Trajectories of functional limitation in early rheumatoid arthritis and their association with mortality

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Abstract

Objective. This study aimed to identify subgroups with distinct trajectories of functional (HAQ) progression over 10 years following diagnosis of RA and identify baseline characteristics associated with the trajectories and their prognostic value for mortality.

Methods. Between 1986 and 1998, 1460 patients with RA symptoms <2 years and prior to disease-modifying treatment (DMARDs) were recruited to an inception cohort (Early RA Study). Standard clinical, functional and laboratory assessments were performed at presentation and annually. Deaths were tracked by the National Health Service Central Register. Growth mixture modelling was used to identify distinct trajectories of HAQ score progression and survival analysis employed to compare all-cause mortality across the trajectory classes.

Results. Four HAQ score progression classes were identified: moderate increasing (46%), low stable (6%), moderate stable (28%) and high stable (20%). Only the moderate-increasing class exhibited an accelerated decline in function over normal ageing. Compared with the moderate-increasing class, individuals with high-stable HAQ scores were more likely to be female, have more severe disease and other coexistent conditions. Low-stable class patients were more likely to be male and report less pain. The high-stable class had increased risk of mortality compared with the moderate-increasing class after adjusting for potential confounding factors, whereas low-stable and moderate-stable classes were at reduced mortality risk.

Conclusion. The effect of RA on function is set within the first few years and is affected by comorbidity. Identifying distinct groups of patients may help to target those at greater risk of poor functional outcome and mortality.

Key words: rheumatoid arthritis, function, disability, HAQ, growth mixture model.

Introduction

RA is a chronic inflammatory condition with a fluctuating course that varies from clinical remission to progressive structural damage, despite the availability of new and more effective therapies. Functional limitation is a central outcome of RA and can lead to disability and work loss [1, 2], impaired health-related quality of life and psychological well-being [3–5], and joint replacement surgery [6] and is the strongest predictor of mortality [7, 8].

Functional decline can occur very early in the course of RA, mainly driven by disease activity [9, 10]. Over time, progressive structural damage is increasingly important [11]. Age, sex and comorbidity influence function [12–15], but despite its importance, rates of functional decline and contributing factors in RA are not well understood.

The HAQ is the most widely used measure of function in observational studies and one of the key measures of...
efficacy in clinical trials in RA. In contrast to the irreversible nature of structural and X-ray damage, HAQ scores can fluctuate considerably over time [11], and when related to disease activity is amenable to drug therapies. HAQ score progression is considered a crucial indicator of control of RA. In order to identify the impact and cost effectiveness of modern biological therapies we need to know the rates of HAQ score progression in patients receiving conventional DMARDs over time, and what factors affect these rates, including those in clinical remission who continue to progress. Since clinical trials are short-lived, we rely on observational studies for long-term data.

Results from previous studies have been inconsistent, other than the HAQ score at an earlier time, prognostic factors for HAQ score progression are lacking [16]. Previous and our own reports showed the mean HAQ score over time followed a J-shaped curve [17, 18], with initial improvement, from the presumed effect of DMARDs, followed by a gradual and insidious decline. At the individual level, HAQ score progression does not in general follow a linear trend, with considerable heterogeneity observed across individuals [10].

Previous research has generally focused on the average course of functional change in RA or has used ad hoc methods to investigate trajectories in longitudinal cohorts. In this inception cohort with >10-years follow-up, we use latent growth mixture modelling (GMM), which effectively tests whether the population under study is composed of a mixture of discrete groups of individuals with differing profiles of progression. The aim is to identify a distinct number of trajectories for HAQ score progression over time and to examine the predictors associated with these trajectories and their prognostic value for mortality.

Patients and methods

Patients

Consecutive patients diagnosed with RA with symptoms <2 years (median 6 months) and prior to disease-modifying treatment were recruited into the Early RA Study (ERAS) from nine hospitals in different regions of England between 1986 and 1998. Of the total of 1460 patients, 884 (61%) completed 10-years of follow-up; those who did not were due to death (n = 332), moved (n = 67), social reasons (n = 54), remission (n = 28), discharged (n = 92) and not known (n = 3).

All centres followed the UK published framework of the 1990s for management of RA, which included early use of sequential monotherapy, step-up combination therapy for severe disease and judicious use of steroids. The choice of DMARDs was based on the physician’s preference, which was mainly SSZ followed by MTX, standard practice for this era in the UK [7]. Biological agents have only been available since 2001. Ethical approval for ERAS was given by the West Herefordshire Hospitals NHS Trust.

Demographic and clinical variables

Standard clinical, functional and laboratory assessments were performed at baseline, 6 months and annually as previously described [19], including HAQ, swollen and tender joint counts (SJC and TJC, respectively), pain visual analogue scale (VAS), grip strength, ESR, RF and ANA titres, BMI and hands/feet radiographs scored using Larsen’s method [20]. The original three-variable DAS based on tender and swollen joint counts and ESR was used [21], standard practice when ERAS started. Outcome measures, including extra-articular and coexistent medical conditions, work status, in-patient episodes and orthopaedic surgery were recorded on a standard outcome form at annual review. Comorbidity was based on patient self-report, medical records and drug charts and coded using the International Classification for Disease (ICD-10). For analysis, individual conditions were categorized into extra-articular manifestations (EAMs), complications of RA or coexistent disease [22], and the Charlson comorbidity index (CCI), which weights 18 medical conditions based on their predictive strength of 1-year mortality in medical inpatients [23]. Cigarette smoking was included from 1992 and collected retrospectively when possible in patients recruited prior to this. The HLA-DRB1 shared epitope (SE) was assessed in a subgroup (n = 1011) [24].

Socio-economic status was assessed according to the Registrar General’s classification for social class and the highest level of educational qualification. Both were dichotomized, social class IV or V categorized as low social class, and left school with no educational qualifications categorized as low education. The 1987 revised ARA criteria [25] were not used formally by ERAS clinicians, although all items were recorded as part of yearly assessments. When applied, 70% fulfilled the minimum four ARA criteria for diagnosis of RA at baseline and 96% at some stage by last visit. The National Health Service Central Register provided death certificates (nmissing = 5) coded using ICD-10 by the Office for National Statistics, as previously described [7].

Statistical analysis

GMM analysis was conducted using Mplus 5.2 in the 10-years follow-up cohort. The estimation method, full-information maximum likelihood, allows all available data to be used in analysis under the assumption that missing data are missing at random (MAR) [26]. Sensitivity analysis was conducted to check the MAR assumption. Specifically, the pattern-mixture modelling approach proposed by Roy [27] indicated that allowing time of dropout from the sample to influence latent class membership (i.e. to be not missing at random) did not change the GMM estimates in terms of the number of classes selected, class membership proportions and random effect means. It was thus assumed that dropout was ignorable and the MAR assumption robust.

Conventional growth modelling approaches, such as hierarchical linear models [28], assume that individuals come from a single population and that a single trajectory (defined by random intercept and slope parameters) adequately approximates the entire population. GMM relaxes this assumption using latent trajectory classes
that allow for different classes of individual trajectories [29, 30]. A model with four classes of trajectories was accepted as providing the best fit, as indicated by standard model comparison techniques: Bayesian Information Criterion, Akaike Information Criterion and the Lo–Mendell–Rubin likelihood ratio test [31, 32]. Supplementary data (growth mixture modelling section, available at Rheumatology Online) provide a detailed description of the analysis.

For each trajectory class, Kaplan–Meier survival curves were calculated in Stata 11.1 to compare mortality rates between classes derived from GMM. Cox proportional hazards regression was undertaken using class membership as the predictor variable, weighted by the probability of class membership. Initially crude unadjusted hazard ratios were computed and then adjusting for baseline demographic and clinical features. We included age, sex, BMI, employment status, low education attainment, CCI, pain VAS, SJC, TJC, ESR, grip strength, year of diagnosis, time between diagnosis and first outpatient visit, and time to first DMARD in the adjustment model. Clinical variables were first included as baseline values and then as time-varying covariates. Smoking and SE status were excluded due to high levels of missing data, but were considered in a sensitivity analysis.

Results

Descriptive analysis

The HAQ score varied in distribution, with the full range observed at each follow-up interval over 10 years (Fig. 1). On average, the HAQ score decreased over the first 2 years, a presumed effect of DMARDs. After around 3 years the HAQ score increased in a linear manner, with a mean increase of 0.051 units/year (95% CI 0.45, 0.58) between 2 and 10 years.

Of course, the average trend indicated in Fig. 1 does not apply to all individuals. Taking a clinically significant improvement and worsening in the HAQ score as −0.09 and 0.15 units, respectively [33], 57.1% of 1377 individuals with HAQ scores at both baseline and 1 year showed an improvement in function, 17.7% stayed about the same and 19.5% deteriorated. This marked variability was also seen at other time points, demonstrated in Fig. 2, which plots the observed HAQ scores for 20 randomly selected individuals with less than three missing observations. In the majority there was an initial improvement in HAQ score. The trajectories can be described as linear for the majority there was an initial improvement in HAQ score. The trajectories can be described as linear for only a few, with a variety of non-linear patterns observed for others. In two patients the pattern was chaotic, the smoothed line not fitting closely to the data points.

Growth mixture model

The estimated trajectories of the four classes are plotted in Fig. 3. Forty-six per cent followed the prototypical J-shaped trajectory, with improvement in the HAQ score over the first year followed by a gradual worsening thereafter (moderate increasing). For this class the initial functional improvement was washed out by 5 years. Six per cent showed mild limitation initially, then improved and remained stable, close to zero (low stable), 28% showed a moderate HAQ score that improved initially and then slowly worsened with time (moderate stable) and 20% experienced persistently high HAQ score (high stable). Only the moderate-increasing group exhibited a rate of decline in function greater than would be expected due to normal ageing.

Demographic and clinical correlates of trajectory classes

Demographic and baseline clinical profiles for each trajectory class are shown in Table 1, including the statistical significance of the overall differences in means or proportions or pairwise comparisons between trajectory classes. The moderate-increasing class is used as a comparison since it depicts the average trajectory for the whole cohort.

Compared with the moderate-increasing class, both the low-stable and moderate-stable classes were significantly more likely to have favourable baseline features. These included socio-economic background, paid employment, less likelihood of HLA-SE, DMARD starts within 12-weeks of the first visit, use of MTX, fewer DMARDs during the first year, less biologic use ever and first visit after 1993 (all \( P < 0.05 \)). All disease markers as measured by VAS pain, Larsen, SJC, TJC, ESR and DAS at baseline, 3 and 5 years indicated milder RA (all \( P < 0.05 \)). No difference between the classes was observed for baseline BMI, erosions, RF, ANA or smoking status. The profiles of the low-stable and moderate-stable classes were similar to
each other, although the low-stable class was significantly more likely to be younger, male, report less baseline VAS pain and fewer tender joints and use steroids within the first year (all \( P < 0.05 \)).

In contrast to this, patients in the high-stable class had fewer favourable features compared with the moderate-increasing class and were significantly more likely to be female, have lower levels of education, worse grip strength and have higher VAS pain, DAS, and SJC and TJC scores (all \( P < 0.05 \)). This was true for clinical variables at all time points. Within the first year steroid use was lower but the average number of DMARDs was higher (both \( P < 0.05 \), reflecting greater use of step-up and combination therapies. The high-stable class had significantly higher ESR levels at baseline but not at the 3- or 5-year follow-up, and significantly higher Larsen damage at 3 years only. Interestingly, there was no difference between these two classes in baseline RF, ANA, HLA-SE, timing of first visit or MTX and biologic use.

Across all classes, patterns of change in pain were comparable to changes in function. In the low-stable, moderate-stable and moderate-increasing classes, pain improved between baseline and 3-year assessments. Between 3 and 5 years pain was unchanged in the low-stable, moderate-stable and high-stable classes. Increases in Larsen scores between baseline and 3 years were greater depending on the level of HAQ disability at baseline, increasing between 3 and 5 years only in the moderate-increasing class.

Comorbidity and mortality
Although there were significant overall differences across the trajectory classes for the number of comorbidities and CCI at baseline, pairwise comparisons revealed no
significant difference between the moderate-increasing class compared with the low-stable, moderate-stable or high-stable classes (Fig. 4). Compared with the moderate-increasing class, the high-stable class had significantly more comorbidity after 3 and 5 years follow-up (total, CCI and EAM), whereas the low-stable and moderate-stable classes had less comorbidity at 5 years ($P < 0.05$).

Restricting the analysis to the 10-year follow-up, there were 322 deaths within 11 913 person-years of follow-up. For analysis, the low-stable and moderate-stable classes were combined due to low mortality in the low-stable class. Mortality rates were lowest in the low-stable and moderate-stable classes (74 deaths, 14%), higher in the moderate-increasing class (144 deaths, 22%) and highest in the high-stable class (104 deaths, 36%). Fig. 5 depicts the unadjusted Kaplan–Meier survival functions for the four classes.

### Table 1
Demographic and clinical characteristics for the ERAS cohort by trajectory class ($n = 1460$)

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>Low stable (6%)</th>
<th>Moderate stable (28%)</th>
<th>Moderate increasing (46%)</th>
<th>High stable (20%)</th>
<th>$\chi^2$</th>
<th>$P$</th>
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<td>Age at onset, years</td>
<td>55.3 (0.4)</td>
<td>51.0 (1.8)</td>
<td>53.4 (0.8)</td>
<td>55.2 (0.6)</td>
<td>59.9 (0.9)</td>
<td>44.1</td>
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<td>Female, %</td>
<td>66</td>
<td>49</td>
<td>62</td>
<td>67</td>
<td>78</td>
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<td>Smoker, %</td>
<td>22</td>
<td>20</td>
<td>23</td>
<td>22</td>
<td>21</td>
<td>0.2</td>
<td>0.979</td>
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<td>Low education, %</td>
<td>43</td>
<td>31</td>
<td>37</td>
<td>43</td>
<td>55</td>
<td>25.0</td>
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<td>Low social class, %</td>
<td>49</td>
<td>44</td>
<td>42</td>
<td>51</td>
<td>54</td>
<td>12.7</td>
<td>0.005</td>
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<tr>
<td>Working, %</td>
<td>46</td>
<td>58</td>
<td>55</td>
<td>45</td>
<td>29</td>
<td>52.0</td>
<td>0.000</td>
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<td>Baseline visit $\geq$ 1993, %</td>
<td>38</td>
<td>50</td>
<td>43</td>
<td>34</td>
<td>37</td>
<td>16.3</td>
<td>0.008</td>
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<td>SE status: $+/-++$, %</td>
<td>70</td>
<td>59</td>
<td>66</td>
<td>73</td>
<td>73</td>
<td>4.0</td>
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<td>Charlson comorbidity $\geq 1$, %</td>
<td>16</td>
<td>15</td>
<td>13</td>
<td>18</td>
<td>21</td>
<td>8.4</td>
<td>0.039</td>
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<td>Extra-articular features, %</td>
<td>19</td>
<td>15</td>
<td>17</td>
<td>20</td>
<td>23</td>
<td>5.3</td>
<td>0.153</td>
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<td>Erosions (hand/feet), %</td>
<td>25</td>
<td>27</td>
<td>25</td>
<td>25</td>
<td>28</td>
<td>0.7</td>
<td>0.875</td>
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<td>RF positive, %</td>
<td>73</td>
<td>66</td>
<td>73</td>
<td>75</td>
<td>73</td>
<td>1.6</td>
<td>0.871</td>
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<td>DMARD within 12 weeks, %</td>
<td>72</td>
<td>56</td>
<td>67</td>
<td>73</td>
<td>83</td>
<td>40.6</td>
<td>0.003</td>
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<td>MTX use, %</td>
<td>42</td>
<td>19</td>
<td>30</td>
<td>48</td>
<td>52</td>
<td>75.6</td>
<td>0.000</td>
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<td>Biologic use, %</td>
<td>4</td>
<td>0</td>
<td>1</td>
<td>6</td>
<td>4</td>
<td>12.2</td>
<td>0.000</td>
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<td>Steroid within 1 year, %</td>
<td>86</td>
<td>97</td>
<td>90</td>
<td>86</td>
<td>80</td>
<td>36.2</td>
<td>0.000</td>
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<td>Number of DMARDs within 1 year</td>
<td>0.9 (0.02)</td>
<td>0.6 (0.06)</td>
<td>0.7 (0.03)</td>
<td>0.9 (0.03)</td>
<td>1.2 (0.05)</td>
<td>89.3</td>
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<td>ESR, mm/h</td>
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<tr>
<td>0 years</td>
<td>40.6 (1.0)</td>
<td>34.9 (3.0)</td>
<td>36.4 (1.5)</td>
<td>43.6 (1.2)</td>
<td>50.9 (2.1)</td>
<td>41.4</td>
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<td>3 years</td>
<td>26.6 (0.8)</td>
<td>19.3 (2.4)</td>
<td>22.4 (1.3)</td>
<td>30.6 (1.2)</td>
<td>33.3 (2.0)</td>
<td>48.3</td>
<td>0.000</td>
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<td>5 years</td>
<td>27.6 (0.8)</td>
<td>19.9 (2.3)</td>
<td>22.0 (1.2)</td>
<td>30.6 (1.2)</td>
<td>30.5 (2.1)</td>
<td>49.5</td>
<td>0.000</td>
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<tr>
<td>0 years</td>
<td>5.1 (0.4)</td>
<td>3.3 (0.2)</td>
<td>3.8 (0.1)</td>
<td>4.2 (0.1)</td>
<td>5.0 (0.1)</td>
<td>140.6</td>
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<td>3 years</td>
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<td>1.7 (0.1)</td>
<td>2.5 (0.1)</td>
<td>3.2 (0.1)</td>
<td>4.5 (0.1)</td>
<td>305.0</td>
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<td>5 years</td>
<td>3.1 (0.1)</td>
<td>1.7 (0.1)</td>
<td>2.5 (0.1)</td>
<td>3.4 (0.1)</td>
<td>4.2 (0.2)</td>
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<td>VAS pain</td>
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<tr>
<td>0 years</td>
<td>44.5 (1.0)</td>
<td>29.0 (2.8)</td>
<td>38.8 (1.3)</td>
<td>45.3 (1.1)</td>
<td>53.2 (1.6)</td>
<td>86.9</td>
<td>0.000</td>
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<td>3 years</td>
<td>30.0 (1.0)</td>
<td>8.9 (1.9)</td>
<td>22.0 (1.3)</td>
<td>31.8 (1.2)</td>
<td>49.0 (2.0)</td>
<td>281.0</td>
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<td>5 years</td>
<td>33.4 (1.0)</td>
<td>7.9 (1.7)</td>
<td>23.4 (1.5)</td>
<td>39.5 (1.4)</td>
<td>48.0 (2.4)</td>
<td>328.2</td>
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<td>Larsen score</td>
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<td>0 years</td>
<td>4.3 (0.3)</td>
<td>2.1 (0.4)</td>
<td>2.6 (0.3)</td>
<td>5.1 (0.5)</td>
<td>5.8 (0.8)</td>
<td>20.85</td>
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<td>3 years</td>
<td>15.5 (0.6)</td>
<td>7.2 (1.3)</td>
<td>12.7 (0.9)</td>
<td>16.2 (0.9)</td>
<td>21.0 (1.5)</td>
<td>37.26</td>
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<tr>
<td>5 years</td>
<td>16.9 (0.7)</td>
<td>6.9 (1.5)</td>
<td>13.3 (1.0)</td>
<td>19.1 (1.1)</td>
<td>21.1 (1.8)</td>
<td>31.62</td>
<td>0.000</td>
</tr>
</tbody>
</table>

Mean (s.e.) or percentage with test for equality across subgroups.

Fig. 4 Prevalence of any comorbidity and Charlson comorbidity (CCI $\geq 1$) at baseline and after 3 and 5 years of follow-up across the latent trajectory classes.
Cox proportional hazards regression entering only the disability trajectory classes indicated a significant overall effect for class membership ($\chi^2(2) = 40.92, P < 0.001$). Compared with the moderate-increasing class, risk of death in the low-stable and moderate-stable classes was reduced by around 40% [hazard ratio (HR) = 0.62, 95% CI 0.47, 0.83] and was increased by almost 2-fold [hazard ratio (HR) = 0.57, 95% CI 0.32, 1.03] in the high-stable class (HR = 1.91, 95% CI 1.48, 2.47).

Adjusting for baseline demographic and clinical factors, the overall effect remained significant ($\chi^2(2) = 11.99, P < 0.001$). The effect remained significantly increased for the high-stable class compared with the moderate-increasing class (HR = 1.48, 95% CI 1.05, 2.10), but was reduced to non-significant for the low-stable and moderate-stable classes (HR = 0.82, 95% CI 0.48, 1.17).

Adjusting for clinical factors as time-varying covariates and using the moderate-increasing class as a comparator, the effect for the high-stable class remained significant (HR = 1.53, 95% CI 1.09, 2.15), but remained non-significant for the low-stable and moderate-stable classes (HR = 0.90, 95% CI 0.63, 1.29).

Sensitivity analyses including smoking and SE status resulted in no substantive change in the estimates for the trajectory classes (see supplementary data mortality section, available at Rheumatology Online).

It is important to consider whether the disability trajectory classes offer explanatory power over the HAQ score assessed at other specified time points. The HAQ score assessed at baseline was not related to increased mortality risk after adjustment for baseline clinical and demographic factors (HR = 1.05, 95% CI 0.82, 1.35). However, the HAQ score assessed at 1 year was a significant predictor of mortality after adjustment for baseline clinical and demographic factors (HR = 1.43, 95% CI 1.17, 1.75), indicating that a one unit increase in the HAQ score at 1 year provides similar explanatory power compared with membership in the high-stable class, who score around one unit higher than the moderate-increasing class at 1 year.

Variations in mortality risk resulted largely from differences in primary deaths due to respiratory causes (low/moderate stable = 4%; moderate increasing = 9%; high stable = 16%) rather than cardiovascular (low/moderate stable = 8%; moderate increasing = 12%; high stable = 9%), stroke (low/moderate stable = 2%; moderate increasing = 5%; high stable = 5%) or cancer (low/moderate stable = 7%; moderate increasing = 11%; high stable = 9%).

**Discussion**

Functional limitation in RA is one of the most important factors affecting patients’ health-related quality of life. This study has characterized distinct trajectories of functional limitation over 10 years following diagnosis of RA and identified the baseline characteristics associated with the trajectories. An important finding was the impact of comorbidity on functional progression by 3 years. Knowledge of the features associated with different trajectories of disease progression helps to identify patients for specific interventions. It is clear from this research that the disease course is set within the first few years, and, since disease activity was related to the HAQ score, provides further support to recommendations for intensive therapies at early stages [34, 35].

We have identified four classes with distinct trajectories of HAQ score progression. Confirming our own and other studies, the average HAQ score followed a J-shaped trajectory, initially improving then declining gradually at around 0.05 HAQ units annually [10, 11, 17, 18]. However, this trajectory, with functional decline accelerated compared with normal ageing [36], was only observed for one of the four distinct trajectory classes, accounting for 46% of the sample. For the remaining three classes minimal progressive deterioration in function was observed. In the low-stable (6%) and moderate-stable classes (28%), initial improvements in function were followed by stable and low HAQ score levels. The rate of decline did not exceed what would be expected due to normal ageing [36]. In the high-stable class (20%), function was markedly impaired at baseline and remained so throughout the 10 years of follow-up.

Compared with the prototypical moderate-increasing trajectory, individuals with persistently high HAQ score levels were more likely to be female, have more severe disease in terms of pain, tender and swollen joints, ESR and DAS, and have less favourable socio-economic backgrounds. No difference was observed between the high-stable and moderate-increasing class in baseline RF, ANA or shared epitope. The high-stable class was also related to major comorbidity, but only by 3 and 5 years, raising an intriguing question concerning cause and effect between the HAQ score and comorbidity on the course of RA. The low-stable class was more likely to be male and report less pain and steroid use, suggesting an acute onset and prompt treatment. Increased MTX use was seen in the high-stable and moderate-increasing groups, suggesting more severe clinical RA. Incidence of treatment effects is limited by the non-randomized design of this...
observational study and confounding by indication, since decisions could have been influenced by baseline features, including functional status.

Survival analysis revealed that patients in the high-stable class had increased mortality risk even after adjusting for potential confounding factors, whereas those in the low- and moderate-stable classes had reduced risk. This is consistent with previous reports using this cohort, as well as the wider literature, and confirms that function is the strongest predictor of mortality in RA [7, 8]. Age, sex, low educational attainment and comorbidity were also found to be independent predictors of mortality, whereas traditional clinical variables including pain, joint counts, ESR and RF were not. The present study suggests that the excess mortality risk attributable to functional limitation is mainly due to individuals with high HAQ score at baseline not improving with DMARD therapy.

Current guidelines for the management of early RA include the principles of treating to a low disease activity target [34, 35, 37], based on consistent evidence of the benefits of targeted approaches, employing specific criteria for the use of biologics [34, 38]. However, DAS levels outside these criteria in the presence of moderate or high HAQ scores can also result in adverse outcomes [39]. The HAQ score has not been proposed as a candidate measure to target models of care in the UK. Nevertheless, it is used in cost-effectiveness modelling, as it reflects changes in quality of life related to disease activity [40]. In line with some studies [15, 16], our data show that HAQ score changes are related to factors other than treatment effects, comorbidity being an important one. We have recently reported the substantial impact of comorbidity on function in RA and the importance of the recognition, prevention and treatment of comorbidity in the management of early RA, since many are potentially remedial [41]. Knowledge of the progression of the HAQ score in patients receiving conventional DMARDs provides important information in assessing the benefits of biologic treatments in the long term. This is critical for informing cogent discussions with NICE in the UK [42].

Reports on HAQ score progression vary. Centile charts for the HAQ have shown progression from an initial average of 0.8 to 1.4 by 18 years [43], depending on age and sex. However, individual patients show a more chaotic pattern and do not progress along centile lines in an organized manner due to considerable within-individual variation [10, 44]. Subgroup-based trajectory modelling approaches, such as GMM, incorporate within-individual differences in trajectories and provide a useful method to examine individual differences in disease progression in rheumatic conditions. Future studies planned for this cohort will focus on the longitudinal association of the HAQ score with disease activity and radiological progression that will also consider variability in the HAQ score as well as the underlying trajectory. Since this cohort reflects the pre-biologic era only, we intend to validate these findings in more recent independent cohorts. The finding that those recruited later in this cohort were more likely to be in classes with better functional outcomes suggests there may be a shift in outcomes with time. This may be related to the increasing use of more intensive therapies but requires further examination.

Limitations of this study include attrition rates (only 61% completed 10 years of follow-up), a common problem of longitudinal studies. However, the analytical technique is less restrictive than traditional methods, allowing inclusion of all available data under the assumption that data are missing at random. CCI was designed for medical inpatients and does not include common comorbidities seen in rheumatology outpatients. One explanation for respiratory rather than cardiovascular conditions being more common primary causes of death in the high HAQ score subgroup could be differences in chronicity, with chronic obstructive pulmonary disease (COPD) and/or its complications being a major cause.

The limitations of the novel GMM method include the considerable computational load in estimating a GMM and the possibility of spurious results in the presence of non-normal observed variables [45] (discussed in detail as supplementary data in the growth mixture modelling limitations section, available at Rheumatology Online). The HAQ score is skewed in this sample, at least early in the course of the disease, although not enough to adversely influence the findings. Despite these limitations, GMM provides extended utility over methods employed by previous studies. Further research is ongoing to validate these findings in contemporary cohorts; indeed, this type of analysis has already confirmed these findings in a preliminary study of an similar independent cohort [46]. Furthermore, these models have the potential for developing prognostic tools to predict HAQ score progression and thus target groups of patients at greater risk of poor functional outcome and mortality.

In summary, we extend the findings of previous studies of functional limitation in this large RA inception cohort [17–19] to show four distinct trajectories of HAQ score progression. Factors associated with progressive functional limitation were sex, age, socio-economic status, comorbidity and disease severity. Consistently high and increasing HAQ scores were independently associated with increased mortality risk. These easily measured features could help identify patients at high risk of poor outcomes in RA in routine clinics.

### Rheumatology key messages

- Four functional progression trajectories were identified for patients in the Early Rheumatoid Arthritis Study.
- Persistent disability in RA was related to female sex, greater comorbidity and increased mortality risk.
- Trajectories of function are set early in RA, supporting early and intensive treatment strategies.

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Supplementary data

Supplementary data are available at Rheumatology Online.

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