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# Secular Changes in Clinical Features at Presentation of Rheumatoid Arthritis: Increase in Comorbidity But Improved Inflammatory States

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***Objective.*** **To examine secular trends in demographics, clinical manifestations, and comorbidity on first presentation of rheumatoid arthritis (RA) prior to disease-modifying antirheumatic drug treatment.**

***Methods.*** **A total of 2,701 patients were recruited over 25 years to 2 UK-based RA inception cohorts: the Early Rheumatoid Arthritis Study (9 centers; 1986–2001) and the Early Rheumatoid Arthritis Network (23 centers; 2002–2012). Trends in demographic and baseline clinical/laboratory and radiographic variables and comorbidities were estimated using mixed-effects models, including random effects for recruitment center.**

***Results.*** **Age at onset increased from 53.2 to 57.7 years in 1990 and 2010, respectively (2.6 months/year; 95% confidence interval [95% CI] 1.2, 4.1). Sex ratio, the proportion living in deprived areas, and smoking status were unchanged ($P > 0.05$) and there were no changes in the proportion seropositive or erosive at baseline ($P > 0.05$). After controlling for treatment at the time of assessment, erythrocyte sedimentation rate decreased and hemoglobin increased over time ($P > 0.05$); however, the Health Assessment Questionnaire (HAQ), the Disease Activity Score (DAS), the DAS in 28 joints, and joint counts were unchanged ($P > 0.05$). The overall prevalence of comorbidity increased from 29.0% in 1990 to 50.7% in 2010, mainly due to cardiovascular and non-cardiac vascular conditions, including hypertension. There was a significant increase in body mass index (0.15 units/year; 95% CI 0.11, 0.18), resulting in an increase in the prevalence of obesity from 13.3% in 1990 to 33.6% in 2010.**

***Conclusion.*** **Age at onset and comorbidity burden, especially obesity, have increased at RA presentation over 25 years, reflecting wider demographic trends at the population level. In contrast, there were no accompanying changes in disease severity assessed by composite markers of disease activity, radiographic erosions, seropositivity, or HAQ at presentation. Treatment strategies in early RA should take greater account of the impact of comorbidity on outcomes.**

## INTRODUCTION

The need to better understand patterns of disease expression in rheumatoid arthritis (RA) and also wider patient characteristics is well recognized in modern day rheumatology practice and stratified medicine. Several studies report a decreasing severity of RA over time, though some controversy remains (1–5). Reports on long-term outcomes of disease (6–10) attribute the reduction in RA severity mainly to the use of earlier and more intensive disease-modifying treatments (11). These data are compromised by the majority

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## Significance & Innovations

- Increasing age and level of comorbidity were observed at presentation of rheumatoid arthritis (RA) over a 25-year period.
- In contrast, RA disease severity remained stable over time, prior to disease-modifying treatment.
- Modern management of RA should incorporate a detailed assessment of comorbidities in order to better inform treatment stratification.

of studies not allowing for an assessment of disease severity on first presentation, prior to disease-modifying antirheumatic drug (DMARD) therapy or long-term steroids, due to the nature of the data collected. As a result, trends at presentation may be confounded by treatment commencement prior to the completion of disease severity assessments. Furthermore, there are very little data on the presence of comorbidities in early RA, although these have an influence on treatment efficacy and disease outcomes. An important reason for this is failure or variation in the capture of this information.

Ascertaining the burden of comorbidities in RA is important in clinical practice for several reasons, and requires an incorporation of strategies to manage these from the time the patient first presents, as well as suppressing the inflammatory burden of RA with traditional DMARDs. This is exemplified by the well-recognized independent influence of RA on adverse cardiovascular outcomes (12). Furthermore, the impact that comorbidities can have on DMARD and biologic agent tolerability and efficacy requires careful treatment selection to optimize outcomes. Therefore, the treatment strategy selected at first presentation of RA should be reflective of the index condition as well as all other coexisting factors.

An increased prevalence of obesity and conditions such as diabetes mellitus have been reported in the general population (13,14) but not specifically in RA (1). The primary objective of this study was therefore to determine whether demographics, clinical characteristics, and the presence of comorbidities at RA presentation, prior to the initiation of DMARD therapy, have changed over the past 25 years. The study uses data from 2 consecutive UK inception cohorts and hypothesizes that 1) in line with a reduced incidence, age at symptom onset would have increased, 2) due to wider societal trends and increasing age at onset, obesity and the presence of comorbidities will have increased, and 3) based on previous literature, and due to better general population health (e.g., greater awareness of the effects of smoking) disease severity as indicated by clinical characteristics, inflammatory markers, and symptoms would have decreased.

## PATIENTS AND METHODS

**Patient databases.** The Early Rheumatoid Arthritis Study (ERAS) and Early Rheumatoid Arthritis Network (ERAN) are multicenter inception cohorts of early RA, which recruited from 9 rheumatology centers in England between 1986 and 2001, and 23 centers in England, Wales, and Ireland from 2002 to 2012, respectively, as previously described in detail (10). Recruitment figures and median followup for ERAS and ERAN were 1,465 and 10 years (maximum 25 years) and 1,236 and 6 years (maximum 10 years), respectively. ERAS and ERAN are consecutive studies with similar design and patients, recruited within the first 2 and 3 years from symptom onset, respectively, and prior to DMARD therapy in ERAS and the greatest majority of ERAN.

**Clinical, laboratory, and radiographic variables.** Standard demographic, clinical, and laboratory variables were recorded at the time of patient visit (baseline visit) and yearly thereafter and strictly prior to DMARD use in ERAS; although in ERAN a small proportion of patients were recruited after DMARD initiation (indicated on the database). Variables recorded in both cohorts included sex, age at disease onset, recruitment year, baseline rheumatoid factor and/or anti–cyclic citrullinated peptide, hemoglobin, erythrocyte sedimentation rate (ESR), and Health Assessment Questionnaire (HAQ) disability index (15). Individuals in both cohorts were classified as living in a deprived area based on their postal code being ranked in the lowest quintile of areas in England by the Index of Multiple Deprivation 2007. There were some differences in the recording of certain variables relating to disease activity between ERAS and ERAN, namely in the recording of the tender (TJC) and swollen joint count (SJC) variables, and patient global assessment (PGA). In ERAS, disease activity was calculated based on the original 3-variable Disease Activity Score (DAS) (16,17), whereas in ERAN the 4-variable DAS in 28 joints (DAS28) ESR method was used (18–20). In line with the change to the DAS28 score, joint counts changed from 44 joints to 28, and the focus of PGA changed from pain to disease activity, respectively. A formula was used to convert the ERAS DAS scores to DAS28 scores (21) to make them comparable across both cohorts, though since they are not interchangeable they were examined separately in the 2 cohorts. Data on comorbidities and extraarticular manifestations were recorded at every visit in the medical notes and on the case reporting forms, and the comorbidities subsequently coded based on the International Classification of Diseases, Tenth Revision coding system. These codes were used to generate a numeric count from which the weighted Charlson Comorbidity Index (CCI) (21) was generated. Since RA is the index condition for this study it was excluded from the CCI score (modified CCI).

**Treatment profiles.** All centers followed the framework of published UK guidelines for management of RA, although treatment choice was ultimately left at the discretion of the treating clinician (10). In ERAN, a small proportion of patients used synthetic DMARDs prior to recruitment into the study. Steroid use in primary care prior to rheumatology review was recorded where available. Nonsteroidal antiinflammatory drug (NSAID) use was not recorded and was therefore not included in the analysis.

**Table 1. Demographic and clinical characteristics at baseline visit***

| Variable | ERAS (n = 1,465) | | ERAN (n = 1,236) | |
|---|---|---|---|---|
| | Value | No. missing | Value | No. missing |
| Year of onset, median (IQR) | 1992 (3.0) | 0 | 2006 (3.0) | 0 |
| Age at onset, mean ± SD years | 55.3 ± 14.6 | 0 | 57.0 ± 14.2 | 0 |
| Female, no. (%) | 973 (66.4) | 0 | 839 (67.9) | 0 |
| BMI, mean ± SD† | 25.6 ± 4.5 | 199 | 27.6 ± 5.3 | 117 |
| Obese, no. (%) | 187 (14.8) | 199 | 303 (27.7) | 142 |
| Socially deprived area, no. (%) | 259 (18.7) | 83 | 143 (16.0) | 343 |
| Smoker, no. (%)‡ | 199 (21.9) | 558 | 310 (25.5) | 19 |
| Comorbidity, no. (%) | 431 (29.4) | 0 | 653 (52.8) | 0 |
| Symptoms duration, median (IQR) months | 6 (7.0) | 0 | 6 (9.0) | 91 |
| HAQ, median (IQR) | 1.0 (1.3) | 5 | 1.0 (1.1) | 37 |
| ESR, (mmHg) median (IQR) | 37 (3) | 7 | 25 (3) | 183 |
| Hemoglobin, mean ± SD | 12.6 ± 1.6 | 5 | 13.1 ± 1.4 | 32 |
| DAS, mean ± SD | 5.0 ± 1.2 | 13 | 4.5 ± 1.6 | 46 |
| TJC, median (IQR) | 10 (12.0) | 5 | 5 (9.0) | 6 |
| SJC, median (IQR) | 15 (19.0) | 3 | 4 (8.0) | 5 |
| RF and/or anti-CCP positive, no. (%) | 914 (62.8) | 9 | 639 (60.5) | 179 |
| Erosions, no. (%) | 368 (25.7) | 32 | 330 (29.4) | 114 |
| Steroid prior presentation, no. (%)§ | 0 (0.0) | 0 | 125 (10.1) | 0 |
| DMARD prior presentation, no. (%)§ | 0 (0.0) | 0 | 168 (13.6) | 0 |

* ERAS = Early Rheumatoid Arthritis Study; ERAN = Early Rheumatoid Arthritis Network; IQR = interquartile range; BMI = body mass index; HAQ = Health Assessment Questionnaire; ESR = erythrocyte sedimentation rate; DAS = Disease Activity Score; TJC = tender joint count (out of 44 in ERAS and 28 in ERAN); SJC = swollen joint count (out of 44 in ERAS and 28 in ERAN); RF = rheumatoid factor; anti-CCP = anti–cyclic citrullinated peptide; DMARD = disease-modifying antirheumatic drug.
† Obesity defined as BMI >30.
‡ Smoker indicates current/previous smoking history.
§ Prior indicates use of these drugs prior to enrollment into the study.

**Statistical analysis.** Mixed-effects models, accounting for clustering of patients within centers with a random effect, were used to estimate the annual change in demographic and clinical variables at first presentation to the rheumatologist. The demographic or clinical variable was entered into separate models as the outcome, and calendar year of onset was included as a predictor. Linear models were used for continuous variables and logistic models for binary variables. All analyses were undertaken in Stata, version 12.1. For variables that were identical across both cohorts (e.g., age at onset, sex, ESR), linear trends over time were compared to nonlinear trends estimated using restricted cubic splines (knots at 1990, 1995, 2000, and 2005), and piecewise models with linear trends estimated separately within each cohort. Based on visual inspection of the estimated trends and the comparison of model fit using Bayesian Information Criterion, trends over time for all variables were adequately approximated by a linear function. Therefore, only linear trends are displayed in the results. Note that for logistic models, estimates of prevalence are curvilinear due to transformation from the logit scale. SEs for all models were estimated using bootstrap approach with 1,000 resamples. Trends in baseline demographic variables were adjusted for age, sex, and the time between symptom onset and baseline visit. Trends in clinical variables were adjusted for age, sex, and use of steroids or disease-modifying treatment prior to the baseline visit. ESR was log-transformed for analysis and then back-transformed for display.

## RESULTS

**Trends in demographic variables.** Demographic and clinical characteristics by cohort are given in Table 1. The estimated trends for variables that were assessed in the same manner across both cohorts are shown in Figure 1. Age at symptom onset increased from 53.2 years in 1990

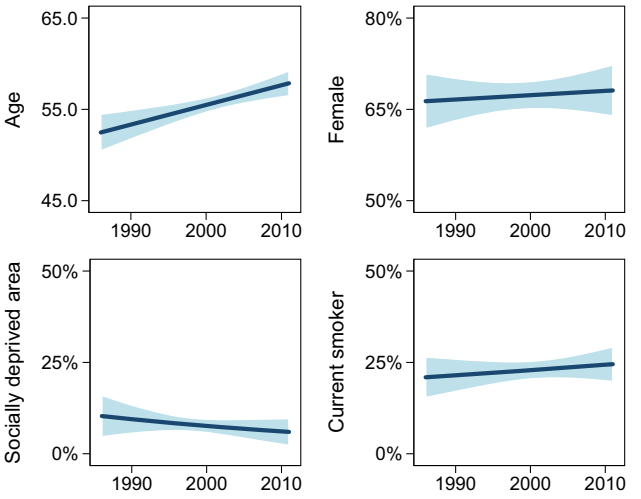


**Figure 1.** Trends in demographic variables and clinical characteristics. Color figure can be viewed in the online issue, which is available at http://onlinelibrary.wiley.com/journal/doi/10.1002/acr.23014/abstract.

**Table 2. Comorbidity burden and extraarticular manifestations across ERAS and ERAN on presentation***

| Type of condition | Baseline, no. (%) |
|---|---|
| Non-cardiac vascular, e.g., hypertension, peripheral vascular disease | 404 (15) |
| Endocrine, e.g., diabetes mellitus, thyroid disease | 253 (9.4) |
| Cardiovascular, e.g., ischemic heart disease, congestive cardiac failure | 173 (6.4) |
| Respiratory, e.g., COPD, asthma | 141 (5.2) |
| Osteoarthritis, primary or secondary | 124 (4.6) |
| Psychiatric, e.g., anxiety, depression, psychotic illness, anorexia | 81 (3.0) |
| Gastrointestinal, e.g., gastritis, inflammatory bowel disease, diverticulitis | 79 (2.9) |
| Solid cancer, organ-based cancer, e.g., lung, prostate | 79 (2.9) |
| Dermatologic, e.g., psoriasis, eczema | 70 (2.6) |
| Spinal, e.g., disc disease, spinal stenosis | 51 (1.9) |
| Cerebrovascular, e.g., ischemic/hemorrhagic stroke | 40 (1.5) |
| Neurologic, e.g., Parkinson's disease, myasthenia gravis | 36 (1.3) |
| Renal, e.g., chronic kidney disease, renal calculi | 28 (1.0) |
| Hematologic, e.g., anemia | 24 (0.9) |
| Ophthalmologic, e.g., cataract formation | 25 (0.9) |
| Gynecologic, e.g., nonmalignant ovarian or uterine disease | 16 (0.6) |
| Hepatic, e.g., alcoholic liver disease | 7 (0.3) |
| Hematologic malignancy, e.g., leukemia, lymphoma | 4 (0.1) |
| Extraarticular manifestations | |
| All, major, e.g., vasculitis, ILD; minor, e.g., nodules, peripheral nerve entrapment | 323 (12) |

* ERAS = Early Rheumatoid Arthritis Study; ERAN = Early Rheumatoid Arthritis Network; COPD = chronic obstructive pulmonary disease; ILD = interstitial lung disease.

to 57.7 years in 2010, an increase of 2.6 months/year (b = 0.22 years/year; 95% confidence interval [95% CI] 0.10, 0.34). The proportion of patients that were female, living in a socially deprived area, and were current smokers did not change significantly over the 25-year period of recruitment to the 2 cohorts ($P > 0.05$).

**Overall comorbidity burden.** Table 2 shows the overall comorbidity burden by type of comorbidity at baseline across both cohorts. The main conditions reported were non-cardiac vascular, mainly hypertension, followed by endocrine disease (mainly thyroid problems), cardiovascular (mainly ischemic heart disease), and respiratory diseases (mainly chronic obstructive pulmonary disease and asthma). Diabetes mellitus was reported in 2.0% (n = 54) and osteoporosis in 1.3% at baseline (n = 34; 13 in ERAS, 21 in ERAN). Psychiatric comorbidity represented 3% of comorbidities at baseline, including depression and anxiety (n = 68) and, less commonly, anorexia and psychosomatic disease (n = 13).

Extraarticular RA disease was present in 12% of patients at baseline and included rheumatoid nodules, pulmonary interstitial lung disease (ILD), and secondary Sjögren's syndrome. ILD in particular was reported in 0.7% (n = 18; 5 in ERAS, 13 in ERAN).

**Trends in comorbidities.** Trends in comorbidities over time are shown in Figure 2, with further information in Supplementary Figure 1, (on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23014/abstract). Presence of a comorbid medical condition increased substantially with time, from 29.0% in 1990 to 50.7% in 2010, relating to a 5% increase in the odds of prevalent comorbidity per year of later onset, across the observed period (odds ratio [OR] 1.05, 95% CI 1.03, 1.07). Similar relative increases in the presence of CCI (modified CCI excluding RA) (9.6–19.8%; OR 1.04, 95% CI 1.02, 1.07), cardiovascular conditions (1.9–6.8%; OR 1.07, 95% CI 1.03, 1.11), and non-cardiac vascular conditions (3.6–30.4%; OR 1.13, 95% CI 1.10, 1.16) including hypertension were observed. There was a

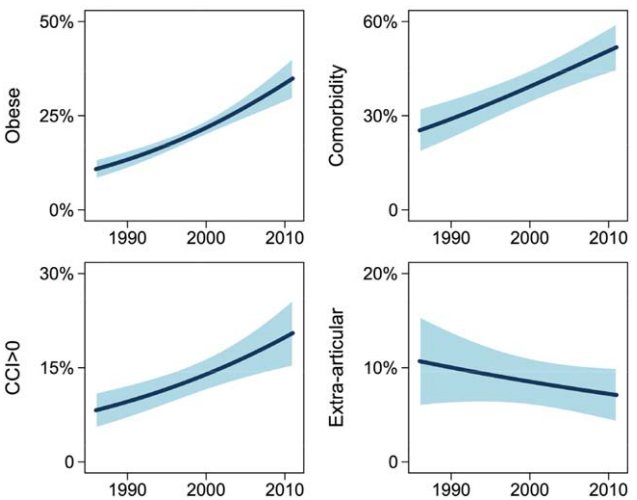


**Figure 2.** Trends in comorbidities over time. CCI = Charlson Comorbidity Index. Color figure can be viewed in the online issue, which is available at http://onlinelibrary.wiley.com/journal/doi/10.1002/acr.23014/abstract.

considerable increase in body mass index (BMI) over time (b = 0.15, 95% CI 0.11, 0.18). This related to an increase in the prevalence of obesity from 13.3% in 1990 to 33.6% in 2010 (OR 1.06, 95% CI 1.04, 1.08). The presence of extraarticular conditions (mainly nodules, Raynaud's phenomenon, and Sjögren's syndrome) reduced slightly though nonsignificantly. Small but nonsignificant increases were observed for diabetes mellitus (1990: 1.3%; 2010: 2.5%; OR 1.04, 95% CI 0.99, 1.08), respiratory conditions (1990: 4.5%; 2010: 5.6%; OR 1.01, 95% CI 0.99, 1.04), and gastrointestinal conditions (1990: 2.3%; 2010: 2.7%; OR 1.01, 95% CI 0.97, 1.05). Trends in other conditions including interstitial lung disease and vasculitis are not displayed due to low prevalence at baseline.

**Trends in disease severity.** Trends in disease severity, adjusting for age at disease onset, sex, symptom duration, and treatment prior to the baseline assessment, are shown in Figure 3 (see Supplementary Figures 2 and 3, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr. 23014/abstract). Controlling for age at disease onset, sex, symptom duration, and treatment prior to the baseline assessment, there was a reduction in baseline ESR (logarithmic scale: b = −0.02, 95% CI −0.02, −0.01) and an increase in hemoglobin (b = 0.04, 95% CI 0.03, 0.05). However, controlling for the same variables, HAQ did not change over the period of observation (b = 0.00, 95% CI −0.01, 0.01).

Figure 4 displays the estimated trends within each cohort for variables assessed in different ways across the 2 cohorts. DAS28, TJC, and SJC were assessed differently in each cohort. In ERAS, DAS28 converted from the original 3-variable DAS with 44 joint counts did not change significantly over time (DAS28: b = −0.01, 95% CI −0.03, 0.01; SJC44: b = 0.06, 95% CI 0.09, 0.20; TJC44: b = −0.01, 95% CI −0.16, 0.13). Similarly, in ERAN, the DAS28, SJC, and TJC did not change significantly over time (DAS28: b = −0.01, 95% CI −0.09, 0.06; SJC28: b = −0.15, 95% CI −0.048, 0.18; TJC28: b = −0.18, 95% CI −0.50, 0.14).

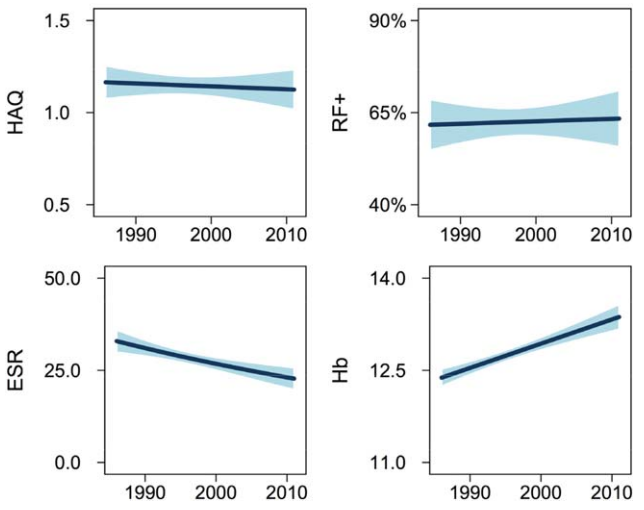


**Figure 3.** Trends in disease severity. HAQ = Health Assessment Questionnaire; RF = rheumatoid factor; ESR = erythrocyte sedimentation rate.

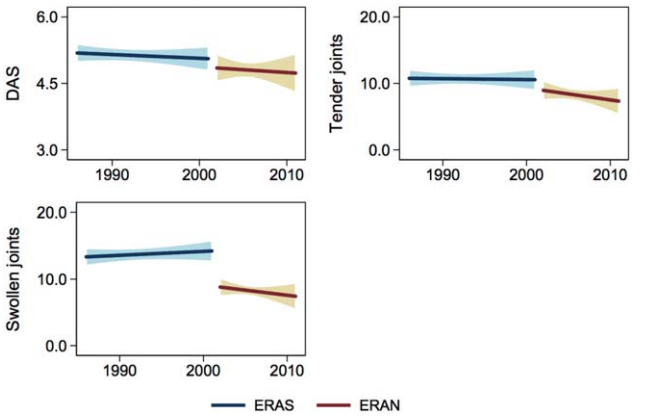


**Figure 4.** Trends of variables assessed in different ways across ERAS (Early Rheumatoid Arthritis Study) and ERAN (Early Rheumatoid Arthritis Network Study). Swollen and tender joints recorded out of 44 joints in ERAS and 28 joints in ERAN. DAS = Disease Activity Score.

**Sensitivity analysis.** Although the trends in disease variables reported above were adjusted for treatment at baseline, a further sensitivity analysis was undertaken to examine whether earlier treatment explained the lower levels of inflammation. Excluding individuals prescribed steroids or DMARDs prior to the baseline assessment, the trends for ESR (logarithmic scale: b = −0.02, 95% CI −0.03, −0.02) and hemoglobin (b = 0.03, 95% CI −0.02, −0.04) remained significant.

## DISCUSSION

This study provides insights into the changing circumstances of the first presentation of RA over 25 years, which may have important clinical and health economic implications for, as an example, the screening and management of comorbid diseases, treatment stratification, and resource allocation. The detailed analysis of patient and disease characteristics and comorbidities at RA presentation, prior to DMARD use and controlling for the small number of patients who received steroids prior to study entry, demonstrates 1) an increasing age at symptom onset, 2) increasing comorbidity burden, and 3) reduced inflammatory states and unchanged patient symptoms and measures of disease activity.

The prevalence of comorbid conditions on presentation of RA has significantly increased over 25 years with rising levels of cardiovascular and non-cardiac vascular morbidity (including hypertension), as well as the overall CCI score. Our findings are in line with the considerable changes in population demography seen in the UK over time, with a rising prevalence of multimorbidity (22) and obesity (23). The obesity "epidemic" has been a highly researched topic across the world, with a recent review supporting increasing levels of obesity (24), which has a wider public health relevance. A possible explanation for this change, aside from it representing a true increase in

certain comorbidities, is an increased awareness of certain conditions over time and better diagnostic and reporting modalities. Although nonsignificant, there was also an increasing trend in endocrine, respiratory, and gastrointestinal conditions at baseline.

Whether these observed changes in comorbidity represent a real increase in conditions or are alternatively due to improved recognition, the fact is that the recognized burden of comorbidity has increased and as such this should impact on modern rheumatology management. The increase in conditions including obesity, hypertension, ischemic heart disease, and anxiety/depression at RA presentation make it increasingly important that early assessment of new cases includes a broad clinical assessment. Each of these comorbid conditions carries a health burden worthy of treatment and amelioration. Similarly, diabetes mellitus, osteoporosis, and extraarticular ILD, although less common at baseline, are associated with significant morbidity and should be screened at baseline.

Aside from their direct impact on disease outcomes, comorbidities influence the choice of pharmacotherapy, e.g., steroid use in patients with diabetes mellitus, osteoporosis, and obesity; interstitial lung disease and use of methotrexate, leflunomide, or tumor necrosis factor inhibitors; and gastrointestinal disease and use of NSAIDs. Therefore, the emphasis at first presentation of RA should not just be on the index disease (RA) but also on other coexisting conditions. Treat-to-target strategies are now widely accepted as best clinical practice, resulting in better outcomes. Emerging evidence, however, demonstrates that multimorbidity negatively impacts treatment of RA to target, with lower achievement of disease remission in multimorbid patients (22–26). Reasons for this include concerns regarding treatment intensification in the presence of multiple coexisting conditions. While treatment intensification should still remain a priority in poorly controlled disease, it is inevitable that in the presence of comorbidity, this will need to be carefully considered and tailored to the individual patient. However, despite existing national and international guidelines on the importance of taking into account comorbidities (27), there is little guidance on how to best manage these patients.

We propose that clinicians in busy clinical settings should screen for comorbidity, at the very least for the specific conditions we have identified in this report, based on their frequency, potential impact on RA outcome, and the availability of relative simple screening tools, with care plans in place for rapid referral to other specialists as necessary. The negative influence on outcome conferred by a delay in initiating DMARDs, which did not improve over the course of the 25-year study period, versus the potential use of suboptimal treatment combinations because of the presence of comorbidity is an important issue that clinicians should be aware of, with respect to both short- and long-term disease outcomes.

It is interesting that while comorbidities are increasing at disease onset, they are accompanied by an unchanged RA severity. The improvement in ESR observed over time somewhat contradicts the significant increase in BMI and obesity, as these contribute to a higher inflammatory load. However the significant rise in hemoglobin may in part explain the fall in ESR.

The later onset age of RA observed in this study may indicate decreasing RA incidence. This is supported by previous studies showing similar trends (20,21) and suggesting a birth cohort effect, that is, a decreasing likelihood of developing RA with successive generations. An alternative explanation could be a gradual lowering of the clinical threshold for diagnosing RA in older people, pointing towards a period effect rather than a cohort effect. This explanation is less likely because our results show a shift in the entire age distribution (with SDs remaining unchanged) and the level of clinical variables remains largely unchanged. Another explanation relates to diagnostic criteria, but there is no suggestion that the proportion of people fulfilling criteria for a diagnosis for RA has changed over time. No sex differences were seen over time, similar to other studies (13), and there was no significant change in the proportion of people living in socially deprived areas at the time of recruitment.

Evidence based on longitudinal observational studies, including this study, is important and provides real-life data as opposed to clinical trial data, which include stringent inclusion and exclusion criteria that often exclude patients with multimorbidity. However, this study demonstrates that the burden of comorbidity is high and is increasing over time, at the onset of disease and prior to DMARD use. Data from other studies, including the Norfolk Arthritis Register, that attempt to account for treatment add to the ambiguity of the findings in this field (4). Extraarticular manifestations of RA were collected routinely in ERAS and ERAN, some of which are features of established, poorly controlled disease. Despite small numbers at disease onset, there was a trend towards a reduction, but this was nonsignificant.

The real life setting of the ERAS and ERAN cohorts, the large patient numbers, and long patient followup covering a quarter of a century are important strengths of this study. Furthermore, the recruitment of patients within the first 3 years of disease and the availability of information on medical treatments add to the value of the study and enable the examination of disease presentation prior to external influences, importantly disease-modifying treatments. Limitations of the study include the drop off in numbers of patient recruitment as ERAS wound down and ERAN started, which could have introduced some bias to the results. However, sensitivity analysis using piecewise models and models allowing for nonlinear trends with restricted cubic splines showed no issue with this, and trends were estimated treating year of onset as a continuous variable to avoid problems with precision. Furthermore, assessment of steroid use in primary care may be underestimated, and other treatment use that may impact on inflammation, particularly NSAIDs but potentially also statins, was not known. This may partially explain the trends for reduced inflammation.

A further limitation relates to the self-reported nature of comorbidities, which may have led to underestimation of the prevalence. For example, the prevalence of depression was lower than expected. We observed a prevalence of 3% for all psychiatric comorbidities, which is considerably lower than the estimated prevalence of 17% for depressive disorder alone (28). Furthermore, previous research using

the ERAS cohort has shown that the prevalence of self-reported clinical depression is far lower than expected in comparison to using a screening tool (29).

In summary, this study demonstrates rising levels of comorbid conditions on first presentation of RA, especially obesity, and along with the older age at disease-onset, highlights the need for more comprehensive packages of care required at these early stages. Our findings support intensification of screening and addressing of risk factors for comorbidities as part of the overall management of RA in order to improve responses to treatment and improved patient outcomes. We also found decreasing levels of inflammation on presentation of RA, whereas other disease activity features and patient symptoms have remained largely unchanged.

## AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be submitted for publication. Dr. Nikiphorou had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

**Study conception and design.** Dixey, Walsh, Kiely, Young.
**Acquisition of data.** Dixey, Walsh, Kiely, Young.
**Analysis and interpretation of data.** Nikiphorou, Norton, Carpenter, Young.

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