# Effect of Smoking on Remission Proportions Differs Between Male and Female Patients with Rheumatoid Arthritis: A Study Based on the IORRA Survey

Yasushi Inoue, Ayako Nakajima, Eiichi Tanaka, Eisuke Inoue, Akiko Kobayashi, Daisuke Hoshi, Naoki Sugimoto, Yohei Seto, Atsuo Taniguchi, Shigeki Momohara, and Hisashi Yamanaka

***ABSTRACT.*** ***Objective.*** To analyze sex difference in the effect of smoking on remission proportions in patients with rheumatoid arthritis (RA).

***Methods.*** Subjects were Japanese patients with RA who participated in the IORRA survey conducted in April 2011 and reported smoking status. Clinical characteristics, treatment status, and the percentages achieving remission were compared between subjects stratified by sex and smoking status. To confirm the differential effects of sex and smoking status on remission, we used multivariate logistic regression models with the dependent variable as 28-joint Disease Activity Score (DAS28) remission.

***Results.*** Among 810 men and 4206 women, 162 (20.0%) and 3173 (75.4%), respectively, were never smokers; 208 (25.7%) and 314 (7.5%), respectively, were current smokers. In men, never smokers tended to have higher remission proportions than past and current smokers. In contrast, smoking status seemed not to affect remission in women. Except for lower corticosteroid dose in male never smokers, no significant differences were observed in comparing treatment status. By multivariate analyses, male past and current smokers were negatively associated with DAS28-erythrocyte sedimentation rate remission compared to male never smokers [OR 0.66 and 0.61, 95% CI (0.44–0.98) and (0.39-0.96), respectively]. However, female past and current smokers were not associated with remission compared to female never smokers [OR 1.04 and 1.19, 95% CI (0.86–1.25) and (0.91–1.54), respectively].

***Conclusion.*** We demonstrated that the effect of smoking on remission proportions differed between men and women. Our findings suggest that both sex and smoking status are important considerations when planning a treatment strategy for patients with RA. (J Rheumatol First Release March 15 2015; doi:10.3899/jrheum.140376)

*Key Indexing Terms:*
RHEUMATOID ARTHRITIS SMOKING SEX DIFFERENCES
DISEASE ACTIVITY REMISSION

It is well known that rheumatoid arthritis (RA) has a strong sex bias, which accounts for differences between men and women in important disease aspects such as incidence rates, clinical characteristics and outcomes, and mortality rates[1]. Several studies have shown that male patients with RA respond more favorably to treatment than female patients[2,3,4,5]. In a large observational cohort study of Japanese patients with RA, we also observed that female patients exhibited more progressive functional disability compared to males[6].

*From the Institute of Rheumatology, Tokyo Women's Medical University, Tokyo; Fukuoka Red Cross Hospital, Fukuoka, Japan.*

*Y. Inoue, MD, PhD, Institute of Rheumatology, Tokyo Women's Medical University (present address, Fukuoka Red Cross Hospital); A. Nakajima, MD, PhD, Associate Professor; E. Tanaka, MD, PhD; E. Inoue, PhD; A. Kobayashi, MD; D. Hoshi, MD; N. Sugimoto, MD; Y. Seto, MD, PhD; A. Taniguchi, MD, PhD, Professor; S. Momohara, MD, PhD, Professor; H. Yamanaka, MD, PhD, Professor and Director, Institute of Rheumatology, Tokyo Women's Medical University.*

*Address correspondence to Dr. A. Nakajima, Institute of Rheumatology, Tokyo Women's Medical University, 10-22 Kawada-cho, Shinjuku-ku, Tokyo, Japan 162-0054. E-mail: ayakonkj@ior.twmu.ac.jp*

*Accepted for publication January 16, 2015.*

Smoking is the greatest known environmental risk factor for developing RA[7,8]. The interaction between smoking and genetic factors can potentially trigger the production of citrullinated proteins in the lung prior to clinical synovitis[8,9]. Smoking has also been associated with the formation of rheumatoid nodules, rheumatoid factor (RF) positivity, and radiographic progression[10,11]. Further, smokers with RA in several studies have demonstrated poorer therapeutic response[12,13,14,15,16,17,18,19,20,21].

Although smoking adversely affects treatment response in RA, whether the effect of smoking on RA disease activity differs between men and women has not been fully investigated. Thus, this cross-sectional study aimed to evaluate the effects of smoking on treatment status and remission proportions, and to examine the effect of the interaction between sex and smoking status on remission proportions in Japanese patients with RA.

## MATERIALS AND METHODS

*IORRA cohort.* The IORRA (Institute of Rheumatology, Rheumatoid Arthritis) cohort is a large observational cohort of patients with RA seen in daily practice at the Institute of Rheumatology, Tokyo Women's Medical

University, since October 2000. The characteristics of the IORRA cohort have been described elsewhere[22,23,24]. Briefly, all patients diagnosed with RA were asked to register in the IORRA. After providing informed consent, patients were invited to participate in the IORRA survey by completing a questionnaire biannually (April and October) during the period of treatment at our institute. Data were collected on each patient's global assessment (PtGA) through a visual analog scale, disability using the Japanese Health Assessment Questionnaire (J-HAQ; validated in 2003)[25], and the physician's evaluation of disease activity, as measured by the swollen joint count (SJC) and tender joint count (TJC). Additional clinical laboratory variables included the erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and RF. Patients provided information on smoking status as well as the use of drugs, such as corticosteroids (frequency and dose converted to prednisolone equivalent), nonsteroidal antiinflammatory drugs, methotrexate (MTX), and biologics, and dosages. More than 5000 patients with RA participated in the survey, 98% of whom returned completed questionnaires by prepaid mail. The Ethics Committee of Tokyo Women's Medical University approved this study (#2952).

*Subjects*. The study cohort comprised Japanese patients with RA who participated in the IORRA survey in April 2011. We performed a cross-sectional analysis of patients who had complete data on smoking status, age, disease duration, J-HAQ score, CRP, and the 28-joint disease activity score (DAS28)-ESR. Subjects were divided on the basis of smoking status into 3 groups: (1) never smokers, (2) current smokers, and (3) past smokers.

*Statistical analysis*. We expect a clinically significant difference in DAS28 remission (10% difference) between male and female never smokers. In IORRA, the numbers of male and female never smokers were 162 and 3173, respectively. In this setting, the statistical power by the chi-squared test is 0.71. If the remission proportion difference is 15%, we will archive the statistical power of 0.97. We determined the proportions of male and female subjects in each smoking status category (never smokers, past smokers, and current smokers) stratified by decade of age. Baseline patient characteristics were summarized using descriptive statistics and reported as the median and interquartile range (IQR). To examine sex differences in the effect of smoking on patients with RA, the background characteristics and treatment status were compared separately by sex and smoking status (never smokers, past smokers, and current smokers). Similarly, remission as defined by the DAS28-ESR (primary outcome) and other remission criteria for secondary outcomes defined by the Simplified Disease Activity Index (SDAI), clinical disease activity index (CDAI), and the Boolean-based remission criteria for clinical trials (Boolean trial), were compared after stratification by sex and smoking status[26,27]. Comparisons were performed using the Kruskal-Wallis test for continuous variables and a chi-squared test for categorical variables.

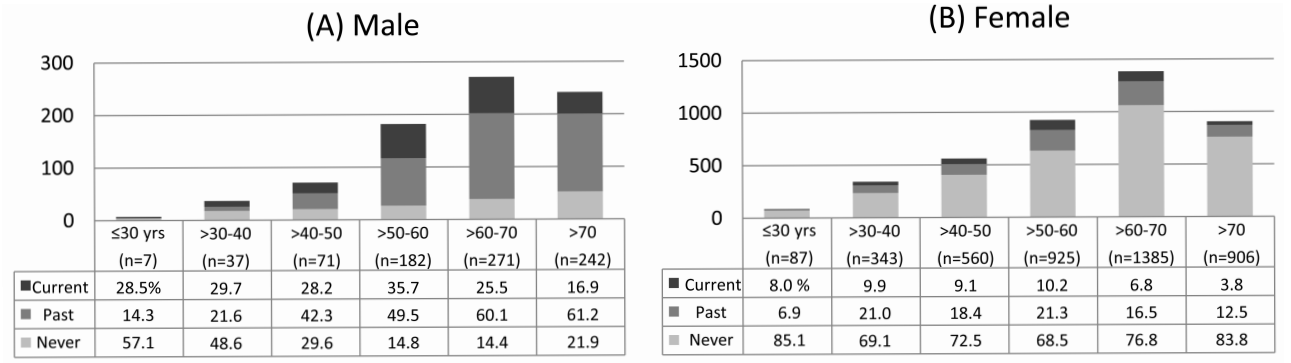
The effect modification of sex on the relation between smoking status and remission was assessed by the following procedures. First, to analyze the relationship between 3 levels of smoking status and remission, we constructed the initial model, which was the logistic model with the dependent variable of DAS28-ESR remission. Searching for confounders, age, body mass index (BMI), disease duration, RF positivity, J-HAQ score, MTX use, and biologics use were added to the initial model one at a time, and we investigated the changes in the regression coefficient of smoking status (the main effect) before and after adding those variables. Among the variables leading more than 10% changes in the main effect, we picked up the variable deriving the greatest change as a confounder and updated the initial model by including it in the initial model. We repeated this step whenever the changes were more than 10%. Finally, the effect modifications by sex were assessed by adding an interaction term of smoking status and sex to the updated model, the statistical significance of which was analyzed by the chi-square test for the deviance of the models with and without the interaction term. Secondary outcomes were evaluated by the same procedures. A p value $< 0.05$ was considered significant. All statistical analyses were conducted using JMP version 9.0 software (SAS Institute) and the R version 3.1.0 software.

## RESULTS

Data on smoking status, age, disease duration, J-HAQ score, CRP, and each item of the DAS28-ESR were available for 5016 of 5356 (93.6%) patients with RA. Figure 1 shows the numbers and proportions of patients with RA in each category of smoking status stratified by sex and decade of age. As shown in Figure 2, 3335 patients (66.5%) were never smokers, 522 (10.4%) were current smokers, and 1159 patients (23.1%; 440 males and 719 females) were past smokers. More than 95% (3173/3335) of never smokers and nearly 60% (314/522) of current smokers were female (Figure 2A). Of the 5016 patients, 162 of the 810 males (20.0%) and 3173 of the 4206 females (75.4%) were never smokers; 208 males (25.7%) and 314 females (7.5%) were current smokers (Figure 2B).

Table 1 displays the characteristics of 370 male and 3487 female patients stratified by smoking status. Among the men, significant differences were observed in age ($p < 0.01$), DAS28-ESR scores ($p < 0.05$), SDAI scores ($p < 0.05$), serum CRP levels ($p < 0.05$), and ESR levels ($p < 0.01$). In women, significant differences were observed in age ($p < 0.01$), disease duration of RA ($p < 0.01$), ESR levels ($p < 0.01$), and J-HAQ scores ($p < 0.05$); however, scores for DAS28-ESR, CDAI, and SDAI showed no significant difference. In both sexes, serum RF levels were the highest in current smokers and the lowest in never smokers. In examining the treatment status, we saw that the proportions of MTX users, corticosteroid users, and biologic users did not differ significantly in either sex (Table 1). The median doses of MTX were also comparable for both men and women. The dose of corticosteroid showed significant difference in male patients ($p < 0.05$); the median doses of corticosteroid in male never smokers were lower than in past and current smokers.

Figure 3 shows the proportions of patients achieving remission based on the DAS28-ESR, SDAI, CDAI, and Boolean-based remission criteria for clinical trials. Among men, never smokers tended to have higher remission proportions compared to past smokers, and past smokers tended to have higher remission proportions than current smokers. In contrast, smoking status seemed not to affect remission in women regardless of remission criteria. To test differential effects of sex and smoking status on remission, logistic regression analyses were performed. In the initial model analysis, smoking status was associated with DAS28-ESR remission ($p < 0.001$). We picked up the confounders in this order: J-HAQ, RF positivity, BMI, and biologics use. Deviance analysis showed a significant association of the interaction of sex and smoking status ($p = 0.03$). Table 2 showed that male never smokers had the highest DAS28-ESR remission proportion, but female never smokers showed no significant difference in DAS28-ESR remission proportion compared to female past and current smokers, after adjusting by confounders. For secondary endpoints, deviance




| | ≤30 yrs (n=7) | >30-40 (n=37) | >40-50 (n=71) | >50-60 (n=182) | >60-70 (n=271) | >70 (n=242) |
|---|---|---|---|---|---|---|
| Current | 28.5% | 29.7 | 28.2 | 35.7 | 25.5 | 16.9 |
| Past | 14.3 | 21.6 | 42.3 | 49.5 | 60.1 | 61.2 |
| Never | 57.1 | 48.6 | 29.6 | 14.8 | 14.4 | 21.9 |

| | ≤30 yrs (n=87) | >30-40 (n=343) | >40-50 (n=560) | >50-60 (n=925) | >60-70 (n=1385) | >70 (n=906) |
|---|---|---|---|---|---|---|
| Current | 8.0 % | 9.9 | 9.1 | 10.2 | 6.8 | 3.8 |
| Past | 6.9 | 21.0 | 18.4 | 21.3 | 16.5 | 12.5 |
| Never | 85.1 | 69.1 | 72.5 | 68.5 | 76.8 | 83.8 |

*Figure 1*. Number and proportion of RA patients stratified by smoking status, sex, and age. Percentages may not sum to 100% because of rounding.

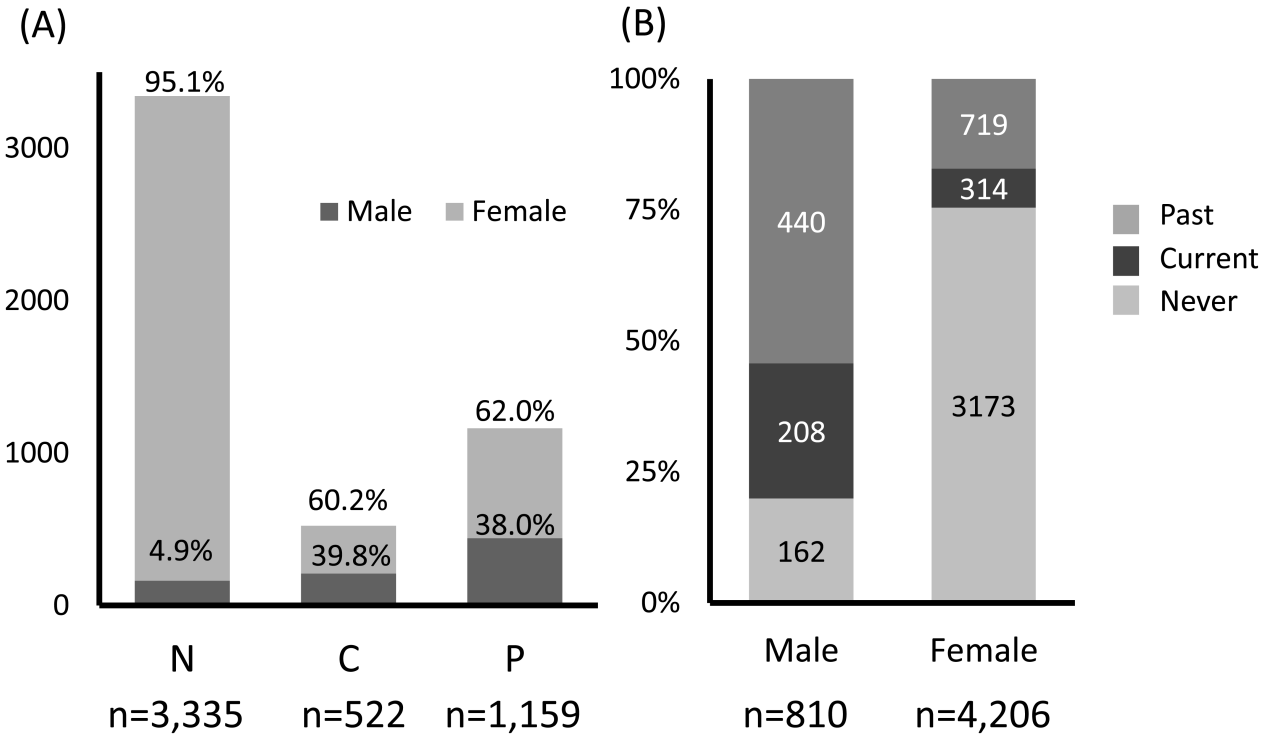



*Figure 2*. Number and proportion of subjects stratified by smoking status (A) and sex (B). N: never smokers; C: current smokers; P: past smokers.

analyses showed no significant relationships with the interaction term of sex and smoking status (Boolean: 0.51, CDAI remission: 0.07, SDAI remission: 0.16).

## DISCUSSION

In our study, our examination of smoking status in a large cohort of Japanese patients with RA led to several important clinical observations. As shown in Figure 1, age-specific proportions of never smokers in patients with RA were much higher in women than in men. This difference is not just limited to patients with RA; this is a characteristic feature of Japanese smoking culture[28,29]. Male patients in each smoking status were more likely to have lower disease activity scores in all the composite measures than female patients (Table 1), and male never smokers tended to show higher remission proportions than past and current male smokers (Figure 3). These results might be affected by the presence of less active disease among men, or the instruments might privilege male patients in terms of disease activity[3]. Except for corticosteroid dose, which showed significant difference according to smoking status in male patients, treatment status did not significantly differ according to smoking status in either sex (Table

*Table 1*. Difference of demographic and clinical features or treatment status according to smoking status. Results are percentages or medians (interquartile range) and compared separately for each sex.

| | Male, n = 810 | | | Female, n = 4206 | | |
|---|---|---|---|---|---|---|
| | Never Smokers, n = 162 | Past Smokers, n = 440 | Current Smokers, n = 208 | Never Smokers, n = 3173 | Past Smokers, n = 719 | Current Smokers, n = 314 |
| Age, yrs | 63.2 (48.6, 72.8) | 65.6 (58.8, 72.1) | 61.6 (54.4, 68.1) † | 62.3 (51.7, 69.6) | 59.2 (50.0, 66.5) | 56.7 (47.5, 64.0) † |
| Disease duration, yrs | 10 (5, 17) | 11 (6, 18) | 10 (5, 16.8) | 13 (6, 20) | 10 (6, 16) | 10.5 (5, 16) † |
| BMI, kg/m$^2$ | 22.9 (21.0, 25.1) | 22.9 (20.9, 24.5) | 22.6 (20.6, 24.6) | 20.7 (19.1, 22.6) | 20.8 (19.1, 23.1) | 20.5 (18.8, 22.6) |
| DAS28-ESR | 2.33 (1.67, 3.10) | 2.62 (1.89, 3.48) | 2.61 (1.62, 3.49) * | 3.03 (2.33, 3.77) | 3.03 (2.27, 3.83) | 2.85 (2.17, 3.62) |
| CDAI | 3.6 (1, 6.9) | 3.8 (1.3, 7.4) | 5 (1.9, 8.2) | 5.3 (2.03, 9.3) | 5.5 (2.2, 9.8) | 5.1 (2, 8.8) |
| SDAI | 3.9 (1.1, 7.2) | 4.3 (1.6, 8.6) | 5.3 (2.1, 9.4) * | 5.6 (2.3, 9.9) | 5.8 (2.4, 10.3) | 5.4 (2.1, 9.5) |
| TJC28 | 0 (0, 1) | 0 (0, 1) | 0 (0, 1) | 0 (0, 1) | 0 (0, 2) | 0 (0, 1) |
| SJC28 | 0 (0, 1) | 0 (0, 1) | 0 (0, 1) | 0 (0, 2) | 0 (0, 2) | 1 (0, 2) |
| PtGA, VAS, mm | 15 (4, 42) | 17 (6, 40) | 21 (6, 46) | 23 (8, 50) | 24 (8, 52) | 22 (8, 43) |
| CRP, mg/dl | 0.14 (0.05, 0.65) | 0.26 (0.07, 0.85) | 0.26 (0.08, 0.9) * | 0.13 (0.04, 0.51) | 0.12 (0.04, 0.5) | 0.11 (0.04, 0.45) |
| ESR, mm/h | 12.5 (6, 26) | 19 (9.0, 38) | 16 (6.4, 31) † | 24 (14, 40) | 22 (12, 39) | 20 (11, 33) † |
| RF, IU/ml | 22.5 (4, 76) | 51.5 (15.8, 165.5) | 93 (21.5, 362.5) † | 44 (16, 104) | 63 (21.5, 186.5) | 77 (22, 217) † |
| J-HAQ | 0 (0, 0.63) | 0.13 (0, 0.63) | 0.13 (0, 0.5) | 0.5 (0, 1.25) | 0.5 (0, 1.13) | 0.38 (0, 1) * |
| MTX use (%) | 69.8 | 65.9 | 73.1 | 72.1 | 72.5 | 76.4 |
| Corticosteroid use (%) | 34.6 | 43.6 | 37.5 | 38.0 | 39.9 | 38.9 |
| Biologics use (%) | 9.9 | 12.3 | 9.1 | 15.4 | 16.7 | 12.1 |
| MTX dose, mg/week | 7.85 (6, 10) | 8 (6, 10) | 8 (6, 10) | 8 (6, 10) | 8 (6, 10) | 8 (6, 10) |
| Corticosteroid dose, PSL equivalent, mg/day | 2.75 (2, 5) | 4 (2.225, 5) | 4 (2, 5) * | 3.1 (2, 5) | 3 (2, 5) | 3.9 (2.15, 5) |

* p value < 0.05. † p < 0.01 by Kruskal-Wallis test or chi-squared test. BMI: body mass index; DAS28: 28-joint Disease Activity Score; ESR: erythrocyte sedimentation rate; CDAI: Clinical Disease Activity Index; SDAI: Simplified Disease Activity Index; TJC: tender joint count; SJC: swollen joint count; PtGA: patient's global assessment; VAS: visual analog scale; CRP: C-reactive protein; RF: rheumatoid factor; J-HAQ: Japanese Health Assessment Questionnaire; MTX: methotrexate; PSL: prednisolone.

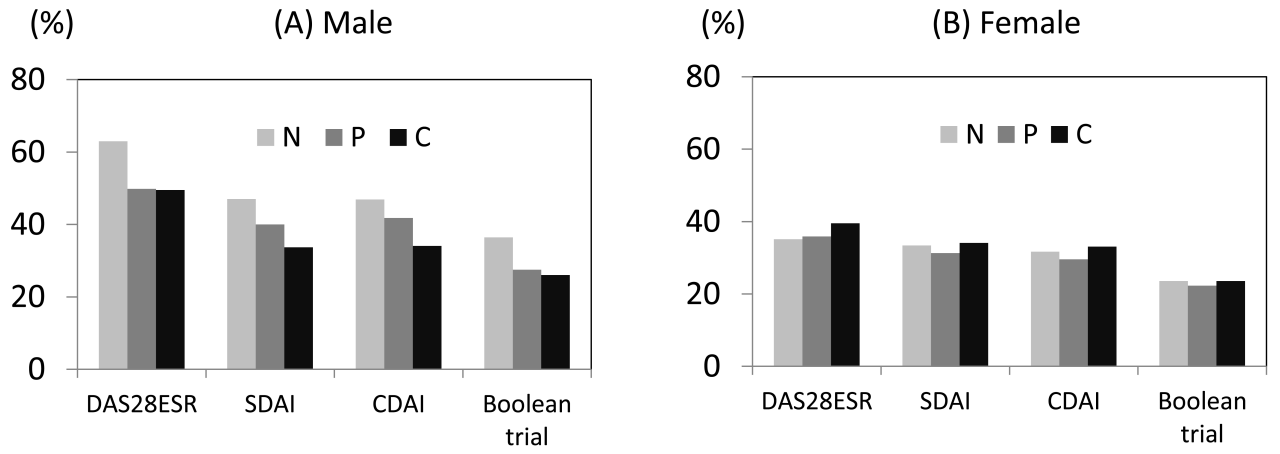



*Figure 3*. Sex difference in remission proportions according to smoking status. N: never smokers; C: current smokers; P: past smokers; DAS28: 28-joint Disease Activity Score; ESR: erythrocyte sedimentation rate; SDAI: Simplified Disease Activity Index; CDAI: Clinical Disease Activity Index; Boolean trial: Boolean-based remission criteria for clinical trials.

1). In multivariate analysis, the effects of smoking on remission proportions differed between men and women (Table 2). Both past and current smoking compared to never smoking were negatively associated with DAS28-ESR remission for male patients, whereas no association was observed for women. Together, these findings suggest that smoking may affect male and female patients with RA differently.

Several studies have cited smoking as a poor predictor of remission in patients with RA. Forslind, *et al* evaluated 678 patients with early RA mostly treated with nonbiologic disease-modifying antirheumatic drugs and determined that current smoking was an independent negative prognostic factor for DAS28-ESR remission after 5 years[2]. In an analysis of 1612 patients with RA treated with infliximab,

*Table 2*. OR for DAS28 remission according to sex and smoking status, adjusted by the confounders. OR were described by using the references of male never smokers and female never smokers, which were calculated from the same logistic regression model.

| | OR (95% CI) | p |
|---|---|---|
| Reference: Male Never | | |
| Male past | 0.66 (0.44–0.98) | 0.04 |
| Male current | 0.61 (0.39–0.96) | 0.03 |
| Female never | 0.47 (0.33–0.67) | < 0.01 |
| Female past | 0.49 (0.33–0.72) | < 0.01 |
| Female current | 0.56 (0.36–0.86) | < 0.01 |
| Reference: Female Never | | |
| Male never | 2.13 (1.48–3.07) | < 0.01 |
| Male past | 1.40 (1.12–1.75) | < 0.01 |
| Male current | 1.30 (0.96–1.76) | 0.09 |
| Female past | 1.04 (0.86–1.25) | 0.68 |
| Female current | 1.19 (0.91–1.54) | 0.19 |

The confounders adjusted for in the analysis included the Japanese Health Assessment Questionnaire scores, rheumatoid factor positivity, body mass index, and biologics use.

Hyrich, *et al* noted that current smoking was an independent negative predictor for higher European League Against Rheumatism (EULAR) response at 6 months[12]. Despite the cross-sectional design of our present study, our results were consistent with those of previous longitudinal studies showing that male patients who never smoked had better remission proportions than current smokers.

Ours is the largest study to date, to our knowledge, examining the influence of sex on the effect of smoking on remission proportions among patients with RA, and it is the first study showing the sex differences of the smoking effect by multivariate analysis. Sex differences in the effect of smoking were investigated previously by Saevarsdottir, *et al*, who analyzed a smaller population of 487 patients with early RA treated with MTX monotherapy[30]. The study found that male, non-current smokers and low HAQ score were predictive of a good response to MTX after 3 to 4 months. Female non-current smokers also experienced higher remission proportions than female current smokers, although statistical significance was not reported. Our results were similar to these longitudinal findings regarding the larger effect of smoking on disease activity observed in males compared to females. Although we used a cross-sectional design, our sample size was larger than that reported in Saevarsdottir, *et al*. Of the 5356 RA participants in our study, 5016 (93.6%) had complete datasets. Missing data were minimal, and thus patient selection bias, if any, was considered small. Moreover, our study also demonstrated statistically significant differences in multivariate analysis.

In men, significant associations between smoking status and DAS28-ESR remission proportion (primary outcome) were shown, but no significant relationships were found for secondary endpoints (SDAI, CDAI, and Boolean trial). This is presumably due to the larger weight on ESR in DAS28 than in the other instruments[31], and the relatively low disease activity in our subjects. With regard to measures of remission in our male subjects, significant differences according to smoking status were observed in CRP and ESR levels but not in TJC28, SJC28, and PtGA score. In the previous study to determine smoking influences on treatment response in RA patients with higher median DAS28-ESR score than our subjects (5.3 vs 2.96, respectively), current smokers showed significantly higher values of ESR, TJC, and SJC than never smokers after MTX treatment, although sex difference was not considered[19]. As management of RA has improved over the last 10 years, disease activity of patients has gradually decreased in clinical practice[32,33]. It is important information, therefore, that the interaction of sex and smoking status was significantly associated with whether clinical remission is achieved, even in patients with lower disease activity.

RF production has been reported to be associated with smoking[34,35]. Serum levels of RF were significantly associated with smoking status in both males and females in our study. These findings were consistent with previous reports[10,11,14,18,36,37]. Therapies including the use of anti-tumor necrosis factor (TNF) drugs have been reported to influence the remission proportions of patients with RA[38]. In our study, patients were treated based on individual disease activity, comorbidities, and to some extent, the physician's own protocol. However, in comparing treatment in each smoking status by sex, no significant differences were observed except for lower corticosteroid dose in male never smokers. This finding suggests that treatment status did not account for the sex differences observed regarding the effect of smoking.

In our present study, we identified sex differences regarding the effect of smoking on RA remission. The importance of these differences and the underlying mechanisms contributing to these differences remain unclear because we could not fully address these issues in this cross-sectional observational study. However, because RA seems to be a highly heterogeneous disease[9,39,40], it is reasonable that male and female smokers displayed different phenotypes, and that this difference could contribute to apparent differences in remission proportions, particularly in patients who exhibit relatively mild disease activity.

There are some limitations to our study. First, we did not consider pack-year smoking history or the time since quitting smoking. If female current and past smokers have a lower pack-year history, they may be affected less by smoking compared to males. Variations in smoking intensity may be an important factor to consider when evaluating the effect of smoking on disease activity. Mattey, *et al* reported that the intensity of previous smoking was associated with poor response to TNF antagonists for patients with RA[15]. Westhoff, *et al* showed that nonsmokers and those with < 20 pack-years had a better treatment response than heavy

smokers[14]. However, in another study, high smoking intensity did not predict poor EULAR response at 6 or 12 months in patients with RA treated with their first anti-TNF drug, although heavy smokers had the poorest drug survival[21]. Therefore, if smoking intensity in male subjects in our present study was higher than that in female subjects, this difference may not necessarily account for sex differences of remission proportions. A second limitation is that we did not evaluate HLA-shared epitopes (SE) and anticitrullinated protein antibodies (ACPA), representative factors associated with both smoking and RA risk[39,41]. Although genetic factors cannot be examined in daily practice, Molenaar, *et al*[42] and Saevarsdottir, *et al*[19] reported that HLA SE were not associated with persistent remission or treatment response. The relationship between ACPA and the effect of smoking on disease activity should be evaluated longitudinally in future studies. A third limitation is that we did not consider sociological differences between the sexes. Sociological status should be included in future studies because it is an important factor associated with smoking status and intensity and has implications for etiology and the natural history of autoimmune diseases[43].

This is the first study, to our knowledge, to demonstrate a significant sex difference in the effect of smoking on remission proportions by multivariate analysis. In men, past and current smoking compared to never smoking were negatively associated with DAS28-ESR remission, whereas no association between smoking status and remission was observed in women. A careful assessment is still needed because smoking or sex are not the only risk factors for remission, and the problem remains unresolved whether male never smokers have better response to RA treatment or are simply underestimated by disease activity assessment instruments used in our study. However, our findings suggest that both sex and smoking status should be considered when developing a treatment strategy for patients with RA. Further longitudinal research is warranted to determine the influence of sex differences on the effect of smoking on RA treatment response.

## REFERENCES


1. Weyand CM, Schmidt D, Wagner U, Goronzy JJ. The influence of sex on the phenotype of rheumatoid arthritis. Arthritis Rheum 1998;41:817-22.
2. Forslind K, Hafström I, Ahlmén M, Svensson B. Sex: a major predictor of remission in early rheumatoid arthritis? Ann Rheum Dis 2007;66:46-52.
3. Sokka T, Toloza S, Cutolo M, Kautiainen H, Makinen H, Gogus F, et al. Women, men, and rheumatoid arthritis: analyses of disease activity, disease characteristics, and treatments in the QUEST-RA study. Arthritis Res Ther 2009;11:R7.
4. Jawaheer D, Olsen J, Hetland ML. Sex differences in response to anti-tumor necrosis factor therapy in early and established rheumatoid arthritis - results from the DANBIO Registry. J Rheumatol 2012;39:46-53.
5. Jawaheer D, Maranian P, Park G, Lahiff M, Amjadi SS, Paulus HE. Disease progression and treatment responses in a prospective DMARD-naive seropositive early rheumatoid arthritis cohort: Does gender matter? J Rheumatol 2010;37:2475-85.
6. Iikuni N, Sato E, Hoshi M, Inoue E, Taniguchi A, Hara M, et al. The influence of sex on patients with rheumatoid arthritis in a large observational cohort. J Rheumatol 2009;36:508-11.
7. Sugiyama D, Nishimura K, Tamaki K, Tsuji G, Nakazawa T, Morinobu A, et al. Impact of smoking as a risk factor for developing rheumatoid arthritis: a meta-analysis of observational studies. Ann Rheum Dis 2010;69:70-81.
8. Arend WP, Firestein GS. Pre-rheumatoid arthritis: predisposition and transition to clinical synovitis. Nat Rev Rheumatol 2012; 8:573-86.
9. McInnes IB, Schett G. The pathogenesis of rheumatoid arthritis. N Engl J Med 2011;365:2205-19.
10. Wolfe F. The effect of smoking on clinical, laboratory, and radiographic status in rheumatoid arthritis. J Rheumatol 2000;27:630-7.
11. Saag KG, Cerhan JR, Kolluri S, Ohashi K, Hunninghake GW, Schwartz DA. Cigarette smoking and rheumatoid arthritis severity. Ann Rheum Dis 1997;56:463-9.
12. Hyrich KL, Watson KD, Silman AJ, Symmons DP; British Society for Rheumatology Biologics Register. Predictors of response to anti-TNF-alpha therapy among patients with rheumatoid arthritis: results from the British Society for Rheumatology Biologics Register. Rheumatology 2006;45:1558-65.
13. Burmester GR, Ferraccioli G, Flipo R-M, Monteagudo-sáez I, Unnebrink K, Kary S, et al. Clinical remission and/or minimal disease activity in patients receiving adalimumab treatment in a multinational, open-label, twelve-week study. Arthritis Care Res 2007;59:32-41.
14. Westhoff G, Rau R, Zink A. Rheumatoid arthritis patients who smoke have a higher need for DMARDs and feel worse, but they do not have more joint damage than non-smokers of the same serological group. Rheumatology 2008;47:849-54.
15. Mattey DL, Brownfield A, Dawes PT. Relationship between pack-year history of smoking and response to tumor necrosis factor antagonists in patients with rheumatoid arthritis. J Rheumatol 2009;36:1180-7.
16. van der Woude D, Young A, Jayakumar K, Mertens BJ, Toes RE, van der Heijde D, et al. Prevalence of and predictive factors for sustained disease-modifying antirheumatic drug-free remission in rheumatoid arthritis: results from two large early arthritis cohorts. Arthritis Rheum 2009;60:2262-71.
17. Abhishek A, Butt S, Gadsby K, Zhang W, Deighton CM. Anti-TNF-[alpha] agents are less effective for the treatment of rheumatoid arthritis in current smokers. J Clin Rheumatol 2010;16:15-8.
18. Söderlin MK, Petersson IF, Bergman S, Svensson B. Smoking at onset of rheumatoid arthritis (RA) and its effect on disease activity and functional status: experiences from BARFOT, a long-term observational study on early RA. Scand J Rheumatol 2011; 40:249-55.
19. Saevarsdottir S, Wedrén S, Seddighzadeh M, Bengtsson C, Wesley A, Lindblad S, et al. Patients with early rheumatoid arthritis who smoke are less likely to respond to treatment with methotrexate and tumor necrosis factor inhibitors: observations from the Epidemiological Investigation of Rheumatoid Arthritis and the Swedish Rheumatology Register cohorts. Arthritis Rheum 2011;63:26-36.
20. Khan A, Scott DL, Batley M. Smoking, rheumatoid factor status and responses to rituximab. Ann Rheum Dis 2012;71:1587-8.
21. Söderlin MK, Petersson IF, Geborek P. The effect of smoking on response and drug survival in rheumatoid arthritis patients treated with their first anti-TNF drug. Scand J Rheumatol 2012;41:1-9.
22. Nakajima A, Inoue E, Tanaka E, Singh G, Sato E, Hoshi D, et al.

Mortality and cause of death in Japanese patients with rheumatoid arthritis based on a large observational cohort, IORRA. Scand J Rheumatol 2010;39:360-7.
23. Tanaka E, Mannalithara A, Inoue E, Hara M, Tomatsu T, Kamatani N, et al. Efficient management of rheumatoid arthritis significantly reduces long-term functional disability. Ann Rheum Dis 2008;67:1153-8.
24. Yamanaka H, Inoue E, Tanaka E, Nakajima A, Taniguchi A, Terai C, et al. Influence of methotrexate dose on its efficacy and safety in rheumatoid arthritis patients: evidence based on the variety of prescribing approaches among practicing Japanese rheumatologists in a single institute-based large observational cohort (IORRA). Mod Rheumatol 2007;17:98-105.
25. Matsuda Y, Singh G, Yamanaka H, Tanaka E, Urano W, Taniguchi A, et al. Validation of a Japanese version of the Stanford Health Assessment Questionnaire in 3,763 patients with rheumatoid arthritis. Arthritis Care Res 2003;49:784-8.
26. Felson DT, Smolen JS, Wells G, Zhang B, van Tuyl LH, Funovits J, et al. American College of Rheumatology/European League Against Rheumatism provisional definition of remission in rheumatoid arthritis for clinical trials. Arthritis Rheum 2011;63:573-86.
27. Felson DT, Smolen JS, Wells G, Zhang B, van Tuyl LH, Funovits J, et al. American College of Rheumatology/European League against Rheumatism provisional definition of remission in rheumatoid arthritis for clinical trials. Ann Rheum Dis 2011;70:404-13.
28. Funatogawa I, Funatogawa T, Yano E. Trends in smoking and lung cancer mortality in Japan, by birth cohort, 1949-2010. Bull World Health Organ 2013;91:332-40.
29. Fukuda Y, Nakamura K, Takano T. Socioeconomic pattern of smoking in Japan: income inequality and gender and age differences. Ann Epidemiol 2005;15:365-72.
30. Saevarsdottir S, Wallin H, Seddighzadeh M, Ernestam S, Geborek P, Petersson IF, et al. Predictors of response to methotrexate in early DMARD naive rheumatoid arthritis: results from the initial open-label phase of the SWEFOT trial. Ann Rheum Dis 2011;70:469-75.
31. Aletaha D, Nell VP, Stamm T, Uffmann M, Pflugbeil S, Machold K, et al. Acute phase reactants add little to composite disease activity indices for rheumatoid arthritis: validation of a clinical activity score. Arthritis Res Ther 2005;7:R796-806.
32. Yamanaka H, Inoue E, Singh G, Tanaka E, Nakajima A, Taniguchi A, et al. Improvement of disease activity of rheumatoid arthritis patients from 2000 to 2006 in a large observational cohort study IORRA in Japan. Mod Rheumatol 2007;17:283-9.
33. Yamanaka H, Sugiyama N, Inoue E, Taniguchi A, Momohara S. Estimates of the prevalence of and current treatment practices for rheumatoid arthritis in Japan using reimbursement data from health insurance societies and the IORRA cohort (I). Mod Rheumatol 2014;24:33-40.
34. Aho K, Heliõvaara M, Maatela J, Tuomi T, Palosuo T. Rheumatoid factors antedating clinical rheumatoid arthritis. J Rheumatol 1991;18:1282-4.
35. Jónsson T, Thorsteinsson J, Valdimarsson H. Does smoking stimulate rheumatoid factor production in non-rheumatic individuals? APMIS 1998;106:970-4.
36. Papadopoulos NG, Alamanos Y, Voulgari PV, Epagelis EK, Tsifetaki N, Drosos AA. Does cigarette smoking influence disease expression, activity and severity in early rheumatoid arthritis patients? Clin Exp Rheumatol 2005;23:861.
37. Manfredsdottir VF, Vikingsdottir T, Jonsson T, Geirsson AJ, Kjartansson O, Heimisdottir M, et al. The effects of tobacco smoking and rheumatoid factor seropositivity on disease activity and joint damage in early rheumatoid arthritis. Rheumatology 2006;45:734-40.
38. Katchamart W, Johnson S, Lin HJ, Phumethum V, Salliot C, Bombardier C. Predictors for remission in rheumatoid arthritis patients: A systematic review. Arthritis Care Res 2010;62:1128-43.
39. Baka Z, Buzás E, Nagy G. Rheumatoid arthritis and smoking: putting the pieces together. Arthritis Res Ther 2009;11:238.
40. Lee DM, Weinblatt ME. Rheumatoid arthritis. Lancet 2001;358:903-11.
41. Willemze A, Trouw LA, Toes RE, Huizinga TW. The influence of ACPA status and characteristics on the course of RA. Nat Rev Rheumatol 2012;8:144-52.
42. Molenaar ET, Voskuyl AE, van der Horst-Bruinsma IE, Schreuder GM, Zanelli E, Dijkmans BA. Influence of HLA polymorphism on persistent remission in rheumatoid arthritis. Ann Rheum Dis 2002;61:351-3.
43. Borchers AT, Gershwin ME. Sociological differences between women and men: implications for autoimmunity. Autoimmun Rev 2012;11:A413-21.