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Predictors for orthopaedic surgery in patients with rheumatoid arthritis: results from a retrospective cohort study of 1010 patients diagnosed from 1972 to 2009 and followed up until 2015

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Objectives: To investigate how patient characteristics, time of diagnosis, and treatment affect the need for orthopaedic surgery in patients with rheumatoid arthritis (RA).
Method: We reviewed the medical history of 1544 patients diagnosed with RA at Haukeland University Hospital in Bergen, Norway, from 1972 to 2009, of whom 1010 (mean age 57 years, 69% women) were included in the present study. Relevant orthopaedic procedures were obtained from the Norwegian Arthoplasty Register and the hospital's administrative patient records. In total, 693 procedures (joint synovectomies 22%, arthrodeses 21%, prostheses 41%, and forefoot procedures 12%) were performed in 315 patients. Survival analyses were completed to evaluate the impact of different factors such as age, gender, radiographic changes, and year of diagnosis, on the risk of undergoing surgery.
Results: Patients diagnosed in 1972–1985 and 1986–1998 had a relative risk of undergoing surgery of 2.4 and 2.2 ($p < 0.001$), respectively, compared to patients diagnosed in 1999–2009. Radiographic changes at diagnosis and female gender were also significant risk factors. Anti-rheumatic medication was significantly different in the three time periods.
Conclusion: Patients with a diagnosis in the early years had a greatly increased risk of having orthopaedic surgery performed. This is probably due to the year of diagnosis being a proxy for the type and intensity of medical treatment.

Rheumatoid arthritis (RA) causes pain, swelling, and erosions in affected joints. Medical treatment in the form of classical synthetic disease-modifying anti-rheumatic drugs (DMARDs) or newer biological treatment has been introduced increasingly earlier to achieve disease control, and many believe this to be the reason why the disease course of patients with RA has become milder in recent years (1, 2). Surgery still comprises a necessary part of treating these patients, when medication fails to prevent joint destruction. Orthopaedic corrective procedures are considered a reliable and objective proxy for a destroyed joint, and are an important outcome measure in RA (3). Studying time trends in orthopaedic surgery thus gives valuable information regarding the prognosis of RA patients.

In the past, estimates have shown that 25% of patients with RA would undergo joint replacement during the course of the disease (4), but the results of later studies indicate a declining incidence of prosthesis surgery (5–9). In 2015, our group published a study investigating the incidence of orthopaedic surgery in Norwegian patients with RA from 1994 to 2012, and found a significant decrease in performed procedures (10). As seen in other studies, this decline coincided with the increasing use of synthetic and biological DMARDs (11–13), and in our study continued into the biological era and throughout the study period. That study described only the general use of orthopaedic surgery in Norway, and therefore could not give information on the outcomes of individual patients with diverse patient characteristics receiving different treatment.

In 1998, Wolfe and Zwillich published a large study on the long-term outcomes of RA, and found that variables that indicated disease activity and severity, such as erythrocyte sedimentation rate (ESR), predicted later joint replacement (4). In a Swedish study on 183 RA patients with onset of disease in 1985–1989, the Health Assessment Questionnaire score, C-reactive protein (CRP), and ESR at disease onset, and radiographic changes in small joints after 1 year were associated with an increased risk of undergoing arthroplasty surgery of large joints (14). Concerning treatment, findings from Moura et al (15) and Widdifield et al (16) suggest that longer exposure to

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DMARDs soon after RA diagnosis is associated with longer time to joint replacement surgery.

Using Haukeland University Hospital's extensive administrative patient system, we now wished to investigate how patient characteristics, treatment, and year of diagnosis affect the need for surgical procedures in Norwegian patients diagnosed with RA in the years 1972–2009, and whether this has changed since the description of earlier cohorts.

Method

Our data originate from Haukeland University Hospital, which delivers specialist care to approximately 500 000 inhabitants in western Norway. As only two private practising rheumatologists operate in this area, the great majority of patients with rheumatic disease are cared for by the hospital's Department of Rheumatology. In general, patients are referred at the time of suspected inflammatory rheumatic disease, and a random selection of these patients is likely to be representative of patients in the region. Some patients with stable disease are later managed by their general practitioner, but most continue to be followed until death or inactive disease.

From the hospital's administrative patient records, we have data available from 1972 to the present. A search on disease codes for RA using International Classification of Diseases (ICD) revisions 8, 9, and 10 detected 6318 unique patients from 1972 to 2014. As most patients with RA are in specialist care for several years after diagnosis, we excluded patients with four or fewer hospital contacts, assuming that these patients were miscoded, initially wrongly diagnosed, or followed up at a different institution. This left us with 3053 patients. We chose to exclude patients with their first encounter later than 2009 to ensure that all patients were observed for at least 6 years, unless diseased, and selected our study subjects from the remaining 2679 patients aged 16 years or older at diagnosis.

The selection process is described in Figure 1. Each medical record was reviewed for the following information: weight, height, affected joints within 2 years of diagnosis, whether the 2010 American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) classification criteria for RA were fulfilled, serological status, ESR, and CRP. As the medical records did not contain radiographic images, the radiologist's interpretation of these as normal or consistent with arthritis or osteoarthritis was recorded. Medication used in the first year and during the course of the disease was also registered. Supplementary data were taken from the Norwegian Arthritis Registry (http://www.norartritt.no) for patients in this register.

Patient characteristics

During the study period, there has been a great change in available medication and intensity of follow-up, and we wished to investigate the outcomes of patients diagnosed in different periods. As methotrexate was introduced to our patient group in 1986, and biological treatment in the form of tumour necrosis factor-α inhibitors in 1999, we split the group into three, depending on diagnosis in different treatment eras: time period 1 from 1972 to 1985, time period 2 from 1986 to 1998, and time

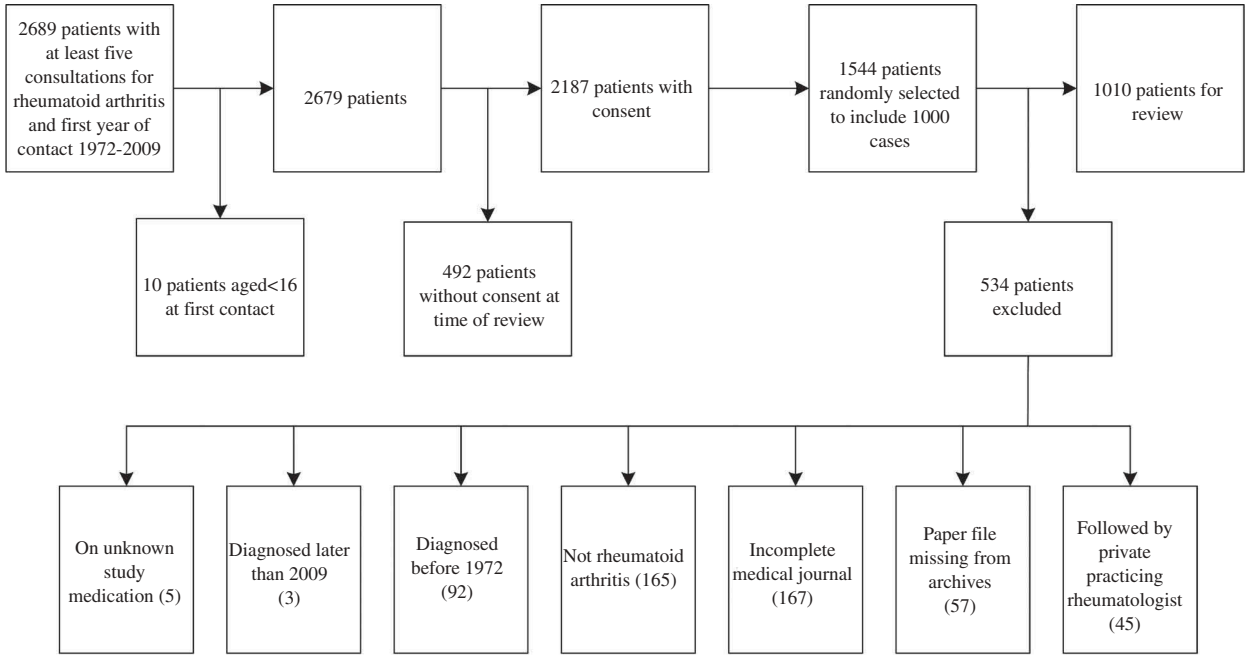

Figure 1. Selection process.

period 3 from 1999 to 2009. Patient characteristics for each group and in total are described in Table 1. Treatments used in the first year and during the course of the disease are presented in Figure 2.

In the years 1986–1998, more patients aged 70 years or above were prescribed methotrexate in the first year of the disease than patients younger than 70 years (37% vs 22%, p = 0.01). In 1999–2009, receiving methotrexate in the first year of the disease seemed to be more common in patients aged below 70 years, but this was not statistically significant (67% vs 58%, p = 0.062). The proportion of patients receiving methotrexate in the first year of the disease increased from 6.3% in 1986 to 48% in 1999 and to 78% in 2009. In 2009, there was no significant difference in prescription rates between older and younger patients.

Surgical procedures

For the selected 1010 patients, information on orthopaedic surgery was obtained from the Norwegian Arthroplasty Register (NAR) and the hospital's administrative patient records. The NAR was established in 1987, initially as a register of total hip replacements, but since 1994 it has been a register of all artificial joints in the Norwegian population. Haukeland University Hospital's administrative patient system has registered all procedures performed since 1972, and the data from NAR gave extra security for completeness of data in the years since the register's establishment. The archives of two other local hospitals which up until the early 1990s performed some surgery in this patient group were also investigated. We searched for joint synovectomies, arthrodesis, and prosthesis procedures using the coding systems NCSP (NOMESCO Classification of Surgical Procedures) and SIFF (Norwegian Institute of Public Health). When excluding surgery conducted earlier than 1 year before diagnosis, we found 693 procedures performed in 315 patients (31%). The procedures performed within 1 year before diagnosis were counted as performed at diagnosis since we had reason to assume an association between surgery and diagnosis.

Five events per 100 patient-years occurred during the whole study period. Forty-one per cent of procedures were arthroplasties, 21% were arthrodeses, 22% were joint synovectomies, and 14% were combined procedures, of which forefoot procedures were the most frequent. The distribution of different procedures in diverse joints is described in Table 2. The areas most frequently operated on were the ankle/foot and the wrist/hand, on which, respectively, 26% and 23% of procedures were performed. Eleven per cent of the 1010 patients had undergone one or more surgical procedure on the hips, 10% ankle or foot surgery, 9.1% hand or wrist surgery, and 8.5% knee surgery, whereas 2.8% and 2.5%, respectively, had undergone shoulder and elbow surgery.

The main outcome of interest was the time from RA diagnosis to the first orthopaedic procedure. The impact of patient characteristics such as age, gender, body mass index (BMI), whether the diagnostic criteria were fulfilled, level of inflammatory parameters during the first 2 years of disease, number and type of affected joints, and radiographic findings at diagnosis on the risk of undergoing surgery was investigated.

Statistical analyses

Descriptive statistics were used for the presentation of patient characteristics. The unpaired t-test was used for

Table 1. Characteristics in each time period and in total.

	1972–1985	1986–1998	1999–2009	Total	
	(n = 154)	(n = 315)	(n = 541)	(n = 1010)	p
Observation time (years), mean ± SD	21 ± 10	17 ± 6.2	9.7 ± 3.2	14 ± 7.3	
Age (years), mean ± SD	57 ± 12	57 ± 16	58 ± 16	57 ± 15	> 0.4
Gender (% female)	73	70	68	69	0.41
Fulfilled ACR/EULAR criteria (%)*	84	84	86	85	0.74
> 10 joints affected within first 2 years (%)	63	64	52	57	0.001
Rheumatoid factor positive (%)†	71	68	59	63	0.004
ESR ≥ 60 mm/h within first 2 years (%)‡	44	40	28	34	< 0.001
Radiographic arthritis initially (%)§	43	30	17	25	< 0.001
Arthrodesis during disease course (%)	22	12	3.1	8.9	< 0.001
Prosthesis during disease course (%)	31	28	11	19	< 0.001
Synovectomy during disease course (%)	22	14	3.7	9.6	< 0.001
Combined procedure during disease course (%)	20	8.9	0.7	6.1	< 0.001

*2010 American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) classification criteria for rheumatoid arthritis.
†Among available (1006).
‡Among available (1009).
§Percentage among patients with initial radiographic examination (922 in total).
ESR, erythrocyte sedimentation rate.

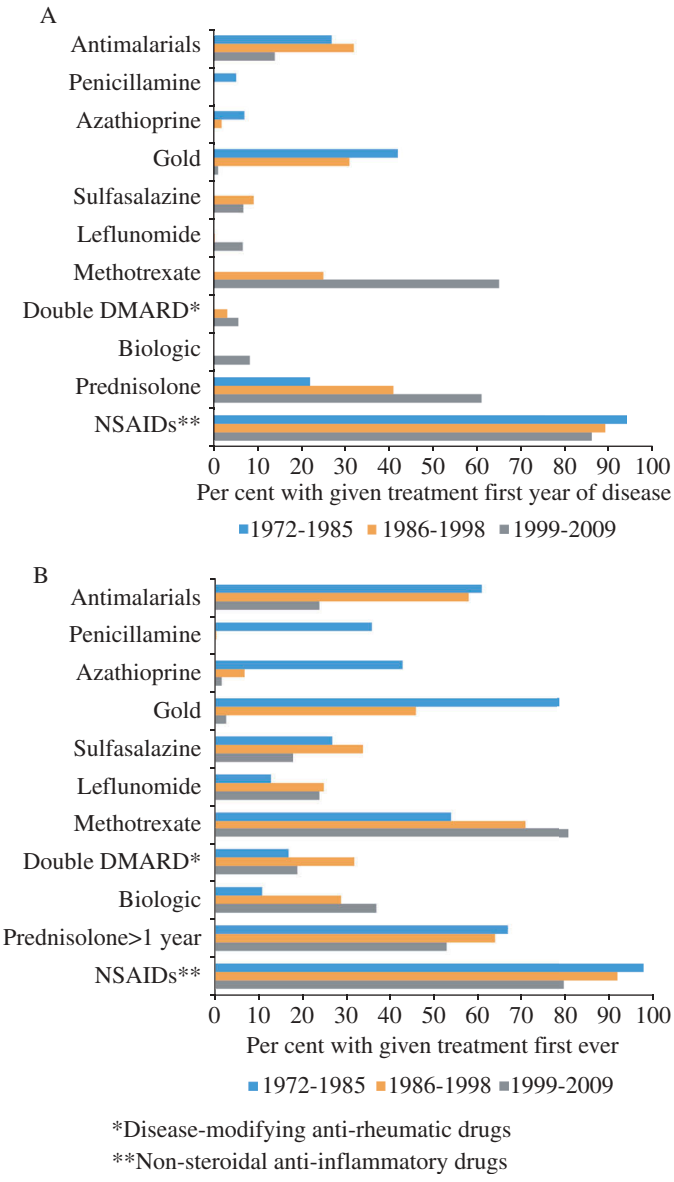

Figure 2. Percentage of patients with the given treatment in each time period: (A) first year of disease; (B) ever. Because of the low numbers, cyclosporine and triple synthetic disease-modifying anti-rheumatic drugs were excluded from the figure.

continuous variables and the chi-squared test for categorical data. Person-time was accumulated from RA diagnosis until the first occurrence of orthopaedic surgery, death, or the end of the study period (31 December 2015). Cumulative incidence rates were calculated for the entire study period as the number of events per 100 patient-years. As follow-up duration was different for individual patients, the impact of each factor on the risk of undergoing surgery was analysed using Kaplan–Meier plots and log-rank analyses for significance. Where a statistically significant difference was found, further analyses using univariate and multivariate Cox proportional hazards regression models were performed. Unless otherwise stated, analyses included all subjects and the outcome was the first occurrence of arthroplasty, arthrodesis, or synovectomy.

When observing the Kaplan–Meier plot of risk of surgery according to time of diagnosis, we saw that patients diagnosed in 1986–2009 had more surgery performed in the early years of disease compared to patients diagnosed in 1972–1985. We therefore supplemented the analysis with Kaplan–Meier analyses of events occurring, excluding the first 4 years.

To account for the increasing use of arthroplasty surgery for osteoarthritis (10), we also performed analyses using orthopaedic surgery exclusive of arthroplasty surgery of the hip and knee as outcome, to look only at the most RA-specific procedures. As others have found a reduction in procedures in the hands and feet, but not in large joint prosthesis surgery (12), we included separate analyses for hip and knee replacements.

We also performed subanalyses of factors affecting the risk of synovectomy, arthrodesis, and prosthesis separately.

In additional analyses using any procedure as outcome, we used a propensity score model to control for

Table 2. Type and localization of surgical interventions.

Procedure	Joint area	No.	% of total
Arthroplasties	Shoulder	20	2.9
	Elbow	9	1.3
	Wrist	4	0.6
	Fingers	8	1.2
	Hip	139	20
	Knee	93	13
	Ankle	3	0.4
	Foot	4	0.6
	Other/unknown	3	0.4
Synovectomies	Shoulder	17	2.5
	Elbow	21	3.0
	Wrist/hand	81	12
	Knee	27	3.9
	Ankle/foot	5	0.7
Arthrodeses	Wrist/hand	50	7.2
	Ankle	2	0.3
	Foot	82	12
	Other/unknown	10	1.4
Combined	Ankle	2	0.3
	Forefoot	81	12
	Hand	13	1.9
Other		19	2.7
Total		693	100

systematic differences and imbalance in the measured covariates. The propensity score is the probability of having a certain treatment conditioned on observed baseline characteristics. Propensity score models aim to perform as a randomized clinical trial (RCT). Instead of using regression adjustment, as in a Cox model, to adjust for differences in baseline characteristics, we use the propensity score model to eliminate the effects of possible known confounders (17). In this study, we used age, gender, radiographic changes at diagnosis, numbers of joints affected, fulfilment of the 2010 ACR/EULAR classification criteria for RA, and serological status as covariates describing the three time periods. These covariates are all factors that affect the treatment assignment. The analyses were performed pairwise.

Statistical analyses were performed in SPSS versions 22 and 23, and in R software version 3.3.0. The level for statistical significance was set to $p < 0.05$.

The study was approved by the regional committee for medical and health research ethics (2014/1923/REC West).

Results

The factor with the greatest impact on the risk of a surgical procedure during the course of the disease was the year of diagnosis. The effect of different time periods of diagnosis on the risk of orthopaedic surgery is shown in Figure 3. Patients diagnosed in 1972–1985 and 1986–1998 had a relative risk (RR) of surgery of 2.4 and 2.2 ($p < 0.001$), respectively, compared to patients diagnosed in 1999–2009 (Table 3).

Female gender and radiographic changes at diagnosis were also significant risk factors (Table 3). No significant effects of number or type of affected joints, rheumatoid factor, or anti-cyclic citrullinated peptide (anti-CCP) positivity, initial level of inflammatory parameters, or whether the diagnostic criteria were fulfilled at time of diagnosis were found, and their presence did not change the significance of the above-mentioned factors. Obesity, defined as BMI ≥ 30 kg/m^2, was not significantly different between the groups, and it did not affect the outcome.

When analysing the impact of whether methotrexate was used in the first year of diagnosis (applicable for patients in time periods 2 and 3) in univariate Cox regression analysis, patients who were prescribed methotrexate had a significantly lower risk of later surgical procedures, with methotrexate decreasing the risk by an RR of 0.60 [95% confidence interval (CI) 0.46 to 0.76, $p < 0.001$]. Any use of biological drugs during the course of the disease did not affect the outcome.

When considering only surgery performed later than 4 years since diagnosis, Cox regression analysis of the same parameters (age, gender, radiographic changes at diagnosis, and time of diagnosis) showed that patients diagnosed in 1986–1998 had an RR for surgery of 3.0, and patients diagnosed in 1972–1985 had an RR of 5.3.

When excluding joint replacement surgery of the hip and knee, patients diagnosed in 1972–1985 and 1986–1998 had RRs for surgical procedures of 3.6 and 2.9, respectively ($p < 0.001$), compared to patients diagnosed in 1999–2009. For prosthesis surgery of the hip and knee, the increased risk (RR 1.6 in 1972–1985 and RR 1.4 in 1986–1998, compared to 1999–2009) was not statistically significant ($p = 0.065$ and 0.067, respectively).

When using the propensity score model to analyse surgical interventions during the entire time span. We found an RR of 2.1 (95% CI 1.49 to 3.10, $p < 0.001$) for time period 1 (1972–1985) compared to time period 3 (1999–2009), and an RR of 2.3 (95% CI 1.70 to 3.04) when comparing time period 2 (1986–1998) to time period 3 (1999–2009).

When performing subanalyses of how age, gender, radiographic changes at diagnosis, and time period of

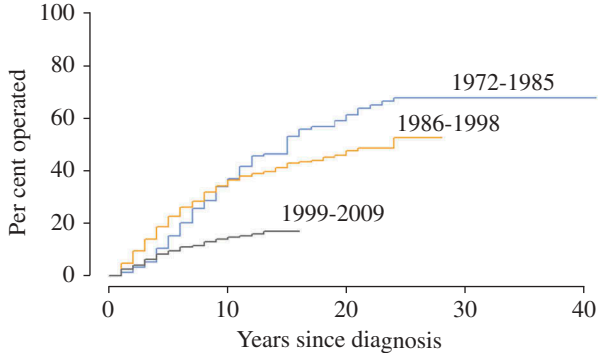

Figure 3. Percentage of patients operated on depending on the time period of diagnosis.

Table 3. Percentage of patients operated on at 5 and 10 years' duration of disease, and relative risk (RR) of surgery according to major explanatory factors.

Variable category	5 years*	10 years*	RR	95% CI	p
Age (years)					
< 70	15	27	1		
≥ 70	22	31	1.04	0.77–1.42	0.78
Gender					
Male	13	22	1		
Female	19	30	1.35	1.02–1.77	0.035
Radiographic changes at diagnosis					
No arthritis	12	21	1		
Possible arthritis, or MRI findings only	19	26	1.01	0.66–1.57	0.92
Arthritis	23	34	1.46	1.10–1.94	0.008
Osteoarthritis	35	55	2.81	1.94–4.05	< 0.001
Time period					
1999–2009	12	18	1		
1986–1998	25	38	2.16	1.62–2.87	< 0.001
1972–1985	15	37	2.38	1.71–3.31	< 0.001

*Five year and 10 year survival, in per cent.
MRI, magnetic resonance imaging; CI, confidence interval.

diagnosis affected the risk of synovectomy, arthrodesis, or prosthesis, we found that patients diagnosed in 1972–1985 had an RR of 4.4 ($p < 0.001$), and patients diagnosed in 1986–1998 an RR of synovectomy of 3.1 ($p < 0.001$) compared to patients diagnosed in 1999–2009. Younger age (< 70 years) was also a risk factor (RR 2.2, $p = 0.036$). For arthrodeses, there was an increased risk of 3.6 ($p < 0.001$) for patients diagnosed in 1972–1985 and 2.4 ($p = 0.004$) for patients diagnosed in 1986–1998 compared to patients diagnosed in 1999–2009, and female gender was a significant risk factor (RR 2.5 $p = 0.004$). For prosthesis surgery, osteoarthritis in radiographic images at diagnosis was the strongest risk factor (RR 4.2, $p < 0.001$). Time of diagnosis was also a significant risk factor; RR 1.8 ($p = 0.006$) for patients diagnosed in 1972–1985 and RR 1.7 ($p = 0.007$) for patients diagnosed in 1986–1998, compared to those diagnosed in 1999–2009. Older age (≥ 70 years) at diagnosis significantly increased the risk of prosthesis surgery (RR 1.6, $p = 0.011$).

Discussion

This study's main finding is that diagnosis in earlier years increased the risk of undergoing orthopaedic surgery. In addition, female gender and radiographic changes consistent with arthritis or osteoarthritis at diagnosis were associated with increased risk of surgery.

Although RCTs are the gold standard in research, they can be difficult to use when investigating late outcomes such as terminal joint destruction with subsequent orthopaedic surgery. RCTs also have other limitations, particularly concerning generalizability (18), as they demonstrate the effect of treatment under ideal conditions. Observational studies have other disadvantages, but describe to a greater extent the prognosis of patients in real life. In this study, we observed the patients for a mean duration of 13.1 years (range 0–42 years), which would be impossible in an RCT, as would the assignment of outdated treatment regimens to current patients.

Female gender is a known predictor of worse outcome of RA (19), and our study confirms that women are more prone to be in need of orthopaedic surgery.

When performing subanalyses for the different procedures, we found that diagnosis in the earlier time periods was a significant risk factor for all procedures, but strongest for synovectomies and weakest for prosthesis surgery. This may be because of the general increase in prosthesis surgery seen in later years. In the subgroup analyses, radiographic arthritis at diagnosis was not a significant risk factor for subsequent surgery, probably because of the reduced number of cases when splitting the cohort.

The use of synthetic and biological DMARDs changed significantly during the study period (Figure 2), with more patients receiving methotrexate and biological treatment both in the first year of disease and during the course of the disease, in later years. Whereas prednisolone is increasingly used in the first year of disease, the proportion using prednisolone for more than 1 year is diminishing. Widdifield et al studied patients aged 66 years and above, and raised the question of whether methotrexate is prescribed to a lesser extent in older patients (16). Investigation of our material did not support this.

In our study, we found the strongest risk factor to be diagnosis in earlier time periods. The survival curves for the different time periods are not proportional, and hence a prerequisite for Cox regression is not strictly present, since use of the Cox regression model requires hazard functions that are proportional over time for all three study periods. We found that the RR was even higher

when investigating events after 4 years, from which time the relative hazards were constant. It is possible that surgical intervention has become more aggressive, and that necessary procedures were performed sooner in later decades, which could explain the higher rates of surgery during the early years of diagnosis in the later cohorts. In that case, some time has to pass before the number of events in each group is comparable, when used as a proxy for joint damage. The propensity score model used does not have the same prerequisite of proportionality, and confirmed the results from fitting the traditional Cox model.

Patients diagnosed in earlier years have a longer time of observation than patients in the latest time period. This may be a confounding factor. However, all patients were included within 2009, but no later, to ensure the possibility of at least 6 years' observation time.

One could argue that the lower risk of surgery is a secular trend indicating higher disease activity among patients diagnosed in 1972–1985 and 1986–1998. Our data do indeed show that patients diagnosed in earlier years included a significantly greater proportion with ESR ≥ 60 mm/h, more than 10 joints affected, and signs of arthritis on initial radiographs. Time of diagnosis was, however, still a significant risk factor, both in multivariate Cox analysis and in the propensity score model correcting for these factors.

Previous studies claim to show that the improved prognosis of patients with RA is due not to secular changes, but to improved treatment (20). In addition, it is probable that the increased disease activity found during the first 2 years of disease among our patients diagnosed in the 1970s and 1980s was caused by later referral to specialist care, and a delay in of or lack of response to an initial treatment that was less intensive in those decades.

Our patients were all treated within the same facility, providing care for the entire region of western Norway. The indication and approval of the costly biological treatments have, since their introduction, been considered for each individual patient by a committee consisting of three rheumatologists, none of whom is the patient's physician. The indication may have changed over time, but there is every reason to believe that all patients in a given year were treated similarly. The use of the synthetic DMARDs was decided by each physician, who all worked within the same treatment tradition, following the same guidelines. We therefore believe that the year of diagnosis may be considered a proxy for the treatment received.

The type and number of affected joints within the first 2 years of diagnosis was not found to be a predictive factor. This is probably because we counted both tender and swollen joints as affected, as according to the ACR/EULAR criteria, and thus a large number (57%) of patients had more than 10 joints involved. According to clinical experience, it is also probable the patient's long-term outcome can be predicted not by initial disease activity, but by how he or she responds to treatment (21). This was confirmed in a study published in 2016 finding that < 20% improvement 1 year after baseline, but not swollen joint count at baseline, was a significant predictor of the number of joints with deformities 18 years after baseline (22). Because there was no uniform registration of clinical response in earlier years, we did not record this in the present study. In our analyses, no significant effects of other signs of initial disease activity, ESR, or fulfilment of the ACR/EULAR criteria were found, and rheumatoid factor positivity did not increase the risk. Previous studies have, however, shown variables expressing disease activity at baseline to be a predictor of poor prognosis and later surgery (4). Because of the long inclusion period of this study, data on anti-CCP were lacking for one-third of patients. Positive anti-CCP was, however, not found to be a significant risk factor among the patients tested.

In this study, 25% of patients had radiographic signs of arthritis initially, and these patients had an increased risk of subsequent surgery, as shown previously (4). The proportion of patients with radiographic arthritis at baseline decreased significantly over the years. Because our cohort went as far back as 1972, we did not have access to the radiographic images, but instead recorded the concluding remarks in the description performed by the evaluating radiologist. Pathology in any image (small or large joint) was recorded. The change may indicate more severe disease in earlier time periods, but is more probably caused by later specialist referral in previous decades.

Radiographic signs of osteoarthritis were seen in 8.6% of the patients at diagnosis. The incidence of arthroplasty surgery in patients with osteoarthritis has increased significantly in later years (10), and this is a possible confounder when considering orthopaedic surgery in patients with RA. When patients with inflammatory rheumatic joint disease develop osteoarthritis, it can be difficult to distinguish primary osteoarthritis from osteoarthritis secondary to inflammatory arthritis. Previous studies have shown that while hand and foot surgery rates in RA have declined, large joint replacements have remained unchanged (12, 23), and that the most RA-specific procedures have declined the most (10). When excluding joint replacement surgery of the hip and knee, which are the more common locations for primary osteoarthritis in need of intervention (24), earlier time of diagnosis is an even stronger risk factor for orthopaedic surgery. This confirms that treatment in later years has decreased the risk of an unfavourable outcome.

Methotrexate has, in later years, been introduced increasingly early (25) and in higher doses (26) to achieve sufficient disease control, and patients are subject to tight management. It is difficult to separate the effect of this from the effect of the introduction of biological DMARDs. In our study, the risk of surgery

was lower among patients diagnosed after the introduction of biologicals, but it is hard to say whether this indicates that biological DMARDs reduce the risk of orthopaedic surgery. Aaltonen et al did not find evidence for this in a study from 2013 (27), but in contrast to their results, we did not find that use of biological medication at any time of the disease was associated with an increased risk of surgery. As users of biologicals are probably the patients with the highest disease activity, this may be considered an indirect indication of their effect.

Conclusion

Patients with a diagnosis in the early years had a greatly increased risk of having an orthopaedic procedure performed. This could be caused by secular changes, but is most probably due to the year of diagnosis being a proxy for the type and intensity of medical treatment received, which we found to have changed significantly during our study's inclusion period.

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Supporting Information

Additional Supporting Information may be found in the online version of this article.

Supplementary table S1. Per cent operated with synovectomy at 5 and 10 years' duration of disease, and relative risk of surgery according to major explanatory factors.
Supplementary table S2. Per cent with arthrodesis at 5 and 10 years' duration of disease, and relative risk of surgery according to major explanatory factors.
Supplementary table S3. Per cent with prosthesis at 5 and 10 years' duration of disease, and relative risk of surgery according to major explanatory factors

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