Smokers and non-smokers with rheumatoid arthritis have similar clinical status: data from the multinational QUEST-RA database

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Abstract

Objectives

To analyse clinical severity/activity of rheumatoid arthritis (RA) according to smoking status.

Methods

The QUEST-RA multinational database reviews patients for Core Data Set measures including 28 swollen and tender joint count, physician global estimate, erythrocyte sedimentation rate (ESR), HAQ-function, pain, and patient global estimate, as well as DAS28, rheumatoid factor (RF), nodules, erosions and number of DMARDs were recorded. Smoking status was assessed by self-report as "never smoked", "currently smoking" and "former smokers". Patient groups with different smoking status were compared for demographic and RA measures.

Results

Among the 7,307 patients with smoking data available, status as "never smoked," "current smoker" and "former smoker" were reported by 65%, 15% and 20%. Ever smokers were more likely to be RF-positive (OR 1.32;1.17-1.48, p<0.001). Rheumatoid nodules were more frequent in ever smokers (OR 1.41;1.24-1.59, p<0.001). The percentage of patients with erosive arthritis and extra-articular disease was similar in all smoking categories. Mean DAS28 was 4.4 (SD 1.6) in non-smokers vs. 4.0 (SD 1.6) in those who had ever smoked. However, when adjusted by age, sex, disease duration, and country gross domestic product, only ESR remained significantly different among Core Data Set measures (mean 31.7mm in non-smokers vs. 26.8mm in ever smoked category).

Conclusion

RA patients who had ever smoked were more likely to have RF and nodules, but values for other clinical status measures were similar in all smoking categories (never smoked, current smokers and former smokers).

Key words
rheumatoid arthritis, smoking, HAQ, DAS

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Introduction

Smoking is associated with an increased risk and a higher prevalence of many diseases, and it has been implicated in the pathogenesis of rheumatoid arthritis (RA), particularly when associated with antibodies, cyclic citrullinated peptides (anti-CCP) and the shared epitope (1-3). In fact, it is postulated that the sequence of events begins with protein citrulination in a subclinical phase before the symptoms start (2). The first study with evidence of an association between smoking and RA risk was an epidemiological investigation of effects of sex hormones on RA (4). Later publications confirmed the association of tobacco and RA, but especially in RF-positive RA (5-8). The studies relating to smoking with RA clinical characteristics have demonstrated an association of smoking with rheumatoid factor (RF), rheumatoid nodules (9-11), higher clinical disease activity (12), need of more treatment (13), and with a greater erosion score (12). However, other studies could not confirm an association of RA severity with smoking (14, 15). Thus, conflicting data are reported concerning severity of RA as measured by the American College of Rheumatology (ACR) Core Data Set and other clinical measures in relationship to smoking status. The QUEST-RA (Quantitative Standard Monitoring of Patients with Rheumatoid Arthritis) (16) multinational database of RA patients seen in usual clinical care at several clinics in different countries provided us an opportunity to analyse the relationship between smoking and the clinical status of RA patients (clinical severity and disease activity).

Patients and methods
Establishment of database

QUEST-RA was established in 2005 with the objectives to promote quantitative assessment in usual rheumatology care, and to develop a baseline cross-sectional database of consecutive RA patients seen outside of clinical trials in regular care in many countries. Three or more rheumatologists from each participating country were asked to enrol 100 consecutive unselected patients (16).

As of June 2009, the QUEST-RA multinational database included 8,039 patients from 86 sites in 32 countries including Argentina, Brazil, Canada, Denmark, Egypt, Estonia, Finland, France, Germany, Greece, Hungary, India, Ireland, Italy, Japan, Kenya, Kosovo, Latvia, Lithuania, Morocco, the Netherlands, Norway, Poland, Romania, Russia, Serbia, Spain, Sweden, Turkey, the United Arab Emirates, the United Kingdom, and the United States.

Ethics committee approvals

The study was carried out in compliance with the Helsinki Declaration. Ethics Committees or Internal Review Boards of participating institutes approved the study, and a written informed consent was obtained from the patients.

Physician assessment measures

Patients were evaluated according to a standard protocol to evaluate RA (SPERA), which includes a 3-page clinician assessment and 4-page patient self-report questionnaire (17). The rheumatologists performed a clinical assessment involving a review of clinical features including ACR 1987 RA classification criteria, disease duration, all previous and present disease-modifying anti-rheumatic drugs (DMARDs as well as biologic agents), a joint count which includes swollen and tender joint on a 28-joint count, and doctor global assessment of disease activity. Past or current presence of rheumatoid nodules was recorded as well as erosive/nonerosive disease in the last hands and feet radiographs. Laboratory tests included erythrocyte sedimentation rate (ESR) and positive RF according to the local reference values measured at any time over the disease course. Extra-articular disease was considered in the case of pulmonal fibrosis, pericarditis, vasculitis, Felty's syndrome or scleritis.

Patient self-report questionnaire measures

Patients completed a 4-page self-report questionnaire, which included demographic data: date of birth, gender, years of formal education and smoking status, reported as "never smoked", "currently

smoking" and "former smokers". A standard Health Assessment Questionnaire (HAQ) (18) assessed physical function in activities of daily living with 4 response categories: 0 = without any difficulty, 1 = with some difficulty, 2 = with much difficulty, 3 = unable to do. Visual analogue scales (VAS; 0 = best to 10 = worst) were completed for pain and patient estimate of his/her global health. Disease activity score (DAS28) was calculated from physician joint counts, ESR, and patient global estimate of health status (19).

The gross domestic product (GDP) of each country was obtained from a database of the International Monetary Fund and is expressed as 1000 United States dollars (USD) per capita (20). Countries were categorised as "high GDP" when their GDP per capita was >24K USD (16 countries), and "low GDP" countries those with a GDP per capita <11K USD (16 countries).

Statistical methods
Descriptive statistics concerning smoking status were calculated for men and women in each country. Analyses for demographic and ACR Core Data Set measures (swollen and tender joint count, pain, patient and doctor global assessment of disease activity, ESR, DAS28 and HAQ) as well as RF, nodules, erosions and number of DMARDs were performed according to smoking status. Statistical significance of possible differences was calculated using *t*-tests and chi-square tests for continuous and categorical variables respectively. Regression models were used to estimate a relationship between categorical variables, adjusted for age, sex, disease duration, and GDP.

The effect of smoking on DAS score index was also analysed by multilevel models, because data consist of clusters (observations on individuals are nested in countries). First, a variance components model with DAS28 and country was conducted to estimate the average value of DAS (constant), the different components of the variance and the intraclass correlation coefficient or percentage of DAS variability due to countries. Then, a full model was used with DAS28 value as a dependent variable

and individual variables (smoking, age, sex, disease duration and number of DMARDs used) as independent variables. The constant was modelled by the country GDP plus a random component using a random intercept model. Stata 10.0 (StataCorp LP, College Station, TX) statistical software package was used for multilevel analysis of data.

Results
Smoking status, sex and country
Among the 7,307 patients with self-report information about smoking status, "never smoked," "current smoker" and "ex-smokers" was reported by 71.5%, 12.4% and 16.0% of women, and 39.0%, 25.1% and 35.8% of men, respectively. The frequency of ever smoked ranged between 68% in Canada to 4% in Egypt (Table I). Apart from male sex, smokers were older, with higher education levels and from high GDP countries (Table II). The percentage of never smoked women was higher in low GDP coun-

tries (80.4%) than in high GDP countries (63.7%) (*p*<0.001).

Smoking status and disease severity
RF and nodules were more frequent in ever smokers (OR 1.32;1.17–1.48 and 1.41;1.24–1.59 respectively). The percentage of nodules was 10 in RF-negative patients and independent of smoking status. However, this figure was 28.3% in RF-positive male smokers *versus* 23.6% in non-smokers (25.6% *vs*. 19.9% in females). Nodules were also more frequent in current versus former smokers (Table II).

The frequency of patients with erosive arthritis and extra-articular disease was similar in all smoking categories.

The use of DMARDs was similar in all smoking categories (Table I; Fig. 1).

Smoking status and disease activity
In univariate models, never smokers had higher disease activity compared to those who ever smoked according to all

Table I. Smoking status per country and sex (%) in patients with rheumatoid arthritis in the multinational QUEST-RA database.

Country	Male			Female		
	Never smoked	Current Smokers	Former smokers	Never smoked	Current smokers	Former smokers
Argentina	25	42	33	56	19	25
Brazil	52	14	33	65	14	21
Canada	19	24	57	35	32	33
Denmark	28	36	42	49	29	31
Egypt	87	8	5	99	1	0
Estonia	37	50	12	73	8	19
Finland	30	22	48	72	12	16
France	32	24	44	68	17	15
Germany	31	11	58	59	13	27
Greece	44	19	37	78	15	7
Hungary	29	35	35	65	23	12
India	78	8	13	98	1	1
Ireland	45	31	24	55	21	24
Italy	30	23	47	67	14	19
Japan	40	33	27	80	12	8
Kosovo	71	14	14	95	4	1
Morocco	45	27	27	100	0	0
Kenya	64	9	27	96	1	3
Latvia	9	56	35	87	6	6
Lithuania	40	25	35	91	3	6
Netherlands	32	32	36	48	18	34
Poland	35	20	45	71	10	19
Romania	47	27	26	77	9	13
Russia	46	42	12	90	6	4
Serbia	27	45	27	80	14	6
Spain	24	31	45	74	12	14
Sweden	31	20	48	45	18	37
Turkey	29	14	57	81	12	6
UAE	63	26	11	85	3	12
UK	31	28	41	60	16	23
USA	42	24	34	58	16	26

Table II. Smoking and disease characteristics in patients with rheumatoid arthritis in the multinational QUEST-RA database.

	All	Never smoked	Ever smokers	Current smokers	Former smokers	p never vs. ever	p current vs. former
Number of patients	7307	4749	2558	1091	1467		
% of patients	100	65	35	15	20		
Age (years), mean	55,17	54,6	56.2	53.0	58.5	<0.001*	<0.001*
Women %	5773	71.5	28.5	12,4	16.0	<0.001**	0.25**
Men %	1468	39.0	61.0	25.1	35.8		
Patients from countries with "High" Gross domestic product, %	4097	56.8	43.2	18.0	25.1	<0.001**	0.19**
Patients from countries with "Low" Gross domestic product, %	3210	75.4	24.6	10.9	13.6		
Education (years), mean	11.1	11.0	11.2	11.3	11.2	0.02**	0.24**
Disease duration (years), mean	10.9	11.9	10.3	9.0	11.3	0.002*	<0.001*
Positive rheumatoid factor %	74.3	72.5	77.7	78.6	77.1	<0.001**	0.38**
Nodules %	19.4	17.5	23.0	25.5	21.2	<0.001**	0.01**
Severe extraarticular disease[a] %	6.5	6.6	6.7	5.7	7.4	0.88**	0.10**
Radiographic erosions %	61.4	62.1	60.2	58.6	61.5	0.14**	0.15**
Number of DMARDs, mean	2.6	2.5	2.6	2.5	2.7	0.05***	0.04***
TNF antagonists %	21.2	19.1	25.2	25.3	25.1	0.10***	0.84***
RA Core Data Set measures							
DAS28-ESR, mean	4.2	4.4	4.0	4.0	4.0	0.28***	0.43***
Swollen joints, mean	4.2	4.3	4.0	4.1	3.9	0.09***	0.38***
Tender joints, mean	6.7	7.3	5.7	5.9	5.6	0.09***	0.64***
MD global, mean	2.9	3.0	2.6	2.6	2.6	0.24***	0.98***
ESR, mean	30.0	31.7	26.8	25.6	27.7	<0.001 &	0.19***
HAQ Function, mean	1.0	1.0	0.9	0.9	0.9	0.23***	0.42***
Pain, mean	4.1	4.1	3.9	4.0	3.8	0.09***	0.06***
Pt Global, mean	4.0	4.1	3.9	3.9	3.8	0.13***	0.06***

[a]Includes pulmonal fibrosis, pericarditis, vasculitis, Felty syndrome, and scleritis.

*T-test, **Chi square test, ***Adjusted by age, sex, disease duration and country gross domestic product &Adjusted by age, sex, disease duration, country gross domestic product, and number of DMARD and biologics.

7 Core Data Set measures: 28 swollen and tender joint count, physician global estimate, ESR, HAQ-function, pain, and patient global estimate, as well as DAS28 (Fig. 2). A higher DAS28 in never smokers was found both in RF positive RA and RF negative RA (p<0.001).

Multivariate models concerning disease activity and smoking status

In a regression model that included smoking status, age, sex, and disease duration as independent variables and DAS28 as the dependent variable, DAS28 was statistically significantly higher in never smokers (p<0.001). However, when GDP was included in the model, the effect of smoking on DAS28 disappeared. In regression models with each of the Core Data Set variables as a dependent variable, only ESR remained statistically significantly lower in ever smokers (Table II). The variance components model showed that country GDP was responsible for 26% of the variability of disease activity. The full model (random-intercept model) showed that the inclusion of the country economy causes the loss of effect of smoking on DAS28 (p=0.927) (Table III).

Discussion

Since 1987 we have known that cigarette smoking is a risk factor for RA, especially in men with RF-positive RA who are heavy smokers (4, 8, 21, 22). Later it was verified that the relation of smoking was more intense with the CCP, interacting with the shared epitope (2, 3, 23-26). Recently, an interaction between the polymorphisms in glutathione S-transferases and smoking in highly active RA has been observed (27). It is also known that smokers in the general population have an increased frequency of elevated RF (28).

In the present study we also found, as other authors (9-11, 29, 30), an association between smoking and nodules but exclusively in RF-positive smokers.
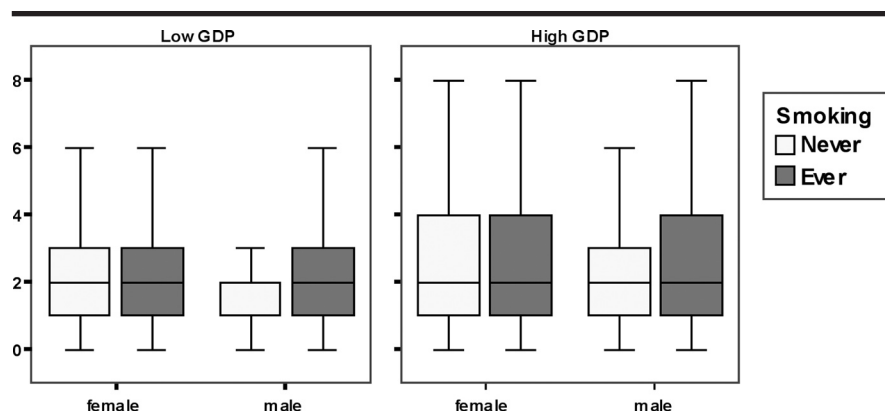

Fig. 1. Disease-modifying anti-rheumatic drugs (DMARD) use according to smoking status, sex, and gross domestic product (GDP). Countries were categorised as "high GDP": GDP per capita >24K USD; and "low GDP": GDP per capita <11K USD.

Fig. 2. DAS28 according to smoking status, sex, and gross domestic product (GDP). Countries were categorised as "high GDP": GDP per capita >24K USD; and "low GDP": GDP per capita <11K USD.
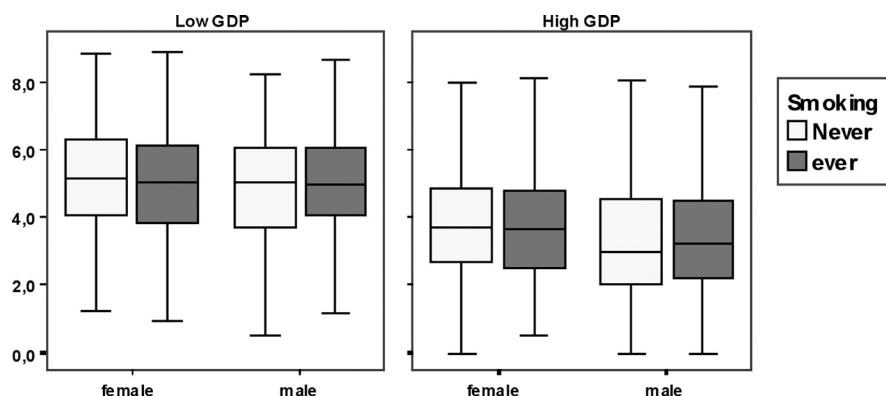
Table III. Multilevel model; the effect of smoking on DAS28 in patients with rheumatoid arthritis in the multinational QUEST-RA database.

Fixed effects	Unconditional model		Random intercept model**	
	Coefficient	p-value	Coefficient	p-value
Constant	4.42	0.000	3.48	
Smoking			0.004	0.927
Female			0.31	0.000
Mean age			0.01	0.000
Mean				
Disease duration			0.003	0.129
Mean number of DMARD			0.07	0.000
Country economy			1.44	0.000
Random effects				
Level 2 variance (countries)	0.85		0.51	
Level 1 variance (individuals)	1.44		1.43	
Intraclass correlation coefficient	0.26*		0.11	

*Variance components model with DAS28 and country economy to calculate the percentage of DAS variability due to countries.
**Full model: DAS28 value as a dependent variable and individual variables as independent variables. The constant was modeled by the country economy plus a random component.

Smoking and disease severity

If it is clear that smoking intervenes somehow in the pathogenesis of the disease, controversy exists on the effect of tobacco use on disease activity and severity. In fact, several prospective studies have obtained conflicting results in this aspect. The effect of smoking on joint damage in Wolfe's study (31) was only detected in patients with very long smoking exposure history, and in Saag's cohort the association was driven by the association between RF and joint damage (9). Moreover, regarding radiological severity the results are conflicting, both in cross-sectional (9, 11, 28) and in prospective studies (12-14, 29). Two large prospective studies with arthritis of different disease duration suggested that cigarette smoking does not accelerate RA disease progression (13, 14).

However, in one of these studies more need of treatments in current smokers was observed (13). Moreover, RA patients with a history of heavy smoking seem to be more likely to show a poor response to TNF antagonists (32). However, another study shows that patients who continue taking their initial biologic medication have a similar smoking status to those requiring switching or discontinuation (33).

Regarding the association of smoking and extra-articular disease, conflicting results have been observed in a few studies (13, 15, 28, 34, 35). Finally, one paper showed association of cigarette smoking with interstitial lung disease (36).

Smoking and disease activity

The effect of smoking on DAS28 has been analysed in few research articles;

in some it is concluded that smoking does not have an influence on DAS (13, 14), whereas in another an increase of DAS in current and former smokers was found (29). In the study by Westhoff *et al.* (13) those who stopped smoking after disease onset had the highest DAS28 when compared to never, former and current smokers. In our study patients who have never smoked appeared to have poorer clinical status than patients who smoked or discontinued smoking, but in a regression model the influence of smoking status on DAS28 was lost when GDP was included. In the multilevel analysis, the effect of country GDP on DAS28 was as high as 26%, and 11% in the adjusted model.

Female patients from low GDP countries have a more active arthritis. In fact, in two reported articles of QUEST-RA multinational database, women have poorer scores than men in all Core Data Set measures (37) and disease activity levels were higher in "low GDP" than in "high GDP" countries at much greater levels than according to whether patients were taking or not taking methotrexate, prednisone and/or biological agents (38). In our study the only activity measure that persisted significant after adjusting for GDP was the ESR, which was higher in never smoked, findings opposite to those reported in a few studies (13, 29).

Smoking and pain

Some authors postulate that smoking may simultaneously have two conflicting influences on disease outcome: a detrimental influence mediated by RF, and also a yet unexplained protective effect (14, 39). In fact, we did not find any association between the activity and severity of RA and smoking status. However, we cannot prove or disprove these two theories. When analysing a larger number of RA patients we could not find the association proven in small studies. On the other hand, several population studies have found a statistically significant association between current and former smoking and the prevalence, intensity and range of pain (40-43). However, results on pain tolerance of smokers and non-smokers are conflicting; in one study it was

observed that nicotine had an effect on increase in pain threshold in men but not in women (44). In a mouse model of collagen-induced arthritis, neither smoking nor nicotine exposure aggravates development of arthritis; both were associated with a lower level of anti-collagen II antibodies and a delay of arthritis onset (45).

Regardless of the outcome of RA activity status in non-smokers, smokers, and former smokers, RA patients should still be strongly encouraged to stop smoking because of the known substantial effects of smoking on cardiovascular disease, additional to the known effects of longstanding disease activity on the cardiovascular system (46, 47).

Limitations of our study
A potential limitation of a cross-sectional analysis includes: first, left censoring (a probable higher mortality rate among smokers prior to acquisition of these data in a rheumatology clinic), and lack of ascertainment of data on pack-years. Second, a cross-sectional database does not allow us to establish a causal relationship between exposure and outcome. Third, we do not have a detailed radiographic damage score given that we only gathered information for the presence or absence of erosions in last available x-rays. Fourth, anti-CCP status was not available in all the participating centres.

Conclusion
RA patients who had ever smoked were more likely to have positive RF and nodules, but values for other clinical status measures were similar in all smoking categories (never smokers, current smokers and former smokers). Though we have not found differences in disease activity and severity of RA and our data cannot confirm this assertion, it must be remembered that cigarette smoking is harmful to the health, not only increasing the risk of RA but also increasing the risk of cardiovascular disease (already raised in RA), bronchitis and cancer.

Acknowledgments

Appendix
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References

1. PADYUKOV L, SILVA C, STOLT P, ALFREDSSON L, KLARESKOG L: A gene–environment interaction between smoking and shared epitope genes in HLA-DR provides a high risk of seropositive rheumatoid arthritis. *Arthritis Rheum* 2004; 50: 3085-92.
2. KLARESKOG L, PADYUKOV L, ALFREDSSON L: Smoking as a trigger for inflammatory rheumatic diseases. *Curr Opin Rheumatol* 2007; 19: 49-54.
3. KLARESKOG L, STOLT P, LUNDBERG K *et al.*: A new model for an etiology of rheumatoid arthritis: smoking may trigger HLA-DR (shared epitope)-restricted immune reactions to autoantigens modified by citrullination. *Arthritis Rheum* 2006; 54: 38-46.
4. VESSEY MP, VILLARD-MACKINTOSH L, YEATES D: Oral contraceptives, cigarette smoking and other factors in relation to arthritis. *Contraception* 1987; 35: 457-64.
5. UHLIG T, HAGEN KB, KVIEN TK: Current tobacco smoking, formal education, and the risk of rheumatoid arthritis. *J Rheumatol* 1999; 26: 47-54.
6. COSTENBADER KH, FESKANICH D, MANDL LA, KARLSON EW: Smoking intensity, duration and cessation and the risk of rheumatoid arthritis in women. *Am J Med* 2006; 119: 503-11.
7. KARLSON EW, MIN LEE I, COOK NR, MANSON JE, BURING JE, HENNEKENS CH: A retrospective cohort study of cigarette smoking and risk of rheumatoid arthritis in female health professionals. *Arthritis Rheum* 1999; 42: 910-7.
8. STOLT P, BENGTSSON C, NORDMARK B *et al.*: Quantification of the influence of cigarette smoking on rheumatoid arthritis: results from a population based case-control study, using incident cases. *Ann Rheum Dis* 2003; 62: 835-41.
9. SAAG KG, CERHAN JR, KOLLURI S, OHASHI K, HUNNINGHAKE GW, SCHWARTZ DA: Cigarette smoking and rheumatoid arthritis severity. *Ann Rheum Dis* 1997; 56: 463-9.
10. NYHÄLL-WÅHLIN BM, JACOBSSON LT, PETERSSON IF, TURESSON C, BARFOT STUDY GROUP: Smoking is a strong risk factor for rheumatoid nodules in early rheumatoid arthritis. *Ann Rheum Dis* 2006; 65: 601-6.
11. MIKULS TR, HUGHES LB, WESTFALL AO *et al.*: Cigarette smoking, disease severity and autoantibody expression in African Americans with recent-onset rheumatoid arthritis. *Ann Rheum Dis* 2008; 67: 1529-34.
12. MANFREDSDOTTIR VF, VIKINGSDOTTIR T, JONSSON T *et al.*: The effects of tobacco smoking and rheumatoid factor seropositivity on disease activity and joint damage in early rheumatoid arthritis. *Rheumatology* 2006; 45:734-40.
13. WESTHOFF G, RAU R AND ZINK A: Rheumatoid arthritis patients who smoke have a higher need for DMARDs and feel worse, but they do not have more joint damage than non-smokers of the same serological group. *Rheumatology* 2008; 47: 849-54.
14. FINCKH A, DEHLER S, COSTENBADER KH, GABAY C, SWISS CLINICAL QUALITY MANAGEMENT PROJECT FOR RA: Cigarette smoking and radiographic progression in rheumatoid arthritis. *Ann Rheum Dis* 2007; 66: 1066-71.
15. WESTEDT ML, HAZES JM, BREEDVELD FC, STERK PJ, DIJKMAN JH: Cigarette smoking and pulmonary diffusion defects in rheumatoid arthritis. *Rheumatol Int* 1998; 18: 1-4.
16. SOKKA T, KAUTIAINEN H, TOLOZA S *et al.*: quantitative clinical assessment of patients with rheumatoid arthritis seen in standard rheumatology care in 15 countries. *Ann Rheum Dis* 2007; 66: 1491-6.
17. PINCUS T, BROOKS RH, CALLAHAN LF: A proposed standard protocol to evaluate rheumatoid arthritis (SPERA) that includes measures of inflammatory activity, joint damage, and longterm outcomes. *J Rheumatol* 1999; 26: 473-80.
18. FRIES JF, SPITZ P, KRAINES RG, HOLMAN HR: Measurement of patient outcome in arthritis. *Arthritis Rheum* 1980; 23: 137-45.
19. PREVOO MLL, VAN'T HOF MA, KUPER HH, VAN LEEUWEN MA, VAN DE PUTTE LBA, VAN RIEL PLCM: Modified disease activity scores that include twenty-eight-joint counts: Development and validation in a prospective longitudinal study of patients with rheumatoid arthritis. *Arthritis Rheum* 1995; 38: 44-8.
20. http://www.imf.org/external/ns/cs.aspx?id http://www.imf.org/external/ns/cs.aspx?id= 28=28 (accessed 12 December 2008).
21. MASDOTTIR B, JÓNSSON T, MANFREDSDOTTIR V, VÍKINGSSON A, BREKKAN A, VALDIMARSSON H: Smoking, rheumatoid factor isotypes and severity of rheumatoid arthritis. *Rheumatology* (Oxford) 2000; 39:1202-5.
22. SUGIYAMA D, NISHIMURA K, TAMAKI K *et al.*: Impact of smoking as a risk factor for developing rheumatoid arthritis: a meta-analysis of observational studies. *Ann Rheum Dis* 2010; 69: 70-81.
23. LEE DM, PHILLIPS R, HAGAN EM, CHIBNIK LB, COSTENBADER KH, SCHUR PH: Quantifying anti-cyclic citrullinated peptide titres: clinical utility and association with tobacco exposure in patients with rheumatoid arthritis. *Ann Rheum Dis* 2009; 68: 201-8.
24. KARLSON EW, CHANG SC, CUI J *et al*: Gene-environment interaction between HLA-DRB1 sharedepitope and heavy cigarette smoking in predicting incident rheumatoid arthritis. *Ann Rheum Dis* 2010; 69: 54-60.
25. MORGAN AW, THOMSON W, MARTIN SG *et al.*: Reevaluation of the interaction between HLA-DRB1 shared epitope alleles, PTPN22, and smoking in determining susceptibility to autoantibody-positive and autoantibody-negative rheumatoid arthritis in a large UK

Caucasian population. *Arthritis Rheum* 2009; 60: 2565-76.

26. LUNDSTRÖM E, KÄLLBERG H, ALFREDSSON L, KLARESKOG L, PADYUKOV L: Gene-environment interaction between the DRB1 shared epitope and smoking in the risk of anti-citrullinated protein antibody-positive rheumatoid arthritis: all alleles are important. *Arthritis Rheum* 2009; 60:1597-603.

27. BOHANEC GRABAR P, LOGAR D, TOMSIC M, ROZMAN B, DOLZAN V: Genetic polymorphisms of glutathione S-transferases and disease activity of rheumatoid arthritis. *Clin Exp Rheumatol* 2009; 27: 229-36.

28. JONSSON T, THORSTEINSSON J, VALDIMARSSON H: Does smoking stimulate rheumatoid factor production in non-rheumatic individuals? *APMIS* 1998; 106: 970-4.

29. MATTEY DL, DAWES PT, CLARKE S *et al.*: Relationship among the HLA-DRB1 shared epitope, smoking, and rheumatoid factor production in rheumatoid arthritis. *Arthritis Rheum* 2002; 47: 403-7.

30. PAPADOPOULOS NG, ALAMANOS Y, VOULGARI PV, EPAGELIS EK, TSIFETAKI N, DROSOS AA: Does cigarette smoking influence disease expression, activity and severity in early rheumatoid arthritis patients? *Clin Exp Rheumatol* 2005; 23: 861-6.

31. WOLFE F: The effect of smoking on clinical, laboratory, and radiographic status in rheumatoid arthritis. *J Rheumatol* 2000; 27: 630-7.

32. MATTEY DL, BROWNFIELD A, DAWES PT: Relationship between pack-year history of smoking and response to tumor necrosis factor antagonists in patients with rheumatoid arthritis. *J Rheumatol* 2009; 36: 1180-7.

33. OEI HB, HOOKER RS, CIPHER DJ, REIMOLD A: High rates of stopping or switching biological medications in veterans with rheumatoid arthritis. *Clin Exp Rheumatol* 2009; 27: 926-34.

34. KIM SK, PARK SH, SHIN IH, CHOE JY: Anti-cyclic citrullinated peptide antibody, smoking, alcohol consumption, and disease duration as risk factors for extraarticular manifestations in Korean patients with rheumatoid arthritis. *J Rheumatol* 2008; 35: 995-1001.

35. NYHÄLL-WÅHLIN BM, PETERSSON IF, NILSSON JA, JACOBSSON LT, TURESSON C, BARFOT STUDY GROUP: High disease activity disability burden and smoking predict severe extra-articular manifestations in early rheumatoid arthritis. *Rheumatol*ogy (Oxford) 2009; 48: 416-20.

36. GOCHUICO BR, AVILA NA, CHOW CK *et al.*: Progressive preclinical interstitial lung disease in rheumatoid arthritis. *Arch Intern Med* 2008; 168: 159-66.

37. SOKKA T, TOLOZA S, CUTOLO M *et al.*, QUEST-RA GROUP: Women, men, and rheumatoid arthritis: analyses of disease activity, disease characteristics, and treatments in the QUEST-RA study. *Arthritis Res Ther* 2009; 11: R7.

38. SOKKA T, KAUTIAINEN H, PINCUS T *et al.*: Disparities in rheumatoid arthritis disease activity according to gross domestic product in 25 countries in the QUEST-RA database. *Ann Rheum Dis* 2009; 68: 1666-72.

39. HARRISON BJ, SILMAN AJ, WILES NJ, SCOTT DG, SYMMONS DP: The association of cigarette smoking with disease outcome in patients with early inflammatory polyarthritis. *Arthritis Rheum* 2001; 44: 323-30.

40. BRAGE S, BJERKEDAL T: Musculoskeletal pain and smoking in Norway. *J Epidemiol Community Health* 1996; 50: 166-9.

41. ERIKSEN WB, BRAGE S, BRUUSGAARD D: Does smoking aggravate musculoskeletal pain? *Scand J Rheumatol* 1997; 26: 49-54.

42. JOHN U, HANKE M, MEYER C, VOLZKE H, BAUMEISTER SE, ALTE D: Tobacco smoking in relation to pain in a national general population survey. *Prev Med* 2006; 43: 477-81.

43. PALMER KT, SYDDALL H, COOPER C, COGGON D: Smoking and musculoskeletal disorders: findings from a British national survey. *Ann Rheum Dis* 2003; 62: 33-6.

44. JAMNER LD, GIRDLER SS, SHAPIRO D, JARVIK ME: Pain inhibition, nicotine, and gender. *Exp Clin Psychopharmacol* 1998; 6: 96-106.

45. LINDBLAD SS, MYDEL P, JONSSON M, SENIOR RM, TARKOWSKI A, BOKAREWA M: Smoking and nicotine exposure delay development of collagen-induced arthritis in mice. *Arthritis Res Ther* 2009; 11: R88.

46. NARANJO A, SOKKA T, DESCALZO MA *et al.*: Cardiovascular disease in patients with rheumatoid arthritis: results from the QUEST-RA study. *Arthritis Res Ther* 2008; 10: R30.

47. KREMERS HM, CROWSON CS, THERNEAU TM, ROGER VL, GABRIEL SE: High ten-year risk of cardiovascular disease in newly diagnosed rheumatoid arthritis patients: a population-based cohort study. *Arthritis Rheum* 2008; 58: 2268-74.