

Influence of Age and Sex on Disease Course and Treatment in Rheumatoid Arthritis

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Objective: More than 50% of patients with rheumatoid arthritis (RA) are >65 years at diagnosis. Age of onset and sex may influence the disease course, outcome and treatment. This study follows a large cohort of patients with early RA to assess contributions of age and sex to disease outcomes.

Methods: Patients from the BARFOT cohort, n=2837 (68% women), were followed for eight years at predefined time points to assess inflammation, function, joint destruction and treatment with disease modifying anti-rheumatic drugs (DMARDs) and glucocorticoids (GC). The patients were divided by sex and age at inclusion (<40, 40–54, 55–69 and ≥70 years).

Results: For both sexes, disease activity, function and pain improved over time, significantly more in men than in women in all age groups. In men, those <40 years displayed significantly lower DAS28 compared with all other groups. This group was also the least represented group in the study. The Sharp van der Heijde Score (SHS) increased over time in both sexes and all age groups. Women ≥70 years showed less improvement in disability and the highest progression of SHS mainly due to increased joint space narrowing. Patients <40 years were more likely to receive biological DMARDs, while those ≥70 years more often received only GC treatment.

Conclusion: There were significant age- and sex-dependent differences in the medical treatment and in outcome of RA 8 years after diagnosis. The differences were most pronounced in men <40 and women ≥70 years, but whether they are due to disease phenotype or treatment is unclear.

Keywords: rheumatoid arthritis, disease course, treatment, age- and sex-dependent differences

Plain Language Summary

Rheumatoid arthritis (RA) is a chronic inflammatory joint disease that often results in joint destruction and disability. It affects approximately 1% of the population and more often women than men. The demographics of the Western world are changing and today, more than 50% of RA patients are older than 65 years at diagnosis.

The aim of this study was to look at the influence of age and sex on the outcome and treatment of RA. To this end, we have examined a cohort of 2837 RA patients from disease onset and over the following 8 years.

The patients were divided into groups by sex and age at inclusion (<40, 40–54, 55–69 and ≥70 years). For all patients, disease activity and pain improved over time, but joint destruction increased. Generally, men were doing better compared to women. Women ≥70 years had a more destructive disease compared with all other patients. Biologic anti-rheumatic drugs were introduced during the collection of the cohort and were mainly

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prescribed to younger patients, preferentially men. Less than 20% of the patients were treated with glucocorticoids only, but the majority of these patients were ≥ 70 years.

We suggest that advanced age, especially for women, should be considered a risk factor for worse disease outcome and that specific treatment guidelines are desirable for patients ≥ 70 years at disease onset.

Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory joint disease that often results in joint destruction and disability. The prevalence is 0.5–1% in European and North-American populations. In Sweden, the prevalence of RA is 0.77% and the overall incidence is 41 per 100,000 inhabitants, which peaks between 70–79 years. The prevalence of RA is 2–3 times higher in women than in men, but this ratio decreases with age at onset.¹ Women generally have a worse outcome than men with respect to disease activity^{2,3} and disability,³ while joint destruction is the same for women and men.^{2,4} The demography in the Western world is changing and more than 50% of all patients with RA are over 65 years of age at diagnosis.¹ Aging is associated with increased prevalence of cardiovascular disease and osteoporosis, both of which are over-represented as comorbidities in patients with RA compared with the general population.⁴ They contribute, alongside RA per se, to the impairment of quality of life, and this combination of morbidities magnifies the socio-economic costs of supporting patients with RA relative to healthy individuals.⁵

International treatment guidelines recommend that treatment with disease modifying anti-rheumatic drugs (DMARDs) at diagnosis, irrespective of sex and age and the presence of poor prognostic factors, should be pursued actively.^{6,7} Although the guidelines do not discriminate on the basis of sex or age, younger patients seem to receive more treatment with both conventional synthetic (cs) and biological (b) DMARDs,^{8–10} whereas elderly patients are more likely to receive glucocorticoids (GC) only¹¹ and less likely to receive DMARD¹² especially bDMARDs.^{11–14}

Previous studies found that age at diagnosis and sex may influence the choice of treatment in RA. However, they were performed during different time periods, had varying lengths of follow-up and varying age stratifications, suggesting a need for further studies. Long-term follow-up studies are necessary to study the disease outcome. However a long-term study means that changes in treatment strategies as well as classification criteria may

occur. In this study, the patients were grouped according to sex and age at inclusion and followed for eight years. The rationale for the age group division at disease onset was based on estimated sex hormone levels. Women have the highest incidence of RA around the age of menopause and for men there is an increase in incidence after 40 years of age.² Sex hormones are believed to contribute to the pathogenesis of RA. The age groups were: < 40 years (no menopause; normal testosterone levels), 40–54 years (woman enters menopause; testosterone levels might start to slowly decrease), 55–69 years (all women have entered menopause; testosterone levels continue to slowly decrease) and ≥ 70 years (other factors such as comorbidities become important).² In this paper we examined the impact of age and sex on the disease course as to disease activity, function, joint destruction and treatment in the BARFOT (Better Anti Rheumatic Pharmacotherapy) long-term cohort that included patients with early RA.

Method

Patients

This study included 2837 BARFOT patients (1916 women and 921 men). BARFOT is a multicenter longitudinal observational study of RA patients in southern Sweden.¹⁵ In short, patients with newly diagnosed RA were consecutively included between 1992 and 2006; inclusion criteria were disease duration of 12 months or less and fulfilling the ACR 1987 classification criteria.¹⁶ The patients were assessed at inclusion, 3 and 6 months, at 1, 2, 5 and 8 years according to the same structured protocol, see “Clinical assessments” below. Assessments of the 15-year outcomes are ongoing. Smoking habits (current, previous or never smoker) and rheumatic factor (RF) according to respective hospital standards were assessed at inclusion. As antibodies to cyclic citrullinated peptides (anti-CCP) were not routinely collected at the standard time-points, for the majority of patients they were determined subsequently from serum samples taken at inclusion. Seropositive patients were defined as being RF positive, anti-CCP positive or positive for both these markers, whereas seronegative patients were those negative for both, or RF negative with anti-CCP status unknown.

The patients were grouped according to sex and age at inclusion. The age groups were: < 40 years, 40–54 years, 55–69 years and ≥ 70 years.

Clinical Assessments

Disease activity was assessed through the composite disease activity score (DAS28), calculated on swollen and tender 28-joint counts (SJC and TJC), erythrocyte sedimentation rate (ESR) and patient's assessment of global health on a visual analogue scale (GH-VAS) range 0–100 mm (best to worst).¹⁷ Similarly, patients reported pain on a VAS (pain-VAS) and functional disability using the Swedish version of Stanford Health Assessment Questionnaire, HAQ, range 0–3.¹⁸ The radiographs of hands and feet were scored chronologically using the Sharp van der Heijde scoring method (SHS) by two experienced readers who were blinded to clinical data. The SHS provides separate scores for joint space narrowing (JSN) and erosions (erosion score, ES).¹⁹

Medical Treatment

Treatments were registered as: no DMARD, methotrexate only, sulfasalazine only, other csDMARD, combination of at least two csDMARDs or bDMARD alone or in combination. Whether or not the patient received GC was also recorded. At inclusion, the patients were treated with DMARDs in accordance with the recommended therapy strategy in Sweden at that time. This strategy specified in early 1990s initial DMARD monotherapy and early use of low-dose GC, and a “step-up” combination therapy reserved for those with a more severe disease, and from early 2000s recommended the possibility to initiate treatment with biologics when the first DMARD or combination of DMARDs failed.

Ethics Approval and Consent to Participate

The study complied with the Declaration of Helsinki and was approved by the Regional Ethical Review Boards at Gothenburg University (Ggb Ö 282-01), Lund University (398–01) and Karolinska Institute (02–075, T2016/297-31/1). Informed, written consent was obtained from the participants before enrolment.

Statistical Analysis

The patients were grouped according to sex and age at inclusion (< 40 years, 40–54, 55–69 and ≥ 70 years). For each sex, the median for continuous variables was compared between age groups with the Kruskal–Wallis test at inclusion, 1 and 8 years. At the same time points, categorical variables were compared according to the chi-square

of independence. To facilitate comparisons with other published studies, the mean values are also presented. For continuous variables, 95% confidence interval of the median was calculated using bootstrap samples (2000 samples generated with replacement). For proportions, the standard error of proportion was used. To counteract inflation of type I error due to multiple testing, a Bonferroni-Holm²⁰ correction was used for each time point individually. The p-values are ranked from smallest to highest and each p-value is compared against a significance level that is adjusted for the number of multiple tests as well as the rank of the p-value: $\alpha(\text{rank}) = \alpha / (n - \text{rank} + 1)$, where α is set to 0.05 and n is the number of multiple tests. The analyses included all patients, regardless of whether they had been assessed at all time-points or not. The term significant is used for differences that are statistically significant at a 95% confidence level.

All statistical analyses were conducted with MATLAB R2015a (MATLAB and Statistics Toolbox Release 2015a, The MathWorks, Inc., Natick, Massachusetts, United States) and SPSS Statistics Version 25 (IBM Corporation).

Results

General Characteristics of the Study Population at Onset of Disease

Figure 1 gives an overview of the number of participants with available DAS28 data at each follow-up time together with causes of exclusion between the visits. Of the participants present at inclusion, 22% were not available for the 8-year examination. Among the 624 patients who were not assessed at 8 years, the main causes for non-participation were death (70%), unwillingness to participate (9%), development of other disease (6%), relocation (6%), and unknown causes (9%). The non-participating patients were on average 11 years older at inclusion (mean age 66 years, $p < 0.001$), more likely to be men (27% of the men vs 20% of the women were missing, $p < 0.001$). An additional 265 patients had missing DAS28 data at this time point even though they were still included in the study (no information available regarding the cause of missing data).

The patients in this new onset RA cohort had a median age of 60 years (range 15–93 years) at inclusion, 68% were women and 67% were seropositive (Table 1). In total, 33% were current smokers. The median DAS28 score of participants at inclusion was 5.3, containing a median presentation of 7 tender joints and 10 swollen joints. The most represented age group among both

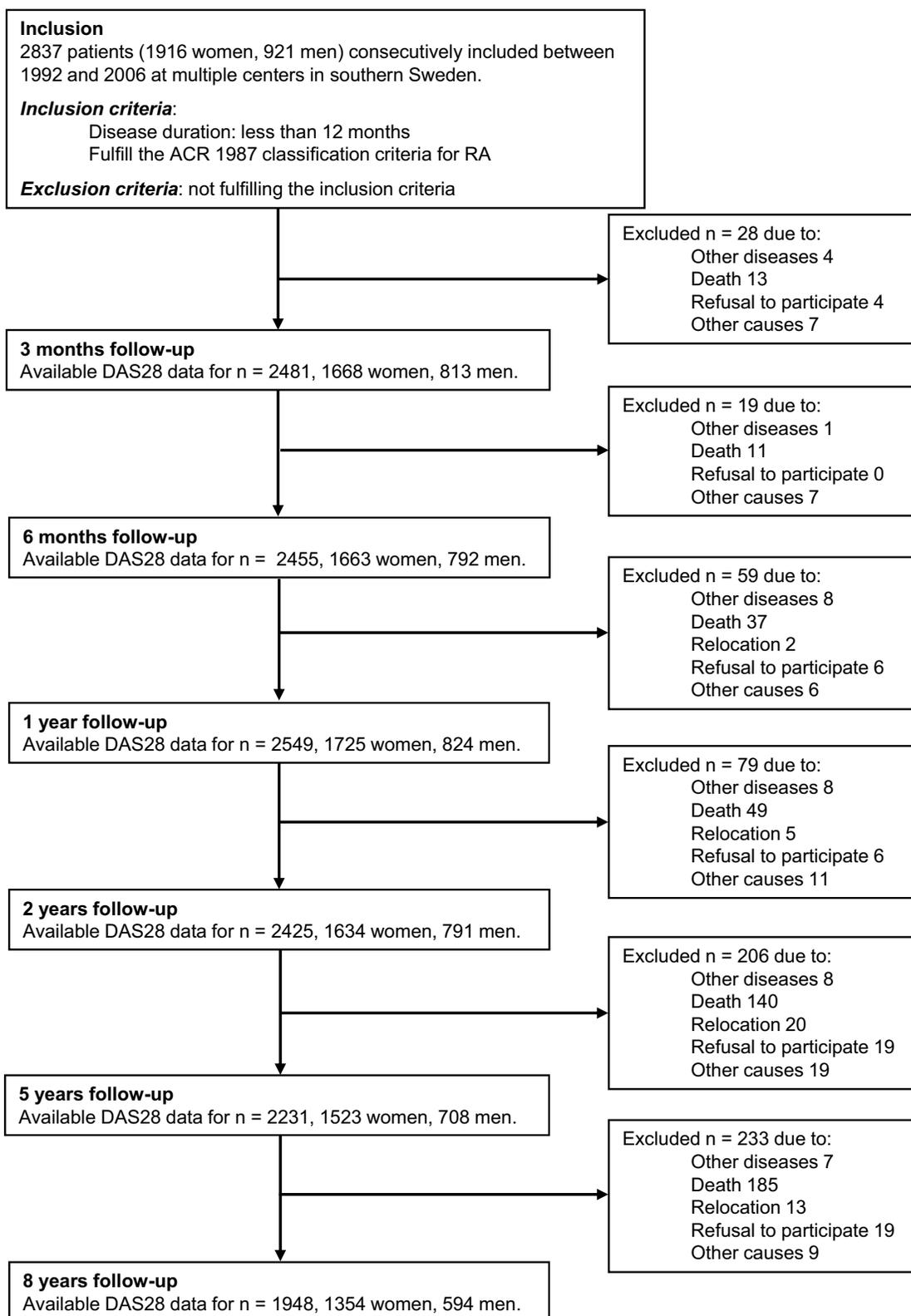


Figure 1 Overview of the number of patients with available DAS28 data at each time point and causes of exclusion. The number of excluded patients between each time point is registered, and excluded patients did not enter the study again. Some patients with missing information at a certain time point have available data at later visits and are included at those visits. No data are available for the cause of absence at a follow-up.

Table 1 Demographic, Clinical and Radiographic Characteristics of All Patients, and Divided into Women and Men at Inclusion

	All	Women	Men
N	2837	1916	921
Age, years	60 [59, 60]	58 [57, 59]	62 [61, 64]
Disease duration, month	6 [6, 6]	6 [6, 6]	6 [5, 6]
Seropositive, n (%)	67%	67%	66%
Smoking status	(n=2698)	(n=1818)	(n=880)
Current smokers, %	33%	28%	43%
Previous smokers, %	27%	26%	27%
Never smokers, %	40%	46%	30%
DAS28 (0–9.6)	5.3 [5.2, 5.4]	5.3 [5.3, 5.4]	5.2 [5.1, 5.3]
Tender joints (0–28)	7 [7, 7]	7 [7, 8]	6 [6, 7]
Swollen joints (0–28)	10 [9, 10]	10 [9, 10]	10 [10, 11]
ESR, mm/h	30 [28, 31]	30 [28, 31]	29 [27, 32]
GH-VAS (0–100)	46 [45, 47]	48 [47, 49]	42 [40, 45]
Pain-VAS (0–100)	47 [46, 48]	48 [47, 50]	42 [40, 45]
HAQ (0–3)	1.0 [0.9, 1.0]	1.0 [1.0, 1.0]	0.9 [0.8, 0.9]
SHS (0–448)	1 [0.5, 2]	1 [0, 1]	2 [1, 2]
Erosion score (0–280)	0 [0, 0]	0 [0, 0]	0 [0, 0]
Joint space narrowing (0–168)	0 [0, 0]	0 [0, 0]	0 [0, 0]

Notes: Data are reported as median [95% lower, upper confidence limits] for continuous variables and as percentages for seropositivity and smoking status.

Abbreviations: DAS28, 28-joint disease activity score; ESR, erythrocyte sedimentation rate; GH-VAS, global health on a visual analogue scale; VAS, visual analogue scale; HAQ, Health Assessment Questionnaire; SHS, Sharp van der Heijde Score for joint destruction.

women and men was the 55–69 years-old, with 634 (33%) women and 355 (39%) men. The least represented group were younger men, n=78 (9% of the male participants). The ratio of women to men decreased with age, being 4:1 in the youngest age group falling to less than 2:1 among those older than 70 years (Tables 2 and 3). Sex differences are summarized in Table 4.

Autoantibodies, Symptom Duration Before Diagnosis and Smoking Habits

The results are shown separately in women (Table 2) and men (Table 3). The majority of the patients studied were seropositive, with the lowest proportions in the age group ≥ 70 years (women 56%: men 51%) and the highest in the age group 40–54 years, (women 73%: men 78%). The median time between self-reported onset of symptoms and inclusion was shortest for women and men ≥ 70 years, and longest for women < 40 years. Smoking habits at inclusion differed significantly between age groups for both women and men: for both sexes, the proportion of

“never smokers” was largest in the age group < 40 years (57%). Except for those < 40 years, more men than women were smokers. The proportion of “current smokers” within age groups differed between the sexes, with most women smokers in the age group 55–69 years (32%) and most men smokers in the ≥ 70 age group (50%).

Disease Activity Measured as DAS28 and Its Components

Figure 2 shows the median DAS28 for women (A) and men (B) over 8 years from diagnosis. The number of participants on which the DAS28 statistics were calculated are presented in Supplementary Table 1, by sex and age group. In all age groups and for both sexes DAS28, as well as number of tender and swollen joints, decreased most during the first year after inclusion in the study. At inclusion, DAS28 differed significantly between age groups for women ($p < 0.001$, Figure 2A and Table 4) and women aged older than 55 years had the highest DAS28 (median 5.5, Table 4). For men, DAS28 at inclusion did not vary

Table 2 Clinical Measures for Women at Inclusion, 1 Year and 8 Years

Age Groups Total n = 1916	< 40 Years n = 337	40–54 Years n = 462	55–69 Years n = 634	≥ 70 years n = 483	p-value	Rank of p-value ^A	Bonferroni- Holm Adjusted Significance Level, $\alpha(a)$ ^B	Significant According to Bonferroni- Holm $p < \alpha(a)$
Symptom duration before inclusion (mo)	7 [6, 8] 9.0 (11.4)	6 [6, 7] 7.8 (7.4)	6 [6, 6] 8.0 (10.0)	5 [5, 6] 7.8 (13.2)	2.6e-04	10	0.013	S
Smoking status (%)					3.3e-08	6	0.006	S
Current smoker	19 [14, 22]	29 [24, 32]	32 [27, 34]	30 [25, 33]				
Previous smoker	24 [20, 29]	35 [31, 40]	29 [27, 34]	15 [12, 19]				
Never smoker	57 [52, 63]	36 [32, 41]	39 [35, 43]	55 [51, 60]				
Seropositive (%)	68 [62, 73]	73 [68, 77]	71 [68, 75]	56 [51, 60]	3.3e-05	9	0.01	S
ESR (mm/h)								
Inclusion	24 [21, 26] 28.6 (22.7)	24 [22, 26] 29.1 (21.6)	34 [32, 36] 38.6 (26.1)	40 [36, 44] 45.7 (28.2)	3.8e-30	3	0.005	S
1 year	12 [10, 13] 15.5 (13.9)	12 [12, 13] 17.4 (15.1)	16 [15, 18] 21.3 (17.2)	20 [18, 23] 27.3 (22.5)	4.4e-23	2	0.006	S
8 years	10 [9, 12] 14.3 (12.0)	13 [12, 15] 17.2 (15.4)	17 [16, 18] 20.9 (16.7)	21 [18, 23] 25.4 (19.3)	2.0e-19	1	0.006	S
GH-VAS (0–100)								
Inclusion	49 [47, 54] 47.5 (26.0)	48 [45, 50] 46.9 (26.5)	48 [46, 50] 48.2 (26.1)	47 [45, 49] 46.9 (24.8)	0.82	13	-	NS
1 year	25 [21, 32] 31.8 (30.0)	26 [21, 31] 31.9 (26.9)	24 [22, 26] 28.8 (22.4)	25 [21, 28] 30.0 (24.9)	0.74	9	-	NS
8 years	26 [19, 33] 31.9 (28.4)	30 [27, 34] 33.1 (25.4)	24 [22, 28] 29.6 (24.6)	35 [30, 41] 35.0 (25.0)	0.03	6	0.013	NS
Tender joints (0–28)								
Inclusion	8 [7, 9] 9.4 (6.8)	7 [6, 8] 8.4 (6.5)	7 [6, 8] 8.5 (6.3)	8 [7, 9] 8.4 (6.3)	0.21	11	-	NS
1 year	2 [1, 2] 3.7 (5.0)	2 [2, 3] 4.0 (5.2)	2 [2, 2] 3.4 (4.4)	1 [1, 2] 3.0 (4.5)	0.005	6	0.0125	S
8 years	1 [0, 2] 3.2 (4.7)	1 [0, 1] 2.7 (4.1)	0 [0, 1] 2.0 (3.4)	0 [0, 0] 1.7 (3.4)	1.2e-04	5	0.01	S
Swollen joints (0–28)								
Inclusion	9 [8, 10] 9.7 (5.9)	8 [8, 9] 9.4 (5.7)	10 [9, 10] 10.0 (5.5)	11 [10, 12] 11.2 (5.6)	1.4e-06	7	0.007	S
1 year	1 [1, 2] 2.7 (3.6)	2 [1, 3] 3.5 (4.4)	2 [2, 3] 3.5 (4.0)	2 [2, 3] 3.5 (4.3)	0.02	7	0.017	S (borderline)
8 years	0 [0, 1] 2.4 (3.9)	0 [0, 1] 2.3 (3.7)	1 [0, 1] 2.0 (3.3)	0 [0, 1] 1.5 (2.7)	0.30	9	-	NS
Pain-VAS (0–100)								
Inclusion	49 [46, 51] 48.8 (24.3)	48 [45, 50] 47.7 (24.1)	49 [46, 50] 49.1 (24.1)	47 [45, 49] 46.3 (24.9)	0.26	12	-	NS
1 year	27 [23, 32] 32.6 (27.2)	28 [23, 32] 32.9 (26.8)	24 [22, 27] 29.6 (23.4)	26 [22, 27] 29.6 (25.3)	0.28	8	-	NS
8 years	25 [20, 31] 31.8 (27.5)	29 [25, 33] 33.4 (24.6)	25 [21, 28] 30.0 (24.7)	33 [27, 38] 33.5 (24.8)	0.10	7	-	NS

(Continued)

Table 2 (Continued).

Age Groups Total n = 1916	< 40 Years n = 337	40–54 Years n = 462	55–69 Years n = 634	≥ 70 years n = 483	p-value	Rank of p-value ^A	Bonferroni- Holm Adjusted Significance Level, $\alpha(a)$ ^B	Significant According to Bonferroni- Holm $p < \alpha(a)$
HAQ (0–3)								
Inclusion	0.9 [0.8, 1.0] 1.0 (0.6)	1.0 [0.9, 1.0] 1.0 (0.6)	1.0 [1.0, 1.0] 1.1 (0.6)	1.3 [1.1, 1.4] 1.3 (0.7)	3.4e-09	5	0.006	S
1 year	0.4 [0.3, 0.5] 0.6 (0.6)	0.6 [0.5, 0.8] 0.7 (0.6)	0.6 [0.5, 0.7] 0.7 (0.6)	0.8 [0.6, 0.9] 0.8 (0.7)	1.2e-05	4	0.008	S
8 years	0.4 [0.3, 0.5] 0.6 (0.6)	0.6 [0.5, 0.8] 0.7 (0.6)	0.6 [0.6, 0.7] 0.7 (0.6)	0.9 [0.6, 1.0] 1.0 (0.8)	1.5e-10	3	0.007	S
Joint destruction (SHS)								
Total score (0–448)								
Inclusion	0 [0, 0] 1.6 (3.9)	0 [0, 0] 3.4 (7.6)	2 [1, 3] 5.9 (9.4)	4 [3, 5] 8.5 (11.6)	2.9e-33	2	0.004	S
1 year	0 [0, 1] 4.5 (7.7)	2 [1, 3] 7.1 (11.8)	5 [4, 6] 10.0 (12.9)	8 [7, 11] 13.3 (15.6)	1.1e-22	3	0.007	S
8 years	5 [3, 7] 14.6 (21.8)	11 [9, 14] 20.2 (27.0)	15 [12, 18] 24.3 (26.5)	19 [14, 21] 26.6 (27.3)	9.8e-10	4	0.008	S
Erosion score (0–280)								
Inclusion	0 [0, 0] 0.7 (1.8)	0 [0, 0] 1.2 (3.5)	0 [0, 0] 1.6 (3.2)	0 [0, 0] 1.9 (3.9)	3.5e-06	8	0.008	S
1 year	0 [0, 0] 1.9 (3.5)	0 [0, 0.5] 2.5 (4.9)	1 [0.5, 1] 3.0 (4.9)	0.5 [0, 1] 3.4 (5.9)	0.001	5	0.01	S
8 years	1 [0, 2] 5.3 (8.6)	2 [1, 3] 6.6 (11.9)	2 [1, 3] 6.8 (9.9)	1 [1, 2] 6.7 (9.9)	0.12	8	-	NS
Joint space narrowing (0–168)								
Inclusion	0 [0, 0] 0.9 (2.7)	0 [0, 0] 2.2 (5.3)	0 [0, 1] 4.3 (7.3)	4 [3, 5] 6.6 (8.9)	5.0e-40	1	0.004	S
1 year	0 [0, 0] 2.6 (5.4)	0 [0, 1] 4.7 (8.6)	3 [2, 4] 7.0 (9.8)	6 [4, 7] 9.9 (11.5)	4.2e-29	1	0.006	S
8 years	3 [0, 4] 9.4 (14.3)	8 [6, 10] 13.6 (17.2)	11 [9, 13] 17.5 (18.4)	15 [12, 20] 20.0 (19.5)	3.1e-13	2	0.006	S

Notes: Data are reported as median [95% lower, upper confidence limits] and mean (standard deviation). Percentages describing smoking status and seropositivity refer only to patients' status at inclusion. P-values were calculated according to the chi-square test of independence for smoking status and proportion of seropositive patients, and the Kruskal–Wallis test for the remaining items. ^Ap-values are ranked, within each time point individually (inclusion, 1 year and 8 years). ^BThe Bonferroni-Holm adjustment – for multiple testing – was calculated for each time point individually $\alpha=0.05$, n =number of tests, rank= rank of the exact p-values. Bonferroni-Holm adjusted level not shown for tests where the original p-value is not significant.

Abbreviations: ESR, erythrocyte sedimentation rate; GH-VAS, global health on a visual analogue scale; VAS, visual analogue scale; HAQ, Health Assessment Questionnaire, SHS, Sharp van der Heijde score; S, significant; NS, not significant.

significantly across age groups, but men <40 years had a significantly lower disease activity over time compared with men from other age groups (Figure 2B), due to lower ESR and GH-VAS (Tables 2 and 3). The DAS28 components are shown in Tables 2 and 3; ESR increased significantly with age at inclusion and after 1 and 8 years, for both sexes. Significant differences in GH-VAS between the age groups were detected only in men at 1 year. The number of swollen joints increased significantly with age

at inclusion and after 1 year in women, but not in men. There was no significant difference in tender joints at inclusion, either in men or women. The number of tender joints increased very slightly, but significantly, with age in women at 1 and 8 years.

Pain and Disability

In both sexes and in all age groups, pain-VAS and HAQ decreased during the first year. After 1 year, pain-VAS was

Table 3 Clinical Measures for Men at Inclusion, 1 Year and 8 Years

Age Groups Total n = 921	< 40 Years n = 78	40–54 Years n = 198	55–69 Years n = 355	≥ 70 Years n = 290	p-value	Rank of p-value ^A	Bonferroni- Holm Adjusted Significance Level, $\alpha(a)$ ^B	Significant According to Bonferroni- Holm $p < \alpha(a)$
Symptom duration before inclusion (mo)	6 [5, 7] 7.6 (6.5)	6 [5, 7] 8.3 (8.4)	6 [5, 6] 8.8 (16.9)	5 [5, 6] 6.9 (11.3)	0.02	6	0.006	NS
Smoking status (%)					2.2e-11	1	0.004	S
Current smoker	19 [10, 27]	38 [31, 44]	45 [39, 49]	50 [43, 55]				
Previous smoker	24 [14, 33]	36 [30, 44]	32 [28, 38]	16 [12, 21]				
Never smoker	57 [47, 69]	26 [19, 31]	23 [19, 28]	34 [29, 40]				
Seropositive (%)	72 [61, 81]	78 [72, 84]	70 [65, 75]	51 [45, 57]	1.3e-07	4	0.005	S
ESR (mm/h)								
Inclusion	17 [12, 21] 23.8 (21.1)	24 [22, 26] 31.6 (24.9)	32 [28, 35] 37.4 (25.3)	35 [32, 39] 39.5 (24.3)	8.5e-09	2	0.004	S
1 year	6 [4, 7] 10.4 (11.6)	10 [9, 11] 13.5 (13.2)	11 [10, 12] 17.6 (17.4)	14 [12, 16]	3.5e-08	1	0.006	S
8 years	6 [4, 8] 10.0 (12.6)	12 [10, 14] 14.8 (13.4)	13 [12, 14] 19.4 (18.9)	16 [13, 20]	1.9e-08	1	0.006	S
GH-VAS (0–100)								
Inclusion	40 [28, 49] 39.2 (26.6)	47 [44, 50] 42.9 (24.8)	42 [39, 45] 41.5 (24.9)	41 [36, 46] 39.6 (25.6)	0.43	12	-	NS
1 year	12 [5, 19] 18.1 (20.1)	24 [19, 27] 28.3 (22.3)	17 [14, 22] 23.6 (22.7)	14 [8, 18] 20.9 (21.3)	3.0e-04	4	0.008	S
8 years	16 [11, 22] 21.5 (22.6)	18 [14, 22] 25.2 (24.2)	19 [14, 23] 25.8 (24.7)	15 [8, 20] 23.9 (24.4)	0.54	9	-	NS
Tender joints (0–28)								
Inclusion	8 [6, 10] 8.5 (6.1)	7 [6, 8] 7.7 (5.0)	6 [5, 7] 7.5 (6.4)	6 [5, 7] 7.6 (6.6)	0.22	9	-	NS
1 year	1 [0, 2] 2.6 (3.6)	1 [1, 2] 3.3 (5.0)	1 [0, 1] 2.8 (4.6)	0 [0, 1] 2.1 (3.8)	0.02	7	0.0167	NS
8 years	0 [0, 0] 1.4 (3.0)	0 [0, 0] 1.9 (3.6)	0 [0, 0] 1.5 (3.0)	0 [0, 0] 1.1 (2.9)	0.20	5	-	NS
Swollen joints (0–28)								
Inclusion	11 [10, 12] 10.4 (6.0)	9 [8, 10] 9.8 (5.3)	10 [9, 11] 11.1 (6.1)	11 [10, 12] 11.6 (5.9)	0.03	7	0.007	NS
1 year	1 [0, 2] 3.3 (4.3)	2 [1, 3] 3.5 (4.2)	2 [1, 2] 3.3 (4.7)	1 [0, 2] 2.7 (3.8)	0.04	8	0.025	NS
8 years	0 [0, 0] 1.7 (4.1)	1 [0, 1] 2.3 (3.5)	0 [0, 0] 2.0 (3.5)	0 [0, 0] 1.3 (2.2)	0.04	3	0.007	NS
Pain (0–100)								
Inclusion	42 [35, 51] 43.5 (22.4)	45 [38, 49] 44.6 (23.8)	43 [38, 47] 43.8 (25.1)	40 [36, 45] 40.8 (24.5)	0.28	11	-	NS
1 year	12 [6, 19] 17.7 (21.1)	23 [19, 28] 27.6 (22.5)	16 [14, 20] 24.4 (23.8)	11 [8, 15] 19.3 (20.8)	2.3e-05	3	0.007	S
8 years	14 [5, 19] 23.3 (25.7)	20 [15, 26] 27.5 (24.8)	19 [14, 23] 26.4 (25.8)	15 [10, 23] 23.8 (24.3)	0.28	6	-	NS

(Continued)

Table 3 (Continued).

Age Groups Total n = 921	< 40 Years n = 78	40–54 Years n = 198	55–69 Years n = 355	≥ 70 Years n = 290	p-value	Rank of p-value ^A	Bonferroni- Holm Adjusted Significance Level, $\alpha(a)$ ^B	Significant According to Bonferroni- Holm $p < \alpha(a)$
HAQ (0–3)								
Inclusion	0.8 [0.5, 0.9]	0.8 [0.6, 0.9]	0.9 [0.8, 1.0]	0.8 [0.7, 0.9]	0.57	13	-	NS
1 year	0.8 (0.5) 0.1 [0.0, 0.1]	0.8 (0.5) 0.4 [0.3, 0.5]	0.9 (0.6) 0.3 [0.1, 0.4]	0.9 (0.7) 0.4 [0.3, 0.5]	0.01	6	0.013	S
8 years	0.3 (0.4) 0.0 [0.0, 0.0]	0.5 (0.5) 0.4 [0.3, 0.5]	0.4 (0.5) 0.3 [0.1,0.4]	0.5 (0.6) 0.5 [0.4, 0.8]	2.2e-05	2	0.006	S
0.3 (0.4)	0.5 (0.5)	0.5 (0.6)	0.7 (0.7)					
Joint destruction (SHS)								
Total score (0–448)								
Inclusion	0 [0, 0] 4.0 (11.7)	0 [0, 1] 3.4 (8.6)	2 [1, 3] 5.1 (8.9)	3 [2, 4] 6.7 (9.6)	1.2e-06	5	0.006	S
1 year	2 [0, 3] 5.4 (12.7)	2 [1, 3] 6.5 (10.6)	4 [3, 5] 8.4 (11.6)	5 [3, 7] 9.1 (11.8)	0.002	5	0.01	S
8 years	12 [3, 16] 15.0 (19.1)	11 [7, 14] 15.7 (17.4)	13 [10, 16] 20.8 (23.6)	13 [8, 19] 18.5 (19.2)	0.29	7	-	NS
Erosion score (0–280)								
Inclusion	0 [0, 0] 1.6 (4.5)	0 [0, 0] 1.5 (4.1)	0 [0, 0] 2.1 (4.4)	0 [0, 0] 1.8 (3.5)	0.24	10	-	NS
1 year	0 [0, 1] 2.6 (5.3)	0 [0, 1] 2.8 (5.2)	1 [0, 2] 3.3 (5.6)	0 [0, 1] 2.9 (5.2)	0.52	9	-	NS
8 years	2 [0, 3] 4.7 (8.6)	2 [1, 3] 4.9 (7.6)	3 [2, 5] 6.9 (9.9)	1 [0, 2] 4.5 (6.5)	0.31	8	-	NS
Joint space narrowing (0–168)								
Inclusion	0 [0, 0] 2.3 (8.1)	0 [0, 0] 1.9 (4.9)	0 [0, 1] 3.1 (5.5)	2 [0, 3] 4.9 (7.5)	5.0e-08	3	0.005	S
1 year	0 [0, 1] 2.8 (8.3)	1 [0, 2] 3.7 (6.4)	2 [1, 3] 5.0 (7.5)	4 [3, 6] 6.5 (8.6)	3.0e-06	2	0.006	S
8 years	7 [2, 12] 10.8 (13.7)	7 [5, 10] 10.8 (12.5)	9 [7, 12] 13.9 (15.6)	10 [7, 14] 14.2 (14.7)	0.15	4	-	NS

Notes: Data are reported as median [95% lower, upper confidence limits] and mean (standard deviation). Percentages describing smoking status and seropositivity refer only to patients' status at inclusion. P-values were calculated according to the chi-square test of independence for smoking status and proportion of seropositive patients, and the Kruskal–Wallis test for the remaining items. ^Ap-values are ranked, within each time point individually (inclusion, 1 year and 8 years). ^BThe Bonferroni-Holm adjustment – for multiple testing – was calculated for each time point individually. $\alpha=0.05$, n =number of tests, rank= rank of the exact p-values Bonferroni-Holm adjusted level not shown for tests where the original p-value is not significant.

Abbreviations: ESR, erythrocyte sedimentation rate, GH-VAS, global health on a visual analogue scale, VAS, visual analogue scale, HAQ, Health Assessment Questionnaire, SHS, Sharp van der Heijde score; S, significant; NS, not significant.

relatively constant in both women and men within the age groups (Table 2 and Table 3). A significant difference between age groups was only seen in men at 1 year; men

< 40 years and men ≥ 70 years had the lowest scores and men 40–54 years had the highest. Men < 40 years had significantly lower HAQ after one year compared with all

Table 4 Clinical Outcomes, Given as Median Values, Compared Across Age Groups and Between Sexes

Time Point, Age-Group	Women	Men	P-value Comparison Between Sexes ^A
DAS28			
Inclusion, <40 yrs	5.2	4.9	NS
Inclusion, 40–54 yrs	5.1	5.2	NS
Inclusion, 55–69 yrs	5.5	5.2	<0.01
Inclusion, ≥70 yrs	5.5	5.3	<0.001
P-value within sex for age-groups ^A	<0.001	0.3, NS	
1 year, <40 yrs	3.3	2.4	<0.001
1 year, 40–54 yrs	3.4	3.1	0.03
1 year, 55–69 yrs	3.6	2.8	<0.001
1 year, >70 yrs	3.4	2.8	<0.001
P-value within sex for age-groups ^A	0.05	0.01	
8 years, <40 yrs	2.8	1.9	<0.001
8 years, 40–54 yrs	3	2.6	<0.01
8 years, 55–69 yrs	2.9	2.4	<0.001
8 years, >70 yrs	3.1	2.5	<0.001
P-value within sex for age-groups ^A	0.4, NS	<0.01	
HAQ (0–3)			
Inclusion, <40 yrs	0.9	0.8	<0.01
Inclusion, 40–54 yrs	1	0.8	<0.001
Inclusion, 55–69 yrs	1	0.9	<0.001
Inclusion, ≥70 yrs	1.3	0.8	<0.001
1 year, <40 yrs	0.4	0.1	<0.001
1 year, 40–54 yrs	0.6	0.4	<0.001
1 year, 55–69 yrs	0.6	0.3	<0.001
1 year, >70 yrs	0.8	0.4	<0.001
8 years, <40 yrs	0.4	0	<0.001
8 years, 40–54 yrs	0.6	0.4	<0.001
8 years, 55–69 yrs	0.6	0.3	<0.001
8 years, >70 yrs	0.9	0.5	<0.001
Pain-VAS (0–100)			
Inclusion, <40 yrs	49	42	0.08
Inclusion, 40–54 yrs	48	45	0.13
Inclusion, 55–69 yrs	49	43	<0.01
Inclusion, ≥70 yrs	47	40	<0.01
1 year, <40 yrs	27	12	<0.001
1 year, 40–54 yrs	28	23	0.08
1 year, 55–69 yrs	24	16	<0.001
1 year, >70 yrs	25.5	11	<0.001
8 years, <40 yrs	25	14	0.01
8 years, 40–54 yrs	29	20	<0.01
8 years, 55–69 yrs	25	19	0.01
8 years, >70 yrs	33	15	<0.001

(Continued)

Table 4 (Continued).

Time Point, Age-Group	Women	Men	P-value Comparison Between Sexes ^A
SHS (0–448)			
Inclusion, <40 yrs	0	0	0.13
Inclusion, 40–54 yrs	0	0	0.75
Inclusion, 55–69 yrs	2	2	0.64
Inclusion, ≥70 yrs	4	3	0.06
1 year, <40 yrs	0	2	0.59
1 year, 40–54 yrs	2	2	0.68
1 year, 55–69 yrs	5	4	0.15
1 year, >70 yrs	8	5	<0.01
8 years, <40 yrs	5	12	0.29
8 years, 40–54 yrs	11	11	0.53
8 years, 55–69 yrs	15	13	0.13
8 years, >70 yrs	19	13	0.05

Note: ^AP-values are given according to the Mann–Whitney test.
Abbreviations: DAS28, 28-joint disease activity score, HAQ, Health Assessment Questionnaire, VAS, visual analogue scale, SHS, Sharp van der Heijde Score for joint destruction; NS, not significant.

other groups. HAQ was higher among women compared with men for all age groups and at all time points (p<0.001, Table 4). For both sexes, the most favorable HAQ was seen for those < 40 years (p<0.001).

Joint Destruction

At one year after inclusion, 2613 (92%) patients were assessed and of those 71% had radiographic assessment of hands and feet. At the 8-year follow-up, 2213 patients (78%) were assessed and 73% of these had radiographic assessments.

The SHS differed significantly between age groups for women at all time points (Table 2) and at inclusion and 1 year for men (Table 3). Joint destruction increased steadily over time, and women ≥ 70 years consistently had the highest SHS at all time points compared with all other groups. Men < 40 years had less joint destruction at inclusion and at 1 year compared with all other groups (Table 3). There were no differences in SHS between men and women under the age of 70 years, whereas older

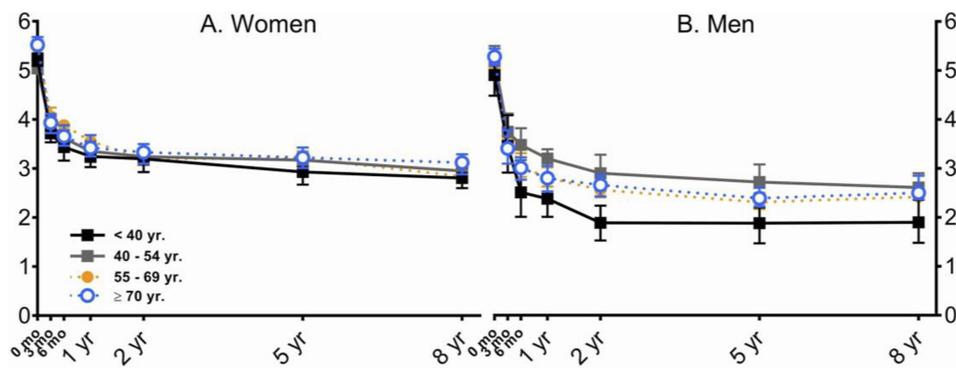


Figure 2 Median disease activity score over the course of the study. Disease activity in (A) women and (B) men over 8 years from diagnosis, measured using the composite disease activity score (DAS28) at all assessment time points for subjects divided by age group: black cube < 40 years; grey cube 40–54 years; closed circle 55–69 years; open circle >70 years. Symbols show median values, error bars represent 95% confidence intervals.

women had marginally higher SHS than older men (Table 4).

Medical Treatment

Figure 3 shows the percentage of patients receiving methotrexate only, sulfasalazine only or bDMARD alone or in combination (Figure 3 A–F) and/or GC (Figure 3 G–H). Methotrexate was the most common csDMARD, and bDMARDs were the least common treatment at inclusion. The usage of bDMARDs increased over time and younger patients were more likely than older patients to receive bDMARDs. Treatment with GC, given alone or together with a DMARD, was similar across all age groups and between sexes, except that they were less often prescribed for men < 40 years. Less than 20% of the patients received GC in monotherapy, however those patients were preferentially women and men ≥ 70 years (Supplementary Figure 1). At 8 years, men ≥ 70 years had, compared with all other groups, the highest proportion of no treatment, ie neither DMARD nor GC.

Discussion

This study investigated the influence of sex and age of onset on the disease course and treatment of more than 2000 early RA patients during 8 years. The striking result that emerges is the great consistency of disease courses measured (Figure 2) in view of the variety of management strategies covered (Figure 3, Supplementary Figure 1). All patients showed significant improvement in most clinical measures immediately on commencement of treatment and throughout the first year, after which disease activity (DAS28) remained fairly constant. Nonetheless, we find that our choice of 4 age bands, formulated specifically to

match the maturation of hormone profiles in patients of both sexes, not only provides a useful breakdown of the stages of disease ensuing for patients of different age at onset, but also reveals sex differences that may otherwise be masked.

The notable example of such a sex difference is in the group of men <40 years old at onset: from 6 months and onwards, they showed more improvement in DAS28 than all other groups, both male and female, despite there being no significant difference at inclusion. Nevertheless, at 8 years, there was no difference in joint destruction compared to older men. However, this is the age group that was least represented in our study ($n=78$, representing 9% of the male participants and only 3% of the entire BARFOT cohort) and these results should be interpreted with care, as these findings might be confounded by the low sample size. At inclusion, women older than 55 years had a significantly elevated median DAS28 compared with age-matched men. During the eight years of follow-up, there was almost no difference in DAS28 between the age groups in women, whereas men younger than 40 years consistently had a lower DAS28 compared with the other age-groups. Tender and swollen joint count decreased strongly and consistently throughout the follow-up and were between 0 and 1 for all groups at 8 years. As previously reported,⁴ the remaining components of DAS28, ESR and GH-VAS, had a greater impact on DAS28 and might not reflect just joint inflammation. It is however noteworthy that ESR in both men and women falls dramatically on commencement of treatment, in all age groups. Moreover, our results are in line with the knowledge that ESR increases with age, particularly in women,²¹ which could mean that the higher DAS28 in

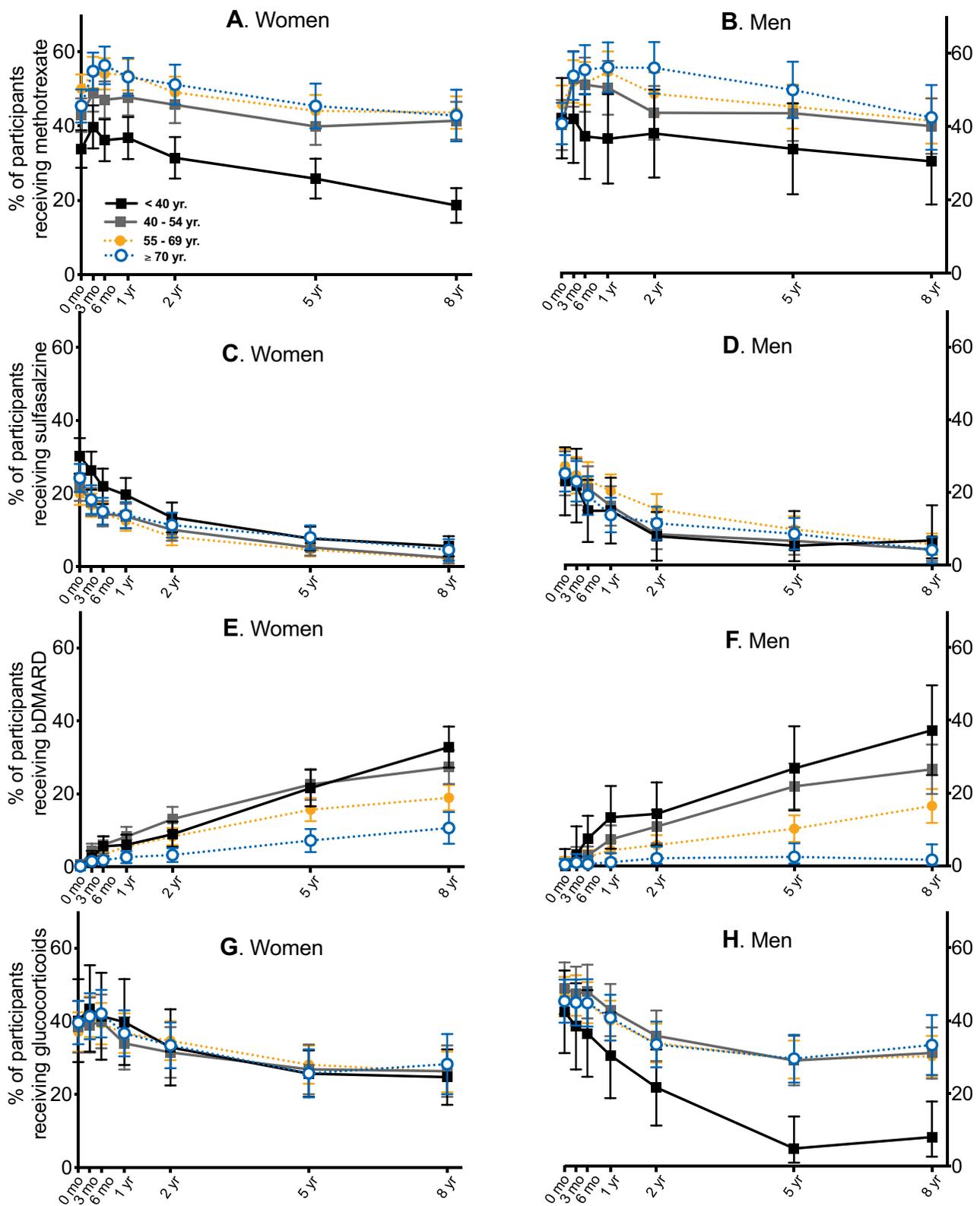


Figure 3 Distribution of drug treatments amongst the study population. Percentages of subjects receiving DMARD and/or glucocorticoid treatment over the course of the study are given for methotrexate (A and B), sulfasalazine (C and D), biological DMARDs (E and F) and glucocorticoids (both alone and in combination with DMARDs) (G and H). Panels (A, C, E, G) show data from women, panels (B, D, F, H) are from men; subjects are divided by age group: black cube <40 years; grey cube 40–54 years; closed circle 55–69 years; open circle >70 years. Symbols show median values, error bars represent 95% confidence intervals.

older women was probably attributed to the measures of disease activity rather than to the disease activity per se. Thus, differences in age and sex should be taken into account when interpreting DAS28.

Women generally had higher HAQ compared with men as has been previously found.^{22,23} Camacho et al found that a sex-independent higher rate of increased disability (HAQ) associated with increased age of symptom onset. The same study showed that after 5 years the HAQ scores were higher than at baseline for patients 55 years and older.²² Arnold et al¹³ found that older-onset patients (≥ 64 years) start and end the first year after diagnosis worse in terms of DAS28 and HAQ compared with younger patients. In the current study, irrespective of age, HAQ decreased during the first year and was thereafter relatively stable. Women ≥ 70 years showed a slight increase after 1 year but the HAQ scores at 8 years were still below baseline level at inclusion.

In contrast to all other measures, radiographically assessed joint destruction increased steadily over time. In women, the SHS increased significantly with age group at all time points, mainly due to joint space narrowing. However, joint space narrowing is not specific for RA. Coexisting osteoarthritis has been shown to contribute to a higher joint space narrowing score at inclusion in patients over 55 years of age relative to their younger counterparts.²⁴ In men, the increase with age was significant at inclusion and after one year but this difference was no longer evident at the 8 years timepoint. Previously, Ahlmén et al²⁵ found no significant differences in SHS between women and men, whereas other studies found men to have a greater radiological destruction at 24 months compared with women.¹² In the present study, we found no significant differences between men and women, except for the ≥ 70 years women who had higher SHS than men at all time points. Further, this group had consistently the highest SHS among women. There was no difference in the erosion score for men and only a marginal increase for women older than 55 years at one-year follow-up. This indicates that the SHS changes seen in women ≥ 70 years were mainly due to increased joint space narrowing. Hence, by introducing age as a factor, the different trajectories of changes in joint architecture experienced by men and women are disclosed.

For the individual patient, treatment is chosen after careful considerations that include disease activity, age,

estimated prognosis, desire to have children for those of reproductive age, and comorbidities. As expected, methotrexate was by far the most commonly used DMARD in the BARFOT cohort. We found that the proportion of younger patients, in particular women less than 40 years, who were treated with methotrexate was lower compared with all other age groups. This could be due to the fact that Methotrexate has teratogenic side effects and is not prescribed before conception or during pregnancy and lactation.²⁶ bDMARDs were introduced during the collection of the BARFOT cohort, which means that only the patients included during 1999–2006 (about half of the patients) had access to treatment with bDMARDs. As seen in other studies,^{11–14} the prescription of bDMARDs was highest for younger patients and decreased with age at onset. GC in monotherapy was used in $< 20\%$ of the patients, however, the patients who were most likely to receive this treatment were women and men ≥ 70 years. Patients younger than 40 years were the least likely to receive GC as the only treatment. Otherwise, no differences for GC as monotherapy or in combination with a DMARD were found. Our findings are in coherence with an epidemiological study on DMARD prescription, covering 87% of the German population, which found that treatment during the first year after onset of RA differed with respect to both sex and age;¹⁴ women were less likely to receive cDMARD, bDMARD and GC during the first year compared with men. The same study found that patients ≥ 65 years were less likely to receive DMARDs and more likely to receive only GC compared with patients < 35 years even though these patients had the highest DAS28 levels.⁴ These findings were contradicted in a large multinational cohort of patients with manifest RA, where no differences in treatment strategies between the sexes were found even though women had a worse disease outcome.³ One possible explanation for GC as monotherapy is the occurrence of comorbidities, since RA patients with late onset have a heavier burden of comorbidities compared with younger ones.¹¹ Notably, GC treatment has been reported to be more common in patients with late onset.^{11,12}

Access to bDMARDs and targeted synthetic DMARDs have improved the disease outcome immensely and today the treatment aim is clinical remission, or at least low disease activity.⁷ The perfect treatment is an act of balance between too little and too much immunosuppression, and particularly among older RA patients there is often

a tension between the likely benefit of treating the active disease and the risk of adverse events due to frailty or comorbidities.^{27,28}

Separating out those participants who were >70 years old at diagnosis confirmed previous reports that the frequency of RF was lower in the elderly, who more frequently had large joint involvement and disease distribution was more equal between the sexes.^{1,29} Thus, our study reinforces the question posed by other previous studies whether RA in elderly is the same disease as RA in younger persons.^{12,13}

Our study has some limitations. The patients were collected to the BARFOT cohort 1992–2006 and treatment strategies as well as classification criteria have changed. Long-term follow-up studies of RA outcomes are necessary and these limitations are unavoidable. As shown earlier, the patients included in the 2000s (half of the patients) were more often treated with MTX and biologics than those included in 1990s.³⁰ However, despite greater reduction in disease activity for the more actively treated patients, the gender difference persisted during 8 years, with men achieving lower DAS28 than women. Therefore we suggest the present findings also to be valid for more actively treated patients and more recent cohorts.

Comorbidities such as hypertension and diabetes may have influenced at least partially the responsiveness to glucocorticoids. All patients, irrespective of comorbidity, were included in the study. However, the information regarding comorbidities was not consistently recorded, which makes it impossible to estimate their impact on our results.

Of the participants present at inclusion, 22% were not available for the 8-year examination. The non-participating patients were on average 11 years older at inclusion and more likely to be men. They did not differ from the participants in regard to any of the disease activity indicators, with the exception of JSN at inclusion (median 2 vs 0 in the participants, $p < 0.001$) which is non-specific for RA and may indicate comorbidity for osteoarthritis and associate with higher age. Taken together, the loss of non-participants might have rendered our findings regarding age differences at 8-years as slightly conservative, potentially more so for men. The BARFOT cohort encompasses more than 2800 patients. However, the division of the patients into eight subgroups resulted in small numbers of participants in some of the subgroups, especially for the

younger men which is an important group for the purpose of this study. This shortcoming limited both the number of statistical analyses we were able to perform and the power of those we performed, and the results regarding younger men should be interpreted with caution. Nonetheless, we consider this approach to have provided us with useful insights.

The aim of this study was to investigate the influence of sex and age on disease development and treatment choices, but our understanding of the influence of age alone on disease development is blurred by the variety of treatment choices across age groups in the cohort.

Conclusions

This large cohort study of patients with early RA over the 8 years following their diagnosis reveals that the disease course for all ages and both sexes was similar, regardless of the details of treatments given, but useful insight was provided by differential analysis using specific function-related age bands and sex as factors.

Men < 40 years of age had the most favorable functional outcome over the study period. The significantly lower DAS28 over time was manifest despite no obvious difference at diagnosis. This group (together with women < 40 years) was also more likely to be treated with bDMARDs. Results for this group should be cautiously interpreted due to the low sample size.

Women ≥ 70 years experienced the smallest improvement with respect to disability and joint destruction over the study period, and were, together with men in the same age group, more likely to receive treatment with only GC.

Whether the differences in outcome are due to the phenotype of the disease or its treatment is not clear. However, late age onset might be a risk factor for a worse disease outcome and appropriate treatment is important irrespective of age. Our results indicate that there is a need for specific treatment guidelines for patients older than 70 years.

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Disclosure

The authors report no conflicts of interest in this work.

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