# Incidence of Clinically Important 10-year Health Status and Disease Activity Levels in Population-Based Cohorts with Rheumatoid Arthritis

SIGRID ØDEGÅRD, TORE K. KVIEN, and TILL UHLIG

*ABSTRACT.* ***Objective.*** To calculate the average age- and sex-specific annual incidence of rheumatoid arthritis (RA) linked to clinically important levels of health status after 10 years, and to study time trends in 10-year disease status during a 6-year period.

***Methods.*** Patients between 20 and 79 years of age with onset of RA from 1988 to 1993 (n = 550) were asked to participate in a 10-year followup examination. Two hundred sixteen patients in different age and sex groups from 6 different annual cohorts met during the period 1998-2003. Study variables included demographic variables, medication, swollen, tender and deformed joint counts, erythrocyte sedimentation rate, Disease Activity Score (DAS28), Health Assessment Questionnaire, and pain and fatigue on a 100 mm visual analog scale and Arthritis Impact Measurement Scale 2. Age- and sex-specific incidences of RA exceeding clinically important levels 10 years after disease onset were calculated using the Poisson distribution with 95% confidence intervals. Analysis of covariance and logistic regression were used to test the influence of time on 10-year DAS28 and presence of deformed joints.

***Results.*** The average annual incidence of cases exceeding clinically important levels in disease activity and health status 10 years after disease onset increased with higher age and was highest among women. There was a tendency to lower disease activity 10 years after disease onset in the latest cohorts compared to the earliest cohorts.

***Conclusion.*** These results from population-based RA incidence cohorts provide important information to healthcare planners and support findings of secular decline in disease burden. (First Release Nov 15 2007; J Rheumatol 2008;35:54–60)

*Key Indexing Terms:*
RHEUMATOID ARTHRITIS HEALTH STATUS DISEASE ACTIVITY SCORE
10-YEAR OUTCOME ANNUAL INCIDENCE

Rheumatoid arthritis (RA) is a chronic inflammatory disease with an overall annual incidence of 25–50/100,000 in the adult population[1-4]. It has been suggested that the incidence as well as the severity of RA have decreased over recent decades[5-10].

Information on incidence of RA and consequences of the disease are important for healthcare planners. However, knowledge about incidence linked to health outcomes at followup is scarce. Such information would be particularly important since RA is a heterogeneous disease with course varying from mild to severe[11-13].

*From the Department of Rheumatology, Diakonhjemmet Hospital, and Faculty of Medicine, University of Oslo, Oslo, Norway.*

*Financed with grants from the Norwegian Foundation for Health and Rehabilitation and the Norwegian Women's Public Health Association.*

*S. Ødegård, MD; T.K. Kvien, MD, PhD, Professor, Department of Rheumatology, Diakonhjemmet Hospital and Faculty of Medicine, University of Oslo; T. Uhlig, MD, PhD, Department of Rheumatology, Diakonhjemmet Hospital.*

*Address reprint requests to Dr. S. Ødegård, Department of Rheumatology, Diakonhjemmet Hospital, N-0319 Oslo, Norway.*
*E-mail: sigrid.odegard@diakonsyk.no*

*Accepted for publication August 3, 2007.*

We have earlier reported that the annual incidence of RA in Oslo over the period from 1988 to 1993 was 25.7/100,000[4]. In this study we have examined the patients from these 6 annual population-based inception RA cohorts 10 years after disease onset. Our aim was to calculate the average age- and sex-specific annual incidence of RA linked to clinically important levels of health status after 10 years. A second aim was to study time trends in 10-year disease status for this 6-year period with disease onset.

## MATERIALS AND METHODS

*Oslo RA register (ORAR).* A register of patients with RA was established in the county of Oslo that continuously includes new cases of RA in Oslo[14,15]. To be included in the register, patients must satisfy the American College of Rheumatology classification criteria for RA[16] and have a residential address in Oslo. Ascertainment of the RA diagnosis is done by rheumatologists by a review of individual patient records. At inclusion the presence of rheumatoid factor (RF) from available examinations was recorded. Patients were classified as seropositive if the Waaler-Rose reaction (IgM RF) had been positive with a titer ≥ 64. In a prevalence study of the ORAR, the register was found to be 85% complete[14]. The incidence of RA in Oslo (age 20–79 yrs) in the period from 1988 to 1993 was 25.7/100,000, 36.7/100,000 for women and 13.8/100,000 for men. These annual numbers of new cases were linked to levels of disease severity after a followup (postal survey in 1996) 3, 4, and 5 years from disease onset[4].

*Patients in the 10-year followup*. Patients between 20 and 79 years of age with onset of RA in the period from 1988 to 1993 (n = 550) who were still living 10 years after disease onset were asked to participate in a 10-year followup examination, which was performed in the period from 1998 to 2003. After 10 years' disease duration, 77 (14%) patients had died. The overall attrition rate among the 473 patients being eligible for a followup examination was 57.7%, and this rate differed across age groups, i.e., in the oldest age group (80–89 yrs at 10-year examination) the attrition rate was 80% of the living patients. Original incidence numbers were censored by December 31, 1995, but for the 10-year followup we also examined a few patients (n = 16) who were identified later, i.e., they had disease onset during the period 1988-1993 but were included into ORAR after 1995. Two hundred sixteen patients in different age and sex groups from 6 different annual cohorts met during the period 1998-2003 for a 10-year followup examination. We used a time variable for the statistical analyses in which each year of onset was coded with a value from 0 to 5 ("0" representing the oldest cohort with RA onset in 1988 and "5" the youngest cohort with RA onset in 1993).

*Data collection*. Collection of data was performed 10 years after disease onset during the period from 1998 to 2003 and included questionnaires, interviews, and examinations with joint counts by one trained research nurse.

Demographic variables included age (at onset) divided into 6 age-groups, disease duration in years, years of education (dichotomized as ≤ 12 yrs and > 12 yrs for use in the statistical analysis) and comorbidities (yes/no). Smoking habits were recorded (current, previous, or never) and dichotomized as never/ever smoked for use in statistical analysis.

Disease activity was assessed by 28 tender and swollen joint counts, patients' and investigators' global assessment of disease activity on a 100 mm visual analog scale (VAS), and the erythrocyte sedimentation rate (ESR). The Disease Activity Score was computed using 28-joint counts (DAS28)[17]. Radiographs of hands were taken, but scores were not available for our study. Joint damage was instead assessed by the number of deformed joints (score 0–20, the metacarpophalangeal and proximal interphalangeal joints for each finger were counted as one joint)[18]. For use in the statistical analysis the deformed joint count was dichotomized with an upper value of ≥ 2 deformed joints, which corresponds to ≥ 10 Larsen score units, a level of joint damage characterizing a severe RA condition[19].

Functional health status was assessed by the Health Assessment Questionnaire (HAQ; range 0–3, high values representing worse health)[20]. The HAQ scores were upgraded for devices or help from other persons. Grip strength was used as the performance-based measure for muscle strength and physical function and was measured by hand-dynamometer (kg, average of right and left arms, the best performance out of 2 attempts on each hand)[21,22].

Other self-reported health status measures included the social interaction and the affect subscales in the Arthritis Impact Measurement Scales (AIMS2)[23] (range 0–10, 0 = best score) as well as pain severity and fatigue on a 100 mm VAS[24,25].

Use of glucocorticosteroids, nonsteroidal antiinflammatory drugs (NSAID), cyclooxygenase-2 selective inhibitors (coxibs), and disease modifying antirheumatic drugs (DMARD) was registered by the nurse and assessed as categorical variables (never user, previous user, current user). Current use of tumor necrosis factor-α (TNF-α) inhibitors was registered (yes = 1, no = 0). Prednisolone and DMARD use was dichotomized as never/ever used for statistical analysis.

The patients gave written consent before participation, and the study was approved by the regional ethics committee.

*Statistical analyses*. Age- and sex-specific incidences of RA exceeding clinically important levels 10 years after disease onset were calculated. The percentage of patients exceeding clinically important levels in each age and sex group was multiplied with the corresponding known incidence of RA using the Poisson distribution with 95% confidence intervals (CI). For the calculation of incidences linked to health outcomes we assumed that the examined patients were representative for the entire cohort, thus extrapolating the group findings to the entire number of patients with disease onset in the period 1988-1993. We applied the same limits for clinically important levels of health status as in an earlier study[4] [AIMS2 scales > 4.0 (social interaction and affect), VAS > 40 mm (pain and fatigue), for HAQ > 1.0 and > 2]. Levels of DAS28 were categorized into remission < 2.6, low disease activity ≤ 3.2, moderate disease activity 3.3–5.1, and high disease activity > 5.1[26]. Descriptive variables were presented as means with 95% CI, and for dichotomous variables as percentages.

To test the null hypothesis that all the 6 annual cohorts were similar regarding demographic variables, disease activity, health status measures, and proportion of patients treated with antirheumatic drugs, one-way analysis of variance (ANOVA) was performed for continuous variables and Pearson's chi-square or Fisher's exact tests for counts. A p value ≤ 0.05 indicates that at least one of the annual cohort is statistically significantly different from the other cohorts.

Analysis of covariance (ANCOVA) was used to test the influence of time on the development of DAS28, and logistic regression was used to test the influence of time on the risk for developing deformed joints. Adjusting factors in both models were age, sex, RF, education, comorbidity, smoking, and current use of TNF-inhibitors. The influence of TNF-inhibitor treatment was not constant in the 6-year period, and current use of TNF-inhibitors was therefore introduced as a covariate. The time variable with values from 0 to 5 was introduced as a continuous variable. These models were also tested with additional adjustment for "ever used prednisolone" and "ever used DMARD." In the ANCOVA model the interaction-term sex × RF was found to be statistically significant and was therefore included into the final model.

Data were analyzed using SPSS version 14.0. The level of significance was set to 0.05.

## RESULTS

*Differences between respondents and nonrespondents*. Characteristics of the populations with all incident cases from 1988 to 1993 (n = 550), living patients (n = 473), living nonrespondents (n = 273), and the 10-year followup population (n = 216) are shown in Table 1. Living nonrespondents were older than the respondents and the proportion of RF positivity was lower. Numbers of respondents in sexes, age groups, and in each of the annual incident cohorts are displayed in Tables 2, 3, and 4, respectively.

*Disease severity and incidence of cases exceeding clinically important levels in sex- and age-specific group after 10-year disease duration*. The overall annual incidence of RA linked to health outcomes after 10 years is shown in Table 2. For example, the annual incidence of RA with high disease activity after 10 years was found to be 5.3 per 100,000 and for disabled RA after 10 years as indicated by HAQ > 1.0 the annual incidence was 12.0 per 100,000 (Table 2). Incidence rates for remission and low, moderate, and high disease activity as well as for health status above defined levels were numerically higher among women than men (Table 2) and generally increased with higher age (Table 3). Many of these differences were statistically significant as demonstrated by separated confidence intervals. The annual incidence of patients with RA and with HAQ higher than 1 after 10 years' disease duration was in women (men) 18.4 (5.0) per 100,000 population (Table 2), whereas the annual incidence rate for RA with high disease activity (DAS28 > 5.1) after 10 years in the youngest (oldest) age group was 1.4 (8.7) per 100,000 (Table 3).

*Time trends in burden of disease*. In unadjusted analyses 10-year disease outcome as measured by disease activity, investi-

*Table 1.* Patient characteristics with means (95% CI) for continuous variables or counts (%).

| Characteristic | Incident Cases, 1988–1993, n = 550 | Living Patients, n = 473 | Living Nonrespondents, n = 273 | Respondents, 1998–2003, n = 216 |
|---|---|---|---|---|
| Age, RA onset, yrs | 57.2 (55.9–58.5) | 55.2 (53.8–56.7) | 57.4 (55.4–59.4) | 51.8 (49.9–53.7) |
| Female, % | 74.4 | 75.5 | 76.9 | 74.5 |
| RF-positive, % | 38.7 | 38.0 | 38.0 | 42.3 |
| Disease duration in 1996, yrs | 5.5 (5.3–5.6) | 5.5 (5.4–5.7) | 5.5 (5.3–5.7) | 5.6 (5.2–5.8) |

RA: rheumatoid arthritis; RF: rheumatoid factor.

*Table 2.* Levels of disease activity and health status measures (means with 95% CI) in female, male, and all incident RA patients after 10 years' followup, percentages of RA patients exceeding clinically important levels, and calculated incidence (95% CI) of RA exceeding these levels.

| No. of Incident Cases/Respondents (n) | Female, 409/161 | Male, 141/55 | All, 550/216 |
|---|---|---|---|
| Mean DAS28 (0–10) | 4.1 (3.9–4.3) | 3.7 (3.3–4.1) | 4.0 (3.8–4.2) |
| DAS28 < 2.6, remission, % | 15.2 | 26.7 | 18 |
| Incidence/100,000 | 5.6 (3.5–8.5) | 3.7 (1.9–6.4) | 4.6 (3.2–6.5) |
| DAS28 ≤ 3.2, low disease activity, % | 27.5 | 37.8 | 30.1 |
| Incidence/100,000 | 10.1 (7.1–13.9) | 5.2 (3.0–8.3) | 7.7 (5.8–10.1) |
| DAS28 3.3–5.1, moderate disease activity, % | 50.0 | 46.7 | 49.2 |
| Incidence/100,000 | 18.4 (5.6–11.7) | 6.4 (4.0–9.8) | 12.6 (10.2–15.5) |
| DAS28 > 5.1, high disease activity, % | 22.5 | 15.6 | 21.0 |
| Incidence/100,000 | 8.3 (5.6–11.7) | 2.1 (0.9–4.4) | 5.3 (3.8–7.3) |
| Mean HAQ (0–3) | 1.04 (0.94–1.14) | 0.76 (0.56–0.96) | 0.97 (0.88–1.06) |
| HAQ > 1, % | 50.0 | 36.5 | 46.6 |
| Incidence/100,000 | 18.4 (14.5–23.0) | 5.0 (3.0–7.8) | 12.0 (9.7–14.6) |
| HAQ > 2, % | 5.2 | 3.8 | 4.9 |
| Incidence/100,000 | 1.9 (0.8–3.7) | 0.5 (0.1–1.9) | 1.2 (0.6–2.3) |
| Mean AIMS social interaction (0–10) | 4.1 (3.8–4.3) | 3.9 (3.4–4.4) | 4.0 (3.8–4.3) |
| AIMS social interaction > 4, % | 45.7 | 42.9 | 45.0 |
| Incidence/100,000 | 16.8 (13.1–21.2) | 5.9 (3.6–9.0) | 11.6 (9.3–14.2) |
| Mean AIMS affect (0–10) | 3.2 (2.9–3.5) | 2.7 (2.3–3.1) | 3.1 (2.8–3.3) |
| AIMS affect > 4, % | 32.0 | 14.0 | 27.4 |
| Incidence/100,000 | 11.7 (8.6–15.6) | 1.9 (0.8–4.0) | 7.0 (5.3–9.2) |
| Mean Pain VAS (0–100) | 34.0 (30.2–37.8) | 31.2 (24.3–38.1) | 33.3 (30.0–36.6) |
| Pain VAS > 40 mm, % | 37.4 | 34.6 | 36.7 |
| Incidence/100,000 | 13.7 (10.4–17.8) | 4.8 (2.8–7.5) | 9.4 (7.4–11.8) |
| Mean Fatigue VAS (0–100) | 47.9 (43.3–52.5) | 33.3 (26.1–40.4) | 44.2 (40.2–48.1) |
| Fatigue VAS > 40 mm, % | 61.0 | 35.8 | 54.6 |
| Incidence/100,000 | 22.4 (18.1–27.4) | 4.9 (3.0–7.7) | 14.0 (11.6–16.9) |

RA: rheumatoid arthritis; DAS: Disease Activity Score; HAQ: Health Assessment Questionnaire; AIMS: Arthritis Impact Measurement Scale; VAS: visual analog scale.

gator global assessment, and joint deformities improved during the 6-year period (Table 4). Figure 1 shows the trend towards improvement in unadjusted 10-year values in DAS28 and HAQ. Disease activity measured with DAS28 showed an independent significant improvement for onset of RA after 1988 and until 1993 adjusted for age, sex, RF, education, comorbidity, smoking, and current use of TNF-inhibitors (Table 5). Increasing age, female sex, and the interaction terms female × RF-positive and male × RF-positive also increased 10-year disease activity.

Every year of RA onset later than 1988 reduced the risk for developing 2 or more deformed joints. Positive RF and current use of TNF-inhibitors were independent explanatory factors for increased risk for deformed joints after 10-year disease duration (Table 6). Adjusting for "ever used prednisolone," "ever used DMARD," and disease duration did not change the main findings in Tables 5 and 6 (data not shown).

## DISCUSSION

Ours is the first study that reports annual incidence rates of RA per 100,000 inhabitants linked to disease outcomes 10 years after disease onset. Several publications have shown

*Table 3.* Levels of disease activity and health status measures (means with 95% CI) in age groups of incident RA patients after 10 years' followup, with percentages of RA patients exceeding clinically important levels and calculated incidence (95% CI) of RA exceeding these levels.

| | Age Group, yrs | | | | | |
|---|---|---|---|---|---|---|
| | 20–29 | 30–39 | 40–49 | 50–59 | 60–69 | 70–79 |
| No. of incident cases/respondents | 39/18 | 54/28 | 67/40 | 101/56 | 141/54 | 148/20 |
| DAS28 (0–10) | 3.6 (2.8–4.5) | 3.7 (3.2–4.2) | 3.9 (3.4–4.4) | 4.1 (3.7–4.5) | 4.4 (4.0–4.7) | 3.3 (2.5–4.2) |
| DAS28 < 2.6 | 31.3 | 29.2 | 12.9 | 14.3 | 10.2 | 35.7 |
| Incidence/100,000 | 2.4 (0.8–5.6) | 3.1 (1.3–6.4) | 2.2 (0.6–5.6) | 5.7 (2.3–11.8) | 5.9 (1.9–13.9) | 21.8 (7.1–50.8) |
| DAS28 ≤ 3.2 | 37.5 | 33.3 | 35.5 | 24.5 | 20.4 | 57.1 |
| Incidence/100,000 | 2.9 (1.1–6.3) | 3.6 (1.5–7.1) | 6.0 (3.0–10.7) | 9.8 (5.1–17.1) | 11.9 (5.7–21.8) | 34.8 (15.0–68.6) |
| DAS28 3.3–5.1 | 43.8 | 54.2 | 48.4 | 55.1 | 49.0 | 28.6 |
| Icidence/100,000 | 3.4 (1.4–7.0) | 5.8 (3.1–9.9) | 8.2 (4.6–13.5) | 22.1 (14.5–32.1) | 28.5 (18.3–42.4) | 17.4 (4.7–44.6) |
| DAS28 > 5.1 | 3 (18.8) | 3 (12.5) | 5 (16.1) | 10 (20.4) | 15 (30.6) | 2 (14.3) |
| Incidence/100,000 | 1.4 (0.3–4.2) | 1.3 (0.3–3.9) | 2.7 (0.9–6.4) | 8.2 (3.9–15.0) | 17.8 (10.0–29.4) | 8.7 (1.0–31.5) |
| Mean HAQ (0–3) | 0.65 (0.33–0.97) | 0.65 (0.46–0.85) | 0.97 (0.73–1.20) | 0.95 (0.79–1.12) | 1.19 (1.00–1.39) | 1.12 (0.76–1.48) |
| HAQ > 1 | 27.8 | 23.1 | 37.8 | 54.7 | 58.4 | 57.9 |
| Incidence/100,000 | 2.1 (0.7–5.0) | 2.5 (0.9–5.4) | 6.4 (3.5–10.8) | 21.9 (14.7–31.5) | 34.0 (23.1–48.3) | 35.3 (17.6–63.15) |
| HAQ > 2 | 5.6 | 0 | 8.1 | 0 | 7.5 | 10.5 |
| Incidence/100,000 | 0.4 (0.01–2.4) | 0 (0–1.5) | 1.4 (0.3–4.0) | 0 (0–2.79) | 4.4 (1.2–11.2) | 6.42 (0.78–23.18) |
| Mean AIMS social interaction (0–10) | 3.6 (2.8–4.3) | 4.0 (3.4–4.6) | 4.0 (3.6–4.5) | 3.7 (3.2–4.2) | 4.7 (4.2–5.3) | 3.6 (2.9–4.4) |
| AIMS social interaction > 4 | 23.5 | 48.0 | 44.4 | 40.4 | 60.8 | 31.6 |
| Incidence/100,000 | 1.8 (0.5–4.7) | 5.2 (2.7–9.0) | 7.5 (4.3–12.2) | 16.2 (10.0–24.7) | 35.4 (24.0–50.2) | 19.2 (7.1–41.9) |
| Mean AIMS affect (0–10) | 2.8 (2.0–3.5) | 2.6 (2.0–3.3) | 3.4 (2.7–4.1) | 2.6 (2.2–3.0) | 3.7 (3.2–4.2) | 3.2 (2.4–4.0) |
| AIMS affect > 4 | 16.7 | 21.7 | 33.0 | 15.1 | 42.0 | 30.0 |
| Incidence/100,000 | 1.3 (0.3–3.8) | 2.3 (0.8–5.4) | 5.6 (2.9–7.7) | 6.0 (2.6–11.9) | 24.4 (15.1–37.4) | 17.9 (5.8–41.8) |
| Mean pain VAS (0–100) | 27.8 (15.9–39.7) | 30.0 (21.4–38.7) | 35.0 (26.9–43.1) | 31.4 (24.4–38.3) | 37.4 (30.9–44.0) | 33.8 (21.7–46.0) |
| Pain VAS > 40 mm | 22.2 | 40.7 | 39.0 | 35.2 | 38.9 | 38.9 |
| Incidence/100,000 | 1.7 (0.5–4.4) | 4.4 (2.2–7.8) | 6.6 (3.6–10.6) | 14.1 (8.5–22.0) | 22.6 (14.0–34.6) | 23.7 (9.5–48.8) |
| Mean fatigue VAS (0–100) | 44.7 (31.6–57.7) | 37.5 (25.4–49.6) | 51.8 (42.3–61.4) | 42.1 (34.2–49.9) | 45.9 (38.5–53.2) | 39.5 (22.4–56.6) |
| Fatigue VAS > 40 mm | 61.1 | 48.1 | 63.9 | 46.3 | 61.1 | 44.4 |
| Incidence/100,000 | 4.7 (2.4–8.7) | 5.2 (2.7–8.8) | 10.8 (6.7–16.2) | 18.5 (12.0–27.4) | 35.6 (24.5–50.0) | 27.1 (11.7–53.4) |

RA: rheumatoid arthritis; DAS: Disease Activity Score; HAQ: Health Assessment Questionnaire; AIMS: Arthritis Impact Measurement Scale; VAS: visual analog scale.

that the incidence of RA is between 25 and 50 per 100,000 inhabitants[4]. Our study adds relevant information for healthcare planning by linking the incidence of RA to health status levels after 10 years of disease duration.

The incidence rates for RA with scores exceeding clinically important levels for physical function, pain, fatigue, and mental and social health for all patients in this 10-year study were comparable to findings 5 years after disease onset. The fact that the incidence rates of clinically important self-reported health status were similar at both 5 and 10 years' followup may be a consequence of the "well-being homeostasis" or adaptation theory in chronically ill patients[27,28]. In addition to health status measurements we measured DAS28 and calculated incidence rates for different levels of DAS28 in patients with 10-year disease duration. The mean level of disease activity was similar to what is reported in 2 other studies after 9 and 12 years' followup[29,30]. No other studies are available for comparison of age- and sex-specific incidence rates for RA exceeding clinically important levels in health status or disease activity at 10-year followup.

The annual incidence rates of RA with scores of disease severity exceeding clinically important levels were higher among women than men for most of the health status measures, but the difference was less pronounced for the disease activity measures. Sex differences in mean values for different health status measures in the direction of worse health in women have been reported; however, statistically significant differences were found only for some measurements[31].

The overall mean level in physical disability after 10 years' disease duration is comparable with findings from other studies[29,32,33]. Studies reporting data about psychological health 10 years after disease onset are scarce[34,35], but the proportion of all patients with clinically important levels of psychological involvement was 27%, and comparable[34] to the findings in our study.

The second focus of our study was to address time trends in disease severity after 10 years' disease duration in the 6-year observation period. We found a statistically significant association between subsequent year of onset and decline in DAS28 as well as decline in risk for developing deformities in 2 or more joints. The cohort with the latest onset had the highest percentage with patients ever treated with DMARD, indicating a more aggressive treatment strategy over time. There is now a body of evidence on declining disease burden in RA over recent decades[8,9,19,36-40] in an era with more aggressive treatment with DMARD[41,42]. Milder disease itself and earlier referral of patients with arthritis to rheumatologists in general are possible explanatory factors[9,43].

*Table 4*. Demographic variables, disease activity, health status, and medication at 10-year followup in 6 annual incidence cohorts with RA [means (95% CI) or %].

| | Onset of RA | | | | | | |
|---|---|---|---|---|---|---|---|
| | 1988 | 1989 | 1990 | 1991 | 1992 | 1993 | p* |
| No. of incident cases each year 1988–93 | 92 | 82 | 92 | 96 | 100 | 88 | |
| No. of patients in the 10-yr followup | 40 | 33 | 29 | 45 | 39 | 30 | |
| Age, yrs | 59.9 (55.4–64.4) | 61.4 (55.6–67.1) | 64.9 (59.9–69.8) | 63.7 (59.0–68.3) | 62.1 (57.7–66.5) | 61.2 (56.7–65.6) | 0.74 |
| Female, % | 80.0 | 75.8 | 86.2 | 66.7 | 66.7 | 76.7 | 0.35 |
| Rheumatoid factor-positive, % | 38 | 50 | 43 | 24 | 46 | 61 | 0.05 |
| Earlier/current smoking, % | 30.0/35.0 | 36.4/36.4 | 33.3/33.3 | 42.9/9.5 | 35.1/27.0 | 22.2/37.0 | 0.70/0.06 |
| > 12 years education, % | 17.9 | 42.4 | 34.6 | 38.5 | 31.4 | 27.6 | 0.28 |
| ≥ 1 comorbid condition, % | 57.5 | 51.5 | 55.2 | 55.6 | 53.8 | 66.7 | 0.88 |
| DAS28 (0–10) | 4.6 (4.2–5.0) | 4.3 (3.9–4.7) | 4.1 (3.6–4.7) | 3.4 (2.9–3.9) | 3.9 (3.4–4.5) | 3.7 (3.2–4.1) | 0.004 |
| Investigator global (VAS 0–100) | 24.7 (18.3–31.1) | 22.9 (15.9–29.9) | 26.7 (16.1–37.2) | 11.8 (8.0–15.6) | 18.2 (13.4–22.9) | 9.7 (7.1–12.3) | < 0.001 |
| ≥ 2 deformed joints, % | 55 | 30 | 24 | 23 | 38 | 30 | 0.03 |
| HAQ (0–3) | 1.01 (0.81–1.22) | 0.96 (0.74–1.18) | 1.19 (0.94–1.43) | 0.96 (0.72–1.20) | 0.90 (0.66–1.13) | 0.83 (0.60–1.07) | 0.47 |
| Grip strength, average right/left hand, kg | 18.2 (15.1–21.3) | 19.4 (16.2–22.6) | 17.9 (14.2–21.6) | 23.0 (19.7–26.2) | 20.1 (16.5–23.8) | 21.7 (17.8–25.6) | 0.21 |
| AIMS social interaction (0–10) | 4.0 (3.4–4.6) | 4.1 (3.5–4.8) | 4.5 (3.7–5.2) | 3.8 (3.3–4.3) | 4.0 (3.6–4.4) | 4.0 (3.2–4.7) | 0.65 |
| AIMS affect (0–10) | 3.1 (2.7–3.6) | 3.1 (2.5–3.7) | 3.7 (3.0–4.4) | 3.0 (2.3–3.7) | 2.9 (2.3–3.6) | 2.7 (2.2–3.3) | 0.44 |
| Pain VAS (0–100) | 36.7 (29.9–43.5) | 32.2 (23.3–41.0) | 38.4 (27.6–49.2) | 32.4 (24.8–39.9) | 32.8 (24.1–41.5) | 27.2 (18.9–35.6) | 0.56 |
| Fatigue VAS (0–100) | 48.8 (39.2–58.5) | 36.2 (26.1–46.3) | 50.6 (37.8–63.4) | 43.8 (35.1–52.5) | 42.2 (33.3–51.1) | 43.5 (32.9–54.2) | 0.42 |
| Ever used NSAID, % | 90.0 | 71.9 | 82.8 | 75.6 | 78.9 | 90.0 | 0.26 |
| Ever used prednisolone, % | 67.5 | 74.2 | 71.4 | 75.6 | 73.7 | 63.4 | 0.87 |
| Ever used DMARD, % | 82.5 | 75.8 | 72.4 | 57.8 | 79.5 | 86.7 | 0.07 |
| Current TNF inhibitors, % | 0 | 0 | 0 | 2 | 10 | 3 | 0.06 |

*Comparisons between cohorts with one-way ANOVA for continuous variables and Pearson's chi-square or Fisher's tests for counts. RA: rheumatoid arthritis; DAS: Disease Activity Score; HAQ: Health Assessment Questionnaire; VAS: visual analog scale; AIMS: Arthritis Impact Measurement Scale; NSAID: nonsteroidal antiinflammatory drugs; DMARD: disease modifying antirheumatic drug; TNF: tumor necrosis factor.

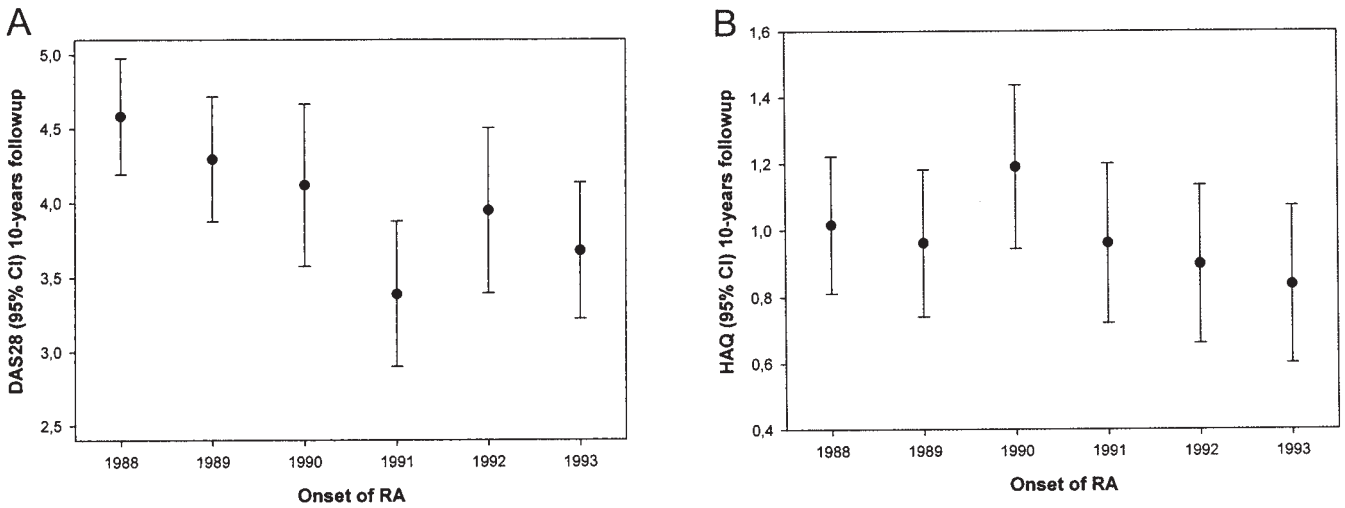


*Figure 1*. Time trends in unadjusted 10-year measures of (A) disease activity (DAS28) and (B) physical function (HAQ) with mean and 95% CI.

An important limitation in our study is missing data at disease onset, which makes adjustment for baseline disease activity and joint deformity impossible. Treatment regimens introduced as adjusting factors in test models will come out as explanatory factors for more severe disease (confounding by indication)[44], whereas in our analyses the significant association between year of onset and declining disease burden remained present after adjustment for treatment regimens. Baseline data on disease severity and more detailed data about duration of treatment, dosage, and type of DMARD used could have altered our findings. Thus our data sample alone does not warrant conclusions and explanations for the observed reduction in 10-year disease burden of RA.

Welsing, *et al*[8] found discrepancy between time trends in disease activity versus patient-assessed physical disability (HAQ). Disease activity was found to be lower in the more recent cohorts, while HAQ worsened in recent years. In our study there was a trend towards improvement in 10-year val-

*Table 5*. Explanatory factors for DAS28 at 10 yrs followup. ANCOVA model adjusted for current tumor necrosis factor inhibitor treatment, education, comorbidity, and smoking.

| Independent Variable | Beta (95% CI) | Standard Error | p |
|---|---|---|---|
| Intercept | 2.74 (1.14; 4.35) | 0.81 | 0.001 |
| Year of onset (range 1988-93) | –0.24 (–0.36; –0.13) | 0.06 | < 0.001 |
| Age at onset | 0.02 (0.006; 0.034) | 0.01 | 0.005 |
| Female*RF-positive | 1.28 (0.66; 1.89) | 0.31 | < 0.001 |
| Female*RF-negative | 0.90 (0.30; 1.50) | 0.30 | 0.004 |
| Male*RF-positive | 1.56 (0.79; 2.33) | 0.39 | < 0.001 |
| Male*RF-negative | 0[†] | | |

DAS: Disease Activity Score; RF: rheumatoid factor. [†] Reference.

*Table 6*. Explanatory factors for deformed joints (≥ 2) at 10 yrs followup. Results after logistic regression adjusted for age, sex, education, comorbidity, and smoking.

| Independent variable | Coefficient | Standard Error | p | Odds ratio (95% CI) |
|---|---|---|---|---|
| Year of onset (range 1988–93) | –0.31 | 0.106 | 0.003 | 0.73 (0.60; 0.91) |
| RF-positive | 1.18 | 0.36 | 0.001 | 3.25 (1.61; 6.57) |
| Current TNF inhibitor | 3.40 | 1.21 | 0.005 | 29.91 (2.80; 319.46) |

RF: rheumatoid factor; TNF: tumor necrosis factor.

ues of both DAS28 and HAQ over the 6-year period (Figure 1), although findings were not statistically significant for physical disability.

The most important strength of our study is the use of a register that is representative for the general population within the area of Oslo and the longitudinal observation over 10 years, with opportunities for calculation of age- and sex-specified incidence rates of defined levels of both disease activity (DAS28) and health status measures. Another strength is examination of all patients by the same research nurse, avoiding interobserver disagreement in joint evaluation.

Other limitations include a relatively low proportion of respondents after 10 years, especially in the oldest age group. Further, nonrespondents were older and we may have underestimated the incidences of cases exceeding defined levels of disease severity by assuming similar outcomes in respondents and older nonrespondents. Missing data among respondents is also a limitation, especially concerning the composite measure DAS28, which was missing in 15%–20% of the total cases.

We found that the average annual incidence of cases exceeding clinically important levels in disease activity and health status 10 years after disease onset increased with higher age and was highest among women. The results indicated a stable incidence from 5- to 10-year followup according to defined levels of physical function, pain, fatigue, and mental and social health measures. Analyzing time trends in 10-year disease severity during the period with disease onset from 1988 to 1993 demonstrated a tendency towards declining consequences of RA in the more recent cohorts. Less favorable outcomes in RA have been revealed in studies with disease duration up to 20 years[45], and also the ORAR will in the future be able to provide data on disease severity in the second decade of RA disease. Documentation of longterm outcome in RA is important for healthcare planners when estimating needs for health service and medication in patients with RA during the disease course.

## ACKNOWLEDGMENT

We thank the research nurse, Margareth Sveinsson, for her patient examination and data collection. Additionally we thank Inge C. Olsen and Petter Mowinckel for their meaningful contributions regarding the statistical analyses.

## REFERENCES

1. Alamanos Y, Voulgari PV, Drosos AA. Incidence and prevalence of rheumatoid arthritis, based on the 1987 American College of Rheumatology criteria: a systematic review. Semin Arthritis Rheum 2006;36:182-8.
2. Chan KW, Felson DT, Yood RA, Walker AM. Incidence of rheumatoid arthritis in central Massachusetts. Arthritis Rheum 1993;36:1691-6.
3. Symmons DP, Barrett EM, Bankhead CR, Scott DG, Silman AJ. The incidence of rheumatoid arthritis in the United Kingdom: results from the Norfolk Arthritis Register. Br J Rheumatol 1994;33:735-9.
4. Uhlig T, Kvien TK, Glennås A, Smedstad LM, Førre Ø. The incidence and severity of rheumatoid arthritis, results from a county register in Oslo, Norway. J Rheumatol 1998;25:1078-84.
5. Kaipiainen-Seppanen O, Kautiainen H. Declining trend in the incidence of rheumatoid factor-positive rheumatoid arthritis in Finland 1980-2000. J Rheumatol 2006;33:2132-8.
6. Silman AJ. Trends in the incidence and severity of rheumatoid arthritis. J Rheumatol 1992;19 Suppl 32:71-3.
7. Uhlig T, Kvien TK. Is rheumatoid arthritis disappearing? Ann Rheum Dis 2005;64:7-10.
8. Welsing PM, Fransen J, van Riel PL. Is the disease course of rheumatoid arthritis becoming milder? Time trends since 1985 in an inception cohort of early rheumatoid arthritis. Arthritis Rheum 2005;52:2616-24.

9. Walji S, Bykerk VP. Rheumatoid arthritis: is the disease becoming milder or is treatment improving? J Rheumatol 2004;31:1023-5.
10. Silman AJ. Will rheumatoid arthritis still be an important health problem in the 21st century? Scand J Rheumatol 2000;29:143-5.
11. Glennas A, Kvien TK, Andrup O, Karstensen B, Munthe E. Recent onset arthritis in the elderly: a 5 year longitudinal observational study. J Rheumatol 2000;27:101-8.
12. Sany J. Clinical and biological polymorphism of rheumatoid arthritis. Clin Exp Rheumatol 1994;12 Suppl 11:S59-61.
13. van der Pouw Kraan TC, van Gaalen FA, Kasperkovitz PV, et al. Rheumatoid arthritis is a heterogeneous disease: evidence for differences in the activation of the STAT-1 pathway between rheumatoid tissues. Arthritis Rheum 2003;48:2132-45.
14. Kvien TK, Glennås A, Knudsrod OG, Smedstad LM, Mowinckel P, Førre Ø. The prevalence and severity of rheumatoid arthritis in Oslo. Results from a county register and a population survey. Scand J Rheumatol 1997;26:412-8.
15. Kvien TK, Uhlig T. The Oslo experience with arthritis registries. Clin Exp Rheumatol 2003;21 Suppl 31:S118-122.
16. Arnett FC, Edworthy SM, Bloch DA, et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis Rheum 1988;31:315-24.
17. Prevoo ML, van 't Hof MA, Kuper HH, van Leeuwen MA, van de Putte LB, van Riel PL. Modified disease activity scores that include twenty-eight-joint counts. Development and validation in a prospective longitudinal study of patients with rheumatoid arthritis. Arthritis Rheum 1995;38:44-8.
18. Orces CH, Del Rincon I, Abel MP, Escalante A. The number of deformed joints as a surrogate measure of damage in rheumatoid arthritis. Arthritis Rheum 2002;47:67-72.
19. Sokka T, Kautiainen H, Hakkinen A, Hannonen P. Radiographic progression is getting milder in patients with early rheumatoid arthritis. Results of 3 cohorts over 5 years. J Rheumatol 2004;31:1073-82.
20. Fries JF, Spitz P, Kraines RG, Holman HR. Measurement of patient outcome in arthritis. Arthritis Rheum 1980;23:137-45.
21. Escalante A, Haas RW, Del Rincon I. Measurement of global functional performance in patients with rheumatoid arthritis using rheumatology function tests. Arthritis Res Ther 2004;6:R315-25.
22. Massy-Westropp N, Rankin W, Ahern M, Krishnan J, Hearn TC. Measuring grip strength in normal adults: reference ranges and a comparison of electronic and hydraulic instruments. J Hand Surg 2004;29:514-9.
23. Meenan RF, Mason JH, Anderson JJ, Guccione AA, Kazis LE. AIMS2. The content and properties of a revised and expanded Arthritis Impact Measurement Scales health status questionnaire. Arthritis Rheum 1992;35:1-10.
24. Wolfe F. Fatigue assessments in rheumatoid arthritis: comparative performance of visual analog scales and longer fatigue questionnaires in 7760 patients. J Rheumatol 2004;31:1896-902.
25. Wolfe F, Michaud K, Pincus T. Preliminary evaluation of a visual analog function scale for use in rheumatoid arthritis. J Rheumatol 2005;32:1261-6.
26. Fransen J, van Riel PL. The Disease Activity Score and the EULAR response criteria. Clin Exp Rheumatol 2005;23 Suppl 39:S93-9.
27. Cummins RA. Objective and subjective quality of life: an interactive model. Social Indicators Research 2000;52:55-72.
28. Postulart D, Adang EM. Response shift and adaptation in chronically ill patients. Med Decis Making 2000;20:186-93.
29. Drossaers-Bakker KW, de Buck M, van Zeben D, Zwinderman AH, Breedveld FC, Hazes JM. Long-term course and outcome of functional capacity in rheumatoid arthritis: the effect of disease activity and radiologic damage over time. Arthritis Rheum 1999;42:1854-60.
30. Welsing PM, van Gestel AM, Swinkels HL, Kiemeney LA, van Riel PL. The relationship between disease activity, joint destruction, and functional capacity over the course of rheumatoid arthritis. Arthritis Rheum 2001;44:2009-17.
31. Kvien TK, Uhlig T, Ødegård S, Heiberg MS. Epidemiological aspects of rheumatoid arthritis: the sex ratio. Ann NY Acad Sci 2006;1069:212-22.
32. Lindqvist E, Saxne T, Geborek P, Eberhardt K. Ten year outcome in a cohort of patients with early rheumatoid arthritis: health status, disease process, and damage. Ann Rheum Dis 2002;61:1055-9.
33. Odegard S, Landewé R, van der Heijde D, Kvien TK, Mowinckel P, Uhlig T. Association of early radiographic damage with impaired physical function in rheumatoid arthritis: A ten-year, longitudinal observational study in 238 patients. Arthritis Rheum 2006;54:68-75.
34. Odegard S, Finset A, Mowinckel P, Kvien TK, Uhlig T. 10-year course of pain and psychological health status in patients with recent onset rheumatoid arthritis. Ann Rheum Dis 2007;66:1195-201.
35. Strating MM, Suurmeijer TP, van Schuur WH. Disability, social support, and distress in rheumatoid arthritis: results from a thirteen-year prospective study. Arthritis Rheum 2006;55:736-44.
36. Finckh A, Choi HK, Wolfe F. Progression of radiographic joint damage in different eras: trends towards milder disease in rheumatoid arthritis are attributable to improved treatment. Ann Rheum Dis 2006;65:1192-7.
37. Heiberg T, Finset A, Uhlig T, Kvien TK. Seven year changes in health status and priorities for improvement of health in patients with rheumatoid arthritis. Ann Rheum Dis 2005;64:191-5.
38. Krishnan E, Fries JF. Reduction in long-term functional disability in rheumatoid arthritis from 1977 to 1998: a longitudinal study of 3035 patients. Am J Med 2003;115:371-6.
39. Pincus T, Sokka T, Chung CP, Cawkwell G. Declines in number of tender and swollen joints in patients with rheumatoid arthritis seen in standard care in 1985 versus 2001: possible considerations for revision of inclusion criteria for clinical trials. Ann Rheum Dis 2006;65:878-83.
40. Sokka T, Kautiainen H, Hannonen P. Stable occurrence of knee and hip total joint replacement in Central Finland between 1986 and 2003 — An indication of improved long-term outcomes of rheumatoid arthritis? Ann Rheum Dis 2007;66:341-4.
41. Kremers HM, Nicola P, Crowson CS, O'Fallon WM, Gabriel SE. Therapeutic strategies in rheumatoid arthritis over a 40-year period. J Rheumatol 2004;31:2366-73.
42. Ward MM. Trends in the use of disease modifying antirheumatic medications in rheumatoid arthritis, 1980-1995: results from the National Ambulatory Medical Care Surveys. J Rheumatol 1999;26:546-50.
43. Uhlig T, Kvien TK. Has rheumatoid arthritis become a milder disease? Drug Discovery Today Disease Mechanisms 2005;2:331-6.
44. Caplan L, Wolfe F, Russell AS, Michaud K. Corticosteroid use in rheumatoid arthritis: prevalence, predictors, correlates, and outcomes. J Rheumatol 2007;34:696-705.
45. Scott DL, Symmons DP, Coulten BL, Propert AJ. Long-term outcome of treating rheumatoid arthritis: Results after 20 years. Lancet 1987;16:1108-11.