Effect of Rheumatoid Arthritis on Longterm Sickness Absence in 1994-2011: A Danish Cohort Study

Sofie Mandrup Hansen, Merete Lund Hetland, Jacob Pedersen, Mikkel Østergaard, Tine Steen Rubak, and Jakob Bue Bjorner

ABSTRACT. ***Objective.*** By linkage of national registries, we investigated the risk of longterm sickness absence (LTSA) ≥ 3 weeks in a large cohort of Danish patients with rheumatoid arthritis (RA) and non-patients. The study aimed to (1) estimate the risk of LTSA for patients with RA compared with the general population, (2) examine whether the risk of LTSA has changed in recent years, and (3) evaluate the effect of other risk factors for LTSA (e.g., physical work demands, age, sex, education, and psychiatric and somatic comorbidities).

Methods. A total of 6677 patients with RA aged 18–59 years in the years 1994–2011 were identified in registries and compared with 56,955 controls from the general population matched by age, sex, and city size. The risk of LTSA was analyzed using Cox proportional hazards models with late entry, controlling for other risk factors and assuming separate risks in the first year after diagnosis and the following years.

Results. Compared with the general population, patients with RA had increased risk of LTSA in the first year after diagnosis (HR 5.4 during 1994–1999, 95% CI 4.2–6.8) and in following years (HR 2.4, 95% CI 2.1–2.8). For established RA (> 1 yr after diagnosis), the excess was 20% lower in 2006–2011 (HR 1.9, 95% CI 1.7–2.2) compared with 1994–1999 ($p < 0.001$). For patients with RA and controls, older age, shorter education, a physically demanding job, and somatic and/or psychiatric comorbidities increased the risk of LTSA.

Conclusion. While improvements were observed from 1994–1999 to 2006–2011, patients with RA have significant increased risk of LTSA, in particular in the first year after diagnosis. (First Release February 15 2016; J Rheumatol 2016;43:707–15; doi:10.3899/jrheum.150801)

Key Indexing Terms:
RHEUMATOID ARTHRITIS SICK LEAVE EMPLOYEE WORK LOAD
REGISTRY COHORT STUDY COX PROPORTIONAL HAZARDS MODEL

Rheumatoid arthritis (RA) is a chronic inflammatory disease, which has a large effect on a patient's physical function and somatic and mental health. Two-thirds of individuals who are diagnosed with RA are at working age[1], and therefore risk longterm sickness absence (LTSA) and work disability. The risk seems to be highest in the first year after RA diagnosis and stabilizes at a lower level with small annual increases during the subsequent years[2,3]. During the past 15 years, the treatment of RA has changed toward earlier and more aggressive treatment with synthetic and biologic disease-modifying antirheumatic drugs[4,5,6,7]. This appears to have reduced the risk of LTSA[2,3]. In addition to RA severity and duration, the risk of LTSA may also be influenced by personal and environmental factors such as sex, age, lifestyle, physically demanding jobs, lower educational level, and socioeconomic status[7,8,9]. LTSA is an important outcome for

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Supported by The Working Environment Research Fund [20110013129/1], The Danish Rheumatism Association [R83-A1466-B554], and an unrestricted research grant from Pfizer Denmark. M.L. Hetland has received consultancy fees or research grants from Pfizer. M. Østergaard has received consultancy/speaker fees and/or research support from Pfizer.

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Accepted for publication December 18, 2015.

patients with RA, both from an individual and a societal perspective. For the individual patient, LTSA often leads to reduced income and loss of contact with colleagues. Further, LTSA puts the patient at higher risk for permanent exclusion from the labor market. From a societal perspective, LTSA represents a significant loss of production and is a substantial economic burden[10]. By linkage of national registries in Denmark, we simultaneously investigated, to our knowledge, for the first time several aspects of the risk of LTSA in a large cohort of patients with RA. The aims of our study were (1) to estimate the risk of LTSA for patients with RA compared with the general population, (2) to study whether the risk of LTSA has changed over the last decades, and (3) to evaluate the effect of other risk factors for LTSA, such as physically demanding jobs, sex, education, and comorbidities.

MATERIALS AND METHODS

Data sources. We identified patients with RA from the nationwide DANBIO registry and the Danish National Patient Registry (NPR), and matched them with controls from the general population. The DANBIO is a nationwide registry that provides data on the disease course of adult patients with inflammatory rheumatic joint diseases[11,12,13]. The NPR includes all hospital admissions (since 1977) and outpatient activities (since 1995) in Denmark, and patients were registered by diagnoses according to the International Classification of Diseases codes (1978–1993: ICD-8; 1994–2011: ICD-10)[14]. The NPR was also used to identify comorbidity in combination with the Danish National Prescription Registry (PRESCRIBE), which provides information on all prescribed medications dispensed from Danish pharmacies since 1995. We were not able to obtain information about biological treatment because biologic drugs are dispensed by the hospitals and not registered in PRESCRIBE.

We retrieved individual data on LTSA from the Danish Register of Evaluation of Marginalization (DREAM) register, which provides weekly information on social transfer payments for all residents in Denmark (since July 1991). It is based on data from the Danish ministries of Employment, Social Affairs, and Education, and has been shown to be suitable for followup of social consequences of disease[15]. To be eligible for sickness absence benefit, the employee must have worked a minimum of 120 h during the last 13 weeks[16].

Data from these registers were linked through the central personal register number, a unique personal identifier given at birth to all Danes.

The study cohort: patients with RA and controls. From the DANBIO, which has an estimated coverage of 79%, we identified a cohort of patients with RA aged 18–59 years at the time of RA diagnosis and who were diagnosed with the disease between 1991 and 2011 (n = 4865)[17]. For each patient, 10 controls from the general population were identified in the nationwide registers of Statistics Denmark, matched for sex, age, and city size. To identify additional patients with RA who were not registered in the DANBIO, the control group was screened in the NPR for individuals who had been hospitalized or received outpatient treatment with an RA diagnosis 3 or more times. This has been shown to be a valid approach to identify patients with RA in the NPR[18]. Thus, the following codes from the ICD-8 and ICD-10 were used: 712.19 (Syndroma Felty), 712.39 (Arthritis rheumatoides alia et non specificata), 712.59 (Fibrositis rheumatoides chronica nodularis), DM05 (Arthritis rheumatoides seropositiva), and DM06 (Arthritis rheumatoides alia) except DM06.1 (Still's disease)[18]. Such patients (n = 1812) were included in the RA group and excluded from the control group (total number of patients with RA = 6677). Individuals with uncertain RA status (i.e., only 1 or 2 relevant RA diagnoses in the NPR) were excluded from the analysis. The controls were then rematched to the merged population by sex, age, and city size, leading to a minimum of 8 controls per patient and a maximum of 10 controls per patient with RA, the median being 9 controls per patient with RA. In sensitivity analysis, comparing results with and without patients with RA from the NPR, we found no difference in HR, but increased estimate precision when NPR patients were included.

Primary outcome variable. Individuals were classified as having LTSA if receiving sickness absence benefits for a period of at least 3 weeks. Briefly, this definition was used because the sickness absence became registered in the DREAM at 3 or more weeks of sickness absence when the municipalities became responsible for managing the sickness absence cases[19,20]. Followup started January 1, 1994, and ended April 1, 2011.

Covariates. Ten variables were included in the analysis: (1) RA classified as seronegative (including nonspecific RA) or seropositive, (2) calendar year (1994–1999, 2000–2005, or 2006–2011), (3) sex, (4) age (18–29, 30–39, 40–49, or 50–59 yrs), (5) immigrant status (immigrant, immigrant descendant, or Danish), (6) household composition (single or cohabitants with or without children, including singles living with children), (7) city size (capital center, closest suburbs, the metropolitan area, city > 100,000 inhabitants, city 10,000–100,000 inhabitants, or the rest of the country), (8) highest obtained education (at most high school, vocational training, tertiary/polytechnic school, higher education, e.g., Master, PhD), (9) physical job exposure (0 kg/day, 1–5999 kg/day, ≥ 6000 kg/day), and (10) somatic and psychiatric comorbidities. In addition, we controlled for seasonal variations in LTSA.

To control for diseases that could be competing causes of LTSA, we adjusted for 18 groups of chronic, somatic comorbidities (cancer, thyroid diseases, diabetes, other endocrine, nutritional and metabolic diseases, obesity, neurological diseases, chronic diseases of the ears, hypertension, chronic pulmonary diseases including asthma, cardiac disease, stroke, inflammatory bowel disease, diseases of the liver, diseases of the skin, kidney diseases, gynecological diseases, and transplantations) and 4 groups of psychiatric comorbidities (dementia, substance abuse, anxiety, and depression). These comorbidities were selected by an expert panel prior to data analysis.

Physical job exposure was estimated from job type (retrieved from the DREAM) using a job exposure matrix that is based on the Danish version of the International Standard Classification of Occupations (DISCO-88)[14,21]. The job exposure matrix is described elsewhere[22,23]. For our present study, physical job exposure was categorized into 3 groups according to estimated kilograms lifted per work day: 0 kg/day, 1–5999 kg/day, and ≥ 6000 kg/day.

All variables except sex and immigrant status were treated as time-dependent variables, thus taking into account that individuals may change status during the period of observation.

Analysis. The HR of LTSA for employees was estimated using the Cox proportional hazards model (SAS 9.2 PROC PHREG) with latent entry, i.e., the patient was included in the analysis when he or she was diagnosed with RA, and the matched controls appeared at the same time. LTSA was treated as a repeated event by the use of a frailty model[24,25]. Using frailty models is a common way to quantify the person variation that arises when subjects have more than 1 period of LTSA. It allows dependence of multiple events in the analysis, and it makes use of the heterogeneity in this type of dataset when estimating hazards[25]. *A priori*, our analyses of LTSA assumed separate risks in the first year after diagnosis, and the subsequent years after diagnosis. The assumption of proportionality has been investigated by visual inspection of cumulative hazard curves for each covariate.

Subjects were censored if they died, turned 60 years, emigrated, became unemployed, received disability pension, or at the end of the observation period (2011), whichever came first. Subjects were temporarily out of risk if they were on maternity leave, other kinds of leave, or students. Initial analyses were performed separately for the 2 sexes, but because the results were similar, the final analysis was performed on the combined population, controlling for sex. We analyzed the risk of LTSA for seronegative and seropositive patients with RA and found no difference. Thus, the 2 groups were combined in the final analysis. We analyzed the HR in 3 models of

increasing complexity. In model 1, analyses were controlled for sociodemographic confounders (age, sex, ethnicity, urbanization, highest obtained education, and family type). In model 2, we also controlled for somatic and psychiatric comorbidities. In model 3, interactions between RA and all the covariates were added as well, 1 at a time. Only results that were significant are shown (interactions between RA and calendar year, sex, and somatic and psychiatric comorbidities). Each analysis was controlled for the 10 covariates.

Ethics approval. The study was approved by the Danish Data Protection Agency, journal number: 2015-41-3828.

RESULTS

Sample characteristics. Table 1 describes the characteristics of the study population at entry. Age, sex, household status, level of education, physically demanding jobs, and urbanization were largely similar between patients and controls, whereas more patients were of Danish origin. Compared with the controls, more patients experienced somatic, but not psychiatric, comorbidities.

Events of LTSA. For patients with RA, 983 events (start of LTSA) were observed in the first year after diagnosis [out of 2735 person-years (PY) of observation]. Thus, the rate of LTSA was 0.36 events/PY. In subsequent years, 2951 events were observed during 19,577 PY for a rate of 0.15 events/PY. For controls, 2417 events were observed within the first year of diagnosis of the index patient (out of 30,399 PY, rate = 0.08 events/PY). In subsequent years, 21,404 events were observed during 266,270 PY for a similar rate of 0.08 events/PY.

Cumulative hazards stratified by calendar years. Figure 1 shows the cumulative hazards (risk of LTSA) for the 2 groups stratified on the 3 periods with separate graphs for the first year after diagnosis (Figure 1A) and subsequent years (Figure 1B). For the control group, the cumulative hazards increased from 1994–1999 to 2000–2005 and also increased slightly from 2000–2005 to 2006–2011. The RA group followed the same pattern for the periods 1994–1999 and 2000–2005, whereas the 2006–2011 period showed lower cumulative hazards than 2000–2005.

Table 1. Characteristics of patients with RA and of the controls when entering the study. Values are %.

Characteristics		RA Population, n = 6677	Control Population, n = 56,955
Year of diagnosis	1994–1999	38.5	—
	2000–2005	31.9	—
	2005–2011	29.6	—
Sex	Female	73.6	73.3
	Male	26.4	26.7
Age, yrs	≤ 29	7.5	7.2
	30–39	18.7	19.7
	40–49	33.1	33.8
	50–59	40.8	39.3
Immigrant status	Danish	94.6	87.0
	Immigrant	5.2	12.8
	Descendants	0.3	0.2
Household composition	Cohabitants with or without children, and singles living with children	77.4	77.3
	Singles	22.6	22.7
City size	Capital center	14.1	12.6
	Closest suburbs	13.9	15.5
	The metropolitan area	6.5	7.6
	City > 100,000	9.9	12.1
	City 10,000–100,000	29.4	27.5
	Rest of the country	26.2	24.8
Highest education obtained	High school	33.7	33.2
	Vocational training	39.6	35.8
	Tertiary/polytechnic school	20.9	22.2
	Higher education, e.g., Master, PhD	4.2	5.9
	NA	1.6	2.9
Physical job exposure	0	43.3	44.5
Estimated kg lifted per day	1–5999	31.5	32.3
	≥ 6000	25.2	23.2
Somatic comorbidity	0	69.4	75.7
	≥ 1	30.6	24.3
Psychiatric comorbidity	0	91.3	92.2
	≥ 1	8.7	7.8

RA: rheumatoid arthritis; NA: not applicable.

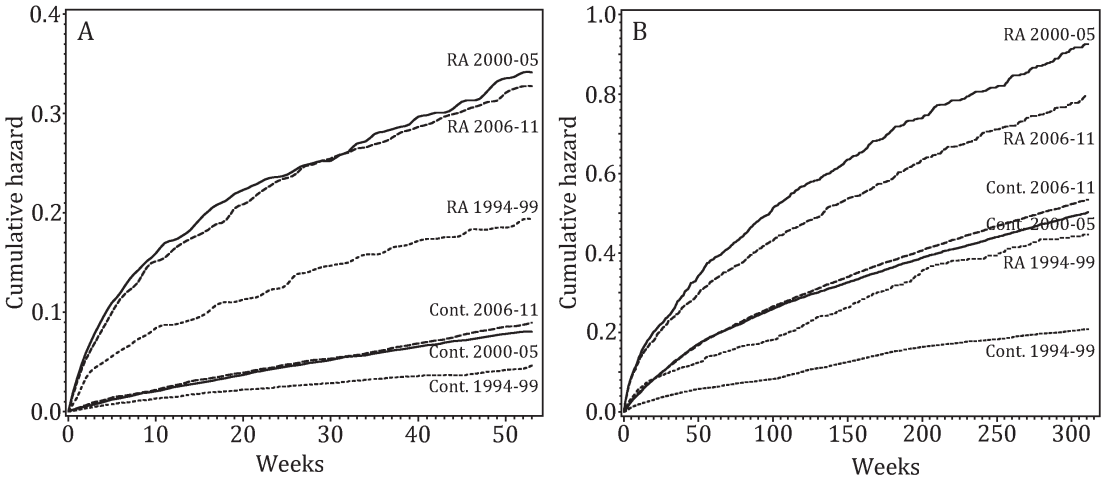

Figure 1. Cumulative hazard for longterm sickness absence in patients with RA and their controls stratified by calendar year of diagnosis. (A) The cumulative hazards for the first year after RA diagnosis. (B) The cumulative hazards for following years. The cumulative hazards for the controls are calculated from the time of diagnosis of their matched patient with RA. Note that Figure 1A is on a scale from 0.0 to 0.4 and at 52 weeks, while Figure 1B is on a scale from 0.0 to 1.0 and at 312 weeks. RA: rheumatoid arthritis; Cont.: controls.

Risk of LTSA: Model 1. Patients with RA had an HR of LTSA of 4.1 in the first year after diagnosis (Table 2, model 1) and 1.8 in subsequent years (Table 3, model 1) compared with the general population. In general, risk of LTSA was higher in the years 2000–2005 and 2006–2011 compared with 1994–1999. Also, the risk was lower for men than for women. The risk of LTSA decreased with higher educational level with an HR of about 0.5 for individuals with at least a college degree compared with those with only elementary schooling or high school degree. A physically demanding job significantly increased the risk of LTSA.

Risk of LTSA: Model 2. In model 2, the risk for LTSA was higher for persons with somatic or psychiatric comorbidity, but the inclusion of these variables did not change the risk estimates for RA (Table 2 and Table 3, model 2).

Risk of LTSA: Model 3. Significant interactions were found between RA and sex, calendar year, and somatic and psychiatric comorbidities (Table 2 and Table 3). We also tested for interactions between RA and the other covariates as well as between education and physical job exposure, but did not find significant results. The HR of LTSA during the years 1994–1999 for a woman with RA and no comorbidity was 5.4 (95% CI 4.2–6.8) in the first year after diagnosis and 2.4 (2.1–2.8) in subsequent years (Table 2 and Table 3, model 3). The interaction effect was < 1 between RA diagnosis and the years 2000–2005 and 2006–2011. Thus, the excess risk of LTSA in patients with RA through more than 1 year was reduced by 20% (HR 0.8, 95% CI 0.7–0.9) in the years 2006–2011 compared with 1994–1999 (Table 3). These interaction effects were not significant in the first year after diagnosis, but highly significant in subsequent years ($p < 0.001$; Table 3). An interaction effect above 1 between male sex and RA through more than a year ($p < 0.05$; Table 3) indicates that the sex difference in LTSA was less pronounced among patients with RA than among the general population. We found interaction effects < 1 between RA diagnosis and somatic and psychiatric comorbidities, which reflected that although RA diagnosis as well as other somatic and psychiatric diseases increased the risk of LTSA, the interaction effect was less than the product of the individual effects.

Effect of certain risk factors on LTSA in RA: the interaction variables. Table 4 illustrates the implications of the interaction variables from model 3 in Table 2 and Table 3 for comparisons between patients with RA with and without certain risk factors. For example, patients with RA with psychiatric comorbidity had an HR 1.2 of LTSA within the first year of diagnosis compared with patients with RA without psychiatric comorbidity. In subsequent years, the HR was 1.5.

Combination of risk factors for LTSA in RA compared with controls. Table 5 compares the risks within particular risk groups or years for persons with RA compared with controls based on the variables from model 3. For any combination of risk factors for LTSA, an RA diagnosis constituted a considerable additional risk factor both in the first year after diagnosis (HR 2.7–5.4) and in subsequent years (HR 1.5–2.4).

DISCUSSION

Our results show that patients with RA had substantially increased risk of LTSA, both in the first year after diagnosis and in subsequent years. Thus, in the years 2006–2011, a woman with RA had an HR of 4.8 for LTSA in the first year after diagnosis and an HR of 1.9 in subsequent years. These results are in line with previous studies[2,3], but the large size of our study allowed more precise estimation of the risk and more detailed analyses of potentially modifiable factors.

Table 2. Results from analyses by proportional hazards models of longterm sickness absence during the first year after diagnosis with RA. All analyses were controlled for ethnicity, urbanization, season, and family type.

Variables	Model 1		Model 2		Model 3	
	HR	95% CI	HR	95% CI	HR	95% CI
RA†						
No	1		1		1	
Yes	4.1***	3.8–4.5	4.0***	3.6–4.3	5.4***	4.2–6.8
Calendar yr						
1994–1999	1		1		1	
2000–2005	1.8***	1.7–2.0	1.6***	1.5–1.8	1.7***	1.5–1.9
2006–2011	2.0***	1.8–2.2	1.7***	1.5–1.9	1.7***	1.5–2.0
Sex						
Female	1		1		1	
Male	0.7***	0.6–0.7	0.7***	0.6–0.8	0.7***	0.6–0.7
Highest education obtained						
Elementary school/high school	1		1		1	
Vocational training	1.0	0.9–1.0	1.0	0.9–1.1	1.0	0.9–1.0
Tertiary/polytechnic school	0.8***	0.8–0.9	0.8***	0.8–0.9	0.8***	0.7–0.9
Higher education, e.g., Master, PhD	0.4***	0.3–0.5	0.4***	0.3–0.5	0.4***	0.3–0.5
NA	1.2	1.0–1.6	1.2	1.0–1.6	1.2	1.0–1.6
Physical job exposure, kg/day						
0	1		1		1	
1–5999	1.6***	1.5–1.8	1.6***	1.5–1.8	1.6***	1.5–1.8
≥ 6000	2.0***	1.8–2.2	1.9***	1.8–2.1	1.9***	1.7–2.1
Somatic comorbidity‡						
No	—		1		1	
Yes	—		1.5***	1.4–1.6	1.6***	1.5–1.8
Psychiatric comorbidity						
No	—		1		1	
Yes	—		2.0***	1.8–2.2	2.2***	2.0–2.5
RA × calendar yr						
1994–1999	—		—		1	
2000–2005	—		—		1.0	0.8–1.2
2006–2011	—		—		0.9	0.7–1.1
RA × sex						
Female	—		—		1	
Male	—		—		1.1	0.9–1.3
RA × somatic comorbidity‡						
No	—		—		1	
Yes	—		—		0.7**	0.6–0.9
RA × psychiatric comorbidity						
No	—		—		1	
Yes	—		—		0.6***	0.4–0.7

† Patients with RA (n = 6677) and matched controls (n = 56,955). ‡ Somatic morbidity except RA. ** $p < 0.01$. *** $p < 0.001$. RA: rheumatoid arthritis; NA: not applicable.

For both the patient and general population, the risk of LTSA increased from 1994–1999 to 2000–2005, probably because of the changing conditions in the Danish labor market (with a possible additional effect of improved registration)[26]. The risk remained high for the general population during 2006–2011, but decreased for patients with RA — in particular, over a year after diagnosis. The HR of LTSA for patients with RA was reduced by 20% when we compared recent years (2006–2011) with the earliest period of observation (1994–1999). Previous studies have shown positive results of treatment with biological drugs on LTSA. In a cohort study comparing patients with RA starting biological treatment with the general population, a decrease of almost 30% in LTSA was observed during the first year of biological treatment[27]. The study included only patients with RA who completed the biological treatment, which may have biased the result. Also, a decrease in LTSA as a result of treatment with biologics was shown in 2 randomized controlled trials[28,29]. In the first study, the odds for favorable employment status were ~1.5 in patients treated with combination treatment [adalimumab + methotrexate (MTX)] versus MTX alone[29]. In the second study, combination treatment (certolizumab pegol + MTX) led to a cumulative annual gain of ~40 full work days and ~30 fewer days with reduced

Table 3. Results from analyses by proportional hazards models of longterm sickness absence more than 1 year after diagnosis with RA. All analyses were controlled for ethnicity, urbanization, season, and family type.

Variables	Model 1		Model 2		Model 3	
	HR	95% CI	HR	95% CI	HR	95% CI
RA[†]						
No	1		1		1	
Yes	1.8***	1.7–1.9	1.8***	1.8–1.9	2.4***	2.1–2.8
Calendar yr						
1994–1999	1		1		1	
2000–2005	2.3***	2.1–2.4	2.0***	1.9–2.1	2.0***	1.9–2.1
2006–2011	2.3***	2.2–2.4	1.9***	1.8–2.0	2.0***	1.8–2.1
Sex						
Female	1		1		1	
Male	0.7***	0.7–0.7	0.8***	0.7–0.8	0.7***	0.7–0.8
Highest education obtained						
Elementary school/high school	1		1		1	
Vocational training	0.9***	0.9–1.0	0.9***	0.9–1.0	0.9***	0.9–1.0
Tertiary/polytechnic school	0.8***	0.8–0.9	0.8***	0.8–0.9	0.8***	0.8–0.9
Higher education, e.g., Master, PhD	0.5***	0.5–0.6	0.5***	0.5–0.6	0.5***	0.5–0.6
NA	1.0	0.9–1.1	1.0	0.9–1.1	1.0	0.9–1.1
Physical job exposure, kg/day						
0	1		1		1	
1–5999	1.4***	1.3–1.4	1.4***	1.3–1.4	1.3***	1.3–1.4
≥ 6000	1.6***	1.5–1.6	1.5***	1.5–1.6	1.5***	1.5–1.6
Somatic comorbidity[‡]						
No	—		1		1	
Yes	—		1.5***	1.5–1.6	1.5***	1.5–1.6
Psychiatric comorbidity						
No	—		1		1	
Yes	—		1.9***	1.8–1.9	1.9***	1.8–2.0
RA × calendar yr						
1994–1999	—		—		1	
2000–2005	—		—		0.9	0.8–1.1
2006–2011	—		—		0.8***	0.7–0.9
RA × sex						
Female	—		—		1	
Male	—		—		1.1*	1.0–1.3
RA × somatic comorbidity[‡]						
No	—		—		1	
Yes	—		—		0.8***	0.7–0.9
RA × psychiatric comorbidity						
No	—		—		1	
Yes	—		—		0.8**	0.7–0.9

[†] Patients with RA (n = 6677) and matched controls (n = 56,955). [‡] Somatic morbidity except RA. * $p < 0.05$. ** $p < 0.01$. *** $p < 0.001$. RA: rheumatoid arthritis; NA: not applicable.

productivity compared with placebo + MTX[28]. These results suggest that modern treatment strategies including but not limited to[30,31] the use of biologics reduce LTSA for patients with RA. In our study, however, we did not have access to data that could support this hypothesis. Other factors may also have influenced the risk of LTSA, e.g., improved treatment strategies for conventional drugs, earlier diagnosis, and advances on health education programs.

Similar to the general population, patients with RA with a short education and/or high physical strain at work had an increased risk of LTSA. This is an important finding because level of education and the amount of physical job strain are potentially modifiable factors. Other important risk factors identified in our study (age, family type, and education) also similarly influenced the risk for LTSA for patients with RA and the general population, and therefore are not specific for patients with RA. Generally, women had a higher risk of LTSA than men, and although this was also the case for patients with RA, the difference between male and female patients with RA was less than in the general population. We had expected the risk to be higher for patients with seropositive RA, but this was not the case. We did not have access to data on anticyclic citrullinated peptide antibody status. Patients with RA and somatic or psychiatric comorbidity had

Table 4. HR for longterm sickness absence for patients with rheumatoid arthritis with or without particular risk factors*.

Variables		First Yr		Subsequent Yrs	
		HR	95% CI	HR	95% CI
Calendar yr	1994–1999	1		1	
	2000–2005	1.6	1.3–2.0	1.9	1.6–2.2
	2006–2011	1.5	1.3–1.9	1.6	1.3–1.8
Sex	Female	1		1	
	Male	0.7	0.6–0.9	0.8	0.8–0.9
Somatic comorbidity	No	1		1	
	Yes	1.2	1.0–1.4	1.3	1.1–1.4
Psychiatric comorbidity	No	1		1	
	Yes	1.2	1.0–1.5	1.5	1.3–1.7
Highest education obtained	Elementary school/ high school	1		1	
	Vocational training	1.0	0.9–1.0	0.9	0.9–1.0
	Tertiary/polytechnic school	0.8	0.7–0.9	0.8	0.8–0.9
	Higher education, e.g., Master, PhD	0.4	0.3–0.5	0.5	0.5–0.6
	NA	1.2	1.0–1.6	1.0	0.9–1.1
Physical job exposure, kg/day	0	1		1	
	1–5999	1.6	1.5–1.8	1.3	1.3–1.4
	≥ 6000	1.9	1.7–2.1	1.5	1.5–1.6

* For risk factors where an interaction effect was found, the combined effect was calculated as the product of the interaction and the main effect (e.g., the HR in the first year after diagnosis for patients with RA in 2006–2011 compared with 1994–1999 was calculated as the product of the HR for 2006–2011 (= 1.7) and the RA × period interaction effect (= 0.9; Table 2). NA: not applicable.

a higher risk for LTSA than patients without, but the risk ratios were lower for patients with RA than for the general population.

A major strength of our study is that it was a cohort study based on a nationwide registry, including > 6600 patients with RA at working age in Denmark who were compared with a large control group of 8–10 persons per patient with RA. This enabled us to calculate the HR of LTSA for patients with RA. Importantly, we investigated changes in risk across the decades, during which the treatment of RA changed to earlier and more aggressive treatment strategies. This was made possible by the combined use of administrative databases with high coverage[15,18] and the DANBIO registry with diagnoses of high validity[13].

The increase in HR of LTSA for patients with RA was robust even after controlling for a large number of covariates. Although residual confounding may exist, the results show that individuals who get RA have up to a 5-time increased risk of LTSA across, for example, sex, age, and socioeconomic factors during the first year of disease, indicating that there is substantial room for further improvement in the handling of recent-onset RA.

We had expected physical job exposure to be a specific risk factor for patients with RA, but this was not the case in our analyses. Physical exposure was defined using job codes linked with the number of kilograms lifted per day. This is a good proxy for physically demanding jobs[22,23], but it may not be the ideal way to define hard work for patients with RA who may have greater trouble with gripping and fine movements of the hands. The DANBIO contains high-quality records of the patients' disease course since 2000, but because we did not have those data for the preceding years of our study period, we chose not to include those records. Future studies may evaluate the effect of other disease-specific variables on the HR of LTSA. Our patient group may be influenced by selection bias because the DANBIO started in the 2000, i.e., patients with RA between 18 and 59 years old who died between 1994 and 1999 were not registered in the DANBIO and were only included in the study if identified from the NPR controls. Because such patients would be expected to have serious illness, our risk estimate for LTSA for the period 1994–1999 and the reduction in HR from 1994–1999 to 2006–2011 may be underestimated.

RA increased the risk of LTSA about 5 times during the first year after diagnosis and twice during subsequent years compared with the general population. Compared with

Table 5. HR for longterm sickness absence for patients with RA compared with the general population for different combinations of risk factors*.

Variables		Status on Other Variables	General Population	RA			
				First Yr		Subsequent Yr	
				HR	95% CI	HR	95% CI
Calendar yr	1994–1999	Female, no somatic or psychiatric comorbidities	1	5.4	4.2–6.8	2.4	2.1–2.8
	2000–2005		1	5.1	4.3–6.3	2.3	2.0–2.5
	2006–2011		1	4.8	4.0–5.8	1.9	1.7–2.2
Sex	Female	Yrs 2006–2011, no somatic or psychiatric	1	4.8	4.0–5.8	1.9	1.7–2.2
	Male	comorbidities	1	5.2	4.1–6.5	2.2	1.9–2.5
Somatic comorbidity	No	Female, yrs 2006–2011, no psychiatric	1	4.8	4.0–5.8	1.9	1.7–2.2
	Yes	comorbidities	1	3.6	3.0–4.3	1.6	1.4–1.7
Psychiatric comorbidity	No	Female, yrs 2006–2011, no somatic comorbidities	1	4.8	4.0–5.8	1.9	1.7–2.2
	Yes		1	2.7	2.0–3.5	1.5	1.3–1.8

* The combined effect was calculated as the product of the relevant interaction and main effects (e.g., the HR in the first yr after diagnosis for patients with RA in 2006–2011 compared with the general population was calculated as the product of the HR for RA in 1994–1999 (= 5.4) and the RA × period interaction effect (= 0.9; Table 2). RA: rheumatoid arthritis.

1994–1999, the excess longterm risk after the first year after diagnosis decreased by about 20% in 2006–2011.

ACKNOWLEDGMENT

Mette Andersen Nexø is acknowledged for writing assistance. We thank Niels Steen Krogh for assisting with management of the DANBIO data and Kathrine Carlsen for support with data management and statistical analysis concerning somatic and psychiatric comorbidities.

REFERENCES

1. Puolakka K, Kautiainen H, Pohjolainen T, Virta L. Rheumatoid arthritis (RA) remains a threat to work productivity: a nationwide register-based incidence study from Finland. Scand J Rheumatol 2010;39:436-8.
2. Puolakka K, Kautiainen H, Pekurinen M, Mottonen T, Hannonen P, Korpela M, et al; FIN-RACo Trial Group. Monetary value of lost productivity over a five year follow up in early rheumatoid arthritis estimated on the basis of official register data on patients' sickness absence and gross income: experience from the FIN-RACo trial. Ann Rheum Dis 2006;65:899-904.
3. Neovius M, Simard JF, Askling J; ARTIS Study Group. How large are the productivity losses in contemporary patients with RA, and how soon in relation to diagnosis do they develop? Ann Rheum Dis 2011;70:1010-5.
4. Ziegler S, Huscher D, Karberg K, Krause A, Wassenberg S, Zink A. Trends in treatment and outcomes of rheumatoid arthritis in Germany 1997-2007: results from the National Database of the German Collaborative Arthritis Centres. Ann Rheum Dis 2010;69:1803-8.
5. Rantalaiho VM, Kautiainen H, Jarvenpaa S, Virta L, Pohjolainen T, Korpela M, et al. Decline in work disability caused by early rheumatoid arthritis: results from a nationwide Finnish register, 2000-8. Ann Rheum Dis 2013;72:672-7.
6. Hetland ML, Østergaard M, Ejbjerg B, Jacobsen S, Stengaard-Pedersen K, Junker P, et al; CIMESTRA study group. Short- and long-term efficacy of intra-articular injections with betamethasone as part of a treat-to-target strategy in early rheumatoid arthritis: impact of joint area, repeated injections, MRI findings, anti-CCP, IgM-RF and CRP. Ann Rheum Dis 2012;71:851-6.
7. Hallert E, Husberg M, Bernfort L. The incidence of permanent work disability in patients with rheumatoid arthritis in Sweden 1990-2010: before and after introduction of biologic agents. Rheumatology 2012;51:338-46.
8. Verstappen SM. Outcomes of early rheumatoid arthritis—the WHO ICF framework. Best Pract Res Clin Rheumatol 2013;27:555-70.
9. Puolakka K, Kautiainen H, Mottonen T, Hannonen P, Hakala M, Korpela M, et al; FIN-RACo Trial Troup. Predictors of productivity loss in early rheumatoid arthritis: a 5 year follow up study. Ann Rheum Dis 2005;64:130-3.
10. Poulsen OM, Aust B, Bjorner JB, Rugulies R, Hansen JV, Tverborgvik T, et al. Effect of the Danish return-to-work program on long-term sickness absence: results from a randomized controlled trial in three municipalities. Scand J Work Environ Health 2014;40:47-56.
11. Hetland ML, Christensen IJ, Tarp U, Dreyer L, Hansen A, Hansen IT, et al; All Departments of Rheumatology in Denmark. Direct comparison of treatment responses, remission rates, and drug adherence in patients with rheumatoid arthritis treated with adalimumab, etanercept, or infliximab: results from eight years of surveillance of clinical practice in the nationwide Danish DANBIO registry. Arthritis Rheum 2010;62:22-32.
12. Dreyer L, Mellemkjær L, Andersen AR, Bennett P, Poulsen UE, Juulsgaard Ellingsen T, et al. Incidences of overall and site specific cancers in TNFα inhibitor treated patients with rheumatoid arthritis and other arthritides - a follow-up study from the DANBIO Registry. Ann Rheum Dis 2013;72:79-82.
13. Hetland ML. DANBIO—powerful research database and electronic patient record. Rheumatology 2011;50:69-77.
14. International Labour Organization. ISCO International Standard Classification of Occupations 1988. [Internet. Accessed January 7, 2016.] Available from: www.ilo.org/public/english/bureau/stat/isco/isco88/index.htm
15. Hjollund NH, Larsen FB, Andersen JH. Register-based follow-up of social benefits and other transfer payments: accuracy and degree of completeness in a Danish interdepartmental administrative database compared with a population-based survey. Scand J Public Health 2007;35:497-502.
16. Ministry of Employment. [Employment requirements in relation to the employer, sickness benefits to employees]. [Article in Danish] [Internet. Accessed January 7, 2016.] Available from: prodstoragehoeringspo.blob.core.windows.net/17f83085-b67e-4c5e-9b35-ba4a60715355/Bekendtg%C3%B8relse%20om%20opg%C3%B8relse%20af%20besk%C3%A6ftigelseskrav%20og%20beregning%20af%20sygedagpenge%20m%20v.pdf
17. Hetland ML, Jensen DV, Krogh NS. Monitoring patients with rheumatoid arthritis in routine care: experiences from a treat-to-target strategy using the DANBIO registry. Clin Exp Rheumatol 2014;32 Suppl 85:S141-6.
18. Pedersen M, Klarlund M, Jacobsen S, Svendsen AJ, Frisch M. Validity of rheumatoid arthritis diagnoses in the Danish National Patient Registry. Eur J Epidemiol 2004;19:1097-103.
19. Nexo MA, Watt T, Pedersen J, Bonnema SJ, Hegedus L, Rasmussen AK, et al. Increased risk of long-term sickness absence, lower rate of return to work, and higher risk of unemployment and disability pensioning for thyroid patients: a Danish register-based cohort study. J Clin Endocrinol Metab 2014;99:3184-92.
20. Rudbeck M. Variation in patients' sick leave between general practitioner practices. Scand J Public Health 2014;42:621-6.
21. Statistics Denmark. DISCO-88. [Website in Danish] [Internet. Accessed January 7, 2016.] Available from: www.dst.dk/da/Statistik/dokumentation/Nomenklaturer/DISCO-88.aspx
22. Rubak TS, Svendsen SW, Andersen JH, Haahr JP, Kryger A, Jensen LD, et al. An expert-based job exposure matrix for large scale epidemiologic studies of primary hip and knee osteoarthritis: the Lower Body JEM. BMC Musculoskelet Disord 2014;15:204.
23. Rubak TS, Svendsen SW, Søballe K, Frost P. Total hip replacement due to primary osteoarthritis in relation to cumulative occupational exposures and lifestyle factors: a nationwide nested case-control study. Arthritis Care Res 2014;66:1496-505.
24. Pedersen J, Bjorner JB, Burr H, Christensen KB. Transitions between sickness absence, work, unemployment, and disability in Denmark 2004-2008. Scand J Work Environ Health 2012; 38:516-26.
25. Christensen KB, Andersen PK, Smith-Hansen L, Nielsen ML, Kristensen TS. Analyzing sickness absence with statistical models for survival data. Scand J Work Environ Health 2007;33:233-9.
26. Johansen K, Bihrmann K, Mikkelsen S, Lynge E. Trends in sickness absence in Denmark. Scand J Work Environ Health 2009; 35:334-41.
27. Olofsson T, Englund M, Saxne T, Joud A, Jacobsson LT, Geborek P, et al. Decrease in sick leave among patients with rheumatoid arthritis in the first 12 months after start of treatment with tumour necrosis factor antagonists: a population-based controlled cohort study. Ann Rheum Dis 2010;69:2131-6.
28. van Vollenhoven RF, Cifaldi MA, Ray S, Chen N, Weisman MH. Improvement in work place and household productivity for patients with early rheumatoid arthritis treated with adalimumab plus methotrexate: work outcomes and their correlations with clinical

and radiographic measures from a randomized controlled trial companion study. Arthritis Care Res 2010;62:226-34.
29. Kavanaugh A, Smolen JS, Emery P, Purcaru O, Keystone E, Richard L, et al. Effect of certolizumab pegol with methotrexate on home and work place productivity and social activities in patients with active rheumatoid arthritis. Arthritis Rheum 2009;61:1592-600.
30. Rantalaiho V, Puolakka K, Korpela M, Hannonen P, Möttönen T. Long-term results of the FIN-RACo trial; treatment with a combination of traditional disease-modifying anti-rheumatic drugs is an excellent option in early rheumatoid arthritis. Clin Exp Rheumatol 2012;30 Suppl 73:S27-31.
31. Rantalaiho V, Kautiainen H, Korpela M, Puolakka K, Blåfield H, Ilva K, et al; FIN-RACo Study Group. Physicians' adherence to tight control treatment strategy and combination DMARD therapy are additively important for reaching remission and maintaining working ability in early rheumatoid arthritis: a subanalysis of the FIN-RACo trial. Ann Rheum Dis 2014;73:788-90.