

## Concise report

# Lifetime risk of knee and hip replacement following a diagnosis of RA: findings from a cohort of 13 961 patients from England

Edward Burn <sup>1</sup>, Christopher J. Edwards<sup>2</sup>, David W. Murray<sup>1</sup>, Alan Silman<sup>1</sup>, Cyrus Cooper<sup>1,3</sup>, Nigel K. Arden<sup>1,3</sup>, Rafael Pinedo-Villanueva<sup>1</sup> and Daniel Prieto-Alhambra<sup>4</sup>

## Abstract

**Objective.** To estimate the lifetime risk of knee and hip replacement following a diagnosis of RA.

**Methods.** The analysis was undertaken using routinely collected data from the English NHS. Diagnosis of RA was identified using primary care records, with knee and hip replacement observed in linked hospital records. Parametric survival models were fitted for up to 15 years of follow-up, with age, sex, Charlson comorbidity score, socioeconomic status, BMI and smoking status included as explanatory variables. A decision model was used to combine and extrapolate survival models to estimate lifetime risk.

**Results.** The number of individuals with a diagnosis of RA and included in the study was 13 961. Lifetime risk of knee replacement and hip replacement was estimated to be 22% (95% CI: 16, 29%) and 17% (95% CI: 11, 26%) following a diagnosis of RA for the average patient profile (non-smoking women aged 64 with no other comorbidities, BMI of 27 and in the top socioeconomic quintile). Risks were higher for younger patients.

**Conclusion.** The lifetime risk of knee and hip replacement for individuals with a diagnosis of RA is approximately double that of the general population. These findings allow for a better understanding of long-term prognosis and healthcare resource use, and highlight the importance of timely diagnosis and effective treatment.

**Key words:** rheumatoid arthritis, surgery, epidemiology, knee, hip

### Rheumatology key messages

- The lifetime risk of knee and hip replacement following an RA diagnosis was not known.
- Lifetime risk is around 20% for the average patient profile.
- The risk for RA is approximately double that of the general population.

## Introduction

RA is characterized by persistent synovitis and systemic inflammation and can lead to the progressive destruction and secondary osteoarthritis of both small and large joints. Surgical procedures may help to relieve pain, maintain or restore function, correct deformity or instability,

and prevent or treat failure of structures. Knee and hip replacement are two of the most common surgeries for individuals with RA [1].

There have been substantial advances in management of RA over recent decades, with numerous effective disease modifying agents introduced coupled with improvements in both diagnostic and management strategies. Likely as a result, while rates of knee and hip replacement have been increasing over recent years in the general population [2–4], rates among those with RA have remained relatively stable [5].

Fifty-year-old men and women from the general population in the UK have an 8 and 11% lifetime risk of knee replacement and a 7 and 11% risk of hip replacement, respectively [6]. Risks are lower for older individuals with, for example, 80-year-olds having a 3–4% lifetime risk of knee and hip replacement [6]. It is not known

<sup>1</sup>Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences, University of Oxford, Oxford, <sup>2</sup>NIHR Wellcome Trust Clinical Research Facility, University Hospital Southampton, <sup>3</sup>MRC Lifecourse Epidemiology Unit, Southampton University, Southampton, UK and <sup>4</sup>GREMPAL Research Group, Idiap Jordi Gol and CIBERFes, Universitat Autònoma de Barcelona and Instituto de Salud Carlos III, Barcelona, Spain

Submitted 8 February 2019; accepted 16 March 2019

Correspondence to: Rafael Pinedo-Villanueva, Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences, University of Oxford, Oxford B4495, UK.  
E-mail: rafael.pinedo@ndorms.ox.ac.uk

whether the improvements in the management of RA have led to this risk being reduced to that of the general population, or whether there remains an increased risk of knee and hip replacement for individuals with RA.

Understanding the lifetime risk of knee and hip replacement following a diagnosis of RA would help provide patients and clinicians with an indication of long-term prognosis and future health care utilization. Therefore, in this study we estimated the lifetime risks of knee and hip replacement following a diagnosis of RA and the effect of patient characteristics at time of diagnosis on this risk.

## Methods

### Study participants and data collection

Patient-level data from the English NHS were used. Primary care records were extracted from practices within the Clinical Practice Research Datalink (CPRD), which contains medical records and demographic details for around 7% of the UK population and is broadly representative of the general population [7]. These data were linked to hospital records from Hospital Episode Statistics Admitted Patient Care, which has data on all admissions to English NHS hospitals and admissions to independent sector hospitals paid for by the NHS [8], and mortality data from the Office for National Statistics. The linked dataset covered 1997–2014. Ethical approval for the study was granted by the CPRD Independent Scientific Advisory Committee.

Individuals were included if they had an incident diagnosis of RA recorded in CPRD during the study period. RA was identified using an established diagnostic algorithm with high validity for CPRD, with >80% sensitivity and specificity [6]. Individuals were excluded from the study if they had a history of knee or hip replacement prior to diagnosis, although no minimum prior observation time was required for inclusion into the study. A sensitivity analysis was performed with study participants excluded if they had less than a year of observation time prior to diagnosis. Individuals were also excluded if they were younger than 40 years of age at time of diagnosis as there was insufficient follow-up to plausibly estimate lifetime risk for them.

The following patient characteristics at time of diagnosis were extracted: age, sex, Charlson score, index of multiple deprivation (IMD), BMI and smoking status. Charlson scores, which provide a measure of comorbidity, were categorized as 0 or 1+ as relatively few study participants had multiple comorbidities. IMD, a measure of socioeconomic status, was extracted with individuals grouped by quintile (where quintile 5 represented the most deprived). Smoking status (classified as non-smoker, ex-smoker or current smoker) and BMI were identified using records from within the year prior to diagnosis, with the record closest to time of diagnosis used.

Study participants were followed for up to 15 years after diagnosis. Knee and hip replacement were identified using procedure codes within Hospital Episode Statistics Admitted Patient Care. Mortality was identified using Office for National Statistics records.

### Estimating lifetime risk

Analyses were undertaken separately for risk of knee and hip replacement. Parametric survival models were estimated for cause-specific risks of knee or hip replacement and death following diagnosis of RA. Age, sex, Charlson score, IMD quintile, BMI and smoking status were included as explanatory variables in the models. There was evidence of non-proportionality in age for risks of knee and hip replacement and so models were estimated separately for age groups based on quartiles of the distribution and with continuous age included as an explanatory variable within each of the stratified models.

A range of distributions were considered for the parametric survival models, with distributions chosen on the basis of their fit to the observed data and, if required, the plausibility of their extrapolation. Under an exponential distribution the hazard is expected to be constant over time, while under Weibull and log-normal distributions the hazard is expected to be either declining or increasing as time passes. Meanwhile, a spline-based distribution allows for more flexible shapes, for example where the hazard first decreases but later increases. Knots (inflection points) for spline models were fitted at 33 and 67% quantiles of log time. When incorporating continuous explanatory factors (age and BMI), non-linearity was accounted for using quadratic terms if the Akaike information criterion was reduced compared with if they were specified as linear.

To estimate lifetime risk, the survival models were combined using a state-based Markov model. Risk of knee and hip replacement was extrapolated over the remaining lifetimes. Risk of mortality was based on the relevant parametric models for the first 15 years following diagnosis, after which they were assumed to revert to estimates based on age- and sex-specific life tables for the UK. Models were run for individuals with average characteristics (median for continuous variables and mode for categorical ones). To estimate the partial effect of explanatory factors on lifetime risk, models were re-run with participant profiles varying in the explanatory factor of interest, while holding other characteristics constant at their average.

## Results

The number of individuals diagnosed with RA and included in the analysis was 13 961. A study flowchart is provided in Supplementary Fig. S1, available at *Rheumatology* online and patient characteristics at time of diagnosis are given in Table 1.

Over observed follow-up, 672 individuals had a knee replacement and 493 had a hip replacement following a diagnosis of RA. The 15-year cumulative incidence of knee and hip replacement was 9.69% (95% CI: 8.75, 10.73%) and 7.69% (95% CI: 6.80, 8.71%), respectively. The lifetime risk of knee replacement and hip replacement was 22% (95% CI: 16, 29%) and 17% (95% CI: 11, 26%), respectively, for the average patient profile (age: 64 years; sex: female; Charlson score: 0; IMD quintile: 1; BMI: 27 kg/m<sup>2</sup>; smoking status: non-smoker).

The cumulative incidence stratified for the different explanatory factors is summarized in detail in Supplementary Table S1,

**TABLE 1** Study participant characteristics at time of RA diagnosis

Characteristic	(n = 13 961)
Age, median (IQR), years	64.0 (54.0–73.0)
Age, n (%)	
≥40 to <54	3216 (23.0)
≥54 to <64	3720 (26.6)
≥64 to <73	3212 (23.0)
≥73 to ≤99	3813 (27.3)
Sex, n (%)	
Women	9468 (67.8)
Men	4493 (32.2)
Charlson score, n (%)	
0	12 399 (88.8)
1+	1562 (11.2)
BMI, median (IQR), kg/m <sup>2</sup>	27.1 (23.9–31.4)
BMI group, n (%)	
Normal or underweight	1701 (12.2)
Obese class I	988 (7.1)
Obese class II	431 (3.1)
Obese class III	225 (1.6)
Overweight	1788 (12.8)
Missing	8828 (63.2)
IMD, n (%)	
1 (least deprived)	3132 (22.4)
2	3118 (22.3)
3	2988 (21.4)
4	2700 (19.3)
5 (most deprived)	2001 (14.3)
Missing	22 (0.2)
Smoking status, n (%)	
Non-smoker	2465 (17.7)
Ex-smoker	2452 (17.6)
Current smoker	1642 (11.8)
Missing	7402 (53.0)

IMD: index of multiple deprivation; IQR: interquartile range.

available at *Rheumatology* online. Timing to knee and hip replacement differed across the age stratified models. In general, risks were closer to being constant over time for younger patients whereas risks peaked shortly after diagnosis for older patients (see Supplementary Figs S2–S9, available at *Rheumatology* online, for details). The effect of age on risk of knee and hip replacement appears to be non-linear with increasing age first associated with an increased risk for younger patients but then a falling risk for older patients, while risk of mortality increased as age increased (see Supplementary Tables S2 and S3, available at *Rheumatology* online). The effect of age on mortality, and so time at risk, appeared to drive differences in lifetime risk with younger age at diagnosis associated with a higher lifetime risk (see Fig. 1).

Lifetime risk estimates were similar by gender (see Fig. 1), socioeconomic status (see Supplementary Fig. S11, available at *Rheumatology* online) and smoking status (see Supplementary Fig. S13, available at *Rheumatology* online). Point estimates implied that

having comorbidities at time of diagnosis was associated with a lower lifetime risk of knee and hip replacement (see Supplementary Fig. S10, available at *Rheumatology* online), with differences mainly due to the effect of comorbidities on risk of mortality (see Supplementary Tables S2 and S3, available at *Rheumatology* online). Point estimates also suggested that a higher BMI at diagnosis was associated with increased lifetime risks, particularly for knee replacement (see Supplementary Fig. S12, available at *Rheumatology* online), driven by an estimated effect on cause-specific risks for surgery (see Supplementary Tables S2 and S3, available at *Rheumatology* online).

Requiring a year of observation time led to 9% of study participants being excluded. This had relatively little impact on estimated lifetime risk for individuals with an average patient profile or older (see Supplementary Fig. S13, available at *Rheumatology* online). For younger individuals, however, lifetime risk was estimated to be lower with fewer knee and hip replacements within the youngest age group.

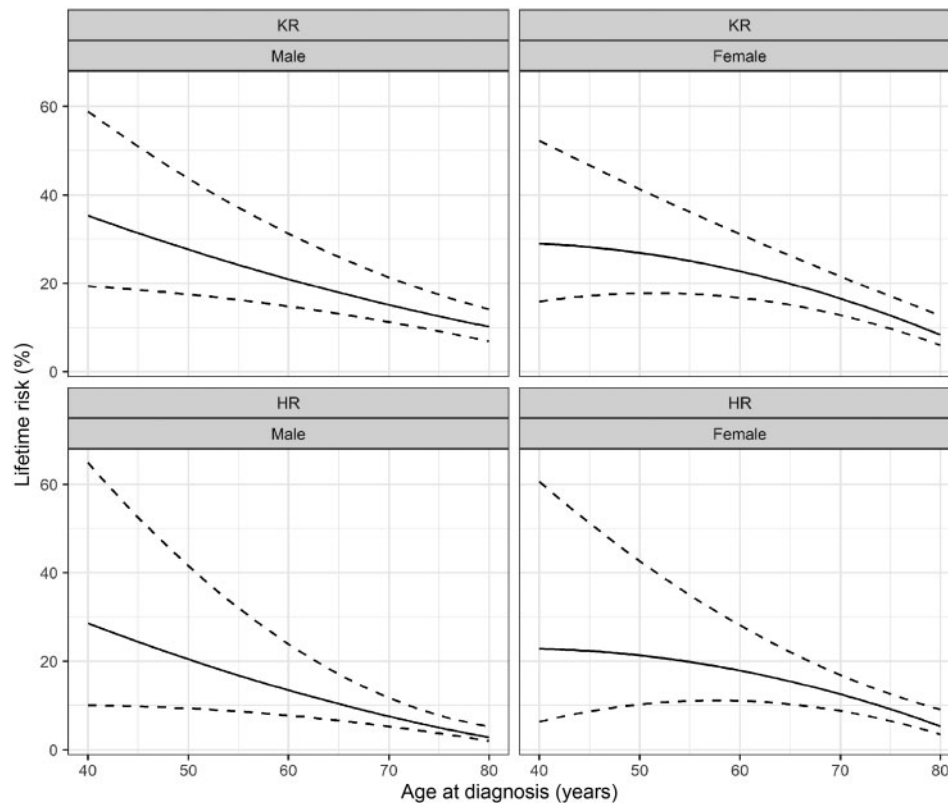
## Discussion

Lifetime risk of knee replacement and hip replacement was estimated to be 22% (95% CI: 16, 29%) and 17% (95% CI: 11, 26%), respectively, following a diagnosis of RA for the average patient profile. Risks were found to be higher for younger patients, but were similar by gender, socioeconomic status and smoking status. Point estimates implied that comorbidities and a higher BMI at time of diagnosis may increase lifetime risks.

The lifetime risks of knee and hip replacement for 50-year-olds from the general UK population has previously been estimated respectively as 11 and 12% for women and 8 and 7% for men [7], with primary osteoarthritis being the most common indication for surgery. Based on our findings, despite the improvement in the diagnosis and treatment of the disease, RA is still associated with a lifetime risk of both knee and hip replacement approximately double that of the general population. A number of studies have described rates of knee and hip replacement for individuals with RA [8–15], and our findings of lifetime risks are broadly in line with what would be expected based on these studies.

While being older has been associated with an increased risk of orthopaedic surgery for people with RA [10], those aged over 80 have been seen to have lower risk of knee and hip replacement compared with younger patients [9]. Patients over 80 who underwent surgery also had their procedure more quickly following diagnosis than younger patients [9]. A similar relationship between age and risk for surgery was seen in this study, with non-proportionality in hazards (with older patients more likely to have surgery shortly after diagnosis) and age having a non-linear association with risks of knee and hip replacement (with risks first increasing and then decreasing as age at diagnosis increased).

The strength of this study include that it was informed by real world, routinely collected data with a large and representative study cohort. Fitting parametric survival

**Fig. 1** Partial effect of age and sex on lifetime risk of knee replacement and hip replacement

Point estimates with 95% CI. HR: hip replacement; KR: knee replacement.

models allowed lifetime risk to be estimated and the impact of patient characteristics on this risk to be assessed, but the required extrapolation leads to sizeable uncertainty particularly for younger patients (as reflected in the wide CIs and the impact of requiring study participants to have a year of observation time prior to diagnosis). The estimates from this study were based on hospital procedures funded by the NHS and so are likely to have missed some of the surgeries done in the private sector, leading to lifetime risk being somewhat underestimated. While individuals were excluded if they had a record of knee or hip replacement prior to diagnosis, 9% of study participants had less than a year of prior observation time and 39% had less than 5 years, hence limiting our ability to definitely exclude those with a previous knee or hip replacement. Another limitation of the study is that while the effects of patient characteristics identified at time of diagnosis were considered, factors such as BMI and comorbidities may change over time and so may have a time-varying effect on risks. In addition, there are a number of other factors not collected in the data we used that are likely to influence risks. In particular, disease severity at time of diagnosis can be expected to have a substantial impact on the risks, with baseline functional disability previously found to be a strong predictor for undergoing surgery [10]. Treatment following diagnosis

can also be expected to have an important effect on lifetime risk, with immediate initiation of treatment with disease-modifying antirheumatic drugs found to reduce risk of surgery when compared with a delayed start [15].

In summary, an individual with an average profile at diagnosis of RA has a slightly lower than 1 in 5 chance of having a knee replacement and a slightly higher than 1 in 5 chance of hip replacement over his or her remaining lifetime. This is approximately double the risk of the general population. Risks are higher for those at a younger age when diagnosed.

### Acknowledgements

D.P.A. is funded by a National Institute for Health Research Clinician Scientist award (CS-2013-13-012). The authors would like to thank Miss Susan Thwaite (National Rheumatoid Arthritis Society) for her role as the patient and public representative and her role in the study steering committee. E.B., C.J.E., D.W.M., A.S., C.C., N.K.A., D.P.A. and R.P.V. all made substantial contributions to conception and design of the study. E.B., R.P.V. and D.P.A. undertook the statistical analysis. E.B., R.P.V. and D.P.A. drafted the manuscript with C.J.E., D.W.M., A.S., C.C. and N.K.A. revising it for important intellectual content. All authors read and approved

the final manuscript. CPRD data with Hospital Episode Statistics linkage were provided under a licence that does not permit sharing. Data are obtainable from CPRD subject to a full application.

**Funding:** This article presents independent research funded by the National Institute for Health Research (NIHR). The views expressed are those of the authors and not necessarily those of the NHS, the NIHR or the Department of Health. This work was supported by the NIHR Biomedical Research Centre, Oxford.

**Disclosure statement:** N.K.A. has received personal fees from Freshfields Bruckhaus Deringer, Bioventus, Flexion, Merck, and Regeneron, all outside the submitted work. D.P.A. reports grants from Amgen, Servier and UCB Biopharma, and non-financial support from Amgen, all outside the submitted work. D.W.M. reports grants and personal fees from Zimmer Biomet. In addition, D.W.M. has various patents related to Unicompartmental Knee Replacement (Zimmer Biomet) with royalties paid, all outside the submitted work.

## Supplementary data

Supplementary data are available at *Rheumatology* online.

## References

- James D. Orthopaedic intervention in early rheumatoid arthritis. Occurrence and predictive factors in an inception cohort of 1064 patients followed for 5 years. *Rheumatology* 2003;43:369–76.
- Culliford DJ, Maskell J, Beard DJ *et al.* Temporal trends in hip and knee replacement in the United Kingdom. *J Bone Joint Surg Br* 2010;92-B:130–5.
- Cram P, Lu X, Kates SL *et al.* Total knee arthroplasty volume, utilization, and outcomes among Medicare beneficiaries, 1991–2010. *JAMA* 2012;308:1227.
- Cram P, Lu X, Callaghan JJ *et al.* Long-term trends in hip arthroplasty use and volume. *J Arthroplasty* 2012;27:278–85.e2.
- Hawley S, Cordtz R, Dreyer L *et al.* Association between NICE guidance on biologic therapies with rates of hip and knee replacement among rheumatoid arthritis patients in England and Wales: an interrupted time-series analysis. *Semin Arthritis Rheum* 2018;47:605–10.
- Thomas SL, Edwards CJ, Smeeth L *et al.* How accurate are diagnoses for rheumatoid arthritis and juvenile idiopathic arthritis in the general practice research database? *Arthritis Care Res* 2008;59:1314–21.
- Culliford DJ, Maskell J, Kiran A *et al.* The lifetime risk of total hip and knee arthroplasty: results from the UK general practice research database. *Osteoarthritis Cartilage* 2012;20:519–24.
- Shourt CA, Crowson CS, Gabriel SE *et al.* Utilization of orthopedic 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.
- Waljee J, Zhong L, Baser O *et al.* The incidence of upper and lower extremity surgery for rheumatoid arthritis among Medicare beneficiaries. *J Bone Joint Surg Am* 2015;97:403–10.
- Gwinnutt JM, Symmons DPM, MacGregor AJ *et al.* Predictors of and outcomes following orthopaedic joint surgery in patients with early rheumatoid arthritis followed for 20 years. *Rheumatology* 2017;56:1510–7.
- Wolfe F, Zwiilich SH. The long-term outcomes of rheumatoid arthritis: a 23-year prospective, longitudinal study of total joint replacement and its predictors in 1,600 patients with rheumatoid arthritis. *Arthritis Rheum* 1998;41:1072–82.
- Da Silva E, Doran MF, Crowson CS *et al.* Declining use of orthopedic surgery in patients with rheumatoid arthritis? Results of a long-term, population-based assessment. *Arthritis Rheum* 2003;49:216–20.
- Massardo L, Gabriel SE, Crowson CS *et al.* A population based assessment of the use of orthopedic surgery in patients with rheumatoid arthritis. *J Rheumatol* 2002;29:52–6.
- 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.
- Verstappen SMM, Hoes JN, Ter Borg EJ *et al.* Joint surgery in the Utrecht Rheumatoid Arthritis Cohort: the effect of treatment strategy. *Ann Rheum Dis* 2006;65:1506–11.