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Original article

Abrupt and unexpected stressful life events are followed with increased disease activity in spondyloarthritis: A two years web-based cohort study

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ABSTRACT

Objective: The contribution of environmental factors to spondyloarthritis (SpA) course remains poorly characterized. We previously reported a possible triggering of disease flares by stressful life events and vaccination. The objective of the present study was to specify the types of vaccine and life event that may influence disease activity.

Methods: A prospective cohort of adult SpA was followed for two years. Patients logged on to a secured website every month to complete a standardized auto-questionnaire. They reported whether they had been exposed to stressful life events, vaccinations or other environmental factors. Patients were asked to rate the distress resulting from exposure to life events on a numerical rating scale (NRS: 0–10). Primary outcome variable was the variation of Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) measured on two consecutive connections. Months where an event occurred were compared to months without events. The cut-off value of 1 is defined as the minimal clinically important variation for the BASDAI.

Results: The 272 enrolled SpA patients returned 3,388 questionnaires. Months where an abrupt and unexpected traumatic event occurred were associated with a significant increase of BASDAI of 0.57 [95%CI: 0.29; 0.85] ($P < 0.001$). The higher the rating of distress, the larger the impact on BASDAI, reaching a clinically meaningful increase of 0.99 [0.17; 1.82] for a VNS ≥ 9. The effect of stressful events on BASDAI persisted during a median of 3 months. No other environmental factor was significantly associated with BASDAI variations.

Conclusion: Among stressful life events, abrupt and unexpected events were associated with transient worsening of disease activity in SpA, which reached a clinically meaningful increase for the highest rating of distress. Association between vaccines and disease flare was not confirmed.

1. Introduction

Spondyloarthritis (SpA) is one of the most common inflammatory rheumatic diseases, affecting 0.40–1% of the adult Caucasian population [1]. The most characteristic symptoms of SpA are chronic pain and stiffness predominating in the axial skeleton, i.e. the spinal, pelvic and thoracic joints. Sustained inflammation

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can lead to structural damage such as erosions evolving into bony ankylosis of the sacro-iliac joints and the inter-vertebral disks and spinal ligaments. Peripheral arthritis, enthesitis and extra-articular inflammation, including anterior uveitis, psoriasis and inflammatory bowel disease (IBD) may also frequently occur in SpA. All these manifestations concur to functional impairment and a decrease in quality of life [2].

Albeit the exact cause of SpA remains largely unknown, heritability of this disorder is high [3]. The *HLA-B27* allele is the most important genetic factor identified nearly 45 years ago and accounting for 30% to 50% of the overall genetic risk [3]. Several other genetic polymorphisms associated with SpA predisposition have recently been identified through large-scale genome-wide association studies [4]. However, a major part of SpA heritability still remains to be explained, as for other complex disorders.

On the other hand, the relative contribution of environmental factors to disease triggering and/or progression remains poorly characterized [2]. The disease course is typically characterized by a succession of flares and partial remissions that can readily be monitored by using self-administered validated questionnaires, such as the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) [5]. We previously conducted a prospective cohort study to investigate the putative impact of environmental factors on the triggering of SpA flares [6]. In this previous study, patients were asked to complete a standardized self-questionnaire, every three months, designed to evaluate disease activity, and to identify if they had been exposed since the previous connection to one of a predefined list of environmental factors suspected of being non-specific stimulants of inflammatory response. Results showed that stressful life events, and to a lesser extent vaccines, may indeed influence the course of SpA [6]. However, this study had some limitations, such as a relatively long interval (i.e. 3 months) between two connections that exposed to memory biases. Moreover, no details were obtained regarding the type of stressful life event or the type of vaccine to which the patients were exposed. Also, the magnitude of variation of the different measures was rather mild at the population level, frequently below the minimal clinically important variations.

In order to investigate more thoroughly the relationships between SpA disease activity and environmental exposures, a new cohort was prospectively followed. The purpose of this new study was to expand and refine the previous results by using a shorter period between each questionnaire and by obtaining a detailed description of incoming stressful life events and vaccinations.

2. Methods

2.1. Patients' recruitment

The study population consisted of a dedicated cohort of adult (age $\geq$ 18 yrs) SpA patients fulfilling internationally validated classification criteria [7,8]. They were recruited on a voluntary basis through the Rheumatology Department of Ambroise-Paré Hospital (Boulogne Billancourt, France) or through the "Association Française des Spondylarthritiques", a self-help organisation for SpA patients. 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 informations collected before inclusion: personal history of inflammatory back pain, buttock pain, peripheral arthritis, enthesitis, dactylitis, efficacy of non-steroidal anti-inflammatory drugs, uveitis, psoriasis, IBD, family history of SpA, advanced radiographic sacroiliitis (according to the modified New York criteria), evidence of sacroiliitis on magnetic resonance imaging and *HLA-B27* status. Consent 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 fulfilling ASAS and/or Amor classification criteria for SpA were included in the analysis [7,8]. Part of the study population corresponded to a carryover of a first cohort, which was followed from December 2005 through October 2008 [6]. Participants who entered the present study were not informed of the results of the previous one, in order to minimize the risk of influencing their responses.

2.2. Study conduct

This longitudinal observational study was carried during two years from May 2010 through April 2012. Patients were asked to log on every month to a secured website developed by the UMRS 1136, as previously described [6], and to complete a standardized auto-questionnaire. Patients were enrolled from May 2010 through June 2011 and followed-up until the end of the study period.

The following data were collected at the time of the first connection: demographic (age, gender, disease duration, history of present illness), socio-economical information, SpA disease history (independently assessed for validation of diagnosis), current cigarette-smoking habits (including Fagerstrom score [9], alcohol consumption and addiction [French version of CAGE score]) [10], disease activity and severity by self-assessment measures (French versions of the BASDAI and Bath Ankylosing Spondylitis Functional Index [BASFI]) [11,12], and the Hospital Anxiety and Depression Scale (HADS) [13]. The cut-off values of 1 for BASDAI and 0.7 for BASFI are defined as the minimal clinically important variations for these variables.

At the next connections they reported whether they had been exposed since the previous connection to one of a predefined list of environmental factors suspected of being non-specific stimulants of inflammatory response, and completed the BASDAI, and BASFI. In all cases it was specified that assessment of disease parameters should reflect symptoms over the week preceding each connection.

To test if disease activity was different between patients dropping out before study completion and those who carried on, we compared the mean trimestral BASDAI score during the last three months of participation of the formers to the BASDAI score of the same trimester of the latters. Such comparison was repeated every 3 months.

2.3. Environmental factors studied

At each follow-up connection, patients were asked to report their exposure since the previous connection (i.e. in the last month) to any of the following 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 [6,14–22].

Vaccinations: all the vaccinations recommended for adults by the French health authorities were listed in the questionnaire. Patients were asked to identify if they had received one or several of them.

Stressful life events: patients were asked to report the occurrence of life events that were felt to be stressful, difficult or traumatic. The proposed stressful events were derived from the Paykel list [23]. Abrupt and unexpected stressful life events were clearly identified (natural disasters, assault or sudden death of a loved one for example). In case of positive reply, patients were asked to complete a numerical rating scale (NRS), rating from 0 (least) to 10 (worst) the distress weight of the occurring life event.

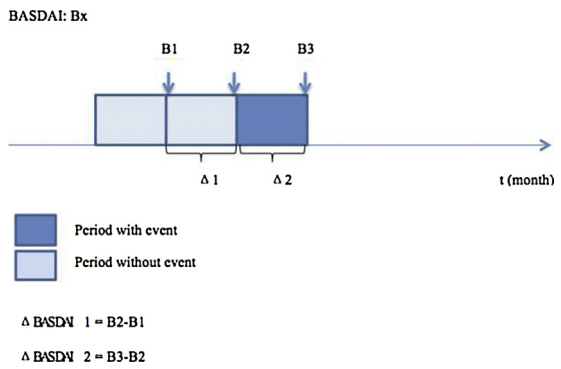

Fig. 1. Study design for calculating changes in BASDAI (ΔBASDAI) in months during which an exposition to an environmental factor occurred, as compared to months during which no exposition to an environmental factor occurred.

Dust exposure: patients were asked if they had been exposed to a very dusty atmosphere, for example, via construction work or removal of dust (yes or no answer).

Solvent exposure: patients were asked if they had used any solvents, either in an occupational setting or while carrying out any "do-it-yourself" activity (yes or no answer).

Surgical intervention: patients were asked if they had had a surgical operation (yes or no answer).

2.4. Missing data

Last observation carried forward (LOCF) was applied for patients who did not connect to the study site between 45 and 59 days since the last connection. The procedure was repeated if no connection had occurred between 60 and 90 days. When a patient did not connect to the study site for more than 90 days, his subsequent connections were deleted from the analysis. With this procedure, 10.6% of observations were added and 12.6% were deleted.

2.5. Statistical analyses

The aim of the statistical analysis was to estimate changes in BASDAI measures according to the occurrence of environmental factors. The primary outcome variable was the change in a given measure over a one month period, computed as the difference of this measure at the end minus this measure at the start of the period (ΔBASDAI). Working with the change in measure as a variable, rather than with the absolute level of it, allowed controlling for patients' characteristics that may affect its absolute level. The effect of exposure to a given environmental factor, vaccination for instance, was tested by comparing change in outcome measure over one month period where vaccination had occurred (i.e. "exposed periods") to change over periods where vaccination was not reported (i.e. "non-exposed periods").

For each patient and each type of event, we searched for all the sequences of two consecutive "non-exposed" and one "exposed" months (Fig. 1). The ΔBASDAI of each of these consecutive months were calculated, and their means were compared with the paired Student *t*-test. Similar analyses were conducted for BASFI.

As multiple comparisons were performed, the Bonferroni correction was applied for endpoint analyses and the corrected *P*-value for statistical significance was set at 0.003.

The persistence of an influence of incoming events on BASDAI was determined by Kaplan-Meier analysis. For this, we defined persistence as the period of time during which the BASDAI remained above the value reported just before the stressful event. Patients who remained above were censored at the time of the last report.

We also compared the average ΔBASDAI between patients with an HADS anxiety score beneath 8 and those with a score at 8 and above, and between patients with an HADS depression score beneath 8 and those with a score at 8 and above (student *t*-test).

All statistical analyses were conducted using R 2.15. package.

2.6. Funding statement

The funders had no role in the design and conduct of the study; analysis, and interpretation of the data and preparation or approval of the manuscript.

3. Results

Three hundred and seven patients having a diagnosis of SpA were recruited for enrolment in this study. Among them 27 could not be reached for classification criteria ascertainment, 4 never accessed to the website, 4 accessed only once for the baseline assessment and 272 patients answered at least to one monthly follow-up questionnaire. Finally, the analyses were conducted on 3,388 patient-connections made by 272 patients during the study period, of which 166 had participated to our previous study [6] and 106 were new participants.

The average duration of participation was 505 days (±159). The mean duration between two connections was 38.9 days (±18.5). Each patient answered to an average of 13.0 (±6.0) monthly questionnaires.

The baseline characteristics of the patients are shown in Table 1. Patients already included in the former study were older, had a longer disease duration and had a lower BASDAI at inclusion than those newly included [6]. On the HADS scoring, the mean level of anxiety was rather high (9.1), while the depression level was in the normal range of less than 8 (6.5). A majority of participants reported drinking alcohol (72.8%), but only 17 patients had a possible addiction. Smokers represented 22.8% of the participants. More than half of the patients (57%) had a professional activity at the time of inclusion.

The average trimestral BASDAI score did not vary significantly according to the duration of participation ($P = 0.42$; [Appendix A, table S1; See the supplementary material associated with this article online]).

The impact of the occurrence of the studied events on BASDAI is shown in Table 2. Months where an abrupt and unexpected stressful life event had occurred were associated with a mean increase of BASDAI of 0.57 [95% Confidence Interval (CI): 0.29; 0.85], compared to months without such occurrence ($P < 0.001$). This increase was not different between patients with an HADS anxiety score beneath 8 and those with a score at 8 and above ($P = 0.82$), nor between patients with an HADS depression score beneath 8 and those at 8 and above ($P = 0.15$). Only the events with the higher rating of distress (i.e. VNS ≥ 9) reached a clinically meaningful increase (mean ΔBASDAI: 0.99 [0.17; 1.82]). The effect of abrupt and unexpected stressful life event on BASDAI persisted for a median of 3 months (95% CI 2–4) and 25% of the patients remained affected more than 8 months (95% CI: 4–18) (Fig. 2).

Among other environmental factors, two showed nominal *P*-value for statistical association with increased BASDAI, although not significant after Bonferroni correction: dust heavy exposure (mean ΔBASDAI: +0.33 [0.01; 0.64], $P = 0.04$) and seasonal influenza vaccination (mean ΔBASDAI: 0.40 [0.02; 0.78], $P = 0.04$) (Table 2).

Similarly as for BASDAI, the months where an abrupt and unexpected stressful life event had occurred were associated with a mean increase of BASFI of 0.27 [95% CI: 0.13; 0.41], compared to months without such occurrence ($P < 0.001$) (Table 3). This increase

Table 1
Characteristics of patients at inclusion according to their participation to a previous cohort [6].

Characteristics	All(n = 272)	Carryover population(n = 166)	Entering population(n = 106)	P
Age at inclusion in years, mean ± SD	48.0 ± 11.8	49.1 ± 11.1	46.2 ± 12.7	0.05
Male percentage, (%)	38.6	38.6	38.7	ns
BMI, mean ± SD	25.3 ± 5.1	25.5 ± 5.3	25.0 ± 4.6	ns
Age at onset in years, mean ± SD	25.6 ± 9.8	24.7 ± 9.9	26.9 ± 9.6	ns
Disease duration in years, mean ± SD	22.4 ± 12.6	24.3 ± 11.7	19.4 ± 13.4	0.002
HLA-B27 positivity, %	78.5	81.7	73.3	ns
Axial manifestations				
Inflammatory back pain, %	95.6	95.2	96.2	ns
Radiographic sacroiliitis, %[a]	44.6	47.1	40.6	ns
Peripheral manifestations				
Peripheral arthritis, %	34.3	35.8	32.1	ns
Dactylitis, %	18.1	20	15.2	ns
Heel pain, %	51.1	51.5	50.5	ns
Extra-articular manifestations				
Uveitis, %	25.3	28	21	ns
Psoriasis, %	28.3	29.1	26.9	ns
Inflammatory bowel disease, %	7.4	6.1	9.5	ns
Classification criteria fulfillment				
New York, %	44.6	47.1	40.6	ns
Amor, %	98.9	99.4	98	ns
ASAS Axial SpA, %	83.6	86.1	79.8	ns
ASAS Peripheral SpA, %	10.9	10.4	11.9	ns
BASDAI (0–10), mean ± SD	4.23 ± 2.04	3.98 ± 1.97	4.62 ± 2.10	0.01
BASFI (0–100), mean ± SD	33.9 ± 24.5	32.8 ± 23.9	35.7 ± 25.4	ns
Treatment				
NSAIDs, %	43.8	39.8	50	ns
Corticosteroids, %	5.9	7.2	3.8	ns
DMARDs, %	17.3	15.1	20.8	ns
Biologics, %	40.4	41.6	38.7	ns
HADS anxiety (0–21), mean ± SD	9.1 ± 4.1	8.8 ± 4.1	9.6 ± 4.2	ns
HADS depression (0–21), mean ± SD	6.5 ±3.9	6.3 ± 4.1	6.8 ± 3.5	ns
Current smokers, %	22.8	21.1	25.5	ns
Fagerström score (0–10), mean ± SD	2.4 ± 2.5	2.4 ± 2.6	2.4 ± 2.6	ns
Alcohol consumption (occasional or regular), %	72.8	72.9	72.6	ns
CAGE score (0–4), mean ± SD	0.3 ± 0.8	0.4 ± 0.8	0.3 ± 0.7	ns
Employment, %	57	60.9	50.9	ns

The registered manifestations correspond to those present at the time of examination, or retrieved from past-medical history. SD: standard deviation; BMI: body mass index; ASAS: Assessment of SpondyloArthritis Society; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; BASFI: Bath Ankylosing Spondylitis Functional Index; NSAIDs: non-steroidal anti-inflammatory drugs; DMARDs: disease modifying anti rheumatic drugs; HADS: Hospital Anxiety and Depression scale; CAGE: Cut-down, Annoyed, Guilty, Eye-opener.

[a] Refers to radiographic sacroiliitis ≥ grade II bilateral or grade III unilateral.

Table 2
Changes of BASDAI during periods with and without events.

Types of exposure	Number of events during the study periods	Number of patients in which the events occurred	Mean of ΔBASDAI of period without events (sd)	Mean of ΔBASDAI of period with events (sd)	Mean difference of ΔBASDAI between periods with and without events [95%CI]	P-value[a]
Abrupt and unexpected stressful life events	169	107	−0.19 (1.13)	0.38 (1.08)	0.57 [0.29; 0.85]	< 0.001
Rating of distress < 5	38	31	−0.12 (1.09)	0.07 (1.11)	0.19 [−0.41; 0.79]	0.52
Rating of distress ≥ 5	131	87	−0.21 (1.14)	0.47 (1.06)	0.68 [0.36; 1.00]	< 0.001
Rating of distress ≥ 7	76	58	−0.16 (1.18)	0.53 (1.02)	0.69 [0.25; 1.13]	0.003
Rating of distress ≥ 9	22	21	−0.28 (1.34)	0.71 (0.94)	0.99 [0.17; 1.82]	0.020
Stressful life events	219	96	0.07 (1.33)	0.04 (1.29)	−0.03 [−0.32; 0.26]	0.86
Financial problem	125	78	0.12 (1.27)	0.04 (1.14)	−0.08 [−0.43; 0.26]	0.64
Work-related problem	56	35	−0.16 (1.60)	0.10 (1.34)	0.25 [−0.38; 0.89]	0.42
Couple problem	153	84	−0.07 (1.23)	0.06 (1.18)	0.13 [−0.20; 0.46]	0.43
Bereavement	116	82	−0.12 (1.16)	0.24 (1.30)	0.36 [−0.03; 0.75]	0.07
Problem with children	123	76	0.05 (1.40)	−0.18 (1.30)	−0.24 [−0.64; 0.17]	0.26
Vaccinations (all vaccines)	116	77	−0.12 (1.14)	0.19 (1.22)	0.32 [−0.05; 0.68]	0.09
Influenza	104	66	−0.17 (1.16)	0.23 (1.13)	0.40 [0.02; 0.78]	0.04
Other	24	23	0.08 (0.95)	−0.23 (1.38)	−0.31 [−1.11; 0.49]	0.43
Surgical intervention	57	49	0.06 (1.25)	−0.05 (1.52)	−0.11 [−0.80; 0.58]	0.75
Dust heavy exposure	149	96	0.00 (1.14)	0.33 (1.20)	0.33 [0.01; 0.64]	0.04
Exposure to agricultural dust	68	43	−0.19 (0.88)	0.15 (1.01)	0.34 [−0.03; 0.72]	0.07
Solvent exposure	138	82	0.15 (1.13)	0.04 (1.12)	−0.11 [−0.40; 0.18]	0.47

[a] The corrected P-value for statistical significance was set at 0.003.

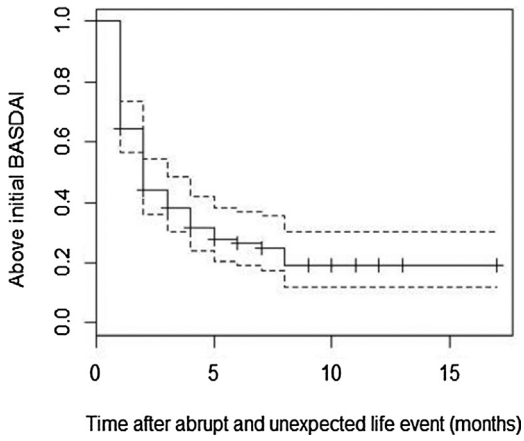

Fig. 2. Persistence of the influence of acute and unexpected stressful life on BASDAI (proportion of patients). The Kaplan-Meier graph shows evolution of the proportion of patients with increased BASDAI over time (months), following occurrence of an acute and unexpected stressful life event.

was close to the minimal clinically important cut-off value only for events with a VNS ≥ 9 (mean ΔBASFI: 0.66 [95% CI: 0.26; 1.06]). A significant increase of BASFI was also observed after dust heavy exposure (0.26 [0.10; 0.42], $P = 0.001$). No other event occurrence was associated with a BASFI modification.

4. Discussion

This prospective study confirms that stressful events are followed by a slight increase of SpA disease activity, as assessed by BASDAI variation. Only stressful life events that are abrupt and unexpected and that are rated as highly distressing reach a clinically meaningful increase. No other environmental factor studied here has a significant impact on disease activity, including vaccines. Noteworthy however, dust heavy exposure was associated to a significant (but non clinically meaningful) worsening of SpA functional score but not of disease activity.

This study showed that abrupt and unexpected life events only, not ongoing stressors, were associated to BASDAI and BASFI worsening. Putting a date on the beginning of a life event may be challenging in the case of ongoing stressors, such as marital or work-related problems for example. On the contrary, abrupt stressors occurring outside of a person's control, such as natural disasters or assault for example, are easier to date, especially in a prospective study, making them more identifiable to patients. There is a widespread belief that acute psychological stress may lead to disease. Indeed, it has been shown that stress contributes to a variety of disease processes and has measurable impacts on the hypothalamic-pituitary-adrenocortical axis, the sympathetic-adrenal-medullary system and the natural and specific immunity [24–26]. The suspicion that stress and traumatic life events are associated with the course or triggering of SpA, was already reported in some retrospective, cross-sectional or case reports studies [27–31]. Even if it is not yet possible to readily establish straightforward relationship between psychological stress and the human immune system, available evidences suggest that acute and chronic stressors determine different kind of changes in the immune response [32]. There is a large body of evidence demonstrating that stress elevates inflammation and that some stressors may be more important than others [33–37]. This biological plausibility of a differential effect of stressors according to their characteristics, together with the clear temporal relationship and the dose-effect pattern observed in the present study, are arguments that favor a causal relationship between stressful life events and disease activity of SpA. Exploring the relationship between psychological symptoms and inflammation is important because it could help to design interventions aiming at reducing stress and the risk of SpA flare, consequently.

Even if the magnitude of variation of the BASDAI following stressful events was rather mild at the population level, variations could be more important at the patient level, and clinically meaningful in some cases. Indeed, the mean variation of 0.99 for the BASDAI following highly distressing abrupt and unexpected events, almost reaches the cut-off value of 1 defined as the minimal clinically important variation for this variable [38].

Beside abrupt and unexpected stressors, dust heavy exposure was associated with worsening of the functional index (BASFI) but not of the disease activity index (BASDAI). One possible interpretation of this observation is that dust heavy exposure was associated with physically demanding occupations that resulted in functional worsening but had no effect on disease activity.

Table 3
Changes of BASFI during periods with and without events.

Types of exposure	Number of events during the study periods	Number of patients in which the events occurred	Mean of ΔBASFI of period without events (sd)	Mean of ΔBASFI of period with events (sd)	Mean difference of ΔBASFI between periods with and without events [95%CI]	*P*-value[a]
Abrupt and unexpected stressful life events	169	107	3.85 (2.56)	4.12 (2.61)	0.27 [0.13; 0.41]	< 0.001
Rating of distress < 5	38	31	2.71 (1.85)	2.87 (1.81)	0.16 [−0.14; 0.46]	0.29
Rating of distress ≥ 5	131	87	4.19 (2.65)	4.48 (2.70)	0.30 [0.14; 0.46]	< 0.001
Rating of distress ≥ 7	76	58	4.59 (2.72)	5.04 (2.75)	0.44 [0.24; 0.65]	< 0.001
Rating of distress ≥ 9	22	21	4.90 (3.28)	5.55 (3.22)	0.66 [0.26; 1.06]	0.003
Stressful life events	219	96	3.97 (2.61)	3.98 (2.57)	0.02 [−0.11; 0.14]	0.81
Financial problem	125	78	3.85 (2.70)	3.79 (2.56)	−0.06 [−0.23; 0.11]	0.51
Work-related problem	56	35	3.39 (2.48)	3.31 (2.37)	−0.08 [−0.39; 0.22]	0.58
Couple problem	153	84	3.13 (2.35)	3.21 (2.34)	0.08 [−0.05; 0.20]	0.24
Bereavement	116	82	3.94 (2.29)	4.04 (2.34)	0.10 [−0.07; 0.27]	0.25
Problem with children	123	76	4.16 (2.64)	4.12 (2.73)	−0.04 [−0.19; 0.12]	0.62
Vaccinations (all vaccines)	116	77	4.47 (2.62)	4.49 (2.59)	0.02 [−0.15; 0.19]	0.85
Influenza	104	66	4.65 (2.67)	4.70 (2.58)	0.05 [−0.14; 0.23]	0.62
Other	24	23	3.25 (2.34)	2.93 (2.34)	−0.32 [−0.69; 0.04]	0.08
Surgical intervention	57	49	4.24 (2.67)	4.53 (2.80)	0.29 [−0.02; 0.61]	0.07
Dust heavy exposure	149	96	3.59 (2.65)	3.85 (2.75)	0.26 [0.10; 0.42]	0.001
Exposure to agricultural dust	68	43	3.18 (2.71)	3.39 (2.81)	0.21 [0.00; 0.42]	0.05
Solvent exposure	138	82	3.70 (2.60)	3.72 (2.42)	0.02 [−0.16; 0.20]	0.83

[a] The corrected *P*-value for statistical significance was set at 0.003.

Concerns about adverse effects of vaccines are associated with low vaccine coverage rates [39]. The results presented here may help reassure patients with spondyloarthritis that vaccines do not increase disease activity.

The principal strengths of this study were its prospective design, the use of a standardized questionnaire applied to a dedicated SpA cohort and the monthly basis of questionnaire administration that limited memory biases. Moreover, each patient served as its own control, limiting the risk of information biases due to a lack of control population.

This study had some limitation, however. Notably, we measured the impact of environmental factors on the perceived severity of symptoms, but not on objective marker of inflammation. Thus, we could not demonstrate that what we measured truly corresponded to an increase in disease activity, even though the BASDAI is an accepted proxy for this purpose. BASDAI score could partly be explained by psychological distress [40]. For instance, it has been shown in the context of rheumatoid arthritis that depressive symptoms could influence patient-reported symptoms, but had no impact on swollen joints and acute-phase reactants [41]. On the other hand, our results were not affected by the level of depression or anxiety, which militates against such interpretation applying to our study.

To conclude, this study confirms with enhanced methodology our previous demonstration that stressful events, but not vaccines could be followed by a worsening of SpA activity [6]. It also showed that such impact was only significant and clinically meaningful for abrupt stressors with the highest rating of distress and that it could last several months. These conclusions bear strong implication for the care of SpA and for understanding factors that influence the evolution of this chronic disorder.

Disclosure of interest

SK declares having received travel grants from Pfizer Vaccines.

TH declares having received travel grants from Sanofi Pasteur MSD.

The other authors declare that they have no competing interest.

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Appendix A. Supplementary data

Supplementary data (Table S1) associated with this article can be found, in the online version, at:

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