Influence of Environmental Factors on Disease Activity in Spondyloarthritis: A Prospective Cohort Study

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ABSTRACT. ***Objective.*** Spondyloarthritis (SpA) is a complex inflammatory disorder. We investigated the influence of environmental factors on SpA disease activity.

Methods. A prospective cohort of adults with SpA was followed for 3 years. Patients logged on to a secured Website every 3 months to complete a questionnaire. They reported whether they had been exposed to environmental factors such as stressful or traumatic life events, infections, or vaccinations. Outcome variables included the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), the Bath Ankylosing Spondylitis Functional Index (BASFI), and pain and patient global assessment (PGA) on visual numerical scales (each rated 0–10). Analyses were performed using a generalized estimating equation for repeated measures, adjusted for the outcome variable collected by the previous questionnaire.

Results. In total, 272 patients were included in the analysis, completing the questionnaire on 2240 occasions. The average time (mean ± SD) between 2 connections to the Website was 4.0 ± 2.0 months. Occurrence of life events was followed by an increase of 0.5 (95% CI 0.4–0.7) in the BASDAI, 0.5 (95% CI 0.3–0.6) in the BASFI, 0.7 (95% CI 0.5–0.9) in the PGA, and 0.8 (95% CI 0.6–1.0) for pain ($p < 0.0001$ for all variations). A moderately statistically significant link was found between vaccination and an elevation of the BASDAI of 0.3 (95% CI 0.0–0.5; $p = 0.032$). No influence of other factors was detected.

Conclusion. This prospective study in a dedicated SpA cohort shows for the first time a link between stressful events and disease activity. Although this link was statistically highly significant, its clinical meaning remains to be determined because the average magnitude of variation of the different variables studied was rather mild. (J Rheumatol First Release Feb 15 2013; doi:10.3899/jrheum.121081)

Key Indexing Terms:
SPONDYLOARTHRITIS EPIDEMIOLOGY ENVIRONMENT LIFE-CHANGE EVENTS

Spondyloarthritis (SpA) is one of the most frequent chronic inflammatory rheumatic diseases, affecting 0.1%–1% of the adult white population. The most characteristic symptoms of SpA are pain and stiffness predominating in the spinal, pelvic, thoracic, and frequently also peripheral joints and entheses (i.e., the sites of attachment of ligaments, tendons, and joint capsules to the bones). The disease course is typically characterized by a succession of flares and partial remissions. Depending on its presentation, SpA is usually divided into several overlapping subsets: ankylosing spondylitis (AS), which is characterized by advanced radiographic sacroiliitis, psoriatic arthritis, arthritis associated with inflammatory bowel disease (IBD, i.e., Crohn disease or ulcerative colitis), reactive arthritis following an infectious trigger, and undifferentiated SpA.

Susceptibility to SpA is largely genetically determined,

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and its heritability has been estimated to be as high as 90%[1]. The HLA-B27 allele is a major genetic factor explaining 30% to 50% of the overall genetic risk. However, other polymorphisms of lower magnitude have recently been associated with disease predisposition, and it is expected that more will be discovered in the future, as for other complex disorders. On the other hand, the relative contribution of environmental factors to triggering disease and/or progression remains poorly characterized, with the exception of reactive arthritis. This infrequent situation refers to a flare of SpA that follows a bacterial enteric or urethral infection but is not characteristically infectious. It is generally assumed that the triggering microbe acts as a stimulant of the immune response.

The relative paucity of investigations regarding the role of environmental factors in SpA may result in part from difficulties of assessing disease activity and severity, despite the development of validated instruments such as the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and the Bath Ankylosing Spondylitis Functional Index (BASFI)[2,3], and thus prospective longitudinal studies of SpA have remained scarce. A number of studies have identified environmental factors as being associated with disease activity and/or progression, such as dietary habits[4], enteric and upper respiratory tract infections[5,6], and cigarette smoking, which was associated with a worse clinical, functional, and radiological outcome[7]. Also, the putative role of environmental factors such as dust, farming, and solvent exposure has been suspected in other chronic inflammatory diseases[8]. However, none of these studies was longitudinally designed. Events such as stress at work, physical trauma, and infection have been studied retrospectively for their potential role in triggering the onset of AS and other inflammatory rheumatic diseases, but not for their effects on disease course[9].

The aim of our study was to prospectively investigate the influence of several environmental factors, especially stressful events, on disease activity, in a dedicated French cohort of patients with SpA.

MATERIALS AND METHODS

Patient recruitment. The study population consisted of the dedicated Co-Env cohort of adult (age ≥ 18 yrs) patients with SpA fulfilling the Amor criteria[10]. They were recruited through the Rheumatology Department of Ambroise Paré Hospital, Boulogne Billancourt, France, or through the Association Française des Spondylarthritiques, a self-help organization for patients with SpA. The study was approved by the Institutional Review Board of Ambroise Paré Hospital and informed consent was obtained from each participant.

The SpA diagnosis was ascertained by qualified investigators (RSN or MB) based on the following information collected before inclusion: personal history of inflammatory back pain, buttock pain, peripheral arthritis, enthesitis, dactylitis, efficacy of nonsteroidal antiinflammatory drugs, uveitis, psoriasis, IBD, family history of SpA, radiographic sacroiliitis (according to the modified New York criteria), and HLA-B27 status. Willingness to participate, having a confirmed diagnosis of SpA, and regular access to an Internet connection were all required for inclusion in the study. Only patients with axial symptoms and/or who had AS defined by the modified New York criteria were included in the analysis[11].

Study procedure. This was a longitudinal observational study. Patients were asked to log on every 3 months to a secured Website developed by the UMR-S 707 (a research group from the French National Institute of Health and Medical Research that specializes in mathematical modeling, statistics, computer science, and information system technologies as applied to the domain of epidemiology) and to complete a standardized self-questionnaire. At the time our study was designed, we did not know what degree of patient compliance could be expected. By consensus among the investigators, assessments were done every 3 months, considering the tradeoff between feasibility and discrimination. Reminders were sent automatically by e-mail ahead of each connection, as scheduled. Patients who did not log on received further reminders by a direct telephone call from a research technician until they eventually logged on to the Website (referred to as the connection). All patients were enrolled within the first month of the study start date and the followup period for the entire cohort extended over 3 years (December 2005 through October 2008).

The following data were collected at the time of the first connection: age, sex, disease duration, SpA disease history (independently assessed for validation of diagnosis), disease activity and severity by self-assessment measures (French versions of the BASDAI[3] and the BASFI[2]), level of pain, and patient global assessment (PGA) of disease activity, all on visual numerical scales (VNS) rated from 0 to 10.

At the next connection they reported whether they had been exposed since the previous connection to one of a predefined list of environmental factors suspected of being nonspecific stimulants of inflammatory response, and completed the BASDAI, BASFI, and VNS for pain and PGA.

In all cases it was specified that assessment of disease variables should reflect symptoms over the week preceding each connection.

Environmental factors. We investigated the putative role of environmental factors that had previously been reported in the literature as possibly being associated with the triggering or disease activity of SpA or other inflammatory/autoimmune diseases[12,13,14,15,16,17,18,19,20,21,22,23], as follows.

Stressful or traumatic life events: Patients were asked to complete a VNS, rating from 0 to 10 the effect of a potential exposure to one or more life events occurring since the previous connection that were felt to be stressful, difficult, or traumatic. Several examples were given in the questionnaire: death of a family member or another relative; disease or other serious problem affecting family member or another relative; a sudden personal health problem other than SpA; a notable event in relation to work, personal studies, vehicle, or housing; financial problem; legal problem; disease or death of a pet; married life event; other family problem; and stress in relation to holidays.

Infections (respiratory tract infection, gastroenteritis, urinary tract infection): Patients were asked if they had been exposed since the previous connection to these kinds of infection. In the case of a positive answer, they were also asked to describe the corresponding health problem and its medical consequences (consultation or hospitalization, diagnosis, treatments in relation to this event).

Vaccinations: Patients were asked if they had received any of the following vaccines since the previous connection (yes or no answer for each vaccine): diphtheria-tetanus-polio, influenza, pneumococcal invasive disease, hepatitis A or B, rubella, typhoid, meningococcal invasive disease, Japanese encephalitis, tick encephalitis, yellow fever, and rabies (the questionnaire specified all commercial names for each vaccine).

Farming exposure: Patients were asked if they had visited a farm since the previous connection (yes or no answer).

Dust exposure: Patients were asked if they had been exposed to a dusty atmosphere, for example, through construction work or removal of dust, since the previous connection (yes or no answer).

Solvent exposure: Patients were asked if they had used any solvents or if they had carried out any do-it-yourself activity (yes or no answer).

For our study, we considered exposure to environmental factors that could be easily experienced by an individual between 2 connections. Thus,

alcohol intake and tobacco use were not included in this analysis because of their chronic consumption, making it difficult to correctly identify the point of exposure between 2 connections.

Statistical analysis. The aim of the statistical analysis was to model change in outcome measures according to environmental factors, controlling for other factors that may have influenced such measures over time. The primary outcome variable was the change in a given measure over a 3-month period, computed as this measure at the end minus this measure at the start of the period. Working with the change in a measure as a variable, rather than with the absolute level of it, allowed control for patients' characteristics that may have affected its absolute level. The effect of exposure to an environmental factor, for instance vaccination, was tested by comparing changes in outcome measures over 3-month periods where vaccination had occurred (i.e., "exposed periods") to changes over periods where vaccination was not reported ("non-exposed periods"). In these comparisons, sex, age, time on study, and baseline levels were taken into account to control for changes due to ongoing time or progression of the disease.

Given the study design, with repeated measurements obtained in the same patient, we used a generalized estimating equation (GEE) approach to model change in BASDAI, allowing for intrapatient correlation of measurement. The model was further adjusted for time in study and initial level of BASDAI. The result of this analysis was an estimate of the excess BASDAI change over 1 trimester due to a given exposure, compared to the same periods where such exposure did not occur. The same analysis was repeated for each item of the BASDAI, BASFI, pain, and PGA. Only 3-month periods where both the initial and final BASDAI measurements were available were considered. We considered that a stressful event had occurred between 2 connections if the VNS for this item was larger than the cutpoint[5]. A sensitivity analysis was performed on the choice of this cutpoint.

A univariable analysis was first conducted, and all variables with a p value < 0.20 were included in a multivariable regression. Backward selection of variables was conducted until all remaining variables achieved a p value < 0.05. Robust variances were used for tests and CI.

All statistical analyses were conducted using SAS 9.1.

RESULTS

Three hundred eight patients with SpA fulfilling the inclusion criteria at entry were enrolled in the prospective Co-Env cohort. Of these, 33 patients connected only once, 1 patient did not reply to the questions corresponding to the outcome variables, and 2 patients who had only peripheral arthritis were removed from the analysis, leaving 272 patients with axial manifestations (56% females; 2240 total patient connections). The characteristics of these 272 patients are summarized in Table 1. Among them, 88% met the Assessment of Spondyloarthritis International Society (ASAS) criteria for axial SpA[24], and 6% of the remainder satisfied the ASAS criteria for peripheral SpA.

During the 3 years of followup, the mean (± SD) number of connections per patient was 8.2 ± 2.0. The mean time between 2 connections was 4.0 ± 2.0 months.

Table 1. Characteristics of the study population.

Characteristic	N = 272
Sex, % females (no.)	56 (153)
Mean age, yrs (SD)	44.6 (11)
Mean disease duration, yrs (SD)	17.3 (11.6)
Inflammatory back pain, % (no. positive/no. tested)	98.8 (240/243)
Peripheral arthritis, % (no. positive/no. tested)	31 (73/239)
Enthesitis, % (no. positive/no. tested)	66 (160/241)
Dactyliitis, % (no. positive/no. tested)	20 (47/241)
History of uveitis, % (no. positive/no. tested)	31 (74/240)
History of psoriasis, % (no. positive/no. tested)	32 (78/243)
History of IBD, % (no. positive/no. tested)	9 (21/239)
HLA-B27-positive, % (no. positive/no. tested)	75 (146/194)
Radiographic sacroiliitis, % (no. positive/no. tested)*	54.3 (113/208)
ASAS axial criteria, % (no. positive/no. tested)	88 (196/222)
ASAS peripheral criteria, % (no. positive/no. tested)	6 (14/222)

* Definite radiographic sacroiliitis defined according to the modified New York criteria[11] as sacroiliitis ≥ grade II bilateral or III unilateral. IBD: inflammatory bowel disease; ASAS: Assessment of Spondyloarthritis International Society.

Univariable and multivariable analysis

Stressful life events. Figure 1 shows the distribution of the number of stressful life events that occurred during the study period, according to the level of effect rated by the patient on a VNS from 0 (no effect) to 10 (worst imaginable). To evaluate the influence of stressful events on disease activity, these numerical data were transformed into a binary variable: exposure to a stressful event or not. Analysis was conducted considering all values from 1 to 10 as the possible cutoff for a stressful event. A significant relationship was observed between stressful events and outcome variables, whatever the cutoff value. Thus, we show the results obtained with a threshold of 5 (Table 2).

Information relating to the influence of exposure to a stressful event was missing from 312 (14%) patient connections. We treated this missing information in 2 ways: in the first analysis, missing values were replaced with 0 (i.e., no exposure), and in a second analysis the corresponding periods were excluded from the analysis. The results were similar in both analyses and thus we decided to show the results obtained using only the first approach (i.e., missing values considered equal to 0).

Multivariable analysis showed that the occurrence of life events with a cutoff of 5 was followed by an average increase of 0.5 (95% CI 0.4–0.7) in the BASDAI score ($p < 0.0001$ for both cutoff values; Table 2). This increase was significant for each question in the BASDAI (Table 3), with an average increase of 0.7 (95% CI 0.5–1.0) for the first question of the BASDAI, which referred to fatigue ($p < 0.0001$); of 0.7 (95% CI 0.5–0.9) for the second question, which referred to axial pain ($p < 0.0001$); of 0.5 (95% CI 0.2–0.7) for the third question, which referred to pain and/or swelling in peripheral joints ($p < 0.0001$); of 0.5 (95% CI 0.3–0.7) for the fourth question, which referred to pain on pressure ($p < 0.0001$); of 0.6 (95% CI 0.3–0.8) for the fifth question, which referred to intensity of morning stiffness ($p < 0.0001$); and finally of 0.3 (95% CI 0.1–0.5) for the last question, on duration of morning stiffness ($p = 0.0045$).

Life events were also followed by an average increase of all the other outcome variables: 0.5 points (95% CI 0.3–0.6) in the BASFI score ($p < 0.0001$), 0.7 points (95% CI

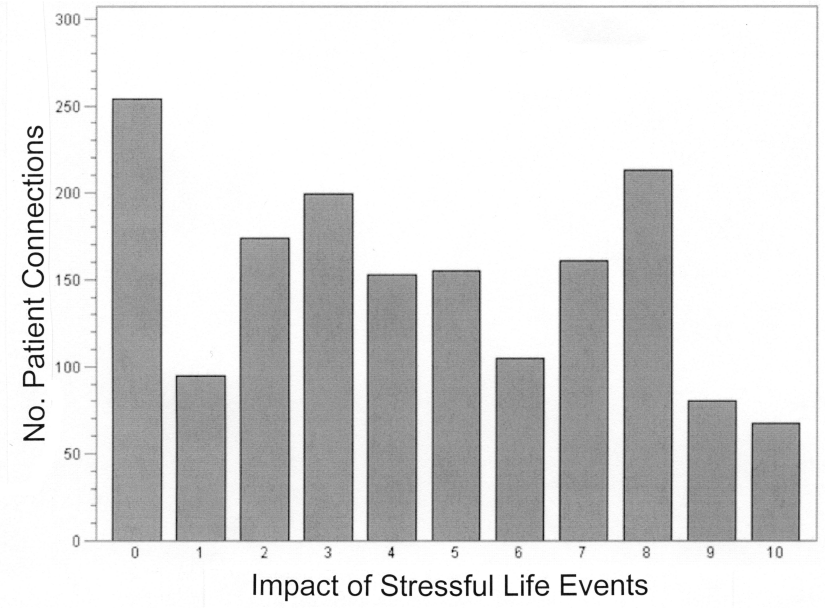

Figure 1. Distribution of stressful life events during the study period, according to their level of influence, rated by the patient on a visual numerical scale from 0 (no impact) to 10 (worst imaginable).

0.5–0.9) on the PGA scale ($p < 0.0001$), and 0.8 points (95% CI 0.6–1.0) on the VNS scale for pain ($p < 0.0001$; Table 2).

Vaccinations. Information relating to vaccine exposure was missing for 118 (5.3%) patient connections (i.e., < 10%). In multivariable analysis, there was a moderate but statistically significant increase in the BASDAI of 0.3 (95% CI 0.0–0.5; $p = 0.032$; Table 2) and of the score corresponding to questions 1, 5, and 6 of the BASDAI after a vaccination (Table 3). No link was found between vaccinations and the BASFI, PGA scale, or VNS for pain.

Other environmental factors. For each of the remaining factors (infection, farming exposure, dust exposure, solvent exposure), missing information accounted for < 10% of patient connections. A weakly significant association was found between dust exposure and the BASDAI, with an increase of 0.2 (95% CI 0.0–0.3; $p = 0.047$) in the first question of the BASDAI (Tables 2 and 3).

No link was found between disease activity and other factors (farming exposure, solvent exposure, infection).

Table 2. Variations in BASDAI, BASFI, PGA, and pain (each criterion rated from 0 to 10) reported following exposure to the studied environmental factors.

	Total No. Patient Connections Analyzed	Univariable Analysis, Mean Change (95% CI)				Multivariable Analysis, Mean Change (95% CI)			
		BASDAI	BASFI	PGA	VNS for Pain	BASDAI	BASFI	PGA	VNS for Pain
Stressful event*	781	0.5 (0.4–0.7) $p < 0.0001$	0.5 (0.3–0.6) $p < 0.0001$	0.7 (0.5–0.9) $p < 0.0001$	0.8 (0.6–1.0) $p < 0.0001$	0.5 (0.4–0.7) $p < 0.0001$	0.5 (0.3–0.6) $p < 0.0001$	0.7 (0.5–0.9) $p < 0.0001$	0.8 (0.6–1.0) $p < 0.0001$
Vaccination	182	0.3 (0.0–0.5) $p = 0.029$	0.1 (–0.1–0.4) $p = 0.321$	0.2 (–0.2–0.5) $p = 0.403$	0.1 (–0.2–0.5) $p = 0.451$	0.3 (0.0–0.5) $p = 0.032$	NS	NS	NS
Infection	478	0.1 (–0.0–0.3) $p = 0.084$	0.1 (–0.1–0.2) $p = 0.484$	0.1 (–0.1–0.4) $p = 0.195$	0.1 (–0.0–0.4) $p = 0.113$	NS	NS	NS	NS
Farming exposure	318	–0.1 (–0.2–0.1) $p = 0.432$	0.0 (–0.1–0.2) $p = 0.873$	–0.0 (–0.3–0.2) $p = 0.809$	–0.1 (–0.3–0.2) $p = 0.584$	NS	NS	NS	NS
Dust exposure	465	0.2 (0.0–0.3) $p = 0.0414$	0.1 (–0.0–0.3) $p = 0.0865$	0.2 (0.0–0.4) $p = 0.0356$	0.1 (–0.1–0.4) $p = 0.151$	0.2 (0.0–0.3) $p = 0.047$	NS	NS	NS
Solvent exposure	430	0.1 (–0.1–0.2) $p = 0.517$	0.0 (–0.1–0.2) $p = 0.707$	0.1 (–0.2–0.3) $p = 0.700$	0.0 (–0.2–0.3) $p = 0.835$	NS	NS	NS	NS

* Patients were considered exposed to a traumatic life event if the influence of the stressful event was equal to or higher than 5, on a scale ranging from 0 (no impact) to 10 (worst imaginable). BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; BASFI: Bath Ankylosing Spondylitis Functional Index; PGA: patient global assessment; VNS: visual numerical scale; NS: not significant.

Table 3. Variations in each question of the BASDAI (each criterion rated from 0 to 10) at the time of connection following exposure to the environmental factors studied: results of the multivariable analysis*.

	Variation in BASDAI Question 1 Mean (95% CI)	Variation in BASDAI Question 2 Mean (95% CI)	Variation in BASDAI Question 3 Mean (95% CI)	Variation in BASDAI Question 4 Mean (95% CI)	Variation in BASDAI Question 5 Mean (95% CI)	Variation in BASDAI Question 6 Mean (95% CI)
Stressful event	0.7 (0.5–1.0) $p < 0.0001$	0.7 (0.5–0.9) $p < 0.0001$	0.5 (0.2–0.7) $p = 0.0001$	0.5 (0.3–0.7) $p < 0.0001$	0.6 (0.3–0.8) $p < 0.0001$	0.3 (0.1–0.5) $p \leq 0.005$
Vaccination	0.3 (0.0–0.6) $p \leq 0.04$	NS	NS	NS	0.4 (0.0–0.7) $p \leq 0.04$	0.4 (0.1–0.7) $p \leq 0.02$
Infection	NS	NS	NS	NS	NS	NS
Farming exposure	NS	NS	NS	NS	NS	NS
Dust exposure	0.3 (0.1–0.5) $p \leq 0.02$	NS	NS	NS	NS	NS
Solvent exposure	NS	NS	NS	NS	NS	NS

* The 6 questions of the BASDAI questionnaire are the following: Question 1: How would you describe the overall level of fatigue/tiredness you have experienced? Question 2: How would you describe the overall level of neck, back, or hip pain you have had? Question 3: How would you describe the overall level of pain/swelling in joints other than neck, back, or hips you have had? Question 4: How would you describe the overall level of discomfort you have had from any areas tender to touch or pressure? Question 5: How would you describe the overall level of morning stiffness you have had from the time you wake up? Question 6: How long does your morning stiffness last from the time you wake up? BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; NS: not significant.

DISCUSSION

To our knowledge, our study was the first to prospectively investigate whether environmental factors may influence the course of SpA. The answer to that question was positive in the case of stressful life events. The most striking result was the significant temporal relationship that appeared between stressful life events and an increase of SpA disease activity measured by the BASDAI. This applied to all functional measures studied to remotely monitor SpA activity/severity. In addition, there was a moderately significant link between vaccination and the BASDAI.

Our results therefore support the hypothesis that stressful events and probably environmental factors can influence the disease activity of SpA. The suspicion that stress and traumatic life events are associated with the course or triggering of SpA had been reported in some retrospective, cross-sectional, or case report studies[4,7,18,25,26]. In terms of vaccinations, only a few cases of reactive arthritis have been reported following vaccine exposure, hepatitis B vaccine being the most frequently cited[27].

Our results appear all the more robust given that all the measures studied varied in the same direction, with an increase in disease activity/severity after exposure to a stressful life event. There is no gold standard for assessing disease activity/severity in SpA or for defining a disease flare. Disease activity cannot be measured by a single variable, which is the reason we used several measures to assess disease activity/severity. Patient-reported disease activity identified by standardized assessment tools is routinely used to guide therapeutic management. Indeed, the BASDAI has been validated for assessment of disease activity and is used as a reference measure for treatment recommendations[2,28,29,30]. The BASFI is a validated functional index used for assessing the severity of SpA[2]. The PGA is considered important for discriminating between low and high disease activity[31]. Importantly, the measures we studied combined the 4 domains retained by the ASAS group of experts as the most important for clinically assessing variation in disease status[32].

The magnitude of variation of the different measures was rather mild at the population level. Average variations of 0.5 for the BASDAI and the BASFI were below the cutoff values of 1 and 0.7, defined as the minimal clinically important variations for these variables, respectively[33]. However, variations could be more important at the patient level, and clinically meaningful in some cases.

Our study had some limitations. First, it is noteworthy that there was a female predominance rather than the more common male predominance seen in axial SpA. This could be explained by the Web-based data collection method, as it has been shown that participants using the Internet can more often be female than male[34]. The same figure has been shown for participation in self-help organizations[35]. However, recent studies also challenged the traditional view of male predominance in axial SPA[36]. Second, we did not evaluate psychopathology or "temperament" in this study. Studies showed a relationship between psychological status (anxiety, depression, helplessness) and the BASDAI or BASFI, because these are self-reported outcome measures[37,38,39,40]. However, we measured life events prospectively, using a standardized questionnaire, with a model taking into account the "baseline" for each patient. Third, given the average delay of 4 months between 2 connections, it is quite possible that some variations in the outcome criteria could have been overlooked, because SpA displays remarkably heterogeneous patterns of change in

disease activity over time[41]. On the other hand, there is no consensus about the maximum time lapse that can be considered meaningful when relating the variation in symptoms to a putative triggering factor. Finally, we measured the influences of environmental factors on the perceived severity of symptoms, but not on objective measures of inflammation, even though the BASDAI and BASFI are accepted proxies for this purpose.

How can stressful life events exacerbate SpA? The biological mechanism linking stressful life events and disease activity has not been determined. Emotional stress may activate or perpetuate preexisting inflammatory arthritis, as suggested for diseases other than SpA[42]. Indeed, alterations in immune function in response to a stressor have been demonstrated in various inflammatory rheumatic diseases[12,14,19]. Understanding the pathways linking the central nervous system to the immune/inflammatory response could provide the basis for treatment approaches that may be either pharmacological or behavioral[43,44].

The prospective design of the study and the standardized questionnaires used to assess both exposure and outcome measures help strengthen the finding of a causal relation between life events (and probably also vaccinations) and increased measures of SpA activity/severity. Even if the effect size was not marked at the population level, it could be important and clinically relevant at the individual level. In any case, identifying the type of event that could be associated with a disease flare will certainly help improve management of SpA (e.g., by postponing a treatment modification in the setting of an "explained" flare or by implementing a psychological intervention, as proposed in the context of other inflammatory diseases[21]). Further research will be necessary to confirm the results of our study and to determine their significance, leading ultimately to improved patient care.

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