Can rheumatologists predict eventual need for orthopaedic intervention in patients with Rheumatoid Arthritis? Results of a systematic review and analysis of two UK inception cohorts

Elena Nikiphorou[1,2,3], Lewis Carpenter[3], Sam Norton[4], Stephen Morris[2], Alex MacGregor[5], Josh Dixey[6], Peter Williams[7], Patrick Kiely[8], David Andrew Walsh[9], Adam Young[1,3]

1) ERAS, Department of Rheumatology, St Albans City Hospital, St Albans, UK
2) Department of Applied Health Research, University College London, UK
3) Centre for Lifespan & Chronic Illness Research, University of Hertfordshire, Hatfield, UK
4) Health Psychology Section, Institute of Psychiatry, King's College London, UK
5) Institute of Musculoskeletal Science, University College London, London, UK
6) Department of Rheumatology, New Cross Hospital, Wolverhampton, UK
7) Department of Rheumatology, Medway Maritime Hospital, Gillingham, UK
8) Department of Rheumatology, St Georges Healthcare Trust, London, UK
9) Arthritis UK Pain Centre, University of Nottingham, UK

Corresponding Author:
Professor Adam Young
Center for Lifespan & Chronic Illness Research,
University Herts,
College Lane,
Hatfield, AL10 9AB
TEL: 01707 285871
FAX: 01707 285136
EMAIL: adam.young@nhs.net

Abstract

Purpose of review: The structural damage caused by rheumatoid arthritis (RA) can often be mitigated by orthopaedic surgery in late disease. This study evaluates the value of predictive factors for orthopaedic intervention.
Methods: A systematic review of literature was undertaken to identify papers describing predictive factors for orthopaedic surgery in RA. Manuscripts were selected if they met inclusion criteria of cohort study design, diagnosis of RA, follow-up duration/disease duration ≥3 years, any orthopaedic surgical interventions recorded, and then summarised for predictive factors. A separate predictive analysis was performed on two consecutive UK Early RA cohorts, linked to national datasets.
Recent findings: The literature search identified 15 reports examining predictive factors for orthopaedic intervention, 4 inception, 5 prospective and 6 retrospective. Despite considerable variation, acute phase, x-ray scores, women and genotyping were the most commonly reported prognostic markers. The current predictive analysis included 1602 procedures performed in 711 patients (25-year cumulative incidence 26%). Earlier recruitment year, erosions and lower haemoglobin predicted both intermediate and major surgery ($P<0.05$).
Summary: Studies report variations in type of, and predictive power of clinical and laboratory parameters for different surgical interventions suggesting specific contributions from different pathological and/or patient-level factors. Our current analysis suggests that attention to non-inflammatory factors in addition to suppression of inflammation are needed to minimise the burden of orthopaedic surgery.

KEY WORDS: Rheumatoid arthritis, orthopaedic surgery, total joint replacement, predictors, outcome measures.

INTRODUCTION

Physicians rely on markers of disease severity for making management decisions in RA. Many studies have examined risk factors for joint damage as measured on radiographs, and standard measures of active disease have featured in most of these [1,2,3] There are fewer reports on structural damage as measured by need for orthopaedic surgery, mainly because such studies require long follow-up and large sample sizes, previously difficult to achieve in inception cohort studies.[4,5]

Several factors other than joint pathology contribute to decisions to undergo surgery, including patient choice, severity of reported pain, comorbidities, accessibility of health resources and orthopaedic surgery. Clinicians would benefit from reliable predictors of subsequent joint surgery in RA, and whether these differ from radiological joint damage, in order to identify reversible risk factors for treatment strategies and to prioritise research in these patients.

The objectives of this study were i) to explore prognostic factors for orthopaedic intervention in RA reported in the literature ii) to identify the most powerful combination of predictive factors for orthopaedic surgery over 25 years in two large ongoing prospective observational studies from the UK.

METHODS

Systematic review.

A systematic review protocol was developed to ensure that objectives and aims where clearly outlined from outset and submitted and approved by PROSPERO. Publications describing predictive factors for orthopaedic surgery in patients with RA were identified by computerised searches of Medline, PubMed, Cochrane Library (incl CENTRAL, CDSR, DARE, HTA) and Scopus supplemented by lateral search techniques: checking reference lists, key word searches in Google Scholar and 'cited by' option in PubMed. In addition, lateral search techniques, such as checking reference lists, performing key word searches in Google Scholar and using the 'cited by' option in PubMed, were used. All databases were searched from January 1st 1975 to February 31st 2015. The search strategy used a mixture of key words and MeSH terms on the title/abstract and full text as appropriate.

The following keywords and combinations were used: (([exp Arthritis, Rheumatoid/] AND ([orthopaedic surgical procedures OR orthopaedic procedures OR orthopaedic interventions OR orthopaedic surgery OR [joint replacement.mp)) OR [hip replacement.mp)) OR [knee replacement.mp)) OR hand surgery OR wrist surgery OR foot surgery OR prosthetic replacement OR prostheses AND predictive factors OR prognostic factors OR risk factors NOT ([exp Arthritis, Juvenile Rheumatoid/] OR [JIA.mp]) NOT ([clinical trial, phase i/ OR clinical trial, phase ii/ OR clinical trial, phase iii/ OR clinical trial, phase iv/ OR controlled clinical trial/ OR randomized controlled trial/] OR [exp case reports/] OR [randomized clinical trial.mp]). Limit to year="1980-2015" and English language.

Manuscripts were selected for review if they met the following inclusion criteria: Prospective or retrospective cohort study design, physician or ARA or ACR or EULAR diagnosis of RA, follow-up duration/disease duration ≥3 years, predictive factors for any orthopaedic surgical interventions recorded.

UK RA orthopaedic datasets

We used two well described multi-centre UK inception cohorts of RA patients recruited prior to DMARD use, the Early RA Study (ERAS, 9 rheumatology centres in England between 1986-1999) and the Early RA Network (ERAN, 23 in England, Wales and Ireland from 2002-2010).[6] Numbers and median follow up was 1465 and 10years (maximum 25years), and 1236 and 6years (maximum 10years) respectively. Time to first DMARD following baseline assessment was 2 and 1 month. Median time from symptom-onset to first visit was 6 months in each cohort.

These consecutive cohorts had very similar design and modes of data collection allowing combined analysis. In view of reports of greater predictive value of first year variables [5,7] both baseline and first year standard parameters have been included. [6] All centres followed the framework of published UK guidelines for management of RA, which included mainly sequential DMARDs in ERAS, standard UK practice for early RA in the 1980s/90s.[6] 'Step-up/add-on' combination therapies were initially reserved for more severe RA only, but gradually became more common.[8] In ERAN, more frequent earlier use of combination DMARDs and biologics were employed in line with contemporary UK guidelines.[9]

Data linkage to national sources was performed through unique NHS number and included Hospital Episode Statistics (HES), which provides information on all National Health Service (NHS) orthopaedic interventions in England, and the National Joint Registry (NJR) which contains information on hip, knee and ankle joint replacement surgery across both the NHS and independent healthcare sectors, as previously documented in greater detail.[6] Orthopaedic interventions undertaken after the diagnosis of RA were categorised by joint type and procedure as previously described.[5,6] Major: primary or secondary large joint replacement surgery. Intermediate: wrist, hand, hind/fore-foot joint reconstructive procedures (excision arthroplasty, synovectomy, arthrodesis). Minor: soft tissue procedures (e.g. tendon surgery). Minor procedures are omitted from this report due to their wide heterogeneity and lack of statistically significant findings from predictive analysis.

Statistical analysis

Survival analysis was used to examine predictive values of variables for time to first orthopaedic intervention. Cox regression, the most widely used method of survival analysis, can produce biased effect estimates in the presence of competing risks, such as death, using non-informative censoring methods. Because of the large number of deaths over the 25year study period, competing-risks regression was used, which accounts for patient follow-up, with the event defined as first orthopaedic intervention and competing-risk defined as death. Patients who did not experience either of these events were censored at end of 2011. Separate models were estimated for intermediate and major surgery, total hip (THR) and knee replacement (TKR). The models employed absolute values of variables, first at baseline then at 1-year.

The following were entered into the model as core covariates of interest, given their importance in RA: gender, age at disease-onset, recruitment year, time to diagnosis at baseline, rheumatoid factor (RF), BMI, HAQ, disease activity score (DAS) based on the original DAS (ERAS) and modified DAS28 (ERAN),[10] and its individual components

including tender (TJC) and swollen joint counts (SJC), patient-reported visual analogue scale (VAS), haemoglobin, ESR, hands and feet x-rays assessed for erosions by each centre (Larsen scores were available in a subgroup of 70% of ERAS patients as previously described).[3] As baseline and 1-year variables did not differ significantly in these patients (data not shown), sub group analysis included Larsen scores.

In order to establish other covariates to include in the model, univariate analysis was undertaken (results not shown). Those significant to $p<0.01$ were also included. In further models, DAS and the proportion of DAS attributable to patient-reported components (TJC and VAS) termed DAS-P were also examined.[11] DAS and DAS-P were only weakly correlated ($r<0.50$), so were included together. Overall missing baseline data were infrequent (around 5%), unlikely to introduce bias. Sensitivity analysis was performed to test robustness of multivariate models by excluding variables with missing data both separately and together in the models (see supplementary material). To assess variance and predictive strength of the regression models, the pseudo R^2 and Area Under the Curve (AUC) were examined for baseline and 1-year models. Those variables with 10 year follow-up were entered as time-varying covariates (TVC), where missing data were imputed using multiple imputation techniques to test the assumption of proportionality over time. Finally, to investigate predictors of multiple surgeries, negative binomial regression was used on the total major or intermediate interventions. All analysis was conducted using Stata (version 13) with significance level of $p<0.05$ assumed.

Results

Systematic review

The literature search initially identified 954 possible relevant paper based on their titles. From these we identified 128 abstracts which appeared to fulfil the appropriate criteria, 39 of which were worthy of full text review. Only 15 reports examined predictive factors for orthopaedic intervention in 17 RA cohorts, 4 inception, 5 prospective and 6 retrospective. 5 were not included because although all were reviews of orthopaedic outcomes in RA, they did not in fact report on predictive factors. There was considerable variation in study recruitment decades and cohort designs, especially in length of follow up and time to surgical intervention from onset of RA. Most reports distinguished between all surgical interventions and TJR, only a few reporting on differences between specific types of surgery. Although there was some variation in the parameters examined for predictive value, most reports included clinical measures of joint disease activity (joint scores, DAS), laboratory acute phase (ESR, CRP), RF and x-ray scores. Some included socio economic and functional measures (e.g. HAQ), HAEMOGLOBIN and genotyping (HLA DR4 & SE). Acute phase, x-ray scores, women and HLA SE were the most commonly reported prognostic markers, RF cited only uncommonly. The 15 reports are summarised in Appendix 1, Table A.1.

Predictive analysis of UK datasets.

During the 25-year observation period, 711 patients from a total of 2701 had undergone at least one type of orthopaedic intervention (n=1602, 25-year cumulative incidence (CI) 26.4%). The 25-year CI, adjusted for death as competing risk, for any major intervention was 22% (95%CI 19–24) and for any intermediate interventions was

22% (95%CI 18–26) (Figure 1). The different types and frequency of orthopaedic interventions and a summary of baseline and 1-year characteristics of patients having surgery are are shown in Appendix 1, Tables A.2 and A.3.

Competing risk regression analysis (Table 1) showed that the risk of both major and intermediate surgeries was reduced in more recent study recruitment years by 6% (SHR 0.94, 95%CI 0.90-0.98) and 7% (SHR 0.93, 95%CI 0.88-0.98) respectively. Older age at disease onset predicted major intervention (SHR 1.01) and female gender more than doubled the risk for intermediate surgery compared to males (SHR 2.11), although not for major surgery. Lower BMI and haemoglobin predicted intermediate surgery in both baseline and 1-year models. Higher VAS or lower ESR at baseline, or higher HAQ or TJC at 1-year, each predicted intermediate surgery. The higher the haemoglobin, or lower the HAQ at 1-year, the lower the risk of major surgery. Higher HAQ at 1-year (Table 1) was associated with >30% increased risk of major surgery. Whereas increased baseline BMI reduced the risk of intermediate surgery (SHR 0.93, [0.0-0.96]), it predicted higher risk of major surgery (SHR 1.03, [1.01-1.06]). Erosions in hands/feet at either baseline or 1-year were predictive for major surgery, but only erosions at 1-year were predictive for intermediate surgery (SHR 1.45, [1.06-1.98]). Higher baseline TJC carried an increased risk, whereas increased SJC at 1-year reduced the risk of major surgery.

High TJC and low SJC might indicate abnormalities of central pain processing, rather than inflammatory disease activity.[11] To explore this further, we examined additional statistical models in which the separate DAS components were replaced by DAS and DAS-P. The results are summarised in Supplementary Data, Appendix 1.

Multiple intermediate and major orthopaedic interventions

Predictors of multiple surgeries (defined as two or more major or intermediate surgeries) using negative binomial regression are shown in Supplementary Data, Appendix 1, Table A.4. Modelling multiple surgical outcomes per patient yielded similar associations to those observed for single first events. Very similar ratios and significant levels were seen for the same predictive variables. Sensitivity analysis on the small proportion of patients who had both major and intermediate surgery showed no difference in effects between surgery types.

Discussion

In this systematic review most studies examining RA outcomes by 5 years reported orthopaedic intervention in around 15%, increasing to around 25% in 20yr+ follow up cohorts. These figures were confirmed by our detailed analysis of a large UK inception cohort. Orthopaedic surgery is an important means of assessing medium to long-term outcomes in RA and is considered both a surrogate marker of joint damage [12] and provides data on unsuccessful medical treatment in RA.[13] Covering both the pre and post-biologic eras, this systematic review and the analysis of orthopaedic interventions in two well-established RA inception cohorts has found consistency in certain predictive factors, and considerable variation in others.

Although few studies distinguished between types of interventions, most reported that women had a higher risk for surgery. In our current analysis this was so for intermediate surgery only, suggesting either more severe disease in women or different thresholds for surgery. Hand surgery in women might be work-related, as in administrative/typing roles, fabrics, kitchen work, and is subject of another study currently being undertaken. Other

possibilities include lower thresholds for surgery stemming from differences in psychological, pain, functional and cosmetic perceptions.

Age was not a consistent marker although the predictive analysis found an increased risk of major surgery in patients older at disease onset. Average age of RA onset has increased in recent decades, and later studies may reflect an increased need for orthopaedic surgery. In the predictive analysis study recruitment year also had an effect, with more recent years predicting lower risk of surgery, most likely reflecting the impact of improved management of RA on outcome, as we have reported recently.[6]

There was fair consistency in the ability of certain clinical and laboratory measures at early stages of RA to predict the eventual need for orthopaedic surgery, including mainly acute phase and radiographic damage. Some studies reported that haemoglobin and genotyping had additional clinically useful predictive value. Some studies reported variations in type of, and predictive power of clinical and laboratory parameters for different surgical interventions suggesting specific contributions from different pathological and/or patient-level factors. Attention to non-inflammatory factors in addition to suppression of inflammation may be needed to minimise the burden of orthopaedic surgery.

One quarter of patients presenting with RA underwent major or intermediate orthopaedic surgery during the following 25 years. We have demonstrated that baseline and 1-year clinical and laboratory variables have clinically useful and independent predictive value for eventual orthopaedic surgery. Similar risk factors for joint destruction as measured on X-ray have been identified, mainly standard measures of active disease.[1-3] However, some unexpected findings have emerged.

Early radiographic damage and low haemoglobin predicted both intermediate and major surgery, whereas variations in predictive power of other parameters for the different surgical interventions suggest specific contributions from different pathological and/or patient-level factors. Erosions at 1-year were predictive for both major and intermediate surgery, although at baseline they were only predictive for major surgery. Baseline variables including erosions are pre-DMARD therapy in these cohorts, and might not adequately reflect potential response to treatment. Joint damage at 1-year reflects suboptimal response to treatment. Patients with progressive damage despite exposure to treatment are more likely to require subsequent orthopaedic surgery than those in whom therapy has retarded progression. 1-year measurements may therefore be better predictors of long term outcomes in RA than baseline, prior to effective treatment.[6,7] The sub-analysis of Larsen scores in ERAS supports this, showing stronger predictive value of Larsen at 1-year ($p<0.001$) compared to baseline ($p<0.05$). A similar explanation could apply for prediction of major and intermediate surgery by HAQ at 1-year only. Prompt and intensive treatment of patients with early RA might be expected to not only improve outcomes, but also permit earlier more accurate prediction of surgical outcomes.

One of the most striking findings in our current analysis was the predictive value of haemoglobin for both major and intermediate surgery, independent of other variables of active disease, the predictive effect being strongest with haemoglobin at 1-year for major surgery. Our findings support the two previous reports that haemoglobin predicts orthopaedic intervention, during the first 5 years after diagnosis [5], and over 25 years follow up in established

arthritis.[13] It is well established that low haemoglobin is a marker of inflammatory disease activity. People with RA display a blunted response to erythropoietin,[14] erythropoietin treatment has been associated with a reduction in inflammatory activity,[15,16] and effective suppression of inflammation is associated with increases in haemoglobin, suggesting a tight coupling between inflammatory activity and haematopoiesis. Iron metabolism might, in addition, be directly involved in joint damage in RA. Higher iron deposition and iron-complexes in synovial fluid and membranes have been associated with decreases in peripheral blood haemoglobin levels during active RA[17] and iron deposition is associated with accelerated joint damage in haemochromatosis.

Although associations with active inflammation may contribute to the overall predictive power of haemoglobin for orthopaedic surgery in RA, another report[18] supports our findings that anaemia-related progression of joint damage might not be restricted to patients with clinically active disease. Non-inflammatory mechanisms might also mediate associations between low haemoglobin and subsequent orthopaedic surgery. Low haemoglobin may also be related to chronic NSAID use, which has been associated with increased joint damage.[19-21] Unfortunately, data on cumulative NSAID use were not available for our cohorts. Whatever the underlying mechanism, our data support the inclusion of haemoglobin in predictive models for joint surgery, in addition to standard measures of inflammation.

We found that different DAS components had opposing predictive values for subsequent orthopaedic surgery, a possible explanation for the weak predictive value of total DAS. Higher TJC at baseline and 1-year had positive predictive value for intermediate joint surgery. SJC at 1-year had the opposite effect, reducing the risk of major surgery. These findings suggest that patient-reported symptoms (pain and tenderness), might be stronger drivers for joint surgery, whereas high objective measures of synovitis might result in surgery being postponed or averted while further attempts are made to suppress inflammatory disease activity. Consistent with this, we found that DAS-P (but not DAS) had positive predictive value for intermediate surgery.

Associations between clinical inflammation and joint damage in RA are often weak and inconsistent,[22-24] in part due to the limited sensitivity and specificity of clinically detected synovitis to predict the presence or activity of synovial pannus.[25] Clinical measurement of disease activity usually depends on composite scores such as DAS, which combine patient-reported (VAS and TJC), physician observed (SJC) and laboratory (ESR or CRP) components. Although each of these components increases with increasing inflammatory activity in RA, individual components may reflect different underlying pathological mechanisms. In particular, it has been proposed that VAS and TJC, or the proportion of DAS attributable to these components (DAS-P) might be more influenced by central pain mechanisms, whereas SJC and ESR might be more directly associated with inflammatory disease activity.[26]

Discrepancies in predictive values of joint scores for hand/foot versus major joint replacement surgery could be due to a number of other factors: higher joint scores can be achieved in hands and feet compared to large joints, in which synovitis maybe less easy to detect; not all joints are included in DAS (e.g. hips); the more demanding nature of major joint surgery can lead to higher thresholds for intervention, not necessarily driven by patient symptoms; higher SJC may lower thresholds for more intensive medical therapies.

Despite an apparently protective effect of high BMI on intermediate surgery, high BMI predicted increased likelihood of major orthopaedic surgery. The influence of BMI on disease activity in RA is unclear. Some studies have shown protective effects of higher BMI, with lower BMI associated with higher disease activity,[27] increased erosions, more severe systemic RA (cachexia) and reduced survival.[28,29] Other studies have shown obesity an independent risk factor for impaired quality of life in RA and poor disease outcomes.[30]

A strong link between obesity and knee osteoarthritis is well-recognised,[31] although reports on the predictive value of high BMI for large joint surgery vary for OA [32] and RA.[33] High BMI may increase loading on already compromised joints, and be associated with OA through genetic or metabolic mechanisms.[34] Such mechanisms may be discrete from those leading to intermediate orthopaedic surgery.

Our current study complements existing data as identified through our literature search. Strengths of our current predictive analysis include the "real life" setting of ERAS and ERAN, reflecting the therapeutic practices of both pre and post-biologics treatment decades; length of study follow up; low attrition rates for orthopaedic data through HES; and corroboration and extension of source data by linkage to national datasets. The use of modern statistical techniques, in particular competing risk regression, has enabled maximum use of data and accounted for both the event of interest (orthopaedic surgery) as well as death allowing for more precise estimates of the effects of independent variables.

Although our observational study design allows identification of associations between baseline variables and orthopaedic interventions, defining causal factors is not possible, especially in the absence of a control group, or placebo-controlled interventions. As allocation of treatment in our study was not randomized, it is possible that the resulting imbalance in underlying risk profiles could introduce bias (confounding by indication).[35] Lack of treatment randomisation precluded adequate investigation of possible effects of steroids and DMARDs on surgical rates, unavoidable in observational studies [6,36], but the presence of widely adopted UK treatment guidelines and the examination of baseline and 1-year variables only should minimise this bias.

Another potential limitation is case definition, i.e. what is considered "RA-related" joint surgery, since coincidental pathophysiological processes, including osteoarthritis and fracture, might have been the main triggers for orthopaedic intervention. Separate analysis of RA-related and unrelated orthopaedic procedures is not possible, due to difficulties with case definition, and potential interactions. RA patients who undergo TKR surgery usually display osteophytes on plain radiographs, but also display more intense synovitis than those undergoing surgery for OA alone.[37] There are currently no definitive classification criteria that permit valid discrimination between OA secondary to RA and comorbid primary OA. Indeed, even in those with primary OA, comorbid inflammatory synovitis might increase rates of structural progression and hasten the need for major joint surgery.[38] Patients with RA, by merit of already being under specialist care, might have facilitated access to orthopaedic surgery even for comorbid conditions.

Generalising our findings to other healthcare systems requires caution, although they have been enhanced by data collection within a nationalised (UK) health service, with extensive linkage to national databases. Finally, we cannot

exclude other possible important contributions to prediction of orthopaedic surgery from factors not measured in our cohorts. Future studies should also examine both the cumulative effects of disease markers over time, and also possible associations between orthopaedic intervention and patient-centred outcomes such as work disability.

Conclusions

This report provides information that could be use for planning future healthcare provision of orthopaedic surgery, in light of the changing prevalence and characteristics of early RA, increasing prevalence of obesity, and an ageing population. Our findings point to multiple and complex mediators of future orthopaedic surgery in people presenting with RA, suggesting that interventions additional to the control of inflammatory disease may be important in minimising the burden of orthopaedic surgery for patients and health care systems in the future. Predicting even late joint destruction and need for surgery up to 25 years later is possible and more accurate at one year of therapy, rather than at the time of RA diagnosis. EULAR recommendations[39] emphasize the importance of early intervention with DMARDs followed by biologics if response is insufficient. Most of the predictive factors identified through previous studies as well as current analysis are potentially reversible with appropriate therapy. It is postulated that stratifying therapies based on these prognostic factors measured at 1-year could further reduce the structural damage that leads to orthopaedic intervention up to 25 years later.

Abbreviation List

anti-TNFa	anti-Tumour Necrosis Factor alpha
BMI	Body Mass Index
CI	Confidence Interval
CRP	C-Reactive Protein
DAS	Disease Activity Score
DAS-P	Disease Activity Score (patient-reported components)
DMARD	Disease-Modifying Anti-Rheumatic Drug
ERAN	Early Rheumatoid Arthritis Network
ERAS	Early Rheumatoid Arthritis Study
ESR	Erythrocyte Sedimentation Rate
EULAR	European League Against Rheumatism
Fe	Iron
HAQ	Health Assessment Questionnaire
HES	Hospital Episode Statistics
HR	Hazard Ratio
IRR	Incidence Rate Ratio

NHS	National Health Service
MRIS	Medical Research Information Service
NICE	National Institute for Health and Care Excellence
NJR	National Joint Registry
NSAID	Non-Steroidal Anti-Inflammatory Drug
RA	Rheumatoid Arthritis
SHR	Sub-Hazard Ratios
SCQM	Swiss Clinical Quality Management
THR	Total Hip Replacements
TJR	Total Joint Replacements
TKR	Total Knee Replacement

Competing Interests

The authors declare that they have no competing interests.

Authors Contribution

EN and AY developed the research questions, recruited and performed follow up assessments in patients for ERAS and ERAN in one rheumatology unit. JD, DW, PK and PW recruited and performed follow up assessments for patients in the study at separate rheumatology units. EN collected, interrogated and cross-validated the data from the clinical cohorts with the national datasets, coded the procedures, analysed the results and performed statistical tests with supervision from AY. SM and AM contributed to the data analysis and statistical tests. LC and SN contributed to the statistical analysis of the results. EN, LC, SN, JD, DW, PW, PK and AY contributed to the drafting the manuscript. All authors read and approved the final manuscript.

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References:

1. Scott DL, Grindulis KA, Struthers GR, et al. Progression of radiological changes in rheumatoid arthritis. Ann Rheum Dis 1984:**43**:8-17.

2. Lindqvist E, Eberhardt K, Bendtzen K, et al. Prognostic laboratory markers of joint damage in rheumatoid arthritis. Ann Rheum Dis 2005;**64**:196-201.

3. Dixey J, Solymossy C, Young A. Is it possible to predict radiological damage in early rheumatoid arthritis (RA)? A report on the occurrence, progression, and prognostic factors of radiological erosions over the first 3 years in 866 patients from the Early RA Study (ERAS). J Rheumatol 2004;**31**(Suppl 69):48-53.

4. Kapetanovic MC, Lindqvist E, Saxne T, et al. Orthopaedic surgery in patients with rheumatoid arthritis over 20 years: prevalence and predictive factors of large joint replacement. Ann Rheum Dis 2008;**67**(10):1412-6.

5. James D, Young A, Kulinskaya E, et al. Orthopaedic intervention in early rheumatoid arthritis. Occurence and predictive factors in an inception cohort of 1064 patients followed for 5 years. Rheumatology 2004;**43**:369-376.

6. Nikiphorou E, Carpenter L, Morris S, et al. Hand and foot surgery rates in RA have declined from 1986-2011, but large joint replacements remain unchanged. Results from two UK inception cohorts. Arthritis & Rheumatology 2014;**66**:1081-1089.

7. Wiles NJ, Dunn G, Barrett EM, et al. One year follow-up variables predict disability 5 years after presentation with inflammatory polyarthritis with greater accuracy than at baseline. J Rheumatol 2000;**27**:2360–6.

8. Young A, Dixey J, Williams P, et al. An evaluation of the strengths and weaknesses of a register of newly diagnosed Rheumatoid Arthritis, 1986-2010. Rheumatology Themed Issue 2010;**50**:176-183.

9. Kiely PDW, Brown AK, Edwards CJ, et al. Contemporary treatment principles for early rheumatoid arthritis: a consensus statement. Rheumatology 2009;**48**:765-72.

10. Prevoo ML, van 't Hof MA, Kuper HH, van Leeuwen MA, van de Putte LB, van Riel PL. Modified disease activity scores that include twenty-eight-joint counts. Development and validation in a prospective longitudinal study of patients with rheumatoid arthritis. Arthritis Rheum 1995;38(1):44-8.

11. McWilliams DF, Zhang W, Mansell JS et al. Predictors of change in bodily pain in early rheumatoid arthritis: an inception cohort study. Arthritis Care Res 2012;**64**:1505-13.

12. Anderson R. The orthopaedic management of rheumatoid arthritis. Arthritis Care Res 1996;9:23-8.

13. Wolfe F, Zwillich S. The long-term outcomes of rheumatoid arthritis. Arthritis Rheum 1998;41:1072-82.

14. Weiss G, Goodnough LT. Anaemia of chronic disease. N Engl J Med. 2005 Mar 10; 352(10):1011-23.

15. Kaltwasser JP, Kessler U, Gottschalk R, et al. Effect of recombinant human erythropoietin and intravenous iron on anemia and disease activity in rheumatoid arthritis.
J Rheumatol. 2001;28(11):2430-6.

16. Peeters HR, Jongen-Lavrencic M, Vreugdenhil G, Swaak AJ. Effect of recombinant human erythropoietin on anaemia and disease activity in patients with rheumatoid arthritis and anaemia of chronic disease: a randomised placebo controlled double blind 52 weeks clinical trial. Ann Rheum Dis. 1996 Oct; 55(10):739-44.

17. Halliwell, B, Gutteridge, JMC, Blake, DR. Metal irons and oxygen radical reactions in human inflammatory joint disease. Philos Trans R Soc Lond B Biol Sci. 1985; 311: 659–671. Philos Trans R Soc Lond B Biol Sci. 1985

18. Möller B, Scherer A, Förger F, et al. Anaemia may add information to standardised disease activity assessment to predict radiographic damage in rheumatoid arthritis: a prospective cohort study. Ann Rheum Dis. 2014;73(4):691-6.

19. Arora J S. Maudslev R H. Indocid arthropathathy of hips. Proc R Soc Med 1968; 61: 669.

20. Milner J C. Osteoarthritis of the hip and indomethacin. J Bone Joint Surg 1973;54B:752.

21. Doherty M, Holt M, MacMillan P, et al. A reappraisal of 'analgesic hip'. Ann Rheum Dis 1986; **45**:272-276.

22. Van Leeuwen MS, van Rijswijk MH, Sluiter WJ, et al. Individual relationship between progression of radiological damage and the acute phase response in early rheumatoid arhtirtis. Towards development of a decision support system. J Rheumatol 1997;**24**:20-7.

23. Matsuda Y, Yamanaka H, Higami K, et al. Time lag between active joint inflammation and radiological progression in patients with early rheumatoid arthritis. J Rheumatol 1998;**25**:427-32.

24. Plant MJ, Williams AL, O'Sullivan MM, et al. Relationship between time-integrated C-reactive protein levels and radiologic progression in patients with rheumatoid arthritis. Arthritis Rheum 2000;**43**:1473-1477.

25. Brown AK, Conaghan PG, Karim Z, et al. An explanation for the apparent dissociation between clinical remission and continued structural deterioration in rheumatoid arthritis. Arthritis Rheum 2008;**58**:2958–67.

26. Joharatnam N, McWilliams DF, Wilson D, Wheeler M, Pande I, Walsh DA. Pain sensitivity, disease activity assessment and fibromyalgia status in rheumatoid arthritis. Arthritis Res Ther (in press) 2015, 17:11 DOI: 10.1186/s13075-015-0525-5

27. Jawaheer D1, Olsen J, Lahiff M, et al. Gender, body mass index and rheumatoid arthritis disease activity: results from the QUEST-RA Study. Clin Exp Rheumatol 2010; **28**:454-61. Epub 2010 Aug 30.

28. Kaufmann J, Kielstein V, Kilian S, et al. Relation between body mass index and radiological progression in patients with rheumatoid arthritis. J Rheumatol 2003;**30**:2350–5.

29. Van Der Helm-Van Mil AH, van der Kooij SM, Allart CF, et al. A high body mass index is protective on the amount of joint destruction in small joints in early rheumatoid arthritis. Ann Rheum Dis 2008;**67**:769–74.

30. Garcia-Poma A, Segami Mi, Mora Cs, et al. Obesity is independently associated with impaired quality of life in patients with rheumatoid arthritis. Clin Rheumatol 2007;**26**:1831–5.

31. Felson DT, Anderson JJ, Naimark A, Walker AM, Meenan RF. Obesity and knee osteoarthritis. The Framingham Study. Ann Intern Med 1988;**109(1):**18-24

32. Conaghan PG, D'Agostino MA, Le Bars M, et al. Clinical and ultrasonographic predictors of joint replacement for knee osteoarthritis: results from a large, 3-year, prospective EULAR study. Ann Rheum Dis 2010;69:644-647.

33. Shourt CA, Crowson CS, Gabriel SE, et al. Orthopaedic surgery among patients with rheumatoid arthritis 1980-2007: A population-based study focused on surgery rates, sex and mortality. J Rheumatol 2012;**39**:481-5.

34. Valdes AM, Spector TD. Genetic epidemiology of hip and knee osteoarthritis. Nature reviews. Rheumatology 2011;7:23-32

35. Landewe RB. The benefits of early treatment in rheumatoid arthritis: confounding by indication, and the issue of timing. Arthritis Rheum 2003;**48**:1-5.

36. Da Silva E, Doran MF, Crowson CS, et al. Declining use of orthopaedic surgery in patients with rheumatoid arthritis? Results of a long-term, population-based assessment. Arthritis Rheum 2003;**49**:216-20.

37. Walsh DA, McWilliams DF, Turley MJ, et al. Angiogenesis and nerve growth factor at the osteochondral junction in rheumatoid arthritis and osteoarthritis Rheumatology 2010, 49, 1852-61.

38. Hill CL, Hunter DJ, Niu J, et al. Synovitis detected on magnetic resonance imaging and its relation to pain and cartilage loss in knee osteoarthritis. Ann Rheum Dis, 2007. 66(12):1599-603.

39. Smolen JS, Landewe R, Breedveld FC, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2013 update. Ann Rheum Dis 2013;**0**:1–18.

Figure 1. Cumulative incidence plots for each type of surgery.

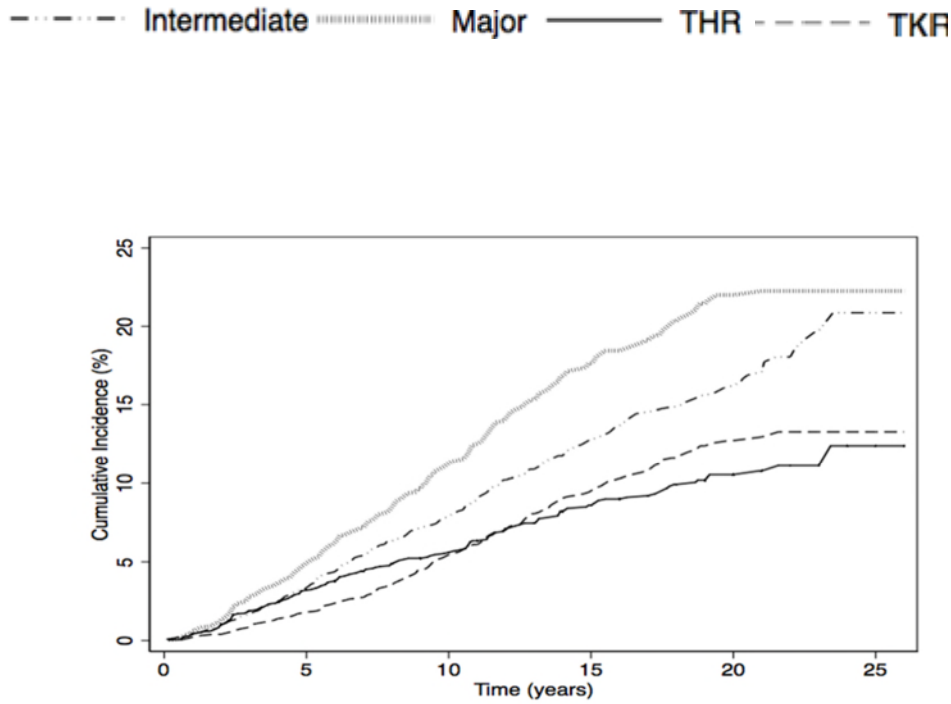

Table 1: Major and intermediate interventions. Competing-risks Multivariate Predictive Model.

		Intermediate Interventions			Major Interventions			Total Hip Only			Total Knee Only		
	Variable	**SHR**	**Wald**	**95% CI**	**SHR**	**Wald**	**95% CI**	**SHR**	**Wald**	**95% CI**	**SHR**	**Wald**	**95% CI**
Baseline Model	Gender	**2.13*** **	3.72	1.43,3.17	1.00	0.02	0.76,1.33	1.03	0.15	0.70,1.51	1.04	0.21	0.71,1.54
	Age at Onset	1.00	-0.90	0.99,1.01	**1.01** **	3.00	1.00,1.02	**1.02*** **	3.35	1.01,1.04	1.01	1.51	1.00,1.02
	Recruitment Yr	**0.95*** **	-3.38	0.92,0.98	**0.94*** **	-4.26	0.92,0.97	**0.95***	-2.55	0.92,0.99	**0.92*** **	-4.00	0.88,0.96
	Diagnosis time	1.00	-0.42	0.98,1.02	1.00	-0.28	0.98,1.01	1.00	-0.30	0.97,1.02	1.00	-0.02	0.98,1.02
	BMI	**0.94*** **	-4.31	0.91,0.96	**1.03***	2.52	1.01,1.06	1.02	0.90	0.98,1.05	**1.08*** **	4.79	1.04,1.11
	Erosions	1.35	1.94	1.00,1.84	**1.39***	2.33	1.05,1.82	1.22	1.00	0.82,1.81	1.22	1.03	0.84,1.77
	Rheum Factor	1.17	1.07	0.88,1.57	0.86	-1.14	0.67,1.11	1.02	0.08	0.71,1.45	0.83	-1.07	0.59,1.17
	SJC	0.99	-0.67	0.97,1.01	0.98	-1.92	0.96,1.00	0.98	-1.36	0.96,1.01	0.98	-1.56	0.95,1.01
	TJC	**1.03***	2.09	1.00,1.05	1.02	1.87	1.00,1.04	**1.03***	2.04	1.00.1.06	1.01	0.58	0.98,1.03
	ESR	**.099***	-2.20	0.99,1.00	1.00	1.27	1.00,1.01	1.00	0.75	1.00,1.01	1.00	1.24	1.00,1.01
	HAQ	1.01	0.10	0.80,1.28	1.11	1.07	0.91,1.36	1.00	0.02	0.77,1.31	1.25	1.71	0.97,1.62
	Haemoglobin	**0.88***	-2.39	0.79,0.98	**0.85** **	-3.09	0.77,0.94	**0.88***	-2.00	0.77,1.00	**0.87***	-2.00	0.76,1.00
1 – Year Model	Gender	**1.79** **	2.74	1.18,2.71	0.82	-1.26	0.61,1.11	0.82	-0.91	0.53,1.26	0.88	-0.64	0.59,1.30
	Age at Onset	0.99	-1.56	0.98,1.00	**1.01***	2.58	1.00,1.02	**1.02** **	3.09	1.01,1.04	1.01	1.08	0.99,1.02
	Recruitment Yr	**0.94** **	-3.12	0.91,0.98	**0.95** **	-3.23	0.93,0.98	0.97	-1.82	0.93,1.00	**0.93*** **	-3.31	0.88,0.97
	Diagnosis time	0.99	-1.07	0.96,1.01	0.99	-1.09	0.97,1.01	0.99	-0.54	0.97,1.02	0.98	-1.06	0.96,1.01
	BMI	**0.93*** **	-4.35	0.90.0.96	**1.03***	2.24	1.00,1.06	1.02	1.03	0.98,1.06	**1.07*** **	4.25	1.04,1.10
	Erosions	**1.51***	2.53	1.10,2.08	**1.34***	2.00	1.01,1.78	1.15	0.66	0.76,1.72	1.24	1.08	0.84,1.82
	Rheum Factor	1.1	0.62	0.81,1.51	0.84	-1.26	0.65,1.10	1.04	0.19	0.71,1.52	0.8	-1.27	0.56,1.13
	SJC	0.98	-1.56	0.95,1.01	**0.97** **	-2.85	0.95,0.99	0.97	-1.81	0.94,1.00	0.98	-1.78	0.95,1.00
	TJC	**1.03***	2.03	1.00,1.07	1.02	1.74	1.00,1.05	**1.04***	1.97	1.00,1.08	1.00	0.06	0.97,1.04
	ESR	1.00	-1.28	0.99.1.00	1.00	1.24	1.00,1.01	1.00	0.87	1.00,1.01	1.00	0.23	0.99,1.01
	HAQ	1.28	1.91	0.99,1.66	**1.40*** **	3.36	1.15,1.71	1.29	1.92	0.99,1.68	**1.43** **	2.72	1.10,1.84
	Haemoglobin	**0.85** **	-2.72	0.75,0.95	**0.81*** **	-4.24	0.73,0.89	**0.81** **	-2.85	0.70,0.94	**0.83** **	-2.95	0.73,0.94

***P<0.05 **P<0.01 ***P<0.001.**

SUPPLEMENTARY MATERIAL

Appendix 1

Statistical details for observational data analysis

The following were entered into the model as core covariates of interest, given their importance in RA: gender, age at disease-onset, recruitment year, time to diagnosis at baseline, rheumatoid factor (RF), BMI, HAQ, disease activity score (DAS) based on the original DAS (ERAS) and modified DAS28 (ERAN),[10] and its individual components including tender (TJC) and swollen joint counts (SJC), patient-reported visual analogue scale (VAS), haemoglobin, ESR, hands and feet x-rays assessed for erosions by each centre (Larsen scores were available in a subgroup of 70% of ERAS patients as previously described).[3] As baseline and 1-year variables did not differ significantly in these patients (data not shown), sub group analysis included Larsen scores.

In order to establish other covariates to include in the model, univariate analysis was undertaken (results not shown). Those significant to $p<0.01$ were also included. In further models, DAS and the proportion of DAS attributable to patient-reported components (TJC and VAS) termed DAS-P were also examined.[11] DAS and DAS-P were only weakly correlated ($r<0.50$), so were included together. Overall missing baseline data were infrequent (around 5%), unlikely to introduce bias. Sensitivity analysis was performed to test robustness of multivariate models by excluding variables with missing data both separately and together in the models (see supplementary material). To assess variance and predictive strength of the regression models, the pseudo R^2 and Area Under the Curve (AUC) were examined for baseline and 1-year models. Those variables with 10 year follow-up were entered as time-varying covariates (TVC), where missing data were imputed using multiple imputation techniques to test the assumption of proportionality over time. Finally, to investigate predictors of multiple surgeries, negative binomial regression was used on the total major or intermediate interventions. All analysis was conducted using Stata (version 13) with significance level of $p<0.05$ assumed.

Appendix 1

Analysis of DAS-P - results

In these models, baseline DAS-P predicted intermediate surgery (35% increase risk), but not major surgery (Appendix I). The associations between surgery and other baseline or 1-year variables were otherwise similar to those identified in the models that used individual DAS components (Appendix I).

For both major and intermediate surgery models, using either DAS components or DAS/DAS-P, the pseudo R^2 was 0.34 for each baseline model, and 0.41 for each 1-year model, suggesting that the models explain 34% and 41% of the total variance respectively. Predictive accuracy measured by AUC of baseline/1-year models was 76/74% for intermediate and 72/63% for major surgery in both the DAS component models and the DAS/DAS-P models. Entering 10-year follow-up data as a TVC in the model revealed no significant interaction between any of the covariates and time, indicating that the effect was proportional over time.

A sub-analysis in ERAS using Larsen scores showed that baseline scores predicted major surgery (SHR 1.02, [1.00-1.03]). 1-year Larsen scores had predictive power ($p<0.001$) for both intermediate and major surgery, an increased risk of 3% for every unit increase in Larsen score. The variables with highest missing data used in the regression models were baseline BMI (13%) and 1-year haemoglobin (8%) and HAQ (9%). Sensitivity analyses indicated that missing data made little difference to the overall results (see supplementary material). Comorbid osteoarthritis (OA) was recorded in ERAS as previously described.[6] Sensitivity analysis excluding these patients undergoing major joint replacement surgery (5.2%) made no difference to effect estimates, suggesting that these did not bias the main analysis.

Table A.1 Summary of reports fulfilling the inclusion criteria for the review. Where more than one report has been derived from the same cohort, these have been identified by *, + or §

Authors/dates/centre	Study type, sample size, FUp	N/% Orth Surg & TJR	Predictive factors & analysis type: Uni/multivariate Cox, Log R
Reilly PA 1990 UK. Unicentre	Inception n=110, 35 survivors at 25yrs	OS=22 (72%) Predictor variables: age/sex, FG	OS Risk: F, FGrade
Eberhardt 1996 Sweden Unicentre *	Inception cohort,2 &5yr FUp n=99	TJR=15 (15%) Predictor variables: HLA SE	OS Risk: HLA SE not related to OS
Kuper 1997 Unicentre Netherlands	Prospective 6yr FUp x-ray scores large joints n=157	OS = 22 (large joints)	None for surgery, mainly X-ray damage large joints
Wolfe F & Zwillich 1998. US Unicentre	Prospective observational 1974-1997 n=1600 23yr FUp	OS=541 (34%) TJR= 36.5% Predictor variables n=14	TJR Risk (UCox): Very high HAQ & high ESR=x3-6 Others: Pain VAS, erosions, Hb, WCC. Smoking protective. RF: NS
Weyand 1998. US 1 county	Retrospective 1970-1985 10yrFUp n=165	OS=67(ops=133) Predictor variables: age/sex	Hand/wrist OS Risk: F (55% v27%) F
Crilly 1999 Unicentre UK	Case control n=65 TJR 15yr FUp	OS=65	TJR risk: HLA DRb1 homozygous = x5 risk OS risk: high ESR , HAQ slight increase
Young 2000 UK + Multicentre	Inception cohort 1986-1998 5yrFUp n=732	OS=117(17%) TJR=55 (8%) Predictor variables n=14	OS risk: Older age & HAQ – NS trends only
Massardo L 2002 US § Population based	Retrospective 1955-1985 n=424 median 14yrs FUp	OS=148 (35%) TJR=76 Predictor variables:	OS risk (UCox): high: youth & nodules low: F & RF+
Da Silva 2003 US § Population based	Retrospective 1955-1995 n=609 FUp 30yr	OS=242 (40%) TJR=85 (%) Predictor variables:	OS risk(U& MCox): F, youth, RF, nodules

James D 2004. UK + Multicentre	Inception cohort 1986-2002 5yrFUp n=1064	OS=181 (17%) TJR=75(7%) Predictor variables n=14	TJR risk: Hb, ESR, DAS, x-ray scores. Hand/foot risk: F, x-ray score, HAQ. All OS: HLA SE LogR: ESR, DAS, HAQ, HLA SE
Lindqvist E 2002 Sweden * Unicentre	Prospective 1985-2000 n=168 10yr FUp	OS=30 (17% all TJR) Predictor variables:	OS risk (LogR): Age, M, HLA SE, RF, HAQ, ESR, SJC
Kapetanovic MC 2008 * Sweden Unicentre	Prospective 1985-2005 n=113 16-20yr FUp	OS=106 (58%) TJR=44(24%) Predictor variables:	OS risk (UniV): x-ray score, HAQ, CRP, Rx, HLA SE Cox: HAQ, CRP/ESR, x-rays
Shourt CA 2012 US § Population based	Retrospective 1980-2007 n=813 FUp 9.6yrs(mean)	OS=189 (%)Predictor variables:	OS risk: F TJR: F, BMI (obese) Minor surgery: smokers
Gossec L France 2004	Retrospective n=300 FUp 12yr	OS=24% TJR=13%	OS: HLA SE not predictive
Verstappen S 2006 Netherlands Unicentre	1990-98 FUp 2-14yrs Early v delayed Rx clinical trial n=482 (mean FUp 7.2yrs)	OS=130 (27%) TJR=10% Predictor variables n=8	OS (UCox): JSc, ESR. Pain, HAQ, x-ray scores, response to Rx, early Rx. Not age, sex, RF, EMS MCox: early Rx,, x-ray scores

***Table references**:*

Crilly A, Maiden N, Capell HA, Madhok. Genotyping for disease associated HLA-DR_1 alleles and the need for early joint surgery in rheumatoid arthritis: a quantitative evaluation. Ann Rheum Dis 1999;58:114–7. -

Da Silva et al., 2003 Doran-Michele-F, Crowson C S, O-Fallon W M, Matteson E L. Declining use of orthopaedic surgery in patients with rheumatoid arthritis? Results of a long-term, population-based assessment. Arthritis-Rheum, 15 Apr 2003, vol. 49, no. 2, p. 216-220. -

Eberhardt KB, Fex E, Johnson U, Wollheim FA. Association of HLA-DR_ and DQ_ genes with two and five year outcome in rheumatoid arthritis. Ann Rheum Dis 1996;55:34–9.

*Gossec L, Bettembourg-Brault I, Pham T, Dougados M. HLA DRB1*01 and DRB1*04 phenotyping does not predict the need for joint surgery in rheumatoid arthritis. A retrospective quantitative evaluation of 300 French patients. Clin Exp Rheumatol. 2004 Jul-Aug; 22(4): 462-4.*

Young A, Cox N, Davies P, Devlin J, Dixey J, Emery P, Gallivan S, Gough A, James D, Prouse P, Williams P, Winfield J. How does functional disability in early Rheumatoid Arthritis (RA) affect patients and their lives? Results of 5yr follow up in 781 patients from the Early RA Study (ERAS). Rheumatology (Oxford) 2000;39:603-11.

*James D, Young A, Kulinskaya E, et al. Orthopaedic intervention in early rheumatoid arthritis. Occurence and predictive factors in an inception cohort of 1064 patients followed for 5 years. Rheumatology 2004;**43**:369-376.*

Kuper HH, van Leeuwen MA, van Riel PLCM et al. Radiographic damage in large joints in early rheumatoid arthritis: relationship with radiographic damage in hands and feet, disease activity, and physical disability. Br J Rheumatol 1997;36:855–60. -

*Kapetanovic MC, Lindqvist E, Saxne T, et al. Orthopaedic surgery in patients with rheumatoid arthritis over 20 years: prevalence and predictive factors of large joint replacement. Ann Rheum Dis 2008;**67**(10):1412-6.*

Lindqvist E, T Saxne, P Geborek, K Eberhardt, Ten year outcome in a cohort of patients with early rheumatoid arthritis: health status, disease process, and damage Annals of the Rheumatic Diseases 2002; 61:1055-1059 .

Massardo L, Gabriel SE, Crowson CS, et al: A population based assessment of the use of orthopaedic surgery in patients with rheumatoid arthritis. J Rheumatol 2002;29:52-56.

Reilly PA, Cosh JA, Maddison PJ, Rasker JJ, Silman AJ. Mortality and survival in rheumatoid arthritis: a 25 year prospective study of 100 patients. Ann Rheum Dis 1990;49:363-9. -

*Shourt CA, Crowson CS, Gabriel SE, et al. Orthopaedic surgery among patients with rheumatoid arthritis 1980-2007: A population-based study focused on surgery rates, sex and mortality. J Rheumatol 2012;**39**:481-5.*

Wolfe F, Zwillich S. The long-term outcomes of rheumatoid arthritis. Arthritis Rheum 1998;41:1072-82. -

Weyand CM, Schmidt D, Wagner U, Goronzy JJ. The influence of sex on the phenotype of rheumatoid arthritis. Arthritis Rheum 1998;41:817-22.) -

Verstappen SM, Hoes JN, Ter Borg EJ, Bijlsma J W, Blaauw AA, Albada-kupers GA et al. Joint surgery in the Utrecht rheumatoid arthritis Cohort: the effect of treatment strategy. Ann Rheum Dis 2006; 65(11): 1506 – 1511.

Table A.2. Number and type of orthopaedic interventions by category over the 25 years of study follow-up.

Type of procedure	Number of episodes (n)	Incidence Rate per 1000	95% CI
TJRs	562	18.2	16.7-19.8
THRs	221	7.2	6.3-8.2
TKRs	277	9.0	8.0-10.1
Other	64	2.1	1.6-2.6
Cervical spine	9	0.3	0.1-0.6
Large joint #	71	2.3	1.8-2.9
All Intermediate	383	12.4	11.2-13.7
Intermediate for #	14	0.5	0.2-0.8
All Minor	527	17.1	15.7-18.6
Minor for #	27	0.9	0.6-1.3
Miscellaneous	50	1.6	1.2-2.1
Total	1602	51.9	49.5-54.4

TJRs=Total Joint Replacements, THRs=Total Hip Replacements, TKRs=Total Knee Replacements, #=fracture.

Table A.3. Baseline and 1-year disease features, patient characteristics, length of follow up and treatments in the "no intervention", "intermediate" and "major" categories.

Variable	No major/intermediate Intervention (n=2173)	Intermediate (n=267)	Major (n=341)	Whole Cohort (n=2701)
Age at disease-onset(yrs), mean ± SD	56.24 ± 14.6	52.5 ± 14.6	57.5 ± 12.7	56.1 ± 14.4
Women, n (%)	14-05 (64.6)	225 (84.3)	248 (72.7)	1812 (67.1)
Length of Follow-up (yrs), median (IQR)	8 (12)	19 (9)	17 (11)	9 (13)
Rheumatoid Factor +ve, n (%)	1223 (61.7)	179 (65.6)	201 (60.2)	1553 (61.8)
Baseline BMI, mean ± SD	26.7 (5.1)	24.9 (4.0)	26.6 (4.9)	26.5 (5.0)
Baseline DAS, mean ± SD	4.7 ± 1.5	5.2 ± 1.2	5.2 ± 1.2	4.8 ± 1.4
Baseline HAQ, mean ± SD	1.1 ± 0.8	1.2 ± 0.8	1.3 ± 0.8	1.1 ± 0.8
Baseline Haemoglobin, mean ± SD	13.0 ± 1.5	12.3 ± 1.4	12.3 ± 1.6	12.8 ± 1.5
Baseline ESR, mean ± SD	35.8 ± 27.1	39.8 ± 26.9	46.9 ± 29.6	37.2 ± 27.5
Baseline erosions, n(%)	478(17.7)	61(2.2)	107(3.9)	646(23.9)
DMARD use by 3 years, n (%)				
Monotherapy	692 (55.1)	95(49.7)	140(50.7)	927 (53.8)
Sequential Monotherapy	191(15.2)	41(21.5)	58(21.0)	290 (16.8)
DMARD Add-on/step-up*	220(17.5)	45(23.6)	57(20.7)	322 (18.7)
Combination 2 DMARD*	61(4.9)	6(3.1)	4(1.4)	71 (4.1)
Combination 3 DMARD*	25(2.0)	1(0.5)	2(0.7)	28 (1.6)
DMARDS + TNF	67(5.3)	3(1.6)	15(5.4)	85 (4.9)
Year 1 DAS, mean ± SD	3.8 ± 1.5	4.3 ± 1.6	4.4 ± 1.5	3.9 ± 1.6
Year 1 HAQ, mean ± SD	0.8 ± 0.8	1.0 ± 0.8	1.1 ± 0.8	0.9 ± 0.8
Year 1 Haemoglobin, mean ± SD	13.1 ± 1.5	12.3 ± 1.5	12.3 ± 1.4	12.9 ± 1.5
Year 1 ESR, mean ± SD	25.3 ± 23.0	31.5 ± 24.9	35.0 ± 26.0	26.9 ± 23.7

*DMARD add-on or step-up therapy refers to single DMARD addition to an existing DMARD sequentially over time, whereas combination 2 or 3 DMARD therapy refers to starting 2 or 3 DMARDs at the same time or within a maximum of one month from each other. Missing baseline data: Rheumatoid factor (4%), DAS28 (2%), HAQ (1.6%), Haemoglobin (1.4%), ESR (7%); BMI (13%). Missing 1-year data: DAS28 (12%), HAQ(19.9%), Haemoglobin (18.8%), ESR (24.4%).

Table A.4: Prediction of Multiple Orthopaedic Interventions. Negative Binomial Regression Model.

		Intermediate Interventions			Major Interventions		
	Variable	**SHR**	**Wald**	**95% CI**	**SHR**	**Wald**	**95% CI**
Baseline Model	Gender	**2.09****	2.96	1.28,3.41	1.12	0.69	0.82,1.53
	Age at Onset	**0.97*****	-5.95	0.96,0.98	1.00	0.43	0.99,1.01
	Recruitment year	**0.88*****	-6.38	0.85,0.92	**0.88*****	-8.60	0.86,0.91
	Time to Diagnosis	1.01	0.56	0.99,1.03	1.00	-0.33	0.98,1.02
	BMI	0.96	-1.87	0.92,1.00	**1.05****	3.23	1.02,1.07
	Erosions	1.17	0.78	0.79,1.75	1.33	1.80	0.97,1.83
	Rheumatoid Factor	1.29	1.32	0.88,1.88	0.86	-1.05	0.65,1.14
	SJC	0.99	-0.48	0.97,1.02	0.99	-1.25	0.97,1.01
	TJC	1.01	0.82	0.98,1.04	1.02	1.83	1.00,1.05
	ESR	**0.99****	-2.62	0.98,1.00	1.00	1.01	1.00,1.01
	VAS	**1.01***	2.10	1.00,1.02	1.00	0.07	0.99,1.01
	HAQ	0.88	-0.85	0.65,1.19	1.09	0.79	0.88,1.35
	Haemoglobin	**0.81****	-2.81	0.70,0.94	**0.86****	-2.58	0.77,0.97
1-Year Model	Gender	**2.05****	2.86	1.25,3.35	1.02	0.14	0.74,1.42
	Age at Onset	**0.96*****	-6.58	0.95,0.97	1.00	-0.45	0.99,1.01
	Recruitment year	**0.88*****	-4.18	0.82,0.93	**0.88*****	-6.80	0.84,0.91
	Time to Diagnosis	1.00	-0.22	0.97,1.03	0.98	-1.68	0.96,1.00
	BMI	**0.93****	-3.01	0.89,0.97	**1.04****	2.66	1.01,1.08
	Erosions	1.10	0.48	0.75,1.60	**1.44***	2.51	1.08,1.92
	Rheumatoid Factor	1.09	0.44	0.74,1.60	0.79	-1.56	0.59,1.06
	SJC	**0.96***	-2.28	0.94,0.99	**0.96****	-2.85	0.94,0.99
	TJC	**1.05***	2.20	1.01,1.09	**1.03***	2.00	1.00,1.06
	ESR	1.00	-1.09	0.99,1.00	1.00	0.36	0.99,1.01
	VAS	1.00	-0.42	0.99,1.01	1.00	-0.57	0.99,1.00
	HAQ	1.27	1.31	0.89,1.82	**1.36***	2.37	1.05,1.75
	Haemoglobin	**0.83****	-2.65	0.73,0.95	**0.81*****	-3.81	0.72,0.90

***P<0.05 **P<0.01 ***P<0.001**