes.

were analysed by a random effects, parametric Weibull 'survival' model, which models the baseline hazard rate and allows for within-individual dependencies between treatment failure episodes. The Weibull survival model had both proportional-hazards (PH) and accelerated failure-time (AFT) parameterisations, and both were reported. Regression coefficients for the PH model were expressed as HRs, with values of >1 indicating an increased risk of 'failure' occurring compared with the reference group at any given time point. For the AFT model, the regression coefficients were expressed as time ratios (TRs), with values of <1 indicating shorter b/tsDMARD 'failure' times.

RESULTS

A total of 988 ARAD participants were included in the study, the majority of whom were of Caucasian ancestry (93%) and spoke English at home (98%). Participants were predominantly female (71%) with a mean age at ARAD entry of 54 years (SD of 11) and a mean disease duration of 2.3 years (SD 1.4). The mean ARAD follow-up time was 6.7 years (maximum 15 years), as outlined in table 1.

Description of trajectories

Using multi-trajectory modelling, study participants were stratified into four, approximately equally sized, distinct pain-related health status groups. Four subgroups were selected based on the best model fit (minimum AIC, BIC and log-likelihood criteria) and a high entropy score (the average posterior probability of class membership) (table 2). Additional information on the model output was reported in online supplemental file.

The fitted multi-trajectories over time for each outcome measure for each group were reported in figure 1. The major difference between the groups was readily identifiable as the location (level) of the scores for each outcome, rather than the shape of the trajectories over time, and in fact, changes over time within each group were relatively small. Importantly, the patterns across each of the five outcome measures were remarkably similar, indicating that they measure the same underlying (latent) pain-related health construct. The four subgroups of study participants were therefore interpreted as an ordered classification of pain-related health status ranging from 'better pain-related health status' in group 1 to 'poorer pain-related health status' in group 4.

Baseline comparisons

Baseline comparisons between the four pain-related health status groups were reported in table 1. There was an increasing female predominance with poorer pain/health status (from 56% in group 1 to 77% in group 4, p<0.001), and a relatively small, but statistically significant, trend for baseline age (from 52 years in group 1 to 54 years in group 4, p=0.003). Importantly, the disease duration at ARAD entry was comparable across all four groups. In terms of other sociodemographic variables, obesity, current smoking, comorbidity index and lower SES indicators (such as education level, being on disability support and IRSAD quintile) were all associated with poorer pain/health status. Of note, 30% of those with poorer pain-related health status had self-reported diagnosis of depression, which was significantly higher than those in the better pain-related health status group (3%) (online supplemental table 1).

In detail, the five pain-related health outcome measures used for the multi-trajectory analysis were each different at baseline between the four groups of participants. When comparing the 'better' (group 1) to 'poorer' (group 4) groups at baseline, the HAQ-DI increased from 0.4 to 1.7, pain VAS from 26 to 61, arthritis condition VAS from 27 to 61, whereas the global health VAS decreased from 76 to 48 and the AQoL utility index decreased from 0.74 to 0.26 (all p<0.001). This was accompanied by an increase in baseline opioid use (from 15% to 52%), prednisolone use (from 39% to 54%), and perhaps surprisingly, lower methotrexate use (from 83% to 70%), which was possibly offset by a statistically non-significant increase in b/tsDMARD use (from 54% to 60%, p=0.17). However, differences in medication use between the pain-related health status groups was subsequently explored in detail over the duration of follow-up.

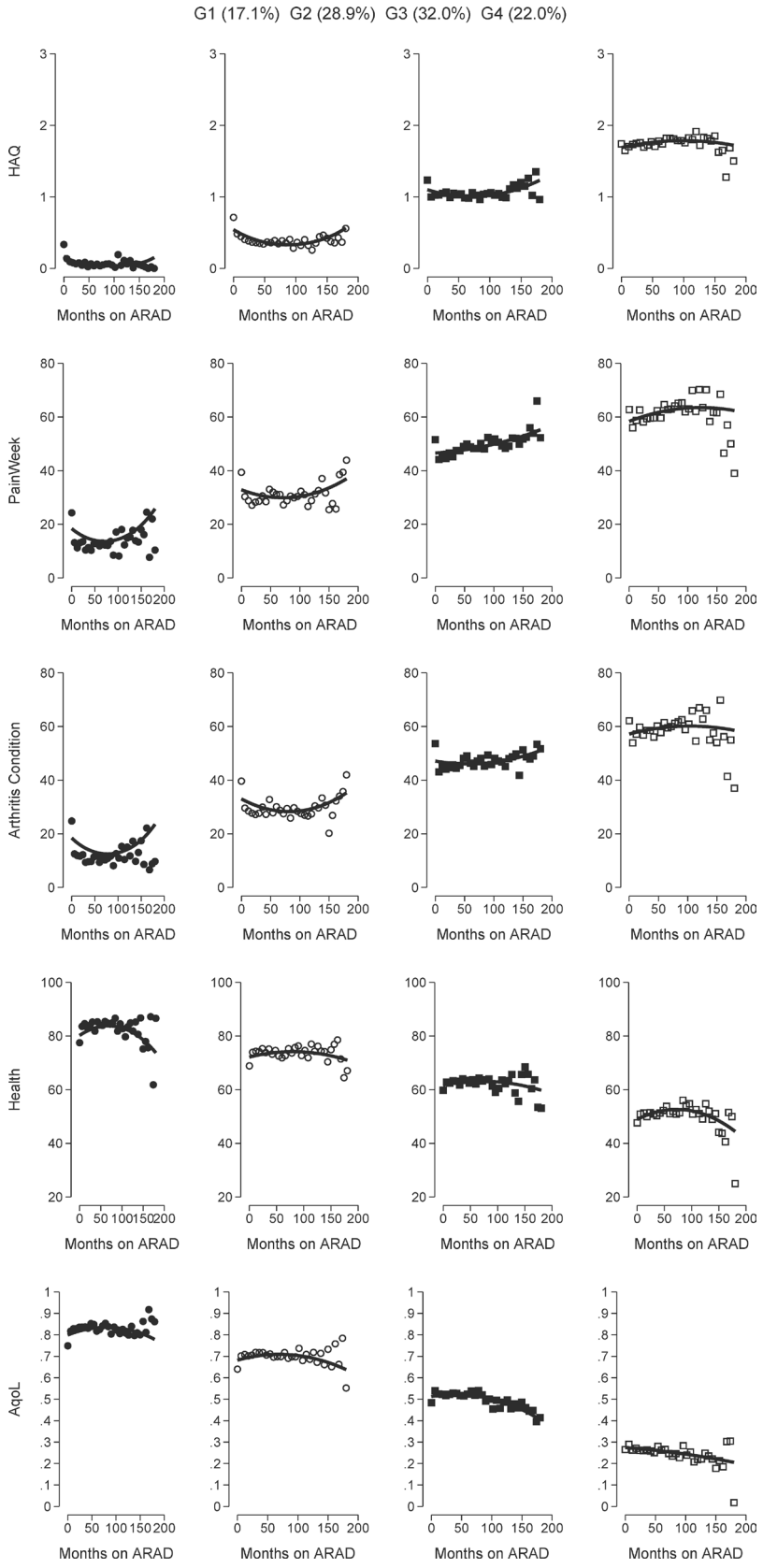

Figure 1 Changes in five self-reported pain-related health status outcomes in rheumatoid arthritis during ARAD follow-up. The outcomes (top to bottom panels) were the Health Assessment Questionnaire Disability Index (HAQ-DI), a pain visual analogue score (VAS), an arthritis condition VAS, patient's global health assessment and the Assessment of Quality of Life (AQoL) utility index. Four different longitudinal trajectory groups were identified (left to right panels). Each panel depicts the fitted regression line (estimated with both linear and quadratic terms for follow-up time) and mean estimates (symbols) at follow-up times for each outcome for each trajectory group. ARAD, Australian Rheumatology Association Database.

Table 3 Longitudinal random effect panel regression modelling analysis of the four pain-related health status trajectory groups as predictors for medication use during Australian Rheumatology Association Database follow-up

Trajectory group	Marginal probability (95% CI)	OR (95% CI)	P value
Opioid use: p_{linear}<0.001			
Group 1 (better)	0.08 (0.05 to 0.10)	1 (base)	
Group 2	0.18 (0.15 to 0.21)	4.7 (2.6 to 8.7)	<0.001
Group 3	0.36 (0.33 to 0.40)	24.9 (13.7 to 45.4)	<0.001
Group 4 (poorer)	0.57 (0.52 to 0.62)	116.1 (61.0 to 221.1)	<0.001
Prednisolone use: p_{linear}<0.001			
Group 1 (better)	0.26 (0.21 to 0.30)	1 (base)	
Group 2	0.36 (0.32 to 0.41)	3.3 (1.5 to 7.2)	0.003
Group 3	0.44 (0.39 to 0.48)	7.5 (3.4 to 16.2)	<0.001
Group 4 (poorer)	0.53 (0.48 to 0.57)	23.0 (9.9 to 53.7)	<0.001
NSAID use: p_{linear}=0.003			
Group 1 (better)	0.27 (0.23 to 0.32)	1 (base)	
Group 2	0.39 (0.35 to 0.43)	2.7 (1.5 to 4.7)	0.001
Group 3	0.41 (0.37 to 0.45)	3.2 (1.8 to 5.6)	<0.001
Group 4 (poorer)	0.37 (0.32 to 0.42)	2.4 (1.3 to 4.3)	0.005
Methotrexate use: p_{linear}=<0.001			
Group 1 (better)	0.78 (0.74 to 0.82)	1 (base)	
Group 2	0.75 (0.71 to 0.78)	0.60 (0.28 to 1.33)	0.21
Group 3	0.65 (0.61 to 0.70)	0.20 (0.09 to 0.44)	<0.001
Group 4 (poorer)	0.68 (0.63 to 0.74)	0.28 (0.12 to 0.65)	0.003
Other csDMARDs use: p_{linear} p=0.001			
Group 1 (better)	0.01 (0.00 to 0.02)	1 (base)	
Group 2	0.02 (0.01 to 0.03)	3.7 (0.6 to 24.7)	0.18
Group 3	0.04 (0.03 to 0.06)	21.9 (3.6 to 134.4)	0.001
Group 4 (poorer)	0.04 (0.03 to 0.05)	15.2 (2.3 to 100.5)	0.005
b/tsDMARD use			
1. No b/tsDMARDs: p_{linear}=0.34			
Group 1 (better)	0.35 (0.30 to 0.39)	1 (base)	
Group 2	0.32 (0.29 to 0.35)	1 (base)	
Group 3	0.32 (0.29 to 0.36)	1 (base)	
Group 4 (poorer)	0.31 (0.27 to 0.35)	1 (base)	
2. TNF inhibitors: p_{linear}=0.002			
Group 1 (better)	0.56 (0.51 to 0.61)	1 (base)	
Group 2	0.55 (0.52 to 0.59)	1.14 (0.6 to 2.2)	0.69
Group 3	0.50 (0.46 to 0.53)	0.85 (0.44 to 1.62)	0.61
Group 4 (poorer)	0.48 (0.44 to 0.53)	0.86 (0.42 to 1.75)	0.68
3. Other b/tsDMARDs: p_{linear}<0.001			
Group 1 (better)	0.09 (0.06 to 0.12)	1 (base)	
Group 2	0.13 (0.10 to 0.15)	2.19 (0.95 to 5.05)	0.065
Group 3	0.18 (0.15 to 0.20)	4.47 (1.98 to 10.09)	<0.001
Group 4 (poorer)	0.21 (0.17 to 0.24)	6.87 (2.87 to 16.46)	<0.001

Results are reported as both marginal probabilities (frequencies) and ORs with 95% CIs. Significance values are derived from both orthogonal polynomial linear contrasts of the marginal probabilities (p_{linear}) reflecting an overall ordinal trend, and Wald tests for individual ORs (p value).
b/tsDMARDs, biologic/targeted synthetic disease modifying anti-rheumatic drugs; csDMARDs, conventional synthetic disease modifying anti-rheumatic drugs; NSAID, non-steroidal anti-inflammatory drug; TNF, tumour necrosis factor.

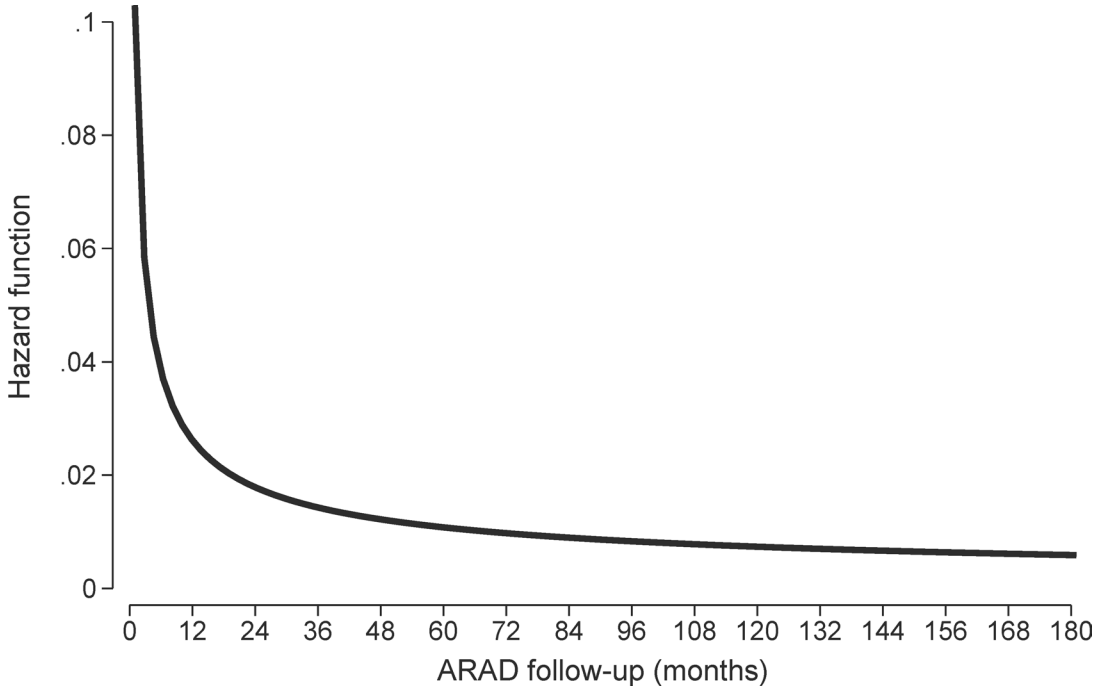

Figure 2 Marginal hazard rate for recurrent biologic/targeted synthetic disease modifying anti-rheumatic drug (b/tsDMARD) modification events estimated from a random effects Weibull parametric time-to-event proportional hazards model. The risk (hazard) of a b/tsDMARD treatment modification was greatest during the first 2 years or so following ARAD entry, and stabilised thereafter. ARAD, Australian Rheumatology Association Database.

Longitudinal (panel) mixed model regression analysis of medication use

Table 3 outlined the time-varying differences in medication use between the pain-related health status trajectory groups during ARAD follow-up.

Opioid, prednisolone and NSAIDs use each increased across the four pain-related health status groups. The difference in opioid use was the most marked, with the marginal probability increasing from 0.08 in the 'better pain-related health status' group (group 1) to 0.57 in the 'poorer pain-related health status' group (group 4) (p_{linear}<0.001). The marginal probability for prednisolone use was overall quite high, with an increase from 0.26 to 0.53 (p_{linear}<0.001).

In terms of DMARD use, the trend towards lower methotrexate use in those with poorer pain-related health status observed at baseline continued during follow-up with marginal probability ranging from 0.78 to 0.68 (p_{linear}<0.001). Although the use of other conventional synthetic DMARDs was low overall, the use of these medications increased with poorer pain-related health status. Overall, b/tsDMARD use was comparable across the four pain-related health status groups (p=0.34) but varied by type of b/tsDMARD. Specifically, tumour necrosis factor (TNF) inhibitor use decreased with poorer pain-related health status (marginal probability decreased from 0.56 to 0.48, p_{linear}=0.002), which was compensated by an increase in the use of other b/tsDMARDs (marginal probability increased from 0.09 to 0.21, p_{linear}<0.001).

Time-to-event analysis of b/tsDMARD modification

A total of 1567 b/tsDMARD modification episodes were identified for 988 participants in this analysis, with a median number of 2 episodes. The underlying hazard rate for b/tsDMARD modification (figure 2) indicated that the risk of b/tsDMARD treatment modification was

Table 4 Time-to-event analysis of recurrent biologic/targeted synthetic disease modifying anti-rheumatic drug treatment modifications

Trajectory group	HR (95% CI)	Time ratio (95% CI)	P value
Group 1 (better)	1 (base)	1 (base)	
Group 2	1.20 (1.01 to 1.42)	0.67 (0.46 to 0.98)	0.041
Group 3	1.58 (1.35 to 1.87)	0.36 (0.25 to 0.52)	<0.001
Group 4 (poorer)	1.78 (1.50 to 2.10)	0.28 (0.19 to 0.41)	<0.001

Analysis was performed by a random effects parametric Weibull time-to-event proportional hazards model, which may be parameterised as either an increased risk (HR) or accelerated failure time (time ratio).

highest within the first 2 years or so after ARAD study entry and plateaued thereafter.

Similar to our other results, there was an ordinal trend across the poorer pain-related health status groups, and the HR for b/tsDMARD modification for the 'poorer pain-related health status' (group 4) compared with the 'better pain-related health status' (group 1) was 1.78 (95% CI 1.50 to 2.10, p<0.001), as outlined in table 4. Alternatively, the AFT parameterisation indicated that the time to b/tsDMARD modification/failure was shorter by approximately 70% for group 4 participants compared with group 1 participants.

DISCUSSION

In this study of patients with rheumatologist-diagnosed RA, we used multi-trajectory analysis to identify subgroups of participants with an increasingly poorer pain-related health status. This type of analysis enabled us to examine risk factors, changes over time and medication use.

Our results highlight the strong interdependency between pain experience and overall health status in patients with RA. In part, pain experience in RA may be a proxy for the overall health status of the individuals. Notably, we observed these parallel patterns of synchronous trajectories of high pain and poor global health and more disability, and vice versa, from the outset and throughout the study follow-up period. Further, the changes over time within trajectory groups were minimal relative to the differences between groups, implying that DMARD treatment alone may not be sufficient to manage chronic pain in RA. However, there may be a window of opportunity early in the course of RA disease to identify patients at high risk of developing persistent pain.

Our study results showed that lifestyle factors, comorbidities and socioeconomic indicators, which are likely inter-related, were risk factors for a persistently poorer pain-related health status. These findings are similar to those from a large French observational study, which highlighted the temporal implications of pain heterogeneity and sociodemographic characteristics throughout the disease course.[44] Over the last two decades, the comorbidity burden at the time of RA diagnosis has risen, implying the need for early identification and better treatment tailoring for these at-risk individuals.[45] Additionally, our study findings have demonstrated high proportions of self-reported depression in those with poorer pain-related health status. The burden of pain in RA is highly correlated with levels of anxiety and depression, highlighting the unmet needs to consider open discussion of any psychological factors early on with these at-risk individuals, and to provide early psychosocial support or interventions as necessary.[30 46]

The use of opioids, prednisolone and NSAIDs throughout follow-up was higher in participants with worsening pain-related health status. The relationship with opioid use was the most marked, and consistent with a prior study of opioid use in the ARAD cohort which concluded that NSAID and DMARD treatment did not obviate opioid use in all patients.[47] Evidence for the benefits of opioid use in treating RA pain is minimal, resulting in a conditional recommendation against opioid use in the latest Australian Living Guideline for the treatment of inflammatory arthritis.[48] Concerningly, a recent American study has demonstrated that despite increasing awareness of the risks and harms associated with opioid use, chronic opioid use approximately doubled in patients with RA between 2002 and 2015, and was associated with pain, antidepressant use, high disease activity and disability.[49] In terms of prednisolone use, the Australian Living Guideline for the treatment of inflammatory arthritis recommends against long-term use of glucocorticoids in RA, and suggest aiming for the lowest dose and shortest possible duration of use of glucocorticoids when used for treatment of disease flare or as a bridging therapy when initiating DMARDs.[50] The relatively high probability of prednisolone use in this study, even in those with better pain-related health status, is potentially of concern. However, there is insufficient information in ARAD in terms of disease activity, prednisolone dose and duration to determine the appropriate prescribing of prednisolone in this study. Overarchingly, our study findings suggest that individuals with poorer pain-related health status did not experience abrogation of their pain level over time, despite greater use of opioids, prednisolone and anti-inflammatories. These at-risk individuals warrant further attentions when it comes to dissecting the underlying natural history of their pain experience, particularly in differentiating inflammatory and non-inflammatory pain in RA. In a proof-of-concept study by Wohlfahrt and her colleagues, lower knee pressure pain thresholds and conditioned pain modulation were shown to be predictive of DAS28 in those with low-moderate disease activity (pre-DMARD) and with higher baseline disease activity (post-DMARD), respectively.[51] Using these indices of pain sensitisation measures, in addition to the standard disease activity composite measures, may allow future personalised mechanism-specific pain interventions in RA, targeting those with PGA-near remission.[52]

The propensity of participants with RA and with poorer pain-related health status to have both used non-TNF inhibitor biological therapy, and experienced more b/tsDMARD treatment modifications, is consistent with more refractory and difficult-to-treat disease. Indeed, a prior study of ARAD participants identified that a lack of treatment response and side effects were the most common reasons for changing b/tsDMARDs, regardless of the line of treatment choice.[53] High pain level at the outset which persisted for up to 12 months was a strong predictor of discontinuation of TNF inhibitors, as shown in a British study of patients with RA.[54] Intriguingly, this was predominantly driven by the patient-reported pain/health components (as opposed to the inflammatory components) of the DAS28.[54]

In the current T2T strategy in managing patients with RA, the best approach to implement PGA in assessing

disease activity in RA remains controversial. Specifically, dilemma remains on how best to incorporate a comprehensive evaluation of the overall well-being and the patient-reported disease impact of individuals living with RA, distinct from the disease inflammation.[17] Although PGA is not necessarily a true reflection of biomarker of disease activity in RA, our study confirms the importance of early and consistent identification and intervention of pain-related health concerns in those at-risk individuals throughout the disease trajectory, as proposed in the current EULAR definition of 'difficult-to-treat' RA.[55] There is emerging evidence that the treatment response with regards to the self-reported pain/health (tender joint counts, global health) components of the DAS28 may be uncoupled from the inflammatory components response in some patients when assessing RA disease activity, suggesting a greater contribution of non-inflammatory factors, including central sensitisation, to pain in these patients.[12 13] In addition, a pragmatic dual-target strategy, focusing on disease inflammation and disease impact as separate composite indices, has been proposed to further refine the definition of disease remission in RA.[17 56 57] Focusing on capturing target information on disease impact, Patient Experienced Symptom State and seven items of Rheumatoid Arthritis Impact of Disease are some of the promising PGA tools that are feasible and universally acceptable for regular use in clinical practice.[17 58 59] Unfortunately, in our study, we were not able to evaluate this factor as disease activity information was not available in the ARAD cohort. Nonetheless, our study results indicate there is an unmet need to incorporate a careful well-being evaluation of patients with high pain and poor health status at diagnosis with the view to the development of appropriate management strategies in addition to suppression of inflammatory disease. Overarchingly, when implemented early from the outset of RA diagnosis, integrative health approaches such as psychological and social welfare access and support, interventions in physical activity and lifestyle factors, and management of comorbidities and related modifiable risk factors may influence the overall outlook of the health status of patients living with RA.[60 61] Timely use of these valuable integrative health strategies may promote more sustainable multidisciplinary care for patients with RA.

This was a long-term longitudinal study of pain-related health outcomes in a well-characterised, well-treated Australian RA cohort. Australia has universal healthcare, and all participants were under the care of a rheumatologist, with access to appropriate medications under the Pharmaceutical Benefits Scheme (PBS). Further, our cohort was homogenous in relation to ancestry and language. Therefore, confounding due to major inequities in access to, and navigation of healthcare were likely to be minimised. However, there are other limitations in our study. First, disease activity information was not available, limiting our study capability to track the relationship between disease activity and pain/health status. Second, medication use was self-reported. Although the accuracy of self-reported medication use by ARAD participants has been previously validated against data from the Australian PBS, dosage information and exact duration of medication use was not available.[62 63] Third, data on other non-inflammatory rheumatological diagnoses were not specifically captured in the ARAD dataset, and therefore, our study results may not be generalisable to patients with RA and other concomitant chronic pain conditions such as fibromyalgia. Fourth, in our trajectory analysis, although we did not perform any training, testing and validation of our study dataset, we have based our optimal model selection on the recommended standard model parameters required for trajectory study reporting, such as the use of AIC, BIC, log-likelihood criteria, entropy and the average posterior probability of class membership.[43]

In summary, poorer pain-related health status in patients with diagnosed RA in this ARAD cohort is associated with sociodemographic and lifestyle factors, and these time-varying factors do not appreciably improve during follow-up despite increased opioids, prednisolone and anti-inflammatory medication use as well as b/tsDMARD treatment modification. Early identification of those potentially at risk of worse prognosis in the context of persistently poorer pain-related health status in RA is necessary. Holistically, there is an unspoken requisite to consider the overall outlook of well-being in patients with RA when assessing disease activity and treatment response, ideally at the time of diagnosis and continuously throughout the disease course. Having better understanding of the evolution of health status in patients living with RA, alongside their pain experience, will fundamentally enrich the opportunities in providing high-quality patient-focused care.

Author affiliations
[1]Discipline of Medicine, The University of Adelaide, Adelaide, South Australia, Australia
[2]Rheumatology Research Group, Basil Hetzel Institute for Translational Health Research, The Queen Elizabeth Hospital, Woodville South, South Australia, Australia
[3]Deaprtment of Rheumatology, The Queen Elizabeth Hospital, Woodville South, South Australia, Australia
[4]Department of Rheumatology, Royal Prince Alfred Hospital, Camperdown, New South Wales, Australia
[5]Institute for Musculoskeletal Health, The University of Sydney and Sydney Local Health District, Sydney, New South Wales, Australia
[6]Sydney School of Public Health, Faculty of Medicine and Health, The University of Sydney, Sydney, New South Wales, Australia
[7]Department of Medicine, The University of Queensland, Brisbane, Queensland, Australia
[8]Department of Rheumatology, Redcliffe Hospital, Redcliffe, Queensland, Australia
[9]Department of Medicine, University of New South Wales, Sydney, New South Wales, Australia
[10]Department of Rheumatology, St George Hospital, Kogarah, New South Wales, Australia
[11]Florance and Cope Professorial Department of Rheumatology, Royal North Shore Hospital, St Leonards, New South Wales, Australia
[12]Department of Rheumatology, Institute of Bone and Joint Research at Kolling Institute, University of Sydney, Sydney, New South Wales, Australia
[13]Department of Epidemiology and Preventive Medicine, School of Public Health and Preventive Medicine, Monash University, Victoria, Australia

Twitter Huai Leng Pisaniello @huaileng_jess, Susan Lester @Lester_Sue1, Oscar Russell @oscar_russell, Rachel Black @dr_rachelblack, Bethan Richards @BethanRichards3, Lyn March @lynmarch1, Rachelle Buchbinder @RachelleBuchbin, Samuel L Whittle @samwhittle and Catherine L Hill @CatherineL_Hill

Acknowledgements The authors sincerely acknowledge and thank the rheumatologists and ARAD participants for their ARAD data contribution. The authors would like to thank the ARAD Steering Committee and the ARAD Database staff members.

Contributors HLP, SEL, SLW and CLH contributed to the conception and design of the work, the acquisition, analysis and interpretation of the data. HLP contributed to the main drafting and the writing of the manuscript and all authors (HLP, SEL, OR, RB, JT, BR, CB, ML, LM, RB, SLW, CLH) contributed to the subsequent drafting and revision of the manuscript. All authors (HLP, SEL, OR, RB, JT, BR, CB, ML, LM, RB, SLW, CLH) read and approved the final manuscript. HLP is responsible for the overall content as the guarantor.

Funding The Australian Rheumatology Association Database (ARAD) receives support of unrestricted educational grants administered through the Australian Rheumatology Association from Pfizer Australia, AbbVie Pty Ltd, Eli Lilly Australia Pty Ltd, Sanofi Australia, Celgene Australian & NZ, Bristol Myers Squibb Australia Pty Ltd, Amgen Australia Pty Ltd, Aventis, AstraZeneca, and Roche. There is no current supporting funding. ARAD was previously supported by an Australian National Health and Medical Research Council (NHMRC) Enabling Grant (ID 384330). Infrastructure support for ARAD is provided by Cabrini Health, Monash University, Royal North Shore Hospital, and the Australian Rheumatology Association (ARA). This manuscript formed part of HLP's Ph.D. work, for which HLP was the recipient of the Ken Muirden Overseas Training Fellowship from the Arthritis Australia, an educational grant funded by the ARA, and HLP also received the Australia Postgraduate Scholarship from the University of Adelaide. RB is funded by an NHMRC Investigator Fellowship (APP1194483).

Competing interests None declared.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and was approved by ARAD has ethics approval obtained from Monash University and other sites, including Central Adelaide Local Health Network (CALHN). This study was granted approval by the ARAD Steering Committee. This study has ethics approval obtained from the CALHN Human Research Ethics Committee. ARAD participants provided informed consent to be enrolled in ARAD. Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request. The dataset used and analysed specific for this study may be made upon reasonable request to the ARAD steering committee (https://arad.org.au).

ORCID iDs
Huai Leng Pisaniello http://orcid.org/0000-0002-0425-1697
Rachelle Buchbinder http://orcid.org/0000-0002-0597-0933

REFERENCES

1 Emery P. Early referral recommendation for newly diagnosed rheumatoid arthritis: evidence based development of a clinical guide. *Ann Rheum Dis* 2002;61:290–7.
2 Heiberg T, Finset A, Uhlig T, *et al*. Seven year changes in health status and priorities for improvement of health in patients with rheumatoid arthritis. *Ann Rheum Dis* 2005;64:191–5.
3 Sparks JA. Rheumatoid arthritis. *Ann Intern Med* 2019;170:ITC1–16.
4 Lacaille D, Avina-Zubieta JA, Sayre EC, *et al*. Improvement in 5-year mortality in incident rheumatoid arthritis compared with the general population-closing the mortality gap. *Ann Rheum Dis* 2017;76:1057–63.
5 Markusse IM, Akdemir G, Dirven L, *et al*. Long-term outcomes of patients with recent-onset rheumatoid arthritis after 10 years of tight controlled treatment: A randomized trial. *Ann Intern Med* 2016;164:523–31.
6 Uhlig T, Heiberg T, Mowinckel P, *et al*. Rheumatoid arthritis is milder in the new millennium: health status in patients with rheumatoid arthritis 1994-2004. *Ann Rheum Dis* 2008;67:1710–5.
7 Lee YC, Cui J, Lu B, *et al*. Pain persists in Das28 rheumatoid arthritis remission but not in ACR/EULAR remission: a longitudinal observational study. *Arthritis Res Ther* 2011;13:R83.
8 Nieuwenhuis WP, de Wit MP, Boonen A, *et al*. Changes in the clinical presentation of patients with rheumatoid arthritis from the early 1990s to the years 2010: earlier identification but more severe patient reported outcomes. *Ann Rheum Dis* 2016;75:2054–6.
9 Prevoo ML, van 't Hof MA, Kuper HH, *et al*. Modified disease activity scores that include twenty-eight-joint counts. development and validation in a prospective longitudinal study of patients with rheumatoid arthritis. *Arthritis Rheum* 1995;38:44–8.
10 van der Heijde DM, van't Hof MA, van Riel PL, *et al*. Disease activity score. *Ann Rheum Dis* 1992;51:140.
11 Barton JL, Imboden J, Graf J, *et al*. Patient-physician Discordance in assessments of global disease severity in rheumatoid arthritis. *Arthritis Care Res (Hoboken)* 2010;62:857–64.
12 McWilliams DF, Zhang W, Mansell JS, *et al*. Predictors of change in bodily pain in early rheumatoid arthritis: an inception cohort study. *Arthritis Care Res* 2012;64:1505–13.
13 Pisaniello HL, Whittle SL, Lester S, *et al*. Using the derived 28-joint disease activity score patient-reported components (Das28-P) index as a discriminatory measure of response to disease-modifying anti-rheumatic drug therapy in early rheumatoid arthritis. *BMC Rheumatol* 2022;6:67.
14 Studenic P, Aletaha D, de Wit M, *et al*. American college of rheumatology/EULAR remission criteria for rheumatoid arthritis: 2022 revision. *Ann Rheum Dis* 2023;82:74–80.
15 Studenic P, Smolen JS, Aletaha D. Near misses of ACR/EULAR criteria for remission: effects of patient global assessment in Boolean and index-based definitions. *Ann Rheum Dis* 2012;71:1702–5.
16 Brites L, Rovisco J, Costa F, *et al*. High patient global assessment scores in patients with rheumatoid arthritis otherwise in remission do not reflect Subclinical inflammation. *Joint Bone Spine* 2021;88:105242.
17 Duarte C, Ferreira RJO, Santos EJF, *et al*. Treating-to-target in rheumatology: theory and practice. *Best Pract Res Clin Rheumatol* 2022;36:101735.
18 Callahan D. The WHO definition of 'health *Stud Hastings Cent* 1973;1:77–88.
19 Health Do. What is health? 2022. Available: https://www.aihw.gov.au/reports/australias-health/what-is-health
20 Rumsfeld JS. Health status and clinical practice: when will they meet *Circulation* 2002;106:5–7.
21 Heiberg T, Kvien TK. Preferences for improved health examined in 1,024 patients with rheumatoid arthritis: pain has highest priority. *Arthritis Rheum* 2002;47:391–7.
22 Minnock P, FitzGerald O, Bresnihan B. Women with established rheumatoid arthritis perceive pain as the predominant impairment of health status. *Rheumatology (Oxford)* 2003;42:995–1000.
23 Sanderson T, Morris M, Calnan M, *et al*. Patient perspective of measuring treatment efficacy: the rheumatoid arthritis patient priorities for pharmacologic interventions outcomes. *Arthritis Care Res (Hoboken)* 2010;62:647–56.
24 Vladimirova N, Jespersen A, Bartels EM, *et al*. Pain Sensitisation in women with active rheumatoid arthritis: A comparative cross-sectional study. *Arthritis* 2015;2015:434109.
25 Zhang A, Lee YC. Mechanisms for joint pain in rheumatoid arthritis (RA): from Cytokines to central sensitization. *Curr Osteoporos Rep* 2018;16:603–10.
26 Courvoisier DS, Agoritsas T, Glauser J, *et al*. Pain as an important Predictor of Psychosocial health in patients with rheumatoid arthritis. *Arthritis Care Res* 2012;64:190–6.
27 Katchamart W, Narongroeknawin P, Chanapai W, *et al*. Health-related quality of life in patients with rheumatoid arthritis. *BMC Rheumatol* 2019;3:34.
28 Malm K, Bergman S, Andersson ML, *et al*. Quality of life in patients with established rheumatoid arthritis: A Phenomenographic study. *SAGE Open Med* 2017;5:2050312117713647.

29 Martinec R, Pinjatela R, Balen D. Quality of life in patients with rheumatoid arthritis - a preliminary study. *Acta Clin Croat* 2019;58:157–66.
30 Vergne-Salle P, Pouplin S, Trouvin AP, *et al*. The burden of pain in rheumatoid arthritis: impact of disease activity and psychological factors. *Eur J Pain* 2020;24:1979–89.
31 Buchbinder R, March L, Lassere M, *et al*. Effect of treatment with biological agents for arthritis in Australia: the Australian rheumatology Association database. *Intern Med J* 2007;37:591–600.
32 Williams MP, Buchbinder R, March L, *et al*. The Australian rheumatology Association database (ARAD). *Semin Arthritis Rheum* 2011;40:e2–3.
33 Fries JF, Spitz P, Kraines RG, *et al*. Measurement of patient outcome in arthritis. *Arthritis Rheum* 1980;23:137–45.
34 Hawthorne G, Osborne RH, Taylor A, *et al*. The Sf36 version 2: critical analyses of population weights, scoring Algorithms and population norms. *Qual Life Res* 2007;16:661–73.
35 Hawthorne G, Richardson J, Osborne R. The assessment of quality of life (Aqol) instrument: a Psychometric measure of health-related quality of life. *Qual Life Res* 1999;8:209–24.
36 Rabin R, de Charro F. EQ-5D: a measure of health status from the Euroqol group. *Ann Med* 2001;33:337–43.
37 Statistics ABo. Census of population and housing: socio-economic indexes for areas (SEIFA). statistical area level 1, indexes 2016. 2016. Available: https://www.abs.gov.au/AUSSTATS/abs@.nsf/DetailsPage/2033.0.55.0012016?OpenDocument
38 England BR, Sayles H, Mikuls TR, *et al*. Validation of the rheumatic disease Comorbidity index. *Arthritis Care & Research* 2015;67:865–72.
39 Jones BL, Nagin DS, Roeder K. A SAS procedure based on mixture models for estimating developmental Trajectories. *Sociological Methods & Research* 2001;29:374–93.
40 Jones BL, Nagin DS. Advances in group-based trajectory modeling and an SAS procedure for estimating them. *Sociological Methods & Research* 2007;35:542–71.
41 Jones BL. A note on a STATA Plugin for estimating group-based trajectory models. *Sociological Methods & Research* 2013;42:608–13.
42 Nagin DS, Odgers CL. Group-based trajectory modeling in clinical research. *Annu Rev Clin Psychol* 2010;6:109–38.
43 van de Schoot R, Sijbrandij M, Winter SD, *et al*. The Grolts-checklist: guidelines for reporting on latent trajectory studies. *Structural Equation Modeling: A Multidisciplinary Journal* 2017;24:451–67.
44 Kumaradev S, Roux C, Sellam J, *et al*. Socio-demographic determinants in the evolution of pain in inflammatory rheumatic diseases: results from ESPOIR and DESIR cohorts. *Rheumatology (Oxford)* 2022;61:1496–509.
45 Nikiphorou E, Norton S, Carpenter L, *et al*. Secular changes in clinical features at presentation of rheumatoid arthritis: increase in Comorbidity but improved inflammatory States. *Arthritis Care Res (Hoboken)* 2017;69:21–7.
46 Backman CL. Psychosocial aspects in the management of arthritis pain. *Arthritis Res Ther* 2006;8:221.
47 Black RJ, Richards B, Lester S, *et al*. Factors associated with commencing and ceasing opioid therapy in patients with rheumatoid arthritis. *Semin Arthritis Rheum* 2019;49:351–7.
48 An Australian living guideline for the pharmacological management of inflammatory arthritis: opioids for pain management. 2022. Available: https://app.magicapp.org/#/guideline/LqRV3n
49 Lee YC, Kremer J, Guan H, *et al*. Chronic opioid use in rheumatoid arthritis: prevalence and predictors. *Arthritis Rheumatol* 2019;71:670–7.
50 An Australian living guideline for the pharmacological management of inflammatory arthritis: glucocorticoid therapy as an adjunct to DMARD therapy in the treatment of rheumatoid arthritis. 2022. Available: https://app.magicapp.org/#/guideline/LqRV3n
51 Wohlfahrt A, Muhammad LN, Song J, *et al*. Pain mechanisms associated with disease activity in patients with rheumatoid arthritis treated with disease-modifying Antirheumatic drugs: A regression tree analysis. *J Rheumatol* 2023;50:741–7.
52 McWilliams DF, Walsh DA. Inflammatory and Noninflammatory disease activity in rheumatoid arthritis: the effect of pain on personalized medicine. *J Rheumatol* 2023;50:721–3.
53 Fletcher A, Lassere M, March L, *et al*. Patterns of biologic and targeted-synthetic disease-modifying Antirheumatic drug use in rheumatoid arthritis in Australia. *Rheumatology (Oxford)* 2022;61:3939–51.
54 McWilliams DF, Walsh DA. Factors predicting pain and early discontinuation of tumour necrosis factor-alpha-inhibitors in people with rheumatoid arthritis: results from the British society for rheumatology Biologics register. *BMC Musculoskelet Disord* 2016;17:337.
55 Nagy G, Roodenrijs NM, Welsing PM, *et al*. EULAR definition of difficult-to-treat rheumatoid arthritis. *Ann Rheum Dis* 2021;80:31–5.
56 Ferreira RJO, Duarte C, Ndosi M, *et al*. Suppressing inflammation in rheumatoid arthritis: does patient global assessment blur the target? A practice-based call for a paradigm change. *Arthritis Care Res (Hoboken)* 2018;70:369–78.
57 Ferreira RJO, Ndosi M, de Wit M, *et al*. Dual target strategy: a proposal to mitigate the risk of Overtreatment and enhance patient satisfaction in rheumatoid arthritis. *Ann Rheum Dis* 2019;78:e109.
58 Duarte C, Santos E, da Silva JAP, *et al*. The patient experienced symptom state (PESS): a patient-reported global outcome measure that may better reflect disease remission status. *Rheumatology (Oxford)* 2020;59:3458–67.
59 Duarte C, Santos EJF, Ferreira RJO, *et al*. Validity and reliability of the EULAR instrument RAID.7 as a tool to assess individual domains of impact of disease in rheumatoid arthritis: a cross-sectional study of 671 patients. *RMD Open* 2021;7:e001539.
60 Gwinnutt JM, Wieczorek M, Balanescu A, *et al*. EULAR recommendations regarding lifestyle Behaviours and work participation to prevent progression of rheumatic and musculoskeletal diseases. *Ann Rheum Dis* 2023;82:48–56.
61 Rausch Osthoff A-K, Niedermann K, Braun J, *et al*. EULAR recommendations for physical activity in people with inflammatory arthritis and osteoarthritis. *Ann Rheum Dis* 2018;77:1251–60.
62 Lynch T, Buchbinder R, *et al*. Predictors of discordant prescription medication self-report in the Australian rheumatology Association database (ARAD) cohort. Australian Rheumatology Association 62nd Annual Scientific Meeting 20-22 May 2022; 2022
63 Lynch T, Barrett C. Assessing self-reported prescription medication validity in the Australian rheumatology Association database (ARAD) using pharmaceutical benefits scheme (PBS) claims data ARA-NSW 2021. 43rd Annual NSW Branch Meeting; Sydney, NSW, Australia, 2021