Health Assessment Questionnaire disability progression in early rheumatoid arthritis: Systematic review and analysis of two inception cohorts

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ABSTRACT

Objective: The Health Assessment Questionnaire is widely used for patients with inflammatory polyarthritis (IP) and its subset, rheumatoid arthritis (RA). In this study, we evaluated the progression of HAQ scores in RA (i) by systematically reviewing the published literature on the methods used to assess changes in functional disability over time and (ii) to study in detail HAQ progression in two large prospective observational studies from the UK.

Methods: Data from two large inception cohorts, ERAS and NOAR, were studied to determine trajectories of HAQ progression over time by applying latent class growth models (LCGMs) to each dataset separately. Age, sex, baseline DAS28, symptom duration, rheumatoid factor, fulfilment of the 1987 ACR criteria and socioeconomic status (SES) were included as potential predictors of HAQ trajectory subgroup membership.

Results: The literature search identified 49 studies showing that HAQ progression has mainly been based on average changes in the total study population. In the HAQ progression study, a LCGM with four HAQ trajectory subgroups was selected as providing the best fit to both cohorts. Old age, female sex, longer symptom duration, fulfilment of the 1987 ACR criteria, higher DAS28 and lower SES were associated with increased likelihood of membership of subgroups with worse HAQ progression.

Conclusion: Four distinct HAQ trajectory subgroups were derived from the ERAS and NOAR cohorts. The fact that the subgroups identified were nearly identical supports their validity. Identifying distinct groups of patients who are at risk of poor functional outcome may help to target therapy to those who are most likely to benefit.

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Introduction

The Health Assessment Questionnaire (HAQ) is the most widely used measure of function in studies of inflammatory polyarthritis (IP) and its subset, rheumatoid arthritis (RA) [1,2]. Worse functional disability is associated with increased cardiovascular and all-cause mortality [3,4], joint damage [5] and work disability in patients with IP and RA [6,7]. Functional disability is mainly...
associated with disease activity in early RA and with radiographic joint damage in patients with established disease. It is therefore often used as an outcome measure to assess the impact of disease over time [8–10]. Predictors of worse functional disability in the long-term include baseline or 1-year HAQ score [11–13], older age [12,14], female gender [12,14], disease activity [11,13–15], rheumatoid factor (RF) positivity or anti-citrullinated protein antibody (ACPA) positivity [16], radiographic damage [5,13,17,18], number of co-morbidities [10,19,20], low education [15] and low socio-economic status (SES) [17,21,22].

Previous research has suggested that the mean HAQ score over time is J-shaped with an initial improvement after treatment commencement followed by an insidious decline in patients with early RA [11,15,23]. However, the focus of most of these studies was on the average change over time in the total study population calculating mean changes in HAQ score over time or applying simple linear regression models to determine the association between disease duration and HAQ progression. In the last two decades, more advanced methods have become available to measure longitudinal data, such as repeated measurement regression analysis. However, in most studies, the change in HAQ scores over time has been measured at the group level. Few studies have attempted to identify subgroups defined in terms of their HAQ trajectory in IP and RA patients or considered their validity across cohorts. In a recent study that included patients with early RA recruited to the Early Rheumatoid Arthritis Study (ERAS) and followed up for 10 years, latent growth mixture modelling (LGMM) was used to determine whether the study population comprises distinct subgroups of patients with differing trajectories of functional disability [24]. It is important to determine if similar results can be found in other RA populations as well. In general, identification of distinct groups of patients who are at risk of poor outcome may help to target therapy to those who are most likely to benefit in the clinic.

The objectives of this study were (i) to give an overview of the methods used in the literature to assess functional disability over time and (ii) to identify common trajectories of HAQ progression over 15 years in two large prospective observational studies from the UK, i.e., ERAS and the Norfolk Arthritis Register (NOAR).

Methods

Systematic literature review

MEDLINE was searched to identify articles describing changes in HAQ scores over time in patients with RA or undifferentiated polyarthritis. The following keywords were used: (((exp Arthritis, Rheumatoid/) OR [inflammatory polyarthritis.mp] OR [undifferentiated arthritis.mp]) AND [health assessment questionnaire$.mp] OR [HAQ.mp] OR [functional.mp AND disability.mp])) NOT (((exp Arthritis, Juvenile Rheumatoid/) OR [JIA.mp]) NOT (((clinical trial, phase i/ OR clinical trial, phase ii/ OR clinical trial, phase iii/ OR clinical trial, phase iv/ OR controlled clinical trial/ OR randomized controlled trial/) OR [exp case reports/] OR [randomized clinical trial.mp])). The search was limited to the years “1980–2012” and English language. Studies were selected if they met the following inclusion criteria: Follow-up duration/disease duration ≥3 years, multiple (i.e., ≥3) cross-sectional assessments of HAQ in case of cross-sectional analysis, (M)HAQ used to measure functional disability and no intervention study (Fig. 1 for selection procedure). References of identified reviews and selected studies were checked for eligible articles.

HAQ trajectory study: Patients recruited to the Early Rheumatoid Arthritis Study (ERAS) and the Norfolk Arthritis Register (NOAR)

ERAS is an inception cohort to which consecutive patients thought to have RA by a consultant rheumatologist were recruited from the outpatient clinics of nine rheumatology departments in the UK between 1986 and 1997. Patients were included if they had a symptom duration of less than 2 years and were disease-modifying anti-rheumatic drug (DMARD) naïve [12,25]. Patients in ERAS were subsequently excluded if the diagnosis changed, for example, apparent early RA evolving to classical lupus or osteoarthritis.

NOAR is a primary care-based inception cohort of patients with early IP recruited in Norfolk, UK. Consecutive patients aged over 16 years with swelling in ≥2 joints that lasted ≥4 weeks were referred via the GP or rheumatologist to NOAR between 1990 and 1994 [26,27]. This analysis included all patients who had not been given a consultant diagnosis other than RA, undifferentiated IP, psoriatic arthritis or post-viral arthritis to explain their symptoms. Patients whose disease has gone into spontaneous long-term remission (no inflamed joints at the 3rd or 5th anniversary and not on disease-modifying anti-rheumatic drugs (DMARDs) or steroids) were followed up beyond the 5th anniversary; otherwise patients were followed up until the 5th anniversary if applicable.

Clinical and laboratory assessments and socio-economic status

Standard clinical assessments were made by trained research nurses in both studies at baseline and included date of symptom onset and number of swollen and tender joints. RA was defined according to the 1987 ACR criteria and applied cumulatively. At each visit, DMARD and biologics use, including start and stop date, was recorded. The two cohorts differed in laboratory assessments. In ERAS, routine haematology tests included the erythrocyte sedimentation rate (ESR) measured according to Westergren test and routine serology including RF. In NOAR, blood was collected and stored in −80°C freezers to measure RF (positive >40 mg/L) and C-reactive protein (CRP). Due to these small differences in data collection and visual analogue scale general well-being missing in NOAR, the 4-component DAS28 score based on ESR values was calculated in ERAS and the three-component DAS28 score based on CRP was calculated in NOAR.

Socio-economic status was defined as an area-level categorical variable, based on the Index of Multiple Deprivation (IMD) 2007. In the IMD, the UK is divided into “super output areas,” with a minimum population of 1000 (mean 1500). Information on income, employment, health, education, barriers to services, crime and living environment is used to assign a deprivation score to each super output area. These scores are then ranked across the country. For this study, we used postal codes to assign each patient...
to a nationwide deprivation rank and then to a nationally determined quartile of deprivation.

All patients completed the disability index of the modified British version of the Stanford Health Assessment Questionnaire (HAQ) [28] at baseline and at subsequent follow-up visits. The HAQ comprises 20 questions in eight categories. A score of 0 (no difficulty), 1 (some difficulty), 2 (much difficulty or need of assistance) or 3 (unable to perform) is given to each question; the highest score in each category represents the score for that category. The sum of scores is then divided by the number of categories, yielding a total score ranging from 0 (best) to 3 (worst). Although patients in ERAS completed the HAQ questionnaire annually after inclusion in the cohort, to resemble the NOAR assessment visits and to ensure that the models were validated using as similar datasets as possible, HAQ scores obtained at 1, 2, 3, 5, 7, 10 and 15 years after inclusion were used for these analyses. Sensitivity analysis using all the ERAS HAQ follow-up data indicated that this did not affect either the number or the shape of the trajectories in the best-fitting model. Patients with missing HAQ data at baseline and a symptom duration > 2 years were excluded from the analysis.

All patients gave written informed consent and both studies were approved by the relevant UK National Health Service Research Ethics Committees.

Statistical analysis

Baseline clinical and demographic data are described for both the cohorts. To determine trajectories of HAQ progression over time, latent class growth models (LCGMs) [29] were applied to the ERAS and NOAR datasets separately and independently. The model captures common characteristics of HAQ trajectories within a subpopulation through latent classes. A mixture of censored normal distributions was used to model the longitudinal HAQ outcomes over time. A censored normal LCGM was chosen because HAQ is a bounded score at 0 and 3. To determine the number of trajectory subgroups, we considered several factors including model-fit statistics such as the Akaike Information Criterion (AIC), the Bayesian Information Criterion (BIC) and the Lo–Mendell–Rubin likelihood ratio test. The best-fitting model was then identified, leaning towards parsimony in the number of trajectory groups. The model is based on a joint likelihood including two parts: an outcome model and a logistic regression model for class membership. Several time-dependent covariates, such as linear, quadratic, cubic and reciprocal (in ERAS) terms of year since registration, were included in the outcome part to model the trajectory shape within subgroups. Age, gender, baseline DAS28, symptom duration, RF, fulfilment of the ACR criteria for RA and SES were included as predictors of class membership. Odds ratios (ORs) and 95% confidence intervals (95% CI) were calculated for each class membership group with the lowest class membership as reference. Each patient was assigned to one of the trajectory groups for which he/she had the highest probability of membership. We also describe the percentage of patients receiving methotrexate and the percentage of patients using biologics during follow-up within each subgroup membership group. The LCGM analyses were performed by using M-Plus or SAS macro PROC TRAJ.

Results of systematic literature review

Description of identified studies

A total of 49 studies were identified: 17 studies including patients with early RA or IP (mean/median disease duration <2 years or including a group of patients with disease duration <2 years) [8,10,13–15,30–41] and 32 studies including patients with a disease duration of more than 2 years [19,20,42–71]. Table 1). The follow-up duration varied between studies ranging from a minimum of 3 years (i.e., inclusion criteria) [38,41,42,55,58,66] to > 15 years [31,33,51,57,67]. Age and gender distribution were representative of a general RA population, except in one study in which only women were included [10].

Methods used to evaluate change in HAQ score over time

Overall, different methods were used to assess change in HAQ score over time in both the early RA group and the established RA group (Table 1, column 8). In 29 studies, HAQ scores were measured cross-sectionally at more than 3 time-points following the same study population over time or for more than 3 groups of patients with increasing disease duration [10,13–15,30–32,34–39,41,42,45–47,51,53–55,58,59,62,64,66,68,69]. A J-shaped trajectory was observed in 12/14 (86%) cross-sectional studies including patients with early disease [10,13–15,30,32,34–39,41] and in 4/9 (44%) studies including patients with established disease [42,58,62,64].

Annual HAQ progression rates are shown in the last column of Table 1. In eight of the 29 cross-sectional studies, change in HAQ score was calculated by the following methods: subtracting HAQ scores obtained at two different time-points divided by the number of years of follow-up, calculating the median difference from ≤ 3 years disease duration groups [51], calculating median change during 3-year intervals [10], calculating mean change from the first assessment [34,37], calculating median change from 0 to 6 months and 2 until 3 years [66], calculating annualised AUC [55], calculating the mean effect size [46] or estimating the annual change in those with early RA and those with established RA [43].

In other studies, linear regression analysis was used to assess the association between disease duration and (change in) HAQ score including one time point per patient [10,15,19,31,33,44,48,61,64,65,68,71], including multiple time-points per patient [49,50,52,70], calculating the annual percentage reduction in average disability [56], including all of the available study observations measured during follow-up by using a dynamic panel data model for repeated measurements applying pooled time-series regression analysis, generalised estimating equations (GEE) [20,33,60,63,69,72], linear mixed-effects models with a random effect for the repeated observations [8,67,71], marginal structural model [40] and generalised linear models [47,60].

In a few studies, different regression models were constructed and the best fit was tested. In one study by Leigh et al. [50], methods used in economics (Tobit, fixed effects and dummy variable for cohort models) were applied to address the problems of censoring, panel data and cohort effects. In another study by Leigh and Fries [73], six different multiple regression analyses were performed, including individual or combinations of covariates (eg, years of disease duration, years of disease duration in gender, education and age). Wolfe [33] constructed various groups and individual linear and non-linear (fractional polynomial) regression models. Three main findings were observed when analysing at a group level: (i) HAQ disability scores were already high at disease onset; (ii) annual HAQ progression was very slow (i.e., ~0.03 units per year) and (iii) the explained variance was only 5%. However, when including covariates to the model, the fit of the model became better and 51% of the variance could be explained. When applying a fractional polynomial model (eg, including HAQ score and HAQ score fraction in the model), the explained variance was 37%.

Overall, change in HAQ scores was mainly based on analysis in the total study population without identification of distinct
<table>
<thead>
<tr>
<th>Study (country)</th>
<th>n</th>
<th>Age</th>
<th>Female gender</th>
<th>Disease duration</th>
<th>Follow-up duration</th>
<th>HAQ baseline</th>
<th>Analysis method</th>
<th>Progression HAQ score</th>
<th>HAQ scores/change over time</th>
</tr>
</thead>
<tbody>
<tr>
<td>van Zeben et al. [30] (NL)</td>
<td>127</td>
<td>DR4+; 34.6 (9.0)</td>
<td>NA</td>
<td>1.7 (1.3) yrs</td>
<td>6.7 (2.2)</td>
<td>0.6 (0.60)</td>
<td>Cross-sectional</td>
<td>Mean (SD) score at 1, 4 and 8 yrs</td>
<td>DR4+; 0.69 (0.6); 0.50 (0.62); 0.67 (0.73); DR4+; 0.70 (0.56); 0.88 (0.68); 1.05 (1.02)</td>
</tr>
<tr>
<td>Wolfe et al. [31], (USA)</td>
<td>561</td>
<td>53.7 (14.4)</td>
<td>72.0 %</td>
<td>1.6 (0.56) yrs</td>
<td>6.5 (1.6)</td>
<td>0.70 (0.56)</td>
<td>Cross-sectional, least square methodology using all time-points for each patient (Figure only)</td>
<td>Mean (SD) score at first visit: 0–2; 2–7; 7–12; 12–17 and 17–22 yrs</td>
<td>Mean (SD) score at first visit: 0–2; 2–7; 7–12; 12–17 and 17–22 yrs</td>
</tr>
<tr>
<td>Guillemin et al. [15] (NL and FR), EURIDISS</td>
<td>NL = 221 FR = 116</td>
<td>54.8</td>
<td>1.9 (M/F)</td>
<td>&lt; 1 yrs</td>
<td>5 yrs</td>
<td>1.18</td>
<td>Cross-sectional crude mean values and mean-adjusted values. Multivariate linear regression.</td>
<td>Mean score and per year increase disease duration (I) and disease duration disease duration6 (II)</td>
<td>&lt; 1 yrs: 0.99 and 1.04 1–2 yrs: 0.83 and 0.94 2–3 yrs: 1.22 and 1.16 3–4 yrs: 1.29 and 1.23 4–5 yrs: 1.55 and 1.43 1: β = 0.10; II: β = –0.13 and β = 0.023</td>
</tr>
<tr>
<td>Munro et al. [32] (UK)</td>
<td>I = 53 (44–60) II=54 (44–64) III=57 (50–65)</td>
<td>I = 75% II = 85% III = 79%</td>
<td>I = 0–2 yrs</td>
<td>I = 1.88 (1.32–2.38)</td>
<td>I = 1.75 (1.19–2.25)</td>
<td>I = 2.00 (1.38–2.38)</td>
<td>Cross-sectional</td>
<td>Median (IQR) score at baseline and at 1, 2, 3, 4 and 5 yrs</td>
<td>Group I: 1.06 (0.53–1.88); Group II: 1.00 (0.13–1.38); Group III: 1.00 (0.44–1.75); 1.13 (0.63–2.00); 1.25 (0.50–2.00), group II: 1.13 (0.66–1.72); 1.25 (0.75–1.83); 1.27 (0.75–1.88); 1.57 (0.88–2.25); 1.81 (1.03–2.22), group III, 1.57 (0.97–2.22); 1.50 (1.00–2.25); 1.75 (1.13–2.38); 1.75 (0.88–2.35); 2.13 (1.23–2.50)</td>
</tr>
<tr>
<td>Dossaeras-Bakker et al. [10] (NL)</td>
<td>112</td>
<td>37 (8.4)</td>
<td>100%</td>
<td>1.0 (0–5) yrs</td>
<td>Median = 12 (range: 10–14) yrs</td>
<td>0.75</td>
<td>Cross-sectional and multiple linear regression at 12 yrs</td>
<td>Median change: 0–3; 3–6 and 6–12 yrs</td>
<td>0 (–1.50; 1.97) 4–6 yrs = 0 (–1.25; 1.29) 6–12 yrs = 1.3 (–1.25; 2.16) β = 0.043 (95% CI: –0.01 to 0.097)</td>
</tr>
<tr>
<td>Wiles et al. [14] (UK)</td>
<td>684</td>
<td>55 (42–68)</td>
<td>67%</td>
<td>5.9 (2.9–11.9)</td>
<td>0.81 (0.25–1.50)</td>
<td>Cross-sectional at different time-points</td>
<td>Median (IQR) score at baseline and at 1, 2, 3 and 5 yrs</td>
<td>0.81 (0.25–1.50); 0.50 (0.125–1.375); 0.625 (0.25–1.375); 0.875 (0.25–1.625)</td>
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<tr>
<td>Wolfe [33] (US)</td>
<td>1843</td>
<td>54.6 (12.7) (S)</td>
<td>72% (S)</td>
<td>16.7 (1.09) yrs</td>
<td>1.08 (0.69)</td>
<td>1) Ordinary least-squares linear regression using one data point in time per patient 2) GEE (all) 3) GEE (S)</td>
<td>Annual change</td>
<td>0.002 (95% CI 0.016–0.24) 0.030 (95% CI 0.027–0.034) 0.020 (95% CI 0.01–0.03)</td>
<td></td>
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<tr>
<td>Kroot et al. [34] (NL)</td>
<td>S: 50</td>
<td>53.3 (18–86)</td>
<td>62%</td>
<td>&lt; 1 yr</td>
<td>10 yrs</td>
<td>0.67 (0.197)</td>
<td>Cross-sectional</td>
<td>Annual mean scores from baseline until 10 yrs (mean difference from baseline)</td>
<td>Baseline = 0.67; 0.49 (–0.25); 0.55 (–0.23); 0.53 (–0.24); 0.56 (–0.18); 0.55 (–0.19); 0.56 (–0.10); 0.63 (–0.01); 0.65 (–0.01); 0.65 (–0.07)</td>
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<tr>
<td>Study</td>
<td>n</td>
<td>Disease duration</td>
<td>Disease severity</td>
<td>Duration</td>
<td>Follow-up</td>
<td>Methodology</td>
<td>Disease activity</td>
<td>Change rate</td>
<td>p-value</td>
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<tr>
<td>Welsing et al. [8]</td>
<td>378</td>
<td>54.8 (14.8)</td>
<td>63.8%</td>
<td>&lt; 1 yr</td>
<td>6.29 (3.8) yrs</td>
<td>0.47 (0.17–1.1)</td>
<td>Adjusted linear mixed model</td>
<td>Adjusted annual change</td>
<td>p = −0.02 units per yr</td>
</tr>
<tr>
<td>Ahlmen et al. [35]</td>
<td>W: 343</td>
<td>W: 54 (16)</td>
<td>62%</td>
<td>&lt; 1 yr</td>
<td>5 yrs</td>
<td>W: 1.05 (0.62)</td>
<td>Mean (SD) score at baseline and at 1, 2 and 5 yrs</td>
<td>W: 1.05 (0.62); 0.62 (0.58); 0.65 (0.65); 0.73 (0.68)</td>
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<tr>
<td></td>
<td>M: 206</td>
<td>M: 61 (13)</td>
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<td></td>
<td>M: 0.84 (0.55)</td>
<td>Mean (range) score at baseline and at 3 and 5 yrs</td>
<td>M: 0.84 (0.55); 0.44 (0.49); 0.47 (0.52); 0.51 (0.56) per yr</td>
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<tr>
<td>Combe et al. [13]</td>
<td>191</td>
<td>50.5 (14.7)</td>
<td>73%</td>
<td>3.6 (2.6) months</td>
<td>5 yrs</td>
<td>1.3 (0–2.75)</td>
<td>Cross-sectional at different time-points</td>
<td>Mean (range) score at baseline and at 3 and 5 yrs</td>
<td>1.3 (0–2.75); 0.5 (0–2.5); 0.6 (0–3.0)</td>
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<tr>
<td>Benton et al. [36]</td>
<td>34</td>
<td>Median = 48.5</td>
<td>62%</td>
<td>Median = 4 months</td>
<td>6 yrs</td>
<td>0.33 (0–1.6)</td>
<td>Cross-sectional at different time-points</td>
<td>Median score at baseline and at 1 and 6 yrs</td>
<td>0.6; 0.16; 0.33</td>
</tr>
<tr>
<td>Persson et al. [37]</td>
<td>158</td>
<td>52 (42–59)</td>
<td>64%</td>
<td>10 (6–14) months</td>
<td>4 yrs</td>
<td>0.92 (0.60)</td>
<td>Cross-sectional at different time-points</td>
<td>Mean (SD) score at baseline and at 1, 2, 3, 4 and 5 yrs</td>
<td>0.918 (0.60); 0.843 (0.56); 0.775 (0.53); 0.957 (0.57); 0.989 (0.58)</td>
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<tr>
<td>Proudman et al. [38]</td>
<td>61</td>
<td>56 (14)</td>
<td>76%</td>
<td>12 (6–104) weeks</td>
<td>36 months</td>
<td>0.9 (0.5)</td>
<td>Cross-sectional at different time-points</td>
<td>Mean (SD) score at baseline and at 12, 24 and 36 months</td>
<td>0.9 (0.5); 0.3 (0.4); 0.2 (0.3); 0.3 (0.4)</td>
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<td>Courvoisier et al. [39]</td>
<td>112</td>
<td>50.4 (12.6)</td>
<td>80.3%</td>
<td>3.9 (2.8) months</td>
<td>10 yrs</td>
<td>1.29 (0.71)</td>
<td>Cross-sectional at different time-points</td>
<td>Mean (SD) score at baseline and at 3, 5 and 10 yrs</td>
<td>1.29 (0.71); 0.53 (0.62); 0.57 (0.62); and 0.75 (0.71)</td>
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<tr>
<td>Farragher et al. [40]</td>
<td>1084</td>
<td>53 (41–66)</td>
<td>65.4%</td>
<td>4 (2–10) months</td>
<td>10 yrs</td>
<td>0.75 (0.25–1.375)</td>
<td>Change over 10 yrs and annual rate, adjusted MDIC treated vs not treated (T vs NT)</td>
<td>Mean (SD) score at baseline and at 1, 2, 3, 4 and 5 yrs</td>
<td>0.24 (95% CI: 0.14–0.33) and NT: 0.13 (95% CI: 0.05–0.21)</td>
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<td>T: -0.062 (0.43); 1.009 (0.60) [0.085 (0.50)]; 0.957 (0.61) [0.049 (0.49)]; 0.989 (0.57) [0.085 (0.53)]</td>
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<td>Adj MDIC: -0.01 (95% CI: -0.20 to 0.19)</td>
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<td></td>
<td>1.15 (0.68); 1.08 (0.66); 1.05 (0.72); 0.98 (0.74)</td>
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<tr>
<td>Benka et al. [41]</td>
<td>116</td>
<td>47.6 (12.4)</td>
<td>85%</td>
<td>22.1 (16.1) months</td>
<td>3 yrs</td>
<td>1.15 (0.68)</td>
<td>Cross-sectional at different time-points</td>
<td>Mean (SD) score at baseline and at 1, 2 and 3 yrs</td>
<td>1.15 (0.68); 1.14 (0.68); 1.10 (0.68); 0.98 (0.74)</td>
</tr>
</tbody>
</table>

### Disease duration > 2 yrs

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>Disease duration</th>
<th>Disease severity</th>
<th>Duration</th>
<th>Follow-up</th>
<th>Methodology</th>
<th>Disease activity</th>
<th>Change rate</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fries et al. [42]</td>
<td>322</td>
<td>~51 yrs</td>
<td>NA</td>
<td>~12 yrs</td>
<td>36 months</td>
<td>0.80</td>
<td>Cross-sectional at different time-points</td>
<td>Mean scores at baseline and at 6, 12, 18, 24, 30 and 36 months</td>
<td>0.80; 0.78; 0.83; 0.83; 0.93; 1.11; 1.18</td>
</tr>
<tr>
<td>Sherrer et al. [43]</td>
<td>681</td>
<td>62 (13)</td>
<td>72%</td>
<td>10 (6) yrs</td>
<td>12 (6) yrs</td>
<td>Cross-sectional: not available</td>
<td>Mean HAQ score at the end of the study</td>
<td>Mean HAQ score and change in HAQ after baseline</td>
<td>0.10 and 0.02</td>
</tr>
<tr>
<td>Wolfe and Cathay [44]</td>
<td>1274</td>
<td>10.3 (12)</td>
<td>71%</td>
<td>7.4 (9.11) yrs</td>
<td>Mean = 3.9 (3.31)</td>
<td>Linear regression at baseline and for change in HAQ after baseline</td>
<td>Mean scores at baseline and at 6, 12, 18, 24, 30 and 36 months</td>
<td>Baseline: β = 0.013 HAQ score per yr increase in disease duration and p = 0.11 change HAQ score per increase in disease duration</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>T: 2.94 (95% CI: 0.14–0.33) and NT: 0.13 (95% CI: 0.05–0.21)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Adj MDIC: -0.01 (95% CI: -0.20 to 0.19)</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1.15 (0.68); 1.08 (0.66); 1.05 (0.72); 0.98 (0.74)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Epstein et al. [45]</td>
<td>574</td>
<td>55</td>
<td>75%</td>
<td>10.2 yrs</td>
<td>5 yrs</td>
<td>1.18</td>
<td>Cross-sectional at different time-points</td>
<td>Unadj and adj mean score at baseline and at 1, 2, 3, 4 and 5 yrs, GEE only p-value shown</td>
<td>Unadj: 1.30 vs 1.09; 1.24 vs 1.08; 1.30 vs 1.16; 1.32 vs 1.16; 1.41 vs 1.21; 1.34 vs 1.00; Adj: 1.18 vs 1.20; 1.24 vs 1.27; 1.25 vs 1.29; 1.35 vs 1.32; 1.08 vs 1.11</td>
</tr>
<tr>
<td>Study (country)</td>
<td>n</td>
<td>Age</td>
<td>Female gender</td>
<td>Disease duration</td>
<td>Follow-up duration</td>
<td>HAQ baseline</td>
<td>Analysis method</td>
<td>Progression HAQ score</td>
<td>HAQ scores/change over time</td>
</tr>
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<tr>
<td>Hawley and Wolfe [46]</td>
<td>157</td>
<td>50.8 (12.5)</td>
<td>75%</td>
<td>6.7 (8.2) yrs</td>
<td>Mean = 9.8 SD 0.75</td>
<td>0.5 (0.5)</td>
<td>Cross-sectional at different time-points</td>
<td>Mean (effect size from baseline) at baseline and at 2, 5 and 10 yrs</td>
<td>0.5 (NA); 0.5 (−0.01); 1.3 (−1.63); 1.6 (−2.39)</td>
</tr>
<tr>
<td>Leigh et al. [47] (US)</td>
<td>L: 209 D: 54 L: 52 (14) D: 66 (10)</td>
<td>L: 86% D: 63% L: 12 (9) yrs D: 18 (9) yrs</td>
<td>8 yrs</td>
<td>L: 1.09 (0.83) D: 1.75 (0.88)</td>
<td>Cross tabulation (L) at follow-up and all (A) patients including deceased Multiple regression pooling data including all time-points. Different models (duration, duration^2 and duration^3)</td>
<td>Annual rate</td>
<td>L cohort: 0.018 per yr L (0–10 yrs) W vs M: 0.017 vs −0.003 L (10–20 yrs) W and M: 0.016 vs −0.010 A (0–10 yrs) W and M: 0.032 vs 0.063. A (10–20 yrs) W and M: 0.029 vs 0.079: Linear model: β = 0.0518</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Guillemin et al. [48] (FR)</td>
<td>82</td>
<td>53.3 (17.8–89.9)</td>
<td>69.5%</td>
<td>7.2 (0–31) yrs</td>
<td>7.2 (0–31) yrs and &lt; 5 yrs (mean 2.3) vs 5 yrs (mean 14.7)</td>
<td>1.5 (0–3)</td>
<td>Multiple regression total sample and for &lt; 5 yrs and &gt; 5 yrs disease duration groups</td>
<td>Annual adjusted: additive model and multiplicative model</td>
<td>Total: β = 0.003 (p &lt; 0.05) and β = 0.002 (p &lt; 0.05); &lt; 5 yrs β = 0.007 (NS) and 0.007 (NS) and &gt; 5 yrs, β = 0.003 (p &lt; 0.05) and β = 0.003 (p &lt; 0.05) β = 0.01 vs β = 0.03; β = 0.007 vs β = 0.02; β = 0.006 vs β = 0.03 β = 0.005 vs β = 0.03; β = 0.01 vs β = 0.03</td>
</tr>
<tr>
<td>Ward and Leigh [49] (US)</td>
<td>188 Married (MA): 54.6 (11.7) Unmarried (UNM): 54.0 (13.4)</td>
<td>78% 94%</td>
<td>13.5 (9.0) yrs 15.0 (9.2) yrs</td>
<td>−9.5 yrs</td>
<td>1.1 (0.8) 1.3 (0.9)</td>
<td>Pooled time-series regression analysis</td>
<td>Mean-adjusted annual rate (MA vs UNM); all patients; patients with complete follow-up; men and women Adjusted rate and mean annual change over 5 yrs</td>
<td>β = 0.019 (SE 0.01) and 0.03 units/yr</td>
<td></td>
</tr>
<tr>
<td>Gardiner et al. [19] (UK)</td>
<td>175</td>
<td>55.4 (range: 18–86)</td>
<td>82%</td>
<td>12.7 (range: 0–43) yrs</td>
<td>5 yrs</td>
<td>1.77 (0.75)</td>
<td>Multiple linear regression analysis using baseline HAQ and change over 5 yrs Using all valid observations during follow-up: 1) Linear regression 2) Tobit regression 3) OLS fixed effects by cohort (I = 0–9, II = 9–19 and III = &gt; 19 yrs disease duration at baseline) 4) Cohort OLS fixed effects</td>
<td>Annual slope</td>
<td>β = 0.014 2) β = 0.014 3) β = 0.019 4) I, β = 0.003; II, β = 0.0001; III, 0.017 5) I, β = 0.0210; II, β = 0.0103; III, β = 0.0293</td>
</tr>
<tr>
<td>Leigh et al. [50] (US)</td>
<td>L: 209 D: 54 L: 52 (14) D: 66 (10) LFU: 67 LFU: 55 (12)</td>
<td>L: 86% D: 63% L: 12 (9) yrs D: until last visit LFU: 14 (9) LFU: until last visit</td>
<td>L: 8 yrs D: until last visit LFU: until last visit</td>
<td>L: 1.16 (0.81) D: 1.75 (0.88) LFU: 1.20 (0.90)</td>
<td>Linear regression 2) Tobit regression 3) OLS fixed effects by cohort (I = 0–9, II = 9–19 and III = &gt; 19 yrs disease duration at baseline) 4) Cohort OLS fixed effects</td>
<td>Annual slope</td>
<td>β = 0.014 2) β = 0.014 3) β = 0.019 4) I, β = 0.003; II, β = 0.0001; III, 0.017 5) I, β = 0.0210; II, β = 0.0103; III, β = 0.0293</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Lassere et al. [51] (AU)
- 358 patients
- 61 (12.7) yrs
- 73.2% women
- Median (QRR): 13.6 (10.4) yrs
- Median difference /C0: 0.250 (0.781)
- Median difference /C0: 0.625 (1.188)
- At mean disease duration: 3.8; 7.8; 12.5; 17.5; 22.2; 26.9; 36.6 yrs

### Ward et al. [52] (US)
- 282 patients
- 52.5 (11.7) yrs
- 84% women
- Median difference /C0: 1.375 (1.25)
- Median difference /C0: 0.875 (0.500)
- Generalised least square regression
- At mean disease duration: 3.8; 7.8; 12.5; 17.5; 22.2; 26.9; 36.6 yrs

### Clarke et al. [53] (CA)
- 130 patients
- 62.4 (9.9) yrs
- 83.1% women
- Median difference /C0: 1.125 (0.75)
- Median difference /C0: 0.875 (0.375)
- Generalised least square regression
- At mean disease duration: 3.8; 7.8; 12.5; 17.5; 22.2; 26.9; 36.6 yrs

### Gordon et al. [54] (CA)
- 289 patients
- 59 (14.3) yrs
- 73% women
- Median difference /C0: 0.875 (1.125)
- Median difference /C0: 0.500 (0.750)
- Generalised least square regression
- At mean disease duration: 3.8; 7.8; 12.5; 17.5; 22.2; 26.9; 36.6 yrs

### Hurst et al. [55] (US)
- 924 patients
- 54.9 yrs
- 72% women
- Median difference /C0: 1.375 (1.25)
- Median difference /C0: 0.875 (0.500)
- Generalised least square regression
- At mean disease duration: 3.8; 7.8; 12.5; 17.5; 22.2; 26.9; 36.6 yrs

### Krishnan et al. [56] (US and CA)
- 3035 patients
- 55 (14.3) yrs
- 76% women
- Median difference /C0: 1.375 (1.25)
- Median difference /C0: 0.875 (0.500)
- Generalised least square regression
- At mean disease duration: 3.8; 7.8; 12.5; 17.5; 22.2; 26.9; 36.6 yrs

### Demange et al. [58] (Europe)
- 542 patients
- 52.5 (12.1) yrs
- 69% women
- Median difference /C0: 1.375 (1.25)
- Median difference /C0: 0.875 (0.500)
- Generalised least square regression
- At mean disease duration: 3.8; 7.8; 12.5; 17.5; 22.2; 26.9; 36.6 yrs

### Baddoura et al. [59] (LB)
- 298 patients
- 51.5 (14.7) yrs
- 87.6% women
- Median difference /C0: 1.375 (1.25)
- Median difference /C0: 0.875 (0.500)
- Generalised least square regression
- At mean disease duration: 3.8; 7.8; 12.5; 17.5; 22.2; 26.9; 36.6 yrs

### Sokka et al. [60] (FI)
- RA: 863
- C: 1176
- 55 (14.3) yrs
- 70% women
- Median difference /C0: 1.375 (1.25)
- Median difference /C0: 0.875 (0.500)
- Generalised least square regression
- At mean disease duration: 3.8; 7.8; 12.5; 17.5; 22.2; 26.9; 36.6 yrs

### Shinozaki et al. [61] (JP)
- 1265 patients
- 57.9 (12.3) yrs
- 81.5% women
- Median difference /C0: 1.375 (1.25)
- Median difference /C0: 0.875 (0.500)
- Generalised least square regression
- At mean disease duration: 3.8; 7.8; 12.5; 17.5; 22.2; 26.9; 36.6 yrs

### Odegard et al. [62] (NO)
- 149 patients
- 50.2 (12.5) yrs
- 76% women
- Median difference /C0: 1.375 (1.25)
- Median difference /C0: 0.875 (0.500)
- Generalised least square regression
- At mean disease duration: 3.8; 7.8; 12.5; 17.5; 22.2; 26.9; 36.6 yrs
<table>
<thead>
<tr>
<th>Study (country)</th>
<th>n</th>
<th>Age</th>
<th>Female gender</th>
<th>Disease duration</th>
<th>Follow-up duration</th>
<th>HAQ baseline</th>
<th>Analysis method</th>
<th>Progression HAQ score</th>
<th>HAQ scores/change over time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Iikuni et al. [70] (JP)</td>
<td>159</td>
<td>55 (11.2)</td>
<td>CS: 76.4%</td>
<td>CS: 10.71 yrs</td>
<td>4 yrs</td>
<td>CS: 0.48 (0.61)</td>
<td>For each patient linear regression analysis for all available HAQ data of that individual</td>
<td>Mean annual rate CS: β = 0.0058</td>
<td>NCS: β = -0.0090</td>
</tr>
<tr>
<td>Gonzalez-Alvaro et al. [63] (ES)</td>
<td>789</td>
<td>61 (13)</td>
<td>72%</td>
<td>~ 13 yrs</td>
<td>4 yrs</td>
<td>1.2 (0.9)</td>
<td>Mean annual rate</td>
<td>Mean annual rate 2004 vs 2000: β = -0.09 (0.03 to 0.15) and adj β = 0.15 (0.07 to 0.22)</td>
<td></td>
</tr>
<tr>
<td>Ranganath et al. [64] (US)</td>
<td>889</td>
<td>56 (14.6)</td>
<td>77%</td>
<td>&lt; 3 yrs</td>
<td>6–12 months</td>
<td>0.57 (0.5)</td>
<td>Cross-sectional in different disease duration groups Multivariate linear regression analysis</td>
<td>Mean (SD) and mean change (SD) in disease duration groups: &lt; 3 yrs, 3–5 yrs and &gt; 5 yrs Change in HAQ per 10 yrs increase disease duration</td>
<td>Adjusted annual rate 0.57 (0.5) and −0.13 (0.5); 0.47 (0.4) and −0.03 (0.4); 0.61 (0.5) and −0.07 (0.4) β = 0.027 (95% CI: 0.002–0.052)</td>
</tr>
<tr>
<td>Iikuni et al. [65] (JP)</td>
<td>4027</td>
<td>57.8 (12.8)</td>
<td>83.5%</td>
<td>W: 10 yrs</td>
<td>One time point per patient 3 yrs</td>
<td>W: 0.63 (0.13–1.38)</td>
<td>Multiple linear regression Cross-sectional at different time-points</td>
<td>Adjusted annual rate</td>
<td>W: 0.0194 M: 0.0067 Change: 0.34 and 0.64</td>
</tr>
<tr>
<td>Bazzani et al. [66] (IT)</td>
<td>1010</td>
<td>60.0 (12.8)</td>
<td>83%</td>
<td>W: 8 yrs</td>
<td>M: 0.25 (0–0.875)</td>
<td>M: 1.46 (0.61)</td>
<td>Overall adjusted annual rate Separate analysis for gender, age, education, smoking status, co-morbidity, year of RA onset, severity of disease and treatment allocation</td>
<td>Overall adjusted annual rate</td>
<td>See article</td>
</tr>
<tr>
<td>Wolfe and Michaud [67]</td>
<td>18,485</td>
<td>59.9 (13.0)</td>
<td>76.7%</td>
<td>9.7 yrs</td>
<td>Lifetime 10 yrs</td>
<td>NA</td>
<td>Annualised lifetime rates of progression Annualised observed rates of progression</td>
<td>Mean per yr</td>
<td>β = 0.016 (95% CI: 0.015–0.017) β = 0.013 (95% CI: 0.010–0.015)</td>
</tr>
<tr>
<td>Michaud et al. [20] (US)</td>
<td>18,485</td>
<td>~60</td>
<td>77%</td>
<td>~ 12 yrs</td>
<td>3.7 yrs</td>
<td>1.06 (0.73)</td>
<td>GEE, adjusted for confounders</td>
<td>Overall adjusted annual rate</td>
<td>0.014 (0.012–0.015) See article</td>
</tr>
</tbody>
</table>
Staples et al. [68]  
(AU)  
1801  55.9 (12.6)  73.0%  13.0 (10.4) yrs  60 months  1.64 (0.66) (derived from EQ-5D)  
Multiple linear regression at baseline and cross-sectional at follow-up  
Adjusted annual rate  
Baseline and 6, 12, 18, 24, 30, 36, 42, 48, 54 and 60 months  
\[\beta = 0.012 \quad (95\% \text{ CI: } 0.009–0.016)\]

Bjork et al. [69]  
(SE and US)  
SE: 149  56 (14)  68%  2.4 (0.7) yrs  5 yrs  0.6 (0.6)  
Cross-sectional at two time-points and GEE  
Mean (SD) score at baseline and 5 yrs.  
Adjusted slope  
SE: mean 0.68 (0.58) and USA: 0.80 (0.65) GEE coefficient –0.28 (95% CI: –0.44 to –0.13)  
Anti-CCP + vs Anti-CCP –:  
1st yr (\(\beta = 0.0335\)); 2nd (\(\beta = 0.0317\)); 3rd yr (\(\beta = 0.0199\))  
RF + vs RF –: 1st yr (\(\beta = 0.0004\)); 2nd yr (\(\beta = 0.0095\)); 3rd yr (\(\beta = 0.0018\))  
Anti-CCP +: \(\beta = 0.00657\)  
Anti-CCP –: \(\beta = 0.00346\)  
RF +: \(\beta = 0.00613\)  
RF –: \(\beta = 0.00617\)  

Shidara et al. [71]  
(JP)  
1226  59 (52–67)  81.6%  10 (4–16) yrs  5 yrs  0.6 (0.1–1.3)  
Multivariate linear regression  
Linear mixed model over 5 yrs  
Adjusted slope at 1st, 3rd and 5th yr  
Anti-CCP +: \(\beta = 0.00657\)  
Anti-CCP –: \(\beta = 0.00346\)  
RF +: \(\beta = 0.00613\)  
RF –: \(\beta = 0.00617\)  

\(n\) = number of participants; data on age, disease duration or follow-up duration are mean (SD) or median (IQR); HAQ = health assessment questionnaire; M-HAQ = modified HAQ; yrs = years; L = alive at follow-up; D = died; LFU = lost to follow-up; NA = not available; W = women; M = men; MA = married; UNM = unmarried; RA = rheumatoid arthritis; C = control; CS = corticosteroids; NCS = not using corticosteroids; MTX = methotrexate; HCQ = hydroxychloroquine; RF = rheumatoid factor; anti-CCP = anti-cyclic citrullinated peptide antibody; DR4 = HLA-DR4+/− antigen negative and positive; MMP3+/− = matrix metalloproteinase positive/negative; RF+/− = rheumatoid factor positive/negative; s = subset; T = treated; NT = untreated; Data on HAQ progression are mean (SD) = mean (stand deviation); \(\beta\) (95% CI) = \(\beta\)-coefficient (95% confidence interval); unadj = unadjusted; GEE = generalised estimating equations; OLS fixed effects = ordinary least square; AUC = area under curve.

\(^a\) Fee for service.
\(^b\) Managed care.
\(^c\) HAQ score was not converted to a 0–3 score.
subgroups. Two studies constructed percentile curve reference charts [51, 57]. Lassere et al. [51] constructed percentile charts stratified by age, gender and disease duration. No overlap between the 10th, 50th and 90th percentile curves was observed when disease duration was included as a time-dependent variable. Wolfe [33] focused on the identification of distinct subgroups of patients with similar progression patterns. In this study, changes at the individual level were examined, observing that HAQ progression did in general not follow a linear trend and could not be readily categorised into distinct subgroups such as remitting, progressive and fluctuating.

In 2013, a novel approach to model individual HAQ progression combined with a form of cluster analysis to identify groups with similar trajectories was published by Norton et al. [24]. This study identified four common progression subgroups. Since this approach is novel and it is not clear whether the results are generalisable, the following section shows the findings in which this approach was repeated in the ERAS cohort, extending the follow-up period to 15 years, and in NOAR.

**Results of HAQ trajectories ERAS and NOAR cohorts**

A total of 1460 ERAS patients and 1027 NOAR patients were included in this study. The corresponding mean (SD) age was 55.2 (14.6) and 53.3 (15.9) years; and 67.1% and 64.8% were women (Table 2). Although symptom duration was almost similar between the two cohorts (~8 months), compared to the NOAR population, mean (SD) disease severity at baseline in the ERAS population was slightly higher, i.e., the DAS28 score was 4.00 (1.43) compared to 5.46 (1.74) and the HAQ score was 0.87 (0.73) compared to 1.15 (0.77), respectively. Furthermore, more patients in ERAS fulfilled the 1987 criteria for RA compared to patients in NOAR (70.6% vs 67.1%, respectively). These differences are probably a reflection of the different referral criteria used for both the cohorts.

**HAQ trajectories**

A total of 1352 patients in ERAS and 830 patients in NOAR with complete data on HAQ and covariates were included in the two separate models. Independently, in both cohorts, a four-subgroup LCGM was selected as providing the best fit and most parsimony. Although AIC or BIC preferred a larger number of subgroups, the likelihood ratio test was in favour of a four-subgroup model against a five (or more)-subgroup model. The subgroups identified were similar in terms of the shape of the trajectories and the distribution of patients between subgroups (Fig. 1). Three subgroups exhibited a J-shaped trajectory (subgroups: “low,” “moderate” and “high”). A fourth subgroup (“severe”) experienced persistently high HAQ scores that increased early in the course of the disease and remained between the 15-year follow-up period. The percentage of patients allocated to each of the four subgroups was also very similar between the two cohorts, ERAS and NOAR, respectively: low (21.3% vs 21.2%); moderate (33.4% vs 31.9%); high (29.5% vs 26.5%); and severe (15.8% vs 20.3%). The percentage of patients using methotrexate at any time during follow-up increased with increasing subgroup of worse HAQ trajectory ranging from 27.8% in the low subgroup membership group to 48.3% in the severe subgroup in ERAS (Fig. 2). The percentage ranged from 8.9% to 38.2% in NOAR. In both the cohorts only 3.8% of patients received a biologics during follow-up. The percentage of patients receiving biologics was 5.3% in the severe subgroup of both cohorts, which was lower than in the high subgroup, 5.9% and 7.7% in ERAS and NOAR, respectively (Fig. 3).

**Predictors of subgroup membership**

In both ERAS and NOAR, older age, female gender and worse DAS28 score were significantly associated with increased likelihood of all subgroup memberships (low = reference, moderate, high and severe) of worse HAQ progression (Table 3). Although less consistent across the cohorts, there was also a statistically significant association or a trend towards a positive association between longer symptom duration, fulfilment of the 1987 ACR criteria of RA and lower SES with higher risk class membership. No association was found between RF and subgroup membership. Actual model coefficients are presented in Appendix.

**Discussion**

This article gives an overview of the methods used to evaluate HAQ changes over time in previous publications and shows the results of a comparison study in two observational cohorts, ERAS and NOAR, including patients with early IP and RA using a latent class growth model. Across previously published studies, between studies using the same database [e.g., the USA National Data Bank for Rheumatic Diseases (NDB)] but applying different statistical methods, there was some variation in mean/median annual change between the studies (ranging from 0.01 to > 0.03), which might partly be explained by differences in disease duration at baseline, HAQ score at baseline, methods used to deal with missing data of patients who were lost to follow-up or died or the statistical methods used. Methods to assess change in HAQ scores over time varied from cross-sectional analysis, calculating raw change score and repeated measurement regression analysis. The advantages of the latter analysis are that they model the sources of variation and correlation that arise from, for example, observations taken from the same subject at multiple time-points, violating assumptions of within-subject independence. Most of these models are useful when assuming that in a given sample, individuals are expected to change in the same direction across time with only the degree of change varying between people. However, we know from individual patient data that both the strength and the direction of change are varying between patients. Wolfe [33] identified three patterns of individual courses: patients who had a high HAQ score at baseline and remained high, patients with fluctuating HAQ scores over time to be associated with variability in inflammation and pain over time and patients who started low and remained low. To address this problem, alternative modelling strategies such as LCGM are available considering multi-nominal heterogeneity in change. Another advantage of a LCGM is that it can be used for incomplete longitudinal data either due to lost to follow-up or due to intermittent missing data by assuming missing.

**Table 2** Demographic and clinical baseline characteristics of patients included in the ERAS cohort and patients included in the NOAR cohort

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>ERAS % missing</th>
<th>NOAR % missing</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age at onset, years</strong></td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>Gender, % female</strong></td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>Symptom duration, months</strong></td>
<td>0</td>
<td>0</td>
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<tr>
<td><strong>HAQ score</strong></td>
<td>0.3</td>
<td>0.3</td>
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<tr>
<td><strong>DAS28 score</strong></td>
<td>0.9</td>
<td>0.9</td>
</tr>
<tr>
<td><strong>Rheumatoid factor, % positive</strong></td>
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<td>1.0</td>
</tr>
<tr>
<td><strong>ACR 1987 criteria for RA, % yes</strong></td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>Socio-economic status, % most deprived</strong></td>
<td>5.7</td>
<td>5.7</td>
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<tr>
<td><strong>DMARDs</strong></td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Values are mean (SD) for continuous variables or numbers (%) for categorical variables. DAS28 = 28 joint Disease Activity Score; HAQ = Health Assessment Questionnaire; DMARDs = Disease-Modifying Anti-Rheumatic Drugs.
at random. Also, a LCGM is a finite mixture model, where the mixture distribution offers a good fit for non-normal distributed outcomes such as HAQ. As far as we know, this is the first time that this model is used to independently identify similar common trajectories of HAQ progression in patients with IP and RA in two observational cohorts, ERAS and NOAR, following a large group of patients with early IP and RA for 15 years. In both the cohorts, four subgroups were identified showing very similar trajectories, i.e., patients who had a high HAQ score at baseline and did not improve (severe subgroup), patients who had a low HAQ score, improved and remained to have low HAQ scores over time (low subgroup) and two classes with a similar pattern, but distinct starting point (moderate and high subgroup). Age, gender, symptom duration, the ACR 1987 criteria for RA, DAS28 score RF and SES were included as indicators into the model. Of the demographic and clinical variables, all but RF were significant predictors for identifying patients in one or more membership subgroups.

The results presented in this article are a first step towards personalised medicine, and these initial findings may further help to develop probability scores of patients belonging to one of the four groups. The information might also be useful in clinic to help target therapy. In this study, we noticed, for example, that compared to the high membership subgroup, the percentage of patients using methotrexate was similar and the percentage of patients using biologics was even lower in the severe subgroup, suggesting that the patients in the severe subgroup need to be treated more aggressively.

The identified predictors were very similar to those reported in the publications reviewed in this article that investigated possible predictors: older age [8,33,43,69], female gender [8,33,43,69], disease duration [33,43] and disease activity [8]. Gardiner et al. [19], however, did not find an association between age, gender or disease duration and change in HAQ score. Although concurrent illness was associated with change in HAQ score in the latter study, an observation seen in other studies as well [24,74,75], we were not able to include co-morbidity as one of the indicators in our models since co-morbidities were not reported consistently between the two cohorts. For that reason we also did not include radiographic joint damage, a predictor seen in some of the reviewed studies. However, since both ERAS and NOAR include patients with early IP or RA, the contribution of baseline radiographic damage to identify subgroups would probably have been minimal. Overall, identification of the four subgroups and their indicators is of importance when assessing patients with early RA in clinic, and the information could be used to tailor treatment to the individual patient.

There were also some limitations to this study. In the comparison study, the referral criteria differed between the two cohorts, resulting in patients recruited to ERAS having slightly higher disease activity and more often being classified as having RA at baseline compared to patients in NOAR. This discrepancy, however, did not result in different models or identification of different predictors. Both IP and RA patients were included in both cohorts, but this is probably also a reflection of a general arthritis population seen in clinic.

The authors conclude that a diverse range of methods exists for assessing the progression of disability in RA. As a consequence, there is no appropriate way to combine previous published research in the field. However, the ERAS and NOAR cohorts showed that HAQ progression could be placed into four HAQ trajectory subgroups. These subgroups were nearly identical between these cohorts, which supports their validity. Identifying distinct groups of patients who are at risk of poor functional outcome is likely to help target therapy to those who are most likely to benefit.
Table 3
Predictors of class membership in ERAS and NOAR

<table>
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<tr>
<th>Class membership</th>
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<td>Odds ratio</td>
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</table>

DAS28 = 28 joint Disease Activity Score; p = p-value for statistical significance; 95% CI = 95% confidence interval odds ratio.

Acknowledgements

We thank the rheumatologists, research nurses and data management teams working for ERAS and NOAR for their major contribution to data collection and data management.

Appendix. Supplementary Information

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.semarthrit.2014.05.003.

References

[14] Wiles N, Dunn G, Barrett E, Silman A, Symmons D. Associations between demographic and disease-related variables and disability over the first five years.


Staples MP, March L, Lassere M, Reid C, Buchbinder R. Health-related quality of life and continuation rate on first-line anti-tumour necrosis factor therapy among rheumatoid arthritis patients from the Australian Rheumatology Association Database. Rheumatology (Oxford) 2011;50:166–75.


