Five Potentially Modifiable Factors Predict Poor Quality of Life in Ankylosing Spondylitis: Results from the Scotland Registry for Ankylosing Spondylitis

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ABSTRACT. ***Objective.*** A chronic inflammatory condition manifesting in young adulthood, ankylosing spondylitis (AS) affects both physical and emotional quality of life (QOL). To inform future intervention strategies, this study aimed to (1) assess the QOL of patients with AS, and (2) identify potentially modifiable factors associated with reporting poor QOL.

Methods. The Scotland Registry for Ankylosing Spondylitis collects clinical and patient-reported data on clinically diagnosed patients with AS across Scotland. QOL is measured using the ASQoL questionnaire [range: 0 (high) to 18 (poor)]. Potentially modifiable factors associated with reporting poor QOL (score 12–18) were examined using Poisson regression models, adjusted for a variety of demographic characteristics, plus various nonmodifiable factors. Results are given as risk ratios (RR) with 95% CI.

Results. Data were available on 959 patients: 74% male, mean age 52 years (SD 13), median ASQoL 7.0 (interquartile range 2–12). Although many factors were univariately associated with poor QOL, 5 were identified as independent predictors: reporting moderate/severe fatigue (RR 1.60, 95% CI 1.13–2.28), poor physical function [Bath Ankylosing Spondylitis Functional Index (BASFI) ≥ 4: 3.46, 1.76–6.82], chronic widespread pain (CWP; 1.92, 1.33–2.75), high disease activity [Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) ≥ 4: 1.52, 1.09–2.12], and poor spinal mobility [Bath Ankylosing Spondylitis Metrology Index (BASMI) ≥ 4: 1.52, 0.93–2.50]. For these factors, population-attributable risks ranged between 20% (disease activity) and 56% (physical function).

Conclusion. We have identified 5 potentially modifiable factors independently associated with poor QOL. These findings provide evidence that in addition to traditional clinical targets (BASDAI, BASFI, and BASMI), focus on nonspecific symptoms (CWP and fatigue), perhaps with nonpharmacological therapies, may yield important improvements in QOL. (J Rheumatol First Release August 1 2017; doi:10.3899/jrheum.160411)

Key Indexing Terms:
ANKYLOSING SPONDYLITIS SPONDYLOARTHRITIS EPIDEMIOLOGY
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Spondyloarthritis (SpA) is one of several diseases sharing genetic predisposition, clinical features, and symptoms. Ankylosing spondylitis (AS), part of the spectrum of axial SpA, is characterized predominantly by low back pain, stiffness, and sacroiliitis. Prognosis is variable and determined in part by the presence of extraspinal manifestations (psoriasis, uveitis, and inflammatory bowel disease), age at diagnosis, and treatment[1,2].

A subjective concept, quality of life (QOL) can be defined as the effect that a disease has on an individual's "life participation" and is affected by a variety of factors, including the severity of symptoms and a number of contextual factors, including marital status, education level, and employment[3,4,5,6]. Within AS, physical functioning and disease activity have been shown to be associated with both physical and mental aspects of QOL[7]. Although recently developed instruments [e.g., the Assessment of Spondyloarthritis international Society (ASAS) Health Index] have focused primarily on items that identify physical functioning with some emotional and social functioning areas included[8], QOL will, arguably, be greatly influenced by other more subjective areas. Specifically, patients frequently report high levels of pain and fatigue, sleep disturbance[9], depression, and

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anxiety[10]. Additionally, there are demonstrable sex differences in QOL among other rheumatic and musculoskeletal disorders[11,12], and one may expect that women with AS will also report poorer QOL[10].

Despite evidence suggesting that patients with AS exhibit poorer QOL compared with the general population, studies rarely have QOL as the primary outcome of interest. In addition, the lack of largescale studies collecting a wide range of demographic, clinical, and patient-reported information greatly limits the understanding of the disease and its effects on QOL, and the power to control for multiple potential confounders. Many previous studies have used generic QOL measures [e.g., the Medical Outcomes Study Short-form Health Survey (SF-12)[13]], which may not adequately identify the areas that patients with AS find most effective. In contrast, the Ankylosing Spondylitis Quality of Life (ASQoL) questionnaire was developed specifically for use with patients with AS and includes domains such as mobility and the ability to perform daily tasks[14].

Developing effective management strategies is of paramount importance to both patients and clinicians, and identifying the modifiable clinical and patient-reported factors associated with poor QOL should therefore be a primary research focus. Thus, the aims of our study were first, to identify and characterize patients with AS by QOL, and second, to identify potentially modifiable risk factors for poor QOL.

MATERIALS AND METHODS

The Scotland Registry for Ankylosing Spondylitis (SIRAS) is a Scotland-wide disease registry that collects clinical and patient-reported information from patients, aged ≥ 16 years, with a clinical diagnosis of AS. The study protocol is published elsewhere[15]. All patients with a diagnosis of AS seen in secondary care rheumatology departments in Scotland between October 2010 and October 2013 were recruited. Clinical data were collected from medical notes, and patients were sent postal questionnaires. The questionnaire included the ASQoL[14], an 18-item questionnaire that results in a single score between 0 (highest QOL) and 18 (poorest). For analysis, this was dichotomized: all individuals in the highest tertile (poorest QOL) were compared with those reporting moderate/high QOL (lower 2 tertiles).

The questionnaire also collected information on chronic widespread pain (CWP) by body manikins [coded as per the American College of Rheumatology (ACR) 1990 classification criteria for fibromyalgia (FM)[16]] and fatigue (Chalder Fatigue Scale, analyzed as moderate/severe fatigue, score ≥ 4, vs absent/mild fatigue, score 0–3)[17].

Clinical measurements included relevant medical history (extraspinal manifestations, peripheral joint involvement), HLA-B27 status, inflammatory markers, treatment history, and the Bath Ankylosing Spondylitis indices for disease activity (BASDAI)[18], function (BASFI)[19], and metrology (BASMI)[20]. These indices all produce outcome scores that range from 0–10 (least to most severe). Prior to analysis, a dichotomous score was created to indicate either low disease activity (BASDAI < 4) or severe disease activity (BASDAI ≥ 4). This cutoff value was chosen to be consistent with UK guidelines for the use of tumor necrosis factor-α (TNF-α) inhibition, as recommended by the UK National Institute for Health and Clinical Excellence; such therapy will be considered only in the presence of a BASDAI score ≥ 4 and efficacy is judged on the reduction of the score below 4. In the absence of commonly accepted cutoffs for BASFI and BASMI, the same cutoff value was used to retain some comparability across the instruments.

Participant postcodes were used to derive a deprivation score based on area of residence — the Scottish Index of Multiple Deprivation, a composite index consisting of several indicators of deprivation including employment, health, education, crime, and housing[21]. Participants were given a score ranging from 1 (most deprived) to 20 (most affluent), and then divided into quartiles for analysis.

Statistical analysis. An *a priori* distinction was made between nonmodifiable factors (e.g., disease duration) and those potentially amenable to change (e.g., smoking status), or potentially modifiable with therapy (e.g., disease activity).

The association between all variables and QOL was examined using chi-square tests, or chi-square tests for trend, as appropriate. These were then quantified using Poisson regression and results were presented as risk ratios, with 95% CI derived from using robust estimates of standard error[22]. Potentially modifiable factors associated with poor QOL at $p \leq 0.2$ were subsequently offered to a forward stepwise Poisson regression model to determine the group of independent factors that best predicted poor QOL. Variables were entered into the model at $p \leq 0.10$ and excluded (if applicable) at $p \geq 0.15$. The model was also adjusted for any nonmodifiable factors associated with poor QOL at $p \leq 0.2$ to control for potential confounding.

Population-attributable risks were calculated for each of the independent risk factors identified, and the performance of the final model was evaluated using the Pearson goodness-of-fit statistic. In addition, a simple count was made totaling the number of independent risk factors each individual had. The risk of poor QOL, and the average ASQoL score, were then examined for each group.

Finally, a sensitivity analysis was conducted to examine questionnaire nonparticipation. Questionnaire respondents/nonrespondents were compared in terms of demographic and clinical characteristics, and for any variable found to be significantly different between the 2 groups, population weights were computed as the inverse of the sampling fraction. A second multivariable model was then created, weighted by these population weights. Thus, subgroups of the clinical population that were underrepresented in the original sample contributed more to the final analysis.

SIRAS received ethical approval from the North of Scotland Research Ethics Service (ref 09/S0802/7). All statistical analysis was undertaken using STATA (StataCorp LP version 13).

RESULTS

Clinical information was collected on 1868 patients, of whom 51% returned a postal questionnaire. Thus 959 patients were included in our current analysis: 74% male; mean age 52 years (SD 13). Pain was common in this population, with almost all participants reporting either moderate (70%) or severe (15%) pain/discomfort. The distribution of ASQoL scores is shown in Figure 1; median 7 (interquartile range 2–12). The top tertile (i.e., the cutoff for poor QOL) equated to a score of ≥ 12.

Nonmodifiable factors. Of the nonmodifiable characteristics assessed, many demonstrated an association with QOL (Table 1). Women were more likely to report poor QOL (risk ratio 1.32, 95% CI 1.05–1.65) and there was some evidence of an association with increasing age, although this was not statistically significant (> 57 yrs vs < 45 yrs: 1.25, 0.93–1.68). Participants not in full-time employment also experienced an increased risk. A significant trend existed between deprivation and QOL, with those residing in the most deprived areas exhibiting an increased risk (1.67, 1.21–2.29). Higher education was associated with an overall decrease in the risk of poor QOL, while those who reported that they did not

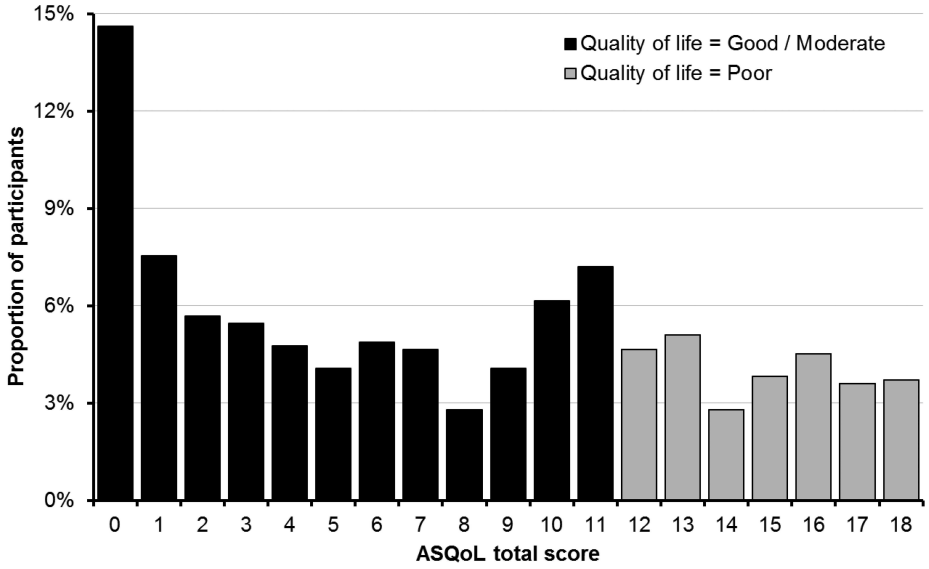

Figure 1. Distribution of quality of life scores among SIRAS participants. SIRAS: Scotland Registry for Ankylosing Spondylitis; ASQoL: Ankylosing Spondylitis Quality of Life.

drive a motor vehicle experienced an increase in risk (2.11, 1.72–2.58). Among nonmodifiable clinical factors, with the exception of peripheral joint disease (1.37, 1.09–1.73), there were no large or significant associations between a history of extraspinal manifestations and the risk of poor QOL (Table 1).

Potentially modifiable characteristics. Compared to never smokers, current and ex-smokers were at an increased risk of reporting poor QOL (1.96, 1.51–2.56 and 1.34, 1.03–1.75, respectively; Table 2). In contrast, current drinkers were less likely to report poor QOL (0.47, 0.36–0.62). Also, participants with CWP (3.27, 2.54–4.20) or moderate/severe fatigue (4.16, 3.16–5.47) experienced more than a 3-fold increase in the risk of poor QOL.

High disease activity (5.17, 3.69–7.22), poor physical function (7.96, 5.13–12.4), and poor spinal mobility (2.23, 1.66–3.01) were all associated with poor QOL. However, although participants with objective measures of inflammation (elevated C-reactive protein/erythrocyte sedimentation rate) experienced a 26% increase in the risk of poor QOL, this was not statistically significant (1.26, 0.99–1.59).

Independent predictors. Of the 8 factors eligible for inclusion in the stepwise model, 5 were accepted into the final model, thus demonstrating independent associations with poor QOL: fatigue, physical function, CWP, disease activity, and spinal mobility (Table 3). The final model also contained 8 nonmodifiable factors, included because they demonstrated a univariate association with QOL at $p \leq 0.2$, and were therefore important potential confounders (Table 3). In addition, the final model was also adjusted for alcohol consumption. Although this is a potentially modifiable factor (and one that met the criterion for inclusion in the stepwise process) because the aim of our current analysis was to model risk effects, this variable was omitted from the stepwise process, but retained in the model to control for potential confounding. The Pearson goodness-of-fit statistic demonstrated that the fit of the final model was good ($p > 0.99$).

Population-attributable risks for each of the 5 variables in the final multivariable model varied from 20% (disease activity) to 56% (physical function; Table 3). Only 16% of participants had none of these risk factors, and the mean ASQoL score for this group was 1.8, compared with a mean of 14.0 among the 11% with all 5 factors. Figure 2 illustrates the increase in the risk of poor QOL with increasing numbers of risk factors in the final model, from 0% (no factors) to 79% (5 factors).

Sensitivity analysis. Questionnaire respondents were found to be slightly older, and a smaller proportion were men compared with the original clinical population. Responders also had lower overall disease activity (BASDAI) and better function (BASFI) compared with nonresponders. However, weighting the multivariable model by the inverse of the sampling fraction for these 4 variables made little difference to the overall risk estimates (Table 3). The risk ratios for moderate/severe fatigue and high BASFI were diminished by 9% and augmented by 12%, respectively, although both retained statistical significance. The interpretation of the final model was unaffected. All other risk ratios were altered by < 3%.

DISCUSSION

We have identified 5 independent, potentially modifiable risk factors for poor QOL among patients with AS. The strongest effect was observed with poor physical function: participants

Table 1. Variables associated with poor quality of life: nonmodifiable factors.

Variables		Quality of Life, n (%)		Probability*	RR (95% CI)
		Poor	Moderate/high		
Patient-reported factors					
Sex	Male	166 (26)	473 (74)	0.018	1.00
	Female	76 (34)	146 (66)		1.32 (1.05–1.65)
Age, yrs	< 45	54 (24)	173 (76)	0.149†	1.00
	45–57	85 (31)	189 (69)		1.30 (0.97–1.75)
	> 57	85 (30)	201 (70)		1.25 (0.93–1.68)
Symptom duration, yrs	< 13	61 (26)	172 (74)	0.104†	1.00
	13–25	59 (26)	165 (74)		1.01 (0.74–1.37)
	> 25	86 (32)	179 (68)		1.24 (0.94–1.64)
Education	Secondary	114 (38)	185 (62)	< 0.001†	1.00
	Apprenticeship	38 (35)	71 (65)		0.91 (0.68–1.23)
	College	63 (25)	185 (75)		0.67 (0.51–0.86)
	University degree	19 (13)	127 (87)		0.34 (0.22–0.53)
	Further degree	8 (16)	43 (84)		0.41 (0.21–0.79)
Employment	Full time	48 (12)	336 (88)	< 0.001	1.00
	Retired	29 (21)	108 (79)		1.69 (1.11–2.57)
	Retired early‡	51 (54)	44 (46)		4.29 (3.11–5.94)
	Unemployed‡	69 (71)	28 (29)		5.69 (4.24–7.63)
	Other	43 (30)	98 (70)		2.44 (1.70–3.51)
Deprivation, quartiles	1, least deprived	39 (21)	146 (79)	< 0.001†	1.00
	2	28 (19)	122 (81)		0.89 (0.57–1.37)
	3	41 (31)	91 (69)		1.47 (1.01–2.15)
	4, most deprived	107 (35)	197 (65)		1.67 (1.21–2.29)
Current driving status	Driver	150 (23)	513 (77)	< 0.001	1.00
	Non-driver	92 (48)	101 (52)		2.11 (1.72–2.58)
Clinical factors: history of…					
Uveitis	No	134 (29)	331 (81)	0.931	1.00
	Yes	79 (29)	198 (81)		0.99 (00.78–1.25)
Psoriasis	No	179 (29)	444 (71)	0.525	1.00
	Yes	27 (26)	78 (74)		0.89 (0.63–1.27)
Inflammatory bowel disease	No	184 (28)	465 (42)	0.495	1.00
	Yes	25 (32)	53 (68)		1.13 (0.80–1.60)
Enthesitis	No	186 (29)	464 (71)	0.505	1.00
	Yes	23 (32)	48 (68)		1.13 (0.79–1.62)
Peripheral joint disease	No	82 (23)	273 (77)	0.005	1.00
	Yes	161 (32)	346 (68)		1.37 (1.09–1.73)

* P value from chi-square test, unless otherwise stated. † P value from chi-square test for trend. ‡ Because of ill health. RR: risk ratio.

with BASFI ≥ 4 experienced a 3.5-fold increase in the risk of poor QOL. Also, the population-attributable risk was high, suggesting that > 50% of all poor QOL cases could be avoided by the eradication of this risk factor (i.e., by a reduction in BASFI to < 4). Other factors independently associated with poor QOL included CWP, moderate/severe fatigue, high disease activity, and poor spinal mobility, again, all with sizable population-attributable risks.

There are several methodological issues to consider. First, within the SIRAS, patients were identified based on clinical diagnosis. No formal criteria were applied (e.g., modified New York or ASAS criteria); because these criteria are not routinely collected in clinic, the proportion of SIRAS participants who fulfill them is not clear. However, these criteria are classification criteria, and although useful for identifying homogeneous patient groups for clinical trials, are not intended for diagnosis. Thus, we would argue that patients identified because of a clinical diagnosis are more closely representative of a real-world clinical population.

The SIRAS included only patients within secondary care. We have previously shown that, in Scotland, only one-third of patients with AS are managed in rheumatology[23]. Excluding patients managed solely in primary care might bias the study toward those with more severe disease. However, the mean ASQoL score (7.54) is within the range demonstrated by other studies (7.2, SD 5.1 to 7.99, SD 4.8)[3,24]. Further, there is no reason to believe that this selection should have affected the internal validity of the study, i.e., the ability to identify risk variables associated with poor QOL, within the study population.

Within the ASQoL, there are several items that assess pain and sleep disturbance/tiredness that may have introduced circularity within our current analysis and in turn may partly explain the association demonstrated between CWP and fatigue with poor QOL. To assess this, posthoc analysis was conducted excluding questions on pain and tiredness (creating a 0–2 scale). Following the same analysis procedure as described in the original study, both CWP and fatigue were retained in the final stepwise model and the risk estimates regarding poor QOL were of similar magnitude. This additional analysis both supports the initial conclusions and the importance of both pain and fatigue in QOL, and

Table 2. Variables associated with poor quality of life: potentially modifiable factors.

Variables		Quality of Life, n (%)		Probability*	RR (95% CI)
		Poor	Moderate/high		
Patient-reported factors					
Smoking status	Never	74 (21)	276 (79)	< 0.001	1.00
	Ex	92 (28)	232 (72)		1.34 (1.03–1.75)
	Current	76 (42)	107 (58)		1.96 (1.51–2.56)
Alcohol consumption	Never	38 (46)	44 (54)	< 0.001	1.00
	Ex	65 (45)	79 (55)		0.97 (0.73–1.31)
	Current	138 (22)	493 (78)		0.47 (0.36–0.62)
Fatigue	None/mild	53 (11)	409 (89)	< 0.001	1.00
	Moderate/severe	184 (48)	202 (52)		4.16 (3.16–5.47)
Chronic widespread pain	No	65 (14)	402 (86)	< 0.001	1.00
	Yes	176 (45)	211 (55)		3.27 (2.54–4.20)
Clinical factors					
Disease activity	BASDAI < 4	35 (10)	329 (90)	< 0.001	1.00
	BASDAI ≥ 4	150 (50)	152 (50)		5.17 (3.69–7.22)
Physical function	BASFI < 4	20 (6)	294 (94)	< 0.001	1.00
	BASFI ≥ 4	144 (51)	140 (49)		7.96 (5.13–12.4)
Spinal mobility	BASMI < 4	49 (17)	237 (83)	< 0.001	1.00
	BASMI ≥ 4	103 (38)	166 (62)		2.23 (1.66–3.01)
Inflammation‡	No	79 (25)	232 (75)	0.056	1.00
	Yes	134 (32)	286 (68)		1.26 (0.99–1.59)

* P value from chi-square test. ‡ Elevated CRP or ESR. RR: risk ratio; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; BASFI: Bath Ankylosing Spondylitis Functional Index; BASMI: Bath Ankylosing Spondylitis Metrology Index; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate.

Table 3.Variables associated with poor quality of life: independent predictors.

Variables		Original Model*		Weighted Model‡	
		RR (95% CI)	PAR, %†	RR (95% CI)	Change, %
Fatigue	None/mild	1.00	22	1.00	—
	Moderate/severe	1.60 (1.13–2.28)		1.46 (1.04–2.06)	9
Physical function	BASFI < 4	1.00	56	1.00	—
	BASFI ≥ 4	3.46 (1.76–6.82)		3.86 (1.97–7.54)	12
Chronic widespread pain	No	1.00	27	1.00	—
	Yes	1.92 (1.33–2.75)		1.94 (1.35–2.79)	1
Disease activity	BASDAI < 4	1.00	20	1.00	—
	BASDAI ≥ 4	1.52 (1.09–2.12)		1.49 (1.09–2.03)	2
Spinal mobility	BASMI < 4	1.00	21	1.00	—
	BASMI ≥ 4	1.52 (0.93–2.50)		1.47 (0.89–2.40)	3

* Model also adjusted for sex, age, education, symptom duration, employment, deprivation, driving status, alcohol consumption, and history of peripheral joint involvement. † Population-attributable risks, based on original (unweighted) model. ‡ Adjusted for all factors in original model. In addition, weighted for nonresponse by inverse of sample fraction with respect to age, sex, BASDAI, BASFI, and history of extraspinal manifestations. PAR: population-attributable risks; RR: risk ratio; BASFI: Bath Ankylosing Spondylitis Functional Index; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; BASMI: Bath Ankylosing Spondylitis Metrology Index.

suggests that circularity is not, in our current analysis, a major concern.

There is currently no validated cutoff published for the ASQoL[25]. Although data granularity is maintained while using a continuous variable, determining the factors associated with a single point change in score is of dubious clinical relevance. The aim of our study was to determine the factors associated with those reporting the poorest QOL; therefore determining a suitable threshold for this was necessary. In the absence of validated cutoffs, creating an arbitrarily high threshold will result in large risk estimates but decreased precision (because of the small number of individuals with the outcome of interest), as manifested by wide CI. In contrast, selecting a very low cutoff may result in an outcome group of little clinical relevance. We believe that our data-driven approach, comparing the top tertile of the distribution (poorest QOL; ASQoL score ≥ 12) with all others, represents a pragmatic balance between the two;

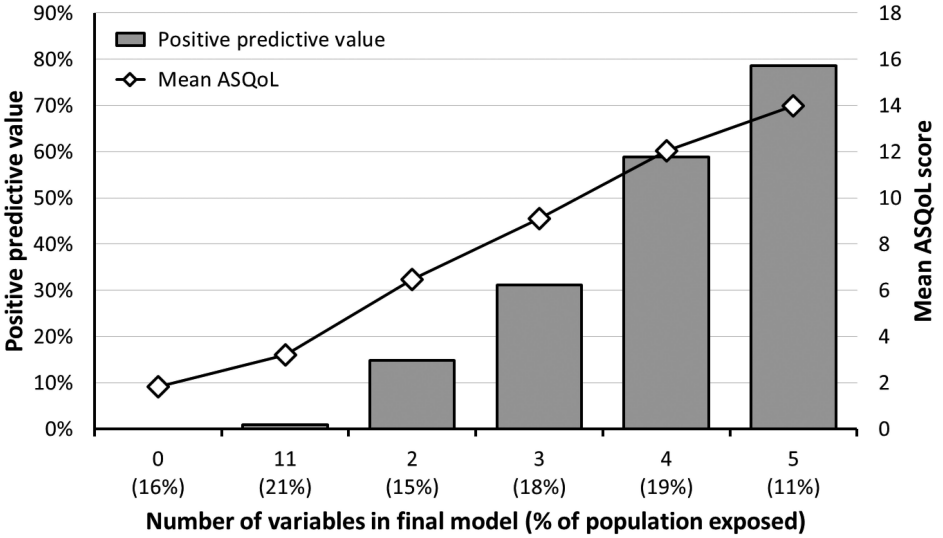

Figure 2. Performance of final multivariable model. ASQoL: Ankylosing Spondylitis Quality of Life.

maintaining the study's ability to identify risk factors with a reasonable degree of precision, while also ensuring an outcome group that is clinically meaningful. However, to ensure that the conclusions were robust to the choice of cutoff, a sensitivity analysis was performed varying the ASQoL threshold for poor QOL (Supplementary Table 1, available with the online version of this article). All risk ratios varied to a minor extent, but there were no changes to overall interpretation of the results.

A number of exposure variables were also categorized for analysis and the cutoff points for these are, to a large extent, arbitrary. We chose to divide BASDAI at a score of ≥ 4 versus < 4. This clinically meaningful cutoff is used as the threshold in the United Kingdom for prescription of biologics. Although no such clinical precedent exists, the same cutoff was used for BASFI and BASMI. All 3 instruments have the same range (0–10) and similar means and SD: 4.1 (2.5), 4.3 (2.8), and 3.9 (2.3), respectively. Thus, for comparability, using the same cutoff was a sensible pragmatic decision. However, to ascertain how vulnerable the final model was to changes in these thresholds, the model was recomputed using cutoff values of 3 and 5. This resulted in no major differences to the models and, crucially, no changes in interpretation (Supplementary Table 2, available with the online version of this article).

Although a variety of validated instruments were included in the postal questionnaire, there are areas that were not collected but that may be important factors, specifically depression and FM. Although CWP (part of the 1990 ACR FM classification criteria[16]) was measured, it was not possible to determine the proportion of participants who have FM. Future studies may consider the inclusion of these factors, perhaps using the self-report FM questionnaire of the ACR modified 2010 criteria[26] to determine the effect that they have on QOL.

Because clinical variables were collected from patient notes, and questionnaires were administered by post, there was a time lag between collection of clinical and patient-reported information — this is especially pertinent for variables that may change over time. The median time between the most recent clinical data collection (BASDAI, BASFI, BASMI, etc.) and the questionnaire (including ASQoL) was about 1 year and 3 months. We have published data previously showing that there is relative consistency in these scores over the mid-term (mos/yrs), albeit some short-time variability[27]. One may expect that in the year between the measurement of Bath indices and questionnaire completion there will have been a mix of improvement and deterioration that will contribute "noise" to the data. This will reduce the ability to identify any associations between these scores and QOL. Despite this, our current study found all 3 Bath indices to be independent predictors of poor QOL, even after multiple adjustment. This supports both their inclusion in our current analysis and their importance when considering targets for future intervention.

It was necessary, because of the low number of observations, to collapse several variables into fewer categories for analysis — e.g., students, part-time workers, and those in unpaid employment were collapsed into a single category. While this permitted inclusion of these variables, one consequence is the inability to examine these risk factors across their full range of values. However, the low prevalence of each of these exposures means that even if the associated risk estimates were large, the population-attributable risks would be small.

During the stepwise regression, the threshold to select variables for the multivariable model was $p \leq 0.2$. This strategy is well established[28] and prevents exclusion of potentially important predictors, or confounders, that do not reach

the conventional threshold ($p \leq 0.05$), but that may become significant when controlled for other factors. This notwithstanding, it is noteworthy that 4 of the 5 variables in the final multivariable model were significant at $p < 0.05$.

Despite several strategies being used to maximize questionnaire response rate, only 51% were returned, and there is the potential for nonresponse bias. Comparison of questionnaire responders/nonresponders revealed few differences, and a sensitivity analysis allowing for these made little difference to the risk estimates in the final model and crucially, no difference in interpretation.

Several clinical variables showed consistent association with poor QOL: high disease activity, poor physical function, and restricted spinal mobility, all of which have shown previous association within other (smaller) studies[3,6,7]. Poor physical function showed the strongest influence on QOL and those who reported a BASFI ≥ 4 experienced a 3.5-fold increase in the risk of poor QOL. Interestingly, although measures of disease activity are routinely collected in clinic (as a principal criterion governing anti-TNF prescription), BASDAI was a weaker predictor of poor QOL than physical function (BASFI), fatigue, or CWP. These findings are consistent with previous work that has shown that pain and fatigue/sleep problems are important factors for daily functioning[8,29]. The current results demonstrate that these symptoms are also important predictors of QOL, independent of function, and that successful treatment may have a greater effect than the common treatment target of a reduction in BASDAI. We do not suggest that a reduction in BASDAI should not be attempted, but rather that pain and fatigue may be powerful additional targets for intervention.

We identified a number of demographic characteristics as well as aspects of clinical presentation that were significantly associated with poor QOL, and although they were nonmodifiable, they were adjusted for in the final model, and they may exert a confounding influence. It is also possible that residual confounding may still exist. While this cannot be ruled out, we included all variables associated in the univariate analysis at $p \leq 0.2$ and it is unlikely that an important confounder in the multivariable model failed to reach this cutoff.

It is important to note that we use the word "predict" to describe the statistical relationship between a risk factor and QOL rather than to infer a causal relationship. All data within our current analysis is cross-sectional and while providing important information on the associations with poor QOL, we recommend that all associations be confirmed in prospective studies.

Of the risk factors we have identified, there is good evidence that areas such as pain may be effectively treated with nonpharmacological interventions such as cognitive behavioral therapy (CBT) and exercise, albeit in non-AS populations[30]. Also, within FM, CBT has shown to be beneficial for pain coping and low mood, while resistance training has been shown to reduce pain and improve physical functioning[31,32]. Such results will need to be tested in the AS patient group, but may prove to be useful additions to standard pharmacological interventions.

We have identified, in a large real-world cohort of patients with AS, 5 factors that independently predict poor QOL. We would argue that the frequent collection of measures, such as pain and fatigue, in addition to clinical "staples" such as the BASDAI, BASFI, and BASMI, may provide useful indicators of treatment effectiveness. Further, in addition to traditional clinical targets, symptoms such as poor physical function, fatigue, and CWP are likely to be the most useful targets, and based on the population-attributable risks observed, may yield substantial improvements in QOL.

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ONLINE SUPPLEMENT

Supplementary material accompanies the online version of this article.

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