Relationship Between Smoking and Patient-reported Measures of Disease Outcome in Ankylosing Spondylitis

DEREK L. MATTEY, SARAH R. DAWSON, EMMA L. HEALEY, and JONATHAN C. PACKHAM

ABSTRACT. ***Objective.*** To investigate the relationship between smoking and disease activity, pain, function, and quality of life in patients with ankylosing spondylitis (AS).

Methods. Patients with AS (n = 612) from areas across the United Kingdom took part in a cross-sectional postal survey. Patient-reported outcome measures including the Bath AS Disease Activity Index, the Bath AS Functional Index (BASFI), a numerical rating scale (NRS) of pain, the AS quality of life questionnaire (ASQoL), and the evaluation of AS quality of life measures (EASi-QoL) were analyzed in terms of smoking status and relationship with pack-year history. The influence of potential confounding factors [age, sex, disease duration, and social deprivation (Townsend Index)] were tested in multivariate logistic regression analyses.

Results. Median scores of BASFI, pain NRS, ASQoL, and the 4 EASi-QoL domains were all higher in the group that had ever smoked compared to those who had never smoked ($p < 0.0001$, $p = 0.04$, $p = 0.003$, $p < 0.02$, respectively). In stepwise multivariate logistic regression analyses, high disease activity and more severe pain were associated primarily with current smoking, disease duration, and Townsend Index score, while decreased function and poor quality of life measures were associated more closely with increasing pack-year history, disease duration, and Townsend Index score. These associations were independent of age and sex.

Conclusion. Smoking has a dose-dependent relationship with measures of disease severity in AS. The association with increased disease activity, decreased function, and poor quality of life in smokers was independent of age, sex, deprivation level, and disease duration. (First Release Oct 1 2011; J Rheumatol 2011;38:2608–15; doi:10.3899/jrheum.110641)

Key Indexing Terms:
ANKYLOSING SPONDYLITIS TOBACCO DISEASE ACTIVITY
QUALITY OF LIFE OUTCOMES

Ankylosing spondylitis (AS) is a condition affecting 0.1%–2% of the population, with the typical age of onset being between 15 and 35 years[1]. The condition involves inflammation of the joints, particularly the sacroiliac joints, causing pain and stiffness. Extraarticular features such as inflammatory bowel disease, acute anterior uveitis, apical lung fibrosis, and cardiac pathology are also associated[2]. Several factors that have been shown to influence the severity of AS and the effect it has on quality of life include age of onset, presence of comorbid conditions, involvement of peripheral joints, current and past physical activity at work, frequency of back exercise, and smoking[3,4,5,6,7,8,9,10,11,12].

Many studies have examined the influence of smoking on the severity of rheumatoid arthritis (RA)[13,14,15,16,17,18,19]. However, relatively few studies have focused on AS and fewer still have specifically looked at the effect that smoking has on disease activity and the quality of life of patients with AS. The studies conducted on patients with AS report varying results, but the majority of studies report smoking to be associated with higher disease activity, worse functional ability, and reduced quality of life[5,6,7,8,9,10,11,12].

Studies of the effect of smoking on disease activity in AS have been small and have produced conflicting data. Kaan and Ferda[6] looked at the effect of smoking on AS disease activity and found that smokers had significantly higher Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) scores than nonsmokers. Similarly, Reed, *et al*[10] found that current but not former smokers had significantly higher BASDAI results. However, they found no relationship between

From the Staffordshire Rheumatology Centre, University Hospital of North Staffordshire, the Institute of Science and Technology in Medicine, Keele University Medical School, and the Arthritis Research UK Primary Care Centre, Keele University, Staffordshire, England.

Supported by the Haywood Rheumatism Research and Development Foundation and an unrestricted educational grant from Wyeth UK (Dr. Packham).

D.L. Mattey, PhD, Staffordshire Rheumatology Centre, University Hospital of North Staffordshire, and Institute of Science and Technology in Medicine, Keele University; S.R. Dawson, MBChB, Keele University Medical School; E.L. Healey, PhD, Arthritis Research UK Primary Care Centre, Keele University; J.C. Packham, DM, Staffordshire Rheumatology Centre, University Hospital of North Staffordshire, Arthritis Research UK Primary Care Centre, Keele University.

Address correspondence to Dr. D.L. Mattey, Staffordshire Rheumatology Centre, Haywood Hospital, High Lane, Burslem, Stoke-on-Trent, Staffordshire, England ST6 7AG. E-mail: d.l.mattey@keele.ac.uk

Accepted for publication July 21, 2011.

cumulative exposure (pack-years) and disease activity scores. Dincer, *et al*[20] found no difference in disease activity between smoking and nonsmoking patients with AS, although that study included only 36 patients.

Several studies have reported that smoking has a negative effect on functional ability in AS[5,6,7,8,9,10]. Smoking has also been associated with more severe radiographic damage in AS[7,11]. There has been less research on the effect of smoking on quality of life of patients with AS[10,12,20]. Reed, *et al*[10] found that current smokers with AS had decreased overall well-being, and scored significantly worse on the AS quality of life questionnaire (ASQoL) assessment. However, no relationship between cumulative exposure and quality of life was found. Dincer, *et al*[20] found that patients with higher levels of disease activity and increased functional disability had a generally poorer quality of life, but there was no association between poorer quality of life and smoking. This finding may be due to the small number of patients or the use of the Medical Outcomes Study Short-Form 36 as a measure of quality of life; it is not AS-specific.

Although few studies have looked directly at quality of life scores, it may be inferred from the results of smoking on functionality and disease activity that quality of life would be reduced in smokers. The current study was carried out on a large population of patients with AS from 10 secondary care centers across the UK; patients were primarily recruited to evaluate a new AS-specific quality of life measure (Evaluation of AS Quality of Life, or EASi-QoL)[21]. This population provided us with the opportunity to carry out the largest study to date on the association of smoking with disease activity, function, pain, and quality of life in AS.

MATERIALS AND METHODS

Between April and July 2007, 1000 patients with AS from 10 secondary care rheumatology centers across the UK (Abergavenny, Bristol, Cambridge, Cannock, Glasgow, Kent, Lancaster, Newcastle-upon-Tyne, Stoke-on-Trent, Torbay) were invited by their consultant rheumatologist to take part in a postal survey consisting of a questionnaire that incorporated both generic and disease-specific patient-reported outcome measures (PROM). The centers were specifically chosen to encompass areas of differing socioeconomic status and geographic populations. Eight of the centers were situated across England, 1 was located in Wales and 1 in Scotland; there were about equal numbers of participants invited from each center.

The North Staffordshire Local Research Ethics Committee and the 10 site-specific National Health Service trusts approved the multicenter cross-sectional study. The main aim of our study was to evaluate EASi-QoL[21]. Three surveys were carried out: at baseline, 2 weeks, and 6 months. Data collected from the baseline survey are reported in our study.

Patients invited to take part in the survey were over 18 years of age, had AS according to the modified New York criteria (1984)[22], and provided written informed consent according to the Declaration of Helsinki. Those with the inability to comprehend English and those with learning difficulties were excluded from the study.

Data collection. Patients eligible to participate were mailed the questionnaire, which they completed and returned in a prepaid envelope. Those who chose not to participate were asked to return the questionnaire uncompleted. Those who had not responded were sent a postcard reminder at 2 weeks and another questionnaire at 4 weeks.

Characteristics obtained from the questionnaire included age, sex, disease duration, and smoking history. Deprivation level was assessed using Townsend Index scores[23], which are based on local area statistics data from the 2001 UK census on the following 4 variables: unemployment, car ownership, home ownership, and overcrowding. The higher the Townsend score, the more deprived and disadvantaged the area is thought to be.

Specific information on smoking included smoking status, smoking duration, average number of cigarettes smoked per day, and age at smoking cessation. Smoking status categorized participants into current smokers, past smokers, and those who had never smoked. In some analyses, patients were grouped into those who had ever smoked (current + past). Pack-years were also calculated (1 pack-year = 20 cigarettes/day for 1 year). Information on pack-years was available on 267/298 (89.6%) smokers. The effects of smoking intensity over time were assessed by categorizing participants according to pack-year history as in previous studies in RA[24,25]; category 1 = 0 pack-years, category 2 = 1–15, category 3 = 16–30, and category 4 = > 30.

Validated, disease-specific PROM were used to assess disease activity (BASDAI), function (Bath AS Functional Index, BASFI), quality of life (ASQoL and EASi-QoL), and pain. The BASDAI is based on 6 questions related to fatigue, spinal pain, peripheral arthritis, enthesitis, and morning stiffness (both severity and duration). The BASFI is a set of 10 questions that consider activities related to functional anatomy and the patient's ability to cope with everyday life. A 10-cm visual analog scale is used to answer questions on the BASDAI and BASFI. Both measures are scored between 0 and 10, with higher values indicating worse disease activity or function. The ASQoL is made up of 18 questions, each with a "yes" or "no" answer[26]. The questions are centered on AS-specific quality of life and so include aspects such as mood, ability to do daily activities, pain, and mobility. The overall score is calculated by adding together the number of "yes" responses. The EASi-QoL, which consists of 4 domains [physical function (PF), disease activity (DA), emotional well-being (EW), and social participation (SP)], also assesses AS-specific quality of life[21]. Instead of a yes/no answering system, a multiple choice answering system is used; there are 5 options ranging from "not limited at all" to "totally limited." Pain was assessed using a 10-cm numerical rating scale (NRS; 0 = no pain, 10 = most severe pain).

Statistical analysis. Data from the completed and returned questionnaires were entered into an SPSS database. All the data were tested for normality and the appropriate parametric or nonparametric tests were selected for analysis. The frequency of smoking in male and female patients was compared using Fisher's exact test. Since the data were nonparametric, the Kruskal-Wallis test was used for comparison of disease measures between groups. To compare disease measures according to pack-year categories, the Jonckheere-Terpstra test for trend was used. Among smokers, Spearman's correlation was used to investigate the relationship between pack-years and disease measures.

To allow further analysis of the data by multivariate logistic regression, the variables were sorted into the following categories: BASDAI (high or low disease activity), BASFI (poor or good function), pain (high or low), according to cutoffs in accord with national guidelines[27]. Participants scoring ≥ 4 on BASDAI, BASFI, and pain NRS were classified as having high disease activity, poor function, and high pain, respectively. In the absence of recognized cutoffs for categorization of ASQoL or EASi-QoL scores, the median level was used as the cutoff for good and poor quality of life measures. Thus patients with an ASQoL score ≥ 7, and those with an EASi-QoL DA score ≥ 8, PF score ≥ 7, EW ≥ 5, or SP ≥ 6 were classed as having a poor quality of life. Forward stepwise analysis was used to determine the variables most strongly associated with disease measures.

Statistical analysis was carried out using version 15 of SPSS for Windows (SPSS, Chicago, IL, USA), or Number Cruncher Statistical System for Windows (NCSS, 2000, NCSS Statistical Software, Kaysville, UT, USA). For all statistical tests, p values < 0.05 were considered statistically significant.

RESULTS

Of the 1000 participants invited, 612 completed the question-

naire. After taking into account deaths and changes of address (n = 44), the adjusted response rate was 64%. Of these, 606 provided information on smoking history. The characteristics of the patients are shown in Table 1.

A history of smoking (past and current) was found in 49.2% of patients, with 21.0% currently smoking. The vast majority of smokers (93.3%) started smoking before disease diagnosis. There was no significant difference in age or disease duration between nonsmokers and current smokers (49.2 vs 49.2 yrs and 16.5 vs 14.6 yrs, respectively), but past smokers were significantly older and had a longer disease duration (54.8 and 20.6 yrs, respectively) than nonsmokers or current smokers ($p < 0.0001$). Patients with a history of smoking were more likely to be men than women, although the difference did not achieve significance (51.4% vs 44.0%; OR 1.34, 95% CI 0.93–1.95, $p = 0.1$). Male smokers had smoked more pack-years than female smokers (23.1 vs 17.1; $p = 0.04$), and current smokers were also more likely to be male than female (23.3% vs 14.9%; 95% CI 1.05–2.89, $p = 0.02$). Current smokers had a greater pack-year history than past smokers (23.0 vs 20.7; $p = 0.04$).

Table 1. Characteristics of patients with ankylosing spondylitis. Values are the median (interquartile range) unless otherwise indicated.

Variable	
Age, yrs	51.0 (42–60)
Disease duration, yrs	15.0 (8–25)
Men, %	72.3
Never smoked, n (%)	308/606 (50.8)
Past smoker, n (%)	171/606 (28.2)
Current smoker, n (%)	127/606 (21.0)
Ever smoke, n (%)	298/606 (49.2)
Disease activity (BASDAI; 0–10)	4.0 (2.0–7.0)
Function (BASFI; 0–10)	4.0 (2.0–7.0)
Pain (NRS; 0–10)	5.0 (3.0–7.0)
Quality of life	
ASQoL (0–18)	7.0 (2.1–13.0)
EASi-QoL	
Physical function (0–24)	7.0 (4.0–13.0)
Disease activity (0–16)	8.0 (4.0–11.0)
Emotional well-being (0–20)	5.0 (2.0–10.0)
Social participation (0–20)	6.0 (3.0–11.0)

BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; BASFI: Bath AS Functional Index; NRS: numerical rating scale; ASQoL: AS Quality of Life; EASi-QoL: Evaluation of AS Quality of Life.

Comparison of disease measures in smokers and nonsmokers. The median scores (interquartile range) for the BASDAI, BASFI, pain NRS, ASQoL, and the 4 EASi-QoL domains for all participants, stratified by smoking status, are shown in Table 2.

The scores for BASFI, pain NRS, ASQoL, and the 4 EASi-QoL domains (PF, SP, EW, and DA) were all higher in the group that had ever smoked compared to those who had never smoked, and all showed statistical significance ($p < 0.0001$, $p = 0.04$, $p = 0.003$, $p = 0.0007$, $p = 0.002$, $p = 0.02$, and $p = 0.01$, respectively). The BASDAI score was also higher in those who had ever smoked compared to those who had never smoked, but it did not reach significance ($p = 0.07$).

When examined by smoking status, there were significant differences between the groups for each disease measure (Table 2). However, there were differences in the relationship between smoking status and different outcome measures. For BASDAI and pain NRS, there was no significant difference between those who had never smoked and past smokers, and only current smokers showed significantly higher scores than those had never smoked ($p < 0.03$). In contrast, the scores for the BASFI, ASQoL, and EASi-QoL PF and SP domains were not statistically different between past and current smokers, and each was significantly higher than those for the nonsmokers. In the case of the EASi-Qol DA and EW domains, only current smokers had higher scores than those who had never smoked ($p < 0.02$).

Quantitative relationship between smoking and disease measures. Among smokers, significant correlations were found

Table 2. Relationship between smoking status and disease measures. Values are median (interquartile range).

	Smoking Status					
	Never, n = 308	Past, n = 171	Current, n = 127	p*	Ever, n = 298	p**
BASDAI	4.0 (2.0–6.0)	4.0 (2.0–7.0)	5.0 (3.0–7.0)	0.10	5.0 (3.0–7.0)	0.07
BASFI	4.0 (2.0–6.0)	5.0 (2.0–8.0)	5.0 (3.0–8.0)	< 0.0001	5.0 (3.0–8.0)	< 0.0001
Pain NRS	4.0 (2.0–7.0)	5.0 (3.0–7.0)	5.0 (3.0–7.0)	0.046	5.0 (3.0–7.0)	0.041
ASQoL	6.0 (2.0–12.0)	8.0 (3.0–12.5)	10.0 (3.0–14.0)	0.005	9.0 (3.0–13.0)	0.003
EASi-QoL						
PF	7.0 (3.0–11.0)	9.0 (4.0–14.2)	8.0 (4.0–14.5)	0.003	9.0 (4.0–14.0)	0.0007
DA	7.0 (4.0–11.0)	8.0 (5.0–11.0)	9.0 (5.0–12.0)	0.007	8.0 (5.0–12.0)	0.002
EW	4.0 (2.0–9.0)	5.0 (2.0–9.0)	6.0 (2.0–12.0)	0.048	6.0 (2.0–10.0)	0.022
SP	5.0 (2.0–10.0)	8.0 (3.0–11.0)	7.0 (3.0–13.0)	0.013	7.0 (3.0–12.0)	0.010

* Kruskal-Wallis test; ** ever vs never smoked. BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; BASFI: Bath AS Functional Index; NRS: numerical rating scale; ASQoL: Ankylosing Spondylitis Quality of Life; EASi-QoL: Evaluation of AS Quality of Life; PF: physical function; DA: disease activity; EW: emotional well-being; SP: social participation.

between pack years and BASDAI (r = 0.21, p = 0.006), BASFI (r = 0.19, p = 0.002), pain NRS (r = 0.20, p = 0.001), ASQoL (r = 0.22, p = 0.0004), and EASiQoL domains: PF (r = 0.20, p = 0.001), SP (r = 0.18, p = 0.003), EW (r = 0.19, p = 0.001), and DA (r = 0.21, p = 0.0005), after controlling for age, sex, and disease duration.

Analysis of the relationship between pack-year categories and disease measures revealed highly significant trends of higher disease scores with increasing pack-year history (Table 3). However, it is noteworthy that there was no significant difference in any of the disease measures between patients who had never smoked and those who had smoked up to 15 pack-years.

Smoking is associated with disease severity independent of social deprivation. We have recently reported that greater social deprivation is significantly associated with greater disease activity and poorer function in patients with AS[28]. Since social deprivation is associated with increased levels of smoking[29], we were interested to see whether the association of smoking with disease severity was independent of this factor.

In an analysis of variables associated with high disease activity (BASDAI > 4), we found that current smoking was associated independently of age, sex, disease duration, and Townsend Index score. In a forward stepwise model that included current smoking and pack-year category, only current smoking was significantly associated (Table 4). A similar independent association with current smoking but not pack-year category was found for more severe pain. However, in the case of the BASFI, the strongest association with poor function was an increasing pack-year history rather than current smoking. This again was independent of the deprivation index and demographic factors. A similar association with pack-year history rather than current smoking was found for each of the EASi-QoL domains, although current smoking was more strongly associated with the ASQoL (Table 5).

DISCUSSION

This is the largest study conducted to date examining the2quantitative effect of smoking in patients with AS. The results provide substantial evidence of a negative effect of smoking on disease activity, pain, function, and quality of life, which is consistent with the findings from previous, smaller studies that have been conducted in AS populations[5,6,7,8,9,10,11,12]. For the first time, we also report a dose-dependent relationship between smoking and outcome measures in patients with AS, and show that this is independent of socioeconomic status. These findings suggest that smoking is unlikely to be just a surrogate of another lifestyle factor or some other health behavior, a suggestion that has been made in previous studies[5,9,10].

The observed dose-dependent relationship could be due to the cumulative effects of smoking, such as increased levels of inflammation and/or a direct effect on the musculoskeletal system. Another possibility is that smoking may interfere with certain treatments used in AS. Recent studies involving patients with RA have shown that smoking is associated with an increased lack of response to treatment with tumor necrosis factor (TNF) antagonists[24,25,30,31,32]. Although anti-TNF is also used in AS, relatively few patients in this cohort were treated in this way (11.6%), so it is unlikely that this could explain the effect of smoking in this group. However, it has been shown that smoking also adversely affects the response to methotrexate in RA[32,33], and that smokers with RA have a greater need for disease-modifying antirheumatic drugs and feel worse than nonsmokers, without having more joint damage[34]. Thus, there may be a more general effect of smoking on therapies that are used in the inflammatory arthritides.

We found that BASDAI scores were higher in smokers than in those who had never smoked. Although an increasing BASDAI score was seen with increasing pack-year history, multivariate analysis suggested that the strongest association was with current smoking, which is consistent with a previous study[10]. Similarly, an increased level of pain was seen in current smokers compared to past smokers or those who had never smoked, and multivariate analysis suggested that pain

Table 3. Association between pack-year categories and disease measures. Values are median (interquartile range).

	Pack-Years				
	0, n = 308	1-15, n = 113	16-30, n = 92	> 30 n = 62	p (trend)*
BASDAI	4.0 (2.0–6.0)	4.0 (2.0–7.0)	5.0 (3.0–6.0)	6.0 (4.0–8.0)	0.01
BASFI	4.0 (2.0–6.0)	5.0 (2.0–7.0)	5.0 (3.0–8.0)	7.0 (4.0–9.0)	< 0.0001
Pain NRS	4.0 (2.0–7.0)	5.0 (2.2–7.0)	5.0 (3.0–7.0)	6.0 (4.0–8.0)	0.008
ASQoL	6.0 (2.0–12.0)	7.0 (2.0–12.0)	9.2 (3.0–13.0)	12.0 (5.0–15.0)	0.001
EASi-QoL					
PF	7.0 (3.0–11.0)	7.0 (4.0–12.5)	8.0 (4.0–15.0)	13.0 (6.0–17.5)	< 0.0001
DA	7.0 (4.0–11.0)	7.0 (4.2–11.0)	8.0 (5.0–11.7)	10.0 (8.0–13.0)	< 0.0001
EW	4.0 (2.0–9.0)	5.0 (2.0–9.0)	6.0 (2.0–10.5)	9.0 (2.7–14.0)	< 0.0001
SP	5.0 (2.0–10.0)	6.0 (3.0–11.0)	7.0 (3.0–12.0)	9.5 (5.0–15.0)	< 0.0001

* Jonckheere-Terpstra test. BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; BASFI: Bath AS Functional Index; NRS: numerical rating scale; ASQoL: AS Quality of Life; EASi-QoL: Evaluation of AS Quality of Life. PF: physical function; DA: disease activity; EW: emotional well-being; SP: social participation.

Table 4. Multivariate stepwise logistic regression analyses of variables most strongly associated with more severe disease activity, function, and pain. All models contained as independent variables age, male sex, disease duration, Townsend Index score, current smoking, and pack-year category. All variables were included simultaneously in the models. Only variables significant after stepwise analysis are shown. For each of the 3 disease measures, a score ≥ 4 is considered high and a score < 4 low. The analysis compares the high and low groups.

Variable	Regression Coefficient (SE)	OR (95% CI)	p
BASDAI			
Townsend Index, per unit	0.134 (0.037)	1.14 (1.06–1.24)	0.0003
Disease duration, per year	0.033 (0.009)	1.03 (1.02–1.05)	0.0002
Current smoker	0.605 (0.248)	1.83 (1.13–2.98)	0.015
BASFI			
Disease duration, per year	0.042 (0.009)	1.04 (1.02–1.06)	< 0.0001
Townsend Index, per unit	0.159 (0.037)	1.17 (1.09–1.26)	< 0.0001
Pack-year category (per category)	0.330 (0.097)	1.39 (1.15–1.68)	0.0007
Male	–0.423 (0.210)	0.65 (0.43–0.99)	0.044
Pain NRS			
Disease duration, per year	0.032 (0.009)	1.03 (1.01–1.05)	0.0002
Townsend Index, per unit	0.102 (0.036)	1.11 (1.03–1.19)	0.005
Current smoker	0.694 (0.249)	2.00 (1.23–3.27)	0.005

BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; BASFI: Bath AS Functional Index; NRS: numerical rating scale.

Table 5. Multivariate stepwise logistic regression analyses of variables most strongly associated with poor quality of life measures. All models contained age, male sex, disease duration, Townsend Index, current smoking, and pack-year category as independent variables. All variables were included simultaneously in the models. Only variables significant after stepwise analysis are shown.

Variables	Regression Coefficient (SE)	OR (95% CI)	p
ASQoL (≥ 7 high, < 7 low)			
Townsend Index (per unit)	0.213 (0.038)	1.23 (1.14–1.34)	< 0.0001
Disease duration (per year)	0.033 (0.008)	1.03 (1.02–1.05)	0.0001
Current smoker	0.697 (0.242)	2.00 (1.25–3.22)	0.004
Male	–0.588 (0.210)	0.56 (0.37–0.84)	0.005
EASi-QoL			
PF (≥ 7 high, < 7 low)			
Townsend Index (per unit)	0.236 (0.040)	1.26 (1.17–1.37)	< 0.0001
Disease duration (per year)	0.034 (0.010)	1.03 (1.01–1.05)	0.0006
Pack-year category (per category)	0.280 (0.098)	1.32 (1.09–1.60)	0.004
Male	–0.497 (0.214)	0.61 (0.40–0.93)	0.02
DA (≥ 8 high, < 8 low)			
Townsend Index (per unit)	0.151 (0.035)	1.16 (1.08–1.24)	< 0.0001
Pack-year category (per category)	0.304 (0.091)	1.35 (1.13–1.62)	0.008
Disease duration (per year)	0.021 (0.008)	1.02 (1.01–1.04)	0.009
EW (≥ 5 high, < 5 low)			
Townsend Index (per unit)	0.163 (0.035)	1.18 (1.10–1.26)	< 0.0001
Pack-year category (per category)	0.214 (0.090)	1.24 (1.04–1.48)	0.02
SP (≥ 6 high, < 6 low)			
Townsend Index (per unit)	0.189 (0.036)	1.21 (1.13–1.30)	< 0.0001
Disease duration (per year)	0.026 (0.008)	1.02 (1.01–1.04)	0.002
Pack-year category (per category)	0.252 (0.092)	1.28 (1.07–1.54)	0.006

ASQoL: Ankylosing Spondylitis Quality of Life; EASi-QoL: Evaluation of AS Quality of Life; PF: physical function; DA: disease activity; EW: emotional well-being; SP: social participation.

was primarily associated with current smoking rather than pack-year history. However, it is difficult to distinguish between the effect of current smoking and the cumulative effects of longterm smoking, especially since current smokers had a greater number of pack-years than past smokers. Further, the association with pack-years is not straightfor-

ward, since patients with up to 15 pack-years appeared to be no worse in terms of pain or disease activity than patients who had never smoked. However, further increases in pack-years, especially beyond 30 pack-years, were associated with significantly higher levels of pain and disease activity.

This is, to our knowledge, the first study to examine the relationship between smoking and pain in patients with AS, although previous studies have reported greater levels of pain in smokers with other musculoskeletal disorders[35,36,37,38]. It has been postulated that this relationship might arise from effects on neurological processing of sensory information, or by damage to musculoskeletal tissues through vasoconstriction, hypoxia, etc.[38]. Alternatively, smokers may demonstrate neuropsychological or sociocultural differences that are reflected by differences in personality or illness behavior; these may include a lower threshold for reporting pain and disability[38].

Apart from 1 small study[20], our finding that smoking was associated with worse functional ability is consistent with other studies[5,6,7,8,9,10]. However, we have shown that there is a dose-dependent effect of smoking, and that this is independent of age, sex, disease duration, and social deprivation. It is unclear why 2 other studies found an association with current smoking but failed to find a relationship with pack-years[9,10]. However, these were smaller studies than ours, so possible associations may have failed to reach significance. Further, no information was provided on the pack-year history in these patient cohorts, so it is possible that differences may be explained by differences in the intensity levels of smoking in different AS populations.

There are many possible mechanisms by which smoking may result in decreased function. An increase in comorbidity and a reduction in physical activity in smokers are likely factors. Smoking may also add to the already poor lung function of these patients, which further decreases their functional ability. Kaan and Ferda[6] found that smokers with AS had reduced vital lung capacity compared to nonsmokers, but were unsure whether this was due to parenchymal damage or to additional fusion of joints in the thorax, causing restriction. A further possibility is that smoking causes increased inflammation in joints, leading to reduced mobility. Two previous studies have found that smokers had worse results for Schober's test, finger-to-floor distance, and occiput-wall distance[6,7], findings that suggest smokers have a reduced range of motion that could lead to reduced function.

Quality of life was also shown to be significantly worse in those who had ever smoked compared to those who had never smoked, as measured by ASQoL and all 4 domains of EASi-QoL. In the latter case, pack-year history appeared to be more strongly associated with these measures than current smoking. This is possibly related to increased disease activity and reduced functioning of patients with AS who smoke. Apart from an effect on disease activity, smoking is likely to have a cumulative effect on cardiac and pulmonary systems, which would lead to lower scores on ASQoL and EASi-QoL. Smoking is also known to be a risk factor for peripheral vascular disease and osteoporosis, which may affect a patient's quality of life.

The increasing severity of outcome measures with increasing pack-year history suggests that cessation of smoking in patients with AS may be beneficial. However, the benefit derived may depend on the amount of damage already accumulated. This is likely to depend on a number of factors, including length of time smoked, number of cigarettes, duration of disease, and age when cessation occurs. Stopping smoking may reduce the chance of further harmful effects, but it is unclear whether accumulated damage can be reversed and whether benefits of smoking cessation are dependent on the length of the cessation. In a cross-sectional study such as ours, it was not possible to directly address the effect of smoking cessation on disease measures, and longterm, prospective studies monitoring the progress of smokers who had quit would be needed to address this question.

Our study has various strengths, including a large sample size, use of multiple centers across the UK, and the use of validated AS-specific outcome measures, which make the results more reliable than some studies conducted to date. However, there are also several limitations. First, information was not obtained on patients failing to respond to the questionnaire, so it was not possible to determine whether there were differences in smoking status or socioeconomic background between participants and nonparticipants. However, the centers chosen were in regions that provided a diverse socioeconomic and geographic population by covering both urban and rural areas across the UK. We therefore believe that our results represent those from a typical population of patients with established AS.

Another possible limitation may relate to the use of PROM, which are subjective measures of disease outcome and may therefore be open to misinterpretation. Third, the use of pack-years as a quantitative measure of smoking may be subject to some inaccuracy due to recall bias or difficulty in accounting for variation in the number of cigarettes smoked by participants over their lifetime. However, by categorizing smokers into 3 broad groups according to pack-year history, we believe that, in a large study such as this, it is possible to get a reasonable estimate of the association with different levels of smoking. Finally, the data were collected at baseline in a cross-sectional study. Cross-sectional studies, although valuable when looking at associations, cannot assess causation. It is possible that patients may have started smoking or smoked more because of more severe disease (reverse causality). However, the vast majority of patients (> 93%) had started smoking long before development of disease (median 15 years), and 57% of smokers had stopped by the time of the study. Further, in those who had stopped smoking, there were still significant dose-dependent associations between previous pack-year history and current outcome measures (data not shown).

Overall, the results of our study strongly support smoking cessation in patients with AS and advocate that more should be done to encourage these patients to quit, or at the very least to attempt to reduce the number of cigarettes they smoke. This could be achieved by promoting specialist smoking cessation clinics and providing more information during clinic appointments about the negative effects of smoking.

ACKNOWLEDGMENT

The authors thank all patients who participated in our study, and consultant rheumatologists, physiotherapists, and research nurses in the EASi-QoL study group: Dr. M. Bukhari (Royal Lancaster Infirmary), Dr. P. Creamer (Southmead Hospital), Prof. H. Gaston (Addenbrookes Hospital), Dr. L. Kay (Freeman Hospital), Dr. S. Linton (Nevill Hall Hospital), Dr. K. McKay (Torbay Hospital), Dr. D. Mulherin (Cannock Chase Hospital), Prof. R. Sturrock (Glasgow Royal Infirmary), and Dr. T. Withrington and Liz van Rossen (Kent and Canterbury Hospital).

REFERENCES

1. McVeigh CM, Cairns AP. Diagnosis and management of ankylosing spondylitis. BMJ 2006;333:581-5.
2. Khan MA. Clinical features of ankylosing spondylitis. In: Hochberg MC, Silman AJ, Smolen JS, Weinblatt MH, editors. Rheumatology. 3rd ed. London: Mosby; 2003:1161-81.
3. Gran JT, Skomsvoll JF. The outcome of ankylosing spondylitis: a study of 100 patients. Br J Rheumatol 1997;36:766-71.
4. Guillemin F, Briancon S, Pourel J, Gaucher A. Long-term disability and prolonged sick leave as outcome measures in ankylosing spondylitis. Possible predictive factors. Arthritis Rheum 1990;33:1001-6.
5. Ward MM. Predictors of the progression of functional disability in patients with ankylosing spondylitis. J Rheumatol 2002;29:1420-5.
6. Kaan U, Ferda O. Evaluation of clinical activity and functional impairment in smokers with ankylosing spondylitis. Rheumatol Int 2005;25:357-60.
7. Averns HL, Oxtoby J, Taylor HG, Jones PW, Dziedzic K, Dawes PT. Smoking and outcome in ankylosing spondylitis. Scand J Rheumatol 1996;25:138-42.
8. Doran MF, Brophy S, Mackay K, Taylor G, Calin A. Predictors of longterm outcome in ankylosing spondylitis. J Rheumatol 2003;30:316-20.
9. Ward MM, Weisman MH, Davis JC, Reveille JD. Risk factors for functional limitations in patients with longstanding ankylosing spondylitis. Arthritis Care Res 2005;53:710-7.
10. Reed MD, Dharmage S, Boers A, Martin BJ, Buchanan RR, Schachna L. Ankylosing spondylitis: an Australian experience. Intern Med J 2008;38:321-7.
11. Ward MM, Hendrey MR, Malley JD, Learch TJ, Davis JC Jr, Reveille JD, et al. Clinical and immunogenetic prognostic factors for radiographic severity in ankylosing spondylitis. Arthritis Care Res 2009;61:859-66.
12. Bodur H, Ataman S, Rezvani A, Bugdayci DS, Cevik R, Birtane M, et al. Quality of life and related variables in patients with ankylosing spondylitis. Qual Life Res 2011;20:543-9.
13. Saag KG, Cerhan JR, Kolluri S, Ohashi K, Hunninghake GW, Schwarz DA. Cigarette smoking and rheumatoid arthritis severity. Ann Rheum Dis 1997;56:463-9.
14. Wolfe F. The effect of smoking on clinical, laboratory and radiographic status in rheumatoid arthritis. J Rheumatol 2000;27:630-7.
15. Masdottir B, Jonsson T, Manfredsdottir V, Vikingsson A, Brekkan A, Valdimarsson H. Smoking, rheumatoid factor isotypes and severity of rheumatoid arthritis. Rheumatology 2000;39:1202-5.
16. Mattey DL, Hutchinson D, Dawes PT, Nixon NB, Clarke S, Fisher J, et al. Smoking and disease severity in rheumatoid arthritis. Association with polymorphism at the gluatathione S- transferase (GST) M1 locus. Arthritis Rheum 2002;46:640-6.
17. Mattey DL, Dawes PT, Fisher J, Brownfield A, Thomson W, Hajeer AH, et al. Nodular disease in rheumatoid arthritis: Association with cigarette smoking and HLA-DRB1/TNF gene interaction. J Rheumatol 2002;29:2313-8.
18. 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.
19. Manfredsdottir VF, Vikingsdottir T, Jonsson T, Geirsson AJ, Kjartansson O, Heimisdottir M, et al. The effect of tobacco smoking and rheumatoid factor positivity on disease activity and joint damage in early rheumatoid arthritis. Rheumatology 2006:45:734-40.
20. Dincer U, Cakar E, Kiralp MZ, Bozkanat E, Kilac H, Dursun H. The pulmonary involvement in rheumatic diseases: Pulmonary effects of ankylosing spondylitis and its impact on functionality and quality of life. Tohoku J Exp Med 2007;212:423-30.
21. Haywood KL, Garratt AM, Jordan KP, Healey EL, Packham JC. Evaluation of Ankylosing Spondylitis Quality of Life (EASi-QoL): Reliability and validity of a new patient-reported outcome measure. J Rheumatol 2010;37:2100-9.
22. Van der Linden S, Valkenburg HA, Cats A. Evaluation of diagnostic criteria for ankylosing spondylitis. Arthritis Rheum 1984;27:361-8.
23. Townsend P, Phillimore P, Beattie A. Health and deprivation: Inequality and the North. London: Croom Helm; 1998.
24. 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.
25. Mattey DL, Dawes PT, Hassell AB, Brownfield A, Packham JC. Effect of psychological distress on continuation of anti-tumor necrosis factor therapy in patients with rheumatoid arthritis. J Rheumatol 2010;37:2021-4.
26. Doward LC, Spoorenberg A, Cook SA, Whalley D, Helliwell PS, Kay LJ, et al. Development of the ASQoL: A quality of life instrument specific to ankylosing spondylitis. Ann Rheum Dis 2003;62:20-6.
27. National Institute for Health and Clinical Excellence. Adalimumab, entanercept and infliximab for ankylosing spondylitis. NICE technology appraisal guidance 143. [Internet. Accessed Aug 30, 2011.] Available from: http://www.nice.org.uk/nicemedia/pdf/TA143Guidance.pdf
28. Healey EL, Haywood KL, Jordan KP, Garratt AM, Packham JC. Disease severity in ankylosing spondylitis: Variation by region and local area deprivation. J Rheumatol 2010;37:633-8.
29. Office for National Statistics. General Lifestyle Survey 2008: Smoking and drinking among adults 2008. London: Office for National Statistics. [Internet. Accessed Sept 20, 2011.] Available from: http://www.ons.gov.uk/ons/publications/re-reference-tables.html?edition=tcm%3A77-49408.
30. Hyrich KL, Watson KD, Silman AJ, Symmons DPM, and The BSR Biologics Register. Predictors of response to anti-TNF-alpha therapy among patients with rheumatoid arthritis: Results from the British Society for Rheumatology Biologics Register. Rheumatology 2006;45:1558-65.
31. Abhishek A, Butt S, Gadsby K, Zhang W, Deighton CM. Anti-TNF-alpha agents are less effective for the treatment of rheumatoid arthritis in current smokers. J Clin Rheumatol 2010;16:15-8.
32. Saevarsdottir S, Wedren S, Seddighzadeh M, Bengtsson C, Wesley A, Lindblad S, et al. Patients with early rheumatoid arthritis who

smoke are less likely to respond to treatment with methotrexate and tumor necrosis factor inhibitors: Observations from the Epidemiological Investigation of Rheumatoid Arthritis and the Swedish Rheumatology Register cohorts. Arthritis Rheum 2011;63:26-6.
33. Saevarsdottir S, Wallin H, Seddighzadeh M, Ernestam S, Geborek P, Peterssson IF, et al. Predictors of response to methotrexate in early DMARD naïve rheumatoid arthritis: results from the initial open-label phase of the SWEFOT trial. Ann Rheum Dis 2011;70:469-75.
34. Westhoff G, Rau R, Zink A. Rheumatoid arthritis patients who smoke have a higher need for DMARDs and feel worse, but they do not have more joint damage than non-smokers of the same serological group. Rheumatology 2008;47:849-54.
35. Amin S, Niu J, Guermazi A, Grigoryan M, Hunter DL, Clancy M, et al. Cigarette smoking and the risk for cartilage loss and knee pain in men with knee osteoarthritis. Ann Rheum Dis 2007;66:18-22.
36. Brage S, Bjerkedal T. Musculoskeletal pain and smoking in Norway. J Epidemiol Community Health 1996;26:49-54.
37. Eriksen WB, Brage S, Bruusgard D. Does smoking aggravate musculoskeletal pain? Scand J Rheumatol 1997;26:49-54.
38. 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.