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Influence of Sex on Early Axial Spondyloarthritis: A Six-Year Longitudinal Analysis From a Large National Cohort

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1 **Manuscript for Arthritis Care and Research**

2 **The influence of sex on early axial spondyloarthritis, 6-year longitudinal**
3 **analyses from a large national cohort**

4
5 **Short title:** Sex-related differences in axSpA

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4

5 **Word count: 3026 words, 46 references, 3 tables, 2 figures, 3 supplementary**
6 **tables, 1 supplementary figure**

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1 **Abstract (N words=243)**
2

3 **Objective:** The objective was to determine sex differences in disease outcomes in
4 recent axial spondyloarthritis (axSpA) over time.

5 **Methods:** We analysed the first 6 years of follow-up of the prospective French
6 multicenter DESIR cohort (NCT01648907). Patients analysed had less than 3 years
7 of disease, were DMARD-naive and fulfilled the ASAS classification criteria for
8 axSpA. Disease activity (ASDAS-CRP), patient global assessment (PGA), C-reactive
9 protein (CRP) and radiographic sacroiliitis were compared between men and women
10 (self-reported sex) by linear and logistic mixed-effect models. Trajectories of disease
11 activity were modelised over 6 years in men and women, using k-means.

12 **Results:** Of 494 patients analysed (mean age 31.9±7.5 years, mean symptoms
13 duration 20.7±11.7 months), 50.4% were men. Over 6 years of follow-up, both men
14 and women showed clear improvements in ASDAS-CRP, PGA and CRP. Women
15 had higher ASDAS-CRP and PGA over time compared to men (both $p<0.0001$) with
16 overall similar CRP levels ($p=0.089$), whereas structural damage increased more in
17 men ($p<0.0001$). One-third of both men (33%) and women (34%) belonged to
18 'persistent high/very high disease activity' trajectories, however, ASDAS-CRP scores
19 were globally higher in women in these trajectories.

20 **Conclusion:** In early axSpA, clinical outcomes (disease activity and symptoms) were
21 worse in women than men over 6 years of follow-up, whereas CRP was similar and
22 structural damage was more frequent in men. Although similarly distributed, disease
23 activity scores were higher in women in 'high/very high disease activity' trajectories.
24 Sex appears to be an important contextual factor in axSpA.

25 **Keywords:** Axial spondyloarthritis; sex
26

1 **Key points**

- 2 • Less improvement in disease activity and patient-reported outcomes were
3 observed in women over time.
4 • Structural damage was more common in men than women over 6 years of follow-
5 up.
6 • Sex is an important contextual parameter to consider in the management of
7 axSpA.

8

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1 In many diseases, sex-related differences have become a major focus of
2 interest.(1) In Rheumatic and Musculoskeletal Diseases (RMDs), it is increasingly
3 being recognized that women differ from men regarding disease expression, clinical
4 manifestations, disease progression and treatment response.(2,3) Sex-related
5 differences may be multifactorial and complex, driven by genetic, hormonal, socio-
6 cultural and/or psychological factors, thus, leading to differing diseases
7 pathophysiology, articular pattern, quality of life and perception of pain between men
8 and women. Recognizing and understanding these disease-specific differences may
9 result in adaptations related to sexes, leading to a tailored management of the
10 disease and better outcomes. (1)

11 Historically, ankylosing spondylitis (AS) was considered a predominantly male
12 disease; however, currently, the male to female ratio is 2-3:1 in radiographic axial
13 spondyloarthritis (axSpA), with an equal sex distribution in its non-radiographic
14 form.(4) Recent data suggest differences in disease phenotypes between men and
15 women with axSpA, in terms of disease activity and disease progression.(5–12)
16 Women seem to have a higher disease burden, worse functional impairment but less
17 structural damage.(13–15) However, data on sex differences in axSpA available
18 today are mostly issued from cross-sectional, retrospective studies or long-standing
19 disease cohorts.

20 In chronic inflammatory arthritis, studying the early period of the disease is key since
21 many changes occur in the early stages.(16) Furthermore, cohort studies allow
22 prospective longitudinal analyses over time.(17) Therefore, identifying the
23 consequences of sex on axSpA in an inception cohort is of interest.

24 We hypothesised that sex may influence disease activity progression and that
25 different factors at baseline might be related to disease progression in men and
26 women. We have previously explored disease activity trajectories in axSpA and
27 homogeneous groups of disease activity were identified.(18) Such methods could be
28 applied to explore the influence of sex in axSpA.

29 The objective of this study was to explore differences in outcomes, including disease
30 activity, patient-reported outcomes (PROs), inflammatory markers and radiographic
31 damage between men and women with axSpA, and to identify sex-specific factors
32 associated with disease activity trajectories, in an inception cohort with a longitudinal
33 follow-up.

34

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37 **MATERIALS AND METHODS**

38

39 **Study design and patients**

40 The DESIR cohort (NCT01648907) is a French longitudinal, prospective, multicenter
41 observational cohort including patients aged >18 and <50 years with early
42 inflammatory back pain (IBP) fulfilling either the Calin or Berlin criteria, symptom
43 duration >3 months and <3 years suggestive of spondyloarthritis according to the
44 rheumatologist's assessment (e.g. score ≥ 5 on a 0 to 10 numerical rating scale
45 where 0 = not suggestive and 10= very suggestive).(19) Of 708 patients included in
46 the cohort, we analysed only patients fulfilling the Assessment of SpondyloArthritis
47 International Society (ASAS) classification criteria of axSpA (20) at entry or at any
48 time point during follow-up visits (**Supplementary Figure 1**). All patients were
49 bDMARD naive. Baseline analyses according to gender have been reported
50 elsewhere;(5) here, the first 6 years of follow-up were analysed (with data collected at

1 0, 6, 12, 18, 24, 36, 48, 60 and 72 months). The DESIR cohort was approved by the
2 French ethical committee and the study was conducted according to Good Clinical
3 Practice guidelines. All participants provided written informed consent.(21)

4

5 **Clinical outcomes**

6 **Sex**

7 Sex as reported by the patient at baseline was the main variable of interest.

8 ***Main outcomes***

9 The outcome criteria collected over time and analysed according to sex were: a) a
10 validated composite disease activity score, the Ankylosing Spondylitis Disease
11 Activity Score-CRP (ASDAS-CRP); (22) b) a PRO, patient global assessment (PGA)
12 using the Bath Ankylosing Spondylitis Patient Global Score (BAS-G) over the past
13 week; c) an acute-phase reactant: C-reactive protein (CRP); and d) radiographic
14 sacroiliitis according to the modified New York criteria (mNY). The first 3 outcomes
15 were evaluated at 0, 6, 12, 18, 24, 36, 48, 60 and 72 months whereas radiographs
16 were obtained and scored at baseline, 2 years and 5 years.

17 ***Patient characteristics***

18 Demographic and clinical data at baseline included age, relevant family history,
19 duration and vertebral level of IBP, HLA-B27 status, extra-articular manifestations
20 (uveitis, inflammatory bowel disease, psoriasis) and other manifestations (dactylitis,
21 enthesitis, arthritis).

22 ***Exploratory outcomes***

23 Secondary analyses were performed for other disease activity scores: Bath
24 Ankylosing Spondylitis Disease Activity Index (BASDAI) [0-100], Ritchie articular
25 index (53 joints weighted from 0 to 3), 28-swollen joint score [0-28], Maastricht
26 Ankylosing Spondylitis Enthesis score (MASES)[0-13]. (22) Physical function and
27 quality of life were assessed using Health Assessment Questionnaire for axSpA
28 (HAQ-AS) and Bath Ankylosing Spondylitis Functional Index (BASFI), Ankylosing
29 Spondylitis Quality of Life Scale (ASQoL) and Short Form-36 health survey
30 questionnaire (SF-36).(22)

31 Treatment intake defined as conventional synthetic disease-modifying anti-rheumatic
32 drugs (csDMARDs) (yes/no), and separately, tumor necrosis factor inhibitor (TNFi)
33 use (yes/no) at each timepoint, were analysed by comparing the sexes using a
34 mixed-effect model.”

35 Radiographs of sacroiliac joints and the spine were assessed by local reading at
36 baseline, 2 years and 5 years. Spine radiographs were scored according to the
37 modified Stoke Ankylosing Spondylitis Spine Score (mSASSS).

38 **Statistical analyses**

1 Baseline characteristics of men and women were compared using t-tests (or Mann-
2 Whitney U tests) for continuous variables and chi-square tests (or Fisher's exact test)
3 for categorical variables. To assess the impact of sex over time taking into account
4 longitudinal repetitive measures, mixed-effect linear and logistic regression models
5 were performed (using lme4 R package) for continuous and binary dependent
6 variables respectively. In the mixed models, sex and time were determined as fixed
7 effects and subjects as random effects (more details in **Supplementary Table 1**). To
8 illustrate the evolution over time, the mean of the last 2 values of each outcome was
9 calculated. Missing data were handled using mixed models, imputation of missing
10 data was not needed and not performed.

11 Trajectories in men and in women separately were modelised through homogeneous
12 clusters of disease activity based on ASDAS-CRP, using the R package kml.(23) The
13 optimal number of clusters (from 2 to 6) was chosen using the Calinski and Harabatz
14 criterion. Only patients for whom at least 3 ASDAS values were available during the 6
15 years of follow-up were included in this analysis, as was done in previous DESIR
16 analyses (**Supplementary Figure 1**). Predisposing baseline factors (demographics,
17 disease phenotype, disease severity, quality of life, radiographic sacroiliitis)
18 associated with the different trajectories were analysed by univariate analysis.
19 Covariates significantly associated with at least one trajectory ($p < 0.1$) in univariate
20 analysis, were included in the multivariable multinomial logit regression, after
21 excluding colinear variables. For the analyses, the "persistent low disease activity"
22 trajectory was used as the reference trajectory because it included the largest
23 number of patients (more details in **Supplementary Table 1**). Statistical analyses
24 were performed using the Software R Studio Version 1.4.1106.
25

1 RESULTS

2
3 Of the 708 patients included in the DESIR cohort at baseline, 494 (69.7%) who
4 fulfilled the ASAS classification criteria for axSpA at any time point were analysed
5 (**Supplementary Figure 1**): mean age was 31.9 ± 7.5 years, mean disease duration
6 was 20.7 ± 11.7 months; 249 (50.4%) were men and 245 (49.6%) were women.

7 **Comparison of baseline characteristics between men and women**

8 At baseline (**Table 1**), mean age was similar between men and women, however, the
9 duration of IBP was longer in women. At baseline, disease activity was high and
10 similar in men and women (mean \pm SD ASDAS-CRP score was 2.6 ± 1.0 in men versus
11 2.6 ± 0.9 in women, $p=0.75$), whereas subjective measures such as PGA and other
12 PROs (SF-36, HAQ-AS, ASQoL, PGA, BASFI), but also objective signs such as
13 tender and swollen joint counts and MASES enthesitis scores, were worse in women
14 at baseline. However, CRP levels and sacroiliitis were more common in men.

15 **Impact of sex on disease outcomes**

16 Main outcomes:

17 **ASDAS-CRP:** Although disease activity was comparable at baseline and decreased
18 in both groups, women had significantly higher ASDAS-CRP scores over 6 years of
19 follow-up ($p<0.0001$ in mixed models, shown in **Figure 1 and Table 2**). To illustrate
20 this, the mean ASDAS-CRP score was 1.9 ± 1.0 in men versus 2.3 ± 0.9 in women at
21 the last 2 time points (**Table 2**, for more details and data availability for each
22 timepoint, see **Supplementary Table 2 and 3**).

23 **PGA:** Women had significantly higher PGA which persisted over 6 years of follow-up
24 ($p<0.0001$ in mixed models, **Figure 1 and Table 2**).

25 **CRP levels:** Although significantly higher CRP levels were seen in men at baseline,
26 overall CRP levels were similar over 6 years of follow-up ($p=0.090$ in mixed models,
27 **Figure 1 and Table 2**).

28 **Radiographic sacroiliitis, mNY criteria:** At baseline and over time, more men had
29 radiographic sacroiliitis ($p<0.0001$ in mixed models, **Figure 1 and Table 2**).
30 Radiographic sacroiliitis was seen in 72 (28.9%) men and 32 (13.1%) women at 5
31 years (**Table 2**). At 6 years, the main outcomes (ASDAS-CRP, PGA and CRP)
32 showed significantly higher values in women compared to men in both radiographic
33 and non-radiographic axSpA (**Supplementary Table 3**).

34 Secondary outcomes:

35 As seen in **Table 2**, women had significantly worse PROs (BASDAI, BASFI, ASQoL,
36 HAQ-AS, SF-36) than men over time, higher MASES enthesitis index, higher
37 tender/swollen joint counts but less sacroiliitis on MRI and less structural spinal
38 damage (mSASSS) over time (all $p<0.05$ in mixed models). Drug intake at least once
39 over follow-up (csDMARDs and TNFi) were similar between sexes over time (**Table**
40 **2**).

42 **Trajectories**

43 When analysing trajectories separately in men and women (total 352 patients), we
44 identified six different trajectories in both in men and women (**Figure 2**,
45 **Supplementary Figure 2**). A nomenclature for trajectories of disease activity in
46 DESIR has been previously described and was used here (18,26). The distribution of
47 patients in different trajectories was globally similar in men and women, eg. 68 (38%)
48 men and 73 (42%) women had an 'inactive or low disease activity' evolution whereas

1 59 (33%) men and 60 (34%) women had a 'high/very high disease' evolution.
2 ASDAS-CRP scores were globally higher in women in 'high/very high disease'
3 trajectories as shown in **Supplementary Figures 2.A and 2.B**. On the other hand,
4 22 (12%) men and 15 (9%) women had 'almost major improvement' on ASDAS-CRP.

5 ***Baseline characteristics associated with each trajectory in men and women***

6 The multivariable analysis showed that higher HAQ-AS scores at baseline were
7 associated with increased odds of being in the of 'persistent high/very high disease
8 activity' group compared to 'persistent low disease activity' in both men and women
9 (**Table 3**). On the other hand, higher HAQ-AS scores at baseline in men (odds ratio,
10 OR=0.09, 95% confidence interval, CI [0.01,0.79]) were significantly associated with
11 decreased odds of being in the "persistent inactive disease activity" compared to
12 'persistent low disease activity'.
13
14

1 DISCUSSION

2 This large cohort of patients with early axSpA demonstrates the differences in
3 disease phenotypes between men and women. For both sexes, disease activity,
4 function and pain improved over time. However, although disease activity was similar
5 between sexes at baseline, there was less improvement in disease activity,
6 functioning and quality of life in women than in men over 6 years of follow-up, leading
7 to higher disease activity and symptoms in women at 6 years. The higher level of
8 disease activity over time was confirmed by a second statistical technique: even
9 though one-third of both men and women had a persistent high/very high disease
10 activity evolution, disease activity scores were globally higher in women in these
11 trajectories. Finally, structural damage and MRI inflammation were more prevalent in
12 men than women, although they had similar acute phase reactants and treatment
13 intake.

14
15 This study has some strengths and limitations. This longitudinal analysis of the
16 impact of sex on disease outcomes in axSpA brings different and valuable
17 information compared to published data which are mainly cross-sectional.(5–
18 8,10,12,13,15,24,25) A strength of our study is the validated methodologies used to
19 analyse longitudinal data: mixed-effects models and trajectory analyses. The use of
20 “k-means” algorithm presents an original and innovative methodology to study
21 longitudinal data; trajectory modeling was recently used in axSpA in previous studies
22 on the same cohort after 3 years and 5 years of follow-up.(18,26) The DESIR cohort
23 included a large sample of patients; however, many patients could not be analysed
24 because they did not satisfy the ASAS criteria for axSpA.The sample of patients
25 allowed us to define distinctive trajectories of disease activity stable over time.
26 However, given the small sample size in each specific trajectory we chose not to
27 (over-)interpret baseline characteristics of the patients in each trajectory. One may
28 argue that PROs included in the ASDAS score may have contributed more than CRP
29 to trajectory clustering. However, both PROs and acute phase reactants are
30 recommended for disease activity monitoring in axSpA.(27) Although treatment
31 intake over time was analysed (and was similar between men and women over time),
32 the types and dosages of TNFi and treatment retention were not analysed. As in
33 many longitudinal studies, there were missing data over time; however, the DESIR
34 cohort is one of the largest cohorts of early axSpA, and using mixed-effects models
35 allowed us to overcome missing data and analyse all the data of patients included in
36 the cohort.

37
38 Our study showed that disease activity scores were higher in women over time
39 as reflected by both ASDAS and BASDAI. This finding is in line with previous cross-
40 sectional and observational studies reporting that female sex was associated with
41 higher disease activity mainly observed on the BASDAI scores;(5–8,10,13,24,25) and
42 a few recent studies also reported higher ASDAS scores in women.(12,28) In this
43 study, women had more peripheral arthritis and enthesitis than men. Past studies
44 have reported similar findings.(6,8,15,25) As for PROs measures, PGA, BASFI,
45 ASQoL, HAQ-AS, SF-36 scores were worse in women determining poor functional
46 status and well-being. This finding is consistent with previous observations showing
47 overall higher disease burden and functional impairment in female sex with axSpA
48 (6,10,15,25,29). On the other hand, there was no difference in CRP levels between
49 sexes over time, therefore, the difference in ASDAS scores was mainly driven by the
50 PROs (axial and peripheral pain, duration of morning stiffness, PGA). This highlights

1 that disease activity scores may be somewhat subjective and driven by central
2 sensitization, in contrast to MRI inflammation which may be a more subjective tool.

3
4 Altogether, in the present study, both disease activity scores and PROs were
5 worse in women. It might be worth noting that similar findings were seen in women
6 with chronic RMDs such as rheumatoid arthritis and psoriatic arthritis (2,30), thus
7 emphasizing increased pain sensitivity widely acknowledged in the female sex.(6,31)
8 Women had a higher percentage of non-radiographic axSpA (nr-axSpA), with higher
9 disease activity scores compared to men. (32) These findings may be partly
10 explained by the higher prevalence of concomitant fibromyalgia among women with
11 axSpA.(33) The ASDAS-CRP score used in our analysis and trajectory modeling is a
12 rather objective score that seems to be less influenced by secondary fibromyalgia in
13 patients with axSpA.(34) Nevertheless, studies have shown that coexistent
14 fibromyalgia characterized by chronic musculoskeletal widespread pain and tender
15 points may impact disease activity scores and treatment response in axSpA (32)
16 making it particularly difficult in the presence of axSpA with enthesal symptoms.(33)
17 Thus, this underlines the challenge to differentiate enthesal tenderness due to
18 central sensitization from enthesitis resulting in real inflammation of the entheses in
19 axSpA patients. It might be of interest to use more objective imaging tools in the
20 evaluation of peripheral symptoms in axSpA as well as pain pathways.

21
22 Because of the association between disease activity and structural
23 progression, (35) one would expect women with higher disease activity to have more
24 structural damage. However, this was not confirmed by our study and other past
25 studies showing significantly more structural progression in men.(7,36–38) Whether
26 men tend to minimize their symptoms leading to worse clinical outcomes, remains
27 unclear. This raises the question of whether lower cut-offs are needed for disease
28 activity scores in men. We also believe this indicates the difficulties to link clinical
29 outcomes to radiographic progression in axSpA, in particular when radiographic
30 progression is overall low as is the case in the DESIR cohort.(39)

31
32 Treatment intake (TNFi and csDMARD) in men and women were similar over
33 time even though women had higher disease activity scores and disease burden.
34 Several hypotheses could justify this finding. We think it could be due to the higher
35 treatment failure and lower time on drug observed in female patients;(7) or on the
36 contrary, due to the better recognition by rheumatologists of the overlap with
37 fibromyalgia resulting in less treatment initiation or switching in women. This needs to
38 be further clarified in future studies.

39
40 Around one-third of men and women remained in 'high/very high disease
41 activity' trajectories, thus, implying an insufficient control of the disease despite the
42 wide use of biologics. This finding was also reported by Molto et al in the analysis of
43 the whole cohort population at 3 years of follow-up.(18) Women had globally higher
44 ASDAS scores in these 2 trajectories which are consistent with the results from
45 mixed models. It is also important to note that coexistent fibromyalgia in women may
46 have influenced the persistence of increased disease activity scores which include
47 subjective elements such as patient global and pain. (40) Furthermore, high HAQ-AS
48 scores at baseline were strongly associated with both high and very high disease
49 activity evolution in both sexes. This finding is probably linked to the existing high
50 correlation between HAQ-AS and other PROs including those comprised in the

1 ASDAS scores. This highlights again the limitations of the ASDAS scores which
2 appear here again to be driven by PROs.(35,41) Factors associated with disease
3 evolution may help physicians predict the evolution of symptoms in axSpA while
4 taking into account sex in the equation.

5 These sex-related differences may be explained by socio-cultural, genetic,
6 hormonal and immunological factors that may result in distinct pathogenesis and
7 phenotypes of the same disease in both sexes and does not seem to be linked to
8 differences in treatment intake. The perception of pain is a subjective experience and
9 differs between sexes. Andromativity and hegemonic masculinity can influence the
10 expression and coping with pain based on gender norms.(31) From a sociocultural
11 perspective, women tend to verbalize and report more pain whereas chronic pain in
12 men may be seen as a sign of weakness and threat to masculine identity.(42) Higher
13 masculinity was shown to be associated with higher pain tolerance and pain
14 thresholds, whereas femininity was associated with greater sensitivity to pain.(31)
15 As for genetic factors, the most relevant one, HLAB27 positivity, appears to be more
16 prevalent in men explaining somewhat the higher structural damage (43). Sex
17 hormones (estrogen and testosterone levels) may also play a role in the dissimilar
18 immune response and pain response between sexes.(44) Cytokine release may also
19 differ: higher levels of TNF-alpha and IL-17 were detected in men with axSpA leading
20 to osteoblastic differentiation, osteoproliferation and stimulation of inflammatory
21 pathways inducing more bone damage.(45,46) Further studies are needed to better
22 identify pathogenic mechanisms and factors causing differential clinical patterns and
23 disease progression between sexes.

24
25 In conclusion, our analysis confirms that women seem to have a different
26 disease phenotype than men in axSpA. Over 6 years of follow-up, women had higher
27 disease activity, worse functioning and well-being but less structural damage. It is
28 important to note that treatment intake was generally similar over time between
29 sexes, though this observational study which did not control for treatment received,
30 may have overlooked more subtle differences in treatments between sexes. It is
31 essential to recognize sex as an important contextual factor in axSpA. Sex
32 differences should be widely recognized and taken into account in the management
33 of the disease. More studies are needed to determine the factors related to sex
34 differences in the view of predicting and improving outcomes.

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28

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10

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16 **Data availability statement:** The data underlying this article were provided by
17 DESIR cohort under permission and cannot be shared publicly. Data will be shared
18 on reasonable request to the corresponding author with permission of the DESIR
19 cohort scientific committee.
20

1 **Table 1. Comparison of baseline characteristics between men and women with**
 2 **axSpA**

	All (n=494)	Men (n=249)	Women (n=245)	p-value
Age, years, mean±SD	31.9±7.5	31.2±7.6	32.6±7.3	0.03
Duration of IBP, years, mean±SD	1.7±1.0	1.7±0.9	1.8±1.0	< 0.0001
Past history of:				
Dactylitis, n (%)	70 (14.2)	32 (12.9)	38 (15.5)	0.40
Enthesitis, n (%)	265 (53.6)	131 (52.6)	134 (54.7)	0.64
Uveitis, n (%)	47 (9.5)	20 (8.0)	27 (11.0)	0.26
Peripheral arthritis, n (%)	138 (28.0)	73 (29.3)	65 (26.5)	0.51
IBD, n (%)	26 (5.3)	10 (4.0)	16 (6.5)	0.21
Psoriasis, n (%)	78 (16.6)	38 (16.0)	40 (17.1)	0.50
HLA-B27 positivity, n (%)	378 (76.5)	201 (80.7)	177 (72.2)	0.02
Tender joint score [0-53], mean±SD	2.6±4.8	1.8±4.0	3.5±5.4	< 0.0001
Swollen joint score [0-28], mean±SD	0.1±0.7	0.1±0.9	0.2±0.3	< 0.0001
MASES Enthesitis score [0-13], mean±SD	2.4±3.0	1.4±2.2	3.4±3.3	< 0.0001
MRI sacroiliitis †, n(%)	220(44.5)	132(53.0)	87(35.5)	0.0002
ASAS criteria clinical arm verified, n(%)	189(40.1)	78(32.9)	111(47.4)	0.0013
ASAS criteria imaging arm verified, n(%)	245(52.0)	147(62.1)	98(41.9)	< 0.0001

3
 4 Continuous variables were expressed as mean and standard deviation (SD) and categorical
 5 variables were expressed as numbers and percentages.

6
 7 *IBP: inflammatory back pain; IBD: Inflammatory Bowel Disease; ASDAS-CRP : Ankylosing*
 8 *Spondylitis Disease Activity Score-CRP, ASQoL : Ankylosing Spondylitis Quality of Life Scale;*
 9 *BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; BASFI: Bath Ankylosing Spondylitis*
 10 *Functional Index; csDMARDs : conventional synthetic disease modifying antirheumatic drugs;*
 11 *CRP: C-reactive protein; HAQ-AS: Health Assessment Questionnaire for axSpA; MASES:*
 12 *Maastricht Ankylosing Spondylitis Enthesis score; MRI: magnetic resonance imaging; mNY :*
 13 *modified New York criteria; SF-36: Short Form-36 health survey questionnaire; TNFi: tumor*
 14 *necrosis factor inhibitors.*

15 † MRI sacroiliitis according to the local investigator.

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1 **Table 2. Effect of sex on different clinical outcomes in axSpA over 6 years of**
 2 **follow-up using mixed-effects models.**

3 # The final value represents the mean of the last 2 values at month 60 and 72 for all clinical
 4 outcomes except for radiographic sacroiliitis, MRI sacroiliitis and mSASSS (only values at month
 5 60).

6 * According to the local investigator.

	Baseline value		Final value [#]		Effect estimate of sex by mixed-effects models over time (N=494)
	Men	Women	Men	Women	
Key outcomes					p-value
ASDAS-CRP, mean±SD	2.6±1.0	2.6±1.0	1.9±1.0	2.25±0.9	<0.0001
PGA [0-10], mean±SD	4.6±2.6	5.2±2.6	2.9±2.5	4.1±2.8	<0.0001
CRP (mg/L), mean±SD	10.7±16.5	6.2±8.3	6.0±11.6	4.9±6.5	0.09
mNY radiographic sacroiliitis during follow-up (local reading*), n (%)	64 (25.7)	42 (17.1)	72 (28.9)	32 (13.1)	<0.0001
Exploratory outcomes					
BASDAI [0-100], mean±SD	40.5±20.2	46.3±18.5	25.7±19.3	37.5±21.2	<0.0001
BASFI [0-100], mean±SD	26.9±21.3	32.4±23.3	15.9±18.3	26.0±22.3	<0.0001
ASQoL [0-18], mean±SD	8.0±5.0	10.1±4.8	4.5±4.7	8.0±5.5	<0.0001
SF-36, mean±SD					
Physical Component Summary (PCS) [0-100]	41.3±8.9	39.0±9.1	47.0±8.7	41.0±9.6	<0.0001
Mental Component Summary (MCS) [0-100]	42.3±11.2	39.6±11.3	47.1±10.1	43.0±11.6	0.0002
HAQ-AS [0-3], mean±SD	0.5±0.5	0.8±0.5	0.3±0.4	0.63±0.5	<0.0001
Tender joint count [0-53], mean±SD	2.5±5.2	4.5±7.5	1.1±3.6	3.8±6.2	<0.0001
Swollen joint count [0-28], mean±SD	0.1±0.3	0.2±0.9	0.02±0.2	0.1±0.7	0.04
MASES enthesitis index [0-13], mean±SD	2.1±3.4	5.4±6.1	1.1±2.9	4.1±5.4	<0.0001
mSASSS [0-72], mean±SD	0.5±1.7	0.2±0.6	1.5±5.1	0.6±2.0	0.02
csDMARDs intake, n (%)	35 (14.5)	33 (14.1)	30 (12.7)	28 (12.0)	0.74
TNFi intake at least once during follow-up, n (%)	0	0	72.5 (30.5)	70 (29.9)	0.85
MRI sacroiliitis during follow-up (local reading*)	132(53.0)	87(35.5)	27(10.8)	19 (7.8)	<0.0001

7 Significant results (p<0.05) are in bold.

8 The p value reflects differences between sexes over time, using all available timepoints, through
 9 mixed models. For illustrative purposes, the baseline and final values of each variable are
 10 presented, though the p-values represent all timepoints.

11
 12 ASDAS-CRP : Ankylosing Spondylitis Disease Activity Score-CRP; ASQoL : Ankylosing
 13 Spondylitis Quality of Life Scale; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index;
 14 BASFI: Bath Ankylosing Spondylitis Functional Index; csDMARDs : conventional synthetic
 15 disease modifying antirheumatic drugs; CRP: C-reactive protein; HAQ-AS: Health Assessment
 16 Questionnaire for axSpA; MASES: Maastricht Ankylosing Spondylitis Enthesis score; MRI:
 17 magnetic resonance imaging; mNY : modified New York criteria; mSASSS: modified Stoke

1 Ankylosing Spondylitis Spine Score; *PGA*: patient global assessment; *SF-36*: Short Form-36
 2 health survey questionnaire; *TNFi*: tumor necrosis factor inhibitors.

3
 4 **Table 3. The association of baseline characteristics with trajectories of disease**
 5 **activity in men and women with early axSpA**
 6

Variables included in the multinomial logit regression*	Trajectory 1 Persistent inactive disease activity (n=69)		Trajectory 2 Persistent low disease activity (n=72)		Trajectory 3 Almost major improvement (n=37)		Trajectory 4 Clinically important improvement (n=55)		Trajectory 5 Persistent high disease activity (n=68)		Trajectory 6 Persistent very high disease activity (n=51)	
	OR [95% CI]		Reference cluster†		OR [95% CI]		OR [95% CI]		OR [95% CI]		OR [95% CI]	
	Men n= 35 (19.8%)	Women n=34 (19.4%)	Men n=33 (18.6%)	Women n=39 (22.3%)	Men n=22 (12.4%)	Women n=15 (8.57%)	Men n=28 (15.8%)	Women n=27 (15.4%)	Men n=31 (17.5%)	Women n=37 (21.1%)	Men n=28 (15.8%)	Women n=23 (13.1%)
HLA-B27 positivity, n(%)	1.61 [0.25,10.45]	NI	-	-	2.72 [0.35,21.42]	NI	0.89 [0.19,4.05]	NI	2.91 [0.45,19.07]	NI	0.42 [0.01,1.84]	NI
Tender joint score [0-53] at baseline, mean ± SD	1.22 [0.69,2.16]	0.89 [0.68,1.15]	-	-	1.71 [1.09,2.69]	1.16 [0.97,1.39]	1.36 [0.88,2.10]	1.01 [0.86,1.18]	1.51 [0.96,2.35]	1.02 [0.89,1.17]	1.52 [0.98,2.37]	1.02 [0.88,1.18]
Swollen joint score at baseline [0-28], mean ± SD	2.59 [0.19,35.90]	NI	-	-	2.88 [0.29,28.69]	NI	1.73 [0.19,16.12]	NI	0.19 [0.01,3.94]	NI	1.49.10 ⁻⁷ [NS]	NI
MASES Enthesitis score at baseline [0-13], mean ± SD	0.64 [0.39,1.05]	0.95 [0.08,1.37]	-	-	0.89 [0.64,1.21]	0.70 [0.50,0.97]	1.03 [0.79,1.33]	0.96 [0.78,1.18]	0.80 [0.58,1.11]	1.05 [0.88,1.26]	0.87 [0.63,1.20]	1.12 [0.91,1.37]
HAQ-AS at baseline [0-3], mean ± SD	0.09 [0.01,0.79]	0.34 [0.07,1.54]	-	-	3.22 [0.55,19.04]	1.34 [0.28,6.40]	4.92 [0.96,25.34]	2.07 [0.58,7.32]	7.72 [1.49,39.97]	5.98 [1.78,20.04]	17.24 [3.13,9.51]	15.00 [3.55,62.40]
Radiographic sacroiliitis on mNY (local reading), n(%)	0.82 [0.22,3.07]	NI	-	-	6.74 [1.72,26.45]	NI	1.63 [0.46,5.80]	NI	1.66 [0.49,5.66]	NI	2.53 [0.70,9.12]	NI

7
 8 *Covariates significantly associated with any trajectory (p<0.1) in univariate analysis, were included in
 9 the model. Variables showing collinearity were excluded from the analysis.

10 † Trajectory 2 “Persistent Low disease activity” was used as the reference trajectory.

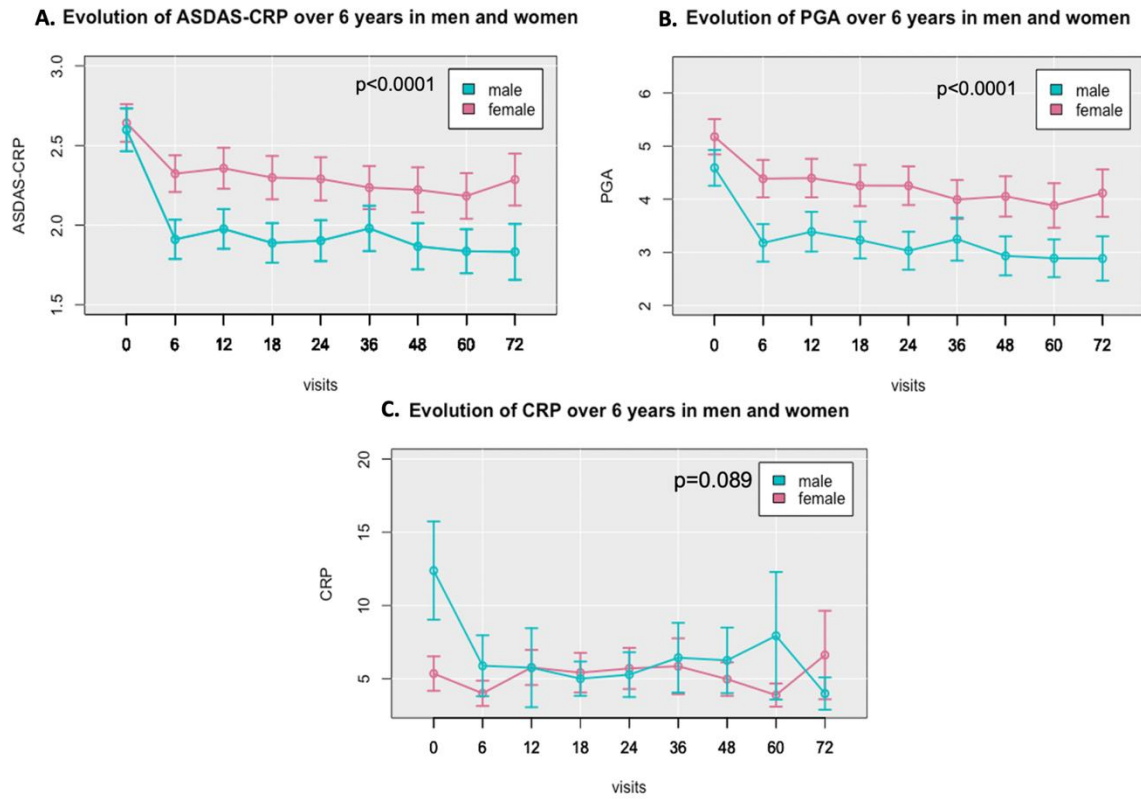
11 NI: not included in the model; NS: not significant.

12 Significant results (p<0.05) are in bold.

13 *HAQ-AS*: Health Assessment Questionnaire for axSpA; *MASES*: Maastricht
 14 Ankylosing Spondylitis Enthesis score; *mNY*: modified New York criteria.

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1 **Figure 1. Comparison of evolution of disease activity (ASDAS-CRP), PGA, and**
 2 **CRP levels over 6 years of follow-up between sexes.**



3 **Figure A.** shows the evolution of ASDAS-CRP over 6 years in men and women.

4 **Figure B.** shows the evolution of PGA over 6 years in men and women.

5 **Figure C.** shows the evolution of CRP over 6 years in men and women.

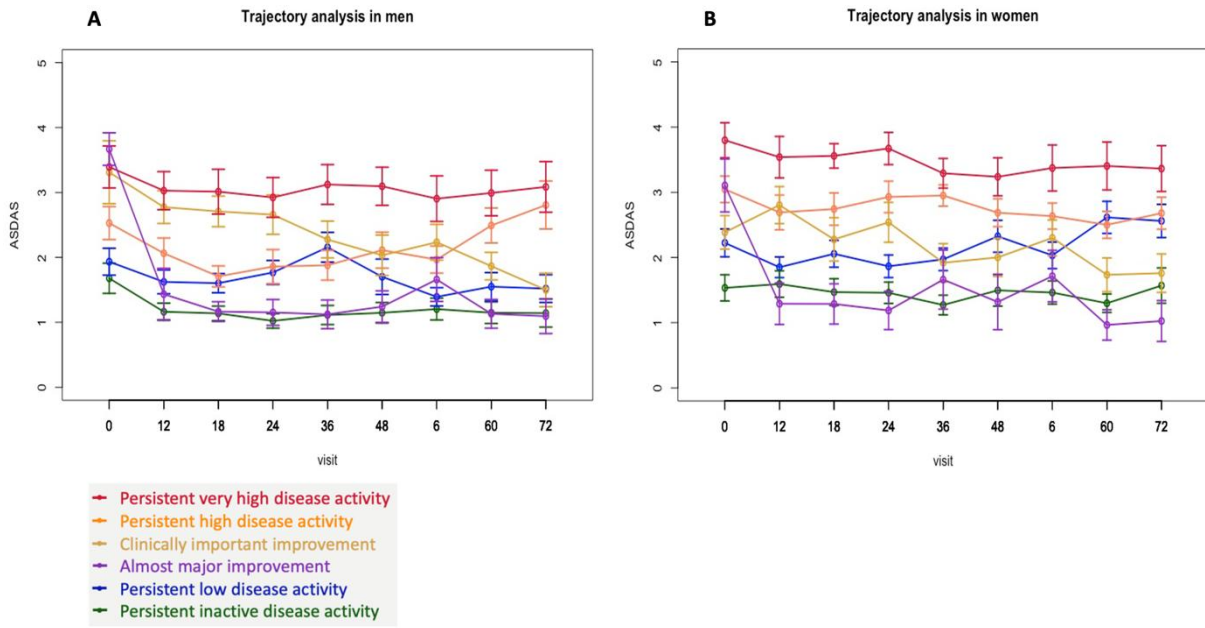
6 x-axis: visits (months)

7 The p-values shown in the figures are the results of linear mixed effect models.

8 ASDAS-CRP: Ankylosing Spondylitis Disease Activity Score-CRP; CRP: C-reactive
 9 protein; PGA: patient global assessment.

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1 **Figure 2. Trajectories of disease activity in men and women with recent axSpA**



2 **Figure A.** represents all the trajectories of disease activity in men.

3 **Figure B.** represents all the trajectories of disease activity in women.

4 **ASDAS-CRP:** Ankylosing Spondylitis Disease Activity Score- C reactive protein

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1 **Supplementary Table 1. Detailed statistical methods used to analyse the effect**
 2 **of sex on outcomes in the DESIR cohort.**

Method		Reasoning
Mixed-effect linear and logistic regression models		To take into account longitudinal repetitive measures, using lme4 R package for continuous and binary dependent variables respectively. In the mixed models, sex and time were determined as fixed effects and subjects as random effects.
Mixed-effect linear and logistic regression models with adjustment and interaction		To explore causes related to sex differences
	With adjustment	Covariates associated with sex in the univariable analysis ($p < 0.20$) were added into the mixed models and retained if being considered clinically a relevant confounder factor. (results not shown)
	With interaction	Potential interactions between sex and other explanatory variables were tested in the model. There was no imputation of missing data (results not shown).
	Correlation matrix and Principal Component Analysis (PCA) focused on sex were performed	To identify covariates with collinearity (correlation coefficient > 0.80) which were excluded from the model.
Trajectory modeling		To explore distinct trajectories of disease activity in men and women. Homogeneous clusters of disease activity were modeled using the variable ASDAS-CRP in function of time. We used the R package "kml" which implements "k-means", a hill-climbing algorithm: each patient was assigned to a cluster, then, two alternating phases "Expectation" and "Maximisation" were repeated until the optimal partition is reached. The center of each cluster was identified during the "Expectation" phase. Each patient was assigned to his/her nearest cluster during the "Maximisation" phase. The optimal number of clusters (from 2 to 6) was chosen using a Clustering Validity index, the Calinski and Harabatz criterion, that corresponds to the ratio of the between-clusters variance and the within-cluster variance.
Univariate analysis		To analyse predisposing baseline factors (demographics, disease phenotype, disease severity, quality of life, radiographic sacroiliitis) associated with the different trajectories were analysed by univariate analysis.
	One-way analysis of variance (ANOVA) (and if not suitable non-parametric Kruskal-Wallis test)	Used to compare means between different trajectories for continuous variables.
	Chi-square	Used to compare proportions between different trajectories for categorical variables.
Multivariable multinomial logit regression		Covariates significantly associated with any trajectory ($p < 0.1$) in univariate analysis, were included in the model. For the analyses, trajectory 2 "persistent low disease activity" was used as the reference trajectory as it included the largest number of patients. ASDAS score was not included since it was the variable used to define the clustering. BASDAI was also not included because of collinearity with ASDAS. Other variables showing collinearity were also excluded from the analysis.

1 **Supplementary Table 2. Evolution over time of disease activity scores: ASDAS-**
 2 **CRP, PGA and CRP levels.**

		M0	M6	M12	M18	M24	M36	M48	M60	M72	Overall
ASDAS-CRP, (mean ± SD)	Men	2.6 ±1.0	1.9 ±0.9	2.0 ±0.9	1.9 ±0.9	1.9 ±0.9	2.0 ±0.9	1.9 ±0.9	1.9 ±0.9	1.8 ±1.0	2.0 ±1.0
	Women	2.6 ±1.0	2.3 ±0.9	2.3 ± 0.9	2.3 ±0.9	2.3 ±1.0	2.2 ±0.9	2.2 ±0.9	2.2 ±0.9	2.3 ±0.9**	2.3 ±0.9**
	n total	472	438	421	371	395	358	327	343	259*	-
PGA, (mean ± SD)	Men	4.6 ±2.6	3.1 ±2.6	3.4 ±2.7	3.2 ±2.5	3.0 ±2.5	3.3 ±2.7	3.0 ±2.4	2.9 ±2.4	2.9 ±2.6	3.3 ±2.6
	Women	5.2 ±2.6	4.4 ±2.6	4.4 ±2.7	4.2 ±2.7	4.3 ±2.7	4.0 ±2.5	4.1 ±2.5	3.9 ±2.8	4.2 ±2.7**	4.3 ±2.7**
	n total	490	452	434	392	409	391	360	357	308*	-
CRP, (mean ± SD)	Men	10.7 ±16.5	5.4 ±10.4	5.4 ±10.9	4.5 ±6.0	5.1 ±7.0	5.8 ±13.2	5.1 ±7.3	7.1 ±15.9	4.8 ±7.3	6.2 ±12.2
	Women	6.2 ±8.3	4.8 ±5.4	5.8 ±8.3	5.2 ±6.0	5.8 ±12.0	5.4 ±7.4	4.7 ±6.6	4.5 ±5.1	5.3 ±7.8	5.3 ±7.5**
	n total	478	442	425	374	403	366	331	348	266	-
mNY Radiographic sacroiliitis, n(%)	Men	64 (25.7)	N/A	N/A	71 (28.5)	N/A	N/A	N/A	72 (28.9)	N/A	N/A
	Women	42 (17.1)	N/A	N/A	51 (16.7)	N/A	N/A	N/A	32 (13.1) **	N/A	N/A
	n total	488	N/A	N/A	394	N/A	N/A	N/A	328	N/A	N/A

3

4 N total(men)=249; n total (women)=245

5 * At Month 72 (M12): missing data for ASDAS-CRP (n=235), PGA (n= 186), CRP (n=228); at M60,
6 missing data for radiographic sacroiliitis (n=166)

7 ** p-value < 0.0001 by univariate analysis at M72

8 N/A: data not available

9 *Ankylosing Spondylitis Disease Activity Score-CRP (ASDAS-CRP), C-reactive*10 *protein (CRP), patient global assessment (PGA), mNY: modified New York criteria.*

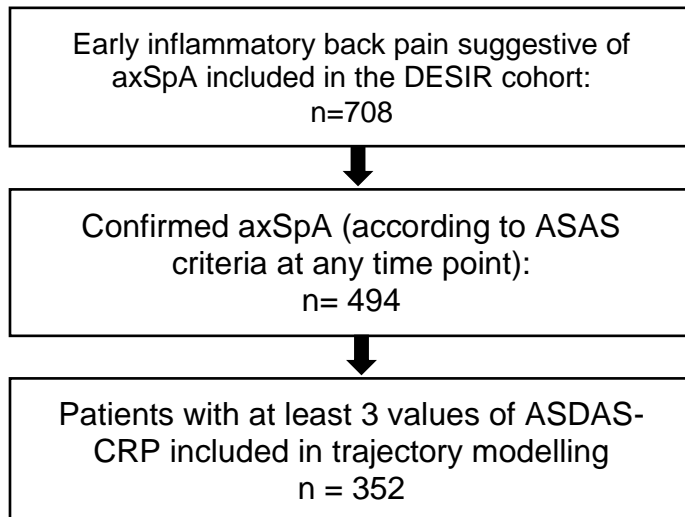
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1 **Supplementary Table 3. Comparison of main clinical outcomes between**
 2 **radiographic and non-radiographic axSpA at 6 years of follow-up.**

Key outcomes at M72	Radiographic axSpA			Non-radiographic axSpA		
	Men	Women	p-value	Men	Women	p-value
ASDAS-CRP, mean±SD	1.9±1.1	2.5±0.9	0.02	1.7±0.9	2.23±0.9	0.0009
PGA [0-10], mean±SD	2.9±2.7	4.5±2.9	<0.0001	2.8±2.5	4.0±2.6	<0.0001
CRP (mg/L), mean±SD	5.9±8.7	7.5±8.5	<0.0001	3.6±6.3	4.6±6.0	<0.0001

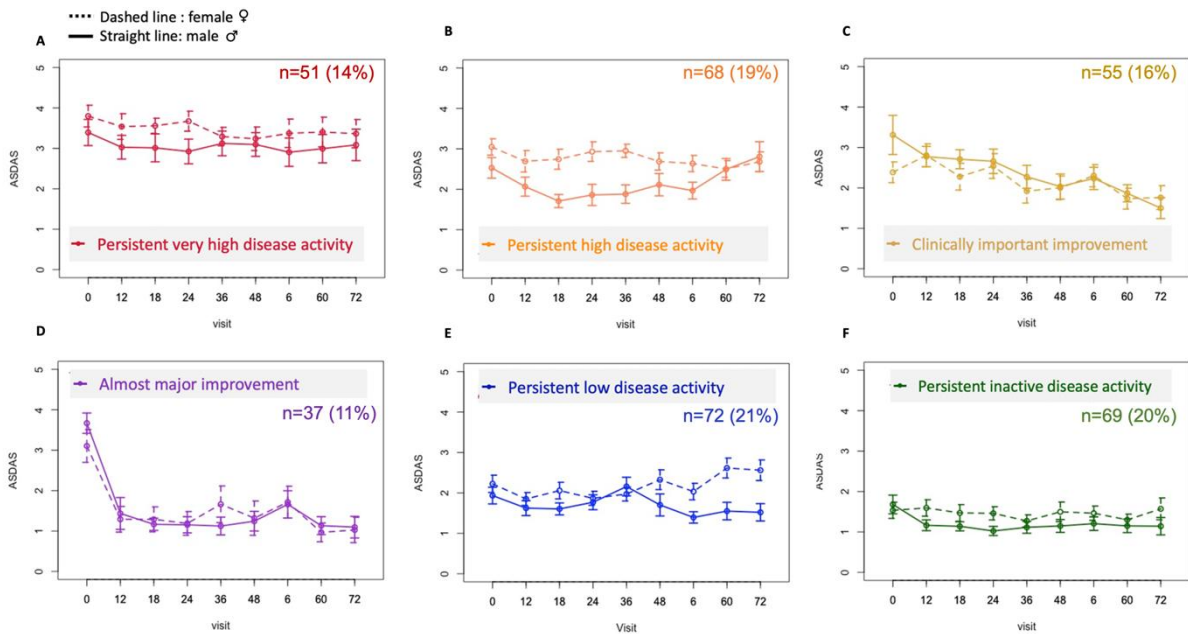
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 4
 5 *Ankylosing Spondylitis Disease Activity Score-CRP (ASDAS-CRP), C-reactive*
 6 *protein (CRP), patient global assessment (PGA).*
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10
 11 **Supplementary Figure 1. Selection of patients for analysis**



28 *ASDAS-CRP: Ankylosing Spondylitis Disease Activity Score-CRP; CRP: C-reactive*
 29 *protein.*
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1 **Supplementary Figure 2. Trajectories of disease activity in men and women**
 2 **with recent axSpA**



- 3
 4 Figure A represents trajectory 6 (t6): ‘patients with persistent very high disease
 5 activity’ (n=51, 14%).
 6 Figure B represents trajectory 5 (t5): ‘patients with persistent high disease activity’
 7 (n=68, 19%)
 8 Figure C represents trajectory 4 (t4): ‘patients with clinically important improvement’
 9 (n=55, 16%)
 10 Figure D represents trajectory 3 (t3): ‘patients with almost major improvement’ (n=37,
 11 11%)
 12 Figure E represents trajectory 2 (t2): ‘patients with persistent low disease activity’
 13 (n=72, 21%)
 14 Figure F represents trajectory 1 (t1): ‘patients with persistent inactive disease activity’
 15 (n=69, 20%)

16
 17 *ASDAS-CRP: Ankylosing Spondylitis Disease Activity Score-CRP; CRP: C-reactive*
 18 *protein, n: total number of patients included in the trajectory. The dashed line*
 19 *represents the female evolution. The straight line represents the male evolution.*
 20
 21