

# Rheumatoid Arthritis: Trends in Antirheumatic Drug Use, C-reactive Protein Levels, and Surgical Burden

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**ABSTRACT. Objective.** Over the past decade, the therapeutic approach used to treat patients with rheumatoid arthritis (RA) has considerably changed. It remains unclear whether these changes have been accompanied by decreased disease severity and surgical treatment burden at the population level. Therefore, we investigated time trends in antirheumatic drug consumption, C-reactive protein (CRP) levels, and use of orthopedic surgery among Danish patients with RA.

**Methods.** Using medical databases, we identified all patients with RA living in Northern Denmark during 1996–2012. For each calendar year, we computed the annual rate of antirheumatic drug use (1996–2010), the median CRP value in mg/l (1996–2011), and the proportions of patients who underwent hip replacement and other orthopedic procedures (1996–2012).

**Results.** Antirheumatic drug consumption per patient increased 5-fold, from 145.0 defined daily doses (DDD) in 1996 to 695.4 DDD in 2010. Median CRP declined from 20.5 mg/l [interquartile range (IQR), 10.0 to 43.5 mg/l] in 1996 to 10.0 mg/l (IQR, 4.2–17.8 mg/l) in 2011. From 1996 to 2012, declining proportions of patients with RA underwent hip replacement (14.9% to 10.1%) and other joint operations (29.1% to 23.4%), while the annual proportion of patients who underwent soft tissue procedures increased from 20.7% to 23.4%.

**Conclusion.** Antirheumatic drug consumption has substantially increased among patients with RA since 1996, in association with reduced disease activity (i.e., lower CRP levels), fewer joint procedures (including hip replacements), and more soft tissue procedures. (First Release November 1 2015; J Rheumatol 2015;42:2247–54; doi:10.3899/jrheum.141297)

## Key Indexing Terms:

ANTIRHEUMATIC AGENTS  
INCIDENCE

RHEUMATOID ARTHRITIS  
PREVALENCE

EPIDEMIOLOGY  
C-REACTIVE PROTEIN

Rheumatoid arthritis (RA) affects about 1.25% of the global population, and substantially limits functional outcome, work ability, and life expectancy<sup>1,2,3</sup>. Early and aggressive medical treatment is recommended to control arthritis and prevent joint damage<sup>4</sup>. Joint replacement surgery is reserved for cases that require improved mobility of deformed joints or where pharmacological and physical therapy have failed to relieve severe pain<sup>5</sup>.

Over the past decade, some studies have reported a decline in total joint replacement surgeries among patients with arthritis<sup>6–17</sup>. This decline could be related to generally lower disease activity caused by (1) improved diagnostic tools

leading to diagnosis earlier in the disease course, (2) updated international treatment guidelines recommending more aggressive treatment with combinations of 2 or more disease-modifying antirheumatic drugs (DMARD)<sup>4,18</sup>, and (3) introduction of biological antirheumatic drugs early in the disease course<sup>19</sup>. However, there is little epidemiological evidence from large population-based studies to support these explanations<sup>20,21,22</sup>.

We therefore conducted a large population-based cross-sectional study to examine trends in antirheumatic drug consumption, C-reactive protein (CRP) levels as a marker of disease activity, and the use of orthopedic procedures among patients with RA in Northern Denmark over a 17-year period (1996–2012).

## MATERIALS AND METHODS

**Setting.** Our study was conducted in Northern Denmark, using prospectively collected data from population-based health registries. The included regions encompass about 2 million inhabitants, about 33% of the entire Danish population. The Danish National Health Service provides tax-supported universal healthcare to all Danish citizens, guaranteeing unfettered free emergency and general admissions to hospitals, and free visits to hospital specialist outpatient clinics and general practitioners. The vast majority of patients with RA in Denmark are treated at hospital outpatient clinics<sup>23</sup>. All Danish citizens are assigned a central person registry (CPR) number — a

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unique 10-digit personal identifier — which permits unambiguous patient tracking and linkage between registries at the individual level<sup>24</sup>. Our study was approved by the Danish Data Protection Agency (J-nr: 2012-41-0377).

**Identification of patients.** The Danish National Patient Register (DNPR) has maintained data on all inpatient hospitalizations to nonpsychiatric hospitals in Denmark since 1977, and on all outpatient and emergency room visits to hospital specialist clinics since 1995. The DNPR includes a patient's CPR number, dates of admission and discharge, and up to 20 discharge diagnoses classified according to the International Classification of Diseases (ICD) 8th edition until the end of 1993, and the 10th edition thereafter<sup>25</sup>. The DNPR also records information on all orthopedic procedures performed in Danish public or private hospitals. These procedures are registered according to a Danish version of the Nordic Medico-Statistical Committee Classification of Surgical Procedures (NCSP)<sup>26</sup>. We also collected demographic details from the Danish Civil Registration System, which has maintained data — including CPR number, vital status, date of death, residence, and migration — for all Danish residents since 1968 and is updated daily<sup>24</sup>. For patients identified between 1996–2010, we obtained all available information regarding antirheumatic drugs from the Aarhus University Prescription Database (AUPD).

Among the residents of Northern Denmark, we identified all in- and out-patients with a primary or secondary diagnosis of RA registered in the DNPR (Supplementary Table 1 has diagnostic codes, and is available from the authors on request). For each calendar year from 1996 to 2012, the cohort at risk was defined as all patients with RA who were alive on January 1 of that year who had at least 1 relevant ICD code in the DNPR between 1977 and the previous calendar year. For example, for the year 2012, the cohort at risk included all patients with RA who were living in Northern Denmark and alive on January 1, 2012, and who were identified as having RA between 1977 and the end of 2011. Thus, we constructed a dynamic cohort of both prevalent and incident patients with RA who contributed person-time for each calendar year.

**Consumption of antirheumatic drugs.** The AUPD tracks all prescriptions for reimbursable drugs dispensed at all community pharmacies and hospital-based outpatient pharmacies in Northern Denmark<sup>27,28,29</sup>. Drugs are coded according to the Anatomical Therapeutic Chemical classification system. Data are available for 4 regions of Northern Denmark: North Jutland (complete since 1992), Aarhus (since 1996), Viborg (since 1998), and Ringkøbing (since 1998). For all patients in our cohort, we obtained

data on the number, dates, and defined daily dose (DDD) values of redeemed prescriptions for DMARD, corticosteroids, and biological drugs from 1996 to 2010 (Supplementary Table 1, available from the authors on request).

**Laboratory data.** The clinical laboratory information system (LABKA) research database records all laboratory analysis results from public and private hospitals in Northern Denmark<sup>30</sup>. The database has included complete coverage of the North Jutland region since 1997 and of the other 3 regions of Northern Denmark since 2000<sup>30</sup>. Analyzed samples are recorded according to Nomenclature for Properties and Units codes, supported by the International Union for Pure and Applied Chemistry subcommittee<sup>30,31,32</sup>. For the 1996–2011 study period we accessed LABKA to collect information on CRP measurements as a proxy measure for systemic inflammation and disease activity. CRP was expressed in mg/l, and presented as the median value among the patients with RA for each calendar year.

**Use of orthopedic procedures.** Using NCSP codes from the DNPR, we collected information on all orthopedic procedures carried out among patients with RA at hospitals in Denmark between 1996 and 2012. We classified these procedures according to indications of the surgery into the following categories: (1) primary or revision total hip replacement procedures (defined as removal or exchange of primary hip implant); (2) procedures for any joint other than the hip, including joint replacement, joint resection, and arthrodesis; and (3) soft tissue procedures, including surgery on synovia, cartilage, ligament, muscles, etc. Hip surgeries have very strict guidelines and indications and are performed in severe cases, whereas subjective assessment and patient preference play important roles in the decision-making process for other joint replacements. Soft tissue surgeries are performed to improve function and reduce stiffness and are not related to joint damage. Supplementary Table 1 lists the NCSP codes used (available from the authors on request).

**Statistical analysis.** Among patients with RA who resided in Northern Denmark and were alive on January 1 of each analyzed calendar year, we estimated the consumption of antirheumatic drugs (both overall and by different drug categories) separately for each calendar year. Consumption was calculated by adding the total number of DDD for antirheumatic drugs dispensed to patients with RA in a calendar year and dividing the sum by the total number of patients with RA alive on January 1 of that calendar year<sup>33</sup>. Antirheumatic drug consumption was expressed as the average number of DDD per patient during a year. Further, we have calculated the

Table 1. Demographic characteristics of the studied rheumatoid arthritis (RA) patients from Northern Denmark according to calendar years 1996–2012.

Year of Inclusion	RA Cases		> 60 Yrs		≤ 60 Yrs		Median Age, yrs (IQR)	Men		Women	
	Prevalent	Incident	n	%	n	%		n	%	n	%
1996	3432	498	1951	57	1481	43	62 (51–71)	954	28	2478	72
1997	3797	488	2182	57	1615	43	62 (52–71)	1069	28	2728	72
1998	4168	516	2419	58	1749	42	63 (52–71)	1166	28	3002	72
1999	4457	452	2614	59	1843	41	63 (52–72)	1245	28	3212	72
2000	4785	488	2812	59	1973	41	63 (52–72)	1346	28	3438	72
2001	5055	441	2992	59	2063	41	63 (52–72)	1435	28	3620	72
2002	5322	460	3119	59	2203	41	63 (52–73)	1518	29	3804	71
2003	5549	450	3256	59	2293	41	63 (52–73)	1574	28	3975	72
2004	5813	478	3423	59	2390	41	63 (52–73)	1656	28	4157	72
2005	6077	465	3620	60	2457	40	63 (52–73)	1732	29	4345	71
2006	6355	492	3812	60	2543	40	63 (53–73)	1802	28	4553	72
2007	6659	504	4016	60	2643	40	63 (52–73)	1871	28	4788	72
2008	6930	500	4227	61	2703	39	64 (52–74)	1935	28	4995	72
2009	7124	420	4380	61	2744	39	65 (53–74)	1989	28	5135	72
2010	7294	446	4498	62	2796	38	64 (53–74)	2056	28	5238	72
2011	7508	494	4648	62	2860	38	64 (53–74)	2149	29	5359	71
2012	7575	329	4751	63	2824	37	65 (53–74)	2165	29	5410	71

IQR: interquartile range.

annual proportion of patients using different DMARD and other drugs, and also patients using 2 or more drugs at the same time.

The median CRP level was computed based on the patients in the cohort who had at least 1 CRP measurement during the analyzed year. If a patient had several measurements available for a calendar year, we used the mean value of those measurements. Because single CRP measurements may have been ordered owing to suspicion of infection rather than RA monitoring, we performed sensitivity analyses by further restricting the analysis to patients who had at least 2 CRP measurements 6 months apart. We also calculated the median CRP level among only those patients who were treated as outpatients.

Finally, we computed the annual cumulative proportions of patients with total hip replacements, other joint procedures, and soft tissue procedures. For example, for 1996, we divided the number of patients registered in the DNPR as having total hip replacement procedures during 1996 by the total number of patients with RA who were alive at the start of 1996. Additionally, we stratified the proportions of orthopedic procedures by age ( $\leq 60$  yrs and  $> 60$  yrs of age during the analyzed calendar year). We also calculated mean age at time of the surgical intervention for each calendar year. Sensitivity analyses were performed by restricting the analyzed study population to patients with at least 2 contacts with diagnosis of RA registered in the DNPR during the 1977–2011 study period.

RESULTS

On January 1, 1996, the DNPR included a total of 3432 patients with RA. For 2012, the number of registered patients with RA had increased to 7575 (Table 1). The annual number of registered incident RA cases increased from 512 in 1996 to 843 in 2007, followed by a decrease to 764 in 2012. The median patient age was 62 years (IQR, 51–71 yrs) in 1996, and increased to 65 years (IQR, 53–74 yrs) in 2012. For all calendar years, about one-third of the patients were men.

*Consumption of antirheumatic drugs.* The total consumption of antirheumatic drugs consistently increased until 2006, and

slowly decreased thereafter, resulting in an overall 4.8-fold increase between 1996 and 2010 (Table 2). The annual use of DMARD per patient increased 5.2-fold from 86.4 DDD in 1996 to 446.6 DDD in 2010. The use of corticosteroids per patient increased 4.2-fold, from 58.6 DDD in 1996 to 248.6 DDD in 2010 (Figure 1). The use of biological drugs per patient was 0.09 in 2007 and 0.1 DDD in 2007 (Figure 1).

The proportion of patients with RA taking DMARD alone or in combination with other drugs increased from 40% in 1996 to 53% in 2010, being about 64% in 2004–2005 (Supplementary Table 2, available from the authors on request). The proportion of patients with RA taking only 1 DMARD varied between 75% and 89% during the period 1996–2010, whereas the proportion of patients taking 2–3 different DMARD varied between 10% and 20% in the same period, showing no clear increase in consumption (Supplementary Table 2). Up to 16% of patients were taking only corticosteroids (Supplementary Table 3, available from the authors on request).

*Laboratory results and RA disease activity.* The proportion of patients with RA who had CRP measurements available increased from 10% in 1996 to 54% in 2000, and to 82% in 2011 (Table 2). The median CRP level was reduced by nearly half from 20.5 mg/l (IQR, 10.0–43.5 mg/l) in 1996 to 10.0 mg/l (IQR, 4.4–17.8 mg/l) in 2011. With the analyses restricted to patients who had at least 2 CRP readings at least 6 months apart within a year, we observed an even larger decrease in median CRP level from 33.9 mg/l (IQR, 10.9–47.0 mg/l) in 1996 to 8.7 mg/l (IQR, 3.5–17.8 mg/l) in 2011. A similar pattern was observed when the analyses were

Table 2. Overall antirheumatic drug use and level of disease activity\* among patients with rheumatoid arthritis (RA) according to calendar years 1996–2011.

Calendar Year	No. RA Patients in the DNPR	Average No. DDD Per RA Patient, Per Yr	No. Patients with RA Who Had CRP Measurement	Median CRP, mg/l (IQR)
1996	3432	145.0	343	20.5 (10.0–43.5)
1997	3797	163.7	753	20.0 (10.8–43.3)
1998	4168	239.0	979	19.0 (11.1–39.4)
1999	4457	244.8	1796	15.5 (10.0–32.2)
2000	4785	249.8	2589	13.6 (8.0–30.4)
2001	5055	264.3	2882	14.7 (8.9–32.0)
2002	5322	401.5	3095	15.0 (8.9–32.4)
2003	5549	429.7	3274	13.3 (8.1–29.6)
2004	5813	530.7	3501	12.1 (7.4–26.2)
2005	6077	660.4	3697	11.6 (6.8–25.3)
2006	6355	792.6	4576	11.2 (6.3–23.5)
2007	6659	670.0	4818	10.8 (6.0–22.5)
2008	6930	751.5	4862	10.4 (6.2–22.0)
2009	7124	724.2	5590	10.0 (4.7–19.2)
2010	7294	695.4	5828	10.0 (4.3–18.3)
2011	7508	—	6137	10.0 (4.2–17.8)

\*Level of disease activity measured with median C-reactive protein (CRP) levels based on at least 1 CRP measurement per patient per year. DNPR: Danish National Patient Register; DDD: defined daily doses; IQR: interquartile range.

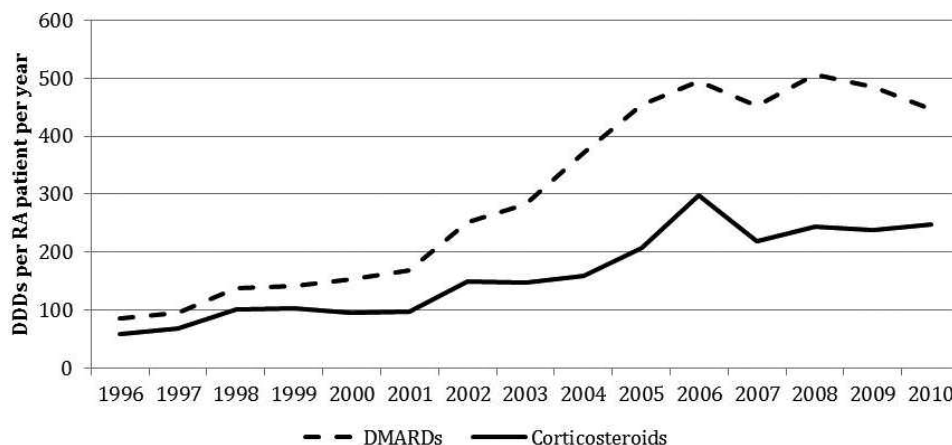


Figure 1. Annual use of DMARD and corticosteroids in patients with rheumatoid arthritis (RA) during 1996–2010 in Northern Denmark. DDD: defined daily doses; DMARD: disease-modifying antirheumatic drugs.

restricted to outpatients with measured CRP levels (data not shown).

*Use of orthopedic procedures.* The mean age at the time of first orthopedic procedure increased from 60.6 years in 1996 to 67.5 years in 2012. The proportion of patients with RA to undergo hip replacement procedures decreased by one-third from 14.9% (512/3432) in 1996 to 10.1% (764/7575) in 2012 (Figure 2). The proportion of patients with RA who underwent other joint procedures decreased by 20% from 29.1% (1000/3432) in 1996 to 23.4% (1770/7575) in 2012 (Figure 2). In contrast, the proportion of patients with RA who underwent soft tissue procedures showed a 13% increase from 20.7% (710/3432) in 1996 to 23.4% (1774/7575) in 2012 (Figure 2).

The annual proportion of patients who underwent hip

replacement procedures clearly decreased over the study period, both among patients less than 60 years of age and among those older than 60 years (Figures 3 and 4). In contrast, the proportions of other joint procedures and soft tissue procedures increased by 28% and 87%, respectively, among patients younger than 60 years of age (Figure 3), but decreased by 57% and 19%, respectively, among those older than 60 years (Figure 4).

Sensitivity analyses restricted to patients with RA with at least 2 RA diagnoses registered in the DNPR during the 1977–2011 study period did not change the magnitude or direction of our estimates (data not shown).

## DISCUSSION

The results of our study showed that antirheumatic drug

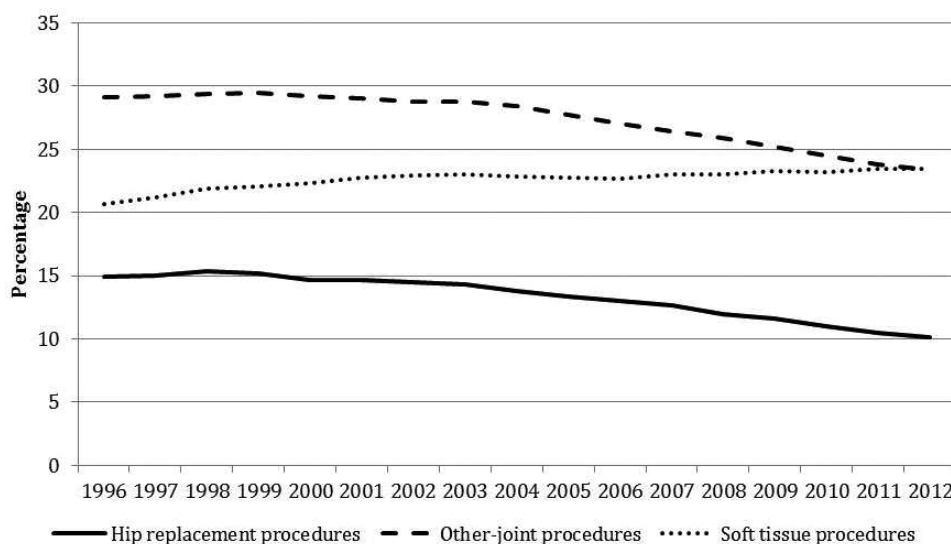


Figure 2. The annual proportion of patients with orthopedic procedures among all patients with rheumatoid arthritis during 1996–2012 in Northern Denmark.



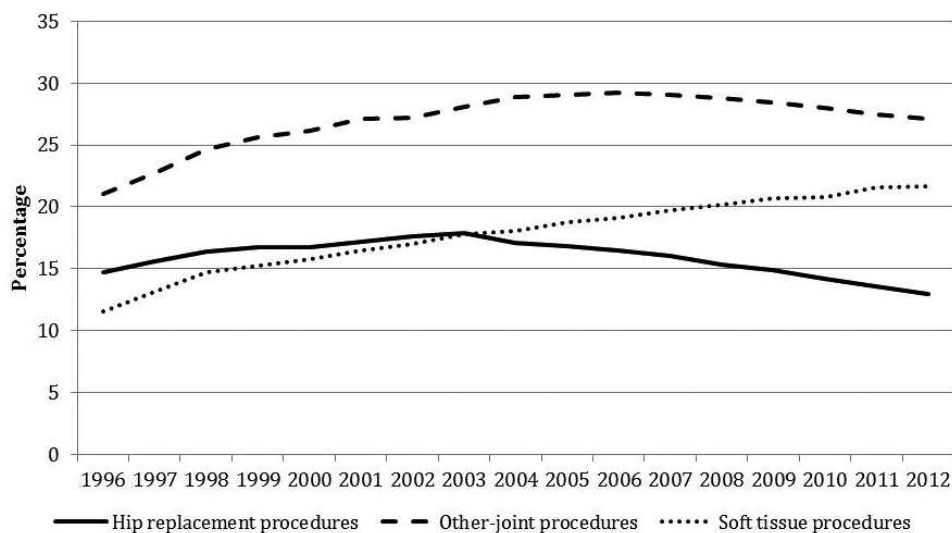


Figure 3. The annual proportion of orthopedic procedures among patients with rheumatoid arthritis who were  $\leq 60$  years old during 1996–2012 in Northern Denmark.

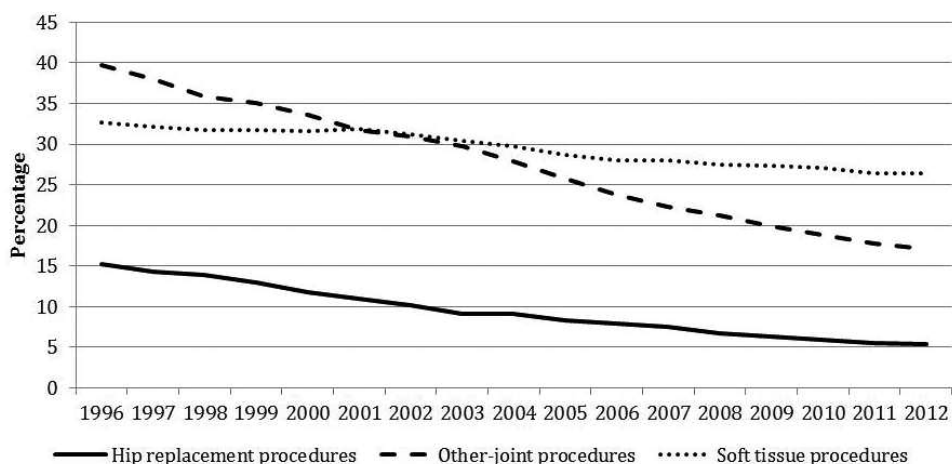


Figure 4. The annual proportion of orthopedic procedures among rheumatoid arthritis patients who were  $> 60$  years old during 1996–2012 in Northern Denmark.

consumption among patients with RA increased 4.8-fold between 1996 and 2011, accompanied by about a 50% reduction in CRP level within this patient population. Additionally, mean age at the time of first orthopedic procedure increased during our study period. The use of hip replacement procedures in patients with RA decreased irrespective of patient age. In contrast, the use of other joint and soft tissue procedures increased among patients with RA below 60 years of age, and decreased in patients with RA older than 60 years.

The presently observed trend of declining hip joint procedures among patients with RA from 1996–2011 is in accordance with previous findings from Europe and the United States between 1955–2010<sup>8,11,16,17,22</sup>. However, a study from

Japan indicated that the number of arthroplasty procedures performed on upper and lower limbs was relatively stable or even increased during the period 1998–2008<sup>34</sup>. The authors speculated that this trend could be due to amelioration of disease activity among patients with established RA who wanted a better quality of life rather than only pain reduction. In contrast to our present population-based design, the Japanese study was based on patients from several university hospitals and it can be questioned whether the procedures rates in these hospitals are representative of the overall trend of surgeries among patients with RA in Japan. We overcame this limitation using a population-based design including patients from all Danish hospitals into the study population, providing a more valid estimate of surgery trend analyses.

The declining use of hip joint procedures since 1996 cannot be explained by increasing use of biological drugs because these were first introduced in 2006 and used very rarely in the first several years.

Also in contrast to our findings, a study of older arthritis patients from Norway reported an increasing use of joint procedures<sup>16</sup>. Mean age at surgery was higher than in our study, suggesting that the analyzed Norwegian patients were diagnosed before treatment recommendation changed to include more aggressive antirheumatic treatment. For the first time, to our knowledge, we reported on the age-specific use of orthopedic procedures in patients with RA using population-based study design.

Previous studies<sup>7,10,15,16</sup> including the above-mentioned Japanese study<sup>34</sup> have reported a general decrease in the use of soft tissue procedures. Based on age-specific estimates of usage of procedures, the present data showed a decrease only among our older patients, while the use of soft tissue procedures doubled among patients 60 years of age or younger. Similarly, Boonen, *et al* examined 285 patients with RA (mean age: 57 yrs) at 5 hospitals in the Netherlands and found increasing use of non-joint-sacrificing procedures (including synovectomy) among patients diagnosed after 1990 compared with those diagnosed before 1990<sup>20</sup>. Soft tissue procedures to control local inflammation may be increasingly used early in the disease course as an adjuvant to medical therapy. However, our findings indicate that the previously suggested shift toward more frequent and earlier non-joint-sacrificing surgery in patients with RA is limited to patients younger than 60 years.

We also observed a large increase in the consumption of antirheumatic drugs over the study period. This corroborates findings from a recent Finnish population-based study, which reported a 2- to 4-fold increase in the use of antirheumatic drugs (mostly DMARD) during the period 1995–2010<sup>21</sup>. In line with our results, those authors also reported a strong relationship between the total annual numbers of joint procedures and methotrexate consumption per patient<sup>21</sup>. In contrast, Kononoff, *et al*<sup>35</sup> found no association between intensification of antirheumatic treatment and decreasing need for joint procedures in a comparison of small cohorts of patients with RA in 1990–1992 and 2000–2001.

Only sparse previous epidemiological data are available regarding changes in RA disease activity in orthopedic disease patients over calendar time. Welsing, *et al*<sup>36</sup> monitored all patients with RA who attended 1 rheumatology clinic in the Netherlands since 1985, and reported decreasing disease activity as assessed by nurses using the Disease Activity Score. However, self-assessed disease activity (evaluated using questionnaires of disease activity and functional disability) indicated worsening over time in the same patient population<sup>36</sup>. The study was too small to draw firm conclusions. Another small cross-sectional study showed also a decrease of median CRP from 15 mg/l in a cohort of

45 arthroplasty patients in 1990–1992 to 5 mg/l among 62 arthroplasty patients in 2000–2002<sup>35</sup>. Use of DMARD combinations was more pronounced in the latter cohort. The presently observed ~50% decrease in median CRP over the study period confirm and extend previous findings by using a population-based design.

*Methodological considerations.* The strengths of our study include the large size and the population-based design within a uniformly organized healthcare system with free access to medical care for all citizens, which reduced the risk of the selection problems that have hampered previous studies. The use of population-based registries enabled identification and complete followup of all patients with RA.

The use of discharge diagnoses may be associated with diagnostic and coding errors. A previous Danish study showed that 59% of RA diagnoses registered in the DNPR between 1997–2001 fulfilled the 1987 American College of Rheumatology (ACR) criteria for RA, with a lower positive predictive value (42%) found among patients with only a single RA diagnosis registered<sup>37</sup>. Therefore, our use of clinical diagnoses of RA made by hospital physicians may have overestimated the true size of the RA population. Correspondingly, our observed RA incidence of 46 per 100,000 person-years was slightly higher than the RA incidence of 35 per 100,000 person-years reported from Southern Denmark in 1995–2001<sup>23</sup>, with the latter based only on patients fulfilling the 1987 ACR criteria. Our presently determined incidence was very similar to those reported in Sweden (41 per 100,000 person-yr)<sup>38</sup>, Finland (45 per 100,000 person-yr)<sup>39</sup>, and Olmsted County, USA (41 per 100,000 person-yr)<sup>40</sup>. Further, restricting our analysis to patients with more than 1 registered RA diagnosis did not materially change our estimates.

We lacked information on RA activity other than CRP level. CRP is an accurate indicator of inflammation<sup>41</sup>; however, it also indicates inflammation caused by, e.g., infection. Additionally, the information on CRP measurements was incomplete, particularly prior to 2000. It is possible that the patients lacking information on CRP level during the early years of the study period were largely patients with low disease activity, and thus some of the observed decrease in CRP level could be explained by more complete registration in the later years. However, a clearly decreasing trend in CRP levels was also observed in the period 2000–2011 for which we had more complete CRP registration. Further, if all patients with RA diagnosed before 1996 were not included in the study population, our present study design would be subject to bias due to left truncation. Although we included all patients with RA diagnosed between 1977–1996, we may have missed some patients diagnosed before 1977, and thus underestimated the study population. Finally, the ecological cross-sectional design<sup>42</sup> of our study does not allow us to draw any firm conclusion on causal associations.

Here we observed a more than 4-fold increase in antirheumatic drug consumption since the mid-1990s among Danish patients with RA. In the same period, we found reduced disease activity in this patient population, as suggested by a roughly halved median CRP level. Additionally, the mean age at the time of first orthopedic procedure increased during our study period. The use of hip replacement procedures decreased irrespective of patient age. In contrast, changes in other joint and soft tissue procedures over time seemed to be age-dependent, with increased frequency among patients below 60 years of age, and decreased frequency among those above 60 years of age.

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