# The Effect of Snuff (Smokeless Tobacco) on Disease Activity and Function in Rheumatoid Arthritis

## *Experiences From the Better Anti-Rheumatic FarmacOTherapy, a Longitudinal Multicenter Study on Early Rheumatoid Arthritis*

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**Background:** It is not known whether snuff (moist smokeless tobacco) affects disease activity in rheumatoid arthritis (RA).

**Objective:** This study aims to study the effect of snuff on disease activity and function in Swedish patients with early RA.

**Methods:** Between 1992 and 2005, 2800 adult patients were included in the Better Anti-Rheumatic FarmacOTherapy (BARFOT) early RA study in Sweden. Disease Activity Score 28 joints (DAS28), Health Assessment Questionnaire, visual analog scale for general health, and drug treatment were registered at inclusion and at follow-up after 1, 2, and 5 years. European League Against Rheumatism response and remission criteria were applied at 1 year. In 2010, a self-completed postal questionnaire was sent to 2102 patients in the BARFOT study enquiring about lifestyle factors such as smoking and use of snuff. Three controls for each patient using snuff were identified.

**Results:** Fifty-one patients who used snuff were identified, together with 145 controls. When we adjusted for socioeconomic class, disease duration, and previous antirheumatic medication, the snuff users had lower DAS28 values at up to 6 months of follow-up than patients who had never smoked, and they had lower DAS28 values than previous smokers at up to 2 years of follow-up. No effect of snuff use on European League Against Rheumatism response was seen at up to 1 year.

**Conclusions:** Snuff users initially had lower DAS28 levels than never smokers and previous smokers.

**Key Words:** rheumatoid arthritis, smokeless tobacco, snuff, epidemiology

(*J Clin Rheumatol* 2013;19: 14–18)

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Funding: This study was supported by grants from the Swedish Society of Medicine, the Swedish Rheumatism Association, the Research Department of the County Council of Halland, the Gothenburg District Rheumatology Foundation, and the Crafoord Foundation.

Conflicts of interest: Dr Maria. K. Söderlin has received speaking fees for educational events from Abbott (<$3,000), MSD (<$1,000), and speaking fees and consultation fees from Pfizer (<$10,000). Dr Stefan Bergman has received fees from speakers bureau from Pfizer (<$5000).

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ISSN: 1076-1608/13/1901–0014
DOI: 10.1097/RHU.0b013e31828214ed

Smoking has been associated with a higher risk of developing rheumatoid arthritis (RA) in patients with shared epitope and positive anti-cyclic citrullinated protein antibodies.[1] Smoking has also been shown to have a detrimental effect on treatment response in patients with RA treated with disease-modifying antirheumatic drugs (DMARDs) in previous studies from the present cohort,[2,3] and other studies have confirmed this.[4–12] However, not all studies show a negative effect of smoking on therapy response in RA.[13,14] Nicotine activates the nicotinic acetylcholine receptors situated in the autonomic ganglia, the central nervous system, neuromuscular junctions, and the adrenal medulla. These receptors are also situated in the bronchial epithelium and the small and the large intestines.[15] Oral nicotine treatment started before the onset of murine collagen–induced arthritis reduced clinical signs of arthritis, joint destruction, and tumor necrosis factor α expression.[16] Nicotine tends to delay the development of arthritis in mice with collagen-induced arthritis.[17] Nicotine has also been shown to reduce the production of interleukin 6 in vitro in stimulated splenocytes.[17]

Snuff ("snus" in Swedish—moist, smokeless tobacco) consists of ground tobacco, salts, and moisturizing and flavoring agents. Nicotine is the main addictive component of snuff. Many carcinogens have been detected in snuff, for example, nitrosamines, polycyclic hydrocarbons, aldehydes, heavy metals, and polonium-210. The tobacco-specific nitrosamines appear to be most important regarding the cancer risk (Swedish National Institute of Public Health). Swedish snuff is pasteurized, which leads to lower concentrations of nitrite and nitrosamines than in American moist snuff, which is fermented.[18] The use of snuff leads to exposure to similar or higher doses of nicotine than tobacco smoking, but not of course to exposure of the airways to tobacco smoke. The use of snuff is associated with oral cancer[19] and with a higher risk of cardiovascular events and lethal myocardial infarction in some studies[20,21] but not all.[22,23] An Indian study has reported a higher risk of all-cause mortality in tobacco chewers.[24]

In 2010, 20% of men and 4% of women used snuff on a daily basis in Sweden. In addition, 6% of men and 3% of women used snuff sporadically during the same year. In Sweden, 13% of women and 12% of men smoked on a daily basis during the same period (Swedish National Institute of Public Health).

In a large Swedish study on 277,000 male construction workers, having ever used snuff was not associated with the risk of developing RA.[25] However, little is known about the effect of snuff on disease activity in RA. The aim of this study was to investigate the effect of snuff on disease activity and function in a longitudinal observational study of early RA in southern Sweden [the Better Anti-Rheumatic FarmacOTherapy (BARFOT) study]. Our hypothesis was that patients using snuff would have the same disease activity and function as patients who had never smoked.

## PATIENTS AND METHODS

During the period of 1992 to 2005, 2800 patients older than 18 years were enrolled in the BARFOT study, a multicenter longitudinal observational study of patients with early RA in southern Sweden.[26–28] In this study, all patients had disease duration of 2years or less. They all fulfilled the American College of Rheumatology RA classification criteria from 1987.[29] The disease activity was evaluated at inclusion and at 3, 6, and 12 months and at 2 and 5 years. The number of swollen joints (28-joint count; SJC), the number of tender joints (28-joint count; TJC), C-reactive protein levels, erythrocyte sedimentation rate (ESR), the Swedish version of the Stanford Health Assessment Questionnaire (HAQ),[30,31] and visual analog scale (VAS) for pain and general health were measured on every follow-up occasion. The Disease Activity Score using 28-joint count (DAS28) was calculated at inclusion and on every follow-up occasion (www.das-score.nl). The disease duration was calculated from the start of the symptoms.

European League Against Rheumatism (EULAR) response was calculated from the DAS28 scores.[32] The DAS28 is a composite score consisting of the number of swollen joints (of 28), the number of tender joints (of 28), ESR, and the patient's global assessment (www.das-score.nl). The patients were classified into 3 EULAR response groups: no response, moderate response, or good response. To be a good responder, a patient had to show an improvement of at least 1.2 units and achieve an absolute score of less than 3.2. Nonresponders had to show an improvement of less than 0.6, or greater than 0.6 and 1.2 or less, and have a final DAS28 score of greater than 5.1. Moderate responses fell in between these criteria. EULAR response was evaluated for up to 1 year in this study. Treatment with DMARDs and glucocorticoids was registered at inclusion and at each follow-up point. The choice of DMARD treatment in the BARFOT study was left to the discretion of the rheumatologist.

### Self-Completion Postal Questionnaire in 2010

Between March and September 2010, all patients who were still alive in the BARFOT study (n = 2102) received a self-completion postal questionnaire assessing smoking, pack-years, use of snuff, second-hand exposure to tobacco smoke, alcohol use, diet, pain, medication, comorbidities, height, weight, waist circumference, activities of daily living function, and physical activity. Demographics such as occupation and immigrant status were also recorded. The occupations were then coded according to the latest version of the socioeconomic status criteria (Socioekonomisk indelning, SEI) in Sweden. In this study, the socioeconomic status was either manual worker, upper or lower white-collar worker (grouped together), or other or self-employed (grouped together) as defined by the SEI.

The snuff question in the 2010 questionnaire was, "Do you use snuff? (yes/no)." The patients in this study who used snuff had either used snuff only all along or were previous smokers who had stopped smoking for at least 2 years before being included in the BARFOT study and had continued to use snuff after stopping smoking. Patients who both smoked and used snuff were labeled as smokers. Smoking status was assessed as reported in the 2010 questionnaire (never smokers, previous smokers, and current smokers). Two reminders were sent to the patients who had not responded to the first and second mailing of the self-completed questionnaire in 2010. All patients received written information about the self-completion postal questionnaire in 2010, and the ethics committee of Lund University approved the BARFOT study and the postal questionnaire in 2010.

### Statistics

Three controls each were found for each patient using snuff. The controls were stratified for sex and smoking status, 1 control each being a never smoker, a previous smoker, or a current smoker. The previous smokers had to have stopped smoking at least 2 years before inclusion in the study. An analysis of variance (ANOVA) was performed to determine whether snuff users differed significantly from never smokers, previous smokers, and current smokers in DAS28 and HAQ at baseline and after up to 5 years of follow-up. These ANOVA analyses were also adjusted for disease duration, the number of previous DMARDs and biologics (grouped together), and SEI class. EULAR response (good vs. no or moderate) at up to 1 year of follow-up was also analyzed. The multiple logistic regression analyses using EULAR response as outcome could not be adjusted for disease duration, the number of previous DMARDs and biologics, or SEI class because of the small number of patients. The variables entered in the regression models were checked for colinearity.

## RESULTS

In total, 1525 (73%) of 2104 patients answered the self-completion postal questionnaire in 2010. Of these, 1460 (69%) were older than 18 years and had a disease duration of 2 years or less, and these patients were included in the study. The patients who did not answer the 2010 questionnaire had higher mean DAS28 (not answered, 5.4 vs. answered, 5.2; $P = 0.006$), had higher mean VAS general health (48 vs. 45 mm, $P = 0.004$), had higher mean SJC (11 vs. 10, $P = 0.02$), had higher mean TJC (8.9 vs. 8.2, $P = 0.045$), and were more often smokers (30% vs. 24%, $P = 0.01$) but less often rheumatoid factor positive (58% vs. 63%, $P = 0.02$) than those who did answer the questionnaire, but did not otherwise differ from the patients who answered the questionnaire.

Table 1 shows the data for the snuff users and the controls. Smoking status at the time of the questionnaire in 2010 was registered for 1379 patients. In total, 514 (37%) of them were never smokers, 634 (46%) were previous smokers, and 231 (17%) were current smokers. Data on smoking for 81 patients were missing in the 2010 questionnaire. We identified 51 patients who used snuff, and 75% of them were men. Forty-nine control patients were never smokers, 48 were previous smokers, and 48 were current smokers. There were no significant differences in baseline disease activity variables or disease duration between the snuff users and the controls (Table 1). There were no significant differences in the number of previous DMARDs and biologics (grouped together; $P = 0.43$) or in the number of ongoing DMARDs and biologics (grouped together; $P = 0.27$) between snuff users and controls, as assessed in the 2010 questionnaire.

### Analysis of Variance and Multiple Logistic Regression Analyses

The HAQ and DAS28 showed high colinearity ($r_s = 0.512$, $P = 0.0001$), and they were thus entered separately in the regression analyses.

### Snuff Users Compared With Never Smokers

There were no significant differences in DAS28 values at inclusion, at 3, 6, and 12 months, and at 1, 2, and 5 years of follow-up between snuff users and never smokers ($P = 0.35$, $P = 0.81$, $P = 0.17$, $P = 0.89$, $P = 0.77$, and $P = 0.74$, respectively). When we had adjusted the DAS28 analyses for SEI class, disease duration, and the number of previous DMARDs and biologics (grouped together), snuff users had significantly

**TABLE 1.** Demographics and Disease Characteristics at Inclusion in the BARFOT Study for the 51 Patients Who Used Snuff and the Controls

| | Snuff Users | Never-Smoking Controls | Previous-Smoking Controls | Current-Smoking Controls | *P* |
|---|---|---|---|---|---|
| Variable | n = 51 | n = 49 | n = 48 | n = 48 | |
| Age, y | 55 (44–61) | 53 (45–60) | 52 (46–60) | 55 (48–62) | 0.66 |
| % men | 75 | 74 | 71 | 71 | 0.97 |
| HAQ | 1.0 (0.6–1.3) | 0.75 (0.5–1.0) | 0.88 (0.4–1.1) | 0.88 (0.5–1.3) | 0.41 |
| DAS28 | 4.9 (4.1–5.8) | 5.2 (4.5–5.9) | 5.1 (4.0–6.1) | 5.3 (4.4–6.0) | 0.72 |
| VAS global, mm | 40 (21–60) | 45 (31–62) | 42 (18–58) | 40 (21–61) | 0.75 |
| VAS pain, mm | 49 (27–60) | 42 (23–61) | 35 (21–54) | 39 (29–61) | 0.56 |
| No. swollen joints (of 28) | 9 (7–13) | 10 (6–13) | 9 (5–14) | 9 (6–11) | 0.58 |
| No. tender joints (of 28) | 6 (2–10) | 7 (3–11) | 5 (2–11) | 8 (3–13) | 0.59 |
| ESR | 24 (13–51) | 31 (16–49) | 28 (12–50) | 26 (12–44) | 0.69 |
| CRP | 20 (9–33) | 18 (9–42) | 24 (9–52) | 16 (9–41) | 0.64 |
| DMARDs, % | 80 | 86 | 83 | 87 | 0.80 |
| Glucocorticoids, % | 22 | 31 | 35 | 38 | 0.35 |
| Current smoker: status at inclusion in the study, % | 0 | 0 | 0 | 100 | NA |
| RF positive, % | 68 | 69 | 54 | 77 | 0.13 |

Unless otherwise stated, the values are presented as median (interquartile range). *P* value denotes the differences between the different patient categories.

CRP, C-reactive protein; RF, rheumatoid factor; NA, not available.

lower DAS28 scores at 3 months of follow-up (mean DAS28, 2.0 in snuff users vs. 3.7 in never smokers; $P = 0.001$) and at 6 months (mean DAS28, 2.1 in snuff users vs. 3.2 in never smokers, $P = 0.003$). For HAQ, the only significant difference was at 2 years of follow-up (mean HAQ for snuff users, 0.4 vs. 0.3 for never smokers; $P = 0.03$), but no differences in HAQ levels were seen at any time point in the adjusted model (data not shown).

There were no differences in EULAR response between snuff users and never smokers up to 1 year of follow-up (data not shown).

## Snuff Users Compared With Previous Smokers

Regarding previous smokers and patients who used snuff, the only significant difference was in DAS28 at 2 years (mean DAS28 score, 2.3 in snuff users vs. 2.8 in previous smokers; $P = 0.048$). When we adjusted the DAS28 model for SEI class, disease duration, and previous antirheumatic medication, there were significant differences at 3 months, 6 months, and 2 years of follow-up, whereby snuff users had lower DAS28 values (3 months: mean DAS28 score, 2.2 for snuff users vs. 3.8 for previous smokers; $P = 0.008$; 6 months: mean DAS28 score, 2.4 for snuff users vs. 3.3 for previous smokers; $P = 0.04$; and 2 years: mean DAS28 score, 2.0 for snuff users vs. 2.9 for previous smokers; $P = 0.02$). There were no differences in HAQ values at any time point, even when the model was adjusted (data not shown).

There were no differences in EULAR outcome between snuff users and previous smokers up to 1 year of follow-up (data not shown).

## Snuff Users Compared With Current Smokers

In the nonadjusted model, there were no differences in DAS28 values between snuff users and current smokers at any time point. In the adjusted model, snuff users had a lower mean DAS28 value at the 3-month follow-up (2.5 in snuff users vs. 4.1 in current smokers, $P = 0.01$). For HAQ, there were no significant differences at any time point, even when the model was adjusted (data not shown). There were no differences in EULAR outcome between snuff users and current smokers up to 1 year of follow-up (data not shown).

Figure 1 shows the nonadjusted data for DAS28 in a 5-year follow-up for the different smoking classes and snuff users.

## DISCUSSION

To our knowledge, this is the first study to consider the use of snuff and its effects on disease activity in RA. In this large Swedish longitudinal observational cohort of patients with RA, the snuff users were compared with controls stratified for sex and smoking status. The main finding was that snuff users

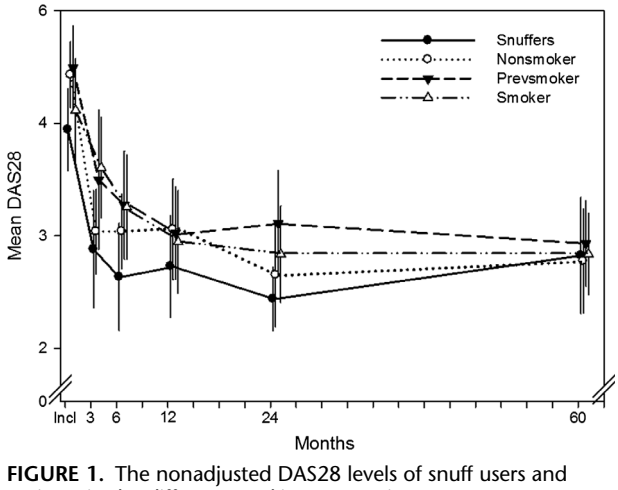


**FIGURE 1.** The nonadjusted DAS28 levels of snuff users and patients in the different smoking categories up to 5 years of follow-up.

generally had lower DAS28 values than never smokers and previous smokers, but this was evident only when we had adjusted for socioeconomic class, previous antirheumatic medication, and disease duration and when we compared them with never smokers at up to 6 months of follow-up and with previous smokers at up to 2 years of follow-up. When we compared snuff users and current smokers, no clear trends emerged. There were no clear trends for HAQ and no differences in EULAR outcome at up to 1 year. Thus, our hypothesis that snuff use would not have any effect on disease activity did not hold true.

Nicotine has been shown to have antiinflammatory effects in mouse models of RA,[16,17] and there is thus a theoretical possibility that nicotine may have an antiinflammatory effect in humans. Our study results may be seen to support this, but we could not detect any effect on function or EULAR outcome. At present, there is no evidence that nicotine is involved in the pathogenesis of RA in men because the use of snuff in male construction workers was not associated with the risk of developing RA in another Swedish study.[25] We have previously reported from the present cohort that smoking has a detrimental effect on outcome at 1 year of follow-up[2] and that smokers lack the "window of opportunity " in early RA,[3] and this has been confirmed in some,[4–12] but not all studies.[13,14] Other studies have shown that smoking has been associated with the risk of developing RA.[1] It is at present not known what component or components in cigarette smoke cause RA and why smokers have a poorer response in RA and what the exact mechanism is. We do not have a good explanation as to why we found only lower DAS28 at 3 months comparing snuff users and current smokers. It would be interesting to study the use of snuff and its effects in RA in a predominantly female population because 75% of our snuff users and controls were men. Men have been shown to have a better prognosis in RA than women, as has also been reported from this same cohort.[2,27]

It must be emphasized that our study is small (51 patients and 145 controls) and that these results must be confirmed in larger studies.

One strength of the present study is that we could compare snuff use stratified for smoking status in controls. Another major strength is also the well-documented follow-up and the cross-sectional data on disease activity and lifestyle factors from the postal questionnaire in 2010. Since the assessment of smoking and snuff use was retrospective, some smokers and snuff users may have been misclassified. It is also possible that the effect on smokers of previous smoking is ongoing, although the users of snuff in this study had stopped smoking at least 2 years before inclusion. We have shown using this same material[2] and others have also shown[4,5] that previous smoking does not affect disease activity at inclusion or prognosis in RA.

Our study results can obviously not be used to promote using snuff, as its use has been shown to be associated with a risk of cardiovascular disease and with lethal myocardial events in some studies.[20,21] Snuff is thus not a "healthier" product than cigarettes.

In conclusion, patients with RA using snuff generally had lower DAS28 values than those who had never smoked at up to 6 months of follow-up, and as compared with previous smokers at up to 2 years of follow-up, but no effect of snuff use was seen on HAQ or EULAR response. Our results must be verified in larger studies.

## KEY POINTS

Patients with RA using snuff initially had lower DAS28 levels than patients who had never smoked and previous smokers adjusted for socioeconomic class, previous antirheumatic medication, and disease duration. There were no differences in EULAR response at 1 year between the patients using snuff and the patients in the different smoking categories.

## ACKNOWLEDGMENTS

*We thank Jan-Åke Nilsson for invaluable help with the statistical analyses. We are also grateful for the help provided by all our colleagues and staff at the hospitals contributing to the BARFOT study, for their cooperation and provision of data.*

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