EXTENDED REPORT

Smokers in early axial spondyloarthritis have earlier disease onset, more disease activity, inflammation and damage, and poorer function and health-related quality of life: results from the DESIR cohort

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ABSTRACT

Objectives To investigate the association of smoking with various clinical, functional and imaging outcomes in patients with early axial spondyloarthritis (SpA).

Methods 647 patients with early inflammatory back pain (IBP) fulfilling at least one of the internationally accepted SpA criteria and with available smoking data were included in the analyses. Clinical, demographic and imaging parameters were compared between smokers and non-smokers at a cross-sectional level. Variables with significant differences in univariate analyses were used as dependent variables in multivariate linear and logistic regression models adjusted for potential confounding/contributing factors.

Results Multivariate analysis showed that smoking was associated with an earlier onset of IBP (regression coefficient (B) = (−1.46), p = 0.04), higher disease activity (ankylosing spondylitis disease activity score B = 0.20, p = 0.03; Bath ankylosing spondylitis disease activity index B = 0.50, p = 0.003), worse functional status (Bath ankylosing spondylitis functional index B = 0.38, p = 0.02), more frequent MRI inflammation of the sacroiliac joints (OR 1.57, p = 0.02) and the spine (OR 2.33, p = 0.001), more frequent MRI structural lesions of the sacroiliac joints (OR 1.54, p = 0.03) and the spine (OR 2.02, p = 0.01), and higher modified Stoke ankylosing spondylitis spine score (B = 0.54, p = 0.03) reflecting radiographic structural damage of the spine. Smoking was also associated with poorer quality of life (Euroquality of life questionnaire 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).

Conclusion In early axial SpA patients, smoking was independently associated with an earlier onset of IBP; higher disease activity, increased axial inflammation on MRI, increased axial structural damage on MRI and radiographs, poorer functional status and poorer quality of life.

The interaction between genetic and environmental factors is important in rheumatic diseases, with rheumatoid arthritis (RA) being the classic example of this gene–environment interaction model. Smoking is the best established and most extensively studied environmental risk factor in RA since an association was first reported in the 80’s.5 Smoking in men,7 in the presence of anticitrullinated protein antibodies,8 and with the human leucocyte antigen (HLA)-DR shared epitope gene9 were each individually found to be risk factors for developing RA. Recent research has also shown additive and multiplicative interactions between PTPN22 and heavy smoking in RA.5 Fewer studies have been performed in ankylosing spondylitis (AS), and none in early axial spondyloarthritis (SpA). Smoking was found to be associated with increased disease activity;6 worse physical functioning6–10 and poorer quality of life,11 but inconsistently associated with radiographic severity7 12 in established AS.

The newly developed Assessment of SpondyloArthritis International Society classification criteria for axial SpA13 14 are more inclusive of patients at an early disease stage. As smoking is a well-established risk factor for developing RA15–17 and other inflammatory diseases, such as systemic lupus erythematosus18 and inflammatory bowel disease,19 and has also been associated with phenotypic variations in AS,6–10 12 it would be worthwhile to clarify the impact of smoking in the axial SpA spectrum, particularly in early stage SpA. The aim of our study was to determine the prevalence of smoking and its association with various clinical, functional and imaging outcomes in early axial SpA.

METHODS

This is a cross-sectional analysis involving data collected during the first visit of the Devenir des Spondylarthropathies Indifférenciées Récentes (DESIR) cohort,20 a large multicentre sample consisting of 708 patients in France. Only patients fulfilling at least one of the following classification criteria for axial SpA or AS were included in the analyses: the modified New York criteria,21 European Spondyloarthropy Study Group criteria,22 Amor criteria,23 or Assessment of SpondyloArthritis International Society classification criteria for axial SpA. Details about the cohort design and data collection were described in previous publications.20 24 In this study, we investigated the influence of smoking on the outcome measures described below. 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 (eg, pack-years). The drinking status was captured in a similar way as the smoking status.
Disease activity, function, mobility and quality of life

Disease activity was assessed using both the Bath ankylosing spondylitis disease activity index (BASDAI) and the ankylosing spondylitis disease activity score (ASDAS).

Mobility was measured by the degree of chest expansion and by the Bath ankylosing spondylitis metrology index (BASMI).

A higher BASMI score represents worse spinal mobility.

Patients also completed the Bath ankylosing spondylitis functional index (BASFI) and the health assessment questionnaire for ankylosing spondylitis (HAQ–AS), 2 to assess functional status. Higher scores represent increased disease activity (ASDAS and BASDAI) and poorer functional status (BASFI and HAQ–AS).

Mobility was measured by the degree of chest expansion and by the Bath ankylosing spondylitis metrology index (BASMI). A higher BASMI score represents worse spinal mobility.

Patients completed the Euro-quality of life questionnaire (Euro-QoL), and the short form 36 (SF-36) to assess health-related quality of life (HRQoL). A higher SF-36 score represents better HRQoL.

Radiographs of the sacroiliac joints and the spine

Radiographs of the cervical spine, lumbar spine and sacroiliac joints were performed. Sacroiliac joint radiographs 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. The modified Stoke ankylosing spondylitis spine score (mSASSS) was calculated from the radiographs of the cervical and lumbar spine. All radiographs were graded by regional radiologists or rheumatologists.

Inflammation and structural lesions in MRI

MRI were performed to look for inflammatory and structural lesions. Similar to radiographs, they were evaluated by regional radiologists or rheumatologists. The MRI were classified as having definite, doubtful or absent inflammatory and/or structural lesions at the spinal and sacroiliac joint levels according to short T1 inversion recovery and T1-weighted fast spin echo images, respectively (1.5 Tesla). Positive images in our analyses were defined as MRI with definite lesions.

Statistical analyses

The χ² statistic and independent samples t test were used to compare categorical and continuous variables between smokers and non-smokers. Variables noted to have differences (with a p value <0.1) in the previous analyses were used as dependent variables in univariate and multivariate linear/logistic regression models.

In addition to smoking status, factors known or expected to be associated with the investigated dependent variables were also tested as regressors in linear/logistic univariate regression analyses. These included: Caucasian race, male sex, HLA-B27 positivity, family history of SpA, age of inflammatory back pain (IBP) onset, duration of IBP, drinking status, CRP, erythrocyte sedimentation rate (ESR), MRI sacroiliac joint inflammatory lesions, MRI spine inflammatory lesions, non-steroidal anti-inflammatory drug (NSAID) use, ASDAS–CRP and BASMI. Independent variables with a p value less than 0.1 in univariate linear/logistic regression analyses were re-tested in multivariate regression models. Interactions between smoking status and gender/HLA-B27 were tested in each model. Separate regression models were built according to gender/HLA-B27 status if such an interaction existed. Variables with a skewed distribution were transformed using natural logarithms in linear regression models (ESR and CRP). The results were reported as OR in logistic regression models, and regression coefficients (B) and standard coefficients (β) in linear regression models. The 95% CI were calculated and p values less than 0.05 were considered statistically significant. All statistical analyses were performed using the statistical product and service solutions package 18.0.

RESULTS

Six hundred and fifty-four patients (92.4% of recruited patients) fulfilled at least one of the internationally accepted SpA criteria. Smoking data were missing in seven of 654 patients (1.1%), resulting in 647 patients included in our analyses. Detailed characteristics of this study population have previously been reported. The number of smokers (past history or concomitant smoking) in the analysed sample was 241 (37.2%).

Table 1 compares the baseline characteristics between smoking and non-smoking early SpA patients. Smokers were more likely to be men, had an earlier onset of IBP and higher disease activity (higher BASDAI and ASDAS–CRP). Functionally, smokers had poorer functional status (increased BASFI and HAQ–AS) and also had poorer HRQoL (increased Euro-QoL and decreased SF-36) and more missing workdays as a result of SpA. On imaging examinations, smokers were more likely to have MRI inflammation and structural damage as well as radiographic lesions in the spine and sacroiliac joints.

Regression analyses

Age of IBP onset as dependent variable

Independent variables tested in univariate analyses included: Caucasian race, male sex, HLA-B27 positivity, family history of SpA, and smoking and drinking status. Significant variables associated with the age of onset of IBP (p<0.01) were: Caucasian race (β=2.5, p=0.03), male sex (β=2.06, p=0.003), HLA-B27 positivity (β=-2.95, p=0.001), family history of SpA (β=1.58, p=0.05) and smoking (β=-1.46, p=0.04). Multivariate analysis showed that Caucasian race (β=0.13, B=3.79, 95% CI 1.55 to 6.04, p=0.001) was independently associated with later age of IBP onset while HLA-B27 positivity (β=-0.44, B=-2.60, 95% CI -4.03 to -1.18, p=0.02), smoking (β=-0.08, B=-1.46, 95% CI -2.87 to 0.06, p=0.04) and male sex (β=-0.10, B=-1.67, 95% CI -3.06 to -0.29, p=0.02) were independently associated with earlier age of IBP onset.

ASDAS–CRP and BASDAI as dependent variables

Independent variables tested in univariate models of ASDAS–CRP included: Caucasian race, male sex, HLA-B27 positivity, family history of SpA, smoking, drinking, MRI sacroiliac joint inflammatory lesions, MRI spine inflammatory lesions and NSAID use. Independent variables with a p value less than 0.1 were: Caucasian race (β=-0.57, p=0.001), HLA-B27 positivity (β=-0.2, p=0.02), smoking (β=0.17, p=0.051), drinking (β=-0.25, p=0.04) and MRI spine inflammatory lesions (β=-0.21, p=0.04).

Independent variables tested in univariate models of BASDAI included: Caucasian race, male sex, HLA-B27 positivity, family history of SpA, smoking, drinking, CRP, ESR, MRI sacroiliac joint inflammatory lesions, MRI spine inflammatory lesions and NSAID use. Independent variables with a p value less than 0.1 were: Caucasian race (β=-1.07, p=0.001), male sex (β=-0.63), smoking (β=-0.25, p=0.04) and MRI spine inflammatory lesions (β=-0.21, p=0.04).
Independent variables tested in univariate models of BASFI and HAQ–AS as dependent variables included: Caucasian race, male sex, HLA-B27 positivity (B=(−0.75), p<0.001), smoking (B=0.31, p=0.06), drinking (B=(−0.59), p=0.01), CRP (B=0.25, p<0.001), ESR (B=0.46, p<0.001) and MRI sacroiliac joint inflammatory lesions (B=(−0.60), p<0.001).

The multivariate analyses for ASDAS–CRP and BASDAI are shown in table 2. Smoking was independently associated with higher ASDAS–CRP and BASDAI scores. BASFI and HAQ–AS as dependent variables

Independent variables tested in univariate models of BASFI and HAQ–AS included: Caucasian race, male sex, HLA-B27 positivity, family history of SpA, duration of IBP, smoking, drinking, MRI sacroiliac joint inflammatory lesions, MRI spine inflammatory lesions, NSAID use, ASDAS–CRP and BASMI.

Independent variables with a p value less than 0.1 in the BASFI model were: Caucasian race (B=(−0.68), p<0.001), male sex (B=−0.57, p=0.002), HLA-B27 positivity (B=(−0.66), p<0.001), smoking (B=0.61, p=0.001), drinking (B=(−0.63), p=0.01), MRI sacroiliac joint inflammatory lesions (B=(−0.39), p=0.04), MRI spine inflammatory lesions (B=0.46, p=0.04), ASDAS–CRP (B=1.30, p<0.001) and BASMI (B=0.64, p<0.001).

Independent variables with a p value less than 0.1 in the HAQ–AS model were: Caucasian race (B=(−0.27), p=0.003), male sex (B=−0.37, p=0.001), HLA-B27 positivity (B=−0.23), smoking (B=0.61, p=0.001), drinking (B=(−0.63), p=0.01), MRI sacroiliac joint inflammatory lesions, MRI spine inflammatory lesions, NSAID use, ASDAS–CRP and BASMI.

The multivariate analyses for ASDAS–CRP and BASDAI are shown in table 2. Smoking was independently associated with higher ASDAS–CRP and BASDAI scores. BASFI and HAQ–AS as dependent variables

Independent variables tested in univariate models of BASFI and HAQ–AS included: Caucasian race, male sex, HLA-B27 positivity, family history of SpA, duration of IBP, smoking, drinking, MRI sacroiliac joint inflammatory lesions, MRI spine inflammatory lesions, NSAID use, ASDAS–CRP and BASMI.

Independent variables with a p value less than 0.1 in the BASFI model were: Caucasian race (B=(−0.68), p<0.001), male sex (B=−0.57, p=0.002), HLA-B27 positivity (B=(−0.66), p<0.001), smoking (B=0.61, p=0.001), drinking (B=(−0.63), p=0.01), MRI sacroiliac joint inflammatory lesions (B=(−0.39), p=0.04), MRI spine inflammatory lesions (B=0.46, p=0.04), ASDAS–CRP (B=1.30, p<0.001) and BASMI (B=0.64, p<0.001).

Independent variables with a p value less than 0.1 in the HAQ–AS model were: Caucasian race (B=(−0.27), p=0.003), male sex (B=−0.37, p=0.001), HLA-B27 positivity (B=−0.23), smoking (B=0.61, p=0.001), drinking (B=(−0.63), p=0.01), MRI sacroiliac joint inflammatory lesions, MRI spine inflammatory lesions, NSAID use, ASDAS–CRP and BASMI.

The multivariate analyses for ASDAS–CRP and BASDAI are shown in table 2. Smoking was independently associated with higher ASDAS–CRP and BASDAI scores. BASFI and HAQ–AS as dependent variables

Independent variables tested in univariate models of BASFI and HAQ–AS included: Caucasian race, male sex, HLA-B27 positivity, family history of SpA, duration of IBP, smoking, drinking, MRI sacroiliac joint inflammatory lesions, MRI spine inflammatory lesions, NSAID use, ASDAS–CRP and BASMI.

Independent variables with a p value less than 0.1 in the BASFI model were: Caucasian race (B=(−0.68), p<0.001), male sex (B=−0.57, p=0.002), HLA-B27 positivity (B=(−0.66), p<0.001), smoking (B=0.61, p=0.001), drinking (B=(−0.63), p=0.01), MRI sacroiliac joint inflammatory lesions (B=(−0.39), p=0.04), MRI spine inflammatory lesions (B=0.46, p=0.04), ASDAS–CRP (B=1.30, p<0.001) and BASMI (B=0.64, p<0.001).

Independent variables with a p value less than 0.1 in the HAQ–AS model were: Caucasian race (B=(−0.27), p=0.003), male sex (B=−0.37, p=0.001), HLA-B27 positivity (B=−0.23), smoking (B=0.61, p=0.001), drinking (B=(−0.63), p=0.01), MRI sacroiliac joint inflammatory lesions, MRI spine inflammatory lesions, NSAID use, ASDAS–CRP and BASMI.
<table>
<thead>
<tr>
<th>Variable</th>
<th>Regression coefficient</th>
<th>Standard coefficient</th>
<th>(95% CI)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smoker</td>
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<td>0.08</td>
<td>0.003</td>
<td>0.002</td>
</tr>
<tr>
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<td>-0.01</td>
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</tr>
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<td>-0.01</td>
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<td>-0.01</td>
<td>0.001</td>
</tr>
<tr>
<td>CRP</td>
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<td>-0.01</td>
<td>0.001</td>
</tr>
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<td>-0.01</td>
<td>-0.01</td>
<td>0.001</td>
</tr>
<tr>
<td>MRI sacroiliac joints</td>
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<td>-0.01</td>
<td>-0.01</td>
<td>0.001</td>
</tr>
<tr>
<td>ASDAS-ESR</td>
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<td>-0.01</td>
<td>-0.01</td>
<td>0.001</td>
</tr>
<tr>
<td>BASMI</td>
<td>0.01</td>
<td>-0.01</td>
<td>-0.01</td>
<td>0.001</td>
</tr>
</tbody>
</table>

The multivariate analyses of BASFI and HAQ–AS are shown in Table 2. Smoking was independently associated with higher BASFI scores. The univariate association between smoking and HAQ–AS was lost in multivariate analysis.

### Euro-QoL and SF-36 as dependent variables

Independent variables tested in univariate models of Euro-QoL and SF-36 physical/mental component scores included: Caucasian race, male sex, HLA-B27 positivity, family history of SpA, duration of IBP, smoking, drinking, ASDAS–CRP, MRI sacroiliac joint inflammatory lesions, MRI spine inflammatory lesions and BASMI.

Independent variables in the Euro-QoL univariate models with a p value less than 0.1 were: Caucasian race (B=−2.44, p<0.001), male sex (B=−2.02, p<0.001), HLA-B27 positivity (B=−1.67, p<0.001), smoking (B=1.67, p<0.001), drinking (B=−1.27, p=0.02), ASDAS–CRP (B=2.75, p<0.001), MRI sacroiliac joint inflammatory lesions (B=−1.39, p=0.001) and BASMI (B=−1.10, p<0.001).

Independent variables in the SF-36 physical component univariate models with a p value less than 0.1 were: Caucasian race (B=9.79, p<0.001), male sex (B=5.65, p<0.001), HLA-B27 positivity (B=5.18, p<0.001), smoking (B=−4.93, p<0.001), drinking (B=4.02, p=0.03), ASDAS–CRP (B=−9.19, p<0.001), MRI sacroiliac joint inflammatory lesions (B=4.81, p=0.001) and BASMI (B=−3.57, p<0.001).

Independent variables in the SF-36 mental component univariate models with a p value less than 0.1 were: Caucasian race (B=12.2, p<0.001), male sex (B=5.68, p<0.001), HLA-B27 positivity (B=5.02, p=0.03), smoking (B=6.51, p<0.001), drinking (B=9.79, p<0.001), ASDAS–CRP (B=−10.14, p<0.001), MRI sacroiliac joint inflammatory lesions (B=4.89, p=0.01) and BASMI (B=3.13, p<0.001).

Table 3 shows the multivariate analyses for Euro-QoL and SF-36. Smoking was independently and positively associated with the Euro-QoL score and negatively associated with the SF-36 physical and mental component scores.

### MRI spine and/or sacroiliac joint inflammation, MRI spine inflammation and MRI sacroiliac joint inflammation as dependent variables

Independent variables tested in univariate models of the above three dependent variables included: Caucasian race, male sex, HLA-B27 positivity, family history of SpA, age at onset of IBP, duration of IBP, CRP, smoking, drinking and NSAID use.

Independent variables in MRI spine and/or sacroiliac joint inflammation models with p value less than 0.1 were: male sex (OR 2.32, p<0.001), HLA-B27 positivity (OR 2.33, p<0.001), age at onset of IBP (OR 0.97, p=0.001), CRP (OR 1.02, p=0.001) and smoking (OR 2.08, p<0.001).

Independent variables in MRI spine inflammation models with a p value less than 0.1 were: male sex (OR 2.47, p<0.001), HLA-B27 positivity (OR 1.73, p=0.01), family history of SpA (OR 1.68, p=0.05), CRP (OR 1.02, p=0.03) and smoking (OR 2.46, p<0.001).

Independent variables in MRI sacroiliac joint inflammation models with a p value less than 0.1 were: Caucasian race (OR 0.59, p=0.05), male sex (OR 2.37, p<0.001), HLA-B27 positivity (OR 2.38, p<0.001), age at onset of IBP (OR 0.96, p=0.01), CRP (OR 1.02, p=0.002), smoking (OR 1.90, p<0.001) and drinking (OR 1.52, p=0.07).
In multivariate analyses, smoking was independently and positively associated with the presence of both sacroiliac joint and spine MRI inflammation (table 4).

MRI spine and/or sacroiliac joint structural lesions, MRI spine structural lesions and MRI sacroiliac joint structural lesions as dependent variables

Independent variables included in univariate models of the above three dependent variables included: Caucasian race, male sex, HLA-B27 positivity, family history of SpA, age at onset of IBP, disease duration, CRP, smoking, drinking and NSAID use.

Independent variables in MRI structural lesion models (spine and/or sacroiliac joints) with a p value less than 0.1 were: HLA-B27 positivity (OR 1.47, p=0.04), duration of IBP (OR 1.19, p=0.06), CRP (OR 1.01, p=0.06) and smoking (OR 1.72, p=0.02).

Independent variables in MRI sacroiliac joint structural lesion models with a p value less than 0.1 were: HLA-B27 positivity (OR 1.67, p=0.01), age at onset of IBP (OR 0.97, p=0.002), CRP (OR 1.01, p=0.04) and smoking (OR 1.74, p=0.005).

The only independent variable with a p value less than 0.1 in MRI spine structural lesion models was smoking (OR 2.02, p=0.01).

The multivariate analyses of the above three dependent variables are shown in table 5. Smoking was found to be positively associated with the presence of both sacroiliac joint and spine MRI structural lesions.

Smoking was found to interact with male sex regarding MRI sacroiliac joint structural lesions. Therefore, separate univariate and multivariate logistic regression models were performed according to gender. Variables with a p value less than 0.1 in the male population were: HLA-B27 positivity (OR 2.41, p=0.01), age at onset of IBP (OR 0.97, p=0.09) and smoking (OR 2.99, p<0.001). Multivariate analysis showed that smoking (OR 2.78, p<0.001) was positively associated with MRI sacroiliac joint structural lesions, while HLA-B27 positivity (OR 1.85, p=0.07) and age at onset of IBP (OR 0.98, p=0.23) were not significantly associated. Variables with a p value less than 0.1 in the female population were: Caucasian race (OR 1.63, p=0.03) and age at onset of IBP (OR 0.97, p=0.02); multivariate analysis showed that both Caucasian race (OR 0.48, p=0.046) and age at onset of IBP (OR 0.97, p=0.03) were associated with MRI sacroiliac joint structural lesions.

Radiographic sacroiliitis and mSASSS as dependent variables

Independent variables included in univariate models of the above two dependent variables included: Caucasian race, male sex, HLA-B27 positivity, family history of SpA, age at onset of IBP, duration of IBP, CRP, smoking, drinking and NSAID use.

Independent variables in radiographic sacroiliitis models with a p value less than 0.1 were: male sex (OR 1.96, p<0.001), HLA-B27 positivity (OR 1.91, p=0.001), age at onset of IBP (OR 0.96, p<0.001), CRP (OR 1.02, p=0.001), smoking (OR 1.44, p=0.04) and drinking (OR 1.77, p=0.02). Independent variables in mSASSS models with a p value less than 0.1 were: male sex (B=0.54, p=0.02), family history of SpA (B=−0.58, p=0.03), age at onset of IBP (B=0.06, p<0.001), CRP (B=0.25, p=0.01) and smoking (B=0.44, p=0.07).

Table 3  Multivariate linear regressions analyses of factors associated with Euro-QoL and SF-36

<table>
<thead>
<tr>
<th>Factor</th>
<th>Standard coefficient (95% CI)</th>
<th>Regression coefficient (95% CI)</th>
<th>p Value</th>
<th>Standard coefficient (95% CI)</th>
<th>Regression coefficient (95% CI)</th>
<th>p Value</th>
<th>Standard coefficient (95% CI)</th>
<th>Regression coefficient (95% CI)</th>
<th>p Value</th>
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</thead>
<tbody>
<tr>
<td>Smoker</td>
<td>0.13 (0.69 to 2.07)</td>
<td>−0.07</td>
<td>&lt;0.001</td>
<td>−0.14 (−7.24 to −2.54)</td>
<td>−0.09</td>
<td>&lt;0.001</td>
<td>−0.14 (−8.99 to −2.81)</td>
<td>−2.56 (−8.46 to −3.72)</td>
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<tr>
<td>Caucasian race</td>
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<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
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<td>NS</td>
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<tr>
<td>Male sex</td>
<td>−0.18 (−1.73 to −1.06)</td>
<td>0.13</td>
<td>&lt;0.001</td>
<td>0.02 (2.08 to 6.66)</td>
<td>−0.09</td>
<td>&lt;0.001</td>
<td>0.11 (1.37 to 7.39)</td>
<td>0.02 (1.10 to 9.98)</td>
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<td>NS</td>
<td>NS</td>
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<td>NS</td>
<td>NS</td>
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<tr>
<td>BASMI</td>
<td>0.12 (0.26 to 0.86)</td>
<td>−0.09</td>
<td>&lt;0.001</td>
<td>−1.42 (−2.45 to −0.39)</td>
<td>0.01</td>
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<tr>
<td>OR (95% CI)</td>
<td>2.15 (2.80)</td>
<td>0.14</td>
<td>&lt;0.001</td>
<td>4.94 (2.56 to 7.32)</td>
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<td>CRP</td>
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<td>−8.32 (−9.41 to −7.21)</td>
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<td>−8.32</td>
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<td>−10.52 (−7.63)</td>
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<tr>
<td>ASDAS-CRP</td>
<td>0.52 (2.47)</td>
<td>−0.52</td>
<td>&lt;0.001</td>
<td>−8.32 (−9.41 to −7.21)</td>
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<td>Male sex</td>
<td>−0.18 (−1.73 to −1.06)</td>
<td>0.13</td>
<td>&lt;0.001</td>
<td>0.02 (2.08 to 6.66)</td>
<td>−0.09</td>
<td>&lt;0.001</td>
<td>0.11 (1.37 to 7.39)</td>
<td>0.02 (1.10 to 9.98)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Male sex</td>
<td>−0.12 (−1.96 to −0.56)</td>
<td>−0.09</td>
<td>&lt;0.001</td>
<td>−1.42 (−2.45 to −0.39)</td>
<td>0.01</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Male sex</td>
<td>−0.12 (−1.96 to −0.56)</td>
<td>−0.09</td>
<td>&lt;0.001</td>
<td>−1.42 (−2.45 to −0.39)</td>
<td>0.01</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Male sex</td>
<td>−0.12 (−1.96 to −0.56)</td>
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<td>&lt;0.001</td>
<td>−1.42 (−2.45 to −0.39)</td>
<td>0.01</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
</tbody>
</table>

Table 4  Multivariate logistic regressions analyses of factors associated with MRI inflammation

<table>
<thead>
<tr>
<th>MRI inflammation (spine or sacroiliac joints)</th>
<th>p Value</th>
<th>MRI sacroiliac joint inflammation</th>
<th>p Value</th>
<th>MRI spine inflammation</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smoker</td>
<td>1.91</td>
<td>1.91</td>
<td>2.33</td>
<td>1.91</td>
<td>2.33</td>
</tr>
<tr>
<td>Caucasian race</td>
<td>NI</td>
<td>NI</td>
<td>NI</td>
<td>NI</td>
<td>NI</td>
</tr>
<tr>
<td>Male sex</td>
<td>1.87</td>
<td>1.80</td>
<td>1.98</td>
<td>1.90</td>
<td>1.90</td>
</tr>
<tr>
<td>HLA-B27 positivity</td>
<td>2.06</td>
<td>2.08</td>
<td>1.90</td>
<td>2.00</td>
<td>2.00</td>
</tr>
<tr>
<td>Drinker</td>
<td>NI</td>
<td>NI</td>
<td>1.10</td>
<td>0.97</td>
<td>0.97</td>
</tr>
<tr>
<td>Family history of SpA</td>
<td>NI</td>
<td>NI</td>
<td>1.02</td>
<td>1.02</td>
<td>1.02</td>
</tr>
<tr>
<td>Age at onset of IBP</td>
<td>0.97</td>
<td>0.97</td>
<td>1.02</td>
<td>1.02</td>
<td>1.02</td>
</tr>
<tr>
<td>CRP</td>
<td>1.02</td>
<td>1.02</td>
<td>1.02</td>
<td>1.02</td>
<td>1.02</td>
</tr>
</tbody>
</table>

ASDAS-CRP, ankylosing spondylitis disease activity score; C-reactive protein based; BASMI, Bath ankylosing spondylitis metrology index; Euro-QoL, Euro-quality of life questionnaire; HLA, human leucocyte antigen; NI, not included in the multivariate model; NS, non-significant in multivariate analysis; SpA, spondyloarthritis.
Multivariate models of radiographic sacroiliitis and mSASSS are shown in table 6. Smoking was found to be independently and positively associated with mSASSS but not with radiographic sacroiliitis.

Interaction between smoking and HLA-B27 positivity

There was no interaction between smoking and HLA-B27 positivity for any of the studied outcomes.

Subgroup analysis

Sacroiliac joint radiographic data were missing in 22/647 patients (3.4%). Subgroup analyses were performed for patients fulfilling (n=181) and not fulfilling (n=444) the modified New York criteria (see supplements 1 and 2, available online only). In the subgroup of patients with radiographic axial SpA smoking was independently and positively associated with BASFI, Euro-QoL, MRI spinal inflammation, MRI spine or sacroiliac joint inflammation and radiographic damage of the spine. Smoking was also negatively associated with SF-36 (physical and mental component scores). In the subgroup of patients with non-radiographic axial SpA smoking was independently and positively associated with BASDAI, Euro-QoL and MRI spinal inflammation. It was negatively associated with age at onset of IBP and SF-36 (physical and mental component scores). Subgroup differences are likely due to loss of statistical power.

DISCUSSION

The negative impact of smoking on AS disease parameters has been reported in previous studies, and confirmed more robustly in our study. Importantly, we confirmed these associations in an early disease stage population with IBP of less than 3 years.

In the general population, smokers were found to have poorer HRQoL, increased alcohol consumption and increased frequency of reported pain.69 10 However, this negative impact might also be mediated by a direct toxic effect of smoking. Notably, cigarette smoke is well known to possess pro-inflammatory effects, via various proposed mechanisms: smokers have increased pro-inflammatory reactants such as tumour necrosis factor α, interleukin (IL) 1, IL-6, IL-8 and granulocyte-macrophage colony-stimulating factor; increased concentration of free radicals; and augmentation of autoreactive B cells.37 Cigarette smoke triggers the nuclear factor-κB pathway and promotes pro-inflammatory cytokine gene expression.38 Moreover, smokers were also found to have increased circulating polymorphonuclear neutrophil counts and T lymphocytes.43

The DESIR cohort is characterised by SpA patients with short disease duration, in contrast with previous studies on AS patients with a longer course of disease. In this early SpA population (average duration of IBP only 1.5 years), smokers had an earlier age of IBP onset, which was not found in smaller studies.8 This demonstrates the enhanced power inherent in the large sample size of the DESIR cohort, allowing us to detect more subtle differences.

The cumulative effects of smoking in RA meta-analyses have established that male smokers are at increased risk but as the quantity of smoking increases, risk between male and female smokers becomes more equal.42 We found an interaction between male sex and smokers regarding MRI sacroiliac joint structural lesions. Given that the quantification of smoking affects the...
gender interaction in RA, it would be of interest to quantify the cumulative effect of cigarette smoking in future studies with SpA patients. Unfortunately, the number of pack-years of smoking is not known in the DESIR cohort. Furthermore, it would have been useful to analyse ‘current smokers’ and patients with a ‘past history of smoking’ separately—however, these data are also not known in DESIR.

The lack of international consensus about the assessment of MRI structural lesions poses another potential limitation to our study. However, in DESIR, the imaging techniques were standardised and the centres involved had to fulfil predefined quality criteria in order to be able to participate in the study, namely regarding previous experience with multicentre, longitudinal epidemiological studies. Therefore, the required high quality standards are expected to have reduced potential bias during the imaging evaluation.

Another concern is whether the physician interview–captured smoking status might have led to an under-reporting of smoking. However, the prevalence of smoking in DESIR is in line with the prevalence of smoking in the French population (37.2% current smokers and ex-smokers in DESIR vs 26.2% current smokers in the French population). Furthermore, a previous study has shown that obtaining a history of tobacco use is an accurate method of detecting smokers in epidemiological studies.

Our study found that, in young axial SpA patients with short disease duration, smoking was independently associated with earlier onset of IBP, higher disease activity, increased axial inflammation and structural damage, poorer functional status and poorer quality of life. This also translated into increased missing workdays as a result of disease (table 1), which may beyond those described for the general population.

The DESIR cohort allowed us to establish the negative impact of smoking in axial SpA; continued follow-up of the cohort may allow detailed quantification of the deleterious impact of smoking at the individual and societal levels. The true magnitude and implications of this effect is yet to be unravelled.

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**REFERENCES**


