# The Influence of Sex on Rheumatoid Arthritis: A Prospective Study of Onset and Outcome After 2 Years

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*ABSTRACT.* ***Objective.*** This prospective study analyzed influence of patient's sex on early rheumatoid arthritis (RA) within one year of disease onset and after 2 years' followup.

***Methods.*** A total of 844 consecutive patients, 538 women, with RA of less than 12 months were studied. Standardized clinical and radiographic assessments were performed at study entry and after 2 years. The association of several variables at study entry with the outcome variables Disease Activity Score (DAS28), functional disability measured by the Health Assessment Questionnaire (HAQ), and, in 390 patients, Larsen score at the 2-year followup were analyzed in men and women separately.

***Results.*** At study entry the women were younger compared with the men and the sexes showed different age distributions. The women had higher DAS28 and HAQ scores. However, women below 50 years of age at study entry had milder disease than older women and close to that of men. At 2-year followup the women still had higher DAS28 and HAQ scores compared to men, who had achieved remission in a higher frequency. Larsen score showed no sex difference either at study entry or after 2 years. Presence of rheumatoid factor (RF) was associated with lower age at study entry and higher DAS28 at followup in men only. Higher DAS28 and HAQ scores at entry were more strongly correlated with severe disease at followup in women than in men. Presence of the "shared epitope" was not associated with age or the outcome variables DAS28 and Larsen score in either sex.

***Conclusion.*** The disease phenotype in early RA was significantly different between men and women, particularly concerning age, disease activity, and functional capacity. There were differences between the sexes concerning early disease characteristics associated with outcome at 2 years of followup. (J Rheumatol 2004;31:214–22)

*Key Indexing Terms:*
RHEUMATOID ARTHRITIS MEN WOMEN DISEASE ONSET
PROGNOSTIC FACTORS OUTCOME

Rheumatoid arthritis (RA) is more prevalent in women than in men[1]. The sex distribution, however, varies in different age groups[2]. Thus, the male/female ratio of incident cases of RA is 1:5 in younger adult patients, but 1:1 after the age of 60 years[3]. For women, the incidence increases steadily with age, whereas for men the incidence is stable over the third through fifth decades and rises thereafter[3,4].

Further, the sex distribution varies with different clinical categories of RA. Thus, in mild to moderate disease there is a female predominance, which has been reported to change into an equal sex distribution in patients with extraarticular manifestations[5]. These sex-related differences might indicate that male and female RA represent different forms of the disease, which phenotypically are heterogeneous regarding presentation and severity, possibly influenced by genetic factors and hormones.

Studies comparing disease patterns and severity in RA in men and women have mainly been performed in established disease with long disease duration, either as case-control studies[5,6] or in tertiary referral clinic patients[7]. In only a few studies have patients with recent onset RA been followed prospectively to analyze the influence of sex on presentation and outcome of RA[8-10]. In the early phase of RA, men have been reported to have a milder disease compared with women[8] and to have a lower degree of radiological joint damage over the first 5 years[9,10], which has also been described for a population-based cohort[11]. As well, men have been reported to go into remission significantly more often than women[12].

This prospective study was performed in a large cohort of patients to clarify the influence of sex on disease phenotype in the early phase of RA. The influence of assumed prognostic markers such as age and rheumatoid factor (RF) on disease onset and outcome in men and women were analyzed. Markers of the sex aspect of outcome not previ-

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*Supported by grants from The Swedish Rheumatism Association*

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*Submitted October 8, 2002; revision accepted July 18, 2003.*

ously investigated were studied in men and women separately, along with smoking, family history of RA, and presence of the "shared epitope" (SE). Disease activity, functional capacity, and joint destruction were chosen as outcome variables.

## MATERIALS AND METHODS

*Patients.* Patients were consecutively recruited into the Barfot (Better Anti-Rheumatic Farmaco Therapy) register, a prospective multicenter observational study of patients with RA, with disease duration of maximum 12 months at time of recruitment into the register[13]. Participating rheumatology units are first-referral centers with well developed contacts with the primary healthcare units in the referral areas and include all the rheumatologists in the area except one. This means that almost all patients with recent onset RA, older than 16 years, referred to rheumatologists in the catchments areas have been included. A total of 844 patients with a diagnosis of RA according to the 1987 revised American College of Rheumatology (ACR) criteria[14] were included between 1993 and 1997. At study entry all patients were questioned for duration of joint symptoms and pattern of joint involvement at onset. Family history was recorded concerning the presence or absence of relatives with RA. If any relative with RA, i.e., including distant relatives, was reported, a positive family history was noted. Disease in first-degree relatives, i.e., parents, children, or siblings, was recorded and analyzed separately. We chose to report results for total heredity, as heredity confined to first-degree relatives did not yield any significant results. The rheumatologists of the study centers regularly followed the patients and the modern model of early, intensive RA treatment with disease modifying antirheumatic drugs (DMARD) and/or glucocorticoids was applied. All patients gave their informed consent and the ethical committees approved the study.

*Assessments.* Disease activity was measured by the Disease Activity Score (DAS), including 28 joints (DAS28), at study entry and at 2-year followup[15]. This composite index includes number of swollen joints, number of tender joints, patients' global assessment of disease activity measured on a visual analog scale (VAS, range 0–100 mm), and the erythrocyte sedimentation rate (ESR, mm/h). A patient is considered to be in remission if DAS28 is < 2.6[16]. DAS28 score between 2.6 and 3.2 is considered low disease activity, between > 3.2 and 5.1 moderate activity, and > 5.1 as high activity[17]. C-reactive protein (CRP), although not included in DAS28, was also measured as titer of RF according to the standard method used at each center.

Functional status was measured at study entry and at 2-year followup using the Swedish version of the Stanford Health Assessment Questionnaire (HAQ)[18], a self-reported instrument measuring capacity to perform activities of daily living. The HAQ score ranges from 0 to 3, where a higher score indicates a higher degree of disability[19].

In a subgroup of patients (n = 399, 47%) comprising consecutive patients included between 1993 and 1995 from 5 of the participating centers, HLA-DR4 determinations were performed to analyze the SE in the third hypervariable region of the HLA-DRB1* chain, which has been linked to predisposition to RA[20] and possibly also to severity of the disease[21]. The DRB1 typing and subtyping was performed by DNA analysis using polymerase chain reaction (PCR) amplification and sequence-specific primers[22-24]. When a single HLA-DRB1 allele could be amplified, the alleles were assumed to be homozygous. Compound heterozygotes constitute those patients who possess more than one of the RA-associated DRB1 alleles analyzed.

Posteroanterior radiographs were taken of hands, wrists, and feet at enrolment and after 2 years. At baseline, 776 patients had records from the responsible clinician in the Barfot protocol, with information about presence of erosions and/or periarticular osteoporosis according to the ACR criteria of radiographic changes[14]. In a subgroup of the patients (n = 329) the radiographs were also scored according to the Larsen method, grading changes in each joint from 0 (normal) to 5 (maximal damage)[25]. Thirty-two joints were evaluated with a theoretical score range of 0–200. These were consecutive patients in the first years of the study in whom radiographs of hands and feet could be identified both at study entry and at followup. The dropout rate was 30% and was mainly due to lost radiographs and insufficient technical quality to assess periarticular osteoporosis. One or 2 blinded assessors read the radiographs in chronological order. Results are reported as the mean value of scores when read by 2 observers.

*Statistical analysis.* Analysis was performed using the Statistica for Windows program (v. 6.0). For differences between sexes the chi-square test was used for categorical data and the Mann-Whitney U-test for continuous data. Correlations between 2 continuous variables were performed with the Spearman rank order correlation test. Multiple linear regression analysis with stepwise backward selection was performed in men and women separately with DAS28 (skewness 0.35) and Larsen score (skewness 0.09 after transformation with square root) at the 2-year followup as dependent variables. HAQ score at 2-year followup was too skewed to perform multiple regression analysis (skewness 1.07) and we were not able to transform this variable to obtain normal distribution. The variables, all recorded at study entry, were tested in bivariate analyses and thereafter in multiple regression analysis. Thus the following independent variables were tested: age, disease duration before study entry, reported heredity, presence of SE, current smoking, presence of RF, CRP, DAS28, HAQ score, presence of radiographic changes by ACR criteria, and Larsen score. In regression models including the SE and Larsen score only patients with these data available were included in the model. Maximum tolerated variables in the final regression models were fourth square root of number of cases in the model. P values < 0.05 were considered statistically significant. P values < 0.05 but > 0.01 are given precisely.

## RESULTS

*Demographic and clinical characteristics at study entry.* Of the 844 patients, 538 were women (64%) and 306 were men (36%). Table 1 shows demographic and clinical characteristics of patients at study entry. Significant difference between sexes was found for age. The median (mean) age was 62 (60.3) years for men and 54 (54.4) years for women ($p < 0.001$). Male and female patients did not only differ concerning mean age at disease onset but also concerning the age distribution (Figures 1 and 2; skewness in distribution –0.67 for men and –0.15 for women). It was apparent that very few men got RA before 40 years of age, and the sex ratio for incidence of RA changed from 1:5 M/F for age between 20 and 30 years at study entry to the ratio 1:1 for age between 60 and 70 years. Men were current or previous smokers in 69% versus 49% in women ($p < 0.001$). Also, the first joint involvement differed, the female patients more frequently having involvement of joints in hands and feet at presentation. Further, women had higher DAS28 and HAQ scores than men. On the other hand, the mean disease duration at study entry, frequency of RF positivity, and frequency of radiographic changes compatible with the ACR criteria for RA classification showed no sex differences.

Thirty-five percent of the patients reported at least one relative with RA and 20% reported a first-degree relative with RA. Presence of family history did not differ between sexes (Table 1). HLA-DR4 analyses were performed in 399 of the patients (266 women, 133 men). Sixty-four percent of

*Table 1.* Demographic and clinical characteristics at study entry of 844 patients with early RA.

| | All Patients | Men | Women | p |
|---|---|---|---|---|
| No. (%) | 844 | 306 (36) | 538 (64) | |
| Age, yrs, mean (SD) | 56.6 (15.9) | 60.3 (13.8) | 54.4 (16.6) | < 0.001 |
| Disease duration, mo, mean (SD) | 6.1 (3.0) | 6.0 (2.9) | 6.2 (3.1) | NS |
| Reported history of RA, % | 35 | 33 | 36 | NS |
| Smoking status, % | | | | |
| Current smokers | 31 | 35 | 29 | NS (p = 0.07) |
| Previous smokers | 25 | 34 | 20 | < 0.001 |
| Never smokers | 43 | 31 | 51 | < 0.001 |
| First symptom, % | | | | |
| Hands and/or feet | 57 | 51 | 61 | < 0.01 |
| Large joints | 25 | 30 | 22 | 0.01 |
| Presence of RF, % | 58 | 59 | 57 | NS |
| CRP, median (interquartile range) | 20 (7–44) | 26 (8–54) | 17 (6–40) | < 0.001 |
| DAS28, mean (SD) | 5.1 (1.3) | 5.0 (1.2) | 5.2 (1.3) | 0.02 |
| HAQ score, median (interquartile range) | 0.88 (0.50–1.38) | 0.75 (0.38–1.30) | 1.00 (0.63–1.38) | p < 0.001 |
| Radiological changes (ACR), % | 27 | 27 | 28 | NS |

p values are differences between men and women. NS: nonsignificant.

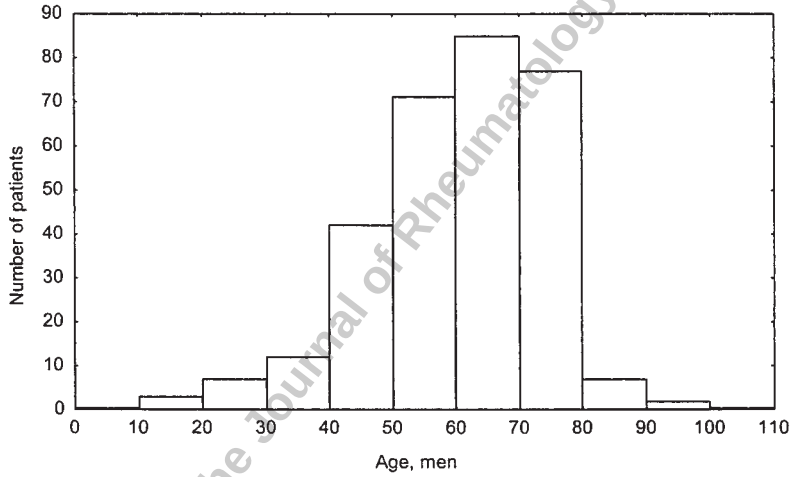


*Figure 1.* Age at disease onset in male patients with RA.

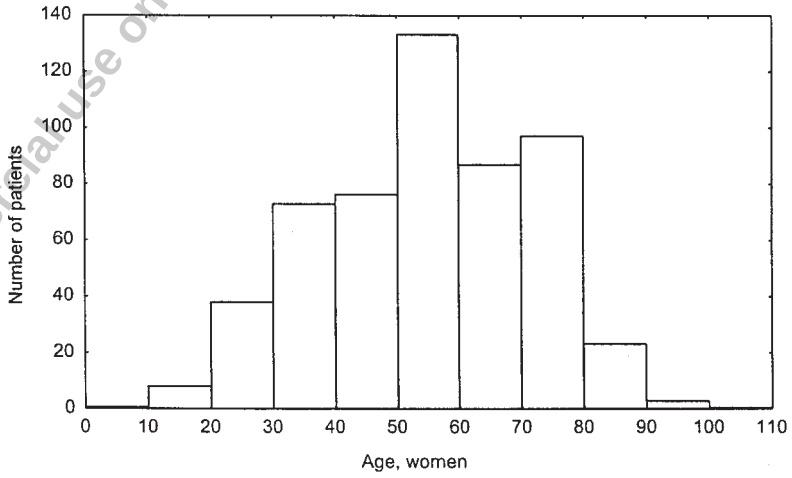


*Figure 2.* Age at disease onset in female patients with RA.

men and 56% of women had the SE, e.g., DRB1*0401, *0404, *0405, or *0408 (nonsignificant between sexes). Among local blood donors the corresponding DRB1 alleles were found in fewer than 18% (personal communication). Altogether 45 patients (30 women, 15 men) carried more than one RA-associated DRB1 allele.

*Associations of patients' characteristics with age at study entry.* In men, presence of RF and presence of relatives with RA correlated significantly with age at onset (Table 2). Men who were younger at disease onset were more likely to be RF positive than older men (difference 3.8 yrs) and more likely to report relatives with RA (difference 3.3 yrs) (Table 2).

In women, smoking correlated with lower age at onset, and CRP, DAS28, HAQ score, presence of radiological changes, and Larsen score all correlated significantly with higher age at onset in bivariate analysis (Table 2). For example, female current smokers were on average 4 years younger than nonsmokers at study entry.

Smoking was thus correlated with lower age at RA onset in women only, and further analysis showed that this was true only for RF negative women. In RF negative women age at disease onset was 47.9 years for current smokers, 52.9 for previous smokers, and 56 years for never smokers ($p < 0.01$ for smokers versus nonsmokers; $p < 0.05$ for ever smokers versus never smokers). In men and RF positive women no correlation between smoking and age at disease onset could be found.

Markers of inflammation, CRP, and DAS28 correlated with higher age at RA onset in women but not in men (Table 2). To find out if these correlations were associated with age or with menopausal status the correlation analyses were also performed in age groups of patients above 55 years and below 45 years, respectively, with age versus CRP, DAS28, HAQ score, and Larsen score (data not included). No significant correlations were found and the regression coefficients were low, in the older women between –0.01 and 0.08 and in the younger women between –0.13 and –0.04. We therefore found it appropriate to compare younger and older patients with a cutoff level between 49 and 50 years in order to analyze (predominantly) premenopausal versus postmenopausal women. The older women were found to have more severe disease than the younger, whereas no significant differences were found between older and younger men (Table 3). The characteristics of the younger women were more like those of the men.

*Table 2.* Correlations between patient characteristics and age at study entry calculated on men and women separately. The number of patients is 844 if not stated otherwise. The directions of the correlations in dichotomous variables are denoted in parentheses. E.g., men reporting a positive family history are younger at disease onset compared with men with a negative family history.

| | Men | Women |
|---|---|---|
| Reported heredity | $p = 0.05$ (–) | NS |
| Presence of SE (n = 399) | NS | NS |
| Current Smoking | NS | $p < 0.01$ (–) |
| Presence of RF | $p < 0.001$ (–) | NS |
| CRP | ($r_s = 0.05$) NS | $r_s = 0.21$, $p < 0.00001$ |
| DAS28 | ($r_s = 0.03$) NS | $r_s = 0.14$, $p < 0.01$ |
| HAQ score | ($r_s = 0.08$) NS | $r_s = 0.11$, $p < 0.01$ |
| Radiographic changes (ACR) | NS | $p < 0.01$ (+) |
| Larsen score (n = 329) | ($r_s = 0.08$) NS | $r_s = 0.18$, $p = 0.01$ |

$r_s$: Spearman regression coefficient. SE: shared epitope. NS: nonsignificant.

*Difference in DAS28 at 2-year followup; influence of patient characteristics on this outcome variable.* In both men and women DAS28 and HAQ scores decreased significantly during the 2 years of observation with no differences between the sexes. Consequently, the higher DAS28 and HAQ scores found at study entry in the women compared with the men were still present after 2 years (Table 4). At the 2-year followup 40% of the men were in remission (DAS28 < 2.6) compared with 28% of the women ($p < 0.001$). There was no significant difference in the proportion of men and women with high disease activity, 11% and 15%, respectively.

In men, the following variables at study entry correlated significantly with DAS28 at 2-year followup in bivariate analysis: disease duration before study entry, presence of RF, DAS28, and HAQ score (Table 5a). For example, RF positive and RF negative men had average DAS28 values of 3.3 and 2.7, respectively, at the 2-year followup. No confounding effect of smoking was found. In women, age, DAS28, and HAQ score at study entry correlated with DAS28 at 2 years in bivariate analyses (Table 5a).

*HAQ scores at 2-year followup.* HAQ scores were still higher in women than in men after 2 years (Table 4). In men, presence of SE, initial DAS28, and HAQ score correlated with HAQ score at 2-year followup (Table 5b). Median HAQ score at 2 years was thus higher in SE positive compared with SE negative men, 0.375 and 0.125, respectively. In women, besides DAS28 and HAQ score, age at study entry also correlated with HAQ score at 2 years (Table 5b).

*Larsen scores at 2-year followup; influence of patients' characteristics on this outcome variable.* There was no significant difference in Larsen score at 2 years between men and women (Table 4). The same proportion of men and women (15%) had Larsen score of 0 after 2 years. In patients younger than 50 years, a larger proportion was without radiographic changes at 2 years in both men (27%) and women (22%) ($p = 0.01$ and $p = 0.02$ for difference between older and younger men and women, respectively).

In men, the presence of RF and Larsen score at study entry correlated with Larsen score at 2 years in bivariate analyses. In women, age, CRP, and DAS28 at study entry in addition to presence of RF and initial Larsen score correlated with Larsen score at 2 years (Table 5c) in bivariate analyses.

*Table 3.* Differences in disease characteristics between younger and older men and women with RA at study entry.

| | Men < 50 yrs, n = 64 | Men ≥ 50 yrs, n = 242 | p | Women < 50 yrs, n = 195 | Women ≥ 50 yrs, n = 343 | p |
|---|---|---|---|---|---|---|
| Disease duration, mo | 6.6 | 5.8 | NS | 6.9 | 5.8 | < 0.001 |
| Presence of RF, % | 63 | 59 | NS | 50 | 61 | 0.01 |
| CRP | 23.5 (9–46.5) | 26 (8–55) | NS | 12.5 (5–31.5) | 20 (8–44) | < 0.001 |
| DAS28 | 4.8 (1.3) | 5.0 (1.2) | NS | 5.00 (1.3) | 5.3 (1.2) | < 0.01 |
| HAQ score | 0.75 (0.25–1.13) | 0.89 (0.38–1.25) | NS | 0.89 (0.5–1.25) | 1.0 (0.63–1.63) | 0.02 |
| Radiographic changes, % (n) | 22 (32) | 28 (104) | NS | 18 (79) | 30 (114) | 0.02 |
| Larsen score | 6 (3.5–10.5) | 6 (4–10) | NS | 4 (1–9) | 7 (2.5–15) | < 0.01 |

DAS28 scores are given in means (SD). CRP, HAQ, and Larsen scores are given in medians (interquartile ranges). P values are differences between younger and older patients for men and women, respectively. NS: nonsignificant.

*Table 4.* Differences in DAS28 scores, HAQ scores, and Larsen scores between men and women at entry and at 2-year follow-up.

| | Men | Women | p |
|---|---|---|---|
| DAS28, study entry | 5.0 (1.2) | 5.2 (1.3) | 0.02 |
| DAS28, 2 years | 3.1 (1.4) | 3.6 (1.4) | < 0.001 |
| HAQ score, study entry | 0.75 (0.38–1.25) | 1.0 (0.63–1.38) | < 0.001 |
| HAQ score, 2 years | 0.25 (0–0.75) | 0.50 (0.25–1.0) | < 0.001 |
| Larsen score, study entry | 6 (4–10) | 6 (2–12) | NS |
| Larsen score, 2 years | 10 (3–24) | 11 (2–23) | NS |

DAS28 scores are given in means (SD); HAQ and Larsen scores are given in medians (interquartile ranges); p values are differences between men and women. Larsen scores were available for 136 men and 193 women. NS: nonsignificant.

Multiple linear regression analyses were performed in men and women separately with DAS28 and Larsen score at 2 years as dependent variables. In men, presence of RF and DAS28 at inclusion correlated independently with DAS28 at 2 years, whereas age, HAQ, and DAS28 at study entry correlated independently with this outcome variable in women. Presence of RF correlated independently with Larsen score at 2 years in both sexes; and in women CRP was also significantly correlated with the radiographic outcome (Table 6).

*Medical treatment during the study years.* Treatment with DMARD was initiated during the first 3 months in 75% of the men and in 71% of the women (nonsignificant). The doses and agents were adjusted according to the physicians' decisions based upon disease activity and side effects. There was no sex difference concerning the first choice of DMARD, but women switched DMARD more frequently than men during their first study year (42% vs 31%; p = 0.01). Glucocorticoids were started at study entry in 53% of the men and 44% of the women (p = 0.02).

## DISCUSSION

This prospective study investigating the influence of sex on disease phenotype during the first year of RA showed that there were significant differences between the sexes, particularly concerning age, disease activity, and functional capacity. Further, there were differences between the sexes concerning which early disease characteristics were associated with worse outcome at 2 years of followup.

The difference in the sex proportion of different age groups at disease onset, with a female preponderance mainly during the reproductive years, confirms other reports[3,4]. Thus, RA was rare in men under age 40 and the ratio of RA incidence between men and women younger than 40 years was 1:5, compared with 1:1 in ages over 60.

The peak incidence of disease onset in women was, with the exception of RF negative smokers, in the years following menopause, when not only estradiol but also testosterone concentrations have declined[26,27]. The peak incidence of onset for men was after 60 years, when biologically active testosterone levels decline[4]. An observation is that the patients in this study were older than those in a study from Finland, where mean age of RA onset for both men and women in nonfamilial cases was 46 years[28]. Age thus has to be considered when evaluating the effect of hormone status on disease onset in RA.

In men, presence of RF was associated with earlier disease onset, whereas in women, smoking was associated with earlier disease onset only for RF negative women. Smoking is associated with earlier menopause, probably partly because smoking induces enhanced metabolism of estrogen in women[29]. Our data may indicate that shortage of estrogens from smoking may be of greater importance in RF negative than in RF positive women with RA.

The difference in age at disease onset between sexes could not be explained by hereditary factors, neither by a positive family history of RA nor by the presence of the SE. However, the uncertainty of the RA diagnoses in self-reported family history must be kept in mind. In one population survey only 35 out of 158 persons self-reporting RA were identified to have the disease[30], and a reported relation of first-degree relatives to patients with RA revealed a false positive reporting rate for family members of 61%[31]. As well, only 2–3% of probands with RA in a population study

*Table 5*. Correlations between patients' characteristics at study entry and the 3 outcome variables. a: DAS28, b: HAQ score, and c: Larsen score, all at 2-year followup given for men and women separately. Only significant values are shown, with one exception. If a correlation was significant in women but not in men, the nonsignificant correlation coefficient in men is given. As the female population is larger, p values are easier to obtain for women. Larsen score at study entry was available in 136 men and 193 women.

| | Men | Women |
|---|---|---|
| a. DAS28 Score | | |
| Age | ($r_s$ = –0.04) NS | $r_s$ = 0.12, p = 0.01 |
| Disease duration | $r_s$ = 0.18, p < 0.01 | NS |
| Reported heredity | NS | NS |
| Presence of SE (n = 399) | NS | NS |
| Current smoking | NS | NS |
| Presence of RF | p < 0.001 (–) | NS |
| CRP | NS | NS |
| DAS28 | $r_s$ = 0.23, p < 0.001 | $r_s$ = 0.28, p < 0.00001 |
| HAQ score | $r_s$ = 0.13, p = 0.04 | $r_s$ = 0.27, p < 0.00001 |
| Radiographic changes (ACR) | NS | NS |
| Larsen (n = 329) | NS | NS |
| b. HAQ Score | | |
| Age | ($r_s$ = 0.07) NS | $r_s$ = 0.16, p < 0.001 |
| Disease duration | NS | NS |
| Reported heredity | NS | NS |
| Presence of SE (n = 399) | p = 0.03 (–) | NS |
| Current smoking | NS | NS |
| Presence of RF | NS | NS |
| CRP | NS | NS |
| DAS28 | $r_s$ = 0.14, p = 0.03 | $r_s$ = 0.25, p < 0.00001 |
| HAQ score | $r_s$ = 0.38, p < 0.00001 | $r_s$ = 0.49, p < 0.00001 |
| Radiographic changes (ACR) | NS | NS |
| Larsen (n = 329) | NS | NS |
| c. Larsen Score | | |
| Age | ($r_s$ = 0.01) NS | $r_s$ = 0.16, p = 0.02 |
| Disease duration | NS | NS |
| Reported heredity | NS | NS |
| Presence of SE (n = 399) | NS | NS |
| Current smoking | NS | NS |
| Presence of RF | p < 0.01 (+) | p < 0.001 (+) |
| CRP | ($r_s$ = 0.13) NS | $r_s$ = 0.22, p < 0.01 |
| DAS28 | ($r_s$ = –0.04) NS | $r_s$ = 0.14, p = 0.04 |
| HAQ score | NS | NS |
| Radiographic changes (ACR) | p < 0.01 (+) | p < 0.0001 (+) |
| Larsen (n = 329) | $r_s$ = 0.57, p < 0.00001 | $r_s$ = 0.66, p < 0.00001 |

$r_s$: Spearman regression coefficient. SE: shared epitope. NS: nonsignificant.

were confirmed to have first-degree relatives with RA[32] compared with 20% in the present study.

The lack of association between age and bearing the SE was in disagreement with reports where an association between the SE and earlier age at onset of RA was found in populations outside Scandinavia[21,33] but also in Finland and Sweden[12,34]. In one study from the United Kingdom[35], with 404 RA cases, no association between age and SE positive alleles was found, corroborating our results. However, we cannot rule out a type II error in our study, i.e., that the sample was too small to detect a significant difference. Median age at study entry for SE positive men was 57 years and for SE negative men 62 years (nonsignificant), while SE positive women were older than SE negative women (median ages 53 vs 51).

The 59% of subjects who carried at least one of the alleles HLA-DRB1*0401, *0404, *0405, and *0408 strongly associated with RA[36,37] was similar for men and women, and this frequency was close to figures of 63–94% in RA patients in northern Europe[21,38], compared to 30–50% of healthy Caucasian populations[39]. The carriage of the SE differs widely among countries, however[38]. The low presence of the SE in our population may have contributed to the lack of association between SE and age.

The finding that women younger than 50 years had milder disease in several aspects compared to older women might depend on the influence of estrogens. The cutoff for age was chosen to differentiate premenopausal from postmenopausal women. The worse disease in the older women may indicate that declining sex hormone levels in women

*Table 6*. Results of multiple regression analyses with DAS28 score (a) and Larsen score (b) as dependent variables.

a. DAS28 Score. Regression summary with DAS28 at 2-year followup as dependent variable.

| N = 250 Men<br>$r^2 = 0.13$ | p | N = 425 Women<br>$r^2 = 0.13$ | p |
|---|---|---|---|
| Duration of disease | 0.01 | Age | 0.03 |
| Presence of RF | < 0.001 | Duration of disease | NS (p = 0.05) |
| DAS28 at study entry | < 0.0001 | HAQ at study entry | < 0.0001 |
| | | DAS28 at study entry | < 0.001 |

b. Larsen Score. Regression summary with Larsen score at 2 years (transformed by square root) as dependent variable.

| N = 125 Men<br>$r^2 = 0.08$ | p | N = 209 Women<br>$r^2 = 0.13$ | p |
|---|---|---|---|
| Smoking | NS | Duration of disease | NS (p = 0.05) |
| Presence of RF | < 0.01 | Presence of RF | < 0.01 |
| HAQ at study entry | NS | CRP at inclusion | < 0.001 |

NS: nonsignificant.

after menopause are also of importance for disease severity. Using the same cutoff age for men, no significant difference was found in disease-specific variables between younger and older men. Reports of the influence of age on disease severity differ in prospective longitudinal studies[8,40,41], where sex was not always considered.

The proportion of patients in remission, measured as DAS28 < 2.6, was 42% in men and 28% in women. It was higher in this study than in other reports, where the remission rate after 2 years of disease varied from 16% to 27% in total cohorts[16,42-44]. When data were separated for sex, our data confirm reports that male sex is associated with a higher remission rate[12,42,45]. However, direct comparisons of remission rates are difficult, as different definitions of remission have been used. Most studies have used the ACR remission criteria[46], sometimes with the duration criterion excluded. However, the European League Against Rheumatism remission criteria used here have been validated and found comparable with the ACR remission criteria[16].

In men not in remission a similar proportion compared to the women had a high disease activity. Thus, it must be emphasized that there is a group of men where the RA disease remains serious/aggressive and difficult to handle[12].

All 3 outcome variables, DAS28, HAQ score, and Larsen score, were associated with age at study entry in women but not in men. However, the associations seemed to be effects of menopause more than of age, as no significant correlations were found if older and younger women were analyzed separately excluding the years surrounding menopause. This does not rule out that age per se is an important factor, although it was not linearly related to the outcome. However, we believe that the influence of menopause is a more plausible explanation. This interpretation is corroborated by the findings of Kuiper and co-workers, although in that study older men had worse outcome than younger men[8]. Their conclusion was that menopausal state explained a major part of sex differences in outcome in RA. In our study, older men hade worse outcome compared with younger men, but the difference did not reach significance. The female population was larger and accordingly statistical significance was easier to measure. However, as our population was larger than reported in their study[8], this does not explain the discrepancies.

DAS28 after 2 years was also correlated with RF positivity at study entry, but only in men. Given that smokers are more frequently RF positive than nonsmokers[5] and considering the different smoking habits in men and women in this study, smoking has to be considered as a possible confounding factor. However, we were not able to determine any confounding effect of smoking on the relationship between RF and DAS28.

In accord with other studies, radiographic damage started early in our patients[11,47]. There was no difference in radiographic damage after 2 years between men and women, a difference that has been described after longer disease duration in some studies[6,11] but not in others[12,48].

Larsen scores at the 2-year followup correlated independently with RF positivity and Larsen score at study entry in both sexes, whereas independent correlations with initial CRP were found in women only. No confounding effect of age on the correlation between inflammation and Larsen score in women could be found. The stronger correlation between markers of inflammation and Larsen score in women compared to men was an unexpected finding. RF and markers of inflammation were thus confirmed to be

prognostic factors of more erosive disease, as in other studies[9,48-50]. However, the sex difference we observed has not been analyzed in previous reports.

The different importance of inflammation between sexes for Larsen score at 2 years was also found for the HAQ score at that time-point, as the correlation between baseline DAS28 and HAQ score at 2 years was much stronger for women than for men. During the first years of disease, inflammation is considered to be the main contributor to the level of disability[51], in agreement with our findings here of both higher DAS28 and higher HAQ scores in women. There is thus only a weak relationship between disability and erosions in the first years of RA disease[52]. Instead, the higher HAQ scores in women probably reflect a more active inflammatory disease[53], but might also confirm that the consequences of joint damage are more pronounced in women[5] and are of greater importance in women's activities and demands, as described[54].

We could not confirm the prognostic importance of bearing the SE or of smoking contributing to a higher Larsen score after 2 years in either sex, which have been reported after longer disease durations[5,11,55-57]. It is possible that 2 years is too short a time to find differences in radiological scores in this cohort of patients who were actively treated with DMARD and glucocorticoids. The Larsen scores at 2 years illustrated the active treatment model, as they were lower than scores previously reported in Swedish patients with early RA after a similar disease duration[11].

In summary, men who were RF positive and reported heredity for RA were significantly younger at disease onset compared with men negative in these aspects. Women smokers were younger at disease onset than nonsmokers, although this finding was confined to RF negative women. Older women had greater disease severity than younger women and the total cohort of men, suggesting hormonal factors at play. Prognostic markers differed between the sexes in ability to predict outcome at 2 years, RF positivity being more important in men and disease activity being more important in women.

## ACKNOWLEDGMENT

We thank Research Nurse Siv Norén for skilful data monitoring and Associate Prof. Lennart Rydberg and assistants at the Regional Blood Center, Sahlgrenska University Hospital, Göteborg, for valuable information concerning HLA-DR4 genotyping procedures and excellent technical assistance.

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