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Do Smoking and Socioeconomic Factors Influence Imaging Outcomes in Axial Spondyloarthritis? Five-Year Data From the DESIR Cohort

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Objective. To investigate the relationship between smoking and imaging outcomes over 5 years in axial spondyloarthritis (SpA) and to assess whether socioeconomic factors influence these relationships.

Methods. Axial SpA patients from the Devenir des Spondylarthropathies Indifférenciées Récentes cohort were included. The following 4 imaging outcomes were assessed by 3 central readers at baseline, 2 years, and 5 years: spine radiographs (using the modified Stoke Ankylosing Spondylitis Spine Score [mSASSS]), sacroiliac (SI) joint radiographs (using the modified New York criteria), magnetic resonance imaging (MRI) of the spine (using the Spondyloarthritis Research Consortium of Canada [SPARCC] score), and MRI of the SI joint (using the SPARCC score). The explanatory variable of interest was smoking status at baseline. Interactions between smoking and socioeconomic factors (i.e., job type [blue-collar or manual work versus white-collar or nonmanual work] and education [low versus high]) were first tested, and if significant, analyses were run using separate strata. Generalized estimating equations models were used, with adjustments for confounders.

Results. In total, 406 axial SpA patients were included (52% male, 40% smokers, and 18% blue-collar workers). Smoking was independently associated with more MRI-detected SI joint inflammation at each visit over the 5 years, an effect that was seen only in patients with blue-collar professions (β = 5.41 [95% confidence interval (95% CI) 1.35, 9.48]) and in patients with low education levels (β = 2.65 [95% CI 0.42, 4.88]), using separate models. Smoking was also significantly associated with spinal inflammation (β = 1.69 [95% CI 0.45, 2.93]) and SI joint damage (β = 0.57 [95% CI 0.18, 0.96]) across all patients, irrespective of socioeconomic factors and other potential confounders.

Conclusion. Strong associations were found, in particular, between smoking at baseline and MRI-detected SI joint inflammation at each visit over a time period of 5 years in axial SpA patients with a blue-collar job or low education level. These findings suggest a possible role for mechanical stress amplifying the effect of smoking on axial inflammation in axial SpA.

INTRODUCTION

Smoking and systemic inflammation, as measured by C-reactive protein (CRP) level or the Ankylosing Spondylitis Disease Activity Score (ASDAS) (1), respectively, have been shown to independently predict spinal radiographic progression in patients with axial spondyloarthritis (SpA) (2,3). At a cross-sectional level, using data from the first visit of patients in the Devenir des

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Spondylarthropathies Indifférenciées Récentes (DESIR) cohort, smoking has been shown to be independently associated with higher disease activity and increased axial inflammation on magnetic resonance imaging (MRI), as well as increased axial structural damage noted on MRI and radiographs (4). In a longitudinal analysis of the Outcome in Ankylosing Spondylitis International Study (OASIS) cohort, smoking amplified the effect of disease activity on spinal progression, suggesting an indirect effect of smoking through inflammation (5). More specifically, for every additional unit increase in ASDAS in smokers, there was an increase in the modified Stoke Ankylosing Spondylitis Spine Score (mSASSS) of 1.9 units per 2 years, compared to only 0.4 units in nonsmokers (5).

The above-mentioned study was the first to suggest that the effect of smoking on radiographic progression was, at least in part, driven by higher disease activity. However, the complex relationships between smoking, inflammation, and radiographic progression have not yet been fully elucidated. In fact, other data fail to confirm an association between smoking and structural progression (6), highlighting the need to further explore these associations.

It has also been argued that certain socioeconomic factors may play a role. For example, similar to smoking, physically demanding jobs are associated with structural damage and have been shown to amplify the effect of inflammation on bone formation (5). In the case of axial inflammation on MRI, the longer-term effects of smoking or socioeconomic factors remain largely unknown, with data limited to early axial SpA at baseline (4).

Whether indicators of poor socioeconomic status such as physically demanding jobs and smoking lead to worse disease outcomes beyond inflammation alone remains to be clearly answered. An important challenge is dissociating socioeconomic factors that tend to cluster, for example, dissociating smokers from people with physically demanding jobs or lower education. This represents a difficult task, especially in analyses of "real-life" cohorts where this kind of clustering is unavoidable. However, these unmet gaps in the literature highlight the need to better understand the intricate relationships between smoking, socioeconomic factors, and axial inflammation and damage, and therefore to understand how these factors potentially interact with and link to more inflammation and damage. We undertook this study to assess the association between smoking and imaging outcomes (both inflammation and structural damage on MRI and conventional radiographs) in axial SpA at each visit over a 5-year time period and the potential role of socioeconomic factors as effect modifiers or confounders of this association.

PATIENTS AND METHODS

Study population. Consecutive patients (ages 18–50 years) with inflammatory back pain lasting ≥3 months but <3 years, and with symptoms suggestive of axial SpA according to the local investigator's assessment (e.g., a score of ≥5 on a 0–10 numerical rating scale [0 nonsuggestive, 10 very suggestive]), were recruited across 25 centers in France as part of the prospective, multicenter longitudinal DESIR cohort (ClinicalTrials.gov identifier: NCT01648907) (7). To be included in this analysis, patients had to fulfill the Assessment of SpondyloArthritis international Society (ASAS) axial SpA classification criteria (8) and have at least one imaging outcome available, as well as baseline information on smoking and socioeconomic factors. Imaging assessments were conducted at baseline, 2 years, and 5 years. The database used for this analysis was locked in June 2016.

Ethics approval. The DESIR study was conducted according to good clinical practice guidelines and was approved by the appropriate local medical ethical committees (Comité de Protection des Personnes Ile de France III). A detailed description of the study protocol is available at the DESIR website (http://www.lacohortedesir.fr/desir-in-english/). The research proposal for this particular analysis was approved by the scientific committee of the DESIR cohort. Written informed consent was obtained from participating patients before inclusion.

Imaging outcomes. Plain radiographs were obtained at all centers, with MRI scans for follow-up occurring only at 9 centers in Paris. Four imaging outcomes were used: spine radiographs (using the mSASSS, range 0–72) (9), sacroiliac (SI) joint radiographs (using modified New York criteria, range 0–8) (10), MRI of the spine (using the Spondyloarthritis Research Consortium of Canada [SPARCC] score, range 0–414) (11), and MRI of the SI joint (using the SPARCC score, range 0–72) (12). The mSASSS and modified New York scoring systems measure the extent of radiographic damage in the spine and SI joints, respectively. Specifically, the mSASSS system measures

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spinal structural damage, with proven validity, feasibility, and sensitivity to change in patients with early axial SpA (13), whereas the modified New York scoring system is the conventional method for assessing SI joint structural damage on radiographs and consists of a semiquantitative scale from 0 (normal) to 4 (total ankylosis) (10). In the present study, the latter was scored using a 0–8 scale, combining scores for both SI joints. The SPARCC indices measure the presence, depth (3-dimensional extent), and signal intensity of active inflammation represented by bone marrow edema in the spine and SI joints. Plain radiographs and MRIs were scored independently by 3 central readers who were blinded with regard to time order (baseline, 2 years, 5 years), clinical information, and imaging findings from other modalities. The average score from all 3 reviewers was used as an absolute value.

Smoking and socioeconomic factors. The main independent variable of interest was smoking, tested as a binary variable to indicate smoking status (current smoker versus noncurrent smoker), recorded at baseline and at every subsequent visit. Socioeconomic variables included age, sex, ethnicity, job type, educational status, marital status, and parental status (number of children). Ethnicity (white versus nonwhite), education status (low [non-university] versus high [university]), and marital status (married versus unmarried) were used as binary variables in the analyses, and parental status (number of children) as a continuous variable. Similarly, job type was based on "collar" profession, handled as a binary variable with blue-collar indicating physically demanding, manual labor and white-collar indicating sedentary, office-based work (14).

Other independent variables of interest, also collected at each visit and tested as potential confounders in the analyses, included clinical variables (extraarticular manifestations, namely uveitis, psoriasis, and inflammatory bowel disease; for all variables, if once positive, they were treated as always positive in subsequent visits), laboratory variables (e.g., CRP level), and treatment variables (namely, nonsteroidal antiinflammatory drugs [NSAIDs], based on computation of the ASAS NSAID score [range 0–400] [15], also tested as a binary variable [NSAID use in the last 6 months], conventional synthetic disease-modifying antirheumatic drugs [csDMARDs], and tumor necrosis factor inhibitor use).

Table 1. Baseline characteristics of the study patients (n = 406)*

	Baseline	5 years
Independent variable		
Age, years	31.6 ± 7.3	–
Male sex, no. (%)	210 (52)	–
Current smoker, no. (%)	162 (40)	–
White ethnicity, no. (%)	363 (89)	–
Low education level (primary/secondary school), no. (%)	145 (36)	–
Blue-collar profession (n = 351), no. (%)	64 (18)	–
Married/in couple, no. (%)	251 (62)	–
No. of children	0.91 ± 1.1	–
HLA–B27 positive, no. (%)	358 (88)	–
Symptom duration, years	1.6 ± 0.9	–
ASDAS-CRP (n = 391)	2.6 ± 1.0	–
CRP, mg/liter (n = 395)	8.5 ± 13.7	–
BASDAI, 0–10 (n = 405)	4.2 ± 2.0	–
BASFI, 0–10 (n = 403)	2.8 ± 2.2	–
History of uveitis, no. (%)	39 (10)	–
History of psoriasis, no. (%)	60 (15)	–
History of IBD, no. (%)	20 (5)	–
History of peripheral arthritis, no. (%)	91 (22)	–
NSAID score in past week, 0–400 (n = 397)	61.9 ± 52.3	–
TNFi use, no. (%)	0 (0)	–
Imaging outcome		
Spine radiograph, mSASSS score, 0–72 (n = 389 at baseline, n = 251 at 5 years)	0.4 ± 1.7	1.0 ± 3.7
SI joint radiograph, modified New York score, 0–8 (n = 396 at baseline, n = 269 at 5 years)	1.7 ± 1.8	2.0 ± 2.0
Spine MRI, SPARCC score, 0–414 (n = 383 at baseline, n = 100 at 5 years)	2.7 ± 8.0	2.2 ± 4.6
SI joint MRI, SPARCC score, 0–72 (n = 391 at baseline, n = 100 at 5 years)	4.5 ± 7.6	3.1 ± 5.5

* Except where indicated otherwise, values are the mean ± SD. ASDAS-CRP = Ankylosing Spondylitis Disease Activity Score using the C-reactive protein level; BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; BASFI = Bath Ankylosing Spondylitis Functional Index; IBD = inflammatory bowel disease; NSAID = nonsteroidal antiinflammatory drug; TNFi = tumor necrosis factor inhibitor; mSASSS = modified Stoke Ankylosing Spondylitis Spine Score; SI = sacroiliac; MRI = magnetic resonance imaging; SPARCC = Spondyloarthritis Research Consortium of Canada.

Statistical analysis. The relationship between smoking status and each imaging outcome was analyzed using separate models. The main models were built using independent variables at baseline and imaging outcomes at each visit for the DESIR cohort (baseline, 2 years, 5 years). A sensitivity analysis was undertaken using models built with both independent and outcome variables tested at each time point over the course of 5 years (i.e., "time-varying" analyses). This approach was used to better understand the relationship and the strength of the relationship between independent and dependent variables at each time point. Generalized estimating equations (GEEs) analyses were conducted, making use of repeated observations per patient and taking within-patient correlations into account. For the latter, the aim was to make use of all data available, allowing for both independent ("explanatory") variables and outcomes to vary over time.

First, potential interactions between smoking and socioeconomic factors were investigated and, if statistically ($P < 0.15$, set a priori) and clinically relevant, subsequent analyses were stratified. Strata for job type or educational level, respectively, were based on whether patients were in a blue-collar profession or not or had attained higher education or not, at baseline. Interactions were tested for smoking status at baseline. For the sensitivity analyses of models built with independent variables and outcomes at each time point, strata for job type or education level, respectively, were based on whether patients were at any time in a blue-collar profession (ever blue-collar versus never blue-collar) or had higher education (ever higher education versus never higher education) over the 5 years of follow-up. Interactions were tested for smoking status at each visit. Subsequently, univariable and multivariable analyses were undertaken. The significance level for entry in to multivariable analyses was set a priori at $P < 0.20$. Variables deemed relevant (e.g., age and sex) were forced into the multivariable models. Forward selection was used to choose the best final model, keeping in the model variables relevant to explain the outcome of interest ($P < 0.05$) or confounders of the main relationship of interest (e.g., smoking and imaging outcomes). Beta coefficients and 95% confidence intervals (95% CIs) were calculated. Stata SE version 14 (StataCorp) was used in all analyses.

RESULTS

A total of 406 patients were included in the present study. The mean ± SD age was 31.6 ± 7.3 years, and 52% of the patients were male. The baseline sociodemographic and clinical characteristics of the patients are summarized in Table 1. Of the patients with a blue-collar job (18%), 81% were male, and 70% had never attained higher education.

Interaction between smoking and socioeconomic factors on imaging outcomes. Significant interactions between baseline smoking and job type ($P = 0.024$) and between baseline smoking and education ($P = 0.036$) on MRI-detected SI joint inflammation were identified. Specifically, the effect of smoking observed by assessing MRI-detected SI joint inflammation was much stronger in patients who had blue-collar jobs (β = 6.20 [95% CI 1.54, 10.87]) compared to those with white-collar jobs (β = 0.67 [95% CI −0.79, 2.12]), and in those who had a lower education level (β = 3.59 [95% CI 0.82, 6.37]) compared to those with a higher education level (β = 0.21 [95% CI −1.15, 1.58])

Table 2. Association (β [95% confidence interval]) between baseline smoking and imaging outcomes at each visit during 5-year follow-up*

	Spine radiograph, mSASSS score, all patients (n = 331)	SI joint radiograph, modified New York score, all patients (n = 328)	Spine MRI, SPARCC score, all patients (n = 377)	SI joint MRI, SPARCC score	
				Blue-collar patients (n = 55)	White-collar patients (n = 264)
Smoking vs. not smoking	0.26 (−0.35, 0.86)	0.57 (0.18, 0.96)†	1.69 (0.45, 2.93)†	5.41 (1.35, 9.48)†	0.24 (−1.13, 1.62)
Age	0.06 (0.01, 0.11)†	−0.03 (−0.06, 0.00)	0.07 (−0.03, 0.17)	−0.05 (−0.32, 0.21)	−0.13 (−0.24, −0.02)
Male vs. female	0.36 (−0.18, 0.89)	0.25 (−0.12, 0.63)	2.39 (1.29, 3.49)†	3.80 (0.15, 7.45)†	2.07 (0.68, 3.47)†
White ethnicity vs. all other ethnic groups	‡	−1.03 (−1.75, −0.30)†	‡	‡	‡
Blue-collar vs. white-collar	0.70 (−0.13, 1.54)§	0.75 (0.24, 1.75)†	‡	‡	‡
Abnormal vs. normal CRP level	0.70 (−0.13, 1.54)§	1.23 (0.77, 1.69)†	4.29 (2.28, 6.31)†	7.41 (1.90, 12.92)†	3.47 (1.63, 5.31)†
BASDAI (0–10)	‡	−0.16 (−0.25, −0.07)†	‡	−1.08 (−2.16, −0.00)§	−0.27 (−0.66, 0.12)
csDMARD use in last 6 months vs. not	‡	−0.75 (−1.28, −0.22)†	−2.39 (−3.79, −0.99)†	−4.29 (−7.54, −1.03)†	−2.41 (−4.17, −0.65)†
Presence of uveitis	‡	‡	−1.97 (−3.24, −0.69)†	‡	‡
Presence of peripheral arthritis	‡	‡	−2.32 (−3.54, −1.10)†	−6.52 (−10.03, −3.00)†	−1.67 (−4.09, 0.74)

* Stratified models for SI joint MRI (SPARCC score) are shown due to identified interactions between smoking and job type. Other independent variables tested ($P > 0.20$ in univariable models) include HLA–B27 status, all socioeconomic variables of interest, ASDAS or BASDAI, and presence of psoriasis or IBD. csDMARD = conventional synthetic disease-modifying antirheumatic drug (see Table 1 for other definitions).
† $P < 0.05$.
‡ Not significant in multivariable models.
§ Confounding effect on the association between smoking and the outcome.

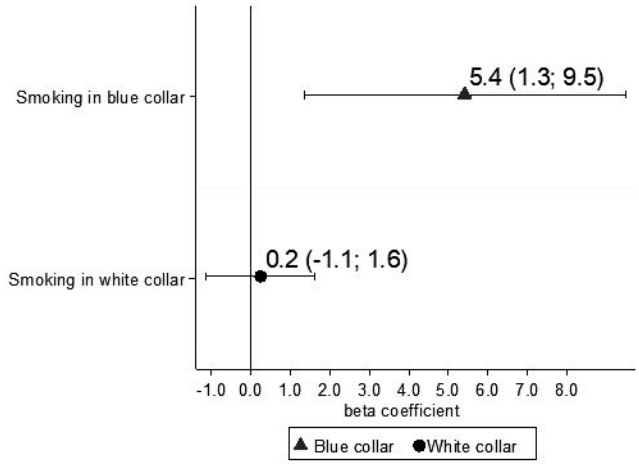

Figure 1. Effect of baseline smoking on magnetic resonance imaging–detected sacroiliac joint inflammation at each visit during the 5 years of follow-up in axial spondyloarthritis patients with blue-collar jobs compared to those with white-collar jobs at baseline. Values in parentheses are the 95% confidence interval.

(Supplementary Table 1, on the *Arthritis & Rheumatology* website at http://onlinelibrary.wiley.com/doi/10.1002/art.41408/abstract). In sensitivity analyses of time-varying models with both predictors and outcomes tested at each time point, interactions between smoking and job type, with MRI-detected SI joint inflammation and modified New York scores as outcomes, were also identified. Similarly, education status also proved to modify the relationship between smoking and MRI-detected SI joint inflammation (Supplementary Table 1).

Association between smoking status at baseline and imaging outcomes at each time point. Univariable analyses are presented in Supplementary Table 2 (http://onlinelibrary.wiley.com/doi/10.1002/art.41408/abstract). In multivariable models, the effect of smoking (at baseline) was significant for SI joint damage, spinal inflammation, and SI joint inflammation at each visit during the 5 year time period. For SI joint inflammation, the effect of smoking was apparent in those with blue-collar jobs. Specifically, a smoker patient with a blue-collar job had 5.41 more SPARCC points at each visit compared to a nonsmoker patient with a blue-collar job. This effect of smoking was independent of age, sex, systemic inflammation (CRP level), or treatment (Table 2 and Figure 1). In multivariable models, CRP level and the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) (16) were tested in different models than the ones that included ASDAS; however, only CRP level was significant and thus kept in the final models. The effect of smoking on SI joint damage and spinal inflammation was also significant.

When the analyses were repeated in separate strata based on level of education (higher versus lower education) in view of interactions identified between smoking and education, similar findings were observed. Smoking was associated with significantly higher inflammation in the SI joints in those with lower education (β = 2.65 [95% CI 0.42, 4.88]) compared to those with higher education (β = 0.36 [95% CI −1.00, 1.71]). This observation was independent of age, sex, systemic inflammation, and treatment (Table 3).

In sensitivity analyses, smoking status at each visit was also significantly associated with MRI-detected SI joint inflammation at each visit, again only in patients who had blue-collar jobs or lower education at any point (Supplementary Tables 3 and 4 and Supplementary Figure 1, http://onlinelibrary.wiley.com/doi/10.1002/art.41408/abstract).

DISCUSSION

The present study, based on 5-year data on axial SpA patients from the DESIR cohort, demonstrates associations of smoking with structural damage and spinal and SI joint inflammation, the latter exclusively in patients with a blue-collar profession or a lower education level. The association of smoking with inflammation, especially in the pelvis, was much stronger than that

Table 3. Association between baseline smoking and SI joint MRI results (SPARCC score) at each visit, in models stratified by level of education*

	SI joint MRI, SPARCC score, β (95% CI)	
	Lower education (n = 134)	Higher education (n = 248)
Smoking vs. not smoking	2.65 (0.42, 4.88)†	0.36 (−1.00, 1.71)
Age	0.05 (−0.09, 0.19)	−0.11 (−0.20, −0.02)†
Male vs. female	3.08 (1.27, 4.90)†‡	1.15 (−0.18, 2.48)
White ethnicity vs. all other ethnic groups	−6.17 (−11.08, −1,25)†	0.09 (−2.01, 2.19)
Abnormal vs. normal CRP level	4.45 (1.72, 7.18)†	2.96 (1.13, 4.80)†
BASDAI (0–10)	−1.04 (−1.65, −0.43)†	−0.38 (−0.74, −0.03)†
csDMARD use in last 6 months vs. not	−3.79 (−6.16, −1.43)†	−2.63 (−4.36, −0.90)†

* Other independent variables tested in models included HLA–B27 status, all socioeconomic variables of interest, ASDAS, presence of psoriasis, IBD, or peripheral arthritis, and use of TNFi. csDMARD = conventional synthetic disease-modifying antirheumatic drug (see Table 1 for other definitions).
† $P < 0.05$.
‡ Confounding effect on the association between smoking and the outcome.

with structural damage. These relationships are not explained by any possible confounders that were assessed, including age, sex, systemic inflammation, or treatment.

Our findings confirm the known independent associations between smoking, inflammation, and structural damage in early axial SpA (4), but they also confirm these for the first time using imaging outcomes up to 5 years after diagnosis. These are interesting, albeit not fully explained, observations, as are the previously observed longitudinal associations between blue-collar work (which entails more mechanical stress) and greater inflammation in smokers (5). These observations were made irrespective of patient sex, disease activity, disease duration, or treatment. Our findings suggest that smoking may amplify the effects of inflammation on SI joints in patients with a lower socioeconomic status, as reflected by job type and level of education (i.e., blue-collar job and lower education). The clustering of specific socioeconomic factors such as job type and education level is not surprising, but it is challenging to elucidate. It is certainly not possible or appropriate to attempt to identify causal links, i.e., to determine whether blue-collar jobs cause more pelvic inflammation or whether smoking does the same, directly or through another factor (residual confounding). Assessing whether mechanical stress and cigarette smoking work synergistically to cause inflammation therefore represents a difficult task and one that may not be easily accomplished using real-life data. Still, our findings support the previously established notion of the proinflammatory effects of smoking and their role in inflammatory pathways (17–20).

The association of smoking with worse disease outcomes is well known, even beyond axial SpA. For example, smoking has been associated with worse disease outcomes in rheumatoid arthritis through various mechanistic pathways, including potentiation of inflammation, oxidative stress, autoantibody formation, and reduced response to treatment (21). This evidence, increasingly observed in axial SpA, strengthens the importance of encouraging and supporting smoking cessation in patients with these diseases, consistent with existing recommendations (22). Our findings also support data from animal studies that mechanical strain can directly result in inflammation and new bone formation (23). The study of job type (physically demanding versus sedentary) as a proxy for "lifetime mechanical stress" on the spine represents a novel approach to better understanding complex relationships between important patient and disease parameters that may drive worse disease outcomes. Furthermore, our findings on the relationship between smoking and MRI-detected SI joint inflammation in models stratified by education align with previous studies that demonstrated an association between lower education and worse disease activity in SpA (24). The findings of lower SI joint inflammation with csDMARD use, especially in patients with blue-collar professions (and also with the presence of peripheral arthritis, suggesting less inflammation in those patients), may simply reflect a different subtype of axial SpA with a predominant peripheral pattern in these patients, combined with the use of more csDMARDs (25).

Our findings are clinically meaningful in that they can help guide clinicians in the provision of more targeted and patient-centric care to axial SpA patients, recognizing those at higher risk, whether due to lifestyle parameters or other sociodemographic factors. In the larger picture, these observations support the role of socioeconomic parameters such as education status and job type in explaining differences in health outcomes. More specifically, our results allow us to speculate that indicators of lower socioeconomic status such as job type and lower education have a negative effect on health outcomes, demonstrated in this case by imaging outcomes in early axial SpA. Perhaps they highlight the need for actively educating patients on disease course and management but also advising, or at least considering, the potential impact of a physical job versus a less-physical job in the context of axial SpA. It is possible that less educated people are less informed and make worse choices when it comes to health and managing their disease. One choice could be smoking; another potential factor that may be less of a choice is job type. Being aware of these factors and their associations can be relevant to routine clinical practice, as they can inform and enable a more holistic and individualistic approach to disease management.

Evidence suggests that in patients with axial SpA, disease activity and inflammatory lesions on spinal MRI are associated, but only in male patients (26). In the present study, patients with blue-collar professions were mainly men, which is consistent with evidence that supports associations between male sex and higher inflammation and structural damage (5,26). In an earlier report on the DESIR cohort, smoking was the main association of interest, with imaging outcomes (radiographs and MRI) driven by previous reports of its independent association with higher disease activity, axial inflammation on MRI, and axial structural damage on MRI and radiographs (4). However, that study focused only on cross-sectional analyses of baseline imaging outcomes, unlike the present study, which examined relationships with independent variables at baseline and imaging outcomes at each visit for up to 5 years. Sensitivity analyses of independent variables and imaging outcomes at each time point confirmed the same associations. In this respect, our data are more robust and more informative, providing greater insight into these relationships.

There are limitations to our study. First, our findings were interpreted on the assumption that blue-collar professions versus white-collar professions are representative of high versus low levels of mechanical stress on the spine, respectively. This formed the basis for speculation on reasons behind the study findings. Although a rather crude dichotomy, it is one that has previously been widely accepted and used (5,27). Furthermore, smoking status was the main association of interest in our study, but information on the intensity/amount of smoking (e.g., number of pack-years) was not available, precluding a more detailed analysis of smoking (and appropriate quantification) and its effects on

outcomes. The effect of smoking on spinal inflammation was also significant, although not as prominent as for SI joint inflammation. Indeed, the interaction between smoking and job type was only significant for SI joint inflammation. This may be explained by the fact that inflammation at the spine is much lower than at the SI joints (28), resulting in a lack of power to detect a significant interaction. Finally, it could be argued that the small amount of damage present in this cohort of patients with early axial SpA and the limited imaging changes over time precluded proper investigation of the effect of smoking and potentially of socioeconomic factors on the damage variables.

Our study has several strengths that also deserve attention. Aside from the real-life setting of DESIR and the large patient sample allowing for the detection of subtle associations between different factors, detailed information on various patient and disease characteristics including socioeconomic factors made it possible to study these complex relationships. In addition, the inclusion of patients with early axial SpA enabled the study of disease predictors and outcomes at crucial early stages of disease. The scoring of images by 3 central readers independently and blinded with regard to time order (baseline, 2 years, 5 years), with average scores used, ensured robust assessment of the imaging outcomes (29).

In conclusion, this study provides new insights into the intricate relationships between smoking, axial damage, and socioeconomic factors in axial SpA. Namely, it was observed that manual (blue-collar) jobs and, consequently, mechanical stress amplify the effect of smoking on axial inflammation in axial SpA. Not only do our findings support the conclusions of translational research, but they reinforce the message that further exploration of the pathway of mechanical stress and inflammation is relevant and necessary in this field. Our study provides greater insight into potential mechanistic links between mechanical stress, smoking, and inflammation. It also suggests the need for more research into this field, including investigation of the type and intensity of physical activity that may enhance disease progression and lead to adverse outcomes observed on imaging in axial SpA.

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All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Nikiphorou had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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