RHEUMATOLOGY

Rheumatology 2022;61:4297–4304
https://doi.org/10.1093/rheumatology/keac139
Advance access publication 8 March 2022

Original article

# The role of comorbidities alongside patient and disease characteristics in long-term disease activity in RA using UK inception cohort data

**Amanda D. Busby [1], James Wason[2], Arthur G. Pratt[3,4], Adam Young[1], John D. Isaacs[3,4] and Elena Nikiphorou[5,6]**

## Abstract

**Objectives.** Control of disease activity in RA is a crucial part of its management to prevent long-term joint damage and disability. This study aimed to identify early predictors of poor disease activity at 5 and 10 years, focusing on comorbidities and clinical/sociodemographic factors at first presentation.

**Methods.** Patients from two UK-based RA cohorts were classified into two groups; low (<3.2) and moderate/high (≥3.2) DAS using 28 joint counts (DAS28) at 5/10 years. Clinical variables (e.g. rheumatoid nodules, erosions), sociodemographic factors (e.g. ethnicity, deprivation) and comorbidities were recorded at baseline and yearly thereafter. The Rheumatic Diseases Comorbidity Index quantified patient comorbidity burden. Binary logistic regression models (outcome low *vs* moderate/high DAS28) were fitted using multiple imputation.

**Results.** A total of 2701 patients living with RA were recruited (mean age 56.1 years, 66.9% female); 5-year data were available for 1718 (63.4%) patients and 10-year data for 820 (30.4%). Baseline Rheumatic Diseases Comorbidity Index was not associated with DAS28 at 5 [odds ratio (OR) 1.05, 95% CI 0.91, 1.22] or 10 years (OR 0.99, 95% CI 0.75, 1.31) in multivariable analyses. Sociodemographic factors (female gender, worse deprivation) and poorer baseline HAQ-Disability Index were associated with DAS28 ≥3.2 at both timepoints. Being seropositive was associated with 5-year DAS28 ≥3.2.

**Conclusion.** This study demonstrates an association between sociodemographic and clinical factors and long-term RA disease activity, in models adjusting for comorbidity burden. The findings call for more holistic and targeted patient management in patients with RA and provide insights for more individualized management plans even on first presentation to rheumatology.

**Key words:** sociodemographic factors, comorbidity, multimorbidity, disease activity, RA

CLINICAL SCIENCE

**Rheumatology key messages**

- Sociodemographic factors are associated with worse disease activity in RA, independently of clinical measures at first presentation.
- Identifying patients at increased risk of moderate/high disease activity at initial review enables targeted management.
- Unlike sociodemographic factors and other clinical measures at baseline, comorbidities were not associated with worse disease activity.

## Introduction

Managing disease activity is a vital aspect of care for patients living with RA. Active disease, measured using patient-reported outcomes, clinical assessment or a combination of the two by use of a composite score [1], can lead to long-term joint damage [2], causing permanent discomfort and/or disability resulting in orthopaedic

[1]Centre for Health Services and Clinical Research, Life and Medical Sciences, University of Hertfordshire, Hatfield, [2]Population Health Sciences Institute, Newcastle University, Newcastle upon Tyne, [3]Faculty of Medical Sciences, Newcastle University Translational and Clinical Research Institute, Newcastle upon Tyne, [4]Musculoskeletal Unit, Newcastle upon Tyne Hospitals NHS Foundation Trust, Freeman Hospital, Newcastle upon Tyne, [5]Centre for Rheumatic Diseases, King's College London and [6]Rheumatology Department, King's College Hospital, London, UK

Submitted 25 September 2021; accepted 26 February 2022

Correspondence to: Amanda D. Busby, Centre for Health Services and Clinical Research, Life and Medical Sciences, University of Hertfordshire, Hatfield AL10 9AB, UK. E-mail: a.busby@herts.ac.uk

© The Author(s) 2022. Published by Oxford University Press on behalf of the British Society for Rheumatology.
This is an Open Access article distributed under the terms of the Creative Commons Attribution-NonCommercial License (https://creativecommons.org/licenses/by-nc/4.0/), which permits non-commercial re-use, distribution, and reproduction in any medium, provided the original work is properly cited. For commercial re-use, please contact journals.permissions@oup.com

surgery [3]. Because of this, the EULAR [4] guidelines recommend focus on disease activity for measuring RA patients' health outcomes. In particular, one of EULAR's four overarching principles targets clinical remission, defined as the absence of significant inflammatory disease activity, or low disease activity as an acceptable alternative [5].

In EULAR's most recent guidelines (updated in 2014), attention was drawn to the role of comorbidities in RA disease management, noting that they had 'potential to preclude treatment intensification' [5]. Aside from this, recent work by the EULAR Task Force on difficult-to-treat RA recognizes that comorbidities can influence the assessment of inflammatory activity in patients with RA [6]. In fact, two points to consider are highlighted through this work and are worth addressing here. The first calls for caution when using composite indices and clinical evaluation in the presence of comorbidities, in particular obesity and FM, since these may directly heighten inflammatory activity and/or overestimate disease activity, respectively [7–10]. It should be noted that comorbidities (such as infections and malignancies) can also contribute to the difficult-to-treat state in RA [11, 12], through misclassification of inflammatory RA activity [13]. Another point of consideration highlights that comorbidities that impact quality of life, either independently or by limiting RA treatment options, should be carefully considered and managed.

Most of the evidence to date is in RA more generally, suggesting a role of comorbidities on physical disability [14], although it remains unclear what effect they have on actual disease activity. As for difficult-to-treat disease, obesity is once again implicated in higher disease activity [15, 16], but the role of other comorbidities on disease activity *per se* is generally less well known. These observations, together with a knowledge that comorbidities are more prevalent in RA patients than the general population [17], and prominent even on first disease presentation [18, 19], have formed the rationale for this work.

The aim of this study was to identify early predictors of poor disease activity in RA at 5 and 10 years, focusing on comorbidities and exploring associations with other clinical and sociodemographic factors.

## Methods

### Study population

Data collected as part of two consecutive prospective cohorts were used in this analysis: the Early Rheumatoid Arthritis Study (ERAS, 1986–2001) and the Early Rheumatoid Arthritis Network (ERAN, 2002–2012). These cohorts were designed to be similar so they can be analysed together, and have previously been described in detail [20]. Recruitment for ERAS took place across nine hospitals in England and for ERAN through 23 centres in England, Wales and the Republic of Ireland. ERAS patients gave informed consent as required at time of enrolment (prior to Good Clinical Practice implementation), approved by the East Hertfordshire Local Research Ethics Committee. ERAN patients gave informed, written consent, approved by the Trent Research Ethics Committee. Patients were followed up 3–6 months after baseline visit, and yearly thereafter. Dates and causes of deaths for patients were obtained from NHS Digital.

### Baseline measures

#### *Comorbidities*

The primary focus of this study was whether baseline comorbidity, measured using the Rheumatic Disease Comorbidity Index (RDCI) [21], predicted future disease activity. The RDCI, used as a continuous variable, was developed as a rheumatic-specific measure of comorbidity, a predictor both of death and of functional outcomes. RDCI scores range from 0 to 9, with higher scores indicating a larger comorbidity burden. Eight disease categories are included, consisting of 11 illness types: lung disease, heart attack/other cardiovascular/stroke, fracture, depression, cancer, ulcer/stomach disease, hypertension, diabetes. The category definitions use the International Classification of Diseases, Ninth Revision, Clinical Modification codes. The overall RDCI score or individual disease category was included in all analyses *a priori*.

#### *Sociodemographic and clinical variables*

Secondary variables included standard demographic data [age at onset (to the nearest year), gender, ethnicity] were collected at baseline. Patient postcodes, recorded at baseline, were used to derive the Index of Multiple Deprivation (IMD) [22]. Quintiles were calculated for each IMD measure and patients assigned a group from 1 (most deprived) to 5 (least deprived), such that comparisons could be made across all nations. Clinical data [BMI, presence of erosions, presence of rheumatoid nodules, haemoglobin levels, presence of RF, presence of anti-CCP autoantibodies (anti-CCP) and ESR] were collected at baseline and then at each subsequent appointment. Patients were asked to complete the HAQ Disability Index (HAQ-DI) at each visit to ascertain their own views of functional disability. Time between onset of RA symptoms to first rheumatology appointment was recorded, measured in months. Time from onset to the commencement of DMARD for those prescribed was also recorded, again in months.

Some variables were reclassified to aid interpretation, for example smoking status (ever/never), serostatus (positive/negative, where positive included RF and/or anti-CCP) and ethnicity (White/minority ethnic groups).

### Outcomes

#### *Five- and 10-year disease activity*

During data collection for ERAS, disease activity was measured using the DAS [23]. As per standard practice at the time, this comprised four components, a

combination of patient (subjective) and clinician (objective) measures. These were: the Ritchie articular index (grading tenderness of 52 joints from 0–3), a general health assessment on a visual analogue scale (from 0, good health to 100, poor health), the 44 swollen joint count and ESR. These were combined to give DAS values which were rounded to scores ranging from 1 (low disease activity) to 9 (high disease activity).

The DAS using 28 joint counts (DAS28) was subsequently developed [24] and was used to measure disease activity in ERAN patients, with simplified joint scores including 28 joints rather than 44/52. Alternative formulas enabled DAS28 to be calculated if no measure of general health was available or if CRP was recorded in place of ESR. DAS28 scores range from 2 to 10, so are not directly interchangeable with DAS scores. ERAS DAS scores were therefore transformed using a tested formula [25] such that they could be compared directly with ERAN DAS28 values, as used in other studies. This formula, which uses all separate components of the DAS, estimates the scores with a higher level of precision than the transformation formula used previously, which tended to overestimate the true DAS28 score, particularly at the higher end of the scale.

DAS28 scores were dichotomized into remission/low ($<3.2$) or moderate/high disease activity ($\geq 3.2$) [26], a well-defined and clinically relevant cut-point. The primary outcome for this study was 5-year DAS28 $\geq 3.2$, with DAS28 at 10 years studied as secondary analysis.

### Statistical analysis

The statistical analysis was prespecified (Supplementary Data S1, available at *Rheumatology* online), although some variables were deemed unsuitable for use due to high levels of missingness (social class, marital status, education level). All analyses were performed using Stata/IC 15.1.

Descriptive statistics were calculated to compare patients with DAS28 $<3.2$ against those with DAS28 $\geq 3.2$ values at 5 and 10 years. For continuous variables, medians and interquartile ranges (IQR) were used and for binary/ordinal, frequencies and proportions. Odds ratios (ORs) were obtained using binary logistic regression models, separately for 5 and 10 years, to compare the groups for each covariate under consideration. Five-year outcomes were not used in 10-year models, since only baseline factors were of interest. Variables with a likelihood ratio test $P$-value $<0.2$ were tested in multivariable analysis.

Models for 5-year and 10-year DAS28 were built using forward selection based on clinical relevance and statistical robustness to obtain ORs and 95% CIs. Age at onset, gender and RDCI were included *a priori*. Variables were added in order of the smallest likelihood ratio test $P$-values (up to $P<0.05$) and retained in subsequent steps even if their $P$-values were increased.

Two interaction terms were deemed necessary for exploration *a priori*: smoking status with education level and smoking with presence of erosions. After obtaining final models, inclusion of interaction terms was tested in exploratory analyses. All possible interactions were considered, using each covariate in turn. This was done by using the selected covariate in interaction with every other covariate already in the model. Those terms with Wald test values of $P<0.15$ were added to the original model and assessed for inclusion with likelihood ratio tests. Stratified models were fitted to the data if appropriate, using complete cases.

Once model building was complete, multicollinearity between covariates was assessed, excluding variables with centred variance inflation factors $>10$. After models were determined using complete cases, multiple imputation by chained equations, performed with 20 imputations, was used. Any missing baseline variables selected in the complete case model, as well as missing DAS28 outcomes, were imputed. Baseline and 5-year values of clinical covariates (measured annually) were included in the imputation model for the 5-year DAS28 model, including RDCI; similarly baseline and 10-year values in the 10-year DAS28 model, if available. Patients who had died prior to the relevant outcome year were excluded from imputation models, so results should be interpreted as conditional on remaining alive. Continuous variables were imputed using linear regression, binary with logistic regression and ordinal using predictive mean matching.

Sensitivity analyses were performed to determine whether any differences were seen depending on the method used to calculate DAS28 scores, described in more detail in Supplementary Data S3.1, available at *Rheumatology* online. A further sensitivity analysis involved fitting a model using all candidate predictors with imputed data is described in Supplementary Data S3.2, available at *Rheumatology* online; this was to mitigate against potential downward bias resulting from the forward selection process. Additionally, any component part of baseline RDCI found to be associated with DAS28 at either timepoint in univariable analysis ($P<0.2$) was used in place of baseline RDCI in final models to ascertain any relationship with the outcome. Details of this process are described in Supplementary Data S3.3, available at *Rheumatology* online.

## Results

### Cohort demographics

There were 2701 patients recruited, with a mean age 56.1 years, 66.9% of whom were female, with a median time of 6 months from disease onset to first outpatient appointment. By year 5, 1718 (63.6%) patients remained enrolled, 185 (6.8%) were known to have died and a further 798 (29.5%) were no longer in follow-up. At year 10, 820 (30.4%) were enrolled, 454 (16.8%) had died and 1427 (52.8%) were not in follow-up. Completeness and availability of patient data are illustrated in the flowchart at Supplementary Data S4, available at *Rheumatology* online. Comparisons between those still enrolled and those no longer followed up are shown in

supplementary Tables S1 and S2, available at *Rheumatology* online. Those still enrolled at 5 years were younger at disease onset than those no longer followed up (median 55.5 years, IQR 45–65 compared with 62, IQR 50–70).

### Outcome: 5-year DAS28

DAS28 scores were available for 1354 patients at 5 years; 808 (59.7%) of patients had values ≥3.2. As shown in Table 1, a higher proportion of patients with DAS28 ≥3.2 were female (71.9% compared with 60.1%) and slightly fewer were of White ethnicity (96.3% *vs* 98.7%). More patients with DAS28 ≥3.2 were in the worst deprivation quintile at baseline (14.7% *vs* 8.4%) and fewer were in the least deprived quintile (25.4% *vs* 30.3%). Of those with DAS28 ≥3.2, 73.3% had no baseline comorbidities compared with 75.6% with DAS28 <3.2. Baseline HAQ-DI was higher among the DAS28 ≥3.2 group (median 1.13, IQR 0.63–1.75 compared with median 0.88, IQR 0.38–1.38).

*Univariable analyses*

Univariable analyses are shown in supplementary Table S3, available at *Rheumatology* online. No association was seen between RDCI, or any components, and 5-

**Table 1** Patient, comorbidity and disease characteristics according to elevated DAS28 status

| | 5-year DAS28 <3.2 | 5-year DAS28 ≥3.2 | 10-year DAS28 <3.2 | 10-year DAS28 ≥3.2 |
|---|---|---|---|---|
| **Total (%)** | 546 (40.3) | 808 (59.7) | 224 (34.4) | 427 (65.6) |
| **Sociodemographic** | | | | |
| Age at onset (years), median (IQR) | 56 (44–64) | 56 (46–65) | 52.5 (43–61) | 53 (45–62) |
| Female, *n* (%) | 328 (60.1) | 581 (71.9) | 131 (58.5) | 318 (74.5) |
| White ethnicity, *n* (%) | 535 (98.7) | 772 (96.3) | 217 (98.6) | 411 (96.9) |
| Ever smoked, *n* (%) | 233 (49.9) | 323 (49.0) | 85 (41.3) | 156 (41.2) |
| IMD quintiles, *n* (%) | | | | |
| 1 (most deprived) | 39 (8.4) | 107 (14.7) | 21 (10.0) | 70 (17.1) |
| 2 | 56 (12.1) | 110 (15.1) | 21 (10.0) | 61 (14.9) |
| 3 | 120 (26.0) | 187 (25.7) | 48 (22.7) | 90 (22.0) |
| 4 | 107 (23.2) | 140 (19.2) | 49 (23.2) | 69 (16.8) |
| 5 (least deprived) | 140 (30.3) | 185 (25.4) | 72 (34.1) | 120 (29.3) |
| **Comorbidity** | | | | |
| RDCI (continuous), median (IQR) | 0 (0–0) | 0 (0–1) | 0 (0–0) | 0 (0–0) |
| Lung disease, *n* (%) | 30 (5.5) | 51 (6.3) | 11 (4.9) | 20 (4.7) |
| Heart attack, other CV, stroke, *n* (%) | 22 (4.0) | 44 (5.4) | 6 (2.7) | 10 (2.3) |
| Fractures, *n* (%) | 2 (0.4) | 2 (0.2) | 1 (0.4) | 1 (0.2) |
| Depression, *n* (%) | 9 (1.6) | 15 (1.9) | 1 (0.4) | 9 (2.1) |
| Cancer, *n* (%) | 9 (1.6) | 13 (1.6) | 2 (0.9) | 6 (1.4) |
| Ulcer or stomach disease, *n* (%) | 13 (2.4) | 27 (3.3) | 8 (3.6) | 7 (1.6) |
| Hypertension, *n* (%) | 55 (10.1) | 85 (10.5) | 14 (6.3) | 23 (5.4) |
| Diabetes, *n* (%) | 12 (2.2) | 12 (1.5) | 7 (3.1) | 6 (1.4) |
| **Clinical measures** | | | | |
| Onset to 1st Appt, median (IQR) | 6 (4-12) | 7 (4-12) | 7 (4-12) | 7 (4-12) |
| | *n* = 542 | *n* = 804 | *n* = 224 | *n* = 427 |
| 1st Appt to 1st DMARD, median (IQR) | 1 (0-3) | 2 (0-4) | 2 (1-6) | 2 (1-6) |
| | *n* = 479 | *n* = 754 | *n* = 182 | *n* = 403 |
| HAQ-DI, median (IQR) | 0.88 (0.38–1.38) | 1.13 (0.63–1.75) | 0.75 (0.25–1.43) | 1.125 (0.625–1.75) |
| | *n* = 536 | *n* = 803 | *n* = 224 | *n* = 427 |
| DAS28, median (IQR) | 4.35 (3.42–5.35) | 5.00 (4.11–5.82) | 4.31 (3.17–5.20) | 4.91 (4.17–5.07) |
| | *n* = 538 | *n* = 791 | *n* = 221 | *n* = 423 |
| BMI (kg/m$^2$), median (IQR) | 25.4 (22.8–28.7) | 26.0 (22.9–29.3) | 24.7 (22.5–27.4) | 25.4 (22.8–28.4) |
| | *n* = 503 | *n* = 744 | *n* = 201 | *n* = 391 |
| Erosions, *n* (%) | 128 (23.9) | 216 (27.4) | 37 (16.9) | 107 (25.5) |
| Nodules, *n* (%) | 34 (6.2) | 53 (6.6) | 13 (5.8) | 29 (6.8) |
| Haemoglobin (g/dL), median (IQR) | 13 (12–14.1) | 12.6 (11.7–13.65) | 12.9 (12–13.8) | 12.6 (11.6–13.65) |
| | *n* = 541 | *n* = 800 | *n* = 221 | *n* = 424 |
| Seropositive, *n* (%) | 379 (73.7) | 598 (77.1) | 153 (69.5) | 322 (77.0) |
| ESR (mm/h), median (IQR) | 26 (13–46) | 35 (18–58) | 27 (12–50) | 37 (20–59) |
| | *n* = 513 | *n* = 774 | *n* = 218 | *n* = 423 |

IMD: Index of Multiple Deprivation 2007; RDCI: Rheumatic Diseases Comorbidity Index; Onset to 1st Appt: time (months) from symptom onset to first outpatient appointment; 1st Appt to 1st DMARD: time (months) from first appointment to starting DMARDs; HAQ-DI: HAQ Disability Index; DAS28: 28 joint count DAS.

year DAS28. Age at disease onset, and being female or of minority ethnicity were associated with DAS28 ≥3.2, each with $P < 0.2$. The odds of DAS28 ≥3.2 increased in the more deprived compared with the least deprived group. Elevated baseline HAQ-DI, DAS28, BMI and ESR, presence of erosions, being seropositive and low haemoglobin were each associated with DAS28 ≥3.2 at 5 years, $P < 0.2$.

*Multivariable analyses*

Results of multivariable analyses are shown in Table 2. Baseline RDCI was not found to be associated with DAS28 at 5 years (OR 1.05, 95% CI 0.91, 1.22). Being female increased odds of DAS28 ≥3.2 by nearly 50% compared with being male (OR 1.47, 95% CI 1.17, 1.85). Baseline HAQ-DI and being seropositive were each associated with increased odds of DAS28 ≥3.2 (OR 1.50, 95% CI 1.28, 1.76, and OR 1.33, 95% CI 1.05, 1.69, respectively). Each increase in IMD quintile, relating to less deprivation at baseline, was associated with reduced odds of DAS28 ≥3.2 (OR 0.88, 95% CI 0.81, 0.95). Although ESR featured in the model, its effect on DAS28 ≥3.2 odds was minimal (OR 1.01, 95% CI 1.00, 1.01). No evidence was found to include interaction terms in the model (further details in Supplementary Data S2, available at *Rheumatology* online).

## Outcome: 10-year DAS28

At 10 years, DAS28 values were available for 651 patients. A higher proportion had DAS28 ≥3.2 values at 10 years than at 5 years (65.6% compared with 59.7%). More females had 10-year DAS28 ≥3.2 (74.5% *vs* 58.5%) and more patients with DAS28 ≥3.2 had positive serostatus (77.0% *vs* 69.5%). Differences in DAS28 according to baseline deprivation remained, with DAS28 ≥3.2 consisting of a higher proportion of the most deprived quintile than DAS <3.2 (17.1% *vs* 10.0%), and conversely fewer in the least deprived group (29.3% *vs* 34.1%).

*Univariable analyses*

Univariable analyses (supplementary Table S3, available at *Rheumatology* online) found no association between RDCI and 10-year DAS28 outcome. A statistically significant difference was seen for depression, ulcer/stomach disease and diabetes groups, but with numbers too small to enable further analysis. As at 5 years, being female, of minority ethnicity and from a deprived area were associated with increased odds of DAS28 ≥3.2 ($P < 0.2$). Baseline HAQ-DI, DAS28, BMI, presence of erosions, haemoglobin, being seropositive and ESR were also associated with DAS28 ≥3.2 ($P < 0.2$).

*Multivariable analyses*

In multivariable analyses (Table 2), no association was seen between baseline RDCI and 10-year DAS28 ≥3.2 (OR 0.99, 95% CI 0.75, 1.31). Baseline HAQ-DI had a smaller effect than that seen at 5 years (OR 1.34, 95% CI 1.06, 1.69) but remained associated. Conversely, being female saw a larger effect on DAS28 ≥3.2 odds at 10 years (OR 1.81, 95% CI 1.22, 2.68). Again, baseline IMD was associated, with each increase in quintile (less deprived) associated with lower odds of DAS28 ≥3.2 (OR 0.82, 95% CI 0.72, 0.93). Although seropositive status was associated in complete case analysis, the association was reduced in the imputed model (OR 1.49, 95% CI 0.96, 2.32). Presence of erosions at baseline was associated with 10-year DAS28 ≥3.2, in contrast to 5 years (OR 1.82, 95% CI 1.16, 2.85). Again, there was no evidence to include interaction terms in the model (Supplementary Data S2, available at *Rheumatology* online).

## Sensitivity analyses

There was no evidence to support the exclusion of patients whose DAS28 scores were calculated using

**Table 2** Sociodemographic and clinical factors associated with DAS28 outcomes

| | 5-year DAS28 ($n$ = 2516) Odds ratio (95% CI) | 10-year DAS28 ($n$ = 2247) Odds ratio (95% CI) |
|---|---|---|
| Baseline RDCI | 1.05 (0.91, 1.22) | 0.99 (0.75, 1.31) |
| Age at onset | 1.00 (0.99, 1.01) | 1.00 (0.99, 1.01) |
| Gender (female) | 1.47 (1.17, 1.85)* | 1.81 (1.22, 2.68)* |
| Baseline HAQ-DI | 1.50 (1.28, 1.76)** | 1.34 (1.06, 1.69)* |
| IMD quintiles | 0.88 (0.81, 0.95)* | 0.82 (0.72, 0.93)* |
| Seropositive status | 1.33 (1.05, 1.69)* | 1.49 (0.96, 2.32) |
| ESR | 1.01 (1.00, 1.01)* | 1.01 (1.00, 1.02)* |
| Erosions | ¥ | 1.82 (1.16, 2.85)* |

Multivariable logistic regression models; gender, age at onset and RDCI included *a priori*. Variables were retained in subsequent steps even if their *P*-values were increased. Variables tested in univariable analysis shown in supplementary Table S3, available at *Rheumatology* online. Variables tested in multivariable analyses: 5-year DAS28: RDCI, age at onset, gender, ethnicity, IMD, DAS28, HAQ, BMI, erosions, haemoglobin, seropositive status, ESR; 10-year DAS28: RDCI, age at onset, gender, ethnicity, IMD, DAS28, HAQ, BMI, erosions, haemoglobin, seropositive status, ESR. *$P$ <0.05; **$P$ <0.001. ¥Not selected in multivariable analysis ($P$ >0.05). RDCI: Rheumatic Diseases Comorbidity Index; HAQ-DI: HAQ Disability Index; IMD: Index of Multiple Deprivation; DAS28: 28 joint count DAS.

CRP instead of ESR (Supplementary Data S3.1 and Supplementary Table S4, available at *Rheumatology* online). Modelling with all candidate predictors had minimal impact on odds ratios for 5- or 10-year DAS28 (Supplementary Data S3.2 and Table S5, available at *Rheumatology* online). No association was found between any RDCI component and DAS28 at 5 years, with too few cases to consider separate conditions at 10 years (Supplementary Data S3.3 and Table S6, available at *Rheumatology* online). Fitting models with baseline DAS28 in place of ESR resulted in issues with multicollinearity and had little impact on the estimates for other covariates (supplementary Table S7, available at *Rheumatology* online).

Models fitted separately for each cohort had minimal effect on odds ratios; although the effect of baseline RDCI on 5-year DAS28 was slightly greater within the ERAN cohort than ERAS, this remained statistically insignificant (data not shown). As DAS28 data were only available for 1354 participants at 5 years and 651 at 10 years, outcome values were imputed for 1434 (57.0%) and 1596 (71.0%) of the combined cohorts, respectively. Fitting models using only those observed had minimal effect on estimated ORs, although presence of erosions at baseline was not found to be significant among those with observed 10-year DAS28 scores in contrast to the imputed values (data not shown).

## Discussion

This study found that baseline comorbidity burden, measured with RDCI, was not associated with DAS28 at either 5 or 10 years. Age at disease onset had no effect on disease activity, but other sociodemographic factors, namely female gender and worse baseline deprivation, were each associated with increased odds of DAS28 $\geq$3.2 at both 5 and 10 years, in line with findings from other studies [27]. Although worse deprivation is known to be associated with poorer HAQ-DI scores, little evidence exists of a relationship with disease activity to date [28]. Among clinical factors tested, being seropositive was associated with 5-year DAS28 and having erosions with 10-year DAS28, as also supported by other literature [29, 30]. Poorer baseline HAQ-DI was found to associate with DAS28 at both timepoints, again in line with existing evidence [31].

Although it is known that a relationship exists between health in early stages of RA and later disease activity [32], this study has attempted to establish a link between comorbidities present at baseline and worse disease outcomes. RA patients are known to be at increased risk of cardiovascular disease [33], malignancies, infections, gastrointestinal diseases, osteoporosis and depression [34], but with little research undertaken to assess the relationship between comorbidities at onset of RA and subsequent disease activity. Those living in areas of the UK with more deprivation are known to have poorer health outcomes [35] and this study has confirmed that this is also true in the case of people living with RA. This highlights the value of considering the whole picture when seeing a patient in clinic for the first time, including sociodemographic as well as clinical factors.

Previous research from our group showed that baseline comorbidities were not associated with later functional outcomes [36], but that sociodemographic factors (increased age at disease onset, female gender and minority ethnicity) were associated with increased odds of HAQ-DI $\geq$1.5 at both 5 and 10 years. Additionally, worse deprivation at baseline was associated with 10-year HAQ-DI $\geq$1.5. Insights from these works will be used to inform risk-stratification of patients and specific pathways to enhance the care of patients with RA. Sociodemographic factors at baseline are informative and bring another important dimension that deserves attention, since they are unlikely to vary in subsequent years—at least, not as much as clinical measures. The role in risk stratification early on, is therefore crucial.

This study is unique in several ways. Firstly, it uses two large early RA cohorts, long in follow-up, rich in clinical, comorbidity and sociodemographic data, and designed such that they could be analysed collectively. Secondly, it studies both biological and non-biological factors, recognizing the impact that comorbidities have on T2T goals. Finally, it investigates sociodemographic factors, particularly deprivation, adding a further dimension and allowing the study of associations with other clinical parameters and the influence on patient outcomes. However, there are also some limitations, including the age of these cohorts, during which time treatment may not have reflected modern approaches, limiting the generalizability of these findings. DAS28 values were available for just 1354 participants at 5 years and 651 at 10 years, with multiple imputation applied to address this. It was assumed that patients without follow-up data were missing at random, but it is possible that they could have had higher disease activity than those remaining in the study. Although similar results were seen among those with measured outcome values, consideration should be given of the high proportion of imputed values when interpreting these results. Few patients who identified as belonging to a minority ethnicity group participated, such that responses could not be meaningfully analysed to represent different communities. Links between ethnicity and deprivation within the UK are well documented [37], but could not be further explored in this dataset. A further limitation is the number of hypotheses tested and lack of multiple testing correction. It is possible that some significant results are false positives, and results should be interpreted as exploratory rather than confirmatory. Overall, despite the use of historical RA inception cohorts, insights from this study are relevant even in modern rheumatology practice, particularly with the added dimension of the potential role of social factors in risk stratification and in informing a more holistic management of patients with RA, at first presentation to rheumatology.

In conclusion, this study found no association between baseline comorbidities and DAS28 outcome at 5 or

10 years in RA patients. However, some sociodemographic and clinical factors recorded at baseline play a role in disease activity in later years, in models adjusted for comorbidity burden. These findings build upon those relating to functional outcome and will accelerate the identification at initial rheumatology appointment of RA patients at increased risk of worse outcomes. Our findings support that tailored intervention can be implemented in a timely manner, in line with national and international recommendations, potentially limiting permanent joint damage and disability and improving quality of life for individuals.

*Funding*: This work was supported by the British Medical Association (BMA) as part of the Doris Hillier award received by E.N.

*Disclosure statement*: The authors declare no conflicts of interest related to this work.

## Data availability statement

The data underlying this article will be shared on reasonable request to the corresponding author.

## Supplementary data

Supplementary data are available at *Rheumatology* online.

## References

1 Anderson J, Caplan L, Yazdany J *et al.* Rheumatoid arthritis disease activity measures: American College of Rheumatology recommendations for use in clinical practice. Arthritis Care Res 2012;64:640–7.

2 Klarenbeek NB, Koevoets R, van der Heijde DMFM *et al.* Association with joint damage and physical functioning of nine composite indices and the 2011 ACR/EULAR remission criteria in rheumatoid arthritis. Ann Rheum Dis 2011;70:1815–21.

3 Nikiphorou E, Norton S, Young A *et al.*; ERAS and ERAN. Association between rheumatoid arthritis disease activity, progression of functional limitation and long-term risk of orthopaedic surgery: combined analysis of two prospective cohorts supports EULAR treat to target DAS thresholds. Ann Rheum Dis 2016;75:2080–6.

4 European Alliance of Associations for Rheumatology (EULAR). https://www.eular.org/eular_about.cfm (15 September 2021, date last accessed).

5 Smolen JS, Breedveld FC, Burmester GR *et al.* Treating rheumatoid arthritis to target: 2014 update of the recommendations of an international task force. Ann Rheum Dis 2016;75:3–15.

6 Nagy G, Roodenrijs NMT, Welsing PMJ *et al.* EULAR points to consider for the management of difficult-to-treat rheumatoid arthritis. Ann Rheum Dis 2021;80:31–5.

7 Bauer EM, Ben-Artzi A, Duffy EL *et al.* Joint-specific assessment of swelling and power Doppler in obese rheumatoid arthritis patients. BMC Musculoskelet Disord 2017;18:99.

8 Sosa J, Perez SK, Santa Cruz MJ *et al.* M-DAS28, M-SDAI and M-CDAI performance in a cohort of RA patients with and without concomitant fibromyalgia [abstract]. Conference: 2017 ACR/ARHP Annual Meeting, 2017.

9 Ranganath VK, Duffy EL, Garg VK *et al.* Obesity impacts swelling of ankle and foot joints in early rheumatoid arthritis patients. J Clin Rheumatol 2019;25:e8–11.

10 Goossens J, Coustet B, Palazzo E, Dieudé P, Ottaviani S. Overweight and obesity affect clinical assessment of synovitis in rheumatoid arthritis: comparison of ultrasonography and clinical exam. Clin Exp Rheumatol 2019;37:49–54.

11 Roodenrijs NMT, van der Goes MC, Welsing PMJ *et al.* Difficult-to-treat rheumatoid arthritis: contributing factors and burden of disease. Rheumatology (Oxford) 2021;60:3778–88.

12 de Hair MJH, Jacobs JWG, Schoneveld JLM, van Laar JM. Difficult-to-treat rheumatoid arthritis: an area of unmet clinical need. Rheumatology (Oxford) 2017;57:1135–44.

13 Roodenrijs NMT, Kedves M, Hamar A *et al.* Diagnostic issues in difficult-to-treat rheumatoid arthritis: a systematic literature review informing the EULAR recommendations for the management of difficult-to-treat rheumatoid arthritis. RMD Open 2021;7:e001511.

14 Radner H, Smolen JS, Aletaha D. Impact of comorbidity on physical function in patients with rheumatoid arthritis. Ann Rheum Dis 2010;69:536–41.

15 Nikiphorou E, Norton S, Young A *et al.*; Early Rheumatoid Arthritis Study and the Early Rheumatoid Arthritis Network. The association of obesity with disease activity, functional ability and quality of life in early rheumatoid arthritis: data from the Early Rheumatoid Arthritis Study/Early Rheumatoid Arthritis Network UK prospective cohorts. Rheumatology (Oxford) 2018;57:1194–202.

16 Nikiphorou E, Fragoulis GE. Inflammation, obesity and rheumatic disease: common mechanistic links. A narrative review. Ther Adv Musculoskelet Dis 2018;10:157–67.

17 Kłodziński Ł, Wisłowska M. Comorbidities in rheumatic arthritis. Reumatologia/Rheumatology 2018;56:228–33.

18 Norton S, Koduri G, Nikiphorou E *et al.* A study of baseline prevalence and cumulative incidence of comorbidity and extra-articular manifestations in RA and their impact on outcome. Rheumatology (Oxford) 2013;52:99–110.

19 Nikiphorou E, Norton S, Carpenter L *et al.*; Early Rheumatoid Arthritis Study and the Early Rheumatoid Arthritis Network Cohorts. Secular changes in clinical features at presentation of rheumatoid arthritis: increase in comorbidity but improved inflammatory states. Arthritis Care Res 2017;69:21–7.

20 Nikiphorou E, Carpenter L, Morris S *et al.* Hand and foot surgery rates in rheumatoid arthritis have declined from 1986 to 2011, but large-joint replacement rates remain unchanged: results from two UK inception cohorts. Arthritis Rheumatol 2014;66:1081–9.

21 England BR, Sayles H, Mikuls TR, Johnson DS, Michaud K. Validation of the rheumatic disease comorbidity index. Arthritis Care Res 2015;67:865–72.

22 Index of Multiple Deprivation 2004. Intelligence. 2005: 1–2. http://www.communities.gov.uk/communities/research/indicesdeprivation/deprivation10 (15 September 2021, date last accessed).

23 van Riel PL. The development of the disease activity score (DAS) and the disease activity score using 28 joint counts (DAS28). Clin Exp Rheumatol 2014;32(5 Suppl 85):S-65-74.

24 van Gestel AM, Haagsma CJ, van Riel PLCM. Validation of rheumatoid arthritis improvement criteria that include simplified joint counts. Arthritis Rheum 1998;41:1845–50.

25 Carpenter L, Norton S, Nikiphorou E *et al.* Validation of methods for converting the original Disease Activity Score (DAS) to the DAS28. Rheumatol Int 2018;38: 2297–305.

26 NRAS. The relevance and importance of DAS28 in your treatment pathway. https://nras.org.uk/resource/the-das28-score/ (15 September 2021, date last accessed).

27 Sokka T, Toloza S, Cutolo M *et al.* Women, men, and rheumatoid arthritis: analyses of disease activity, disease characteristics, and treatments in the QUEST-RA study. Arthritis Res Ther 2009;11:R7.

28 Verstappen SMM. The impact of socio-economic status in rheumatoid arthritis. Rheumatology (Oxford) 2017;56: 1051–52.

29 Aletaha D, Alasti F, Smolen JS. Rheumatoid factor, not antibodies against citrullinated proteins, is associated with baseline disease activity in rheumatoid arthritis clinical trials. Arthritis Res Ther 2015;17:229.

30 Mouterde G, Rincheval N, Lukas C *et al.* Outcome of patients with early arthritis without rheumatoid factor and ACPA and predictors of rheumatoid arthritis in the ESPOIR cohort. Arthritis Res Ther 2019;21:140.

31 Vastesaeger N, Kutzbach AG, Amital H *et al.* Prediction of remission and low disease activity in disease-modifying anti-rheumatic drug-refractory patients with rheumatoid arthritis treated with golimumab. Rheumatology (Oxford) 2016;55:1466–76.

32 Fanouriakis A, Papalopoulos I, Gergianaki I *et al.* In early arthritis patients, high HAQ at baseline and DAS28 at three months predict suboptimal outcomes at two years: a retrospective cohort study. Clin Exp Rheumatol 36:806–13.

33 Urman A, Taklalsingh N, Sorrento C, McFarlane IM. Inflammation beyond the joints: rheumatoid arthritis and cardiovascular disease. SciFed J Cardiol 2018;2: 1000019.

34 Baillet A, Gossec L, Carmona L *et al.* Points to consider for reporting, screening for and preventing selected comorbidities in chronic inflammatory rheumatic diseases in daily practice: a EULAR initiative. Ann Rheum Dis 2016;75:965–73.

35 Marmot M. Strategic Review of Health Inequalities in England post-2010. Fair Society, Healthier Lives: The Marmot review. 2010. https://www.parliament.uk/globalassets/documents/fair-society-healthy-lives-full-report.pdf (15 September 2021, date last accessed).

36 Busby AD, Wason J, Pratt AG *et al.* Predictors of poor function in RA based on two prospective UK inception cohorts. Do comorbidities matter? Rheumatology (Oxford) 2022;61:1563–69.

37 People Living in Deprived Neighbourhoods. 2020. https://www.ethnicity-facts-figures.service.gov.uk/uk-population-by-ethnicity/demographics/people-living-in-deprived-neighbourhoods/latest (15 September 2021, date last accessed).