EXTENDED REPORTS

# Cigarette smoking and rheumatoid arthritis severity

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**Abstract**

***Objectives*—Cigarette smoking may influence rheumatoid arthritis (RA) disease incidence and may have direct biological effects on the lungs and systemically. This study sought to determine if cigarette smoking is associated with RA disease severity.**

***Methods*—Clinical evaluations of patients seen in the University of Iowa rheumatology and orthopaedic ambulatory clinics were conducted. A letter of interest was mailed to 1701 patients who were first assigned an ICD-9-CM diagnostic code for RA in one of these clinics. A total of 857 patients expressed interest and were offered a clinical examination and 395 were evaluated over an 18 month period. Of these, 336 satisfied examiner criteria for prevalent RA and were included in the analysis. The disease characteristics and arthritis care utilisation of these patients seemed representative of prevalent cases in the general community. RA disease severity was assessed by radiographic bone erosions (graded as either present/absent and using the Larsen system), rheumatoid factor seropositivity, and presence of subcutaneous rheumatoid nodules.**

***Results*—Pack years of cigarette smoking was significantly associated with rheumatoid factor seropositivity (p = 0.0001), radiographic erosions (p = 0.024), and nodules (p = 0.051). After adjustment for potential confounders, smokers with ≥25 pack years were 3.1 times more likely to be rheumatoid factor positive (95% CI 1.7, 5.6) and 2.4 times more likely to show radiographic erosions (95% CI 1.2, 4.5) than never smokers. Less severe radiographic disease seemed to be more strongly associated with cigarette smoking than more severe disease.**

***Conclusion*—Cigarette smoking may adversely influence the severity of RA in a potentially dose dependent fashion.**

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Investigation into environmental and constitutional risk factors predicting the severity of rheumatoid arthritis (RA) remains an ongoing challenge that may offer new insights into RA pathogenesis and new approaches to disease prevention. Radiographically detected juxta-articular bone erosions are a characteristic consequence of longstanding, severe RA and provide a cumulative index of joint damage.[1 2] Clinical and epidemiological investigations have shown radiographic evaluation of bone erosions to be a sensitive, valid, and reliable technique that can be quantitated and followed up serially.[1] Extensive erosions in RA are strongly correlated with poor outcome and premature mortality.[3–5] In addition to radiographic abnormalities, severe RA is often accompanied by the presence of high serum titres of rheumatoid factor,[6 7] subcutaneous rheumatoid nodules,[7] and other extra-articular manifestations of RA.[8] Other non-genetic factors often indirectly associated with more severe RA and correlated with a poorer prognosis include increasing age, female sex, lower income, unemployment, less formal education, and single marital status.[9–14] Although these sociodemographic measures are associated with increased morbidity and may strongly impact on arthritis health care utilisation, none of these factors independently predicts worsening radiographic status. Additionally, there are no obvious biological explanations for their direct effects on RA.

Evidence from all three prospective cohort studies and two of three population based case control studies show that cigarette smoking increases a person's risk for developing RA.[15–20] Smoking may have direct biological effects on the RA disease process by increasing serum rheumatoid factor [18 21 22] and changing immune function both in the lung and systemically.[23 24] For instance, cigarette smoking has been shown to increase the white blood cell count [25] and heavy smokers show abnormalities in circulating T lymphocytes, which may predispose to infection or malignancy.[26–28] Although we and others have identified smoking as an important risk factor for the development of RA associated interstitial lung disease (RA-ILD),[29 30] the importance of smoking on RA global disease severity remains unknown.

Given the clinical importance of smoking on RA lung disease, the possible role of smoking

as a risk factor for RA incidence, and the potential immunological effects of tobacco smoke, we hypothesised that smoking would be an independent risk factor for RA disease severity. To consider this hypothesis and explore the nature of this relation, we determined the association between cumulative cigarette smoking and common measures of RA disease severity in a large group of previously well characterised RA patients (n = 336).[30]

## Methods

### SUBJECTS

Using computerised diagnosis codes, we identified all University of Iowa (UI) patients who first visited either the UI rheumatology or orthopaedic outpatient clinics between 1985 and 1992 and were given an ICD-9-CM code (714.0) for RA (n = 1701). All identified subjects were mailed a one page questionnaire to determine their interest in a RA study and to ascertain demographic data and a listing of their current arthritis medications. To avoid a biased response, the nature of our study was intentionally not specified. Interested respondents were invited to the University of Iowa General Clinical Research Center where, after providing informed consent, they were comprehensively evaluated.

Of the 1701 potential study subjects identified and mailed the screening letter, we accounted for 67% of the mailings: 857 (50.3%) responded to the letter and expressed interest in our study; 62 (3.6%) respondents were not interested in participating and 186 (10.9%) letters were either not delivered because the respondent was deceased (n = 35) or had no forwarding address (n = 151). Thirty eight (2.3%) people declined to participate because of a diagnosis other than RA. All of the 857 interested respondents were offered a clinical evaluation and we were able to schedule and evaluate 395 in the University of Iowa General Clinical Research Center (UI-GCRC) between 1993 and 1994.

### CLINICAL EVALUATIONS

A rheumatologist (n = 241) or experienced rheumatology physician assistant (n=154), systematically evaluated all subjects in the UI-GCRC. Evaluation included self completed and clinician assisted questionnaires on RA history (for example, duration of disease and complications), functional status, past/current medication use, co-morbid conditions, sociodemographic data, and a detailed smoking history. Cigarette smoking history was assessed by self report questionnaire mailed to subjects and completed before the research visit using guidelines developed by the American Thoracic Society.[31] Smoking was quantified in pack years for all former or current smokers. Each subject underwent a limited general physical examination and a standardised complete rheumatological evaluation including quantitative joint counts (a maximum of 66 swollen and 69 tender joints) and assessment for extra-articular rheumatoid disease such as the presence of rheumatoid nodules. We also performed latex fixation rheumatoid factors (RapiTex RF, Behring Diagnostics, Inc) on each participant. Rheumatoid factors were reported as positive or negative.

### RADIOGRAPHIC INTERPRETATION

All subjects received a single AP radiograph of both hands. These were initially interpreted by a radiologist as showing/not showing rheumatoid arthritis erosive abnormalities. Additionally, a subset of randomly selected radiographs (n = 212; 54%) were quantitatively interpreted by an experienced rheumatologist (KGS) and two orthopaedic radiologists (KO and MJS) using Larsen's method.[32] The radiographs were interpreted blinded to all identifying subject information. Larsen's method grades 20 hand joints (10 metacarpophalangeal, eight proximal interphalangeal, and two interphalangeal joints of the thumbs) on a 0 to 5 point scale based on the severity of bone erosions and joint space narrowing. Thus, each of the three trained readers assigned a 'damage score' (minimum of 0 to a maximum of 100) to each subject's hand radiograph and the three values were later averaged. Using the Larsen method to grade these radiographs, we found excellent inter and intra-rater reliability (intraclass correlation coefficients 0.89 and 0.98, respectively).[33]

### CHARACTERISATION OF RA

Because of RA misclassification anticipated using our sampling scheme, we characterised subjects according the 1987 American College of Rheumatology (ACR) (formerly Rheumatism Association (ARA)) classification criteria for RA (four of seven current criteria required to satisfy criteria),[34] as well as by our examiner's clinical assessment of 'definite, 'probable, 'possible' or 'unlikely' RA. These ordinal assessments were assigned by our experienced rheumatology clinicians based on clinical impressions and do not correspond to ACR categorisations. Of note, we categorised subjects given a previous diagnosis of RA by any rheumatologist as at least 'possible' RA. Validation studies of RA criteria often use subspecialist report as the 'gold standard'.[35] Three hundred and thirty six, or 73.7% of the 395 subjects were classified as definite (n = 224), probable (n = 67), or possible (n = 45) RA by the rheumatology physician or physician assistant examiner. For the purposes of this report, we included only subjects with definite, probable, or possible RA.

### STATISTICAL ANALYSIS

All data collected were entered into an adapted version of ARION, a computerised database specifically designed for the rheumatic diseases.[36] Data management and statistical analyses were carried out using SPSS (SPSS Inc, Chicago, IL) and SAS (SAS Institutes Inc, Cary, NC) software. We performed univariate screening to identify potentially clinically relevant disease severity and activity measures

associated with cigarette smoking and also to identify possible confounding factors related to both cigarette smoking and to RA disease activity/severity. We evaluated associations of smoking (expressed in pack years) with categorical variables using the Wilcoxon rank sum and Spearman correlation coefficients for continuous measures. Multivariable logistic regression models were constructed to evaluate the independent effect of smoking on three dichotomous disease severity outcomes: serum rheumatoid factor (positive, negative), subcutaneous nodules (present, absent), and radiographic abnormalities (erosions present, absent). Before multivariable model building, we identified all potentially confounding factors from our dataset suspected to be associated with both RA disease severity and smoking. Variables examined included age, sex, body mass index (Quetelet's index = weight in kg/ height in $m^2$), maximal educational level (≤12th grade, other), marital status (married, other), companionship (lives alone, other), and income level (≤$20 000, other). Any of these factors having univariate p values of less than 0.20 were included in the multivariable models. Using the methods of Hosmer and Lemeshow,[37] we built models using a forward step wise procedure with inclusion and exclusion p values of 0.15. Final models included only terms of special interest or those with p values of ≤0.05. All clinically relevant one way interactions were examined for evidence of important effect modifiers. Final logistic associations were expressed as odds ratios and we categorised non-linear independent variables to satisfy the linearity assumption of the logit function.[37] For smoking categorisation, we chose a cut point of 25 pack years corresponding to the 50th percentile of those who smoked. We evaluated logistic regression model performance using the Hosemer-Lemeshow goodness of fit statistic (measuring model calibration) and the c-statistic (measuring model discrimination).[38 39] We additionally explored the association of smoking with the Larsen radiographic damage score. To evaluate trends in this non-normally distributed measure, we categorised the Larsen scores into quartiles.

## Results

The study participants were not significantly different from the RA clinic population as a whole with regard to sex (71.0% women in the population (n = 1701) versus 70.2% in the study group (n = 336), p > .05), and the study participants were only slightly younger than the population overall (mean (SD) age in the overall population 59.9 (16.2) versus 57.2 (13.5) among the participants, p = 0.006). Although only limited additional information was available on survey respondents who did not participate in the study, the arthritis medication use characteristics of the study participants (per cent using non-steroidal anti-inflammatory drugs, prednisone, and second line antirheumatic drugs) were nearly identical to the 857 survey respondents, suggesting a representative sample with regard to previous disease treatment.

*Table 1 Disease characteristics of RA study subjects (n=336)*

| | | |
|---|---|---|
| Patient details | | |
| Sex (% female) | | 70.2 |
| Age (mean (SD)) | | 57.3 (13.5) |
| Race (% White) | | 98.0 |
| Current ACR criteria for RA (%) | | 61.0 |
| Cigarette smoking (%) | Current | 11.6 |
| | Former | 40.5 |
| | Never | 47.9 |
| RA activity (mean (SD)) | | |
| Joint count | Swollen (0–66) | 7.7 (7.6) |
| | Tender (0–69) | 10.1 (12.9) |
| Morning stiffness (h) | | 1.6 (3.4) |
| HAQ DI (0–3) | | 1.0 (0.70) |
| Pain by VAS (0–100) | | 37.6 (25.4) |
| Patient global severity by VAS (0–100) | | 35.5 (23.3) |
| Physician global severity by VAS (0–100) | | 25.1 (22.0) |
| ESR (mm 1st h) | | 36.0 (26.0) |
| RA severity (%, unless otherwise indicated) | | |
| Radiographic bone erosions | | 71.7 |
| Rheumatoid factor positive | | 63.4 |
| Rheumatoid nodules | | 34.2 |
| Mean (SD) disease duration (y) | | 13.9 (11.2) |
| Previous joint surgery | | 51.5 |
| Current medication use (%) | | |
| NSAIDs | | 73.5 |
| Second line drugs | | 61.9 |
| Corticosteroids | | 37.5 |

RA=Rheumatoid arthritis; ACR=American College of Rheumatology; HAQ DI=Health Assessment Questionnaire Disability Index; VAS=Visual Analogue Scale; ESR=erythrocyte sedimentation rate.

Table 1 shows the characteristics of the 336 study subjects with 'definite', 'probable', or 'possible' RA. Two hundred and five, or 61.0% of these subjects satisfied ACR criteria for RA[34] at the time of clinical evaluation. Most subjects with examiner assessment of RA who did not satisfy current ACR criteria (n=131) had diminished disease activity at the time of the clinical encounter. For example, only six (4.6%) showed greater than three swollen joints on the physical examination. Attesting to the potential validity of our examiner classification as a measure of cumulative prevalence (useful in epidemiological studies[40 41]), 84 (64%) of those subjects not satisfying current ACR criteria had physical examination evidence of previously active RA (such as the presence of nodules or other characteristic RA deformities). An additional 34 (26%), while not yet showing physical examination evidence of RA, were currently being treated or had previously been treated with a disease modifying antirheumatic drug.

Table 1 also shows the smoking characteristics of subjects. Smoking start and stop dates were known for 119 (87.5%) of the 136 former smokers. Of the 119 previous smokers, 88 (74%) stopped smoking either after the diagnosis of RA (n = 51) or less than 10 years before the onset of RA (n = 37).

We first explored the association of cigarette smoking (expressed in pack years) on common measures of RA disease activity and severity. Table 2 shows significant associations for the effects of smoking on three traditional disease severity markers: radiographic abnormalities, serum rheumatoid factor positivity, and the presence of rheumatoid nodules. Morning stiffness of greater than one hour (p =0.012) and tender joint count (Spearman's correlation = 0.16, p = 0.004), both measures of disease

*Table 2 Associations of cigarette smoking with RA disease severity measures*

| *Disease severity measure* | *Number of subjects* | *Pack years of smoking Mean (SD) (median)* | *p Value** |
|---|---|---|---|
| Rheumatoid factor | | | |
| Positive | 213 | 18.46 (23.37) (9.55) | 0.0001 |
| Negative | 123 | 9.66 (19.97) (0) | |
| Radiographic erosions | | | |
| Present | 241 | 16.77 (22.71) (4.5) | 0.024 |
| Absent | 95 | 11.33 (21.77) (0) | |
| Subcutaneous nodules | | | |
| Present | 115 | 17.21 (22.78) (7.47) | 0.051 |
| Absent | 121 | 14.21 (22.41) (0) | |

*Wilcoxon rank sum statistic.

activity, also showed a significant positive association with cumulative cigarette smoking. Although we did not observe significant univariate relations between smoking and other measures of disease activity or severity including previous joint surgery, swollen joint count, erythrocyte sedimentation rate or the Health Assessment Questionnaire Disability Index,[42] all associations trended towards more severe or active disease in former or current cigarette smokers (data not shown).

After statistical adjustment for all possible available measures suspected to be associated with both RA disease severity and smoking, cigarette smoking (expressed in pack years) remained a significant predictor of both serum rheumatoid factor positivity and radiographic bone erosions in a pack years dependent fashion as shown in table 3. The presence of subcutaneous rheumatoid nodules also was positively associated with pack years of smoking, although the 95% confidence intervals overlapped 1.0 and there was no dose response relation. Age was the only covariate mildly influencing the association of smoking and rheumatoid factor positivity (OR = 1.14 for a five year increase in age, 95% CI (1.04, 1.24)), while lower body mass index (BMI) was inversely associated with radiographic erosions (OR = 0.94 per one unit change in BMI, 95% CI (0.90, 0.98)). There were no first order interactions between smoking and the sociodemographic variables; in other words, the effects of smoking on radiographic changes or rheumatoid factor positivity did not vary with the level of any sociodemographic factors. Further adjustment for duration of disease (not initially examined as a confounding factor in our models because of its unestablished association with smoking) did not materially influence the results (data not shown). Although the final regression equations for rheumatoid factor and bone erosions showed adequate goodness of fit, they showed only moderate predictive abilities as indicted by the c-statistics (c-statistic = 0.67 and 0.62, respectively). In addition to pack years of smoking, we examined the effects of current cigarette smoking on these same three outcomes. Current smoking was significantly associated only with rheumatoid factor positivity (adjusted OR = 2.6, 95% CI (1.1, 5.9)).

The timing of smoking in relation to the onset of RA was also evaluated. Using never smokers as the referent category, we found a non-significant trend towards an increased risk of erosions for both more recent former smokers and for current smokers at the time of RA diagnosis. A gradient of risk seemed to be present ranging from no risk for former smokers who had stopped more than 10 years before the start of RA (OR = 0.90, 95% CI 0.38 to 1.93), to a trend towards an increased risk among former smokers who had stopped either 10 or less years before RA began or after its onset (OR = 1.71, 95% CI 0.03 to 3.15), to the highest risk among current smokers (OR 1.83, 95% CI 0.79 to 4.26). We also examined the association of bone erosions with pack years of cigarette smoking before RA onset. A trend was again noted with both smokers of ≤25 pack years (OR = 1.37, 95% CI 0.75 to 2.51) and > 25 pack years (OR = 1.46, 95% CI 0.78 to 2.75) more likely to have erosions than never smokers.

Because cigarette smoking was associated with the presence of serum rheumatoid factor, also a disease severity marker, we next explored the relation of rheumatoid factor with bone erosions. As expected, rheumatoid factor positivity was strongly associated with RA radiographic abnormalities (adjusted OR = 4.6, 95% CI (2.8,8.3)). However, when rheumatoid factor was placed into the same statistical model with smoking, the smoking and radiographic erosion association was greatly weakened and no longer statistically significant (above 0 to 25 pack years OR = 0.8, 95% CI (0.4,1,4); ≥25 pack years OR = 1.6, 95% CI (0.8, 3.2)). Of interest, however, the effects of rheumatoid factor on bone erosions varied depending on a person's smoking history: subjects who never smoked had an unadjusted odds ratio of 3.5 (95% CI 1.7, 6.9) compared with an OR of 7.8 (95% CI 3.6 to 17.0) for people with a current or past history of cigarette smoking.

In addition to an effect of cigarette smoking on the presence/absence of bone erosions, smoking was also positively associated with the Larsen damage score, a quantitative measure of RA radiographic disease severity. Because the damage score was skewed towards lower values, and to gain an understanding of the effects of smoking on this severity measure, we stratified the damage scores into quartiles. Table 4 displays the association of ever versus never smoking with the categorised damage score. A significant effect of smoking on overall radiographic severity determined by the Larsen method is seen only across the lower levels of damage. Subjects with a damage score (average of the three readers) of more than 1 but less than 14 were nearly three times more likely to be a current or former smoker than

*Table 3 Adjusted odds ratios (OR)* for the effects of cumulative smoking on RA disease severity*

| *Smoking status (versus never smoker)* | | *OR (95% CI)* | | |
|---|---|---|---|---|
| | | *Rheumatoid† factor positive* | *Radiographic‡ erosions* | *Rheumatoid nodules* |
| Never smoked | | 1.00 (referent) | 1.00 (referent) | 1.00 (referent) |
| Smoking (pack years): | >0–25 | 2.39 (1.36,4.20) | 1.10 (0.62,1.47) | 1.65 (0.93,2.92) |
| | ≥25 | 3.06 (1.67,5.59) | 2.37 (1.23,4.56) | 1.25 (0.70,2.22) |

*Adjusted for age, sex, body mass index, education level, marital status, companionship, and/or income level (if relevant based on univariate associations). †c statistic=0.668, goodness of fit statistic p=0.437. ‡c statistic=0.624, goodness of fit statistic p=0.964.

*Table 4 Effects of cigarette smoking on RA radiographic severity assessed by the Larsen method†*

| | *Number of subjects (%)* with categorised average Larsen damage score (DS)†* | | | |
|---|---|---|---|---|
| | *Stratum 1‡ DS <1* | *Stratum 2 1.1 < DS <14* | *Stratum 3 14.1 < DS <27* | *Stratum 4 27.1 < DS* |
| Smoking status | | | | |
| Never smoked | 34 (32) | 20 (19) | 25 (24) | 27 (25) |
| Ever smoked | 20 (18) | 34 (32) | 26 (25) | 26 (25) |
| Odds ratio (95% CI)‡ | 1.0 (Referent) | 2.9 (1.3,6.2) | 1.8 (0.8,3.8) | 1.6 (0.8,3.5) |

CI=Confidence intervals. *n=212 subjects. †Larsen damage score based on the mean of three radiographic readings (scored from 0 to 100). ‡Referent to stratum 1; stratums determined based on quartiles.

those who had a score of less than 1. An association was attenuated in subjects with more radiographically advanced disease. Of note, the duration of RA was moderately correlated with the Larsen damage score ($\rho = 0.43$, $p<.0001$).

## Discussion

Using a large group of RA patients (n = 336), we identified a consistent pack years dependent association of cigarette smoking with RA radiographic severity, which was independent of sociodemographic and behavioural factors. We also detected a previously described positive association between cigarette smoking and increased serum rheumatoid factor.[20 23 24]

Only a few previous investigations have examined smoking as a co-factor for RA severity. In one report, Wolfe *et al* noted smoking to be a significant risk factor of increased cardiopulmonary mortality in RA (relative risk = 1.5, 95% CI (1.4, 1.7)), but that study did not report on the potential effects of smoking on bone radiographs.[7] Smoking has diverse effects on the immune system both in the lung and systemically.[19 26] Although cigarette smoking has been convincingly associated with an increased risk of RA interstitial lung disease,[29 30] the effects of smoking on other inflammatory conditions are controversial. In slight contrast with our clinical findings, several reports describe a beneficial effect of smoking on bowel inflammation[43–45] and acne.[46] However, an increasing number of studies have detected an increased relative risk (range 1.3 to 2.6) of RA ever smokers compared with never smokers.[16–19] A recent study of monozygotic twins discordant for smoking (n=13) also showed an increased risk for RA in smokers (OR = 12.0, 95% CI (1.78, 513)). [20]

We also analysed the relation between serum rheumatoid factor and radiographic abnormalities and found it to be a stronger correlate of erosions than smoking. This finding is consistent with previous reports of an association between increased serum rheumatoid factor and RA radiographic damage.[6] The results of our stratified analysis further suggest that smoking modifies the effects of rheumatoid factor on radiographic severity. However, the very strong correlation between smoking and rheumatoid factor makes it difficult to statistically discern the independent predictive properties of these two factors. Based on our data and the perceived biology of rheumatoid factor, we postulate that rheumatoid factor may be an intermediate mediator to smoking in a causal pathway that leads to bone erosions. In addition, the effects of smoking on the quantitative Larsen radiographic score argue that smoking may be more important in the initiation of erosive disease than in the perpetuation of the erosive disease process. This hypothesis is consistent with studies showing that smoking is an important aetiological co-factor in disease initiation.

The prevalence of current (11.6%) and former (52.1%) smokers in our study population is comparable to population based rates for the State of Iowa.[47] Importantly, the majority of pack years of smoking were provided by former smokers, approximately 75% of whom discontinued smoking within the period of 10 years before or five years after the onset of their RA. This argues against a significant increase in smoking frequency after disease onset as a driving force in our analysis. With regard to smoking quantity, over 54% of the total pack years of smoking were contributed by former smokers who stopped either after RA began or within 10 years of RA onset, compared with 35% of total pack years contributed by current smokers.

Although we obtained historical information from subject's self report, our data are cross sectional. Prospective data examining variations in both smoking and treatments over time on disease severity would be necessary to optimally consider this question. Cross sectional studies fail to account for people who prematurely die or decline to participate as a result of the outcome of interest. If our study population is under-representative of smokers with severe arthritis (because of smoking related mortality), this would probably bias our results toward the null hypothesis of smoking not influencing RA severity. In this case, our risk estimates would reveal a weaker effect of smoking than was actually present. A bias in the opposite direction seems much less probable. Additionally, cross sectional analyses are limited by difficulties in separating cause from effect and, in turn, accounting for whether subjects may change their behaviours in response to concerns about disease development. Severe RA may lead to depression,[48] a sense of helplessness,[49] and unemployment[11] all of which could increase cigarette consumption. Alternatively, people with severe RA might curtail their smoking either on their own or under medical advice. Based on the small proportion of current smokers and the relatively few former smokers who continued to smoke well beyond the onset of RA, it appears less likely that increased smoking is an effect (rather than a cause) of more severe disease in our analysis.

Although smoking self report has generally good reliability and validity in cross sectional studies,[50–52] recall bias associated with the smoking history is a potential source for misclassification. Patients have been reported to both under and over-report their smoking habit.[51] However, there is no reason to suspect differential misclassification of smoking by the level of disease severity; thus, any bias would be expected to minimise a smoking and RA disease severity association. We also recognise that our case definition may lead to over-ascertainment of true RA. However, our inclusion of subjects not currently satisfying diagnostic criteria for RA, but with previous clinical features of RA, increases the generalisability of our results to patients with less severe RA.

The results of our study are also likely to be generalisable to RA patients in many practice settings. Arthritis care options for the study subject pool were limited. During the study period there were only 24 adult rheumatologists in the state of Iowa; 10 (42%) of whom were at the University of Iowa. Similarly, 43% of the subjects evaluated were actively followed up by UI rheumatologists. Thus, although the subjects are not a community based sample, the subspecialty care utilisation of these subjects may be representative of the distribution of rheumatology resources available throughout our state.

Our study is the first report known to us to suggest smoking is a significant potentially modifiable risk factor for RA disease severity. These results imply that modification of cigarette smoking behaviour may prove to have a significant effect on RA disease severity. Given the absence of other published data supporting our association, we can only speculate on the clinical significance and biological plausibility of our findings. Because of the potential limitations in our study design, we present our findings as hypothesis generating and to stimulate other epidemiological and basic investigations in this area. Prospective studies evaluating the role of smoking as a disease severity factor in RA coupled with an analysis of possible immunogenetic factors that influence this association are needed areas of future research.

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