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# Progression From Subclinical Inflammation to Overt Spondyloarthritis in First-Degree Relatives of Patients in Association With HLA–B27: The Pre-Spondyloarthritis Cohort

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**Objective.** As first-degree relatives (FDRs) of HLA–B27–positive patients with axial spondyloarthritis (SpA) have an increased risk of developing axial SpA, the objectives were 1) to evaluate the presence of highly specific imaging features as well as clinical signs of SpA at baseline and after 1 year of follow-up, and 2) to describe the evolution toward clinical disease within 1 year of follow-up in a cohort of seemingly healthy FDRs of HLA–B27–positive axial SpA patients.

**Methods.** The Pre-SpA cohort is a 5-year prospective inception cohort of seemingly healthy FDRs of HLA–B27–positive axial SpA patients. Clinical and imaging features were collected and recorded.

**Results.** At baseline, 19% of the FDRs reported inflammatory back pain, 32% current arthralgia, 3% arthritis (ever), 5% enthesitis (ever), and 1% dactylitis (ever), and 3% had an extraarticular manifestation. C-reactive protein level was elevated in 16%, and erythrocyte sedimentation rate was elevated in 7%. On magnetic resonance imaging (MRI) views of sacroiliac joints, 10% had a Spondyloarthritis Research Consortium of Canada score of ≥2, 4% had a score of ≥5, and 4% had deep lesions. In total, 1% fulfilled the modified New York criteria for radiographic sacroiliitis. Clinical, MRI, and acute phase findings were equally distributed between HLA–B27–positive and –negative FDRs. After 1 year of follow-up, clinical parameters did not change on the group level, but 6% of the FDRs were clinically diagnosed with axial SpA, of whom 86% were HLA–B27–positive.

**Conclusion.** Features associated with SpA or imaging abnormalities were found in up to 32% of seemingly healthy FDRs, with an equal distribution between HLA–B27–positive and –negative FDRs. Progression to clinical axial SpA within 1 year of follow-up was mainly observed in HLA–B27–positive FDRs.

## INTRODUCTION

Axial spondyloarthritis (SpA) usually presents between ages 18 and 40 years and is characterized by inflammation and structural damage of the spine. In addition, peripheral manifestations (including arthritis, dactylitis, and enthesitis) and extraarticular manifestations (including psoriasis, inflammatory bowel disease [IBD], and uveitis) can be present (1). Diagnosis is challenging and often delayed by several years, resulting in a delay of treatment. This delay can be explained by an insidious disease

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**SIGNIFICANCE & INNOVATIONS**

- HLA–B27 is associated with progression from subclinical inflammation to overt spondyloarthritis rather than the presence of subclinical inflammation.
- Features associated with spondyloarthritis are equally distributed among HLA–B27–positive and –negative first-degree relatives of spondyloarthritis patients.

onset, limited specificity of signs and symptoms, and the lack of diagnostic biomarkers with sufficient positive predictive value. Carriership of HLA–B27 is broadly considered a predisposing factor for axial SpA. First-degree relatives (FDRs) of HLA–B27–positive patients with axial SpA are known to have an increased risk of developing SpA (2–5), and studying them could help to identify clinical signs, imaging abnormalities, and biomarkers that are predictive of development of axial SpA.

Previously we have reported the data of the first 51 participants of the Pre-SpA cohort, an ongoing prospective inception cohort study in which FDRs of HLA–B27–positive axial SpA patients are included and prospectively followed for a period of 5 years (6). Although the FDRs did not have a clinical diagnosis of SpA, we observed clinical features associated with SpA in up to 33% of FDRs. Additionally, there was a high prevalence (20%) of bone marrow edema, suggestive of subclinical sacroiliitis on magnetic resonance imaging (MRI).

Recent studies have reported that up to 23% of MRIs of healthy volunteers, athletes, and women postpartum are scored positive for sacroiliitis according to the Assessment of SpondyloArthritis international Society (ASAS) definition (7–9), suggesting that bone marrow edema itself is not very specific for SpA but rather is omnipresent and related to mechanical stress. In contrast, deep or extensive lesions (a homogeneous, unequivocal increase in signal extending ≥1 cm from the articular surface) on MRI of the sacroiliac (SI) joints were not seen in healthy volunteers and were far more specific for axial SpA patients (10). Scoring of MRI images of SI joints by the Spondyloarthritis Research Consortium of Canada (SPARCC) score rather than by a binomial score was reported to be more specific for axial SpA (10,11). So far, whether these extensive and deep lesions are also present in the at-risk cohort of FDRs of HLA–B27–positive axial SpA patients is not known. More importantly, whether FDRs with clinical or imaging features highly suggestive of SpA, but without a clinical diagnosis of SpA, will develop clinically manifest disease over time is not known.

The objectives of this study were to 1) evaluate the presence of highly specific imaging features as well as clinical signs of SpA suggestive of subclinical disease at baseline and after 1 year of follow-up and 2) describe the evolution toward clinical disease within 1 year of follow-up in a cohort of seemingly healthy FDRs of HLA–B27–positive axial SpA patients.

## MATERIALS AND METHODS

**Study design and FDRs.** The Pre-SpA cohort is an ongoing, multicenter, prospective 5-year inception cohort study (6). FDRs of HLA–B27–positive axial SpA patients were included; all were between ages 18 and 40 years at the time of inclusion. The main exclusion criteria were a clinical diagnosis of SpA or back pain with a previously confirmed nonrheumatic diagnosis. FDRs who were diagnosed with axial SpA at or directly after the baseline visit were judged as a missed diagnosis. Since the aim was to investigate whether FDRs who are at risk will develop SpA, and not to describe features of FDRs with clinically manifest disease at baseline, these FDRs were excluded from the analyses.

To confirm our preliminary findings in the original cohort of 51 FDRs, which showed that a high number of FDRs had clinical and imaging findings suggestive of SpA (2), we analyzed the data of 156 additionally included FDRs whose baseline data were not reported in the previous article on the Pre-SpA cohort. Both cohorts were included in the 1-year analysis.

The study was approved by the medical ethics committee of the Academic Medical Center/University of Amsterdam, The Netherlands. All FDRs gave written informed consent to participate in the study. Participating sites across the Netherlands were the Amsterdam University Medical Center, location AMC and VUMC, Leiden University Medical Center, Maastricht University Medical Center, Maasstad Hospital in Rotterdam, and Reade in Amsterdam.

**Assessments.** Baseline demographic characteristics included year of birth, sex, ethnicity, and smoking status. A complete medical history and family history of SpA (first and second degree relatives with axial SpA, reactive arthritis, psoriasis, psoriatic arthritis, IBD, uveitis, or peripheral SpA) were recorded.

The FDRs were asked about the presence or absence of back pain yearly. If back pain was present, specific features of inflammatory back pain according to the ASAS definition (12) were recorded. Buttock pain and a good response to nonsteroidal antiinflammatory drugs were also recorded. FDRs were asked yearly about the presence or absence of the following SpA features, as diagnosed by a physician in the previous year: dactylitis, enthesitis, uveitis, IBD, and psoriasis.

A physical examination was repeated yearly: swollen and tender joint count (66/68 joints), spinal mobility measures (Bath Ankylosing Spondylitis Metrology Index), chest expansion, occiput to wall distance), Maastricht Ankylosing Spondylitis Enthesitis Score, and evaluation of the presence of dactylitis (recorded as present/absent). The normal reference values used for the Schober and chest expansion were >4.5 cm and >3.6 cm, respectively (13).

Although the FDRs of the Pre-SpA cohort do not have a clinical diagnosis at baseline, at every visit the patient-reported outcomes relevant to axial SpA were collected: global disease

activity on a visual analog scale (VAS, 0–100 mm), Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) score, Bath Ankylosing Spondylitis Functional Index score, VAS total back pain (0–100 mm), and VAS nocturnal back pain (0–100 mm). A VAS physician global disease assessment was filled out at every visit. The Ankylosing Spondylitis Disease Activity Score using the C-reactive protein (CRP) level was calculated for each FDR at every visit (14). Peripheral blood samples were collected at every visit to measure CRP level (mg/liter) and erythrocyte sedimentation rate (ESR; mm/hour). At baseline, HLA–B27 genotyping was performed.

FDRs with symptoms suspicious of axial SpA were discussed by the study team and with an experienced rheumatologist. If the suspicion of clinical disease was high, or in case of doubt, the FDR was referred to a rheumatologist for confirmation of a possible clinical diagnosis. In case of a new clinical diagnosis (confirmed by a rheumatologist), the date of diagnosis and subtype of diagnosis were recorded. All FDRs (both with and without a clinical diagnosis) were followed over time in the Pre-SpA cohort.

**Imaging.** Plain radiographs of the SI joints, lumbar spine, and cervical spine were obtained at baseline. Radiographs of the SI joints were scored according to the modified New York criteria (15) by 2 experienced readers (HMYdJ and RBML). High-grade sacroiliitis was defined as ≥grade 2 bilateral, or ≥grade 3 unilateral. Only radiographs that were scored as high-grade sacroiliitis by both readers were considered as such. Lateral radiographs of the lumbar and cervical spine were scored according to the Modified Stoke Ankylosing Spondylitis Spine Score (mSASSS) (16) by 1 experienced reader (RBML).

MRIs of the SI joints were performed on a 3 Tesla MRI scanner, semicoronal with T1 and STIR sequences and a slice thickness of 4 millimeters. MRIs were scored according to the SPARCC scoring system (17) by 2 experienced readers (JJHdW and RBML). The SPARCC scoring system divides each SI joint in 4 quadrants (upper iliac, lower iliac, upper sacral, lower sacral). The presence of increased signal on STIR images in each of these quadrants was scored as dichotomous (0 = normal, 1 = increased signal). Joints with a lesion with an increased signal were additionally scored when this signal was intense (+1) or deep, defined as a homogeneous, unequivocal increase in signal extending >1 cm from the articular surface. This scoring was repeated in 6 consecutive slices, the maximum score being 72. The mean of the scores of both readers was used for the analyses. Previously we reported abnormalities on MRI suggestive of SpA in up to 20% of the initial cohort (n = 51). The scoring method that was used in the previous report was the ASAS scoring system (18). We extended the evaluation of imaging findings on MRI in the previous cohort by using the SPARCC scoring method, with 2 and 5 as cutoff values as well as a score for deep lesions (10,17).

**Statistical analysis.** Clinical features and imaging data were reported descriptively. All data are presented as median (interquartile range [IQR]) unless stated otherwise. We compared the baseline features of HLA–B27–positive and –negative FDRs. Binary data were analyzed using a chi-square test, and nominal data were analyzed using a Student's *t*-test or Mann–Whitney U test, as appropriate. Interreader agreement on an SPARCC score of ≥2 was investigated using Cohen's kappa coefficient and interpreted according to the standards of Landis and Koch (19). Interreader agreement on absolute SPARCC scores was evaluated using intraclass correlation coefficients (ICCs). Statistical tests were 2-sided and *P* values less than 0.05 were considered significant. The baseline data of the first 51 participants have been reported before (6).

To investigate whether clinical signs of SpA or inflammatory markers changed over 1 year of follow-up, we compared baseline and 1 year follow-up clinical signs of SpA and inflammatory markers of the FDRs who had completed the 1-year follow-up visit (n = 123). Finally, we compared the baseline features of the FDRs who were clinically diagnosed with axial SpA within the first year of follow-up to the baseline features of the FDRs without a clinical diagnosis after 1 year. The data are reported descriptively as median (IQR) unless stated otherwise. Chi-square tests were used to analyze binomial data and Mann–Whitney U tests or Student's *t*-test, as appropriate, for continuous data.

## RESULTS

**FDRs.** In total, 207 FDRs had been included at the time of analyses. The baseline data of 51 FDRs had been reported before (6). An additional 156 FDRs were consecutively included in the Pre-SpA cohort. Of those 156, 5 FDRs were immediately referred to a rheumatologist because of signs and symptoms suggestive of clinical axial SpA. Since the clinical diagnosis was confirmed, these FDRs were considered a previously missed diagnosis rather than healthy FDRs at risk of SpA and were therefore excluded from further analysis.

Therefore, the baseline characteristics of 151 FDRs were analyzed in the current report. In total, 123 participants (from the initial cohort and the current confirmation cohort) had completed the 1-year follow-up visit at the time of the analyses. None were lost to follow-up during the first year of follow-up.

**Confirmation of preclinical signs in an independent cohort of FDRs.** Demographic and baseline characteristics of the confirmation cohort (n = 151) are shown in Table 1. HLA–B27 status was missing in 7 FDRs, imaging data in 12 FDRs. Ninety-eight FDRs (65%) reported back pain at baseline, and 29 (19%) fulfilled the criteria for inflammatory back pain. Severity of back pain was low, as the FDRs who reported back pain

**Table 1.** Demographic and clinical characteristics, laboratory test results, and imaging signs of spondyloarthritis at baseline and stratified by HLA–B27–positive and HLA–B27–negative first-degree relatives*

| | Baseline (n = 151) | Positive (n = 80) | Negative (n = 64) |
|---|---|---|---|
| Male, no. (%) | 90 (60) | 48 (60) | 40 (63) |
| White, no. (%) | 134 (89) | 73 (91) | 55 (86) |
| Age, mean ± SD years | 27.1 ± 6.7 | 27.5 ± 6.7 | 27.2 ± 5.6 |
| HLA–B27–positive, no. (%)† | 80 (53) | 80 (100) | 0 (0) |
| Current smoker, no. (%) | 28 (19) | 13 (16) | 13 (20) |
| Axial disease, no. (%) | | | |
| Back pain (current) | 98 (65) | 54 (68) | 41 (64) |
| Inflammatory back pain (current) | 29 (19) | 18 (23) | 10 (16) |
| Peripheral disease, no. (%) | | | |
| Arthralgia (current) | 48 (32) | 27 (34) | 19 (30) |
| Peripheral arthritis (ever) | 5 (3) | 2 (3) | 3 (5) |
| Enthesitis (ever) | 8 (5) | 5 (6) | 3 (5) |
| Dactylitis (ever) | 1 (1) | 1 (1) | 0 |
| Extraarticular disease, no. (%) | | | |
| Psoriasis (ever) | 2 (1) | 1 (1) | 1 (2) |
| Inflammatory bowel disease (ever) | 0 | 0 | 0 |
| Urethritis/diarrhea (ever) | 1 (1) | 0 | 0 |
| Uveitis (ever) | 1 (1) | 0 | 1 (2) |
| Family history, no. (%) | | | |
| Psoriatic arthritis | 1 (1) | 0 | 1 (2) |
| Psoriasis | 12 (8) | 4 (5) | 8 (13) |
| Inflammatory bowel disease | 12 (8) | 5 (6) | 7 (11) |
| Uveitis | 9 (6) | 7 (9) | 2 (3) |
| Disease activity measures | | | |
| PhGA, 0–100 mm VAS | 0 (0–7) | 0.5 (0–20) | 0 (0–6.8) |
| PtGA, 0–100 mm VAS | 2 (0–26) | 5 (0–25) | 1 (0–36) |
| Patient total back pain, 0–100 mm VAS | 13 (0–33) | 12.5 (0–28) | 15 (0–42) |
| Patient nocturnal pain, 0–100 mm VAS | 0 (0–9) | 0 (0–12) | 0 (0–5) |
| BASDAI | 1.4 (0.7–2.7) | 1.3 (0.7–3) | 1.4 (0.7–2.7) |
| ASDAS-CRP | 1.0 (0.6–1.7) | 1.1 (0.5–1.7) | 0.9 (0.6–1.7) |
| BASFI, range 0–10 | 0.1 (0–0.9) | 0.2 (0–0.8) | 0 (0–0.9) |
| Clinical findings | | | |
| Modified Schober <4.5 cm, no. (%) | 5 (3) | 3 (4) | 2 (3) |
| Chest expansion <3.6 cm, no. (%) | 3 (2) | 2 (3) | 1 (2) |
| TJC >0, range 0–68 | 16 (11) | 11 (14) | 5 (8) |
| SJC >0, range 0–66 | 0 | 0 | 0 |
| MASES >0, no. (%) | 35 (23) | 19 (24) | 25 (25) |
| Laboratory test results | | | |
| CRP, mg/liter | 2 (1–3) | 2 (1–3) | 2 (1–3) |
| ESR, mm/hour | 2 (2–8) | 2 (2–8) | 2 (2–10) |
| Imaging, no. (%) | | | |
| High-grade sacroiliitis on radiograph | 2 (1) | 2 (3) | 0 |
| SPARCC score ≥2 on MRI | 14/139 (10) | 10 (13) | 4 (6) |
| SPARCC score ≥5 on MRI | 5/139 (4) | 4 (5) | 1 (2) |
| Deep lesions on MRI | 5/139 (4) | 3 (4) | 2 (3) |

* Values are the median (interquartile range) unless indicated otherwise. ASDAS = Ankylosing Spondylitis Disease Activity Score; BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; BASFI = Bath Ankylosing Spondylitis Function Index; CRP = C-reactive protein; ESR = erythrocyte sedimentation rate; MASES = Maastricht Ankylosing Spondylitis Enthesitis Score; MRI = magnetic resonance imaging; PhGA = physician global disease assessment; PtGA = patient global disease assessment; SJC = swollen joint count; SPARCC = Spondyloarthritis Research Consortium of Canada; TJC = tender joint count; VAS = visual analog scale.
† HLA–B27 status is missing for n = 7.

(n = 98) had a median VAS total back pain (0–100 mm) of 22 (IQR 11.8–48.5). Forty-eight FDRs (32%) reported the current presence of arthralgia, and in 16 FDRs (11%) at least 1 tender joint was found at clinical examination. No active arthritis was observed. Five FDRs (3%) had a past diagnosis of arthritis confirmed by a physician, 8 (5%) of enthesitis, and 1 (1%) of dactylitis diagnosed in the past. In none of these FDRs was a previous diagnosis of SpA made. Two FDRs (1%) reported the presence of psoriasis, none reported IBD, and 1 (1%) reported a history of uveitis.

Median disease activity measures were low in the total study population, both the patient-reported parameters as well as the serum inflammatory markers. CRP level was elevated (>5 mg/liter) in 24 participants (16%; median 8.8 [IQR 6.8–12.8] mg/liter)

and ESR (>20 mm/hour) in 11 (7.3%; median 27 [IQR 24–34] mm/hour). Very few showed decreased spinal mobility: the Schober test was decreased (<4.5 cm) in 5 FDRs (3%) and chest expansion was decreased (<3.6 cm) in 3 (2%).

Imaging data were available for 139 of 151 FDRs. Two FDRs (1%) formally fulfilled the modified New York criteria for high-grade radiographic sacroiliitis on conventional imaging with grade 2 sacroiliitis bilateral, according to the scoring of both readers. A total of 117 radiographs (84%) were scored as grade 0 bilateral by both readers. None of the FDRs had abnormalities on the radiographs of the lumbar and cervical spine, according to the mSASSS. On MRI images of SI joints, 14 FDRs (10%) had an SPARCC score of ≥2 and 5 (4%) an SPARCC score of ≥5. Deep lesions were present in 5 FDRs (4%). The interreader agreement for the absolute SPARCC score was high (intraclass coefficient 0.94), the kappa for SPARCC scores of ≥2 was substantial (0.68).

When comparing HLA–B27–positive and –negative FDRs, no statistically significant differences were found for demographic, clinical, or imaging findings (Table 1). Between male and female FDRs, only ESR and CRP level were significantly different (median ESR and CRP level in male patients 6 [IQR 2–10] and 2 [IQR 1–5] and in female patients 2 [IQR 2–2] and 1 [IQR 1–3], $P < 0.0001$ and $P = 0.033$, respectively).

**Presence of highly specific MRI lesions in the original cohort of FDRs.** We previously reported a higher incidence of MRI lesions in a first cohort of 51 FDRs using a less stringent scoring method, namely according to the ASAS definition. To assess whether this difference in incidence of MRI lesions was due to the cohort or to the scoring methodology, we reassessed the MRI images of SI joints of all 51 FDRs from the original cohort using the more stringent methodology to assess the presence of abnormalities suggestive of SpA. Eight FDRs (16%) had an SPARCC score of ≥2 and 4 (8%) an SPARCC score of ≥5. One FDR (2%) had a deep lesion on MRI; this FDR had a total SPARCC score of 9.5. The distribution was equal between HLA–B27–positive and –negative FDRs. Interreader agreement on absolute SPARCC scores was excellent (ICC 0.877). These data are in line with the finding reported in the cohort of 151 FDRs, showing imaging findings highly specific of axial SpA in up to 15% of seemingly healthy FDRs.

**Evolution toward clinical SpA during 1 year of follow-up.** At the time of analysis, 123 FDRs had completed 1 year of follow-up. None were lost to follow-up during the first year. Characteristics after 1 year of follow-up are shown in Table 2. One participant had developed new-onset IBD; all other SpA-related features and disease activity parameters remained stable. Within the first year of follow-up, 7 FDRs (6%) were referred to a rheumatologist because they were suspected of axial SpA, as the intensity and frequency of their back pain had increased. All were clinically diagnosed with axial SpA. In all FDRs with a clinical diagnosis after 1 year, disease activity measures had increased at the 1-year follow-up visit compared to baseline: VAS patient global disease activity (0–100 mm) from median 18 (IQR 0–28) to 44 (IQR 19–60; $P = 0.043$), VAS total back pain from 19 (IQR 0–27) to 44 (IQR 16–54; $P = 0.063$), VAS nocturnal back pain from 4 (IQR 0–25) to 27 (IQR 11–50; $P = 0.028$), and BASDAI from 1.4 (IQR 1.0–2.1) to 3.9 (IQR 2.2–4.9; $P = 0.018$).

**Table 2.** Demographic and clinical characteristics, laboratory test results, and imaging signs of spondyloarthritis at baseline and after 1 year of follow-up of 123 first-degree relatives with 1 year follow-up*

| | Baseline (n = 123) | Year 1 (n = 123) |
|---|---|---|
| Male, no. (%) | 72 (59) | – |
| White, no. (%) | 114 (93) | – |
| HLA–B27–positive, no. (%) | 65 (53) | – |
| Current smoker, no. (%) | 33 (27) | 33 (27) |
| Axial disease, no. (%) | | |
| Back pain (current) | 70 (57) | 57 (46) |
| Inflammatory back pain (current) | 22 (18) | 22 (18) |
| Peripheral disease, no. (%) | | |
| Arthralgia (current) | 40 (33) | 20 (16) |
| Peripheral arthritis (ever) | 5 (4) | 4 (3) |
| Enthesitis (ever) | 5 (4) | 5 (4) |
| Dactylitis (ever) | 0 | 0 |
| Extraarticular disease, no. (%) | | |
| Psoriasis (ever) | 3 (2) | 3 (2) |
| Inflammatory bowel disease (ever) | 0 | 1 (1) |
| Urethritis/diarrhea (past/present) | 0 | 1 (1) |
| Uveitis (ever) | 2 (2) | 2 (2) |
| Family history, no. (%) | | |
| Psoriatic arthritis | 3 (2) | 3 (2) |
| Psoriasis | 11 (9) | 11 (9) |
| Inflammatory bowel disease | 8 (7) | 8 (7) |
| Uveitis | 4 (3) | 4 (3) |
| Disease activity measures | | |
| PhGA, 0–100 mm VAS | 0 (0–6) | 0 (0–7) |
| PtGA, 0–100 mm VAS | 2 (0–15) | 1 (0–12) |
| Patient total back pain, 0–100 mm VAS | 6 (0–21) | 4 (0–24) |
| Patient nocturnal pain, 0–100 mm VAS | 0 (0–5) | 0 (0–12) |
| BASDAI | 1.0 (0.5–2.0) | 1.1 (0.5–2.1) |
| ASDAS-CRP | 0.9 (0.5–1.3) | 0.8 (0.5–1.5) |
| BASFI, range 0–10 | 0.1 (0–0.7) | 0.1(0–0.6) |
| Clinical examination findings, no. (%) | | |
| Modified Schober <4.5 cm | 5 (4) | 7 (6) |
| Chest expansion <3.6 cm | 1 (1) | 2 (2) |
| TJC >0, range 0–68 | 15 (12) | 7 (6) |
| SJC >0, range 0–66 | 0 | 0 |
| MASES >0 | 30 (24) | 30 (24) |
| Laboratory test results | | |
| CRP, mg/liter | 2 (1–3) | 2 (1–3) |
| ESR, mm/hour | 5 (2–9) | 5 (2–8) |

* Values are the median (interquartile range) unless indicated otherwise. ASDAS = Ankylosing Spondylitis Disease Activity Score; BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; BASFI = Bath Ankylosing Spondylitis Function Index; CRP = C-reactive protein; ESR = erythrocyte sedimentation rate; MASES = Maastricht Ankylosing Spondylitis Enthesitis Score; PhGA = physician global disease assessment; PtGA = patient global disease assessment; SJC = swollen joint count; TJC = tender joint count; VAS = visual analog scale.

To assess whether specific baseline features may be associated with evolution to clinical axial SpA, baseline characteristics of FDRs who developed clinical disease were compared to baseline characteristics of those who did not develop axial SpA within the first year of follow-up (Table 3). Six of 7 FDRs were HLA–B27–positive, none had extraarticular disease, and 5 of 7 were male. FDRs with a clinical diagnosis after 1 year had significantly more frequent inflammatory back pain (71% versus 15%; $P < 0.001$) and enthesitis (29% versus 3%; $P = 0.001$) at baseline, and thus before a clinical diagnosis was made. Imaging abnormalities suggestive of axial SpA were also more prevalent at baseline in FDRs with a clinical diagnosis after 1 year: high-grade sacroiliitis on radiograph: 29% versus 1% ($P < 0.001$); an SPARCC score of ≥2: 43% versus 12%

**Table 3.** Baseline characteristics of first-degree relatives with and without a clinical diagnosis of spondyloarthritis after 1 year of follow-up*

| | Yes (n = 7) | No (n = 116) | *P* |
|---|---|---|---|
| Male, no. (%) | 5 (71) | 67 (58) | 0.476 |
| White, no. (%) | 7 (100) | 107 (92) | 0.586 |
| Age, mean ± SD years | 26.6 ± 6 | 26.6 ± 6 | 0.914 |
| HLA–B27–positive, no. (%) | 6 (86) | 59 (51) | 0.073 |
| Current smoker, no. (%) | 3 (43) | 30 (26) | 0.324 |
| Axial disease, no. (%) | | | |
| Back pain (current) | 6 (86) | 64 (55) | 0.113 |
| Inflammatory back pain (current) | 5 (71) | 17 (15) | <0.001† |
| Peripheral disease, no. (%) | | | |
| Arthralgia (current) | 3 (43) | 37 (32) | 0.548 |
| Peripheral arthritis (ever) | 0 | 5 (4) | 0.575 |
| Enthesitis (ever) | 2 (29) | 3 (3) | 0.001† |
| Dactylitis (ever) | 0 | 0 | – |
| Extraarticular disease, no. (%) | | | |
| Psoriasis (ever) | 0 | 3 (3) | 0.667 |
| Inflammatory bowel disease (ever) | 0 | 0 | – |
| Urethritis/diarrhea (past/present) | 0 | 0 | – |
| Uveitis (ever) | 0 | 2 (2) | 0.726 |
| Family history, no. (%) | | | |
| Psoriatic arthritis | 0 | 3 (3) | 0.667 |
| Psoriasis | 2 (29) | 9 (8) | 0.061 |
| Inflammatory bowel disease | 0 | 8 (7) | 0.472 |
| Uveitis | 0 | 4 (3) | 0.617 |
| Disease activity measures | | | |
| PhGA, 0–100 mm VAS | 21 (0–23) | 0 (0–5) | 0.021† |
| PtGA, 0–100 mm VAS | 18 (0–28) | 2 (0–13) | 0.158 |
| Patient total back pain, 0–100 mm VAS | 19 (0–27) | 5.5 (0–21) | 0.380 |
| Patient nocturnal pain, 0–100 mm VAS | 4 (0–25) | 0 (0–5) | 0.135 |
| BASDAI | 1.4 (1.0–2.1) | 1.0 (0.5–1.9) | 0.416 |
| ASDAS-CRP | 1.2 (1.1–1.5) | 0.8 (0.5–1.3) | 0.126 |
| BASFI, range 0–10 | 0.4 (0.2–1.4) | 0 (0–0.6) | 0.050† |
| Clinical examination findings, no. (%) | | | |
| Modified Schober <4 cm | 1 (14) | 4 (3) | 0.159 |
| Chest expansion <3.6 cm | 0 | 1 (1) | 0.805 |
| TJC >0, range 0–68 | 1 (14) | 14 (12) | 0.862 |
| SJC >0, range 0–66 | 0 | 0 | – |
| MASES >0 | 3 (43) | 27 (23) | 0.241 |
| Laboratory test results | | | |
| CRP, mg/liter | 2 (1–6) | 2 (1–3) | 0.428 |
| ESR, mm/hour | 10 (2–16) | 5 (2–8) | 0.158 |
| Imaging, no. (%) | | | |
| High-grade sacroiliitis on radiograph | 2 (29) | 1 (1) | <0.001† |
| SPARCC score ≥2 on MRI | 3 (43) | 14 (12) | 0.023† |
| SPARCC score ≥5 on MRI | 1 (14) | 6 (5) | 0.317 |
| Deep lesions on MRI | 1 (14) | 1 (1) | 0.006† |

* Values are the median (interquartile range) unless indicated otherwise. ASDAS = Ankylosing Spondylitis Disease Activity Score; BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; BASFI = Bath Ankylosing Spondylitis Function Index; CRP = C-reactive protein; ESR = erythrocyte sedimentation rate; MASES = Maastricht Ankylosing Spondylitis Enthesitis Score; MRI = magnetic resonance imaging; PhGA = physician global disease assessment; PtGA = patient global disease assessment; SJC = swollen joint count; SPARCC = Spondyloarthritis Research Consortium of Canada; TJC = tender joint count; VAS = visual analog scale.
† Statistically significant.

($P$ = 0.023); and deep lesions on MRI: 14% versus 1% ($P$ = 0.006) at baseline.

## DISCUSSION

The Pre-SpA cohort is a prospective inception cohort of FDRs of HLA–B27–positive axial SpA patients. In this study, we evaluated clinical features and imaging abnormalities that are considered highly suggestive of SpA at baseline, as well as clinical features of SpA and evolution toward clinical disease within 1 year of follow-up. We showed that at baseline, 19% of FDRs had inflammatory back pain, 32% had current arthralgia, 3% arthritis (ever), 5% enthesitis (ever), and 1% dactylitis (ever). In total, 3% of FDRs had extraarticular disease. Sixteen percent had an elevated CRP level and 7% an elevated ESR. Up to 15% of FDRs had MRI findings highly suggestive of axial SpA, but still without signs and symptoms that warranted a clinical diagnosis. All features were equally distributed between HLA–B27–positive and –negative FDRs. Approximately 6% of FDRs developed a distinguishable clinical syndrome of axial SpA over 1 year of follow-up, and all except 1 were HLA–B27–positive. Two of the FDRs who developed clinical axial SpA had high-grade sacroiliitis on radiograph at baseline, and 1 of those additionally had abnormalities on MRI suggestive of SpA.

Even though the Pre-SpA cohort consists of young, (seemingly) healthy FDRs, up to 65% reported current back pain, of which 19% was inflammatory, and up to 30% current arthralgia. It is probable that these findings are not very specific in most individuals, as tender joints are not observed at physical examination, and although inflammatory back pain is regarded as an SpA feature, recent studies have reported that the distinctive impact of inflammatory back pain is lower than previously thought, with a specificity of 25–52% and sensitivity of 74–84% (20,21). We did not score for the presence of degenerative lesions in this cohort as an alternative explanation for back pain, but de Bruin et al previously suggested that the clinical relevance of these lesions might be limited (22). Nevertheless, the percentages of FDRs reporting arthralgia and back pain are high when considering the mean age at inception of 27 years. Additionally, serum inflammatory markers were elevated in a significant number of FDRs, which could be an indication of subclinical disease. In contrast, the number of FDRs with extraarticular disease was low, which could partly be explained by the young age at inception. Taken together, subclinical signs of SpA features were highly prevalent.

In this study, imaging abnormalities suggestive of subclinical inflammation were seen in up to 16% of the FDRs. A recent study showed that scoring MRIs binomially as either highly suggestive of SpA or not, according to the ASAS definition, lacks specificity (23), and MRI results should be interpreted with caution. In accordance with this, another study reported the presence of SI joint bone marrow edema in 17.2% of seemingly healthy individuals age <45 years (24). Here we used the SPARCC score with cutoff values of ≥2 and ≥5, which was previously shown to discriminate between axial SpA patients, patients with nonspecific back pain, and healthy individuals with or without SI strain (10).

The MRI images of SI joints of 10–16% of FDRs were scored with an SPARCC score ≥2, an SPARCC score of ≥5 was seen in 4–8% of FDRs, and deep lesions in 2–4%. All were equally distributed between HLA–B27–positive and –negative FDRs. As these FDRs have additional risk factors for development of axial disease, following these individuals over time will be worthwhile, to determine who will or will not develop clinically manifest disease and whether these highly specific imaging findings pose the same risk for the development of disease.

After 1 year of follow-up in the Pre-SpA cohort, 6% of FDRs were diagnosed with axial SpA. Notably, the assessment of global disease activity by the study physician at baseline, and thus before a clinical diagnosis was made, was higher in the FDRs with a clinical diagnosis at the visit after 1 year of follow-up, indicating that the study physicians already suspected subclinical disease. As expected, the number of FDRs developing SpA in our cohort is much higher than the yearly incidence in a nonselected healthy population (25). Axial SpA usually develops before age 40 years; therefore, with the mean age at baseline of 27, we expect that more FDRs will develop axial SpA in the coming 5–10 years of follow-up. Whether we can extrapolate the incidence of 6% to later years of follow-up, or whether this percentage will be lower in the following years remains to be seen. A recent study by Sepriano et al distinguished 3 groups within the clinical axial SpA domain. One of these groups was "SpA at risk," which shows a close resemblance to part of the Pre-SpA cohort. Those researchers reported that 11% switched from the "SpA at risk" group to a group with clinically manifest disease (26). This finding suggests that possibly a large number of FDRs in the Pre-SpA cohort remain at risk of SpA, with some suggestive clinical symptoms but without enough signs and symptoms to make a diagnosis.

In this cohort, 5 FDRs had a "missed diagnosis," reflecting a well-known but worrying characteristic in the field of axial SpA of many undiagnosed cases. Although clinical serologic and imaging features suggestive of subclinical inflammation at baseline were independent of HLA–B27 status, 6 of 7 FDRs who progressed toward clinical disease were HLA–B27–positive. A strong association between HLA–B27 and progression toward chronic disease was also shown several decades ago for reactive arthritis. The disease was mainly self-limiting in HLA–B27–negative patients, while the patients who progressed toward chronic disease were mainly HLA–B27–positive (27). If our finding that almost all FDRs who progress toward clinical disease are HLA–B27–positive is confirmed during further follow-up, this fact suggests that HLA–B27 is not responsible for initiation of acute subclinical inflammation (or susceptibility to inflammation) but rather determines the progression of subclinical

inflammation to clinically manifest disease in axial SpA. This hypothesis could also fit our previous imaging findings suggesting that sacroiliitis (bone marrow edema according to ASAS) on MRI is a relatively common feature as a consequence of mechanical stress and is transient in general (10), but preferentially in HLA–B27–positive individuals this stress-induced inflammation becomes extended and chronic, with development of structural damage.

One of the limitations of this study is the possible channeling of specifically those FDRs with complaints to participate in this study, as a high number of FDRs reported back pain (65%). However, this back pain was reported upon active questioning, and the majority had not visited a physician or used pain medication because of back pain. Furthermore, the FDRs with back pain reported a low VAS total back pain (median 20.5 [IQR 10–39.5]), indicating that back pain was not a major complaint in their daily lives and probably not the sole reason to participate in the Pre-SpA cohort. We did not formally record how many potential FDRs did not want to participate nor their reasons not to participate. Also, for ethical reasons, we cannot formally check the information that FDRs give about family and medical history. As the number of FDRs included in the Pre-SpA cohort is still limited, we are recruiting more FDRs. Further follow-up will show which FDRs will develop clinical axial SpA.

In conclusion, in seemingly healthy FDRs of axial SpA patients, subclinical signs of SpA features are frequently seen, with an equal distribution between HLA–B27–positive and –negative FDRs. However, progression toward clinical axial SpA is seen mainly in FDRs with HLA–B27 positivity and inflammatory back pain. Further follow-up of the Pre-SpA cohort will give more robust insight into the characteristics of FDRs who progress toward clinical SpA, thereby hopefully enabling the characterization of high-risk FDRs.

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## ADDITIONAL DISCLOSURE

Author Dominique L. P. Baeten is an employee of UCB Pharma.

## AUTHOR CONTRIBUTIONS

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

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**Acquisition of data.** de Jong, de Winter, van Gaalen, van Tubergen, Landewé, Baeten, van de Sande.

**Analysis and interpretation of data.** de Jong, de Winter, van der Horst-Bruinsma, van Schaardenburg, van Gaalen, van Tubergen, Weel, Landewé, Baeten, van de Sande.

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