Reduction in Upper Limb Joint Surgery among Rheumatoid Arthritis Patients

An Interrupted Time Series Analysis using Danish Health Care Registers

Cordtz, René; Hawley, Samuel; Prieto-Alhambra, Daniel; Højgaard, Pil; Zobbe, Kristian; Kristensen, Lars Erik; Overgaard, Søren; Odgaard, Anders; Soussi, Bolette Gylden; Dreyer, Lene

Published in:
Arthritis Care & Research

DOI (link to publication from Publisher):
10.1002/acr.23835

Publication date:
2020

Document Version
Accepted author manuscript, peer reviewed version

DR. RENÉ LINDHOLM CORDTZ (Orcid ID : 0000-0002-5271-2574)

MR. SAMUEL HAWLEY (Orcid ID : 0000-0002-7034-6168)

Article type : Original Article

RUNNING HEAD:

Introduction of Biologic DMARDs and Upper Limb Joint Replacements among Patients with Rheumatoid Arthritis

TITLE:

Reduction in Upper Limb Joint Surgery among Rheumatoid Arthritis Patients: An Interrupted Time Series Analysis using Danish Health Care Registers

AUTHORS:

1. René Cordtz, MD. Center for Rheumatology and Spine Diseases, Rigshospitalet – Gentofte, Copenhagen, Denmark and The Parker Institute, Bispebjerg and Frederiksberg Hospital, Frederiksberg, Denmark
2. Samuel Hawley, DPhil/PhD Student. Pharmaco- and Device Epidemiology, Centre for Statistics in Medicine, NDORMS, University of Oxford, Oxford, United Kingdom.
3. Daniel Prieto-Alhambra, MD, Professor. Pharmaco- and Device Epidemiology, Centre for Statistics in Medicine, NDORMS, University of Oxford, Oxford, United Kingdom and GREMPAL Research Group, Idiap Jordi Gol and CIBERFes, Universitat Autònoma de Barcelona and Instituto de Salud Carlos III, Barcelona, Spain.

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1002/acr.23835

4. Pil Højgaard, MD, PhD. Center for Rheumatology and Spine Diseases, Rigshospitalet – Gentofte, Copenhagen, Denmark and The Parker Institute, Bispebjerg and Frederiksberg Hospital, Frederiksberg, Denmark.
5. Kristian Zobbe, MD. Center for Rheumatology and Spine Diseases, Rigshospitalet – Gentofte, Copenhagen, Denmark and The Parker Institute, Bispebjerg and Frederiksberg Hospital, Frederiksberg, Denmark.
6. Lars Erik Kristensen, MD, Ass. Clinical Professor. The Parker Institute, Bispebjerg and Frederiksberg Hospital, Frederiksberg, Denmark
7. Søren Overgaard, MD, DMSc, Professor. Department of Orthopaedic Surgery and Traumatology, Odense University Hospital, Odense, Denmark and Department of Clinical Research, University of Southern Denmark, Odense, Denmark.
8. Anders Odgaard, MD, DMSc, Ass. Professor. Department of Orthopaedic Surgery, Copenhagen University Hospital, Herlev-Gentofte, Copenhagen, Denmark.
9. Bolette Gylden Soussi, MD, Department of Rheumatology, Aalborg University Hospital, Aalborg, Denmark
10. Lene Dreyer, MD, Professor. Departments of Clinical Medicine and Rheumatology, Aalborg University and Aalborg University Hospital, Aalborg, Denmark; Center for Rheumatology and Spine Diseases, Rigshospitalet – Gentofte, Copenhagen, Denmark and The Parker Institute, Bispebjerg and Frederiksberg Hospital, Frederiksberg, Denmark

FUNDING:

The study was funded by The Danish Rheumatism Association, The Bjarne Jensen Foundation, The Oak Foundation and The Danish Council for Independent Research. This work has been supported by the NIHR Biomedical Research Centre, Oxford. DPA is funded by a National Institute for Health Research Clinician Scientist award (CS-2013-13-012).

ROLE OF FUNDING SOURCE:

The Danish Rheumatism Association, The Bjarne Jensen Foundation, The Oak Foundation and The Danish Council for Independent Research had no influence on or access to the design, analysis or interpretation of the study. This paper presents independent research funded by the National Institute for Health Research (NIHR). The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health.

COMPETING INTERESTS:

RC, SH, PH, KZ, SO, AO and BGS have no competing interests. DPA's research group has received research grants from Servier, UCB, and Amgen; and consultancy fees from UCB outside the present work. LEK has received fees for speaking and/or consultancy from Pfizer, AbbVie, Amgen, UCB, Celgene, BMS, Biogen, Sanofi, MSD, Novartis, Eli Lilly, Janssen Pharmaceuticals. LD has received speaking fees from MSD, Eli Lilly and UCB outside the present work.

CORRESPONDING AUTHOR:

René Cordtz, MD
Center for Rheumatology and Spine Diseases,
Rigshospitalet – Gentofte, Entrance 5, 3rd floor
Kildegaardsvej 28, 2900-Hellerup
Copenhagen, Denmark.
e-mail: rene.lindholm.cordtz.03@regionh.dk. Telephone: +45 22 15 13 14

ABSTRACT

Objectives: Joint replacement surgery is a proxy of severe joint damage in rheumatoid arthritis (RA). The aim of this study was to assess the impact of the introduction of biological DMARDs (bDMARDs) on the incidence rate (IR) of upper limb joint replacements among newly diagnosed RA patients.

Methods: Using the Danish National Patient Register, incident RA patients from 1996-2012 were identified. Each patient was matched on age, sex and municipality with up to 10 general population controls. Age and sex standardised 5-year IR per 1000 person-years (PY) of a composite outcome of any first joint replacement of the finger, wrist, elbow, or shoulder was calculated; and an interrupted time series analysis was undertaken to investigate trends and changes of the IR in the pre-bDMARD (1996-2001) and the bDMARD era (2003-2012) with a 1-year lag period in 2002.

Results: In total, 18 654 incident patients with RA were identified (mean age 57.6 years, 70.5 % women). The IR of joint replacements among RA patients was stable at 2.46/1000 PY (95%CI 1.96-2.96) from 1996 to 2001 but started to decrease from 2003 onwards (-0.08/1000 PY annually, 95%CI -0.20 to +0.02). Compared with RA, the IR among controls in 1996 was 1/17 and it increased continuously throughout the study period.

Conclusion: The IR of upper limb joint replacements started to decrease among RA patients from 2002 onwards, whereas it increased among controls. Our results suggest an association between the introduction of bDMARDs and a lower need of joint replacements among RA patients.

SIGNIFICANCE AND INNOVATIONS

- The incidence of joint replacements in the shoulder, elbow, wrist and fingers among newly diagnosed patients with rheumatoid arthritis was fairly stable prior to the introduction of biological DMARDs, but nonetheless ~17 times higher than in the general population.
- Following introduction of biological DMARDs, the incidence rate of upper limb joint replacement surgery started to decrease among patients with rheumatoid arthritis, whereas it increased in the non-rheumatoid background population.
- However, the overall need of upper limb joint replacements in the first 5 years following diagnosis of rheumatoid arthritis was low in this Danish cohort.

In patients with rheumatoid arthritis (RA), joint replacement surgery is considered a proxy for end-stage or severe joint damage (1). Joint damage occurs with persisting and longstanding inflammation but even short periods of severe inflammation can also result in significant joint damage (2). Moderate or high disease activity in the first five years after diagnosis are risk factors for joint surgery (3). Up to 10 % of RA patients require surgery of the upper limbs within the first five years after disease onset (1); and following RA diagnosis, upper limb surgery is generally performed sooner than lower limb surgery (4,5).

The introduction of biological DMARDs (bDMARDs) in the late 1990s and early 2000s has expanded the treatment repertoire and increased the chances of more favorable clinical and radiographic outcomes for RA patients (6–8). Whether the improved clinical outcomes observed with bDMARDs have resulted in lower rates of upper limb joint surgery is less clear (9,10). There are studies reporting decreases in upper limb joint replacements among patients with RA during recent decades, but in most studies, these changes started in the mid-1990s before bDMARDs were

available (10–16). Other studies suggest that no changes have occurred for rates of joint replacements among RA patients during recent decades (13,17,18).

Thus, we thought it of interest to explore if there was an association between the introduction of bDMARDs in the treatment of patients with RA and the incidence rate of shoulder, elbow, wrist, and finger joint replacement surgery among incident RA patients compared to a cohort of general population controls (controls). To investigate this, we used Danish healthcare register data in an interrupted time series design. As a secondary aim, we investigated the impact of bDMARD introduction on non-joint replacement surgeries in the shoulder and elbow, and the wrist and fingers.

PATIENTS AND METHODS

Study design

This is a nationwide interrupted time-series analysis from Denmark (19,20), investigating if there was an association between the introduction of bDMARDs for the treatment of RA in 2002 and the 5-year incidence rate of upper limb joint replacement and upper limb non-replacement joint surgery. The interrupted time series is an ecological study method to investigate population-level time trends following a specific intervention at a specific point in the time series. Study methods and results are reported in accordance with Strengthening the Reporting of Observational Studies in Epidemiology guidelines (21).

Setting

In Denmark, the healthcare system is tax-financed and offers free access for all residents to hospitals and essential operations. Every resident receives a 10-digit personal identification number at birth or date of immigration. This personal identifier is consistent throughout all national registers making register linkage possible. The study period was January 1st 1996 to 31st December 2017.

Data sources

The Civil Registration System (CRS)**:** The CRS captures all births, migrations and deaths among Danish residents (22).

The Danish National Patient Register (DNPR): contains information on all inpatient (since 1977) and outpatient (since 1995) contacts at private and public hospitals in Denmark (23,24). Discharge diagnoses are registered in accordance with the International Classification of Diseases (ICD) 10th Edition (since 1994). Surgical interventions have been registered and coded in accordance with the Nordic Medico-Statistical Committee (NOMESCO) Classification since 1996. When patients are discharged, information is provided on 1 main diagnosis and up to 19 additional secondary diagnoses along with surgeries if any are performed during the hospital stay. We used DNPR to identify all RA patients, all joint surgeries, and to obtain information on pre-existing comorbidities for descriptive purposes solely (See Supplementary Table 1 for ICD-10 and NOMESCO codes used).

DANBIO: is a nationwide register in Denmark established in 2000 to monitor the use and efficacy of bDMARDs (25). Each year the DANBIO steering committee publishes online reports (26). We used data from these annual reports to establish the time of the interruption (intervention) in the present study.

Study population

RA patients. In DNPR, all patients with a diagnosis of RA between 1996 and 2012 were identified (ICD-10: M05.1, M05.3, M05.8, M05.9, M06.0, M06.8, and M.06.0). Some degree of misclassification is expected when using healthcare registers in epidemiologic studies. To minimise this risk, we restricted our case definition of RA in the primary analysis to patients having RA listed as their main diagnosis at two hospital contacts within 90 days, and each of these had to originate from a department specialised in rheumatology or general internal medicine (27).

General population comparator. Each RA patient identified in DNPR was matched with up to 10 non-RA individuals from the general population of Denmark. Matching criteria were sex, year of birth and municipality at time of diagnosis. Matching was carried out only once and with no replacement following patient exclusions (see exclusion criteria below). In this paper, the date from which patients and controls were followed up, i.e. date of second RA diagnosis and corresponding matching date for controls, is termed 'index date'.

Exclusion criteria. Prevalent RA patients with a first diagnosis of RA recorded prior to January 1st 1996 were excluded, as were individuals aged <18 years at the index date. Furthermore, patients and controls who had received upper limb joint replacement prior to their index date were excluded for the primary analysis. Accordingly, patients who had a secondary outcome of interest prior to the index date were excluded in the respective secondary analyses.

Outcomes

Primary outcome. The primary composite outcome was any first joint replacement of the shoulder, elbow, wrist or fingers within 5 years of the index date. NOMESCO codes were used for identification of the procedures in DNPR (See Supplementary Table 1 for specific codes). If an individual had multiple surgeries within the 5 years of maximum allowed follow-up, only the first joint replacement counted in the analysis.

Secondary outcomes. We had 2 secondary outcomes of interest: 1) any first joint or soft tissue surgery in the shoulder or elbow excluding joint replacements and 2) any first joint or soft tissue surgery in the wrist or fingers excluding joint replacements. See Supplementary Table 1 for specific procedures and NOMESCO codes.

Follow-up

In our primary analysis, follow-up started at the index date and ended at the date of first joint replacement surgery, death, emigration, or at no later than 5 years of follow-up, whichever occurred first. In secondary analyses, follow-up started at the index date and ended at whichever occurred first of non-joint replacement surgery of interest, death, emigration, or at 5 years of follow-up at the latest. To ensure equal follow-up time regardless if patients were diagnosed at the start or end of the study period, we exclusively looked at the first 5 years after the diagnosis for all patients and controls; thus, patients diagnosed later than December 31st 2012 and hence not able to contribute a full 5 years of follow-up were not included in the present study.

Intervention

The intervention in our interrupted time series analysis was the introduction of bDMARDs for the treatment of RA patients in Denmark. Although infliximab was available in 1999, there were three reasons why 2002 was the appropriate choice as intervention time point: First, data from DANBIO showed that it was not until 2002 that the use of TNFi dramatically increased (26). Second, in 2002, three different TNFis were available (adalimumab, etanercept and infliximab), and each of them were increasingly being used (26). Lastly, the now defunct Danish Institute for Rational Pharmacotherapy published their first national treatment guideline for TNFi therapy in rheumatoid arthritis in 2002. Changes in prescription patterns and guideline implementation were likely "phased in" rather than instantaneously changed, and thus to account for this in our time series analysis, we applied a one-year lag period starting January 1st 2002 and ending December 31st 2002.

Statistical analyses

Descriptive data of the study populations are presented in means and standard deviations (SD) and absolute numbers and percentages, as appropriate.

Within each 6-month period from 1996 to 2012, we calculated the 5-year age-and sex standardised incidence rates (IR) of upper limb joint replacement surgery among incident RA patients and controls. Thus, the time series consisted of 32 data points when excluding the 1-year lag period in 2002. The interrupted time series analysis was then carried out with two time segments: the pre-bDMARD era (1996-2001) and the bDMARD era (2003-2012) interrupted by the lag-period in 2002. Using segmented linear regression, we estimated the baseline IR in 1996 (IR /1000 person years), the trend in IR from 1996 to end of 2001 (Δ IR per 1000 person years per 6-month period), the immediate change in the level of the IR in 2003 (Δ IR per 1000 person years) and the changes in trend (Δ IR per 1000 person years per 6-month period) from 2003 to 2012 in the bDMARD era. Using a backward-stepwise procedure, the most parsimonious models was specified (p-entry <0.05; p-exit ≥0.20). This model selection strategy is commonly used in interrupted time series studies. (19,28,29). Results are presented as the 1996 baseline IR (intercept of the model); the pre-bDMARD era trend per year (slope coefficient x 2); level change in IR at start of bDMARD era (difference between level in IR at the end of 2001 and start of 2003); and trend in bDMARD era (slope regression coefficient in pre-bDMARD era x 2 plus slope regression coefficient in bDMARD era x 2). All model parameters are presented with 95% confidence intervals (95% CI).

Statistical analyses were carried out using Stata (v13.1, StataCorp LP, Texas, US) and R 3.1.4 (R Foundation for Statistical Computing, Vienna, Austria).

Sensitivity analyses and model testing

For sensitivity we used another and less strict case definition inspired by Eriksson et al. (30). This included patients with RA listed as a main or contributory diagnosis at two hospital contacts within 1 year in DNPR. This case definition had no requirements with regards to the specialisation of the departments at each contact. All interrupted time series models were tested for first order auto-correlation using Durbin-Watson tests (20).

Ethics

According to Danish legislation, the registration and publication of data from clinical registers and databases do not require patient consent or approval by Ethics Committees. Approval was given by the Danish Data Protection Agency (GEH-2014-043, I-Suite: 03166).

RESULTS

We identified 18 654 adult RA patients diagnosed between Jan 1st 1996 and Dec 31st 2012 and with no prior upper limb joint replacements (see Table 1 and Supplemental Figure 1 for population flow chart).

Primary outcome

Overall, 193 of 18 654 patients with RA (1.0 %) had upper limb joint replacements within the first 5 years from the index date; with a total of 89 196 person years of follow-up, this resulted in a crude IR of 2.16 per 1000 person years (95% CI 1.87 to 2.49) for the entire period of 1996-2012.
In the interrupted time series analysis, the 1996 baseline IR was 2.46 (95% CI 1.96 to 2.96) per 1000 person years and remained so until 2001 (Table 2 and Figure 1). From 2003, the IR started to decrease by 3 % annually.

Among controls, the IR was much lower at 0.14 (95% CI 0.07 to 0.21) per 1000 person years in 1996. Conversely to that observed for RA patients, these rates increased annually by 7 % from 1996 to 2002 and a level increase of +0.17 (95% CI 0.03 to 0.31) following the lag period in 2002 (see Table 2 and Figure 1). At an IR of 0.37 in the beginning of 2003, the rate subsequently increased annually from 2003 to 2012 by the same magnitude as in the pre-bDMARD era.

The incidence rate ratio comparing RA and controls using regression-based values decreased from 17.6 in 1996, to 12.9 in 2001 (end of pre-bDMARD era), to 6.8 in 2003 (beginning of bDMARD era) and 3.5 in 2012 (end of the study period).

Secondary outcomes.

Shoulder and elbow surgery. The IR of shoulder and elbow surgery was stable at 2.76 (95% CI 2.32 to 3.20) per 1000 person years among RA patients in the pre-bDMARD era from 1996 to 2001 (see Table 3 and Figure 2). From 2003, the IR started to decrease with 1 % annually. Among matched controls, the baseline IR was 1/12 of that in the RA cohort (0.23, 95% CI 0.12 to 0.33 per 1000 person years) but with an annual increase of 0.01 (95% CI -0.01 to +0.03) from 1996 to 2017. There was a level increase of 134 % from the end of 2001 to 2003 following the lag-period.

Finger and wrist surgery. In the regression models, the 5-year IR of finger and wrist surgeries in 1996 was 7.98 (95% CI 6.99 to 8.97) with an annual decrease of 2 % from 1996 to 2001 (see Table 3 and Figure 3). In 2003, at the start of the bDMARD era, there was a decrease of 32 % followed by an annual decrease in IR with the same magnitude as in the pre-bDMARD era. Among controls, the IR was 0.90 (95% CI 0.82 to 0.98) surgeries per 1000 person years from 1996 to 2017 with no observed changes throughout the interrupted time series.

Sensitivity analyses. Using the more liberal case definition, 32 584 patients with RA were identified. Applying this case definition resulted in a slightly older cohort (mean 59.0 vs 57.6 years) but with the same proportion of females (70.4 vs 70.5 %) (see Suppl. Table 2). Overall, 372 of 32 584 patients (1.1 %) with RA had a first primary upper limb joint replacement during follow-up. The regression model differed from the main analysis in that there was a level increase in 2003 in the RA cohort, but the rate of decline during 2003 to 2012 was the same as in the main analysis (See Suppl. Table 3 and Suppl. Figure 2). Overall, the results for the secondary outcomes using the liberal case definition were no different than when using the more strict definition (see Suppl. Table 4 and Suppl. Figure 3 and 4).

DISCUSSION

In a nationwide study, we investigated if there was an association between the introduction of bDMARDs for treatment of patients with RA and the 5-year IR of upper limb joint replacements among newly diagnosed RA patients in an interrupted time series design. Our main finding was that following a constant IR of upper limb joint replacements in the pre-bDMARD era from 1996 to 2001, the IR started to decrease after bDMARDs were introduced from 2003 to the end of the study period in 2012. Among controls from the general population, the IR was 1/17 of that in the RA cohort in 1996, but contrasting with the trend among RA patients, the rate increased among controls throughout the whole study period.

Our study contributes to a slowly growing body of evidence, that among patients with RA the need for upper limb joint replacements and joint surgery in general is decreasing. But, what it further adds, is that in Denmark, this decrease mainly started after the bDMARDs became a viable treatment option in 2002. In this study, we were able to demonstrate the use of surgery and changes there in following this major addition to the treatment repertoire in RA. Furthermore, the gradually increasing use of joint replacement in the general population from 2003 and onwards is supported by data from the Danish Shoulder Arthroplasty Register (31,32). We looked at the main diagnoses of the controls who had upper limb joint replacement in DNPR and found that primary and secondary osteoarthritis along with fracture sequelae were more often the indication for surgery from 2002 and onwards.

In the RA population, treatment with conventional synthetic DMARDs and the introduction of the treat-to-target strategy in RA is likely to have contributed as well to the decreased need for joint surgery (33). Accordingly, some studies have shown that rates of joint surgery had already started to decrease before the introduction of bDMARDs. In a study investigating the temporal development in joint surgery in two inception cohorts from UK covering the period from 1986 to 2011, Nikiphorou et al. showed that rates of wrist, hand, and hindfoot/forefoot joint reconstructive procedures started

to decrease before 2000 (13). In addition, Nystad et al. found that in Norway, the incidence of finger joint replacements among RA patients decreased significantly from 1994 to 2012, as did the rates of shoulder and elbow replacements as well as non-joint replacement surgery of these joints although this was not statistically significant (10). In all these prior studies, these decreasing trends started before the millennium.

However, there are also studies with findings that compares well with those presented in the current study: A study from Finland showed a 60 % reduction in shoulder and elbow replacements from 1995 to 2010. The rates of elbow replacements in that study showed a pattern similar to those presented here despite the use of a different denominator population. It would have been interesting to apply the interrupted time series method to the data from Finland, as the biggest reduction in IR occurred post 2003. Likewise, Jenkins et al. showed the same decreasing pattern starting in the early 00s for total elbow replacements performed due to RA using data from the Scottish Arthroplasty Project (34). Also in accordance with our results, Louie and Ward showed in a serial cross-sectional time trend study, that among RA patients aged ≥40 years living in California, rates of total wrist arthroplasty and arthrodesis had started to decrease in the early 1990s, but there was a significant and steep decrease from 2003-2007 (16). Young et al. have recently reported the time trends in joint replacement surgery from the US Nationwide Inpatient Sample, and they too reported a relative decrease in prevalence of RA patients among recipients of total elbow and total shoulder replacements from 2002 to 2012 as did Triplet et al. (35,36). However, in the study by Young et al., although the proportion of patients with RA among shoulder replacement recipients decreased, the absolute numbers of RA patients undergoing shoulder surgery looked as if they increased (35). In a study from Japan, Momohara et al. reported an increase in finger arthroplasty surgery, whereas the number of elbow and wrist joint replacements remained constant from 1998 to 2008 (18).

The overall pattern in the existing literature seems to be a decrease in use of joint surgery among RA patients since the 1990s, but with a few studies where the incidence has not changed. A possible explanation as to the different results could be that many studies include prevalent cohorts of RA. As suggested by Momohara et al. and others (18), it is possible that patients with RA have become more fit for surgery in recent decades, but an increased use of surgery in RA populations due to this phenomenon would mostly affect prevalent RA patients. As we only included newly diagnosed patients with RA, the "fit-for-surgery" theory does not seem the most likely explanation for the present findings.

Our study has some limitations that need be mentioned. The interrupted time series analysis is an ecological method, and our results does not allow for commenting on causality. There is an alternative or contributory explanation for the decreasing rates of surgery among patients with RA: the more intensive treat-to-target strategy with increased use of csDMARD combination therapy although this strategy was not specifically introduced in 2002, it is likely that this has contributed to our results (33,37,38). To investigate the true impact of bDMARDs on the need for joint surgery, studies using individual-level based information on DMARD treatment are needed. Another limitation is the inherent risk of misclassification of RA patients when using health care register-based data, but by using two different case definitions we tried to account for this. A recent Danish study found that using the case definition in our primary analysis resulted in a positive predictive value of ~80 % (27). Applying the 1-year lag period to the analysis of the time series in general population controls can result in models with no biological or meaningful interpretation, given that the introduction of bDMARDs would have no effect on this non-treated population. For instance, we have no biological, political or practical meaningful explanation for the big level increase observed in shoulder and elbow surgery among controls in 2003, other than that merely being the result of applying the same flexible regression modelling as in the RA population.

All patients and controls were only followed up for the first 5 years following diagnosis, allowing us to only capture joint replacements performed within the first years after disease onset. Although this could underestimate the true long-term impact of bDMARDs on our outcomes, it allowed for all patients and controls to have an equal amount of follow-up time regardless if entering the study in the pre-bDMARD or the bDMARD era and therefore made comparisons across the time-series more valid. It's worth noting that other studies have shown that a non-negligible number of RA patients require joint replacement surgery within 5 years of diagnosis and upper limb surgery is reported to be the first type of surgery in at least two studies (3–5). Another limitation is the possibility that the new diagnostic criteria for RA introduced in 2010, with emphasis on earlier diagnosis, could have affected the 5-year IR of surgery in the last two years of the study period. Furthermore, it is also possible that rheumatologists have changed their threshold for referral to orthopaedic surgery.

The strengths of the current study include the nationwide population-based design ensuring complete follow-up in a large population of RA patients as well as matched controls in a universal, tax-funded health care system. Our ability, to compare the observed trends in patients with RA to the secular trends among matched non-RA individuals is another strength. We also believe the interrupted time series method to be a strength of this study: When analysing time series data where interventions occur in the midst of the time series, it is beneficial to know the trend pre and post a given intervention; and to not only calculate the mean change over the entire period or to only calculate incidence rate ratios where information on trends within each calendar period is lost.

In conclusion, we found that the five-year IR of upper limb joint replacements among newly diagnosed RA patients started to decrease following the introduction of bDMARDs. However, given the ecological design of the study, it is a possibility that other factors contributed to this finding. In 1996, the IR of upper limb joint replacements was 17-fold higher among RA patients compared to non-RA individuals. In 2012, it was only 3.5 times

higher. In context, our study supports previous reports of improved outcomes in newly diagnosed RA patients.

ACKNOWLEDGEMENTS

We would like to thank Ass. Professor, consultant orthopaedic surgeon Niels H. Søe for his valuable inputs on relevant surgical procedures in the wrist, hand and finger procedures in relation to rheumatoid arthritis.

REFERENCES

1. James D, Young A, Kulinskaya E, Knight E, Thompson W, Ollier W, et al. Orthopaedic intervention in early rheumatoid arthritis. Occurrence and predictive factors in an inception cohort of 1064 patients followed for 5 years. *Rheumatology (Oxford)* 2004;43:369–76.

2. Schett G, Gravallese E. Bone erosion in rheumatoid arthritis: mechanisms, diagnosis and treatment. *Nat Rev Rheumatol* 2012;8:656–64.

3. Nikiphorou E, Norton S, Young A, Carpenter L, Dixey J, Walsh DA, et al. Association between rheumatoid arthritis disease activity, progression of functional limitation and long-term risk of orthopaedic surgery: combined analysis of two prospective cohorts supports EULAR treat to target DAS thresholds. *Ann Rheum Dis* 2016:annrheumdis-2015-208669.

4. Waljee J, Zhong L, Baser O, Yuce H, Fox DA, Chung KC. The Incidence of Upper and Lower Extremity Surgery for Rheumatoid Arthritis Among Medicare Beneficiaries. *J Bone Jt Surg* 2015:403–410.

5. Osnes-Ringen H, Kvien TK, Henriksen JE, Dagfinrud H. Patients with inflammatory arthropathies undergo feet surgery later in the disease course than hand surgery. *Clin Exp Rheumatol* 28:702–7.

6. Nam JL, Takase-Minegishi K, Ramiro S, Chatzidionysiou K, Smolen JS, Heijde D van der, et al. Efficacy of biological disease-modifying antirheumatic drugs: a systematic literature review informing the 2016 update of the EULAR recommendations for the management of rheumatoid arthritis. *Ann Rheum Dis* 2017:annrheumdis-2016-210713.

7. Verstappen SMM, Jacobs JWG, Veen MJ van der, Heurkens AHM, Schenk Y, Borg EJ ter, et al. Intensive treatment with methotrexate in early rheumatoid arthritis: aiming for remission. Computer Assisted Management in Early Rheumatoid Arthritis (CAMERA, an open-label strategy trial). *Ann Rheum Dis* 2007;66:1443–1449.

8. Grigor C, Capell H, Stirling A, McMahon AD, Lock P, Vallance R, et al. Effect of a treatment strategy of tight control for rheumatoid arthritis (the TICORA study): a single-blind randomised controlled trial. *Lancet (London, England)* 2004;364:263–9.

9. Aaltonen KJ, Virkki LM, Jämsen E, Sokka T, Konttinen YT, Peltomaa R, et al. Do biologic drugs affect the need for and outcome of joint replacements in patients with rheumatoid arthritis? A register-based study. *Semin Arthritis Rheum* 2013;43:55–62.

10. Nystad T, Fenstad A, Furnes O, Havelin L, Skredderstuen A, Fevang B-T. Reduction in orthopaedic surgery in patients with rheumatoid arthritis: a Norwegian register-based study. *Scand J Rheumatol* 2016;45:1–7.

11. Weiss RJ, Ehlin a., Montgomery SM, Wick MC, Stark a., Wretenberg P. Decrease of RA-related orthopaedic surgery of the upper limbs between 1998 and 2004: Data from 54579 Swedish RA inpatients. *Rheumatology* 2008;47:491–494.

12. Jämsen E, Virta LJ, Hakala M, Kauppi MJ, Malmivaara A, Lehto MUK. The decline in joint replacement surgery in rheumatoid arthritis is associated with a concomitant increase in the intensity of anti-rheumatic therapy. *Acta Orthop* 2013;84:331–337.

13. Nikiphorou E, Carpenter L, Morris S, Macgregor AJ, Dixey J, Kiely P, 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 (Hoboken, NJ)* 2014;66:1081–9.

14. Gottenberg J-E, Brocq O, Perdriger A, Lassoued S, Berthelot J-M, Wendling D, et al. Non–TNF-Targeted Biologic vs a Second Anti-TNF Drug to Treat Rheumatoid Arthritis in Patients With Insufficient Response to a First Anti-TNF Drug. *Jama* 2016;316:1172.

15. Gay DM, Lyman S, Do H, Hotchkiss RN, Marx RG, Daluiski a. Indications and reoperation rates for total elbow arthroplasty: an analysis of trends in New York State. *J Bone Jt Surg Am* 2012;94:110–117.

16. Louie GH, Ward MM. Changes in the rates of joint surgery among patients with rheumatoid arthritis in California, 1983-2007. *Ann Rheum Dis* 2010;69:868–71.

17. Mertelsmann-Voss C, Lyman S, Pan TJ, Goodman SM, Figgie MP, Mandl LA. US Trends in Rates of Arthroplasty for Inflammatory Arthritis Including Rheumatoid Arthritis, Juvenile Idiopathic Arthritis, and Spondyloarthritis. *Arthritis Rheumatol* 2014;66:1432–1439.

18. Momohara S, Tanaka S, Nakamura H, Mibe J, Iwamoto T, Ikari K, et al. Recent trends in orthopedic surgery performed in Japan for rheumatoid arthritis. *Mod Rheumatol* 2011;21:337–42.

19. Kontopantelis E, Doran T, Springate DA, Buchan I, Reeves D. Regression based quasi-experimental approach when randomisation is not an option: interrupted time series analysis. *BMJ* 2015;350:h2750.

20. Wagner AK, S.B.Soumerai, Zhang F, Ross-Degnan D. Segmented regression analysis of

interrupted time series studies in medication use research. *J Clin Pharm Ther* 2002;27:299–309.

21. Elm E Von, Altman DG, Egger M, Pocock SJ, Peter C, Gøtzsche P, et al. Strengthening the reporting of observational studies in epidemiology (STROBE) statement: guidelines for reporting observational studies. *Br Med J* 2007;335:19–22.

22. Schmidt M, Pedersen L, Sørensen HT. The Danish Civil Registration System as a tool in epidemiology. *Eur J Epidemiol* 2014;29:541–549.

23. Lynge E, Sandegaard JL, Rebolj M. The Danish National Patient Register. *Scand J Public Health* 2011;39:30–3.

24. Schmidt M, Schmidt SAJ, Sandegaard JL, Ehrenstein V, Pedersen L, Sørensen HT. The Danish National Patient Registry: a review of content, data quality, and research potential. *Clin Epidemiol* 2015;7:449.

25. Ibfelt EH, Jensen DV, Lund Hetland M. The Danish nationwide clinical register for patients with rheumatoid arthritis : DANBIO. *Clin Epidemiol* 2016;8:737–742.

26. The DANBIO Steering Committee. Annual Reports from DANBIO. Available at: https://danbio-online.dk/formidling.

27. Ibfelt EH, Sørensen J, Jensen D V., Dreyer L, Schiøttz-Christensen B, Thygesen PH, et al. Validity and completeness of rheumatoid arthritis diagnoses in the nationwide DANBIO clinical register and the Danish National Patient Registry. *Clin Epidemiol* 2017;Volume 9:627–632.

28. Lu CY, Zhang F, Lakoma MD, Madden JM, Rusinak D, Penfold RB, et al. Changes in antidepressant use by young people and suicidal behavior after FDA warnings and media coverage: quasi-experimental study. *BMJ* 2014;348:g3596.

29. Serumaga B, Ross-Degnan D, Avery AJ, Elliott RA, Majumdar SR, Zhang F, et al. Effect of pay for performance on the management and outcomes of hypertension in the United Kingdom: interrupted time series study. *BMJ* 2011;342:d108–d108.

30. Eriksson JK, Neovius M, Ernestam S, Lindblad S, Simard JF, Askling J. Incidence of rheumatoid arthritis in Sweden: A Nationwide population-based assessment of incidence, its determinants, and treatment penetration. *Arthritis Care Res* 2013;65:870–878.

31. Danish Shoulder Artrhoplasty Register. *Annual Report 2017.*; 2017.

32. Lübbeke A, Rees JL, Barea C, Combescure C, Carr AJ, Silman AJ. International variation in shoulder arthroplasty: Incidence, indication, type of procedure, and outcomes evaluation in 9 countries. *Acta Orthop* 2017;88:592–599.

33. Moura CS, Abrahamowicz M, Beauchamp M-E, Lacaille D, Wang Y, Boire G, et al. Early medication use in new-onset rheumatoid arthritis may delay joint replacement: results of a large population-based study. *Arthritis Res Ther* 2015;17:197.

34. Jenkins PJ, Watts AC, Norwood T, Duckworth AD, Rymaszewski LA, McEachan JE. Total elbow replacement: Outcome of 1,146 arthroplasties from the Scottish Arthroplasty Project. *Acta Orthop* 2013;84:119–123.

35. Young BL, Watson SL, Perez JL, McGwin G, Singh JA, Ponce BA. Trends in Joint Replacement Surgery in Patients with Rheumatoid Arthritis. *J Rheumatol* 2018;45:158–164.

36. Triplet JJ, Kurowicki J, Momoh E, Law TY, Niedzielak T, Levy JC. Trends in total elbow arthroplasty in the Medicare population: a nationwide study of records from 2005 to 2012. *J Shoulder Elb Surg* 2016;25:1848–1853.

37. Graudal N, Hubeck-Graudal T, Faurschou M, Baslund B, Jurgens G. Combination Therapy With and Without Tumor Necrosis Factor Inhibitors in Rheumatoid Arthritis: A Meta-Analysis of Randomized Trials. *Arthritis Care Res (Hoboken)* 2015;67:1487–1495.

38. Graudal N, Jürgens G. Similar effects of disease-modifying antirheumatic drugs, glucocorticoids, and biologic agents on radiographic progression in rheumatoid arthritis: meta-analysis of 70 randomized placebo-controlled or drug-controlled studies, including 112 comparisons. *Arthritis Rheum* 2010;62:2852–63.

Figures:

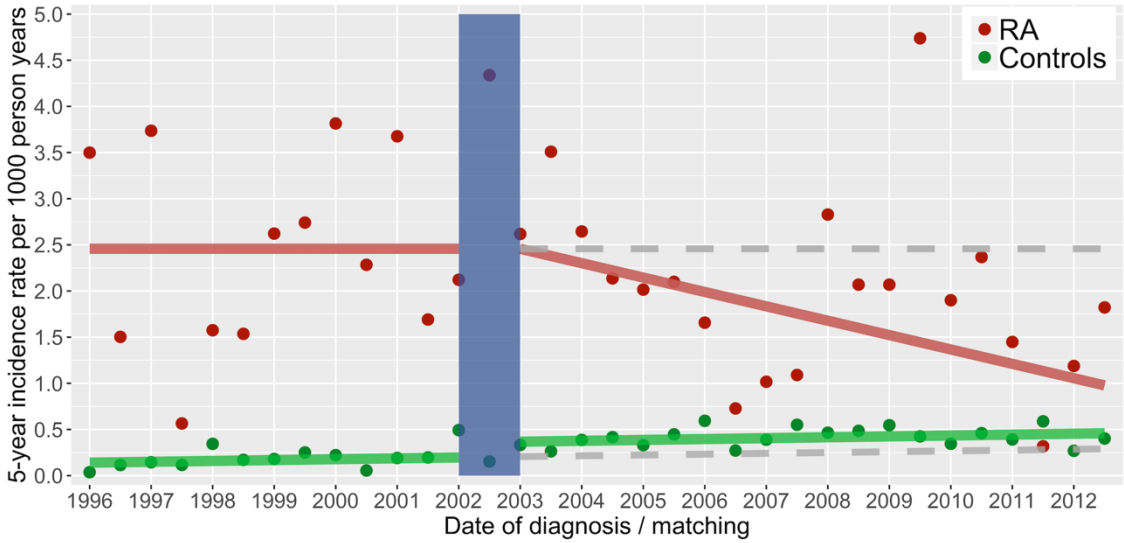

Figure 1. Results of interrupted time series regression analysis investigating the association between introduction of bDMARDs and the 5-year incidence rate (per 1000 person years) of any first upper limb joint replacement among newly diagnosed rheumatoid arthritis patients and matched controls from the general population. Dotted lines represent estimated counterfactual scenarios had there been no change after 2002.

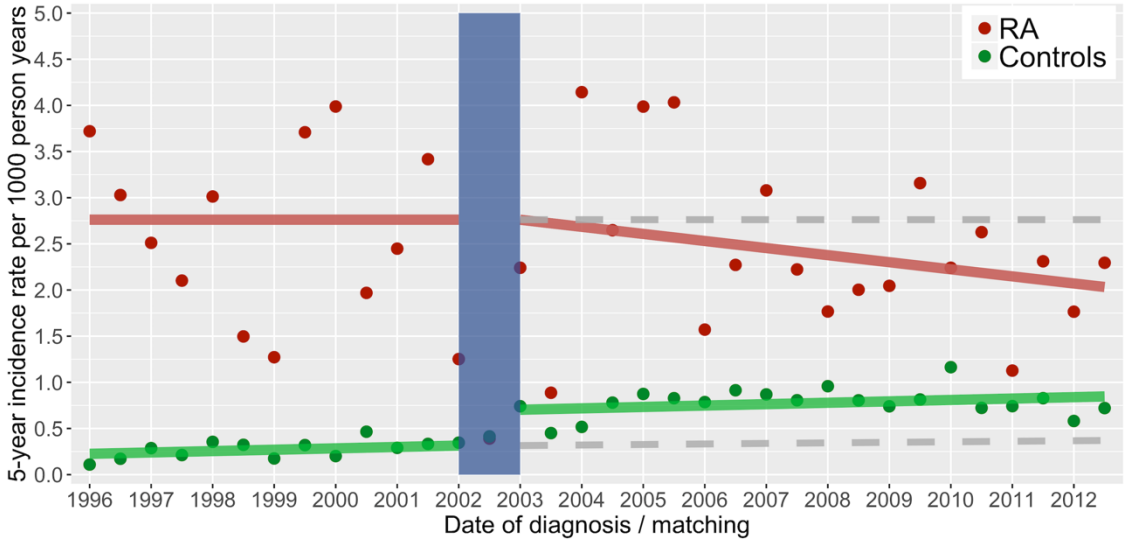

Figure 2. Results of interrupted time series analysis investigating the association between introduction of bDMARDs and the 5-year incidence rate (per 1000 person years) of any first shoulder or elbow surgery (excluding joint replacement) among newly diagnosed rheumatoid arthritis patients and matched controls from the general population. Dotted lines represent counterfactual scenarios had there been no change after 2002.

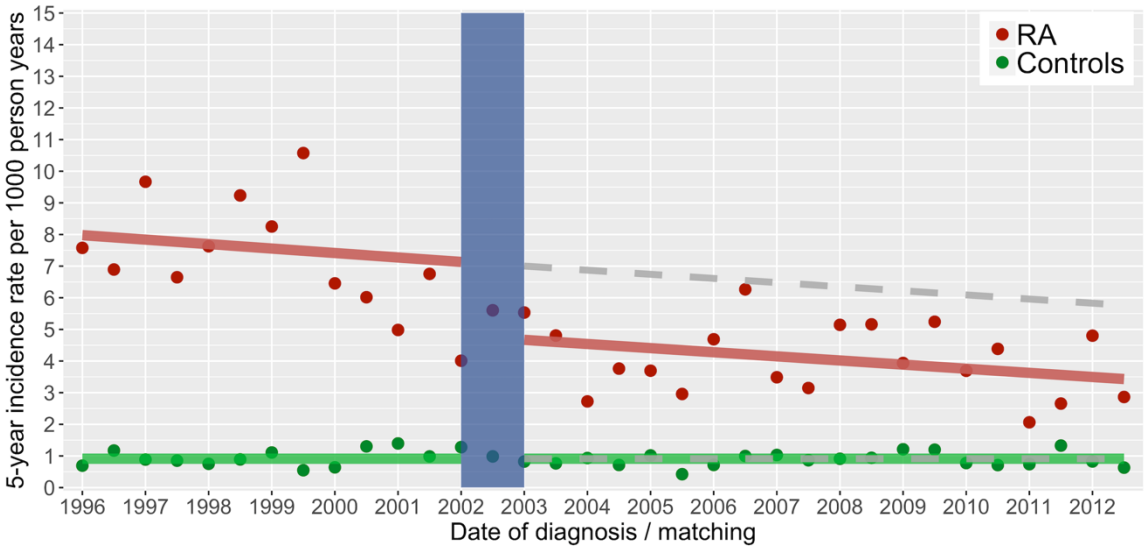

Figure 3. Results of interrupted time series analysis investigating the association between introduction of bDMARDs and the 5-year incidence rate (per 1000 person years) of any first finger or wrist surgery (excluding joint replacement) among newly diagnosed rheumatoid arthritis patients and matched controls from the general population. Dotted lines represent counterfactual scenarios had there been no change after 2002.

Tables:

Table 1. Demographics of incident adult rheumatoid arthritis (RA) patients and matched general population controls from 1996 to 2012.

	RA	Controls	p value
N	18 654	183 065	
Age, years	57.6 ± 15.1	57.4 ± 15.1	0.048
Female, n (%)	13 142 (70.5%)	129 239 (70.6%)	0.683
Chronic obstructive pulmonary disease, n (%)	756 (4.1)	6432 (3.5)	<0.001
Cardiovascular disease, n (%)	1829 (9.8)	16 917 (9.2)	0.019
Diabetes mellitus, n (%)	661 (3.5)	7005 (3.8)	0.045

Table 2: Changes in the 5-year incidence rate of upper limb joint replacement surgery among newly diagnosed rheumatoid arthritis (RA) patients following introduction of biological DMARDs (bDMARDs) compared with secular trends in age, sex and municipality-matched general population controls in an interrupted time series model.

Cohort	N	Person years	Joint replacements, N	Baseline incidence rate/ 1000 PY (95%CI) in 1996	Δ per year* 1996-2001 (pre-bDMARD era)	Δ in level January 1st 2003 (start bDMARD era)	Δ per year 2003-2012 (bDMARD era)
RA	18,654	89,196	193	2.46 (1.96 to 2.96)	No change	No change	-0.08 (-0.20 to +0.02)
Controls	183,152	838,001	291	0.14 (0.07 to 0.21)	+ 0.01 (-0.00 to +0.02)	+0.17 (+0.03 to +0.31)	+ 0.01 (-0.00 to +0.02)

Stepwise backward elimination to produce most parsimonious model: p-entry<0.05 and p-exit>0.2. * Δ per year based on biannual data. Abbreviations: PY, person years; 95%CI, 95 % confidence interval.

Table 3. Changes in the 5-year incidence rate of upper limb joint surgery (excluding joint replacements) among newly diagnosed rheumatoid arthritis (RA) patients following introduction of biological DMARDs (bDMARDs) compared with secular trends in age, sex and municipality-matched general population controls in an interrupted time series model.

Outcome	Cohort	N	PY	N surgeries	Crude incidence rate per 1000 PY 1996-2015	Baseline incidence rate per 1000 PY	Annual change in incidence rate per 1000 PY 1996-2001	Level change per 1000 PY in 2003	Trend 2003-2015
Shoulder and elbow surgeries	**RA**	18,545	88,577	216	2.44 (2.13-2.79)	2.76 (2.32-3.20)	No change	No change	-0.07 (-0.16-0.02)
	Controls	182,831	835,782	529	0.63 (0.58-0.69)	0.23 (0.12-0.33)	0.01 (-0.01-0.03)	0.39 (0.19-0.59)	No change
Finger and wrist surgeries	**RA**	18,321	86,928	437	5.03 (4.58-5.52)	7.98 (6.99-8.97)	-0.13 (-0.32 - 0.06)	-2.33 (-4.29- - 0.37)	-0.13 (-0.32 - 0.06)
	Controls	181,874	830,768	760	0.91 (0.85-0.98)	0.90 (0.82- 0.98)	No change	No change	No change

Stepwise backward elimination to produce most parsimonious model: p-entry<0.05 and p-exit>0.2. * Δ per year based on biannual data. Abbreviations: PY, person years; 95%CI, 95 % confidence interval.