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The effect of smoking on clinical and structural damage in patients with axial spondyloarthritis: A systematic literature review☆,☆☆

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ABSTRACT

Objectives: To evaluate the association between smoking and clinical parameters and structural damage in axial spondyloarthritis (axSpA).
Methods: We systematically searched MEDLINE, EMBASE and Cochrane Library till November 2015. We selected articles that analysed the smoking impact on disease activity, functional status, structural damage, physical mobility and life quality. Independent extraction of articles by 2 authors using predefined data fields was performed. Studies quality was graded according to the Oxford Level of Evidence scale.
Results: A total of 17 articles were selected for inclusion: 2 case–control, 11 cross-sectional and 4 prospective cohort studies, which analysed 4694 patients. Weak evidence suggested a smoking effect on pain, overall assessment of health, disease activity, physical mobility and life quality in ankylosing spondylitis (AS). Moderate-good evidence revealed higher HAQ-AS among smokers (0.025 units/y; 95% CI: 0.0071–0.0429; $p = 0.007$). Every additional unit of ASDAS resulted in an increase of 1.9 vs. 0.4 mSASSS units/2 y in AS smokers vs. non-smokers. Good evidence revealed that cigarette smoking and smoking intensity was associated with spinal radiographic progression in axSpA [mSASSS ≥ 2 units/2 y: OR = 2.75, 95% CI: 1.25–6.05, $p=0.012$; mSASSS progression in heavy smokers (> 10 cigarettes/d): OR = 3.57, 95% IC: 1.33–9.60, $p = 0.012$].
Conclusions: Published data indicate that smoking has a dose-dependent impact on structural damage progression in axSpA. There is worse HAQ among AS smokers compared to non-smokers. Respect to pain, overall assessment of health, disease activity, physical mobility and life quality, although the evidence level is poor, all evidence points in the same direction: smoking AS patients are worse than non-smoking.

Introduction

Spondyloarthritis is a family of chronic arthritis diseases characterised by inflammatory back pain, peripheral arthritis and enthesitis [1]. Ankylosing spondylitis (AS) is the typical disease among the family of spondyloarthritis, and it predominantly involves the axial joints and bilateral sacroiliac joints. It is a potentially debilitating disease, which may lead to progressive limitation of the spinal mobility, loss of the functional ability, and reduced quality of life. Inflammatory rheumatic diseases are considered to be due to a complex interaction between environment and genetic factors, which may lead to immune reactions and cause different rheumatic disorders [2]. The environmental factor might be quite important in the development of chronic rheumatic and immune disease.

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Cigarette smoking, one of the most serious health problems, has been identified as one of the major environmental risk factor of rheumatic diseases, including rheumatoid arthritis [3–5] and systemic lupus erythematosus [6,7]. Fewer studies have been performed in ankylosing spondylitis, and even less in early axial spondyloarthritis (axSpA). Smoking has been associated with increased disease activity and radiographic severity in established AS in some studies [8]. Current but not previous smoking or smoking intensity has been recently reported to be a major risk factor for incident AS, supporting the hypothesis that smoking may be causally related to the development of AS [9].

The newly developed Assessment of SpondyloArthritis International Society classification criteria for axSpA [10,11], are more inclusive of patients at an early disease stage. As smoking is a well established risk factor for developing RA and other inflammatory diseases, such as systemic lupus erythematosus and inflammatory bowel disease and has also been associated with phenotypic variations in AS, it would be worthwhile to determine the impact of smoking in the whole axSpA spectrum, particularly in early stage axSpA. The objective of this study was to evaluate the effect of smoking not only on clinical and structural damage but also on functional status and quality of life in patients with axSpA. We made a systematic literature review in the framework of the drawing up of the axSpA and psoriatic arthritis guidelines of the Spanish Society of Rheumatology.

Materials and methods

A systematic review was conducted to identify all studies published up to November 25, 2015 providing information on the association between smoking and clinical parameters, structural damage, functional status and quality of life in patients with axSpA. This review was elaborated according to the PRISMA statement [12]. An expert committee developed the research question and adjusted it according to the PICO (patients, intervention, comparator and outcome) system. This process was supervised by expert methodologists from the Spanish Society of Rheumatology research unit.

Search strategy

A librarian (M.G.) designed a search strategy for the following biomedical databases: MEDLINE (PubMed) (1950–November 25, 2015), EMBASE (1980–November 25, 2015) and the Cochrane Library (Wiley Online) (up to November 25, 2015). Initially, key search terms in natural language were identified and assessed using the PICO (patients, intervention, comparator and outcome) format to frame the question. A generic search strategy was then designed, consisting of exploited controlled vocabulary (Medical Subject Headings—MeSH, Emtree, and other thesauri) and free language. This was later adjusted to redefine the most relevant terms. The strategy was complemented by field identifiers, wild cards, proximity operators and Boolean operators. This strategy was adopted for the various resources selected. The searches were conducted with a language restriction (English, French and Spanish), but without time or geographical limits. Finally, a hand search was performed by reviewing the references of the included studies and the abstracts of the ACR congress (2013–2015) and the EULAR congress (2013–2015). A description of the search strategy is shown in Appendix Supplementary Material.

Inclusion criteria

The studies retrieved with the above strategies were finally included if they met the following predefined criteria: (1) adult patients fulfilling at least one of the following classification criteria for axSpA or AS: the modified New York criteria [13], European Spondyloarthropathy Study Group criteria [14], Amor criteria [15] or Assessment of SpondyloArthritis International Society classification criteria for axSpA [10,11], (2) smoking status, (3) comparison with non-smokers patients and (4) outcomes measures: swollen and tender joints count; enthesitis; pain (visual analogue scale, NRS, etc.); morning stiffness (minutes); overall assessment of health (VAS, Bath Ankylosing Spondylitis Patient Global Score, etc.); disease activity assessed using both the Bath Ankylosing Spondylitis Disease activity Index (BASDAI) [16] and the Ankylosing Spondylitis Disease Activity Score (ASDAS) [17]; patient's physical mobility [measured by the Bath Ankylosing Spondylitis metrology index (BASMI) [18], etc.]; functional status assessed using both the Bath ankylosing Spondylitis Functional Index (BASFI) [19] and the Health Assessment Questionnaire for Ankylosing Spondylitis (HAQ-AS) [20]; structural damage evaluated with the Bath Ankylosing Spondylitis Radiology Index for the spine (BASRI-s) [21], the modified Stoke Ankylosing Spondylitis Spine Score (mSASSS) [22] and sacroiliitis grading (New York criteria) as established by conventional radiography (grade 2: minimal, grade 3: moderate and grade 4: ankylosis; quality of life measured by the AS Quality of Life (ASQoL) [23], Short Form-36 (SF-36) [24], Short Form-12 (SF-12) [25] and evaluation of AS Quality of Life (EASi-QoL) [26]. Any type of study except case series or case reports was eligible. There was no limitation with regard to the number of patients included in the studies.

Selection of studies and data collection

EndNote X7® software was used to manage the records retrieved by searches of the different electronic databases and manual search methods. Articles were selected, according to the inclusion criteria, by 2 independent reviewers (V.V.G. and T.C.I.). Firstly, articles were selected according to title and abstract, followed by a full-text reading. If any discrepancy arose in either of the 2 selection phases, consensus was reached with the aid of a third reviewer (D.S.). Articles with incomplete data or which did not comply with the inclusion criteria were excluded. Authors were contacted when the full article was not available. Supplementary information was obtained for one of the studies. A reviewer (V.V.G.) compiled the information on the studies included using standardized forms. When the data were not included in the text, they were extracted from the tables and figure to obtain the necessary information.

Assessment of the methodological quality and data analysis

The Oxford Level of Evidence rating scale was used to evaluate the methodological quality of the studies [27]. Due to the small number of studies and their design, we focused on describing the studies in the evidence tables, their results and a qualitative synthesis rather than a meta-analysis.

Results

The search identified 509 studies related to smoking effect on clinical and structural damage in AS and axSpA patients published between 1961 and November 2015 and was screened for inclusion in the study. Of these, 26 were duplicated studies, so potentially eligible citations were assessed and 24 studies met eligibility for data extraction. An additional 7 studies were later excluded for the following reasons: 1 low quality, 4 did not meet study design eligibility, 1 letter to the editor and 1 review. The remaining 17 studies: 2 case–control, 11 cross-sectional and 4 prospective cohort

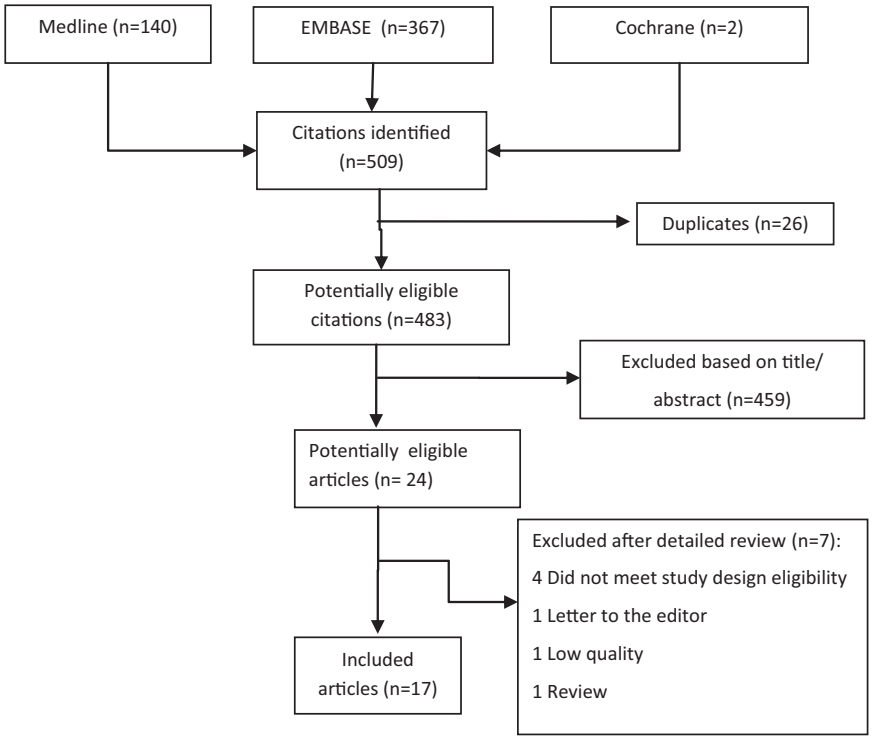

Figure. Search strategy and results of the selection of articles.

studies, met the criteria to be included in this review (Fig.). In total, 4878 patients were analysed. The main characteristics of the studies included in the analysis are shown in Tables 1 and 2. A list of excluded studies and reasons for their exclusion are shown in Table 3.

Swollen and tender joints count and enthesitis

None of the included studies evaluated the smoking effect on swollen and tender joints count and enthesitis.

Pain

Specific information on smoking effect on pain level in AS patients was reported in 3 cross-sectional studies [32,33,36]. Mattey et al. [32] found that there was no significant difference between those who had never smoked and past-smokers and only current smokers showed significantly higher pain scores than those had never smoked ($p < 0.05$), using a 10 cm numerical rating scale (NRS; 0 = no pain, 10 = most severe pain). Averns et al. [36] did not find significant differences between non-smokers, ex-smokers and smokers (pain was assessed using a visual analogue scale), but Zhang et al. [33], found that compared to non-smoking patients those with tobacco use scored significantly higher in nocturnal pain (visual analogue scale) and total back pain (visual analogue scale) ($p < 0.05$).

A cross-sectional analysis of the DESIR cohort [8], showed that smoking was independently associated with earlier onset of inflammatory back pain in patients with axSpA ($B = -1.46$, $p = 0.04$).

Morning stiffness

The association between smoking and morning stiffness was reported in a cross-sectional study [33]. Zhang et al. [33] did not find statistically significant differences between smokers and non-smokers patients with regard to morning stiffness (14.0 ± 26.3 vs. 9.9 ± 17.6; $p = 0.30$).

Overall assessment of health

The smoking effect on overall assessment of health in AS patients was evaluated in 3 studies (1 case–control and 2 cross-sectional studies) [28,30,33]. The value of BAS-G was higher in smoking AS patients than those with non-smoking, but this difference did not show statistical significance (5.20 ± 2.62 vs. 4.46 ± 2.69; $p = 0.305$) [28]. However, Reed et al. [30] found significant difference between smokers and non-smokers in BAS-G (regression coefficient = 1.94; 95% IC: 0.75–3.13; $p = 0.02$).

Compared to non-smoking patients, those with tobacco use scored significantly higher in overall assessment of health (VAS), (6.6 ± 2.7 vs. 5.6 ± 3.3; $p = 0.00$) [33].

Global disease activity

The effect of smoking on disease activity in AS patients was examined in 8 cross-sectional studies [8,9,28–33]. The disease activity was evaluated with *Bath Ankylosing Spondylitis Disease Activity Index* (BASDAI) in all of them. According to these reports, current smokers had significantly higher BASDAI scores than non-current smokers, and current smoking was an independent variable for higher BASDAI after adjusting for confounding factors in the majority of the studies. No difference in BASDAI score between ever smokers and never smokers, and no correlation with pack-years, was found in Reed et al. [30] and Sakellariou et al. [9]. Furthermore, Mattey et al. [32] and Sakellariou et al. [9] reported that current smokers but not ever smokers had higher BASDAI score compared to never smokers and, despite the significant correlation between pack-years and BASDAI, only current smoking and not pack-years was significantly associated with BASDAI ≥ 4 in the multivariate analyses.

Table 1
Characteristics of studies and results

Study	Population	Intervention	Outcome measures	Results	Quality of evidence and comments
Chen et al. [28] Case–control	*N*: 75 male AS patients according to the 1984 modified New York criteria. Mean age 33.55 ± 10.67 y AS patients were divided into 2 subgroups with smoking (*N*: 35 including current smoker and past smoker) and non-smoking (*N*: 40). There was no statistically significant difference between smoking AS patients and non-smoking in age, onset age, disease duration and peripheral joint involvement rate.	Smoking (including current smoker and past smoker). Smoking duration and smoking intensity (pack-years of smoking, the product of years of smoking and packs of cigarette per day) Non-smoking	BASDAI BASFI Bath Ankylosing Spondylitis Patient Global Score (BAS-G) Patient's physical mobility, including tragus-to wall distance, lumbar flexion (modified Schöber's index), intermalleolar distance, cervical rotation, lateral lumbar flexion, fingertip-to-floor distance, chest expansion and occiput-to-wall distance	The values of BASDAI ($p = 0.283$), BASFI ($p = 0.240$) and BAS-G ($p = 0.305$) were higher in smoking AS patients than those with non-smoking The smoking AS patients showed significantly elevated odds ratio (OR; 95% CI) than those with non-smoking in modified Schöber's index (OR = 12.17; 95% CI: 2.60–56.98), lateral lumbar flexion (OR = 4.61; 95% CI: 1.51–14.08), fingertip-to-floor distance (OR = 4.06; 95% CI: 1.14–14.43), chest expansion (OR = 4.44; 95% CI: 1.05–18.78) and occiput-to-wall (OR = 4.61; 95% CI: 1.36–15.6) Among the 35 smoking AS patients, the smoking intensity correlated significantly with BASFI ($r = 0.481$, $p = 0.005$), cervical rotation ($r = -0.401$, $p = 0.031$), fingertip-to-floor distance ($r = 0.485$, $p = 0.004$) and occiput-to-wall distance ($r = 0.473$, $p = 0.005$). The smoking duration also correlated significantly with BASFI ($r = 0.409$, $p = 0.018$), fingertip-to-floor distances ($r = 0.482$, $p = 0.004$) and occiput-to-wall distance ($r = 0.402$, $p = 0.021$)	Oxford 4 Small sample size Low quality 100% male patients
Fallahi et al. [29] Cross-sectional study	*N*: 160 AS patients according to the 1984 modified New York criteria. Male to female ratio: 3.85 61.8% Non-smokers 8.8% Ex-smokers 29.4% Current smokers	Smoking (current smokers). Quantity of smoking (pack-years) Non-current smokers (including ex-smokers and non-smokers)	BASDAI ASQoL BASMI Sacroiliitis established by conventional radiography (New York criteria)	Smoking quantity was significantly higher in the patients with severe sacroiliitis than those with mild or moderate disease ($p = 0.001$). Univariate analysis revealed an association between the pack-years of smoking and the BASDAI [regression coefficient (B) = 0.05, standard error (SE) = 0.02, 95% CI: 0.006–0.10; $p = 0.03$], ASQoL ($B = 0.15$, SE = 0.06, 95% CI: 0.04–0.26; $p = 0.007$) and BASMI ($B = 0.05$, SE = 0.02, 95% CI: 0.006–0.08; $p = 0.03$). A multivariate analysis revealed a significant association between the pack-years of smoking and the BASDAI ($B = 0.05$, SE = 0.02, 95% CI: 0–0.094; $p = 0.05$) and ASQoL ($B = 0.11$, SE = 0.05, 95% CI: 0.003–0.21; $p = 0.04$)	Oxford 4 Low quality Cross-sectional studies, cannot assess causation Lack of radiographic and MRI evaluation for spinal damage

Reed et al. [30] Cross-sectional study	*N*: 126 AS patients according to the 1984 modified New York criteria. Mean age 44.9 ± 12.3 y and a mean duration of AS symptoms of 20.3 ± 11.3 y 72.2 % male 53.97% Never smokers 28.57% Former 17.46% Current smokers	The smoking status was categorised as never, former or current smokers. Cigarette consumption was quantified as total pack-years (1 pack year is equivalent to 20 cigarettes smoked per day for 1 year)	BASDAI BASFI ASQoL BAS-G	Multivariate analysis revealed a significant association between current smokers and BASDAI (B = 1.39; 95% CI: 0.52–2.26; p = 0.002), ASQoL (B = 4.24; 95% CI: 2.16–6.32; p < 0.0001) and BAS-G (B = 1.94; 95% CI: 0.75–3.13; p = 0.02) There was no relation between cumulative exposure (pack-years) and composite indices (data not shown)	Oxford 4 Low quality Spinal radiographic data were not uniformly available and were therefore not presented in the study Lack of data about the relation between cumulative exposure and composite indices
Kaan et al. [31] Case-control	*N*: 48 AS patients according to the 1984 modified New York criteria. Mean age 35.5 ± 8.85 y 85.41 % male There was no significant difference in age, sex, height, weight, body mass index or duration of disease between smokers and non-smokers. 50% Non-smokers 50% Smokers	Smoking was judged as that lasting for at least 5 y and including daily consumption of at least one packet of cigarettes Non-smokers	BASDAI BASFI Chest expansion Lumbar modified Schöber´s test Wall-occiput distance Hand-ground distance Chin-manibrium distance	BASDAI and BASFI were significantly higher in smokers than in non-smokers (p = 0.000 and p = 0.002, respectively). There were correlations between BASDAI and BASFI in chest expansion (r = −0.368, p = 0.01 and r = −6.56, p = 0.000), lumbar modified Schöber's test (r = −0.625, p = 0.000 and r = −0.732, p = 0.000, respectively), wall-occiput distance (r = 0.327, p = 0.02 and r = 0.492, p = 0.000), chin-manibrium distance (r = 0.312, p = 0.01 and r = 0.462, p = 0.001)	Oxford 4 Small sample size Low quality
Mattey et al. [32] Multicenter cross-sectional study	*N*: 612 AS patients according to the 1984 modified New York criteria. Mean age 51.0 (42–60) y Disease duration 15.0 (8–25) y 72.3% male 50.8% Never smoked 28.2% Past smoker 21.0% Current smoker 49.2% Ever smoke	Specific information on smoking included smoking status, smoking duration, average number of cigarettes smoked per day and age at smoking cessation. Smoking status categorised 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)	BASDAI BASFI ASQoL EASi-QoL Pain assessed using a 10 cm numerical rating scale (NRS; 0 = no pain, 10 = most severe pain)	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, more severe pain and poor quality of life (ASQoL) were associated primarily with current smoking (B = 0.605, SE = 0.248, OR = 1.83, 95% CI: 1.13–2.98; p = 0.015; B = 0.694, SE = 0.249, OR = 2.00, 95% CI: 1.23–3.27; p = 0.005 and B = 0.697, SE = 0.242, OR = 2.00, 95% CI: 1.25–3.22; p = 0.004, respectively). Increasing pack-year history was associated with poor quality of life (EASi-QoL): B = 0.280, SE = 0.098, OR = 1.32, 95% CI: 1.09–1.60; p = 0.004	Oxford 4 Data collected from a questionnaire that patients completed and returned in a prepaid envelope. Information was not obtained on patients failing to respond the questionnaire. It was not possible to determine whether there were differences in smoking status between participants and non-participants in the study Cross-sectional study It was not possible to directly address the effect of smoking cessation on disease measures
Zhang et al. [33] Cross-sectional study	N: 425 AS patients according to the 1984 modified New York criteria. Mean age 29.2 ± 8.3 y Disease duration 7.5 ± 5.8 y	Current smoker Pack-years of smoking	BASDAI BASFI BASMI Fingertip-to-floor distance Morning stiffness (minutes) Nocturnal pain (VAS) Total back pain (VAS)	Compared to non-smoking patients, those with tobacco use scored significantly higher in BASDAI, BASFI, BASMI and multiple parameters of functional state including fingertip-to-floor distance, overall assessment of	Oxford 4 Low quality It was not possible to directly address the effect of smoking cessation on disease measures

Table 1 (*continued*)

Study	Population	Intervention	Outcome measures	Results	Quality of evidence and comments
	81.9% male 27.8% Never smoked 72.2% Current smoker	Never smoker (defined as having smoked fewer than 100 cigarettes in the subject´s lifetime)	Overall assessment of health (VAS)	health, nocturnal pain and total back pain ($p < 0.05$) Hierarchical multiple regression analysis was performed with BASDAI as independent variable and smoking as dependent variable (OR = 1.62; 95% CI: 1.03–2.55; $p = 0.04$). Smoking variable contributed 1% change of BASDAI and 1% increase of R^2 value.	The data on smoking was retrospective, which may have caused misclassification of some patients Single center study
Ward et al. [34] Cross-sectional component of the prospective study of outcomes in AS	*N*: 326 AS patients according to the 1984 modified New York criteria and duration of AS for ≥ 20 y Mean age 55.0 ± 10.7 y and a mean duration of AS symptoms of 31.7 ± 10.2 y 73.9% Male 44.5% Non-smokers 44.8% Former smokers 10.7% Current smokers	Current smoker Non-smoker or former smoker	BASFI HAQ-AS	BASFI scores were higher among current smokers compared with former/non-smokers (55.5 vs. 38.9, $p = 0.0002$). In the multivariate analysis, BASFI score was significantly associated with smoking status, using age as the measure of time (11.8 points higher among current smokers than among non-smokers or former smokers, $p = 0.006$). Results for the HAQ-AS were similar to those for the BASFI, with significant associations with smoking status (0.18 points higher among current smokers than among non-smokers or former smokers, $p = 0.005$). Results were also similar when duration of AS was used instead of age as the measure of time (BASFI score = 12.1 points higher among current smokers than among non-smokers or former smokers, $p = 0.005$ and HAQ-AS score = 0.17 points higher among current smokers than among non-smokers or former smokers, $p = 0.006$)	Oxford 4 Low quality Differences in AS activity and associations with treatment were not evaluated
Ward et al. [35] Cross-sectional component of the Prospective Study of Outcomes in AS	*N*: 398 AS patients according to the 1984 modified New York criteria and duration of AS for ≥ 20 y Mean age 55.0 ± 10.8 y and a mean duration of AS symptoms of 23.1 ± 7.8 y 75% Male 45% Non-smokers 45% Former smokers 10% Current smokers Pack-years of smoking: All patients: 11.3 ± 18.7 Ever smokers only: 20.4 ± 21.1	Current smoker Non-smoker	BASRI	Radiographic severity (being in the top quartile of BASRI/duration of AS) was associated with current smoker (OR = 4.72, 95% CI: 2.16–10.30; $p < 0.0001$). Being in the lowest quartile of BASRI/duration of AS was also less likely among current smokers (OR = 0.29; 95% CI: 0.09–0.85; $p = 0.03$).	Oxford 4 Low quality AS activity or certain clinical features such as non-steroidal anti-inflammatory drug use, as potential prognostic factors due to the absence of complete historical data, were not examined
Averns et al. [36] Cross-sectional study	*N*: 53 AS patients according to the 1968 New York criteria	Current smoker Non-smoker or ex-smoker	Pain VAS (cm) Stiffness VAS (cm) Total spine score	There were statistically significant differences between smokers and non-smokers for finger floor	Oxford 4 Small sample size Low quality

	Mean age 47.5 (32–66) y Duration of history 20 (9–48) y 58.49% Never smoked 18.87% Current smokers 22.64% Ex-smokers		Occiput-wall distance (cm) Finger floor distance (cm) Chest expansion (cm) Total spine movement	distance ($p < 0.01$), total spinal movement ($p < 0.001$), occiput-wall distance ($p < 0.01$), stiffness ($p < 0.01$)	Cross-sectional study
Doran et al. [37] Cross-sectional study	*N*: 311 AS patients according to the 1984 New York criteria Mean age 22.9 ± 8.3 y Disease duration 23.5 ± 11.3 y 82% Male 39% Ever cigarette smoker 61% Never smoker	Ever cigarette smoker Never smoker	BASRI BASFI	Multivariate analysis only revealed a significant association between smoking and BASFI ($B = 0.618$; 95% CI: 0.0108–1.22; $p = 0.02$)	Oxford 4 Low quality This study is based in a tertiary referral center and patients with more severe AS may be overrepresented Cross-sectional analyses are limited by difficulties in separating cause from effect Due to the variation in disease duration at time of radiographs, the information on some individuals may be incomplete
Ward et al. [38] Prospective longitudinal study Median duration of follow-up: 5 y	*N*: 212 AS patients according to the 1984 New York criteria Mean age 47.8 ± 13.6 y Disease duration 20.1 ± 13.9 y 70.3% Male 14.6% Current smoker 85.4% Non-smoker	Current smoker Non smoker	HAQ-AS	The rate of progression of the HAQ-AS increased by 0.0006 units/y with each additional year of age, and increased by an additional 0.025 units/y (95% CI: 0.0071–0.0429, $p = 0.007$) among smokers compared to non-smokers To determine if there were additional or unique predictors of the progression of functional disability in early AS, analyses were repeated in the 58 patients who had AS for less than 10 y at entry study. Smoking was also associated with the progression of functional disability in this subgroup of patients (0.0173 units/y; $p = 0.05$)	Oxford 2b Large sample Wide variety of predictors examined Prospective design and moderately long follow-up The generally slow rate of progression may have decreased the statistical power to detect associations with some predictors
Bodur et al. [39] Cross-sectional study	*N*: 962 AS patients according to the Turkish League Against Rheumatism Registry Mean age 47.8 ± 13.6 y Disease duration 11 ± 8.5 y 76.2% Male 47.8% Current smoker 52.2% Non-smoker	Current smoker Non smoker	ASQoL SF-36	ASQoL was found to be poorer in smokers (6.3 ± 5.4 vs. 7.3 ± 5.7) being the difference statistically significant ($p < 0.05$). There was no significant difference between smokers and non-smokers regarding SF-36 subscale scores	Oxford 4 Low quality Cross-sectional analyses are limited by difficulties in separating cause from effect It was not possible to directly address the effect of smoking cessation on disease measures
Ramiro et al. [40] Prospective Cohort (Outcome in Ankylosing Spondylitis International Study: OASIS) Patients were followed up for 12 y, with 2-yearly assessments.	*N*: 184 AS patients according to the 1984 New York criteria Mean age 43 ± 12 y Disease duration 11 ± 9 y 70% Male ASDAS-CRP 2.6 ± 1.0 mSASSS (0–72) 10.8 ± 15.2 39% Current smoker	Smokers Non-smokers	mSASSS Two well-trained readers independently scored all available radiographs per patient, blinded to demographic and clinical data, but with known chronology	Every additional unit of ASDAS resulted in an increase of 1.94 (1.00 to 2.87) vs. 0.35 (0.04–0.65) mSASSS units/2 y in smokers vs. non-smokers ($p < 0.001$). The influence of smoking on the association between ASDAS and radiographic progression was statistically stronger than the effect of job type on this relationship	Oxford 2b Smokers vs. non-smokers were distinguished based on baseline smoking status. If baseline information was not available, patients were retrospectively questioned in order to minimise missing data. However, baseline smoking status was missing for 57 patients

Table 1 (*continued*)

Study	Population	Intervention	Outcome measures	Results	Quality of evidence and comments
	61% Non-smoker				
Sakellariou et al. [9] Cross-sectional study	N: 106 AS patients according to the 1984 New York criteria Mean age 41.5 ± 12.7 y Disease duration 15.6 ± 11.2 y 94.3% Male 52.8% Current smoker 26.4% Past-smokers 79.2% Ever smokers Smoking pack-years (for the ever smokers) 20.3 ± 19.7	Current smoking Smoking pack-years (1 pack year = 20 cigarette/d for 1 y) Ever smokers o never smokers	BASDAI BASFI mSASSS	Current smokers had significantly higher BASDAI ($p < 0.001$) and a trend for higher BASFI ($p = 0.059$). Ever smokers had significantly higher BASFI ($p = 0.035$) and a trend for higher mSASSS ($p = 0.063$) compared to never smokers. Pack-years (smoking intensity) were positively correlated with duration of inflammatory back pain ($r = 0.628$, $p < 0.001$), BASFI ($r = 0.443$, $p < 0.001$) and mSASSS ($r = 0.683$, $p < 0.001$). Multivariate regression analyses showed that current smoking was independently associated with a higher BASDAI score ($B = 14.75$ 95% CI: 7.0–22.49, $p < 0.001$) and increasing pack-years were independently associated with higher mSASSS (B=0.26, 95% CI: 0.08–0.43, $p = 0.005$)	Oxford 4 Low quality Cross-sectional design cannot prove causality High proportion of male patients (the results of association between smoking and radiographic damage may be different in a mixed population with AS) Single-center study Associations with treatment were not evaluated
Chung et al. [8] Cross-sectional analysis involving data collected during the first visit of the Devenir des Spondyloarthropathies Indifférenciées Récentes (DESIR) cohort	*N*: 647 patients with early inflammatory back pain, fulfilling at least one of the following classification criteria for axSpA (European Spondyloarthropathy Study Group criteria, Amor criteria or Assessment of SpondyloArthritis International Society classification criteria for axSpA) 37.2% Smokers (past history or concomitant smoking) 62.8% Non-smokers There was statistically significant difference between smoking patients and non-smoking in sex and mean age at onset of inflammatory back pain (IBP) Smokers were more likely to be men (51% vs 42.9%) and had an earlier onset of inflammatory back pain 31.1 ± 8.3 vs 32.6 ± 9.0 y)	Smoker (In DESIR, smoking status was obtained through interview by the physician, without a standardised questionnaire. It was collected as past history or concomitant smoking, without any reference to the quantity (e.g., pack-years) Non-smoker	BASDAI ASDAS BASMI BASFI HAQ-AS Euro-QoL SF-36 Sacroiliac joint radiographs (they were graded according to the following grading scale: 0, normal; 1, doubtful; 2, obvious; 3, fusion. Radiographic sacroiliitis was defined by at least a unilateral 'obvious' grading scale Spinal radiographs were scored according to the mSASSS. All radiographs were graded by regional radiologists or rheumatologists	Multivariate analysis showed that smoking was associated with an earlier onset of inflammatory back pain ($B = -1.46$, 95% CI: −2.87 to −0.06; $p = 0.04$); higher disease activity (ASDAS $B = 0.20$, 95% CI: 0.02–0.38; $p = 0.03$; BASDAI $B = 0.50$; 95% CI: 0.17–0.83; $p = 0.003$), worse functional status (BASFI $B = 0.38$, 95% IC:0.07–0.69; $p = 0.02$), more frequent MRI inflammation of the sacroiliac joints (OR = 1.57 95% CI: 1.08–2.30; $p = 0.02$) and the spine (OR = 2.33, 95% CI: 1.55–3.51; $p < 0.001$), more frequent MRI structural lesions of the sacroiliac joints (OR = 1.54, 95% CI: 1.05–2.26; $p = 0.03$) and the spine (OR = 2.02; 95% CI: 1.15–3.55; $p = 0.01$) and higher mSASSS ($B = 0.54$; 95% CI: 0.05–1.03; $p = 0.03$) reflecting radiographic structural damage of the spine. Smoking was also associated with poorer quality of life (Euro-QoL $B = 1.38$; 95% CI: 0.69–2.07; $p < 0.001$; SF-36 physical component $B = -4.89$; 95% CI: −7.24 to −2.54; $p < 0.001$ and mental component $B = -5.90$; 95% CI: −8.99 to −2.81; $p < 0.001$	Oxford 4 Cross-sectional design cannot prove causality Current smokers and patients with a past history of smoking are analysed together because of incomplete data in DESIR cohort The number of pack-years of smoking is not known in the DESIR cohort Lack of international consensus about the assessment of MRI structural lesions

Poddubnyy et al. [41] Prospective Cohort (German Spondyloarthritis Inception Cohort: GESPIC) Median duration of follow-up: 2 y	*N*: 210 patients, 115 AS patients according to the 1984 New York criteria and duration of AS $\leq$ 10 y, 95 SpA patients according to the European Spondyloarthropathy Study Group criteria and the maximum duration of symptoms $\leq$ 5 y Mean age 37.1 $\pm$ 10.6 y Disease duration 4.2 $\pm$ 2.7 y 51.0% Male 30.0% Current smoker 25.3% Non-radiographic axSpA current smokers 33.9% AS current smoker	Current smoker Non-smokers	Radiographs of the spine and sacroiliac joints were obtained at baseline and after 2 y. Radiographic sacroiliitis was scored from grade 0 (normal) to grade 4 (ankylosis) according to the modified New York criteria Spinal radiographs were scored according to the mSASSS. Definition of definite radiographic progression: worsening of the mean mSASSS score by $\geq$ 2 units after 2 y Available radiographs were centrally digitised, blinded and scored in random order independently by 2 trained readers. Both readers were blinded to all clinical data	Cigarette smoking was independently associated with spinal radiographic progression (worsening of the mSASSS by $\geq$ 2 units over 2 y: OR = 2.75; 95% CI: 1.25–6.05; p = 0.012) in patients with axSpA. Current smoking was not associated with formation of new syndesmophytes over 2 y (OR = 2.53; 95% CI: 0.90–7.07; p = 0.077)	Oxford 1b
Poddubnyy et al. [42] Prospective Cohort (German Spondyloarthritis Inception Cohort: GESPIC) Median duration of follow-up: 2 y	N: 210 patients, 115 AS patients according to the 1984 New York criteria and duration of AS $\leq$ 10 y, 95 SpA patients according to the European Spondyloarthropathy Study Group criteria and the maximum duration of symptoms $\leq$ 5 y Mean age 37.1 $\pm$ 10.6 y Disease duration 4.2 $\pm$ 2.7 y 51.0% Male 33.8% Smokers at least at 1 time point over 2 y 60.56% Smokers, $\leq$ 10 cigarettes a day 39.44% Smokers, > 10 cigarettes a day	Moderate smokers ($\leq$ 10 cigarettes a day) Heavy smokers (> 10 cigarettes a day) Non-smokers	Radiographs of the spine and sacroiliac joints were obtained at baseline and after 2 y Radiographic sacroiliitis was scored from grade 0 (normal) to grade 4 (ankylosis) according to the modified New York criteria Spinal radiographs were scored according to the mSASSS. Definition of definite radiographic progression: worsening of the mean mSASSS score by $\geq$ 2 units after 2 y Available radiographs were centrally digitised, blinded and scored in random order independently by 2 trained readers. Both readers were blinded to all clinical data	Heavy smoking vs. non-smoking, was associated with mSASSS progression ($\geq$ 2 points): OR = 3.57; 95% CI: 1.33–9.60; p = 0.012. This remained also significant after adjustment for baseline syndesmophytes, C-reactive protein level, gender, presence of definite radiographic sacroiliitis, use of non-steroidal anti-inflammatory drugs and tumour necrosis factor blockers (OR = 3.48; 95% CI: 1.06–11.42; p = 0.039) Heavy smoking vs. non-smoking, was associated too with formation of new syndesmophytes over 2 y (OR = 3.53; 95% CI: 1.25–9.98; p = 0.018). After adjustment for all factors mentioned above, the OR was 4.17 (95% CI: 0.79–22.02), p = 0.093	Oxford 1b

AS, ankylosing spondylitis; SpA, spondyloarthritis; OR, odds ratio; CI, confidence interval; *r*, Spearman's rank correlation test; SE, standard error; *B*, regression coefficient; NRS, numerical rating scale; vs, versus; y, year; e.g., example; MRI, magnetic resonance image; VAS, visual analogue scale; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; BASMI, Bath Ankylosing Spondylitis Metrology Index; BAS-G, Bath Ankylosing Spondylitis Patient Global Score; HAQ-AS, Health Assessment Questionnaire for Ankylosing Spondylitis; Euro-QoL, Euro-quality of life Questionnaire; SF-36, short form-36; BASRI, Bath Ankylosing Spondylitis Radiology Index; mSASSS, Modified Stoke Ankylosing Spondylitis Spine Score.

Table 2
Effects of smoking on clinical, structural, physical mobility and quality of life outcomes in axSpA patients

Outcomes	References	Smokers	Past-smokers	Non-smokers	Statistical association	Study design	LE
Pain	Mattey et al. [32]	5.0 (3.0–7.0)[a]	5.0 (3.0–7.0)[a]	4.0 (2.0–7.0)[a]	$p = 0.046$	Cross-sectional study	4
	Averns et al. [36]	0.5 (5.7–8)[a]	2 (6–0.5)[a]	1.2 (10–2)	NS	Cross-sectional study	4
	Zhang et al. [33]	Nocturnal pain (VAS): 4.8 ± 3.1	–	Nocturnal pain (VAS): 3.9 ± 2.8	$p = 0.01$	Cross-sectional study	4
		Total back pain (VAS): 4.3 ± 2.7		Total back pain (VAS): 3.7 ± 2.4	$p = 0.04$		
	Chung et al. [8]	Onset of IBP (y): 31.1 ± 8.3		Onset of IBP (y): 32.6 ± 9.0	$p = 0.04$	Cross-sectional analysis of the DESIR cohort	4
Morning stiffness	Zhang et al. [33]	14.0 ± 26.3	–	9.9 ± 17.6	$p = 0.30$	Cross-sectional study	4
Overall assessment of health	Chen et al. [28]	5.20 ± 2.62	–	4.46 ± 2.69	$p = 0.305$	Case–control study	4
	Reed et al. [30]	7.0 [5.9–8.8][b]		5.2 [5.0–6.5][b]	$p = 0.02$	Cross-sectional study	4
	Zhang et al. [33]	6.6 ± 2.7		5.6 ± 3.3	$p = 0.00$	Cross-sectional study	4
Global disease activity (BASDAI)	Chung et al. [8]	$B = 0.50$; 95% CI: 0.17–0.83	–	–	$p = 0.003$	Cross-sectional analysis of the DESIR cohort	4
		4.8 ± 2.3				Cross-sectional study	
	Sakellariou et al. [9]	$B = 14.75$; 95% CI: 7.0–22.49	–	3.2 ± 1.5	$p < 0.001$	Case–control study	4
	Chen et al. [28]	4.30 ± 1.91					4
		OR = 2.905, 95% CI: 0.922–9.155	–	3.84 ± 2.11	$p = 0.283$	Case–control study	
			–	–	$p=0.069$		
	Fallahi et al. [29]	4.96 ± 0.33				Cross-sectional study	4
	Reed et al. [30]	6.5 ± 2.1	–	4.35 ± 0.22	$p = 0.13$	Cross-sectional study	4
			4.9 ± 1.9	5.0 ± 2.1	$p < 0.005$		
	Kaan et al. [31]	33.87 ± 11.71				Case–control study	4
	Mattey et al. [32]	OR = 1.83, 95% CI: 1.13–2.98	–	19.54 ± 10.95	$p = 0.000$	Cross-sectional study	4
			–	–	$p=0.015$		
	Zhang et al. [33]	4.2 ± 2.0		3.6 ± 1.9	$p = 0.00$	Cross-sectional study	4
		OR = 1.62, 95% CI: 1.03–2.55	–	–	$p = 0.04$		
Physical mobility	Chung et al. [8]	BASMI	–	BASMI	$p = 0.12$	Cross-sectional analysis of the DESIR cohort	4
		1.6 ± 1.2		1.5 ± 1.1			
	Chen et al. [28]	Tragus-to-wall distance (cm): 14.61 ± 5.44	-	Tragus-to-wall distance (cm): 13.13 ± 3.84	$p = 0.148$	Case-control study	4
		Modified Schober's index (cm): 2.75 ± 1.77	–	Modified Schober's index (cm): 4.30 ± 1.47	$p < 0.001$		
		Intermalleolar distance (cm): 118.30 ± 20.35	–	Intermalleolar distance (cm): 112.83 ± 19.23	$p = 0.199$		
		Cervical rotation (degree): 44.56 ± 17.01	–	Cervical rotation (deg.): 44.56 ± 17.01	$p = 0.034$		
		Lateral lumbar flexion (cm): 9.30 ± 6.02	–	Lateral lumbar flexion (cm): 9.30 ± 6.02	$p = 0.002$		
		Fingertip-to-floor distance (cm): 29.87 ± 28.03	–	Fingertip-to-floor distance (cm): 22.24 ± 23.64	$p = 0.121$		
		Chest expansion (cm): 3.89 ± 1.81	–	Chest expansion (cm): 5.0 ± 1.88	$p = 0.016$		
		Occiput-to-wall distance (cm): 5.71 ± 7.21	–	Occiput-to-wall distance (cm): 1.76 ± 4.47	$p = 0.003$		
	Fallahi et al. [29]	Univariate analysis revealed an association between the pack-years of smoking and BASMI: $B = 0.05$, SE = 0.02, 95% CI: 0.006–0.08	–	–	$p = 0.03$	Cross-sectional study	4
		Hand-ground distance (cm): 23.77 ± 10.19	–	Hand-ground distance (cm): 23.77 ± 10.19	$p = 0.02$	Case-control study	4

	Kaan et al. [31]	Dorsal Schober's test (cm): 3.13 ± 2.11	-	Dorsal Schober's test (cm): 2.39 ± 0.87	$p = 0.082$		
		Lumbar Schober's test (cm): 3.16 ± 1.95	-	Lumbar Schober's test (cm): 4.99 ± 2.01	$p = 0.011$		
		Chest expansion (cm): 2.51 ± 1.87	-	Chest expansion (cm): 3.81 ± 1.32	$p = 0.002$		
		Chin-manibrium distance (cm): 3.71 ± 2.65	-	Chin-manibrium distance (cm): 2.71 ± 1.71	$p = 0.123$		
		Wall-occiput distance (cm): 3.85 ± 6.99	-	Wall-occiput distance (cm): 0.833 ± 0.28	$p = 0.004$		
	Zhang et al. [33]	BASMI		BASMI	$p = 0.00$	Cross-sectional study	4
		2.2 ± 2.3	–	1.5 ± 2.0			
	Averns et al. [36]	Occiput-wall distance (cm): 3.9 (3.5–11.5)	Occiput-wall distance (cm): 0 (5.5–16.5)	Occiput-wall distance (cm): 0 (16–9)	NS	Cross-sectional study	4
		Finger floor distance (cm): 6.3 (20.2–24.5)	Finger floor distance (cm): 1.5 (24.5–9.5)	Finger floor distance (cm): 0 (28.5–20)	NS		
		Chest expansion (cm): 1.2 (−2.3 to 1.6)	Chest expansion (cm): 1.5 (6.9–0.5)	Chest expansion (cm): 1.5 (−4.6 to 2)	NS		
		Total spine movement: 1.9 (6.25–2.9)	Total spine movement: 0.9 (5.3–2.3)	Total spine movement: 1 (8.5–8)	NS		
Functional status	Chung et al. [8]	BASFI	–	–	$p = 0.02$	Cross-sectional analysis of the DESIR cohort	4
		$B = 0.38$, 95% CI: 0.07–0.69					
		HAQ-AS					
		NS	–	–	–		
	Sakellariou et al. [9]	BASFI	BASFI	BASFI	$p = 0.035$	Cross-sectional stud	4
		5.3 ± 2.8	5.0 ± 2.7	3.9 ± 1.9			
	Chen et al. [28]	BASFI		BASFI	$p = 0.240$	Case-control study	4
		2.54 ± 2.30		2.05 ± 2.16			
	Reed et al. [30]	BASFI	BASFI	BASFI	$p < 0.05$	Cross-sectional study	4
		6.3 ± 2.30	5.4 ± 3.2	4.7 ± 2.3			
	Kaan et al. [31]	BASFI	–	BASFI	$p = 0.002$	Case–control study	4
		40.04 ± 18.55		22.75 ± 16.40			
	Mattey et al. [32]	BASFI	BASFI	BASFI	$p < 0.0001$	Cross-sectional study	4
		5.0 (3.0–8.0)	5.0 (2.0–8.0)	4.0 (2.0–6.0)			
	Zhang et al. [33]	BASFI	–	BASFI	$p = 0.00$	Cross-sectional study	4
		2.2 ± 2.2		1.4 ± 1.8			
	Ward et al. [34]	BASFI	–	BASFI (non-smoker or former smoker are included in the same group)	$p = 0.0002$	Cross-sectional component of the Prospective Study of Outcomes in AS	4
		55.5 ± 27.4		38.9 ± 24.8			
		HAQ	–	HAQ (non-smoker or former smoker are included in the same group)	$p < 0.0001$		
		1.1 (0.7–1.4)		0.6 (0.3–1.1)			
	Doran et al. [37]	BASFI	–	–	$p = 0.02$	Cross-sectional study	4
		$B = 0.618$; 95% CI: 0.0108-1.22					
	Ward et al. [38]	HAQ-AS	–	–	$p = 0.007$	Prospective longitudinal study	2b
		0.025, 95% CI: 0.0071–0.0429					
Structural damage	Chung et al. [8]	Smoking was associated with				Cross-sectional analysis of the DESIR cohort	4
		More frequent MRI inflammation of the sacroiliac joints: OR = 1.57; 95% CI: 1.08–2.30	–	–	$p = 0.02$		
		More frequent MRI inflammation of the spine: OR = 2.33, 95% CI: 1.55–3.51	–	–	$p < 0.001$		
		More frequent MRI structural lesions of the sacroiliac joints: OR = 1.54, 95% CI: 1.05–2.26	–	–	$p = 0.03$		
		More frequent MRI structural lesions of the spine: OR = 2.02, 95% CI: 1.15–3.55	–	–	$p = 0.01$		
		Higher mSASSS: $B = 0.54$, 95% CI: 0.05–1.03	–	–	$p = 0.03$		

Table 2 (*continued*)

Outcomes	References	Smokers	Past-smokers	Non-smokers	Statistical association	Study design	LE
	Sakellariou et al. [9]	Pack-years (smoking intensity) were independently associated with higher mSASSS: $B = 0.26$; 95% CI: 0.08–0.43	–	–	$p = 0.005$	Cross-sectional study	4
	Fallahi et al. [29]	Ankylosis in Rx (sacroiliitis grading = 4): 38.3%	–	Ankylosis (sacroiliitis grading = 4): 13.3% (ex-smokers and non-smokers are included in the same group)	$p = 0.001$	Cross-sectional study	4
	Ward et al. [35]	Radiographic severity was associated with current smoker: OR = 4.72; 95% CI: 2.16–10.30		–	$p <$ 0.0001	Cross-sectional component of the Prospective Study of Outcomes in AS	4
	Doran et al. [37]	BASRI NS	– BASRI NS	BASRI NS	 NS	Cross-sectional study	4
	Ramiro et al. [40]	2-year increase in mSASSS per one-ASDAS unit increase (units, 95% CI): 1.94 (1.00–2.87)	–	2-year increase in mSASSS per one-ASDAS unit increase (units, 95% CI): 0.35	$p < 0.001$	Prospective Cohort (outcome in ankylosing spondylitis international Study:OASIS)	2b
	Poddubnyy et al. [41,42]	Smoking was associated with spinal radiographic progression (mSASSS ≥ 2 over 2 y): OR = 2.75; 95% CI: 1.25–6.05		(0.04–0.65)			
		Heavy smoking (> 10 cigarettes a day) was associated with mSASSS ≥ 2 over 2 y: OR = 3.48, 95% CI: 1.06–11.42	–	–	$p = 0.012$	Prospective Cohort (German Spondyloarthritis Inception Cohort: GESPIC)	1b
		Heavy smoking was associated too with formation of new syndesmophytes: OR = 3.53, 95% CI: 1.25–9.98	–	–	$p = 0.039$		
			–	–	$p = 0.018$		
Quality of life	Fallahi et al. [29]	Relation between pack-years of smoking and ASQoL: $B = 0.11$, 95% CI: 0.21–0.003	–	–	$p = 0.04$		
	Reed et al. [30]	ASQoL 13.2 ± 4.7	ASQoL 8.7 ± 4.7	ASQoL 8.6 ± 5.0	$p <$ 0.0005	Cross-sectional study	4
	Mattey et al. [32]	ASQoL $B = 0.697$; SE = 0.249, OR = 2.00; 95% CI: 1.25–3.22 Increasing pack-year history was associated with poor EASi-QoL: $B = 0.280$; SE = 0.098, OR = 1.32; 95% CI: 1.09–1.60	– – –	– – –	$p = 0.004$ $p = 0.004$	Cross-sectional study	4
	Bodur et al. [39]	ASQoL 6.3 ± 5.4 SF-36 There was no significant difference between smokers and non-smokers regarding SF-36 subscale scores (no data provided)	 –	ASQoL 7.3 ± 5.7	$p < 0.05$	Cross-sectional study Cross-sectional analysis of the DESIR cohort	4 4
	Chung et al. [8]	Smoking was associated with poorer quality of life Euro-QoL: $B = 1.38$, 95% CI: 0.69–2.07 SF-36 physical component: $B = -4.89$, 95% CI: −7.24 to −2.54 SF-36 mental component: $B = -5.90$, 95% CI: −8.99 to −2.81	 – – –	 – – –	 $p < 0.001$ $p < 0.001$ $p < 0.001$		

LE, level of evidence; NS, not significant; VAS, visual analogue scale; IB*p*, inflammatory back pain; *B*, regression coefficient; SE, standard error; OR, odds ratio; CI, confidence interval; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; ASQoL, Ankylosing Spondylitis Quality of Life Questionnaire; EASi-QoL, AS quality of life measures; SF-36, Short Form-36; Euro-QoL, Euro-quality of life questionnaire; BASMI, Bath Ankylosing Spondylitis Metrology Index; BASFI, Bath Ankylosing Spondylitis Functional Index; mSASSS, modified Stoke Ankylosing Spondylitis Spine Score; BASRI, Bath AS Radiology Index.

[a] Median (interquartile range).

[b] Mean score (95% CI).

Table 3
Excluded studies and reasons for exclusion

Studies	Reasons for exclusion
Poddubnyy et al. [43]	Did not meet study design eligibility. Specific data about smoking effect on radiographic sacroiliitis progression are not shown in this study.
Poddubnyy et al. [44]	Did not meet study design eligibility. No specific data related to this review objective
Ramiro et al. [45]	Did not meet study design eligibility
Ciurea and Finckh [46]	Letter to the editor
Kydd et al. [47]	Did not meet study design eligibility
Gaber et al. [48]	Low quality
Wendling and Prati [49]	Review

Smoking was independently associated with higher disease activity (measured by BASDAI) in patients with axSpA ($B = 0.50$, $p = 0.003$) in the DESIR cohort [8].

Physical mobility

The association between smoking and physical mobility in AS patients was evaluated in 6 cross-sectional studies [8,28,29,31,33,36]. The measures that were used to examine the physical mobility were as follows: the Bath Ankylosing Spondylitis Metrology Index (BASMI) in 3 studies [8,29,33] and physical examinations [tragus-to-wall distance (cm), modified Schöber's index (cm), intermalleolar distance (cm), cervical rotation (degree), lateral lumbar flexion (cm), fingertip-to-floor distance (cm), chest expansion (cm) and occiput-to-wall distance (cm)] in the other 3 studies [29,31,36]. Compared to the non-smokers, smoking patients had significantly higher BASMI [8,29,33] but no correlation with pack-years, was found by Fallahi el al. [29]. Among the physical mobility parameters, it is of interest that modified Schöber's index, cervical rotation, lateral lumbar flexion and chest expansion were significantly reduced in smoking AS patients as than those with non-smoking. In addition, occiput-to-wall distances were significantly increased in smoking patients than those with non-smoking. Taken together, smoking AS patients showed relatively poor physical mobility than those with non-smoking [28,31,36].

Functional status

Functional status in AS patients, was reported in 10 studies: 9 cross-sectional studies [8,9,28,30–34,37] and 1 longitudinal study [38]. Two measures of functional limitations were used as the Bath AS Functional Index (BASFI) in 9 studies [8,9,28,30–34,37] and the Health Assessment Questionnaire modified for the Spondyloarthropaties (HAQ-AS) in 3 studies [8,34,38]. Regarding function, ever smokers had significantly higher BASFI scores than never smokers and there was a significant positive association between smoking pack-years and BASFI. In 5 studies, current smoking, ever smoking or increasing smoking intensity was an independent variable for higher levels of functional limitation in AS [9,28,29,32,34]. Functional disability in AS (HAQ-AS) progressed more rapidly in smokers. Smoking was also associated with the progression of functional disability in the subgroup of patients who had AS for less than 10 years [38].

A cross-sectional analysis of the DESIR cohort [8], showed that smoking was independently associated with worse functional status (measured by BASFI) in patients with axSpA ($B = 0.38$, $p = 0.02$).

Structural damage

Structural damage was reported in 5 cross-sectional studies [8,9,29,35,37] and 3 prospective cohort study [40–42]. The Bath Ankylosing Spondylitis Radiology Index for the spine (BASRI-s), the modified Stoke Ankylosing Spondylitis Spine Score (mSASSS) and the New York criteria were used to evaluate the radiographic damage.

Fallahi et al. [29] compared sacroiliitis grading (2 minimal, 3 moderate and 4 ankylosis) between current and non-current smokers and ankylosis was significantly more common in current AS smokers ($p = 0.001$). The pack-years of smoking was higher for the AS patients with sacroiliac ankylosis than for those with moderate or minimal sacroiliitis. Radiographic severity (scored by BASRI-s) was associated with current smoker (OR = 4.72; 95% CI: 2.16–10.30; $p < 0.0001$) [35]. There was an independent positive association between smoking pack-years and mSASSS ($B = 0.26$; SE = 0.32; 95% IC: 0.08–0.43; $p = 0.005$) [9]. Ramiro et al. [40] found that every additional unit of ASDAS resulted in an increase of 1.9 vs. 0.4 mSASSS units/2 y in AS smokers vs. non-smokers. The influence of smoking on the association between ASDAS and radiographic progression was statistically stronger than the effect of job type on this relationship in this study (data from OASIS cohort). A cross-sectional analysis of another cohort (DESIR cohort) [8], showed that smoking was independently associated with an increased axial inflammation on MRI (OR = 1.57, $p = 0.02$), increased axial structural damage on MRI (OR = 1.54, $p = 0.03$) and radiographs scored by mSASSS ($B = 0.54$, $p = 0.03$).

Poddubnyy et al. [41] evaluated prospectively the rates and the predictors of spinal radiographic progression scored by mSASSS over 2 years in a cohort of patients with early axSpA. Spinal radiographic progression was independently associated with cigarette smoking (OR = 2.75, $p = 0.012$). The same authors, in a more recent study, found that not only smoking but also smoking intensity (> 10 cigarettes a day), was associated with mSASSS progression: ≥ 2 points (OR = 3.57; 95% CI: 1.33–9.60; $p = 0.012$) after adjustment for baseline syndesmophytes, C-reactive protein level, gender, presence of definite radiographic sacroiliitis, use of non-steroidal anti-inflammatory drugs and tumour necrosis factor blockers (OR = 3.48; 95% CI: 1.06–11.42; $p = 0.039$). Heavy smoking vs. non-smoking, was associated too with formation of new syndesmophytes over 2 years after adjustment for all factors mentioned above (OR = 4.17; 95% CI: 0.79–22.02; $p = 0.093$) [42].

Quality of life

We included 4 cross-sectional studies [29,30,32,39] in which the correlation between smoking and quality of life in patients with AS, was investigated. Three measures of quality of life were used: the AS Quality of Life (ASQoL), Short Form-36 (SF-36) and Evaluation of AS Quality of Life (EASi-QoL). Fallahi et al. [29] found that the pack-years of smoking were positively and independently associated with the higher ASQoL scores [regression coefficient (B) = 0.11; standard error (SE) = 0.05; 95% CI: 0.21–0.003; $p = 0.04$]. Reed et al. [30] found a decrease in quality of life associated with current smoking ($B = 4.24$; 95% CI: 2.16–6.32; $p < 0.0001$). There was, however, no relation between cumulative exposure (pack-years) and composite indices (data were not shown). Regarding SF-36 subscale scores, there was no significant difference between

smokers and non-smokers [39]. Quality of life was shown to be significantly worse in those who had ever smoked compared to those who had never smoked, as measured by EASi-QoL (all 4 domains) [32]. Poor quality of life measures were associated more closely with increasing pack-year history too ($p < 0.05$).

Smoking was also associated with poorer quality of life scored by Euro-Qol ($B = 1.38$, $p < 0.001$), short form 36 physical ($B = -4.89$, $p < 0.001$) and mental component score ($B = -5.90$, $p < 0.001$) in patients with axSpA [8].

Discussion

We conducted a systematic review of the scientific literature to analyse the association between smoking and clinical, functional status, structural damage and quality of life in patients with axSpA.

Most of the included studies were cross-sectional studies with low quality. Four studies (2 EA and 2 axSpA) were prospective cohort studies with appropriate follow-up periods and moderate-good methodological quality. Studies varied substantially in terms of design, outcomes measures and the smoking habit evaluation (some studies evaluated 2 patients groups: current smoker and non-smoker, other studies analysed 3 groups: current smoker, ex-smokers and non-smokers; past-smokers and non-smokers were grouped together in various studies but former smokers were included in the current smokers group in 2 studies. Quantity of smoking (pack-years) was defined in 6 studies.

In our systematic review, we found weak evidence on the smoking effect on pain level and overall assessment of health in AS patients in 3 studies. The association between smoking and morning stiffness was reported in only 1 cross-sectional study. Although this study suggested that smokers had worse morning stiffness compared to non-smoking patients, the level of evidence is weak and based on a low quality study.

The effect of smoking on disease activity in AS patients was examined in 8 of the studies. According to these reports, current smokers had higher scores than non-current smokers. Current smoking was an independent variable for higher BASDAI after adjusting for confounding factors. No correlation between BASDAI and quantity of smoking (pack-years) was found in the studies. However, the evidence level is weak. All the studies were cross-sectional, being impossible to directly address the effect of smoking cessation on disease activity measures. There were also differences between the studies respect to smoking habit evaluation. Chen et al. [28] included current smokers and past-smokers in the same group, while Fallahi et al. [29] and Zhang et al. [33] included past-smokers in the non-smokers group. Most of the studies collected smoking habit by face-to-face interview, but the data on smoking were retrospective in Zhang et al. [33], which may have caused misclassification of some patients and it was not possible to determine whether there were differences in smoking status between participants and non-participants in Mattey et al. [32] study, because data were collected from a questionnaire that patients completed at home and returned by mail and no information was obtained on patients failing to respond the questionnaire.

Respect to physical mobility, although the studies design was heterogeneous and the measures used to determine patient mobility were different, all evidence points in the same direction: smoking AS patients had poor physical mobility than those with non-smoking. No correlation with smoking quantity was found [29].

Our systematic review showed some evidence focused on smoking effect on functional status in AS patients. HAQ-AS progressed more rapidly in smokers. Smoking was also associated with the progression of functional disability in the subgroup of patients who had AS for less than 10 years. The evidence level is moderate and based on a moderate good-quality study. Although this study design was prospective with moderately long follow-up, the sample was large and a wide variety of predictors were examined, the generally slow rate of progression may have decreased the statistical power to detect associations with some predictors.

Current smoking and smoking quantity (pack-years) were significantly associated with worse structural damage. However, the measures to evaluate structural damage in AS patients were different (only 2 studies used the same measure: BASRI), the quality of these studies was low and AS activity or certain clinical features such as non-steroidal anti-inflammatory drug use and potential prognostic factors due to the absence of complete historical data, were not examined. Regarding the smoking effect in patients with axSpA, the strongest level of evidence is based on 2 very good-quality studies [41,42], where spinal radiographic progression scored by mSASSS, was independently associated with cigarette smoking and smoking intensity.

This review found poor evidence respect to the correlation between smoking and quality of life. Current smoking and smoking quantity (pack-years) were positively and independently associated with higher ASQoL and EASi-QoL scores, but there was no significant difference between smokers and non-smokers regarding SF-36 subscale score. Although these studies suggested that smoking has a negative impact on quality of life in AS patients, all of them were cross-sectional low-quality studies, being not possible to directly address the smoking cessation impact on life quality measures.

Conclusion

Published data indicate with good level of evidence, that smoking has a dose-dependent impact on structural damage progression in axSpA. There is higher HAQ among AS smokers compared to non-smokers too. Respect to overall assessment of health, global disease activity, physical mobility and quality of life, although the studies design is heterogeneous and the level of evidence is poor, all evidence points in the same direction: smoking AS patients are worse than non-smoking.

Appendix A. Supplementary material

Supplementary data are available in the online version of this article at http://dx.doi.org/10.1016/j.semarthrit.2016.11.004

References

[1] Zochling J, Brandt J, Braun J. The current concept of spondyloarthritis with special emphasis on undifferentiated spondyloarthritis. Rheumatology (Oxford) 2005;44:1483–91.
[2] Aho K, Heliovaara M. Risk factors for rheumatoid arthritis. Ann Med 2004;36:242–51.
[3] Stolt P, Bengtsson C, Nordmark B, Lindblad S, Lundberg I, Klareskog L, 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.
[4] 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.
[5] Klareskog L, Stolt P, Lundberg K, Källberg H, Bengtsson C, Grunewald J, 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.
[6] Costenbader KH, Kim DJ, Peerdaza J, Lockman S, Nobles-Knight D, Petri M, et al. Cigarette smoking and the risk of systemic lupus erythematosus: a meta-analysis. Arthritis Rheum 2004;50:849–57.

[7] Freemer MM, King TETE Jr, Criswell LA. Association of smoking with dsDNA autoantibody production in systemic lupus erythematosus. Ann Rheum Dis 2006;65:581–4.
[8] Chung HY, Machado P, van der Heijde D, D'Agostino MA, Dougados M. Smokers in early axial spondyloarthritis have earlier disease onset, more disease activity, inflammation and damage, and poorer function and health-realted quality of life: results from the DESIR cohort. Ann Rheum Dis 2012;71:809–16.
[9] Sakellariou GT, Anastasilakis AD, Kenanidis E, Potoupnis M, Tsiridis E, Savvidis M, et al. The effect of smoking on clinical and radiographic variables and acute phase reactants in patients with ankylosing spondylitis. Rheumatol Int 2015;35:2109–14.
[10] Rudwaleit M, Landewé R, van der Heijde D, Listing J, Brandt J, Braun J, et al. The development of Assessment of SpondyloArthritis international Society classification criteria for axial spondyloarthritis (part I): classification of paper patients by expert opinion including uncertainty appraisal. Ann Rheum Dis 2009;68:770–6.
[11] Rudwaleit M, van der Heijde D, Landewé R, Listing J, Akkoc N, Brandt J, et al. The development of Assessment of SpondyloArthritis international Society classification criteria for axial spondyloarthritis (part II): validation and final selection. Ann Rheum Dis 2009;68:777–83.
[12] Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gotzsche PC, Ioannidis JP, et al. The PRISMA statement for reporting systematic reviews and metaanalyses of studies that evaluate health care interventions: explanation and elaboration. Ann Intern Med 2009;151:W65–94.
[13] van der Linden S, Valkenburg HA, Cats A. Evaluation of diagnostic criteria for ankylosing spondylitis. A proposal for modification of the New York criteria. Arthritis Rheum 1984;27:361–8.
[14] Dougados M, van der Linden S, Juhlin R, Huitfeldt B, Amor B, Calin A, et al. The European Spondyloarthropathy Study Group preliminary criteria for the classification of spondyloarthropathy. Arthritis Rheum 1991;34:1218–27.
[15] Amor B, Dougados M, Mijiyawa M. Criteria of the classification of spondyloarthropathies. Rev Rhum Mal Osteoartic 1990;57:85–9.
[16] Garrett S, Jenkinson T, Kennedy LG, Whitelock H, Gaisford P, Calin A. A new approach to defining disease status in ankylosing spondylitis: the Bath Ankylosing Spondylitis Disease Activity Index. J Rheumatol 1994;21:2286–91.
[17] Lukas C, Landewé R, Sieper J, Dougados M, Davis J, Braun J, et al. Development of an ASAS-endorsed disease activity score (ASDAS) in patients with ankylosing spondylitis. Ann Rheum Dis 2009;68:18–24.
[18] Jenkinson TR, Mallorie PA, Whitelock HC, Kennedy LG, Garrett SL, Calin A. Defining spinal mobility in ankylosing spondylitis. The Bath AS Metrology Index. J Rheumatol 1994;21:1694–8.
[19] Calin A, Garrett S, Whitelock H, Kennedy LG, O'Hea J, Mallorie P, et al. A new approach to defining functional ability in ankylosing spondylitis: the development of the Bath Ankylosing Spondylitis Functional Index. J Rheumatol 1994;21:2281–5.
[20] Guillemin F, Briancon S, Pourel J, Gaucher A. Long-term disability and prolonged sick leaves as outcome measurements in ankylosing spondylitis. Possible predictive factors. Arthritis Rheum 1990;33:1001–6.
[21] MacKay K, Mack C, Brophy S, Calin A. The Bath Ankylosing Spondylitis Radiology Index (BASRI): a new, validated approach to disease assessment. Arthritis Rheum 1998;41:2263–70.
[22] Creemers MC, Franssen MJ, van't Hof MA, Gribnau FW, van de Putte LB, van Riel PL. Assessment of outcome in ankylosing spondylitis: an extended radiographic scoring system. Ann Rheum Dis 2005;64:127–9.
[23] 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.
[24] Ware JE, Kosinski M, Dewey JE, Gandek B. SF-36 Health Survey: Manual and Interpretation Guide. Lincoln: Quality Metric Inc; 2000.
[25] Maruish ME, editor. User's Manual for the SF-12 Health Survey. 3rd ed. Lincoln: Quality Metric Inc; 2012.
[26] Haywood KL, Garratt AM, Jordan KP, Healey EL, Packham JC. Evaluation of Ankylosing Spondylitis Quality of Like (EASi-QoL): Reliability and validity of a new patient-reported outcome measure. J Rheumatol 2010;37:2100–9.
[27] Phillips B, Ball C, Sackett D, Badenoch D, Straus S, Haynes B, et al. (2001). Oxford centre for evidence-based medicine levels of evidence. BJU Int 2009;104:1825.
[28] Chen CH, Chen HA, Lu CL, Liao HT, Liu CH, Tsai CY, et al. Association of cigarette smoking with Chinese ankylosing spondylitis patients in Taiwan: a poor disease outcome in systemic inflammation, functional ability, and physical mobility. Clin Rheumatol 2013;32:659–63.
[29] Fallahi S, Jamshidi AR, Gharibdoost F, Mahmoudi M, Ahmadzadeh N, Nicknam MH. The correlation between pack-years of smoking and disease activity, quality of life, spinal mobility and sacroiliitis grading in patients with ankylosing spondylitis. Turk J Rheumatol 2013;28:181–8.
[30] Reed MD, Dharmage S, Boers A, Martin BJ, Buchanan RR, Schachna L. Ankylosing spondylitis: an Australian experience. Intern Med J 2008;38(5):321–7.
[31] Kaan U, Ferda O. Evaluation of clinical activity and functional impairment in smokers with ankylosing spondylitis. Rheumatol Int 2005;25:357–60.
[32] Mattey DL, Dawson SR, Healey EL, Packham JC. Relationship between smoking and patient-reported measures of disease outcome in ankylosing spondylitis. J Rheumatol 2011;38:2608–15.
[33] Zhang S, Li Y, Xu X, Feng X, Yang D, Lin G. Effect of cigarette smoking and alcohol consumption on disease activity and physical functioning in ankylosing spondylitis: a cross-sectional study. Int J Clin Exp Med 2015;8(8):13919–27.
[34] Ward MM, Weisman MH, Davis JCJC Jr., Reveille JD. Risk factors for functional limitations in patients with long-standing ankylosing spondylitis. Arthritis Rheum 2005;53:710–7.
[35] Ward MM, Hendrey MR, Malley JD, Learch TJ, Davis JCJC Jr., Reveille JD, et al. Clinical and immunogenetic prognostic factors for radiographic severity in ankylosing spondylitis. Arthritis Rheum 2009;61:859–66.
[36] Averns HL, Oxtoby J, Taylor HG, Jones PW, Dziedzic K, Dawes PT. Smoking and outcome in ankylosing spondylitis. Scan J Rheumatol 1996;25:138–42.
[37] Doran MF, Brophy S, MacKay K, Taylor G, Calin A. Predictors of longterm outcome in ankylosing spondylitis. J Rheumatol 2003;30:316–20.
[38] Ward MM. Predictors of the progression of functional disability in patients with ankylosing spondylitis. J Rheumatol 2002;29:1420–5.
[39] 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.
[40] Ramiro S, Landewé R, van Tubergen A, Boonen A, Stolwijk C, Dougados M, et al. Lifestyle factors may modify the effect of disease activity on radiographic progression in patients with ankylosing spondylitis: a longitudinal analysis. RMD Open 2015;1:e000153, http://dx.doi.org/10.1136/rmdopen-2015-000153.
[41] Poddubnyy D, Haibel H, Listing J, Märker-Hermann E, Zeidler H, Braun J, et al. Baseline radiographic damage, elevated acute-phase reactant levels and cigarette smoking status predict spinal radiographic progression in early axial spondyloarthritis. Arthritis Rheum 2012;64:1388–98.
[42] Poddubnyy D, Haibel H, Listing J, Märker-Hermann E, Zeidler H, Braun J, et al. Cigarette smoking has a dose-dependent impact on progression of structural damage in the spine in patients with axial spondyloarthritis: results from the German SPondyloarthritis Inception Cohort (GESPIC). Ann Rheum Dis 2013;72:1430–2.
[43] Poddubnyy D, Rudwaleit M, Haibel H, Listing J, Märker-Hermann E, Zeidler H, et al. Rates of predictors of radiographic sacroiliitis progression over 2 years in patients with axial spondyloarthritis. Ann Rheum Dis 2011;70:1369–74.
[44] Poddubnyy D, Conrad K, Haibel H, Syrbe U, Appel H, Braun J, et al. Elevated serum level of the vascular endothelial growth factor predicts radiographic spinal progression in patients with axial spondyloarthritis. Ann Rheum Dis 2014;73:2137–43.
[45] Ramiro S, van der Heijde D, van Tubergen A, Stolwijk C, Dougados M, van der Bosch F, et al. Higher disease activity leads to more structural damage in the spine in ankylosing spondylitis: 12-year longitudinal data from the OASIS cohort. Ann Rheum Dis 2014;73:1455–61.
[46] Ciurea A, Finckh A. Smoking and spondyloarthritis. Joint Bone Spine 2013;80(3):234–5.
[47] Kydd AS, Chen JS, Makovey J, Chand V, Henderson L, Buchbinder R, et al. Smoking did not modify the effects of anti-TNF treatment on health-related quality of life among Australian ankylosing spondylitis patients. Rheumatology 2015;54(2):310–7.
[48] Gaber W, Hassen AS, Ibrahim I, Nawito ZO. Impact of smoking on disease outcome in ankylosing spondylitis patients. Egypt Rheumatol 2015;37:185–9.
[49] Wendling D, Prati C. Spondyloarthritis and smoking: towards a new insight into the disease. Expert Rev Clin Immunol 2013;9(6):511–6.