Descriptive epidemiology of hip and knee replacement in rheumatoid arthritis: an analysis of UK electronic medical records

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Abstract

Objective: To provide descriptive data on rates of total hip replacement (THR) and total knee replacement (TKR) within a large RA cohort and describe variation in risk.

Methods: Incident RA patients (1995 to 2014) were identified from the Clinical Practice Research Datalink (CPRD). First subsequent occurrence of THR and TKR were identified (analysed separately) and incidence rates calculated, stratified by sex, age, BMI, geographic region, and quintiles of the index of multiple deprivation (IMD) score.

Results: There were 27,607 RA patients included, with a total of 1,028 THRs (mean age at surgery: 68.4 years) and 1,366 TKRs (mean age at surgery: 67.6 years), at an overall incidence rate per 1,000 person-years (PYs) [95% CI] of 6.38 [6.00 - 6.78] and 8.57 [8.12 - 9.04], respectively. TKR incidence was similar by gender but THR rates were higher in females than males. Rates of TKR but not THR rose according to BMI. An increasing trend was observed in rates of both outcomes according to age (although not ≥75) but of decreasing rates according to socio-economic deprivation. There was some evidence for regional variation in TKR. The 10-year cumulative incidence was 5.2% [4.9, 5.6] and 7.0% [6.6, 7.4] for THR and TKR, respectively.

Conclusion: We provide generalizable estimates of THR and TKR incidence in the UK RA patient population and note variation across several key variables. Increased BMI was associated with a large increase in TKR but not THR incidence. Increased deprivation was associated with a downward trend in rates of THR and TKR.

Background

RA is a chronic autoimmune disease, clinically characterised by persistent joint inflammation and progressive damage to cartilage and bone (1). The progressive and often permanent nature of radiographic joint damage, in conjunction with associated pain, loss of function and failure to adequately respond to therapeutic options are strong indications for eventual joint replacement surgery (2, 3). While progression of structural damage in RA has been well described (4, 5), long-term clinical outcomes such as the incidence of joint replacement remains less well studied (6). Estimates from the US National Inpatient Sample from 2002 – 2012 indicate that of approximately 2.7 million total hip replacements (THR) and 5.7 million total knee replacements (TKR), approximately 3% were carried out in patients with prevalent RA. Likewise, previous National Joint Registry (NJR) estimates from England, Wales and Northern Ireland indicate that inflammatory arthritis accounts for 1-2% of all THR and TKR procedures performed which is a substantial number given >200,000 hip and knee replacements were carried out across all indications in 2016 alone (7, 8).

Notwithstanding the prior studies reporting on the prevalence of RA amongst larger samples of joint replacement procedures (9-13), good quality data pertaining to the incidence of joint replacement following RA diagnosis is arguably more useful in terms of better understanding the longer-term natural history of RA. However, these data are still only emerging (6, 14-22). Generalizable, population-based estimates of joint replacement incidence among RA patients and the potential influence of demographic and clinical characteristics are scarce. Such data would provide clinicians and other stake holders a more thorough understanding of the long-term prognosis for specific RA patients and allow

a greater ability to plan healthcare resource utilisation. This is a worthwhile consideration given the estimated cost of £6,000 - £7,000 per THR/TKR operation for UK RA patients (23) .

Our aim here was therefore to describe the epidemiology of hip and knee replacement in RA, using routinely collected electronic medical records for a generalizable sample of the entire UK RA population

Methods

Data and participants

With its single healthcare system with near universal coverage and single reimbursement guideline, the UK National Health Service (NHS) represents an ideal healthcare model to explore the natural history of THR and TKR in RA. Primary care health data were obtained from the UK Clinical Practice Research Datalink (CPRD) GOLD dataset for the period April 1995 to September 2014. As of 2013, CPRD GOLD included data on over 11.3 million patients from 674 general practitioner practices and had a coverage of approximately 7% of the United Kingdom (24), although this was lower in the early years of the study (400 practices in 1999) (25). The data resource has previously been shown to be representative of the entire UK population (as measured by national census) in terms of age, sex (24) and ethnicity (26). The database has also broadly been shown to be comparable to the UK NHS Health Survey for England data in terms of BMI distribution (27). Mortality data were obtained from linkage to the Office for National Statistics (ONS) dataset. Incident RA patients were identified using a pre-defined READ code list (appendix file 1) as developed elsewhere (28), with the date of first recorded RA considered as diagnosis date. Data on

gender, age, BMI, Charlson comorbidity score and index of multiple deprivation (IMD) were extracted from CPRD GOLD data. The values for these variables were taken as recorded either on or before the date of RA diagnosis. Patients aged <18 years old and those diagnosed with RA before the study period were excluded as were those with a prior or subsequent diagnosis of a different inflammatory arthritis (to address possible diagnosis/coding errors).

Outcome

Outcome of interest was first occurrence of THR or TKR following RA diagnosis. These were identified using CPRD Read codes (appendix file 2) as used/validated previously in the published literature (29). THR and TKR were considered separately so patients could potentially have both outcomes of interest. Patients were followed up from date of RA diagnosis until the first date of either outcome event, death or lost-to-follow up.

Statistical analysis

Baseline patient characteristics and standard epidemiological descriptive statistics were calculated for the whole study sample. These included incidence rates (per 1,000 person years) and cumulative probability (accounting for death as a competing risk) at 10 and 20 year timepoints. Similarly, incidence rates and cumulative probability at 10 years were generated according to stratification variables. Characteristics explored in this fashion were: gender, age group, body mass index (BMI) category, index of multiple deprivation (IMD) quintile, geographic region and time period. The IMD is the official measure of relative deprivation for 32,844 small areas (lower-layer super output areas) of England, each of approximately 1,500 individuals (30, 31). It is based on a weighted combination of seven

domains of deprivation including: income, education, employment, crime and living environment (30). Univariate Poisson models were used to test for differences in rates across levels of stratification variables. *p*-values from these models were used to assess the conformity of data to what would be expected under the null hypothesis of no difference in rates between strata. Specifically, *p*-values were reported for binary stratification variables while *p*-trend was used to assess evidence of linear trend across ordinal categorical variables. Geographic region was considered a nominal categorical variable (i.e. neither binary nor ordinal) and *p*-values for equality were generated using chi-squared tests.

Missingness in BMI was dealt with using multiple imputation (32), but this technique was considered inappropriate for missingness in IMD as this data was not collected for Wales, Scotland or Northern Ireland and so was considered missing not at random (MNAR). As a sensitivity analysis, results were also generated stratified by BMI categories prior to multiple imputation, with patients missing BMI data included as an additional category.

Results

Baseline Characteristics

Of the total 33,044 RA patients identified, 5,437 were excluded (Supplementary Figure 1). The subsequent study sample consisted of 27,607 incident RA patients with a mean age of 61 [IQR: 50, 72] and of whom 70.6% were female. Mean BMI was 27.3 kg/m^2 (Supplementary Table 1).

Overall incidence

Overall, 1,028 patients received a primary THR during a total of 161,211 person-years (PYs) and median follow-up of 4.9 [IQR: 2.2, 8.7] years. This yielded an incidence rate of 6.38 [95% C.I. 6.00 to 6.78] per 1,000 PYs, with median time from diagnosis to THR being 3.2 [IQR: 1.3, 6.5] years. Similarly, there were 1,366 patients who received a primary TKR during a total of 159,384 PYs at an incidence rate of 8.57 [95% C.I. 8.12 to 9.04] per 1,000 PYs. Median follow-up in the TKR analysis was 4.9 [IQR: 2.1, 8.6] overall and median time from RA until TKR was 3.5 [IQR: 1.5, 6.7] years. The overall 10-year cumulative percentage probability for THR and TKR were 5.2% [95% C.I. 4.9, 5.6] and 7.0% [95% C.I. 6.6, 7.4], respectively (Supplementary Table 1, Figure 1). At 20 years these values were 8.4% [95% C.I. 7.3, 9.7] and 11.1% [95% C.I. 10.0, 12.4], respectively. THR and TKR incidence rates were similar after 2004 than before 2005 (Supplementary Table 1).

Incidence by sex and age

Among those receiving a THR, mean age at surgery was 68.4 years, while this was 67.6 years for the TKR cohort. While rates of THR were significantly higher in women (6.82 [95% C.I. 6.36 – 7.31] per 1,000 PYs) than in men (5.25 [95% C.I. 4.63 – 5.96] per 1,000 PYs), the rates of TKR were approximately equal between genders (Figure 2). Rates were lowest among those aged <45 years of age (2.12 [95% C.I. 1.64 – 2.74] per 1,000 PYs for THR and 3.18 [95% C.I. 2.58, 3.93] per 1,000 PYs for TKR), with rates rising significantly with increasing age up to those aged 65-74 years old (10.46 [95% C.I. 9.44 – 11.64] per 1,000 PYs for THR and 11.69 [95% C.I. 10.60 – 12.90] per 1,000 PYs for TKR) (Figure 3). However, rates then began to decline in those ≥75 years (Figure 3).

Incidence by BMI

BMI appeared to have divergent affects on rates of THR versus TKR (figure 4). THR rates remained approximately stable by BMI, however rates of TKR increased in an almost monotonic fasion with increasing BMI (p<0.001). Specifically, TKR incidence was lowest among those underweight (4.98 [95% C.I. 3.46 – 7.17] per 1,000 PYs) but was nearly three times as large among those with a BMI ≥35 (14.58 [95% C.I. 12.72 – 16.72] per 1,000 PYs) (Supplementary Table 1, Figure 4). Main findings were unchanged in sensitivity analysis where multiple imputation was not used and the 31% of patients missing BMI were included as a separate category instead (Supplementary Table 2).

Incidence by deprivation and geographic region

A significant downward trend in joint replacement rates with greater deprivation was observed for both THR and TKR, p-trend=0.001 and p-trend=0.041, respectively (Supplementary Table 1, Figure 5). Estimated rates of THR were >30% lower in those most deprived versus least deprived (5.07 [95% C.I. 4.02 – 6.40] versus 7.49 [95% C.I. 6.45 – 8.71] per 1,000 PYs) (Supplementary Table 1, Figure 5). For TKR there was an approximate 20% decrease in incidence among those most deprived versus least deprived (7.30 [95% C.I. 6.00 – 8.87] versus 9.06 [95% C.I. 7.90 – 10.39] per 1,000 PYs) (Supplementary Table 1, Figure 5). There was little evidence for regional variation of THR (p-value=0.11), with incidence being lowest in the North East (3.82 [95% C.I. 2.22 – 6.57] per 1,000 PYs) and highest on the South East Coast (7.58 [95% C.I. 6.34 – 9.07] per 1,000 PYs) (Supplementary Table 1, Figure 6). Weak evidence was found for variation of TKR (p=0.034), with incidence being lowest in the North West (6.59 [95% C.I. 5.57 – 7.79] per 1,000 PYs) and highest in the West Midlands (10.34 [95% C.I. 8.79 – 12.16]) (Supplementary Table 1, Figure 6).

Discussion

This is the first UK population-based study to use routinely collected medical records to estimate PY THR/TKR incidence rates following RA diagnosis. As such it provides a better understanding of long-term prognosis for RA patients, both overall and for specific sub-groups. It demonstrates a moderate incidence of major lower limb joint replacement, with some notable variation in rates according to patient profile, as discussed below.

Overall incidence

UK data examining the occurrence of joint replacement in RA are emerging (16-18). Although it is difficult to make direct comparisons due to differences in study design used, our overall cumulative % probabilities for THR and TKR are broadly consistent with these previous studies.

It is interesting to note the 10-year risk of THR and TKR previously reported for the UK general population using CPRD data, by Culliford and colleagues (33). Although direct comparisons should be carried out with caution given differences in study design, it is noteworthy that Culliford's 10-year risk estimates for those aged 60 years old were 3.5% (95% CI: 2.8 – 4.1) and 2.2% (95% CI: 1.7 – 2.7) for THR in females and males, respectively. This is approximately half that of the THR estimates for the RA patients here analysed. Likewise, Culliford's estimates for TKR in the general population were 3.1% (95% CI: 2.5 – 3.7) and 2.6% (95% CI: 2.0 – 3.1) for females and males, respectively, which is again substantially lower than among the present RA sample. Furthermore, these differences are

somewhat conservative given the fact the present results were based on a competing risk model whereas those for the general population were not.

Although we did not here observe significant change in hip or knee replacement rates during latter years of the study, we have previously investigated this issue in detail for a similar cohort (29), and there reported a relative 34% decline in rates of TKR but not THR associated with the introduction of TNFi therapy in 2004. These findings were subsequently replicated among RA patients in Denmark (34). The most likely reason for the lack of a similar reduction in TKR rates in the latter 10 years of the present analysis is due to not accounting for trends (i.e. an upward trend in TKR in the first 10-year period 'cancelling out' an equal but opposite downward trend in the latter 10-year period (29)). The previous study also suggested THR rates may have declined towards the end of the study (from 2009), although there was insufficient data for this to be conclusive and other factors such as potentially milder RA involvement at the hip vs. knee, improved access to joint replacement surgery and increasing rates of arthroplasty for the general population may explain the relatively stable THR rates observed (29, 34). While we have also recently observed a reduction in the rate of THR among older (≥65 years of age) patients using biologics vs. non-biologics (35), the preponderance of established and severe RA in that prior drug registry study is not immediately comparable with the more generalisable sample of the current analysis and more research is needed to confirm and/or further elucidate these findings.

Incidence by age

The increase in THR/TKR incidence according to age at RA diagnosis is something of an expected finding (16, 17, 36) given that joint destruction is progressive among patients with

insufficiently managed RA, leading to accumulated pain and loss of function. However, the incidence of osteoarthritis (37) is also a likely factor. The decline in rates seen here among patients over 75 is not surprising given the heightened risks of complications (38, 39), mortality (40, 41) and diminished benefits for elderly frail patients (42-44).

Incidence by sex

The observation of higher THR rates among females is somewhat supported by prior data indicating female patients have on average higher disease activity and achieve remission less frequently (36). Conversely, the incidence of TKR here was almost identical between the genders (8.54 versus 8.58 per 1,000 PYs), although the 10-year percentage probability of TKR was non-significantly higher among women. Although this is a subject for further research, it could be this divergence in THR but not TKR rates between male and female RA patients is due to the knee being more affected than the hip within the inflammatory processes of RA (29). Need for THR may rather be more influenced by secondary osteoarthritis (the prevalence of which is highest in females (37)).

In terms of prior data for RA patients, James *et al*. found female gender a significant risk factor in relation to intermediate joint replacement (16), although not larger joint replacement (16). Likewise, Leon *et al*. found female gender associated with subsequent orthopaedic surgery but not total joint replacement ($p \geq 0.05$), which was a similar finding to Richer *et al*. (36).

Incidence by BMI

The increase in TKR rates with increasing BMI (*p*-trend <0.001) is a pattern previously reported for osteoarthritis patients (45, 46). Increasing BMI is strongly associated with increased risk of developing incident knee osteoarthritis (47, 48), and to a lesser extent hip osteoarthritis (49). It is also very biologically plausible that greater weight bearing would exacerbate the process of inflammatory-induced cartilage and bone destruction within effected knee joints of RA patients, possibly more so than at the hip. Indeed, the increase in TKR risk with increasing BMI was not here repeated for THR risk (*p*-trend = 0.49). Other reasons for approximately stable THR rates accross BMI values may reflect that, although it is known that high BMI is not a limiting factor for clinically meaningful improvement in terms of pain or function after either TKR (42, 50) or THR (51), complications are known to be higher after THR surgery for patients with higher BMI (43, 52). Likewise, there could be a potential surgeon reluctance to operate at the hip for obese RA patients given greater challenges posed by increased adiposity, which may not be such an issue at the knee. A further tentative explanation could even be the negative impact of obesity on the effectiveness of biologic agents(53), the consequences of which may plausibly be more pertinent at the knee if the hip joint was indeed less involved in RA (29).

Incidence by deprivation

The finding of significant linear trends of decreasing THR and TKR rates according to lower IMD ranking is an interesting finding, albeit similar to previous reports for the general UK population (54). Judge *et al*. report a decline in equity (provision of THR/TKR relative to need) among the general population for those residing in areas of the UK with greater deprivation, with 70% less provision relative to need among people living in the most deprived areas compared with least deprived areas (55).

UK deprivation has previously been found to predict worse outcome of TKR (42) and that better outcomes have been observed following osteoarthritis-induced THR among those with higher socio-economic status (43). Therefore, surgeon preference to operate may be influenced by such a perceived association between deprivation and worse outcome. It has also been suggested that those from more deprived areas may tolerate greater degrees of ill health which make them less likely to demonstrate healthcare-seeking behaviour (42), although factors such as reduced knowledge of or confidence in accessing complex health systems would likely also play a role, as may many other factors. It could also be the case that despite visiting their GPs, individuals residing in more deprived areas are still less likely to receive surgery due to substandard provision (56), despite their willingness to consider arthroplasty (57). While further research is needed to disentangle these issues, given that these are univariate associations in the current study it cannot be ruled out that IMD is here acting more as a proxy for other confounding characteristics, either at the patient-level or small-area-level that may be the primary drivers of the trend. For example it is likely higher deprivation correlates with higher comorbidity, which patients may choose to resolve before elective joint surgery.

Incidence by geographic region

The differences in actual numbers of RA patients diagnosed in each geographic region (Supplementary Table 1) approximately reflects the distribution of GP practices contributing data to CPRD (24). The lack of significant variation in THR across regions is reassuring. Variation in TKR rates is concerning and possibly reflects a disparity between need and provision within the UK (55), which has been shown to be greater for knee replacement

than hip (55, 58, 59). Specifically, in the late 1990s the total deficit of hip replacement surgery in England (compared to estimated need) was 2,500 per year (59), whereas similar estimates for knee replacement showed an annual deficit that was approximately 10-fold larger (26,500) (58). The current study does not demonstrate that the regional variation in TKR rates is necessarily due to unmet need, for example it could be the product of regional variation in management of RA (60) and/or the consequence of other confounding factors. Although considering the previous data on unmet need of TKR within the UK, it would seem these regional variations for TKR are of interest and warrant further investigation in future studies.

Strengths and limitations

Key strengths of the analysis include the large study sample and long follow-up available, allowing PY rates to be estimated not only for the overall RA population but for various sub-groups. CPRD has previously been demonstrated to be broadly representative to the wider UK in terms of age, sex, ethnicity and BMI (24). Linkage to ONS mortality data meant follow-up of each patient accurately took into account when a patient died. Linkage to the HES dataset has previously been leveraged in order to validate the THR/TKR Read code lists against in-hospital secondary care data, which showed a high degree of agreement (29). While the Kaplan-Meier method has been shown to lead to overestimation in contexts of a strong competing risk of an alternative event (e.g. death), this was here addressed by generating cumulative incidence functions incorporating death as a competing risk (61).

There are a number of limitations. One is the likely delay between onset of RA symptoms and coding of the disease in a patient's record (62). Although this should not have a large

impact on the subsequent rates of THR/TKR as reported here, it does mean the estimates of time from diagnosis to event and time-specific cumulative incidence estimates should not be interpreted overly precisely. Furthermore, the lack of individual validation of each patient diagnosis of RA has not been carried out due to lack of an available gold standard. While the approach of including all patients with ≥1 code likely maximises sensitivity and facilitates the inclusion of early/mild RA, it is probable that more complex algorithms including multiple codes and DMARD prescriptions would enhance specificity. We did however exclude patients with prior or subsequent diagnoses of a different inflammatory arthritis to reduce the likelihood of coding errors. Approximately 30% of the sample were missing BMI data and approximately 20% missing a value for IMD, although missing BMI was imputed. Another important caveat to the estimates are that they are unadjusted (given the study aim of providing "real-life" burden of disease estimates), so restraint is required to avoid interpretations not strictly supported by the data given lack of confounder adjustment.

Conclusion

This analysis describes the overall incidence rates of THR (6.38 per 1,000 PYs) and TKR (8.57 per 1,000 PYs) among a large UK cohort of newly diagnosed RA patients over a maximum of 20 years. Cumualtive incidence at 10-years (5% and 7% for THR and TKR, respectively) is approximately double that previously reported in the UK general population. Rates of TKR but not THR increased according to BMI, whilst a declining trend in both outcomes occurred with increasing deprivation. These findings offer clinicians, patients and commissioners a better understanding of the long-term prognosis of RA.

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Figure Legends

FIGURE 1: CUMULATIVE INCIDENCE FUNCTION PLOTS FOR THR AND TKR OVER STUDY FOLLOW-UP

FIGURE 2: INCIDENCE RATE OF THR AND TKR: STRATIFIED BY GENDER

FIGURE 3: INCIDENCE RATES OF THR AND TKR: STATIFIED BY AGE AT DIAGNOSIS

FIGURE 4: INCIDENCE RATES OF THR AND TKR: STRATIFIED BY BMI AT DIAGNOSIS

FIGURE 5: INCIDENCE OF THR AND TKR: STRATIFIED BY INDEX OF MULTIPLE DEPRIVATION

FIGURE 6: INCIDENCE OF THR AND TKR: STRATIFIED BY GEOGRAPHIC REGION

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