Research article

**Women, men, and rheumatoid arthritis: analyses of disease activity, disease characteristics, and treatments in the QUEST-RA Study**

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ACR: American College of Rheumatology; CRP: C-reactive protein; DAS28: disease activity score using 28 joint counts; DMARD: disease-modifying antirheumatic drug; ESR: erythrocyte sedimentation rate; HAQ: Health Assessment Questionnaire; QUEST-RA: Quantitative Standard Monitoring of Rheumatoid Arthritis; RA: rheumatoid arthritis; RF: rheumatoid factor; SJC28: swollen joint count-28; TJC28: tender joint count-28.
Introduction Gender as a predictor of outcomes of rheumatoid arthritis (RA) has evoked considerable interest over the decades. Historically, there is no consensus whether RA is worse in females or males. Recent reports suggest that females are less likely than males to achieve remission. Therefore, we aimed to study possible associations of gender and disease activity, disease characteristics, and treatments of RA in a large multinational cross-sectional cohort of patients with RA called Quantitative Standard Monitoring of Patients with RA (QUEST-RA).

Methods The cohort includes clinical and questionnaire data from patients who were seen in usual care, including 6,004 patients at 70 sites in 25 countries as of April 2008. Gender differences were analyzed for American College of Rheumatology Core Data Set measures of disease activity, DAS28 (disease activity score using 28 joint counts), fatigue, the presence of rheumatoid factor, nodules and erosions, and the current use of prednisone, methotrexate, and biologic agents.

Results Women had poorer scores than men in all Core Data Set measures. The mean values for females and males were statistically significantly higher mean values compared with men in all other disease activity measures ($P < 0.001$) and met DAS28 remission less often than men. Rheumatoid factor was equally prevalent among genders. Men had nodules more often than women. Women had erosions more often than men, but the statistical significance was marginal. Similar proportions of females and males were taking different therapies.

Conclusions In this large multinational cohort, RA disease activity measures appear to be worse in women than in men. However, most of the gender differences in RA disease activity may originate from the measures of disease activity rather than from RA disease activity itself.

Materials and methods The Quantitative Standard Monitoring of Patients with RA (QUEST-RA) program was established in 2005 to promote quantitative assessment in usual clinical care at multiple sites and to develop a database of RA patients seen outside of clinical trials in regular care in many countries. The initial design was to assess 100 patients with RA at each of three or more sites in 10 different countries, with data collection beginning in January 2005. The program has since been expanded to include 6,004 patients from 70 sites in 25 countries as of April 2008. This report includes data from Argentina, Brazil, Canada, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Kosovo, Latvia, Lithuania, The Netherlands, Poland, Russia, Serbia, Spain, Sweden, Turkey, United Arab Emirates, the UK, and the US. The study was car-
ried out in compliance with the Declaration of Helsinki. Ethics committees or internal review boards of participating institutes approved the study, and informed consent was obtained from the patients.

Clinical evaluation
All patients were assessed according to a standard protocol to evaluate RA (SPERA) [30]. Physicians completed three one-page forms: (a) review of clinical features, including classification criteria, extra-articular features, comorbidities, and relevant surgeries; (b) all previous and present disease-modifying antirheumatic drugs (DMARDs), their adverse events, and reasons for discontinuation; and (c) a 42-joint count [31] for swollen and tender joints as well as joints with limited motion or deformity. The review included physician global assessment of disease activity, physician report concerning whether or not the patient had radiographic erosions, and laboratory tests of ESR, C-reactive protein (CRP), and rheumatoid factor (RF) values.

Patient self-report
Patients completed a four-page expanded self-report questionnaire that included the standard Health Assessment Questionnaire (HAQ) [32] as well as items from the multidimensional HAQ (MDHAQ) [33], HAQ II [34], and the Recent-Onset Arthritis Disability questionnaire to assess functional capacity in activities of daily living [35]. The questionnaire also includes visual analog scales (VASs) for pain, patient global status, and fatigue; RA disease activity index (RADAI) self-report joint count [36]; duration of morning stiffness; lifestyle choices such as smoking and physical exercise; height and weight to calculate body mass index; and demographic data, including years of education and work status [29].

Gender and disease activity measures
DAS28 was calculated for current disease activity [37,38] according to 28 swollen (SJC28) and tender (TJC28) joint counts from the formula DAS28 = 0.56*sqrt(TJC28) + 0.28*sqrt(SJC28) + 0.70*Ln(ESR) + 0.014*patient global 0 to 100. DAS28 remission rates (DAS28 of less than 2.6) were calculated for females and males. The HAQ score was calculated without including 'aids and devices' and 'help from other people' given that the availability of aids/devices may differ across countries in a multicultural study such as QUEST-RA. It has been suggested that the HAQ may be calculated without aids/devices/help since inclusion might result in bias.

The proportion of patients who met DAS28 criteria for remission (<2.6) was analyzed in females and males with 0, 1, 2, 3, 4, and 5 swollen joints on a 28-joint count. Levels of individual disease activity measures were calculated for females and males according to SJC28 in arbitrary categories of 0 to 1, 2 to 3, 4 to 6, and 7 or more swollen joints. Swollen joint count was chosen as the standard, although a 'gold standard' measure for disease activity does not exist.

Gender and disease characteristics
Gender differences in disease characteristics, including the prevalence of RF+, nodules, and erosive disease, were studied separately in two groups of countries: 'low' prevalence and 'high' prevalence countries. For example, the prevalence of RF+ ranges between 52% and 92% among countries, with a median of 73.5%. Thus, all countries with a 'low' prevalence of RF+ of between 52% and 73.5% were analyzed together for gender differences of RF+, and countries with a 'high' prevalence of RF+ of between 73.5% and 92% were analyzed together for gender differences of RF+. Two groups of countries ('low' versus 'high' prevalence) were formed similarly to analyze nodules (cut point for prevalence = 20%) and erosive disease (cut point for prevalence = 63%).

Gender and therapies for rheumatoid arthritis
The percentage of patients who were taking prednisone, methotrexate, and biologic agents for RA differed considerably between countries. To study whether females were treated differently from males, countries were studied in two groups, such as for disease characteristics, divided at the median among the 25 countries. Thus, countries with 'low use of a drug' and 'high use of a drug' were analyzed separately. Medians were 50% for prednisone, 62% for methotrexate, and 18% for biologic agents. The delay between the first RA symptoms and initiation of the first DMARDS was calculated and compared between men and women.

Statistical methods
Results for continuous variables are presented as mean, standard deviation, median, and percentages. Statistical significance was tested with the Student t test and nonparametric tests for continuous variables and the chi-square test for categorical variables. The association of gender and outcome variables was calculated for each variable and each country. Effect size was estimated according to two methods: in standardized units of difference (Cohen’s D) and variance-accounted statistics (eta-squared \( \eta^2 \)). Ninety-five percent confidence intervals for Cohen’s D were obtained by bias-corrected bootstrapping (1,000 replications) and for \( \eta^2 \) by noncentrality-based interval estimation. \( \eta^2 \) was calculated using an analysis of covariance model that adjusts for age, disease duration, and country. Cohen’s D standards are small effect 0.2, medium effect 0.5, and large effect 0.8. For \( \eta^2 \), standards are small effect 0.01, medium effect 0.059, and large effect 0.138.

Results
Demographic and clinical characteristics
In April 2008, the QUEST-RA database included 6,004 patients from 70 sites in 25 countries. The demographic characteristics are those of a typical RA cohort with 79% females,
more than 90% Caucasians, and a mean age of 57 years (Table 1), with considerable variation between countries. Significant variation between countries was seen in disease activity, severity, and treatments (Table 1).

Gender differences in disease activity in the entire group
Women had higher scores (indicating poorer status) than men in all Core Data Set measures. The mean values for females and males were SJC28 of 4.5 versus 3.8, TJC28 of 6.9 versus 5.4, ESR of 30 versus 26, HAQ (0 to 3) of 1.1 versus 0.8, visual analog scales (0 to 10) for physician global estimate of 3.0 versus 2.5, pain of 4.3 versus 3.6, and patient global estimate of 4.2 versus 3.7 ($P < 0.001$). DAS28 (0 to 10) was 4.3 in females versus 3.8 in males, and fatigue was 4.6 versus 3.7 ($P < 0.001$). Variables were also compared using nonparametric tests, with identical levels of statistical significance. Cohen’s D effect size of gender was at a medium level (0.2 to 0.5) for HAQ physical function (0.43) followed by DAS28 and fatigue (0.33), pain (0.27), physician global estimate (0.23), tender joint count (0.21), and patient global estimate (0.20) and was at a low level ($<0.20$) for swollen joint count and ESR (0.13 for both). According to $\eta^2$ statistics, the effect of gender was small-medium for all studied variables (Figure 1).

Among the disease activity measures that were studied, SJC28 levels appeared to be most similar between genders. Therefore, other disease activity measures were compared on different SJC28 levels. Among patients who had 0 to 1 swollen joints, women had statistically significantly higher mean values compared with men for all other disease activity measures ($P < 0.001$) (Table 2). Among patients who had 2 to 3 swollen joints, women had significantly higher scores than men in all other measures except TJC and ESR (Table 2). At higher levels of SJC28, differences were most pronounced in pain, fatigue, and HAQ.

More men (30.0%) than women (16.7%) were in DAS28 remission ($P < 0.001$). Among patients with 0 swollen joints, 57.6% of men and 42.0% of women were in DAS28 remission. Among patients with 1 and 2 swollen joints, 30.3% and 20.2% of men and 16.9% and 7.1% of women met DAS28 remission, respectively ($P < 0.001$) (Figure 2). Around 15% of men and 5% of women met criteria for DAS28 remission even when they had 3 to 4 swollen joints on a 28-joint count.

Gender differences in disease activity measures according to country
Standardized units of difference between genders were calculated for each variable according to country and are shown as an example for two variables: HAQ (Table 3) and DAS28 (Table 4). Differences according to gender were greatest on the HAQ (of all Core Data Set measures); females had poorer scores compared with men in all but one country. The effect sizes of gender were high (Cohen’s D $>0.5$) in 5 countries, medium (0.2 to 0.5) in 16 out of 25 countries, and low ($<0.2$) in 4 countries (Table 3). For DAS28, the differences between scores according to gender were high in 2 countries, medium in 9 countries, and low in 14 out of 25 countries (Table 4).

Gender and disease characteristics
RF was equally prevalent among females and males, including 'low' (females 67.2% versus males 69.5%; $P = 0.29$) and 'high' (79.6% versus 80.0%; $P = 0.86$) prevalence countries. Men (24.1%) had rheumatoid nodules more often than women (19.3%). Erosions were more prevalent among women than men (64.3% versus 59.7%; $P = 0.003$), although the difference was not statistically significant in 'low' prevalence countries (53.6% versus 51.6%; $P = 0.36$) and was only marginally significant in 'high' prevalence countries (76.7% versus 71.9%; $P = 0.041$). Men were smokers more often than women: 27.2% versus 14.8% ($P < 0.001$).

Gender and therapies for rheumatoid arthritis
In 'low use' countries, similar percentages of women and men were currently taking prednisone (30.0% versus 31.0%), methotrexate (54.1% versus 54.7%), and biologic agents (7.9% versus 8.1%). Similar proportions of women and men were taking these drugs in 'high use' countries; the percentages were 60.6% versus 61.5% for prednisone, 68.4% versus 72.0% for methotrexate, and 29.1% versus 30.8% for biologic agents, respectively. Similar percentages of women and men had ever taken these drugs over the course of RA (data not shown). The delay between the first RA symptoms and initiation of DMARDs was 10 months in the entire group, with considerable variation between countries (Table 1); no statistically significant gender differences within countries were seen (data not shown).

Discussion
Obvious differences between genders exist in the prevalence, age at onset, and autoantibody production of RA [39]. The majority of patients with RA are middle-aged women, generally greater than 70% in any RA cohort (including the present study), although RA can occur at any age in either gender. Furthermore, gender differences are seen in biologic (hormones) [40] and behavioral (smoking) [41,42] factors that may influence susceptibility and phenotype of RA.

As noted before, the natural history of RA when limited treatment options were available involved severe outcomes in most patients without major gender differences. However, occasional reports of gender differences in RA with unexpected results or interpretations appear to have gained more attention than reports of no gender differences. Ten years ago, a study from the Mayo Clinic [18] compared 55 male patients with 110 female controls with similar disease duration of at least 10 years. Erosive disease was more prevalent and developed earlier in men than in women. Nodules and lung disease were more frequent in men and sicca syndrome was more frequent in women [18]. The investigators suggested that the findings...
| Country     | Sites | Patients | Female, percentage | Age, years | Disease duration, years | DMARD delay, months | RF⁺, percentage | Smoking now, percentage | DAS28 | SJC28 | ESR | Pain | Patient global | HAQ | Taking now, percentage |
|-------------|-------|----------|-------------------|-----------|------------------------|---------------------|------------------|------------------------|-------|-------|-----|------|------------------|-----|---------------------|
| Netherlands | 3     | 317      | 66.3              | 59.2      | 9.2                    | 6.0                 | 68.8             | 22.9                   | 3.1   | 1.0   | 15.0 | 2.5  | 2.7              | 0.8 | 16.1                 |
| Finland     | 3     | 304      | 72.4              | 58.5      | 13.5                   | 7.0                 | 74.8             | 15.5                   | 3.3   | 1.0   | 13.0 | 2.8  | 2.8              | 0.6 | 51.3                 |
| USA         | 3     | 301      | 72.9              | 57.5      | 9.3                    | 9.0                 | 70.9             | 20.5                   | 3.3   | 2.0   | 14.0 | 3.2  | 2.6              | 0.6 | 60.1                 |
| Greece      | 3     | 300      | 75.7              | 58.1      | 11.8                   | 7.0                 | 52.1             | 15.8                   | 3.4   | 0.0   | 23.0 | 2.3  | 2.0              | 0.3 | 70.7                 |
| Denmark     | 3     | 301      | 76.7              | 57.8      | 12.0                   | 11.0                | 73.3             | 31.6                   | 3.4   | 1.0   | 14.0 | 2.6  | 2.8              | 0.6 | 14.6                 |
| Spain       | 3     | 302      | 73.5              | 59.8      | 10.6                   | 14.0                | 72.5             | 17.8                   | 3.5   | 1.0   | 17.0 | 3.1  | 3.6              | 0.9 | 46.7                 |
| France      | 4     | 389      | 77.9              | 55.3      | 12.8                   | 8.0                 | 75.3             | 19.1                   | 3.7   | 1.0   | 16.0 | 3.9  | 3.6              | 0.9 | 60.9                 |
| Sweden      | 3     | 260      | 71.8              | 59.4      | 12.5                   | 12.0                | 81.6             | 19.2                   | 3.8   | 2.0   | 19.0 | 3.3  | 3.3              | 0.9 | 41.2                 |
| UK          | 3     | 145      | 77.9              | 59.6      | 15.0                   | 16.0                | 81.4             | 19.4                   | 4.0   | 1.0   | 19.0 | 4.1  | 3.6              | 0.9 | 28.3                 |
| Ireland     | 3     | 240      | 64.3              | 56.4      | 11.3                   | 11.0                | 79.6             | 24.6                   | 4.1   | 3.0   | 18.0 | 3.4  | 2.9              | 0.8 | 31.7                 |
| Canada      | 1     | 100      | 78.8              | 57.9      | 12.4                   | 11.0                | 82.8             | 30.0                   | 4.1   | 2.0   | 21.0 | 4.6  | 4.0              | 1.0 | 25.0                 |
| Turkey      | 3     | 309      | 85.6              | 52.2      | 11.6                   | 12.0                | 67.6             | 14.1                   | 4.2   | 0.0   | 30.0 | 4.2  | 4.6              | 0.9 | 57.3                 |
| Brazil      | 3     | 115      | 88.6              | 52.3      | 8.5                    | 8.0                 | 79.6             | 13.3                   | 4.2   | 3.0   | 28.0 | 3.2  | 3.5              | 0.6 | 53.9                 |
| UAE         | 2     | 199      | 85.8              | 45.3      | 6.4                    | 11.7                | 75.4             | 6.3                    | 4.3   | 3.0   | 23.5 | 3.7  | 2.8              | 0.6 | 35.2                 |
| Germany     | 3     | 225      | 83.6              | 58.8      | 13.4                   | 15.0                | 60.9             | 13.5                   | 4.4   | 3.0   | 20.0 | 5.0  | 4.9              | 0.8 | 26.7                 |
| Italy       | 4     | 336      | 78.2              | 61.0      | 10.5                   | 9.0                 | 71.4             | 15.9                   | 4.5   | 2.0   | 28.0 | 4.9  | 5.0              | 1.0 | 51.8                 |
| Estonia     | 3     | 168      | 85.5              | 55.8      | 11.8                   | 12.0                | 68.1             | 14.0                   | 4.7   | 4.0   | 24.0 | 4.3  | 4.8              | 1.1 | 43.5                 |
| Russia      | 3     | 73       | 84.5              | 54.2      | 6.2                    | 10.0                | 74.6             | 15.4                   | 5.0   | 5.0   | 24.0 | 3.6  | 4.5              | 1.1 | 38.4                 |
| Hungary     | 3     | 153      | 87.4              | 57.9      | 12.6                   | 12.0                | 92.8             | 25.3                   | 5.1   | 5.0   | 26.0 | 5.2  | 5.1              | 1.4 | 36.6                 |
| Latvia      | 1     | 79       | 79.7              | 53.2      | 13.2                   | 32.1                | 84.6             | 19.2                   | 5.2   | 4.0   | 26.0 | 5.1  | 5.7              | 1.4 | 63.3                 |
| Poland      | 7     | 642      | 86.7              | 53.2      | 11.5                   | 4.0                 | 70.3             | 11.9                   | 5.3   | 6.0   | 31.0 | 5.0  | 4.8              | 1.4 | 58.9                 |
| Argentina   | 2     | 246      | 90.2              | 51.4      | 9.9                    | 13.0                | 90.5             | 21.4                   | 5.3   | 9.0   | 30.0 | 5.0  | 4.7              | 1.0 | 63.4                 |
| Lithuania   | 2     | 300      | 82.9              | 54.1      | 10.7                   | 15.0                | 78.4             | 7.1                    | 5.5   | 3.0   | 29.0 | 5.2  | 5.3              | 1.4 | 82.7                 |
| Serbia      | 1     | 100      | 88.0              | 59.2      | 10.1                   | 11.1                | 71.4             | 18.4                   | 5.9   | 6.0   | 28.0 | 5.1  | 5.3              | 1.6 | 54.0                 |
| Kosovo      | 1     | 100      | 84.0              | 55.0      | 7.8                    | 3.0                 | 80.6             | 10.4                   | 6.0   | 6.0   | 45.0 | 5.1  | 5.0              | 1.6 | 90.0                 |

| Mean values are presented for age, disease duration, and disease activity score using 28 joint counts (DAS28). Median values are presented for other continuous variables. DMARD, disease-modifying antirheumatic drug; ESR, erythrocyte sedimentation rate; HAQ, Health Assessment Questionnaire; MTX, methotrexate; Pred, prednisone; QUEST-RA, Quantitative Standard Monitoring of Rheumatoid Arthritis; RF, rheumatoid factor; SJC, swollen joint count; UAE, United Arab Emirates. |
might help ‘assess the prognosis and tailor the treatment of the individual patient’ with a reaction from the rheumatology community [1].

Our results are consistent with the results of recent studies that indicate major gender differences in DAS28 remission rates: overall, 30% of men and 17% of women in QUEST-RA were in DAS28 remission. Differences were striking in patients who had no swollen joints: much fewer women than men (42% versus 58%) met DAS28 remission. At SJC28 levels of 0 to 1, which indicate no or very little clinical disease activity, gender differences were significant both clinically and statistically in all other American College of Rheumatology (ACR) Core Data Set measures and fatigue. On the other hand, gender differences in measures were less pronounced or nonexistent on higher disease activity levels (that is, higher SJC28 counts) (Table 2). Therefore, recent observations of higher DAS28 remission rates [22,23] and treatment responses in males [19-21] may reflect considerable differences in the measures between genders [27,43-45], including normal ESR levels, which are higher in females than males (especially in older age groups) [28]. Furthermore, women report more symptoms and

Table 2

| Number of swollen joints | DAS28 | TJC28 | ESR | MD global | Pain | Patient global | Fatigue | HAQ |
|-------------------------|-------|-------|-----|-----------|------|----------------|---------|-----|
| 0–1                     |       |       |     |           |      |                |         |     |
| Female                  | 3.2 (1.2) | 3.2 (5.3) | 24 (19) | 1.6 (1.8) | 3.3 (2.6) | 3.3 (2.5) | 3.9 (2.9) | 0.83 (0.75) |
| Male                    | 2.7 (1.2) | 2.0 (3.9) | 20 (21) | 1.2 (1.5) | 2.8 (2.5) | 2.9 (2.6) | 2.9 (2.7) | 0.52 (0.62) |
| P value                 | <0.001 | <0.001 | <0.001 | <0.001    | <0.001 | <0.001    | <0.001    | <0.001 |
| 2–3                     |       |       |     |           |      |                |         |     |
| Female                  | 4.2 (1.1) | 5.2 (5.4) | 29 (22) | 2.8 (1.9) | 4.1 (2.6) | 4.1 (2.4) | 4.5 (2.8) | 1.1 (0.71) |
| Male                    | 3.8 (1.2) | 4.7 (5.7) | 25 (26) | 2.4 (1.8) | 3.6 (2.4) | 3.6 (2.3) | 3.7 (2.6) | 0.74 (0.62) |
| P value                 | <0.001 | 0.26 | 0.11 | 0.013 | 0.010 | 0.010 | 0.001 | <0.001 |
| 4–6                     |       |       |     |           |      |                |         |     |
| Female                  | 4.8 (1.1) | 7.3 (6.0) | 31 (23) | 3.5 (2.0) | 4.7 (2.5) | 4.6 (2.4) | 5.0 (2.7) | 1.2 (0.71) |
| Male                    | 4.6 (1.3) | 6.8 (6.2) | 32 (27) | 3.4 (2.0) | 4.1 (2.5) | 4.4 (2.4) | 4.2 (2.7) | 0.91 (0.64) |
| P value                 | 0.071 | 0.28 | 0.63 | 0.041 | 0.017 | 0.29 | <0.001 | <0.001 |
| ≥7                      |       |       |     |           |      |                |         |     |
| Female                  | 6.0 (1.2) | 13 (8.0) | 38 (25) | 5.1 (2.1) | 5.8 (2.5) | 5.2 (2.5) | 5.8 (2.6) | 1.4 (0.75) |
| Male                    | 5.8 (1.3) | 12 (7.8) | 38 (28) | 4.9 (2.1) | 5.2 (2.3) | 4.9 (2.4) | 5.0 (2.6) | 1.2 (0.68) |
| P value                 | 0.016 | 0.064 | 0.99 | 0.21 | 0.024 | 0.082 | <0.001 | <0.001 |

P values are from Student t test for independent samples. DAS28, disease activity score using 28 joint counts; ESR, erythrocyte sedimentation rate; HAQ, Health Assessment Questionnaire; MD global, doctor global assessment; QUEST-RA, Quantitative Standard Monitoring of Rheumatoid Arthritis; TJC28, tender joint count-28.
poorer scores on most questionnaires [7], including scores for pain [46], depression, and other health-related items [47,48].

Self-report performance in activities of daily living is a strong predictor of further functional loss, work disability, and mortality in RA, in other conditions, and in the general population [49]. HAQ is an important outcome measure in clinical trials and in the documentation of patient status in clinical care [33]. Throughout the history of the HAQ, women have been found to report poorer scores than men [8,50-53]. This is reasonable as women are not as physically strong as men [54,55], which has a major effect in the functional status of patients with RA and of healthy persons [56]. In fact, gender differences in musculoskeletal performance remain even among the best-trained individuals – female and male athletes compete separately! Given that women are a 'weaker vessel' concerning musculoskeletal size and strength and their baseline values are lower than those of men, the same burden of a musculoskeletal disease may be more harmful to a woman than to a man.

Possible reasons for gender differences in RA have been sought on the basis of sex hormones. Disease activity is ameliorated in 75% of women in pregnancy, and after delivery, flares occur in up to 90% [57]. Oral contraceptives may protect against RA [58]. Hormone replacement therapy appears to be beneficial concerning RA disease activity [58]. Estrogen has a dichotomous impact on the immune system by downregulating inflammatory immune responses and upregulating immunoglobulin production [60]. On the other hand, sex hormone metabolism in the synovial tissue [61]. The beneficial effects include restored levels of synovial androgens although restored androgenic (immunosuppressive) activity may explain, in part, the higher likelihood of men to develop serious infections during biologic treatments [24,25].

Radiographs provide a permanent measure of the structural damage of RA, radiographic scores are associated with certain disease activity measures [62]. Gossec and colleagues [63] found no statistically significant differences in radiographic outcomes between genders. In the BARFOT (Better Anti-rheumatic Farmacotherapy) study [64] of patients with early RA, erosive disease was present in 27% of men and 28% of women at the time of diagnosis. Similar percentages of males and females were free of any radiographic changes over the course of 2 years [64], and radiographic scores remained similar between genders during the follow-up of 5 years [44]. In the extensive database of Wolfe and Sharp [65] concerning number of patients and number of years, gender was not among predictors of radiographic progression over the course of two decades. These observations are consistent with early studies from the 1980s [66] indicating that RA presents similarly in both genders in case the extent of structural damage is chosen as the measure of disease severity.

There is a concern that women might be less likely to be treated aggressively for RA compared with men. A report from The Netherlands indicates a longer delay of referral of females to an early arthritis clinic compared with men [67]. Several reports from the cardiology literature indicate that men are treated more intensively than women [68,69]. We did not find significant differences in the proportion of females and males who were taking prednisone, methotrexate, and biologic agents in the QUEST-RA Study. Furthermore, the delay to initiation of therapies was similar for females and males within countries.

Although QUEST-RA represents a unique program, several limitations are recognized. All data were collected as part of clinical care in different clinical environments and traditions to examine and treat patients, which may vary greatly in the participating countries. First, a central laboratory was not used for blood samples, which instead were analyzed locally. Therefore, for example, normal CRP was reported as '<10' in many clinics and DAS28-CRP cannot be calculated for all patients; CRP values of 0 to 9.9 provide DAS28 results different from CRP = 10, especially on low DAS28 levels approaching criteria for remission. Second, although radiographs were taken of participating countries. First, a central laboratory was not used for blood samples, which instead were analyzed locally. Therefore, for example, normal CRP was reported as '<10' in many clinics and DAS28-CRP cannot be calculated for all patients; CRP values of 0 to 9.9 provide DAS28 results different from CRP = 10, especially on low DAS28 levels approaching criteria for remission. Second, although radiographs were taken of participating countries. First, a central laboratory was not used for blood samples, which instead were analyzed locally. Therefore, for example, normal CRP was reported as '<10' in many clinics and DAS28-CRP cannot be calculated for all patients; CRP values of 0 to 9.9 provide DAS28 results different from CRP = 10, especially on low DAS28 levels approaching criteria for remission. Second, although radiographs were taken of participating countries. First, a central laboratory was not used for blood samples, which instead were analyzed locally. Therefore, for example, normal CRP was reported as '<10' in many clinics and DAS28-CRP cannot be calculated for all patients; CRP values of 0 to 9.9 provide DAS28 results different from CRP = 10, especially on low DAS28 levels approaching criteria for remission. Second, although radiographs were taken of participating countries. First, a central laboratory was not used for blood samples, which instead were analyzed locally. Therefore, for example, normal CRP was reported as '<10' in many clinics and DAS28-CRP cannot be calculated for all patients; CRP values of 0 to 9.9 provide DAS28 results different from CRP = 10, especially on low DAS28 levels approaching criteria for remission. Second, although radiographs were taken of participating countries. First, a central laboratory was not used for blood samples, which instead were analyzed locally. Therefore, for example, normal CRP was reported as '<10' in many clinics and DAS28-CRP cannot be calculated for all patients; CRP values of 0 to 9.9 provide DAS28 results different from CRP = 10, especially on low DAS28 levels approaching criteria for remission. Second, although radiographs were taken of participating countries. First, a central laboratory was not used for blood samples, which instead were analyzed locally. Therefore, for example, normal CRP was reported as '<10' in many clinics and DAS28-CRP cannot be calculated for all patients; CRP values of 0 to 9.9 provide DAS28 results different from CRP = 10, especially on low DAS28 levels approaching criteria for remission. Second, although radiographs were taken of participating countries. First, a central laboratory was not used for blood samples, which instead were analyzed locally. Therefore, for example, normal CRP was reported as '<10' in many clinics and DAS28-CRP cannot be calculated for all patients; CRP values of 0 to 9.9 provide DAS28 results different from CRP = 10, especially on low DAS28 levels approaching criteria for remission. Second, although radiographs were taken of participating countries. First, a central laboratory was not used for blood samples, which instead were analyzed locally. Therefore, for example, normal CRP was reported as '<10' in many clinics and DAS28-CRP cannot be calculated for all patients; CRP values of 0 to 9.9 provide DAS28 results different from CRP = 10, especially on low DAS28 levels approaching criteria for remission.
may therefore be ‘left-censored’ in cross-sectional databases, rendering outcomes for men apparently better. Finally, the QUEST-RA data may not be generalizable in all included (or nonincluded) countries.

**Conclusion**

QUEST-RA data indicate that currently used disease activity measures are higher in women than in men. Gender differences for DAS28, fatigue, and ACR Core Data Set measures are most pronounced in patients with low swollen joint counts, suggesting that (especially at low levels of disease activity) one has to be cautious about interpretations of gender differences since disease activity measures themselves may be contaminated by gender.

**Competing interests**

One or more authors of this manuscript have received reimbursements, fees, or funding from pharmaceutical companies. The article-processing charge was not received from any of these companies: Abbott (Abbott Park, IL, USA), Allergan (Irvine, CA, USA), Amgen (Thousand Oaks, CA, USA), Bristol-Myers Squibb Company (Princeton, NJ, USA), Chelsea Therapeutics (Charlotte, NC, USA), GlaxoSmithKline (Uxbridge, Middlesex, UK), Jazz Pharmaceuticals (Palo Alto, CA, USA),

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**Table 3**

| Country       | Female, mean (SD) | Male, mean (SD) | Difference, mean (95% CI) | Effect size<sup>a</sup> (95% CI) |
|---------------|------------------|----------------|---------------------------|----------------------------------|
| Netherlands   | 0.89 (0.69)      | 0.62 (0.61)    | 0.27 (0.12 to 0.43)       | 0.42 (0.16 to 0.62)              |
| Finland       | 0.84 (0.76)      | 0.60 (0.64)    | 0.24 (0.06 to 0.42)       | 0.33 (0.07 to 0.56)              |
| USA           | 0.81 (0.68)      | 0.52 (0.67)    | 0.29 (0.12 to 0.46)       | 0.43 (0.16 to 0.67)              |
| Greece        | 0.61 (0.71)      | 0.29 (0.45)    | 0.32 (0.15 to 0.50)       | 0.49 (0.29 to 0.68)              |
| Denmark       | 0.85 (0.75)      | 0.59 (0.66)    | 0.26 (0.07 to 0.46)       | 0.36 (0.09 to 0.60)              |
| Spain         | 1.10 (0.84)      | 0.75 (0.69)    | 0.35 (0.14 to 0.56)       | 0.44 (0.21 to 0.70)              |
| France        | 0.99 (0.69)      | 0.67 (0.62)    | 0.32 (0.16 to 0.48)       | 0.48 (0.24 to 0.74)              |
| Sweden        | 0.97 (0.65)      | 0.82 (0.63)    | 0.16 (-0.02 to 0.33)      | 0.25 (-0.02 to 0.54)             |
| UK            | 1.06 (0.74)      | 0.80 (0.75)    | 0.26 (-0.04 to 0.55)      | 0.35 (-0.08 to 0.78)             |
| Ireland       | 0.98 (0.71)      | 0.79 (0.75)    | 0.19 (-0.01 to 0.38)      | 0.26 (-0.04 to 0.55)             |
| Canada        | 1.04 (0.72)      | 1.07 (0.73)    | -0.03 (-0.40 to 0.34)     | -0.04 (-0.58 to 0.44)            |
| Turkey        | 1.01 (0.77)      | 0.70 (0.71)    | 0.31 (0.07 to 0.56)       | 0.41 (0.11 to 0.73)              |
| Brazil        | 0.84 (0.74)      | 0.68 (0.72)    | 0.15 (-0.28 to 0.59)      | 0.21 (-0.45 to 0.72)             |
| UAE           | 0.74 (0.63)      | 0.42 (0.46)    | 0.32 (0.07 to 0.56)       | 0.53 (0.19 to 0.81)              |
| Germany       | 0.94 (0.70)      | 0.74 (0.65)    | 0.20 (-0.04 to 0.45)      | 0.29 (-0.04 to 0.65)             |
| Italy         | 1.23 (0.82)      | 0.72 (0.71)    | 0.51 (0.30 to 0.71)       | 0.64 (0.40 to 0.89)              |
| Estonia       | 1.18 (0.74)      | 1.08 (0.76)    | 0.11 (-0.22 to 0.43)      | 0.14 (-0.29 to 0.59)             |
| Russia        | 1.24 (0.73)      | 1.33 (0.59)    | -0.09 (-0.56 to 0.37)     | -0.13 (-0.77 to 0.43)            |
| Hungary       | 1.45 (0.66)      | 0.97 (0.73)    | 0.48 (0.15 to 0.82)       | 0.72 (0.08 to 1.23)              |
| Latvia        | 1.52 (0.66)      | 1.14 (0.64)    | 0.38 (0.01 to 0.74)       | 0.58 (0.03 to 1.16)              |
| Poland        | 1.40 (0.79)      | 1.27 (0.68)    | 0.14 (-0.04 to 0.31)      | 0.17 (-0.04 to 0.38)             |
| Argentina     | 1.18 (0.86)      | 0.97 (0.66)    | 0.22 (-0.14 to 0.57)      | 0.26 (-0.11 to 0.58)             |
| Lithuania     | 1.41 (0.67)      | 1.21 (0.59)    | 0.20 (0.00 to 0.40)       | 0.31 (0.04 to 0.59)              |
| Serbia        | 1.63 (0.71)      | 1.24 (0.80)    | 0.40 (-0.04 to 0.84)      | 0.55 (-0.24 to 1.18)             |
| Kosovo        | 1.58 (0.53)      | 1.34 (0.68)    | 0.25 (-0.06 to 0.55)      | 0.44 (-0.13 to 1.15)             |

All 1.09 (0.78) 0.76 (0.70) 0.33 (0.28 to 0.38) 0.43 (0.37 to 0.49)

<sup>a</sup>Cohen’s D with bias-corrected 95% confidence intervals (CIs) from bootstrapping (1,000 replications). SD, standard deviation; UAE, United Arab Emirates.
Merrimack Pharmaceuticals (Cambridge, MA, USA), MSD (Whitehouse Station, NJ, USA), Pfizer Inc (New York, NY, USA), Pierre Fabre Médicament (Boulogne Cedex, France), Roche (Basel, Switzerland), Schering-Plough Corporation (Kenilworth, NJ, USA), sanofi-aventis (Paris, France), UCB (Brussels, Belgium), and Wyeth (Madison, NJ, USA).

Authors' contributions
The QUEST-RA Study was designed and conducted by TS and TPincus. All authors participated in data collection concerning their clinical patients. Analyses for the present report were designed and coordinated by TS and HK. All authors read and approved the final manuscript.

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| Country      | Female, mean (SD) | Male, mean (SD) | Difference, mean (95% CI) | Effect size<sup>a</sup> (95% CI) |
|--------------|-------------------|-----------------|---------------------------|-----------------------------------|
| Netherlands  | 3.07 (1.19)       | 3.03 (1.37)     | 0.03 (-0.26 to 0.33)      | 0.03 (-0.23 to 0.29)              |
| Finland      | 3.37 (1.35)       | 3.01 (1.60)     | 0.37 (0.01 to 0.73)       | 0.26 (-0.03 to 0.55)              |
| USA          | 3.59 (1.56)       | 2.65 (1.61)     | 0.94 (0.54 to 1.35)       | 0.60 (0.31 to 0.85)               |
| Greece       | 3.52 (1.49)       | 2.72 (1.37)     | 0.79 (0.40 to 1.19)       | 0.55 (0.28 to 0.80)               |
| Denmark      | 3.49 (1.41)       | 3.05 (1.53)     | 0.44 (0.05 to 0.83)       | 0.31 (0.03 to 0.60)               |
| Spain        | 3.59 (1.38)       | 3.33 (1.31)     | 0.26 (-0.10 to 0.62)      | 0.19 (-0.07 to 0.45)              |
| France       | 3.69 (1.41)       | 3.56 (1.74)     | 0.13 (-0.24 to 0.49)      | 0.09 (-0.22 to 0.36)              |
| Sweden       | 3.83 (1.58)       | 3.80 (1.62)     | 0.04 (-0.40 to 0.48)      | 0.02 (-0.24 to 0.30)              |
| UK           | 4.09 (1.41)       | 3.56 (1.34)     | 0.53 (-0.04 to 1.11)      | 0.39 (-0.05 to 0.74)              |
| Ireland      | 4.16 (1.51)       | 4.03 (1.86)     | 0.13 (-0.32 to 0.57)      | 0.08 (-0.25 to 0.34)              |
| Canada       | 4.13 (1.57)       | 4.17 (1.88)     | -0.04 (-0.88 to 0.79)     | -0.03 (-0.60 to 0.57)             |
| Turkey       | 4.16 (1.43)       | 4.12 (1.27)     | 0.05 (-0.44 to 0.54)      | 0.03 (-0.28 to 0.37)              |
| Brazil       | 4.25 (1.41)       | 3.66 (1.52)     | 0.59 (-0.25 to 1.42)      | 0.42 (-0.20 to 1.08)              |
| UAE          | 4.33 (1.72)       | 3.83 (1.90)     | 0.50 (-0.25 to 1.24)      | 0.29 (-0.20 to 0.72)              |
| Germany      | 4.47 (1.63)       | 3.84 (1.97)     | 0.64 (0.03 to 1.25)       | 0.38 (-0.00 to 0.79)              |
| Italy        | 4.51 (1.24)       | 4.38 (1.37)     | 0.13 (-0.22 to 0.48)      | 0.10 (-0.17 to 0.42)              |
| Estonia      | 4.70 (1.43)       | 4.53 (1.83)     | 0.16 (-0.50 to 0.83)      | 0.11 (-0.37 to 0.63)              |
| Russia       | 4.89 (1.46)       | 5.33 (0.86)     | -0.44 (-1.40 to 0.51)     | -0.32 (-0.82 to 0.19)             |
| Hungary      | 5.13 (1.23)       | 4.51 (1.24)     | 0.61 (0.00 to 1.23)       | 0.50 (0.02 to 1.07)               |
| Latvia       | 5.24 (1.59)       | 5.11 (1.41)     | 0.13 (-0.78 to 1.03)      | 0.08 (-0.49 to 0.68)              |
| Poland       | 5.32 (1.44)       | 5.20 (1.43)     | 0.12 (-0.22 to 0.45)      | 0.08 (-0.15 to 0.32)              |
| Argentina    | 5.35 (1.68)       | 5.36 (1.95)     | -0.02 (-0.76 to 0.72)     | -0.01 (-0.48 to 0.54)             |
| Lithuania    | 5.49 (1.30)       | 5.51 (1.30)     | -0.02 (-0.43 to 0.38)     | -0.02 (-0.34 to 0.30)             |
| Serbia       | 5.93 (1.30)       | 5.93 (0.97)     | -0.01 (-0.78 to 0.77)     | -0.00 (-0.45 to 0.51)             |
| Kosovo       | 6.08 (0.95)       | 5.83 (0.99)     | 0.25 (-0.26 to 0.77)      | 0.27 (-0.32 to 0.91)              |

All 4.30 (1.64) 3.76 (1.76) 0.54 (0.43 to 0.65) 0.33 (0.25 to 0.39)

<sup>a</sup>Cohen’s D with bias-corrected 95% confidence intervals (CIs) from bootstrapping (1,000 replications). DAS28, disease activity score using 28 joint counts; SD, standard deviation; UAE, United Arab Emirates.
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