

# 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

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**Objective.** To determine whether cigarette smoking influences the response to treatment in patients with early rheumatoid arthritis (RA).

**Methods.** We retrieved clinical information about patients entering the Epidemiological Investigation of Rheumatoid Arthritis (EIRA) early RA cohort from 1996 to 2006 (n = 1,998) who were also in the Swedish Rheumatology Register (until 2007). Overall, 1,430 of the 1,621 registered patients were followed up from the time of inclusion in the EIRA cohort. Of these, 873 started methotrexate (MTX) monotherapy at inclusion, and 535 later started treatment with a tumor necrosis factor (TNF) inhibitor as the first biologic agent. The primary outcome was a good response according to the

European League Against Rheumatism criteria at the 3-month visit. The influence of cigarette smoking (current or past) on the response to therapy was evaluated by logistic regression, with never smokers as the referent group.

**Results.** Compared with never smokers, current smokers were less likely to achieve a good response at 3 months following the start of MTX (27% versus 36%;  $P = 0.05$ ) and at 3 months following the start of TNF inhibitors (29% versus 43%;  $P = 0.03$ ). In multivariate analyses in which clinical, serologic, and genetic factors were considered, the inverse associations between current smoking and good response remained (adjusted odds ratio [OR] for MTX response 0.60 [95% CI 0.39–0.94]; adjusted OR for TNF inhibitor response 0.52 [95% CI 0.29–0.96]). The lower likelihood of a good response remained at later followup visits. Evaluating remission or joint counts yielded similar findings. Past smoking did not affect the chance of response to MTX or TNF inhibitors. Evaluating the overall cohort, which reflects all treatments used, current smoking was similarly associated with a lower chance of a good response (adjusted ORs for the 3-month, 6-month, 1-year, and 5-year visits 0.61, 0.65, 0.78, 0.66, and 0.61, respectively).

**Conclusion.** Among patients with early RA, current cigarette smokers are less likely to respond to MTX and TNF inhibitors.

In patients with rheumatoid arthritis (RA), early and efficient reduction of inflammatory activity is important for improving long-term outcome (1–3). The panel of effective, yet often expensive, drugs with which

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to achieve this goal is growing. Baseline predictors of response to individual treatments would facilitate a rational choice of therapeutic strategy. In this regard, modifiable predictors, such as cigarette smoking habits, are of particular interest. Since methotrexate (MTX) and tumor necrosis factor (TNF) inhibitors are widely used as first-and second-line treatments for recent-onset RA, efforts to find predictors of response to these drugs are of high priority (4).

Cigarette smoking has, in most studies following patients with early RA or inflammatory polyarthritis, been associated with more use of disease-modifying antirheumatic drugs (DMARDs) and increased occurrence of extraarticular manifestations, including nodules, while findings with regard to disease activity have not been conclusive (5–11). Smoking has also been associated with radiologic progression in advanced RA (8,12), while findings in early disease are less consistent (5,9–11,13). However, only limited data are currently available about the influence of cigarette smoking on the response to individual treatments in early RA. For MTX monotherapy, a report of a randomized controlled clinical trial of 205 patients indicated a not significantly reduced response among smokers (14), and no information exists as to whether previous smoking influences response. With respect to TNF inhibitors, current smoking (15,16) and the number of pack-years smoked (17) have been associated with a reduced response in patients with established RA. Further, the extent to which an apparent effect of smoking on the risk of developing RA may be influenced by genetic factors known to interact with smoking is unknown.

In the present study, we therefore linked baseline information on cigarette smoking (current or past and cumulative dose) from a large population-based cohort of patients with newly diagnosed RA to followup data on disease activity and treatment from the Swedish Rheumatology Register (SRR) and investigated the influence of smoking on treatment response in the overall group, as well as specifically to the subgroup of patients who initially started MTX monotherapy and the subgroup who later started TNF inhibitors as the first biologic agent. Demographic and disease characteristics, serologic factors (rheumatoid factor [RF] and anti-cyclic citrullinated peptide [anti-CCP] antibody status), and genetic susceptibility factors (HLA-DRB1 shared epitope and the *PTPN22*\*620W risk allele) were evaluated as potential confounders or effect modifiers.

## PATIENTS AND METHODS

**Source population of RA patients.** We evaluated RA patients from the Epidemiological Investigation of Rheumatoid Arthritis (EIRA) study. EIRA is a population-based case-control study covering the middle and southern parts of Sweden, including as cases RA patients ages 18–70 years who are within 1 year of diagnosis and, on average, within 10 months of symptom onset. All cases of RA were diagnosed by a rheumatologist, fulfilled the American College of Rheumatology (ACR) 1987 criteria for RA (18), and were predominantly of Caucasian ancestry (97% of the participants). We included in the present study all patients with RA who participated in the EIRA study during its first decade, from 1996 to 2006. Of 2,097 patients included from the participating clinics, 1,998 (95%) answered a questionnaire that included information about smoking habits.

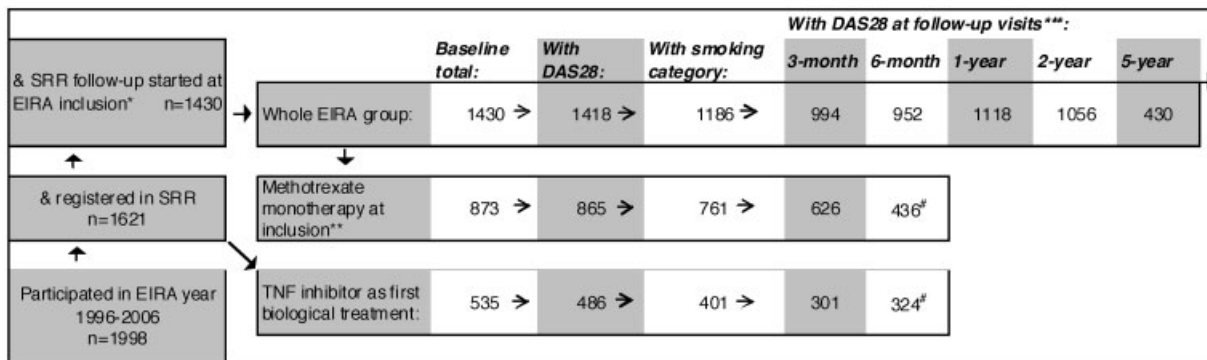
This study was approved by the Ethical Review Board at the Karolinska Institute. All participants gave informed consent.

**Capture of clinical data for EIRA patients from the SRR.** The SRR is a web-based national surveillance system that was started in the mid-1990s and is used optionally by rheumatologists to follow incident RA cases longitudinally as a part of standard care. Information about disease activity, disability, and treatment are registered at each visit, which occurs at predefined time points, although the clinical practice setting allows some flexibility around the intended dates. Also hosted within the SRR is the Anti-Rheumatic Therapy in Sweden (ARTIS) registry, in which patients who receive treatment with biologic agents, including TNF inhibitors, are followed. ARTIS covers more than 90% of patients who have ever taken a biologic agent (ref. 19 and Neovius M: unpublished observations).

By virtue of their early RA, patients included in EIRA are also invited to participate in the SRR. For the purpose of the present study, we linked these two data sources to capture clinical information about disease course and therapy. A unique personal identification number permitted deterministic linkage between the data sources. Of the 1,998 RA patients in the EIRA cohort, 1,621 had been registered in the SRR; 1,430 of these patients started SRR followup at the time of EIRA inclusion (Figure 1) and were thus eligible for the current study.

**DMARD treatment at baseline.** Of the 1,430 patients whose cases were followed from the time of EIRA inclusion, 873 (61%) received methotrexate monotherapy as their first DMARD, 382 (27%) received treatment with other DMARDs or combinations, and 175 (12%) received clinical care without DMARD treatment at baseline. An overview of the DMARD treatments or combinations initiated at baseline is shown in Supplementary Table 1 (available on the *Arthritis & Rheumatism* web site at [http://onlinelibrary.wiley.com/journal/10.1002/\(ISSN\)1529-0131](http://onlinelibrary.wiley.com/journal/10.1002/(ISSN)1529-0131)). In the present study, we focused on MTX as the initial DMARD, since it was the most commonly used first-line treatment. Other treatment options were included in the overall group.

**Therapy with a biologic agent.** Treatment with a TNF inhibitor (infliximab, etanercept, or adalimumab) was initiated as the first biologic agent in 535 patients at a median of 3 years after the diagnosis of RA (Figure 1). Fewer than 30 patients



**Figure 1.** Flow chart showing the distribution of rheumatoid arthritis (RA) patients who entered the Epidemiological Investigation of Rheumatoid Arthritis (EIRA) study during 1996–2006 and were also in the Swedish Rheumatology Register (SRR). The numbers of RA patients who had baseline data in the SRR at EIRA inclusion, had Disease Activity Score in 28 joints (DAS28) data available at the followup time points, and had been categorized as current, past, or never smokers are shown for the overall cohort, for patients receiving methotrexate (MTX) at baseline, and for patients receiving tumor necrosis factor (TNF) inhibitors during the followup until 2007. \* In accordance with the eligibility criteria for the SRR and the EIRA study, the baseline visit in the SRR could occur up to 12 months before, and up to 2.5 months after, inclusion in the EIRA study. \*\* Detailed treatment data for all patients who received MTX monotherapy at baseline is shown in Supplementary Table 1 (available on the *Arthritis & Rheumatism* web site at [http://onlinelibrary.wiley.com/journal/10.1002/\(ISSN\)1529-0131](http://onlinelibrary.wiley.com/journal/10.1002/(ISSN)1529-0131)). \*\*\* Predefined times for followup visits were at 3 months (range 2.5–5 months), 6 months (range 5–7.5 months), 1 year (range 7.5 months to 1.5 years), 2 years (range 1.5–2.5 years), and 5 years (range 4.5–5.5 years). # Patients who continued the same treatment until the followup visit. Reasons for treatment changes were not documented, but most patients changing treatment had no response according to the European League Against Rheumatism criteria.

had started any of the other available biologic agents (rituximab, abatacept, anakinra, or unspecified biologic agent in clinical trials) before the end of the followup period in 2007, usually after treatment with a TNF inhibitor.

**Definition of treatment response.** In accordance with recent guidelines from the European League Against Rheumatism (EULAR) and the American College of Rheumatology (ACR) (20), we used the EULAR response criteria (21), which are based on the Disease Activity Score 28-joint assessment (DAS28), to define response to treatment. The primary outcome of interest was a good response according to the EULAR response criteria (DAS28 <3.2 at the followup visit and >1.2 units decrease compared with the baseline DAS28), and the secondary outcome was remission according to the EULAR response criteria (DAS28 <2.6 units at followup). We evaluated these outcomes at the following predefined time points: the 3-month, 6-month, 1-year, 2-year, and 5-year visits. The numbers of patients with available DAS28 and smoking status data are shown in Figure 1.

**Definition of baseline variables. Smoking status.** We retrieved information on smoking status from the EIRA questionnaire. Patients were classified according to their smoking status at the time of RA diagnosis as never, past, current, or irregular cigarette smokers, as well as other than cigarette smokers (Table 1). The number of pack-years smoked (1 pack-year = 20 cigarettes/day for 1 year) was used to measure the cumulative dose of smoking. Information about cigarette smoking habits was not available for 4.6% of the patients, and 8.2% lacked information about the number of pack-years.

**Other variables.** Baseline parameters that we evaluated as potential confounders or effect modifiers are listed in Table 1 and are described under the statistical analysis section below.

Clinical variables were captured from the SRR. RF status was determined using standard procedures, and anti-CCP antibodies were determined by the standard enzyme-linked immunosorbent assay (Immunoscan RA Mark 2 ELISA; Euro-Diagnostica). The methods for determining the HLA-DRB1 shared epitope alleles and the *PTPN22*\*620W (1858C/T) polymorphism have been previously reported (22–25). At baseline, the following data were not available: DAS28 for 0.8%, Health Assessment Questionnaire (HAQ) score for 3.4%, RF status for 0.5%, anti-CCP antibody status for 4.3%, shared epitope allele status for 2.0%, and *PTPN22*\*R620W status for 3.7%.

**Statistical analysis.** We used 2 approaches to analyze the association between current smoking and a good response or remission according to the EULAR criteria. First, a good response (DAS28 <3.2 at followup and >1.2 units decrease from baseline) as compared with no response (DAS28 >5.1 or <0.6 units decrease) or a moderate response (falls between good response and no response) was evaluated using univariate and multivariate logistic regression analyses. The results were expressed as univariate *P* values and multivariate odds ratios (ORs) with 95% confidence intervals (95% CIs). Separate models were constructed for each time point for the overall EIRA cohort at the 3-month, 6-month, 1-year, 2-year, and 5-year followup visits. For the groups treated with MTX or with TNF inhibitors, we restricted our analyses to the 3-month and 6-month visits and considered only those who continued to take the same treatment, since the reason for treatment changes was not registered (for example, lack of response or side effects). The numbers of patients continuing each treatment are shown in Figure 1. Their smoking habits did not differ significantly from the smoking habits of those who changed treatment.

**Table 1.** Patient characteristics at treatment baseline\*

	All patients with SRR data at inclusion, regardless of treatment	Nonrandomly selected DMARD at baseline as part of standard care		Biologic agents (TNF inhibitors) started later
		MTX monotherapy	No DMARD therapy	
No. with DAS28 data/no. in group	1,418/1,430	865/873	158/175	486/535
Demographics				
Age, median (IQR) years	54 (44–61)	55 (45–62)	54 (44–61)	53 (42–60)
Female, no. (%)	992 (70)	594 (69)	119 (75)	364 (75)
Cigarette smoking†				
Never smokers, no. (%)	406 (30)	246 (30)	50 (32)	146 (32)
Past smokers, no. (%)	402 (30)	239 (29)	50 (32)	128 (28)
Current smokers, no. (%)	368 (27)	225 (28)	35 (23)	127 (27)
Irregular smoking/other tobacco, no. (%)‡	176 (13)	105 (13)	19 (12)	61 (13)
Pack-years smoked, median (IQR)	17 (8–26)	17 (8–26)	18 (9–24)	15 (6–25)
Baseline disease characteristics†				
Rheumatoid factor positive, no. (%)	931 (66)	574 (67)	108 (68)	362 (75)
Anti-CCP antibody positive, no. (%)	859 (63)	539 (65)	104 (67)	333 (77)
Years from diagnosis, median (IQR)	0	0	0	3.0 (1.0–5.0)
DAS28, median (IQR)	5.3 (4.5–6.2)	5.6 (4.8–6.3)	5.0 (4.0–5.7)	5.4 (4.4–6.2)
HAQ score, median (IQR)	1.0 (0.6–1.4)	1.0 (0.6–1.5)	1.0 (0.4–1.4)	1.0 (0.6–1.5)
Therapy				
Any DMARD, no. (%)	1,239 (87)	865 (100)	0	393 (81)
Prednisolone, no. (%)	400 (28)	269 (31)	29 (18)	176 (36)
NSAIDs, no. (%)	763 (54)	495 (57)	72 (46)	270 (56)
Genetic factors†				
Shared epitope haplotype, no. (%)	1,036 (75)	635 (75)	118 (76)	398 (83)
PTPN22*620W risk allele, no. (%)	392 (29)	238 (29)	48 (31)	148 (32)

\* The study population consisted of patients from the Epidemiological Investigation of Rheumatoid Arthritis cohort who had baseline data in the Swedish Rheumatology Register (SRR). Subgroups represent patients who started monotherapy with methotrexate (MTX) or who received no disease-modifying antirheumatic drug (DMARD) at baseline, as well as those who started a tumor necrosis factor (TNF) inhibitor as the first biologic agent during the followup period. DAS28 = Disease Activity Score in 28 joints; IQR = interquartile range; anti-CCP = anti-cyclic citrullinated peptide; HAQ = Health Assessment Questionnaire; NSAIDs = nonsteroidal antiinflammatory drugs.

† Not all patients had available information about smoking status, disease characteristics, or genetic factors. Missing values for each parameter are summarized in Patients and Methods.

‡ Patients in this category were excluded from further analyses of cigarette smoking habits.

The following baseline parameters were evaluated in the multivariate regression model: age at baseline (in 10-year increments), sex, current cigarette smoking, past cigarette smoking, RF status (positive/negative), anti-CCP antibody status (positive/negative), baseline DAS28 (per unit increase), and baseline HAQ score (per unit increase), carriage of the HLA-DRB1 shared epitope (1 or 2 copies versus no copies), and carriage of the *PTPN22*\*R620W risk allele (1 or 2 copies versus no copies), as well as disease duration for those who received TNF inhibitor treatment. Age, sex, past smoking, and baseline DAS28 were included as potential confounders or a priori covariates in all models. In addition, we included concurrent use of prednisolone or nonsteroidal antiinflammatory drugs (NSAIDs) in the models investigating the specific treatments. For the group starting TNF inhibitors during the followup period, we also included disease duration at the start of TNF inhibitor treatment and concurrent use of MTX or other DMARDs. Furthermore, we considered the remaining baseline parameters as potential confounders by assessing whether their addition (one at a time) to the model containing smoking and the a priori covariates altered the OR associated with smoking by more than 10%. None of these factors materially altered the association with smoking. Through strat-

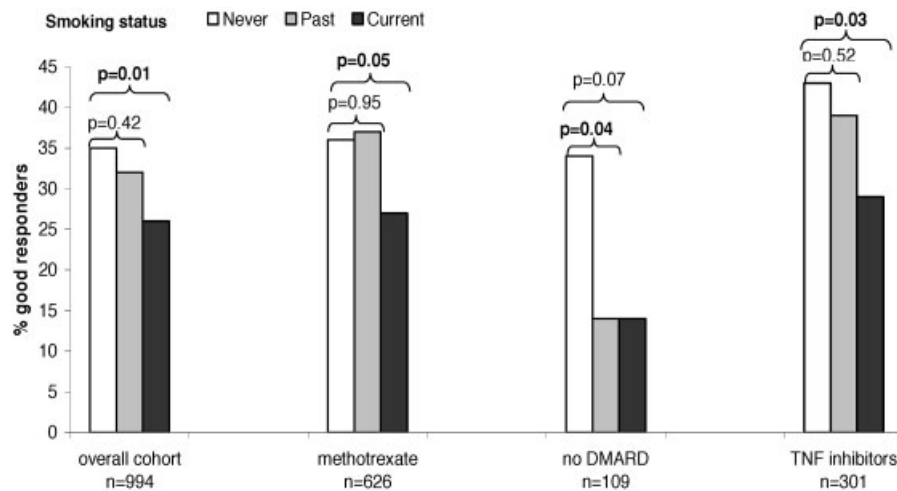
ification, each parameter was also evaluated as a potential effect modifier. All stratum-specific ORs were similar. Thus, the final nonstratified models included only the a priori covariates.

The distribution of DAS28 units on a continuous scale at the 3-month visit was compared between current smokers and never smokers and between past smokers and never smokers by use of *t*-tests, as well as for each of the components of the DAS28 (swollen joint count, tender joint count, erythrocyte sedimentation rate (ESR), patient's assessment of global health status using a 100-mm visual analog scale [VAS]) by use of Wilcoxon's rank sum test, since these parameters were not normally distributed.

Statistical analysis was performed using the SAS version 9.1 software (SAS Institute). All tests were 2-sided, and the significance level was set at 0.05.

## RESULTS

**Eligibility of patients for analyses.** Patients who had available DAS28 data at baseline and were classifiable as current, past, or never smokers constitute the



**Figure 2.** European League Against Rheumatism (EULAR) response in the overall EIRA cohort and in the subgroups receiving MTX or clinical care without a disease-modifying antirheumatic drug (DMARD) at baseline, as well as in those receiving TNF inhibitors later on, according to smoking status. Values are the proportion of patients achieving a good response according to the EULAR criteria at the 3-month visit divided by the number in the smoking category who had DAS28 data available at followup. Numbers across the bottom are the total number with DAS28 and smoking status data. *P* values were determined by univariate logistic regression. See Figure 1 for other definitions.

basis for all analyses (Figure 1). Baseline characteristics of the study patients are shown in Table 1. Baseline characteristics did not differ between RA patients with and those without available DAS28 data.

#### Cigarette smoking and the chance of response.

There was no indication that smokers were more likely to be included in the SRR (data available upon request from the author).

**Findings in the entire EIRA cohort irrespective of treatment.** Overall, 1,430 EIRA patients were followed in SRR from baseline; 1,418 of them had DAS28 data available at baseline (Figure 1), and 1,199 had DAS28 data available at the 3-month visit (994 with smoking status). At the 3-month visit, 32% were good responders according to the EULAR criteria and 24% were in remission. At the 6-month visit, 1,124 had DAS28 data available (952 with smoking status), and 42% of them had achieved a good response and 34% were in remission.

As shown in Figure 2, 26% of current smokers (80 of 305) in the whole cohort achieved a good response according to the EULAR criteria after 3 months, compared with 35% of never smokers (123 of 349;  $P = 0.01$ ). Past smokers had a similar chance of having a good response (32% [110 of 340]) as never smokers ( $P = 0.42$ ).

This decreased chance of a good response in current smokers remained after adjustment for covari-

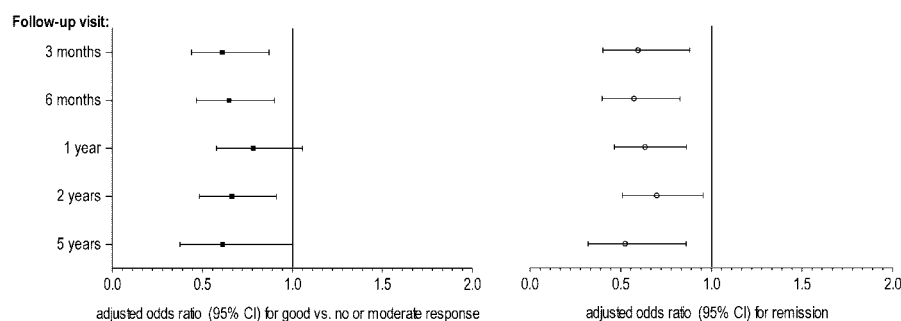
ates at the 3-month followup visit (adjusted OR 0.61 [95% CI 0.44–0.87]) (Figure 3, left) and was similar at later followup visits as compared with baseline (adjusted ORs for the 6-month, 1-year, 2-year, and 5-year visits 0.65, 0.78, 0.66, and 0.61, respectively).

The influence of smoking did not differ significantly between anti-CCP-positive and anti-CCP-negative patients (data not shown).

Current smokers were also less likely to achieve remission at the 3-month followup visit (adjusted OR 0.60 [95% CI 0.40–0.88]) (Figure 3, right), and similar results were observed at all later followup visits (adjusted ORs for the 6-month, 1-year, 2-year, and 5-year visits 0.57, 0.64, 0.70, and 0.52).

The cumulative dose of smoking did not further add to the results among current smokers. Thus, no association was observed between the number of pack-years smoked and a good response according to the EULAR criteria at the 3-month followup visit (adjusted OR per pack-year increase 1.00 [95% CI 0.98–1.02]).

**Findings in the patients starting MTX monotherapy at baseline.** A total of 873 patients started methotrexate (MTX) as the only DMARD treatment at baseline. Of these, 865 had an available DAS28 measure at baseline (Figure 1), and 761 (626 with smoking status) of those who had not changed their treatment before followup had DAS28 data available at the 3-month



**Figure 3.** Association between current smoking and a good response (left) or remission (right) according to the European League Against Rheumatism criteria in the overall group of EIRA patients. Values are the adjusted odds ratios with 95% confidence intervals (95% CIs) determined at the 3-month, 6-month, 1-year, 2-year, and 5-year followup visits, as calculated by multivariate logistic regression, adjusting for age, sex, past smoking, and baseline DAS28. Construction of the models and definition of the covariables are described in Patients and Methods. See Figure 1 for other definitions and numbers of patients in each group.

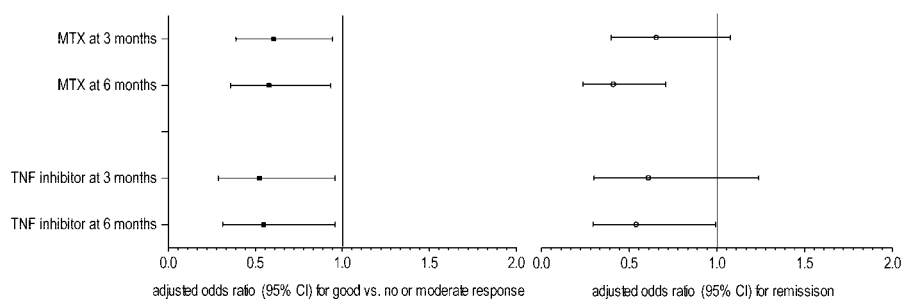
followup visit. We found that 33% were good responders according to the EULAR criteria, and 24% were in remission. At the 6-month followup visit, 522 patients (436 with smoking data) had not changed their treatment and had available DAS28 data, and of that group, 48% had achieved good response and 39% were in remission.

After 3 months of MTX monotherapy, 27% of current smokers (54 of 197) had reached a EULAR good response as compared with 36% of never smokers (78 of 214;  $P = 0.05$ ) (Figure 2), whereas the frequency of good response did not differ between past smokers (37% [79 of 215]) and never smokers ( $P = 0.95$ ).

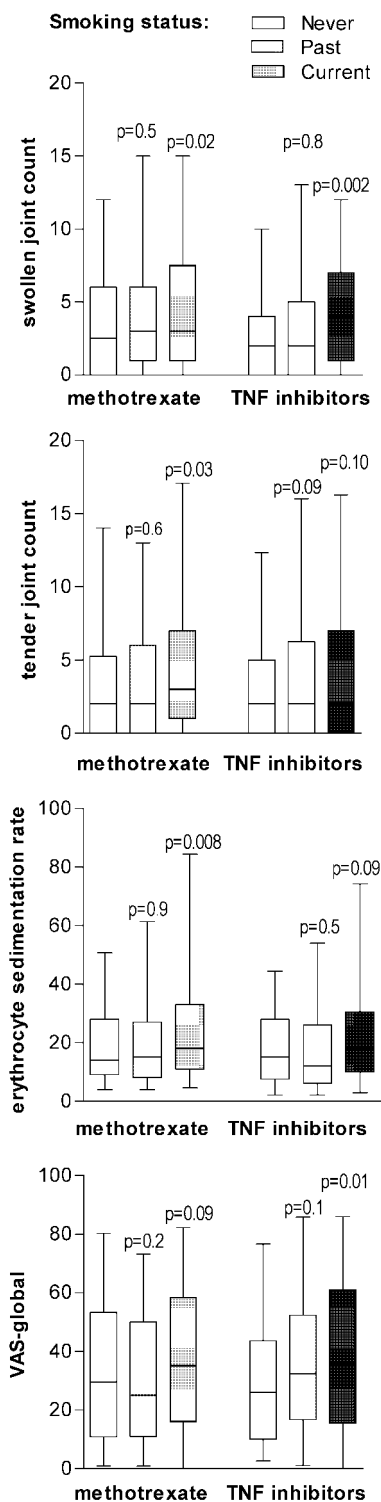
The decreased chance of a good response in

current smokers as compared with never smokers remained in the multivariate model and was not influenced by any of the covariates (adjusted OR 0.60 [95% CI 0.39–0.94]) (Figure 4, left). Similar results for a good response at the 6-month visit were observed (adjusted OR 0.58 [95% CI 0.36–0.94]). Current smokers also tended to be less likely to be in remission after 3 months (OR 0.66 [95% CI 0.40–1.08]) (Figure 4, right), and at the 6-month followup visit, this was significant (OR 0.41 [95% CI 0.24–0.71]).

Among current smokers, the number of pack-years smoked was not associated with the chance of good response after 3 months (adjusted OR per pack-year increase 0.99 [95% CI 0.98–1.02]).



**Figure 4.** Association between current smoking and a good response (left) or remission (right) according to the European League Against Rheumatism criteria in patients starting MTX at baseline and in patients starting a TNF inhibitor as the first biologic agent. Values are the adjusted odds ratios with 95% confidence intervals (95% CIs) determined at the 3-month and the 6-month visits, as calculated by multivariate logistic regression, adjusting for age, sex, past smoking, DAS28 at diagnosis, and concurrent treatment with prednisolone, nonsteroidal antiinflammatory drugs, and in the TNF inhibitor–treated group, MTX. Construction of the models and definition of the covariables are described in Patients and Methods. See Figure 1 for other definitions and numbers of patients in each group.



**Figure 5.** Influence of smoking habits on individual components of the DAS28 in patients receiving MTX or a TNF inhibitor, as determined at the 3-month followup visit. Data are shown as box plots. Each box represents the upper and lower interquartile range. Lines inside the boxes represent the median. Whiskers represent the fifth percentiles. *P* values are versus never smokers, as determined by Wilcoxon's rank sum test (significant at  $P < 0.05$ ). VAS-global = visual analog scale (0–100 mm) for the patient's assessment of global health.

The influence of smoking did not differ significantly between anti-CCP-positive and anti-CCP-negative patients or between patients with and without concurrent prednisolone treatment (data not shown).

None of the DAS28 components differed between current, past, and never smokers at baseline (data not shown). However, consistent with the categorized results above for a good response and remission according to the EULAR criteria, current smokers had significantly higher scores on the DAS28 as a continuous variable than did never smokers (mean 4.10 versus 3.62;  $P = 0.001$ ) at the 3-month followup visit, whereas past smokers and never smokers had similar scores on the DAS28 (mean 3.65 versus 3.62;  $P = 0.83$ ). This also applied to the individual components of the DAS28 (Figure 5), where current smokers as compared with never smokers had higher numbers of swollen joints ( $P = 0.02$ ) and tender joints ( $P = 0.03$ ), a higher ESR ( $P = 0.008$ ), and tended to have higher VAS score for the patient's assessment of global health ( $P = 0.09$ ) at 3 months. These parameters were not significantly different between past smokers and never smokers (swollen joint count  $P = 0.47$ , tender joint count  $P = 0.64$ , erythrocyte sedimentation rate  $P = 0.85$ , and VAS score for the patient's assessment of global health  $P = 0.21$ ).

**Findings in patients who did not start DMARD therapy at baseline.** Eighteen percent of the patients who did not start any DMARD treatment at baseline ( $n = 175$ ) received oral prednisolone treatment, and 46% took NSAIDs regularly. At baseline, 158 of the patients had DAS28 data available, and at the 3-month followup visit, 129 had DAS28 data available (109 with smoking status). At the 3-month visit, 22% of these patients were classifiable as EULAR good responders and 21% were in remission. At the 6-month followup visit, 52 of those with available DAS28 data were still not receiving DMARD treatment, and of those, 27% were classifiable as EULAR good responders and 29% were in remission.

After 3 months, 14% of current smokers (4 of 28) achieved a good response according to the EULAR criteria as compared with 34% of never smokers (15 of 44;  $P = 0.07$ ), and past smokers had a significantly lower chance of achieving a good response (14% [5 of 37]) than did never smokers ( $P = 0.04$ ). The influence of smoking did not differ significantly between patients who did and those who did not receive prednisolone in this non-DMARD-treated group, although those who received prednisolone were more likely to reach a good response (data not shown).

**Findings in the patients who later started a TNF inhibitor as the first biologic agent.** By the end of the followup period in 2007, a total of 535 patients who entered the EIRA cohort during 1996–2006 had started a TNF inhibitor, and 486 of these patients had DAS28 data available at the start of treatment (Figure 1). The median time from RA diagnosis to the start of a TNF inhibitor was 3 years (interquartile range 1–5 years). Of the patients who had smoking status available, 199 received infliximab, 136 received etanercept, and 66 received adalimumab. When pooled, 301 had DAS28 data and smoking category available at the 3-month followup visit. Of these 301 patients, 38% were good responders and 28% were in remission. At the 6-month followup visit, 324 had DAS28 data available, and 44% had achieved a good response and 36% were in remission.

Current smokers were less likely to respond well to TNF inhibitors after 3 months of therapy (29% [28 of 98]) than never smokers were (43% [49 of 113];  $P = 0.03$ ), whereas past smokers (39% [35 of 90]) had a similar frequency of good response as never smokers ( $P = 0.52$ ). The lower likelihood of a good response in current smokers remained in the multivariate model after adjustment for covariates (adjusted OR 0.52 [95% CI 0.29–0.96]). Findings were similar at the 6-month followup visit (adjusted OR 0.55 [95% CI 0.31–0.96]). Using remission as the outcome measure showed a tendency toward an association of current smoking with remission after 3 months (adjusted OR 0.61 [95% CI 0.30–1.24]), which was significant at the 6-month visit (adjusted OR 0.54 [95% CI 0.30–0.99]).

Among current smokers, the number of pack-years smoked was not associated with the chance of good response after 3 months (adjusted OR per pack-year increase for current smokers 1.00 [95% CI 0.96–1.04]).

The influence of smoking did not differ significantly between anti-CCP-positive and anti-CCP-negative patients or between patients who were and those who were not receiving concurrent prednisolone treatment (data not shown).

While none of the DAS28 components differed between the groups of current, past, and never smokers at baseline (data not shown), at the 3-month visit, current smokers had higher DAS28 scores than did never smokers ( $P = 0.003$ ). As shown in Figure 5, this also applied to the individual DAS28 components of swollen joint count ( $P = 0.002$ ) and VAS score for the patient's assessment of global health ( $P = 0.01$ ), whereas a trend was observed for the tender joint count ( $P = 0.10$ ) and the ESR ( $P = 0.09$ ). These parameters did not

differ significantly between past smokers and never smokers.

## DISCUSSION

In this population-based early RA cohort receiving real-life care, we found that current smokers were less likely to respond to MTX treatment and to TNF inhibitor treatment. The decreased chance of response associated with current smoking in both treatment groups was observed for the primary end point of a good response according to the EULAR criteria, for remission according to the EULAR criteria, and for the DAS28 scores or the joint counts at followup and was not explained by other factors. The influence of current smoking was similar at later followup visits and was also observed for the overall group, without regard to which treatment was used. On the other hand, past smoking did not influence the chance of treatment response, although it seemed to have a negative effect in the group that did not start DMARD treatment at baseline.

Our findings provide new information concerning the influence of smoking on the response to MTX monotherapy and extend the information concerning response to TNF inhibitors in patients with longstanding RA (15–17). Previous findings of smoking as a predictor of later disease activity in early RA or inflammatory polyarthritis have been somewhat inconsistent, maybe due to the different treatments used, the outcome measures, and the followup time points, which makes the study results difficult to compare (5,8–11,26). Thus, we evaluated both the likelihood of a good response and remission, which are recommended as outcome measures in the ACR and EULAR joint guidelines (20,21), and found similar results for current smoking up to 5 years later, results which were independent of other baseline parameters.

The strength of our study is that it is population-based, using information about real-life care of patients with early RA, with almost complete information about smoking habits. Compared with clinical trials, the findings may have a higher external validity for routine care, since the only selection criteria applied were being between the ages of 18 and 70 years and having RA of recent onset. The influence of smoking was studied in the context of the main treatment options of today, and most RA patients in whom these treatments were started should have been captured because of the population-based setting and high coverage of the EIRA and SRR registers. Other DMARDs used as part of standard care during the study period (see Supplementary Table 1, available on the *Arthritis & Rheumatism*

web site at [http://onlinelibrary.wiley.com/journal/10.1002/\(ISSN\)1529-0131](http://onlinelibrary.wiley.com/journal/10.1002/(ISSN)1529-0131)) were found in the whole cohort, but the numbers of patients receiving each of these treatments were too low for a meaningful analysis in separate groups.

Another strength of the present study is that the information about smoking was detailed enough to permit analysis of both current and past smoking as well as of the number of pack-years. Furthermore, we had data on genetic risk factors (HLA-DRB1 shared epitope and the *PTPN22*\*620W risk allele) as well as serology (RF and anti-CCP antibodies) for analysis of eventual modifying effects of these factors, which have been shown to interact with smoking in terms of the risk of developing the seropositive form of RA and, in some but not all studies, have been reported to be associated with response to MTX (27–30) or to TNF inhibitors (31,32). The association estimates for current smoking, however, turned out to be unaffected by all covariates tested.

The observational design of this study gives also rise to its main limitations. First, some patients stopped the treatment, received alternative drugs, or received additional drugs before the 3-month or 6-month followup visit when treatment response was evaluated. The reason for changes in medications before the followup visit (lack of response, side effects, etc.) was not recorded, and those patients were therefore excluded from the analyses of individual treatment groups for that time point (see Figure 1). Thus, the numbers of patients with available data for an evaluation of treatment response are likely to be selected on response since they continued to take the same treatment, but a more conservative approach of keeping in the analyses all patients who initiated each treatment yielded similar findings (data not shown).

Treatment changes also made it difficult to evaluate the influence of smoking on the response to particular drugs after the 6-month followup. We did, however, evaluate the whole cohort at later followup visits to give an overall picture of the more long-term influence of smoking, which yielded similar findings of a detrimental effect of smoking. For the TNF inhibitor-treated group, smoking information was retrieved from the time of study entry. This may have introduced bias, but our findings are consistent with those of previous studies (15–17).

Second, some patients were lost to followup in the SRR registry. This might affect the external validity of the results, especially if the smoking habits of those who were lost to followup differed from those who were not, but this was not the case (data not shown). After 2

years, many were lost to followup, partly because they had not yet reached that time point and partly because during the first years of the SRR and the EIRA study, clinicians were instructed to follow their RA cases for only 2 years. Further, some patients were excluded because they did not start their followup in the SRR at the time of EIRA inclusion. It should be noted, however, that the findings were similar if all RA patients with followup data were kept in the analyses.

This study did not intend to explore the reasons why smoking may have a negative effect on response to treatment, but the following factors may be considered. First, smoking may possibly be associated with refractoriness to medications because of pharmacokinetic (PK) or pharmacodynamic (PD) interactions. Accordingly, a recent study in RA patients showed that smokers had lower concentrations of MTX polyglutamates, the active metabolites retained in cells, which indicates that smokers metabolize MTX differently (33). We did not observe any influence of initial MTX dosage on the response frequencies (data not shown). For TNF inhibitors, we are not aware of any studies on the influence of smoking on PK–PD interactions.

Second, it may also be that smokers have a more persistent “natural” disease course of RA, irrespective of treatment. Since only 175 patients did not start any DMARD treatment, only 52 of whom were not receiving any DMARD after 6 months from inclusion, our power to detect differences in disease course that were dependent on smoking was limited. Thus, the observational setting of our study makes it impossible to determine whether it is the underlying disease that is made more severe by smoking or whether smoking specifically affects response to therapy. From a clinical perspective, it is important to know the impact of smoking on disease activity in individuals who are treated with MTX or TNF inhibitors, irrespective of whether the effect of smoking is mainly acting on the underlying disease course (which is then not compensated for by the treatment) or whether the effect of smoking is specific for the actual treatment.

Cigarette smoking is a well-known risk factor for the RA diagnosis, particularly in the subset of patients with anti-CCP antibodies (1), but the anti-CCP status had no modifying effect on the association of current smoking with response. Thus, the mechanisms through which smoking influences susceptibility to RA and its disease course, respectively, may differ.

In conclusion, our findings indicate that cigarette smokers have a diminished chance of responding well to the currently first- and second-line agents of choice in

early RA treatment today: MTX and TNF inhibitors, respectively. This was also observed in the whole group of RA patients during the first years, indicating that smokers have a more persistent disease activity irrespective of which treatment is used. These findings support the idea that smoking should be taken into account when trying to predict response to antirheumatic agents. Whether discontinuation of smoking prior to initiating treatment is beneficial, as suggested by the observation that past smokers responded equally well to treatment as those who had never smoked, remains to be studied further. Meanwhile, the findings provide a strong impetus for clinicians to include measures against smoking as a fundamental part of the therapeutic armamentarium in RA care.

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### AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Saevarsdottir had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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