# Can rheumatologists unequivocally diagnose axial spondyloarthritis in patients with chronic back pain of less than 2 years duration? Primary outcome of the 2-year SPondyloArthritis Caught Early (SPACE) cohort

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CLINICAL SCIENCE

# Can rheumatologists unequivocally diagnose axial spondyloarthritis in patients with chronic back pain of less than 2 years duration? Primary outcome of the 2-year SPondyloArthritis Caught Early (SPACE) cohort

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**Handling editor** Josef S Smolen

► Additional supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/ard-2023-224959).

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Received 4 September 2023
Accepted 29 December 2023



**To cite:** Marques ML, Ramiro S, van Lunteren M, *et al*. *Ann Rheum Dis* Epub ahead of print: [*please include* Day Month Year]. doi:10.1136/ard-2023-224959

## ABSTRACT

**Objectives** To investigate the prevalence of axial spondyloarthritis (axSpA) in patients with chronic back pain (CBP) of less than 2 years (2y) duration referred to the rheumatologist, the development of diagnosis over time, and patient characteristics of those developing *definite (d-)axSpA* over 2y.

**Methods** We analysed the 2y data from SPondyloArthritis Caught Early, a European cohort of patients (<45 years) with CBP (≥3 months, ≤2y) of unknown origin. The diagnostic workup comprised evaluation of clinical SpA features, acute phase reactants, HLA-B27, radiographs and MRI (sacroiliac joints and spine), with repeated assessments. At each visit (baseline, 3 months, 1y and 2y), rheumatologists reported a diagnosis of *axSpA* or *non-axSpA* with level of confidence (LoC; 0-*not confident at all* to 10-*very confident*). Main outcome: axSpA diagnosis with LoC≥7 (*d-axSpA*) at 2y.

**Results** In 552 patients with CBP, *d-axSpA* was diagnosed in 175 (32%) at baseline and 165 (30%) at 2y. Baseline diagnosis remained rather stable: at 2y, baseline *d-axSpA* was revised in 5% of patients, while 8% 'gained' *d-axSpA*. Diagnostic uncertainty persisted in 30%. HLA-B27+ and baseline sacroiliitis imaging discriminated best 2y-*d-axSpA* versus 2y-*d-non-axSpA* patients. Good response to non-steroidal anti-inflammatory drugs and MRI-sacroiliitis most frequently developed over follow-up in patients with a new *d-axSpA* diagnosis. Of the patients who developed MRI-sacroiliitis, 7/8 were HLA-B27+ and 5/8 male.

**Conclusion** A diagnosis of *d-axSpA* can be reliably made in nearly one-third of patients with CBP referred to the rheumatologist, but diagnostic uncertainty may persist in 5%–30% after 2y. Repeated assessments yield is modest, but repeating MRI may be worthwhile in male HLA-B27+ patients.

### WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Long diagnostic delay remains a problem in axial spondyloarthritis (axSpA). The Assessment of SpondyloArthritis international Society stipulates that patients with suspected axSpA should be immediately referred to a rheumatologist. However, data on whether rheumatologists can reliably diagnose axSpA shortly after symptom onset is lacking.

⇒ In 2008, the SPondyloArthritis Caught Early cohort was started to assess the prevalence of axSpA and the reliability of an early axSpA diagnosis in patients with chronic back pain (CBP) of unknown origin.

### WHAT THIS STUDY ADDS

⇒ One-third of patients with CBP of less than 2 years (2y) duration suspected of axSpA referred to the rheumatologist has *definite axSpA (d-axSpA)* after 2y of follow-up.

⇒ Most patients can be unequivocally and reliably diagnosed at their first assessment. However, diagnostic uncertainty persisted in up to 30% of the cases after 2 years: 25% received a most likely diagnosis and 5% a possible diagnosis.

⇒ A single feature with sufficient accuracy to diagnose axSpA does not exist, but HLA-B27 positivity and sacroiliitis on imaging discriminate best between the 2y-*d-axSpA* and 2y-*d-non-axSpA* patients.

⇒ The yield of repeated assessments of SpA features in patients with CBP suspected of axSpA was modest for a new *d-axSpA* diagnosis at 2y.

⇒ Most SpA features were already present at the first assessment, with response to non-steroidal anti-inflammatory drugs and sacroiliitis on MRI appearing as the two most frequent incident SpA features potentially adding to a new *d-axSpA* diagnosis over time.

## INTRODUCTION

In axial spondyloarthritis (axSpA), despite substantial advances in diagnostic process and treatment, diagnostic delays remain a challenge.[1 2] A timely diagnosis is still hard to achieve, with mean worldwide diagnostic delays of about 7 years, which is markedly longer than for other chronic inflammatory rheumatic and musculoskeletal diseases.[3 4]

The most common presenting symptom of axSpA is chronic, often inflammatory, back pain. However, chronic back pain (CBP) is common, can

**HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY**

⇒ This is the first study formally proving that rheumatologists can reliably diagnose axSpA shortly after symptom onset.
⇒ When the diagnosis is uncertain, repeated assessments over time are questionable and most patients can be referred back to the general practitioner. MRI repetition can be considered in HLA-B27+ patients, especially if male.
⇒ The current data unequivocally support prompt access to rheumatologists for patients with CBP suspected of axSpA.

be a symptom of many diseases and particularly in the absence of other symptoms may not immediately raise suspicion of axSpA.[1] This poses a major challenge in clinical practice: how to recognise patients with axSpA among young patients with CBP?

With none of the so-called 'SpA features' being pathognomonic, a diagnosis of axSpA is based on recognising the pattern (the '*Gestalt*') of the disease; a careful consideration of present and absent features, as well as alternative diagnoses.[1 5] While pattern recognition is crucial, new SpA features may also only develop over time, which further complicates an early axSpA diagnosis.

Recently, the Assessment of SpondyloArthritis international Society (ASAS) developed quality standards to improve healthcare for patients with axSpA, stressing the need of immediate referral to a rheumatologist of patients suspected of having axSpA.[6] However, there is clear paucity of data showing that rheumatologists are indeed capable of reliably diagnosing axSpA shortly after symptom onset.[7] Studies that claim that axSpA can be diagnosed in an early stage of the disease are based on retrospective and self-reported data,[8] or a study that received substantial critique because of severe methodological concerns.[9] In a recent systematic literature review, it was found that the term 'early axSpA' is mostly used for symptom duration of less than 5 years.[10] Moreover, data are lacking on which diagnostic strategies to pursue in cases of diagnostic uncertainty.[7]

In 2008, the SPondyloArthritis Caught Early (SPACE) cohort was started aiming at assessing the prevalence of axSpA and the reliability of an early axSpA diagnosis in patients with recent onset CBP of unknown origin referred to a rheumatologist. In this multinational cohort, patients with CBP (at least 3 months and up to 2y duration) and unknown origin were followed over 2y with repeated clinical, laboratory and imaging assessments.[11]

While baseline and up to 1-year follow-up results of this inception cohort have been used to report on various aspects of early axSpA,[12] we now present the primary outcome of SPACE using data of the complete 2y follow-up for the first time. In the present manuscript, we aimed to: (1) assess the 2y prevalence of an axSpA diagnosis among patients with recent onset CBP referred to the rheumatologist; (2) investigate the accuracy of a baseline diagnosis of axSpA when reviewed after 2y; (3) evaluate the yield of repeated assessments of SpA features to make a new definite diagnosis of axSpA over 2y; and (4) describe the characteristics of patients with a new definite diagnosis of axSpA after follow-up.

## METHODS

### Study design

We analysed the 2y data from the SPACE cohort, a European inception cohort of patients (age<45 years) with CBP of recent onset (≥3 months, ≤ 2 years) and unknown origin included from 2008 to 2016. Patients were recruited from rheumatology outpatient clinics in four different countries: the Netherlands, Norway, Sweden and Italy. However, patients from Sweden and Italy did not fulfil the criterion of unknown origin of back pain (either not collected (Sweden) or all patients had already a diagnosis of SpA at the time of inclusion (Italy)). Therefore, only patients included in three centres in the Netherlands (Amsterdam, Leiden and Gouda) and one in Noway (Oslo) could be included in the current analyses. A description of the SPACE cohort has been previously published.[11] For the present analysis, the SPACE database was locked on the 31 December 2021.

Patients were assessed at baseline, and according to the likelihood of having SpA (based on SpA-related features) were eligible for further follow-up as per protocol (online supplemental figure-S1). Patients with ≥1 major or ≥2 minor SpA features were followed for 2y. The major SpA features (positive likelihood ratio (LR) of ≥6.0 for axSpA diagnosis[13]) were: HLA-B27 positivity, family history of SpA, anterior uveitis and sacroiliitis (on radiographs or MRI). The minor SpA features (positive LR of ≥2.5 and <6.0 for axSpA diagnosis[13]) consisted of inflammatory back pain, peripheral arthritis, dactylitis, heel pain, inflammatory bowel disease, psoriasis, good response to non-steroidal anti-inflammatory drugs (NSAIDs), and increased acute phase reactants.

Data were collected using a case report form at each centre. The diagnostic workup consisted of the clinical assessment of SpA features; laboratory tests, namely HLA-B27 carriership and acute phase reactants; and imaging (radiographs and MRI of the sacroiliac joints and spine). This was repeated (except HLA-B27) at 3 months, 1y and 2y visits.

At each visit, the rheumatologist reported a clinical diagnosis of 'axSpA' or 'non-axSpA' with a level of confidence (LoC) varying from 0 (*not confident at all*) to 10 (*very confident*). A 'non-axSpA' diagnosis meant that the CBP was attributed to causes other than axSpA, and the most likely alternative diagnosis (eg, non-specific back pain, fibromyalgia) was asked to be reported in these cases. The cohort's study visits including details on repeated imaging are summarised in online supplemental figure-S2.

### SpA features assessments

To capture the diagnostic assessment by the treating rheumatologist, SpA features were considered as they were used in the diagnostic process (local assessments), thus not necessarily according to standardised definitions. Sacroiliitis on imaging was considered as reported by the local radiologist: for radiographs, according to the modified New York criteria,[14] and, for MRI, if the radiologist identified axSpA-related inflammatory lesions or structural lesions, or both. At baseline, overall, SpA features were categorised as either currently present (yes/no) or ever present (yes/no; for peripheral manifestations and extramusculoskeletal manifestations (EMM), if past occurrence confirmed by a physician). At 2y, variables were categorised as present (yes/no), using a 'once present, always present' approach. Therefore, a newly developed SpA feature was considered if first-ever present during follow-up.

### Main outcome

The clinical diagnosis at 2y was the primary outcome of this study. Herein, we stratified patients by diagnostic likelihood based on the diagnosis, the LoC of that diagnosis and the availability of an alternative diagnosis in patients without SpA (figure 1). At baseline, four categories were defined based on the diagnosis and

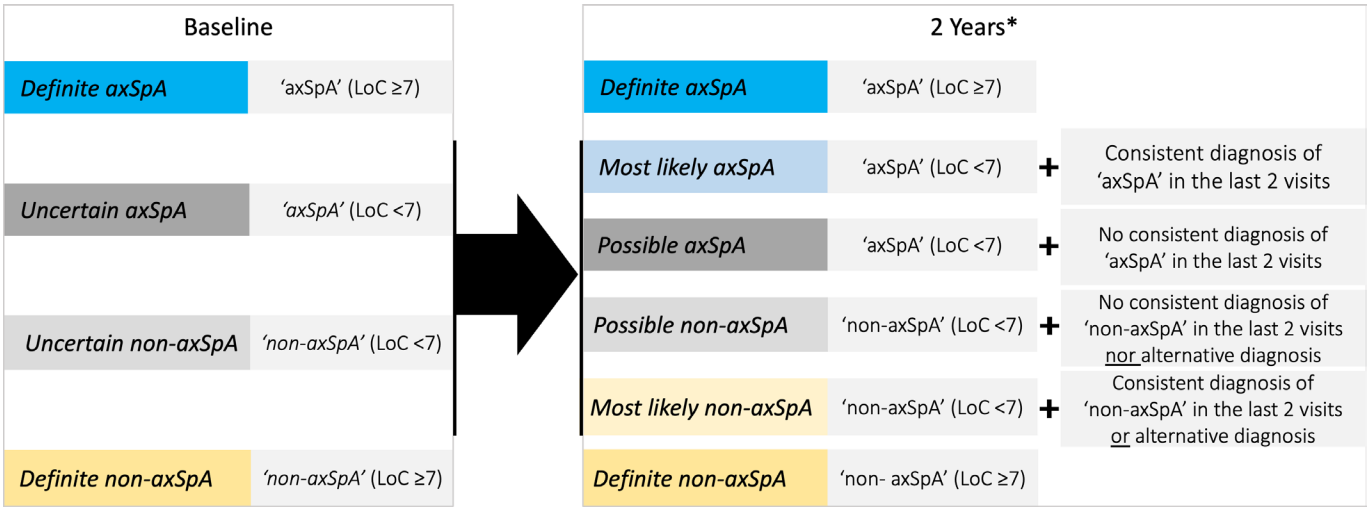


**Figure 1** Diagnosis definitions at baseline and at 2 years. At baseline: definite axSpA/non-axSpA—'axSpA' or 'non-axSpA' diagnosis at baseline with a LoC≥7; uncertain axSpA/non-axSpA—'axSpA' or 'non-axSpA' at baseline (LoC<7). At 2 years (*last observation carried forward approach if 2-year visit data were missing): *Definite axSpA*—'axSpA' (LoC≥7) at 2 years (complete follow-up) or at the two last available visits (missing at the 2 year visit); *Most likely axSpA*—'axSpA' (LOC<7) at 2 years, plus a consistent diagnosis of 'axSpA' in the two last visits (complete follow-up) or 'axSpA' (LoC≥7) at the last visit only (missing at the 2-year visit); *Possible axSpA*—'axSpA' (LOC<7) at 2 years, plus no consistent diagnosis of 'axSpA' in the last two visits (complete follow-up) or 'axSpA' (LoC<7) at the last visit (missing at the 2-year visit); *Possible non-axSpA*—'non-axSpA' (LOC<7), plus no consistent diagnosis of 'non-axSpA' in the last two visits (complete follow-up) or 'non-axSpA' (LoC<7) at the last visit and no alternative diagnosis reported (missing at the 2-year visit); *Most likely non-axSpA*—'non-axSpA' (LOC<7), plus a consistent diagnosis of 'non-axSpA' in the last two available visits (complete follow-up) or 'non-axSpA' (LoC≥7) at the last visit only or if LoC<7, plus an alternative diagnosis reported (missing at the 2-year visit); *Definite non-axSpA*—'non-axSpA' (LoC≥7) at 2 years (complete follow-up) or at the two last available visits (missing at the 2-year visit). axSpA, axial spondyloarthritis; LoC, level of confidence.

LoC of that diagnosis: 'definite (d-) *axSpA/non-axSpA*' when the diagnosis was made with a LoC≥7 and 'uncertain *axSpA/non-axSpA*' when the LoC was <7. At 2y, the categories of *d-axSpA* and *d-non-axSpA* were kept for the diagnosis with the same definition. 'Uncertain' categories were split into two categories per diagnosis (ie, '*most likely*' and '*possible*' *axSpA/non-axSpA*), capturing different levels of diagnostic uncertainty. Here, not only the diagnosis and LoC of that diagnosis were considered but also the (in)consistency of diagnosis over time, and the presence/absence of an alternative diagnosis provided by the treating rheumatologist (*non-axSpA* categories only) (figure 1).

Of note, the 2y-diagnosis categories were applied to all patients. For patients lost to follow-up (n=131 (24%)), a last observation carried forward approach was applied (figure 1). The patients excluded *per protocol* (n=107 (19%)) were labelled with a '*d-non-axSpA*' diagnosis, supported by the very low estimated probability of axSpA development if having no or only one minor SpA-feature after a complete baseline workup.[15]

### Statistical analysis

A flow chart indicating patients followed-up over 2y, missing visits, and losses to follow-up (with respective reasons) was built. For the current analyses, patients could be included if having a diagnosis (and LoC) reported by the rheumatologist at least at baseline. We assessed the prevalence of *d-axSpA* at baseline and 2y. The proportions of the 2y-diagnosis categories were computed. In patients with diagnosis of *d-axSpA* and *d-non-axSpA*, the mean (SD) LoC was computed at baseline and at follow-up. The percentage of fulfilment of the ASAS classification criteria (imaging (local readings) or clinical arm; yes/no) was evaluated at a later stage during data analysis, and applied only in patients with *d-axSpA*. Baseline characteristics are descriptively summarised for the overall cohort and stratified by 2y-diagnosis groups (from *d-axSpA* to *d-non-axSpA*).

The proportions of patients transitioning between diagnostic categories from baseline to 2y were computed. SpA features were investigated over time in patients shifting to *d-axSpA* at 2y. Therefore, the baseline and cumulative (over follow-up) number of patients with each SpA-feature were evaluated. Moreover, both for baseline and follow-up, group-level data (mean (SD) total number of SpA features) and individual-level data (proportion of patients by number of SpA features) were computed.

In secondary analyses, the 2y-diagnosis categories were stratified by centre and year of recruitment. The baseline mean (SD) number of SpA features (including/excluding both HLA-B27 carriership and sacroiliitis on imaging) and the proportion of patients by number of SpA features were computed, overall, and stratified by 2y diagnosis. In addition, we descriptively summarised the baseline characteristics of two 'outlier' subgroups: (1) patients with 2y diagnosis of *non-axSpA* and four or more SpA features at baseline, and (2) patients with 2y diagnosis of *axSpA* and solely one or two SpA-feature(s) at baseline. Finally, the baseline characteristics of a subset of patients newly diagnosed with *d-axSpA* over follow-up despite not developing new SpA features over time were also investigated.

Overall, missing clinical features were considered missing completely at random. Missing SpA features were solely imputed for computing the total number of SpA features and the ASAS classification criteria variable (both using the assumption of absent if missing).

Statistical analyses were performed using *STATA* software V.16.0.

## RESULTS

In total, 555 patients were enrolled in the SPACE cohort from 2008 to 2016 (484 (88%) white, 18 (3%) Asian, 15 (3%) mixed ethnicity (eg, black and white, Asian and white), 9 (2%) black, and 26 (5%) unknown ethnicity (not reported)). In total, 448

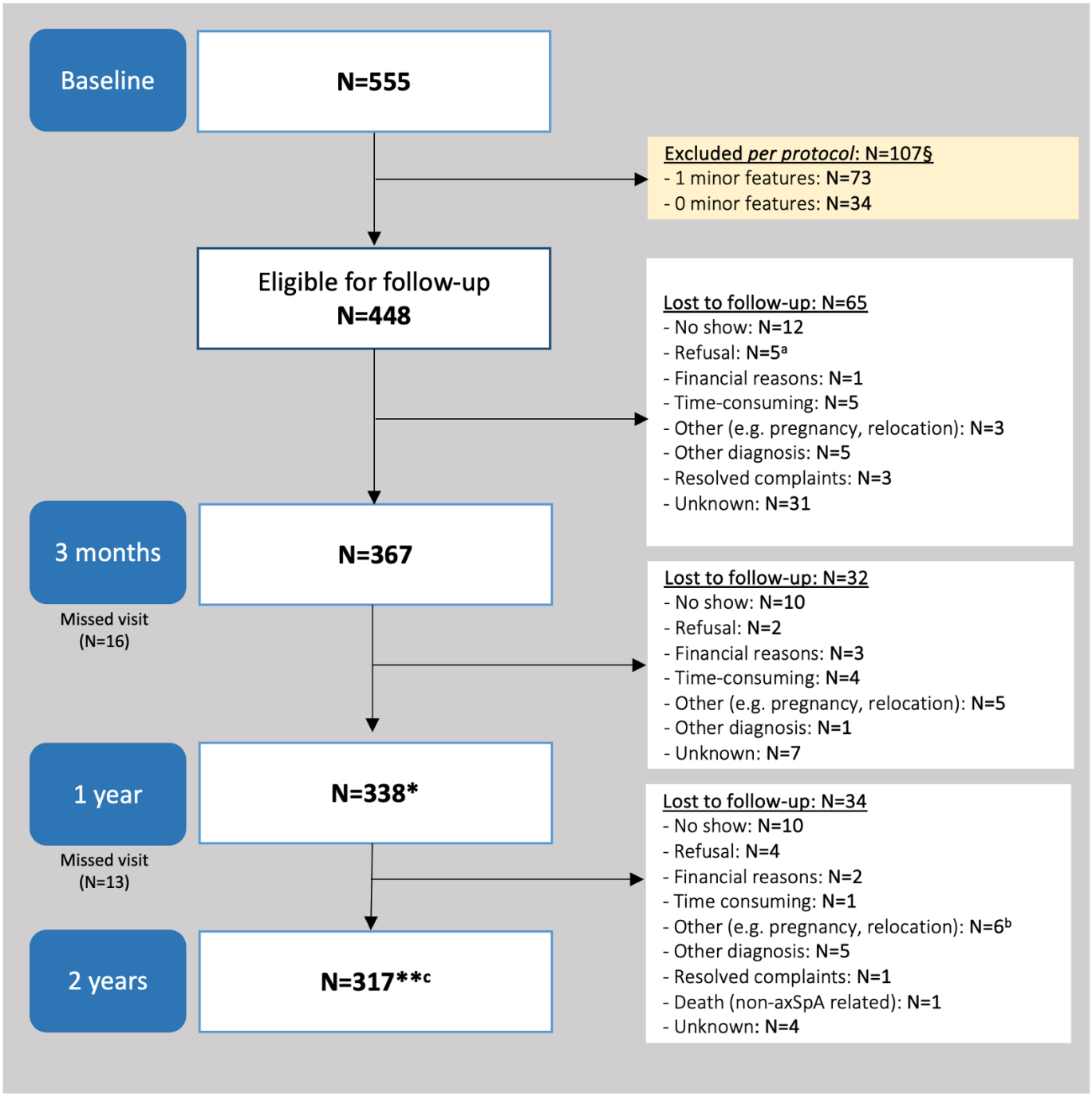


**Figure 2** Flow chart of the individuals with chronic back pain of unknown origin (symptom duration of ≥3 months but ≤2 years, starting before the age of 45 years) included in the SPondyloArthritis Caught Early cohort.[§]n=16 patients with 1 minor feature at baseline were followed up over 2 years (follow-up outside of the protocol) *Including 3 patient who missed the previous follow-up visit. **Including 13 patients who missed the previous follow-up visits. Of the three patients not included in the main analyses of this manuscript because of missing data regarding diagnosis: [a]one had only a baseline visit, refusing to continue in the subsequent study visits; [b]another was lost to follow-up after 1 year because of other reasons (eg, pregnancy, relocation); and [c]another had a complete follow-up.

(81%) patients were eligible for follow-up, with 107 (19%) excluded *per protocol* at this stage (figure 2). At 1 year and 2y, 338/448 (75%) and 317/448 (71%) of patients eligible for follow-up had a study visit, respectively. Details on patients skipping visits and lost to follow-up can also be found in figure 2.

For the current analyses, three patients were excluded because of missing data regarding the diagnosis at baseline. Therefore, 552 patients were ultimately available for analysis (Leiden n=383, Oslo n=94, Amsterdam n=48, Gouda n=27), with a mean (SD) age of 31 (8) years, 35% male, 41% HLA-B27 positive and a mean (SD) symptom duration of 13 (7) months (table 1).

The diagnosis of *d-axSpA* was given to 175/552 (32%) patients at baseline and 165/552 (30%) at 2y; the mean (SD) LoC was 8.1 (1.9) and 8.7 (1.1), respectively. Of the 387 (70%) patients without a *d-axSpA* diagnosis at 2y, 53 had 'most likely axSpA', 13 'possible axSpA', 14 'possible non-axSpA', 84 'most likely non-axSpA' and 223 'd-non-axSpA'.

**Table 1** Baseline characteristics by 2-year diagnosis category of patients with chronic back pain symptom duration of ≥3 months but ≤2 years starting before the age of 45 years

| | Overall population n=552*† | Definite axSpA n=165† | Most likely axSpA n=53† | Possible axSpA n=13‡ | Possible non-axSpA n=14† | Most likely non-axSpA n=84† | Definite non-axSpA n=223† |
|---|---|---|---|---|---|---|---|
| Age at inclusion, years | 30.6 (8.2) | 29.8 (7.7) | 30.4 (8.9) | 33.9 (6.2) | 29.9 (9.8) | 31.1 (8.7) | 31.0 (8.3) |
| Male | 195 (35%) | 86 (52%) | 23 (43%) | 4 (31%) | 3 (21%) | 16 (19%) | 63 (28%) |
| Symptom duration, months | 13.2 (7.1) | 12.8 (7.0) | 13.2 (7.8) | 13.1 (5.7) | 14.4 (6.5) | 13.1 (6.5) | 13.5 (7.4) |
| HLA-B27+ | 226 (41%) | 133 (81%) | 33 (62%) | 8 (62%) | 7 (50%) | 19 (23%) | 26 (12%) |
| Family history of SpA | 248 (45%) | 79 (48%) | 32 (60%) | 8 (62%) | 8 (57%) | 49 (58%) | 72 (32%) |
| Inflammatory back pain | 343 (62%) | 125 (76%) | 32 (60%) | 10 (77%) | 9 (64%) | 48 (57%) | 119 (54%) |
| Good response to NSAIDs | 170 (31%) | 69 (43%) | 21 (41%) | 6 (46%) | 4 (29%) | 22 (27%) | 48 (23%) |
| Peripheral arthritis¶ | 61 (11%) | 26 (16%) | 9 (17%) | 2 (15%) | 2 (14%) | 9 (11%) | 13 (6%) |
| Dactylitis¶ | 19 (3%) | 8 (5%) | 4 (8%) | 1 (8%) | 2 (14%) | 2 (2%) | 2 (1%) |
| Heel pain¶ | 67 (12%) | 31 (19%) | 8 (15%) | 3 (23%) | 1 (7%) | 9 (11%) | 15 (7%) |
| Anterior uveitis¶ | 40 (7%) | 22 (13%) | 6 (11%) | 3 (23%) | 1 (7%) | 2 (2%) | 6 (3%) |
| Inflammatory bowel disease¶ | 36 (7%) | 11 (7%) | 4 (8%) | 0 (0%) | 1 (7%) | 5 (6%) | 15 (7%) |
| Psoriasis¶ | 47 (9%) | 18 (11%) | 6 (11%) | 0 (0%) | 1 (7%) | 8 (9%) | 15 (7%) |
| Increased acute phase reactants§ | 138 (25%) | 61 (37%) | 14 (26%) | 0 (0%) | 3 (21%) | 21 (25%) | 39 (17%) |
| Sacroiliitis on radiographs§ | 47 (9%) | 38 (23%) | 6 (10%) | 1 (8%) | 1 (7%) | 1 (1%) | 0 (0%) |
| Sacroiliitis on MRI§ | 147 (27%) | 108 (67%) | 17 (33%) | 1 (8%) | 2 (15%) | 11 (13%) | 8 (4%) |

Data presented as mean (SD) or n of patients (%). The 2-year diagnosis categories are defined in the methods section and figure 1.
*Three patients not analysed because of missing baseline diagnosis.
†Missing values were inferior to 5% for all variables.
‡No missing values.
§Local assessment/reading.
¶Present or past (if confirmed by a physician)
axSpA, axial spondyloarthritis; HLA-B27, human leucocyte antigen B27; NSAIDs, non-steroidal anti-inflammatory drugs.

Table 1 shows the baseline characteristics of patients, overall and split by diagnostic categories at 2y. Expectedly, SpA features were more prevalent in the 2y-*axSpA* categories when compared with the *non-axSpA* categories. A 1:1 ratio between males and females was observed in the *d-axSpA* category, with female predominance in the remaining categories, especially in *non-axSpA*. A clear HLA-B27 positivity gradient stood out, decreasing across categories from *d-axSpA* (81%) to *d-non-axSpA* (12%). At baseline, sacroiliitis on imaging best discriminated *d-axSpA* from *non-axSpA* (definite, most likely, and possible) 2y-diagnostic categories (table 1). Overall, sacroiliitis on imaging (on radiographs or MRI) was present in 108/165 (67%) patients with 2y-*d-axSpA*, with all patients with sacroiliitis on radiographs (n=38) also showing inflammatory or structural changes on MRI at baseline.

Following figure 3, starting from each baseline category, we subsequently describe the diagnostic changes over 2y.

Most of the patients with *d-axSpA* at baseline kept a high-confidence axSpA diagnosis after 2y (164/175 (94%): 133/175 (76%) with *d-axSpA* and 31/175 (18%) with *most likely axSpA* after 2 years), with only 11 (6%) changing to the *non-axSpA* categories at 2y (7/11 having *d-non-axSpA*, 1/11 having *most likely non-axSpA* and 3/11 having *possible non-axSpA* at 2y). Although still diagnosed as axSpA by the rheumatologist, 31/175 (17%) of the patients with *d-axSpA* at baseline were no longer *d-axSpA* at 2y, reflected by a decrease in the LoC (LoC<7, n=14/31) or

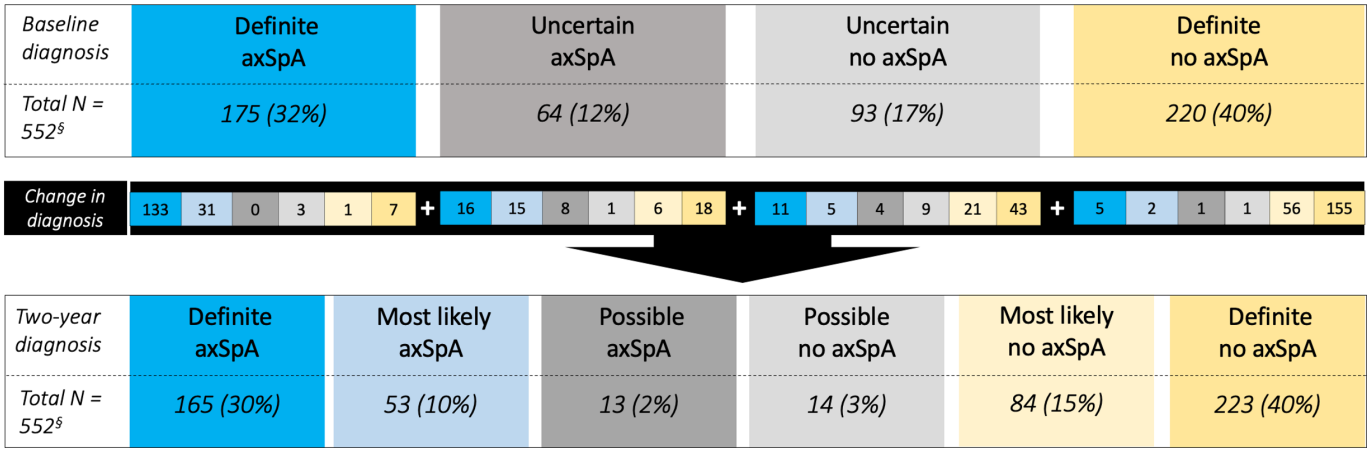


**Figure 3** Course of diagnosis over 2 years in patients with recent onset chronic back pain of unknown origin. The baseline and 2-year diagnosis categories are defined in the Methods section and figure 1. axSpA, axial spondyloarthritis.

due to incomplete follow-up (n=17/31). Of the patients with *d-axSpA*, 154/175 (88%) and 150/165 (91%) fulfilled the ASAS classification criteria, at baseline and 2y, respectively.

In 40% of patients both at baseline and at 2y, the cause of back pain was deemed to be 'd-non-axSpA' (figure 3), with LoC increasing from 7.4 (2.1) at baseline to 8.3 (1.4) over time. The alternative diagnoses for CBP were diverse, with non-specific back pain being reported in most patients both at baseline (n=80 (36%)) and at 2y (n=99 (44%)) (online supplemental table-S1). Of the 220 patients with *d-non-axSpA* at baseline, in 211/229 (96%) the rheumatologists maintained a high confidence regarding the non-axSpA diagnosis after 2y (155/220 (70%) with *d-non-axSpA* and 56/220 (26%) with *most likely non-axSpA* at 2y) (figure 3). Of note, of the 56 patients who transitioned to *most likely non-axSpA*, most (48 (86%)) had an incomplete follow-up precluding us to confirm the *definite* diagnosis at 2y, while in 8 (14%) the LoC decreased <7 after 2y without an alternative diagnosis reported. Finally, only one patient transitioned to *possible non-axSpA*, and 8 (4%) changed into one of the *axSpA* categories (5/8 *d-axSpA*, 2/8 *most likely axSpA* and 1/8 *possible axSpA*).

In nearly 30% (n=157/552) of the patients, the diagnosis was uncertain (of either axSpA or non-axSpA) at baseline and the overall percentage of *uncertain* diagnoses at 2y remained stable (164/552 (30%)) (figure 3). Yet, at 2y, most patients received a *most likely* diagnostic category, and only 5% had a vignette of *possible axSpA* (13/552 (2%)) or *possible non-axSpA* (14/552 (3%)).

Only 8% (n=32/377) of those who did not have a baseline diagnosis of *d-axSpA* 'gained' one at 2y (baseline categories: 16 *uncertain axSpA*, 11 *uncertain non-axSpA*, and 5 *d-non-axSpA*—*figure 3*). In these patients with a *d-axSpA* diagnosis at 2y but not at baseline, a mean of three to four SpA features were already present at baseline (ranging from one to seven), and on average one new SpA feature (ranging from zero to three) developed over 2y (table 2).

In patients with new 2y-d-axSpA who developed new SpA features over time (n=23/32 (75%)), 'good response to NSAIDs' and 'sacroiliitis on MRI' were the two most frequently newly developed features over time, occurring in 9/23 (39%) and 8/23 (35%) patients, respectively (table 2). One-third (3/9) of patients with newly developed good response to NSAIDs, also had new

**Table 2** SpA features of 32 patients changing diagnosis from baseline *non-axSpA* and *uncertain axSpA* to 2-year *definite axSpA*

| Baseline diagnosis | Uncertain axSpA at baseline n=16 | | Uncertain non-axSpA at baseline n=11 | | Definite non-axSpA at baseline n=5 | |
|---|---|---|---|---|---|---|
| | Baseline | Two years* | Baseline | Two years*‡ | Baseline | Two years* |
| Age at inclusion, years | 30.3 (8.6) | – | 35.1 (7.9) | – | 25.8 (6.1) | – |
| Male | 8 (50%) | – | 8 (73%) | – | 2 (40%) | – |
| Symptom duration, months | 12.7 (6.8) | – | 12.5 (6.8) | – | 12.0 (4.7) | – |
| HLA-B27+ | 13 (81%) | – | 6 (55%) | – | 4 (80%) | – |
| Family history of SpA | 8 (50%) | 9 (56%) | 3 (27%) | 4 (36%) | 3 (60%) | 4 (80%) |
| Inflammatory back pain | 14 (88%) | 16 (100%) | 6 (54%) | 7 (64%) | 5 (100%) | 5 (100%) |
| Good response to NSAID | 4 (25%) | 10 (63%) | 5 (45%) | 7 (58%) | 3 (60%) | 4 (80%) |
| Peripheral manifestations¶ | 3 (19%) | 6 (38%) | 1 (9%) | 3 (27%) | 0 (0%) | 1 (20%) |
| Extramusculoskeletal manifestations** | 4 (25%) | 6 (38%) | 3 (27%) | 4 (36%) | 0 (0%) | 1 (20%) |
| Increased acute phase reactants† | 4 (25%) | 4 (25%) | 1 (9%) | 3 (27%) | 2 (40%) | 2 (40%) |
| Sacroiliitis on radiographs† | 0 (0%) | 0 (0%) | 1 (9%) | 2 (16%) | 0 (0%) | 1 (20%) |
| Sacroiliitis on MRI† | 3 (19%) | 8 (50%) | 3 (27%) | 5 (45%) | 0 (0%) | 1 (20%) |
| Total number of SpA features§ | 3.4 (1.1) | 4.6 (1.4) | 2.6 (1.0) | 3.7 (1.3) | 3.4 (0.5) | 4.8 (0.8) |
| 1 SpA feature | 1 (6%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) |
| 2 SpA features | 2 (13%) | 1 (6%) | 7 (64%) | 1 (9%) | 0 (0%) | 0 (0%) |
| 3 SpA features | 6 (38%) | 2 (13%) | 2 (18%) | 6 (55%) | 3 (60%) | 0 (0%) |
| 4 SpA features | 4 (25%) | 6 (38%) | 1 (9%) | 1 (9%) | 2 (40%) | 4 (80%) |
| 5 SpA features | 3 (19%) | 2 (13%) | 1 (9%) | 1 (9%) | 0 (0%) | 0 (0%) |
| 6 SpA features | 0 (0%) | 4 (25%) | 0 (0%) | 2 (18%) | 0 (0%) | 1 (20%) |
| 7 SpA features | 0 (0%) | 1 (6%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) |
| Number of new SpA features over FU§ | – | 1.3 (1.0) | – | 1.1 (0.9) | – | 1.0 (0.7) |
| 0 SpA features | – | 5 (31%) | – | 3 (27%) | – | 1 (20%) |
| 1 SpA feature | – | 4 (25%) | – | 5 (45%) | – | 3 (60%) |
| 2 SpA features | – | 5 (31%) | – | 2 (18%) | – | 1 (20%) |
| 3 SpA features | – | 2 (13%) | – | 1 (9%) | – | 0 (0%) |

Data presented as mean (SD) or n of patients (%). The baseline diagnosis categories are defined in the methods section and figure 1.
*Cumulative numbers over the 2-year follow-up.
†Local assessment/reading.
‡One patient missed the 2-year visit; therefore, only follow-up data up to 1 year was available for this patient.
§Including HLA-B27 and imaging.
¶Uncertain axSpA at baseline (Baseline: peripheral arthritis n=2, heel pain n=2; Two years: peripheral arthritis n=3, dactilitis n=2, heel pain n=3); Uncertain non-axSpA at baseline (Baseline: peripheral arthritis n=1; Two years: peripheral arthritis n=2, heel enthesitis n=1); Definite non-axSpA at baseline (Two years: dactilitis n=1).
**Uncertain axSpA at baseline (Baseline: anterior uveitis n=3, inflammatory bowel disease n=1; Two years: anterior uveitis n=4, inflammatory bowel disease n=2); Uncertain non-axSpA at baseline (Baseline: inflammatory bowel disease n=2, psoriasis n=1; Two years: anterior uveitis n=1, inflammatory bowel disease n=2, psoriasis n=1); Definite non-axSpA at baseline (Two years: inflammatory bowel disease n=1).
axSpA, axial Spondyloarthritis; FU, follow-up; HLA-B27, human leucocyte antigen B27; NSAIDs, non-steroidal anti-inflammatory drugs.

**Table 3** Baseline number of SpA features (including HLA-B27 carriership and sacroiliitis on imaging) of 552 patients with chronic back pain of unknown origin at baseline stratified by diagnosis at 2 years

| | Overall population n=552 | Definite axSpA n=165 | Most likely axSpA n=53 | Possible axSpA n=13 | Possible non-axSpA n=14 | Most likely non-axSpA n=84 | Definite non- axSpA n=223 |
|---|---|---|---|---|---|---|---|
| Number of SpA features | 2.9 (1.8) | 4.4 (1.6) | 3.6 (1.3) | 3.3 (1.0) | 3.0 (1.2) | 2.5 (0.9) | 1.7 (1.3) |
| 0 SpA feature | 34 (6%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 34 (15%) |
| 1 SpA feature | 97 (18%) | 2 (1%) | 2 (4%) | 0 (0%) | 0 (0%) | 8 (10%) | 85 (38%) |
| 2 SpA features | 127 (23%) | 15 (9%) | 10 (19%) | 3 (23%) | 6 (43%) | 45 (54%) | 48 (22%) |
| 3 SpA features | 109 (20%) | 33 (20%) | 13 (25%) | 5 (38%) | 5 (36%) | 20 (24%) | 33 (15%) |
| 4 SpA features | 77 (14%) | 35 (21%) | 14 (26%) | 3 (23%) | 1 (7%) | 7 (8%) | 17 (8%) |
| 5 SpA features | 68 (12%) | 45 (27%) | 11 (21%) | 2 (15%) | 1 (7%) | 4 (5%) | 5 (2%) |
| 6 SpA features | 24 (4%) | 20 (12%) | 2 (4%) | 0 (0%) | 1 (7%) | 0 (0%) | 1 (0.5%) |
| 7 SpA features | 10 (2%) | 9 (5%) | 1 (2%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) |
| 8 SpA features | 4 (1%) | 4 (2%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) |
| 9 SpA features | 2 (0.4%) | 2 (1%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) |

Data presented as mean (SD) or n of patients (%). The 2-year diagnosis categories are defined in the Methods section and figure 1.
axSpA, axial spondyloarthritis.

MRI positivity. Of the patients who developed good reponse to NSAIDs, 5/9 (56%) used NSAIDs at baseline, and the remaining started NSAIDs over follow-up. Of the 8 patients who developed new MRI positivity for sacroiliitis in at least one, the MRI scans repeated over time (3 months, 1 year and 2 years), 7/8 (88%) were HLA-B27 positive and 5/8 (63%) were male.

Regarding secondary analyses, 9 out of the 32 patients who received a new diagnosis of *d-axSpA* at 2y had so without developing new SpA features over time (table 2). In addition to the universal presence of inflammatory back pain (n=9; 100%), these patients had one to four other SpA features (mean (SD): 3.3 (1.0)) already at baseline. HLA-B27 was positive in 5 (56%) of them, but only 2 (22%) patients had sacroiliitis (on MRI).

The percentages of patients *with* 2y-*d-axSpA* and *2y-d-non-axSpA* varied by centre, respectively, from 22% to 54% and from 19% to 48% (online supplemental figure-S3). The proportions of the 2y-diagnostic categories stayed rather similar over time (online supplemental figure-S4).

There was an increasing gradient in number of SpA features (including HLA-B27 and sacroiliitis) from *d-non-axSpA via intermediate categories* to *d-axSpA (table 3)*. On average, we observed a two-and-a-half-times higher number of SpA features in the 2y-*d-axSpA* patients when compared with 2y-*d-non-axSpA* (mean (SD) SpA features of 4.4 (1.6) vs 1.7 (1.3)) (table 3).

When excluding HLA-B27 and sacroiliitis, the mean number of baseline SpA features was nearly one-and-a-half-times higher in 2y-*d-axSpA* when compared with 2y-*d-non-axSpA* patients (mean (SD) of 2.7 (1.4) vs 1.5 (1.2)) (online supplemental table-S2). The gradient across categories was still present, but less pronounced.

Within patients with *non-axSpA* diagnoses at 2y, a subgroup had four to six baseline SpA features (37/321 (12%); 23/37 (62%) *d-non-axSpA*). Briefly, these were mostly females (76%) with inflammatory back pain (92%), fairly low percentage of HLA-B27 positivity (38%), infrequent sacroiliitis (3% on radiographs and MRI), and relatively high prevalence of peripheral arthritis (27%), heel pain (32%) and psoriasis (27%) (online supplemental table-S3). CBP was most frequently attributed to anon-specific back pain (n=16/37 (43%)) (online supplemental table-S4). On the other extreme, among patients with 2y-*axSpA* diagnoses (n=233), 32 (14%) had only one to two SpA-feature(s) at baseline. Patients with only one SpA feature at baseline (n=4/32 [13%]), had sacroiliitis on MRI (n=1), HLA-B27 positivity (n=1) or family history of SpA (n=2).

## DISCUSSION

Patients with recent onset CBP suspected of axSpA referred to the rheumatologist can be unequivocally and reliably diagnosed already at their first presentation to a rheumatologist. Diagnostic judgements remained relatively stable over time, with nearly one-third of the referred patients having *d-axSpA* after 2y.

Notably, this is the first study formally proving that patients with axSpA can be diagnosed by rheumatologists shortly after symptom onset, here with an overall mean symptom duration of 13 months. To help overcoming the diagnostic delay seen in patients with axSpA,[2–4] a timely referral of preselected patients to secondary or tertiary care centres seems crucial. Therefore, our data support the ASAS recommendation of immediate referral of patients with 'suspicion of axSpA' to a rheumatologist.[6] According to ASAS, patients with CBP (≥3 months) starting before 45 years of age should be referred to a rheumatologist if at least one additional SpA feature is present.[16] Although elevation of acute phase reactants and sacroiliitis on imaging (including MRI) are within the listed SpA features, referral must not be postponed if these are not available (or difficult to interpret) in primary care settings.[17] While referral strategies to specialists vary worldwide,[16] data suggest that among general practitioners, who commonly manage CBP, knowledge regarding axSpA is poor.[18] An intensification of educational efforts in targeting first-line professionals seems vital.[19]

This study provides insight into how rheumatologists integrate the 'Gestalt' of axSpA in real-life settings. None of the many SpA features suffices to make a diagnosis of *d-axSpA*. Nevertheless, at baseline, HLA-B27 positivity and sacroiliitis on imaging discriminated best between the 2y-*axSpA* and the 2y-*non-axSpA* categories. The gradient of HLA-B27 positivity decreasing between 2y-diagnostic categories (from *d-axSpA (81%)* to *d-non-axSpA (12%)*) tells us that this well-known genetic marker is a SpA feature considered of important value for diagnostic purposes.[13 20] The other variable of major discriminatory value was imaging. At baseline, imaging sacroiliitis, especially on radiographs, was completely absent in patients with *d-non-axSpA*. While the importance of HLA-B27 positivity and sacroiliitis on imaging are well-known major

SpA features in established axSpA,[13] their major relevance in patients with <2y symptom duration adds robustness to the diagnoses made in the study and *Gestalt* of axSpA irrespective of symptom duration.

Not all patients with *d-axSpA* have clear imaging abnormalities in the sacroiliac joints as detected by the radiologist. While this is not an uncommon finding in axSpA cohorts, an axSpA diagnosis without any objective sign of axial inflammation on imaging is increasingly being questioned.[21–23] Conversely, not all patients with imaging findings (especially on MRI) were given the diagnosis of *d-axSpA*. This is compatible with previous reports showing that bone marrow oedema on MRI is also seen in persons without axSpA.[24–26] Therefore, the sole presence of MRI changes (without additional SpA features) does not suffice to make a *d-axSpA* diagnosis. Of note, imaging sacroiliitis was deliberately considered as per local radiologists' reports taking inflammatory and structural lesions into account (real-life settings) warranting future research using central readings.

On the other hand, the presence of many SpA features also did not automatically lead to a definite diagnosis of axSpA.[27] Also, it is reassuring to observe that fulfilment of ASAS classification criteria (not meant for diagnosis purposes) does not preclude clinicians to give the diagnosis of non-axSpA, and *vice-versa*.[21] The 'pattern' of the SpA features and exploration of alternative diagnoses are key for the rheumatologist's judgement.[28] A paradigmatic example was observed in the subgroup of 37 patients with 2y-*non-axSpA* and 4 or more SpA features at baseline. These paients were mostly females, mostly HLA-B27 negative, with predominant peripheral manifestations and EMM present. While most of them had inflammatory back pain, sacroiliitis on imaging was rarely present, and the CBP was attributed to other causes. This subgroup of patients may perhaps better fit the spectrum of peripheral SpA or psoriatic arthritis.[29 30]

Of note, re-evaluations of diagnosis resulted in various transitions between diagnostic categories, but diagnostic uncertainty persisted in up to 30% of patients with CBP, even though only 5% corresponded to high-degree uncertainty. How to proceed in such cases is of utmost importance in clinical practice. Therefore, it is relevant to understand the value of repeated assessments of SpA features for a definite clinical diagnosis. In our cohort, the yield of repeated assessments of SpA features was modest: only 8% of patients 'gained' a diagnosis of *d-axSpA* after 2y. The development of new SpA features was not strictly necessary for a de novo diagnosis of *d-axSpA* after 2y, *but* response to treatment (NSAIDs) and sacroiliitis on MRI were the two most frequently observed newly developed features, and they could have contributed to a new diagnosis of *d-axSpA*. Interestingly, about half of the patients with newly developed good response to NSAIDs over time were already taking these drugs at baseline, but all with suboptimal response. The rheumatologist's prescriptions after the first assessment, which may include optimisation of dosages, could have contributed to the response to NSAIDs over follow-up.[6]

Additionally, our data suggest that the usefulness of repeating MRI in terms of diagnostic yield is generally very low but perhaps somewhat higher in HLA-B27 positive patients, especially if male. These findings align with the 1-year results from the SPACE cohort.[31] MRI-detected changes in the sacroiliac joints were seen in a minority of patients, and both male sex and HLA-B27 positivity were important determinants of MRI positivity.[31] Also, congruent results were reported in other cohorts of individuals with CBP suspected of axSpA with MRI repetitions varying from 12 weeks to 2y.[32–34] Although axSpA is a disease affecting both genders (1:1 female-to-male ratio in patients with *d-axSpA*),[35] future research is warranted to delve into potential gender differences regarding diagnosis.

This study is not without limitations. Only European (mostly white) patients were included which imposes caution about the generalisability to populations with, for example, known lower HLA-B27 prevalence or regional phenotypes with low susceptibility.[20 36–38] Moreover, our results mainly represent the clinical practice at academic or central hospitals (only 5% of patients included in a peripheral hospital). Notwithstanding, the proportions of diagnostic categories varied across centres, even in hospitals of similar type. This finding unveils that differences between centres are likely multifactorial and not only driven by the type of hospital receiving the patient. Other factors, such as different referral strategies, can also play a role. On the other hand, patients were not necessarily evaluated by the same rheumatologist over time, and the expertise in SpA may have varied across rheumatologists. While some of the transitions in diagnosis may thereby simply have been driven by judgements (including the LoC) from different rheumatologists, this is a reflection of real-life clinical practice and potentially adds to the generalisability of our findings to diverse clinical settings. An under-representation of the 2y-*definite diagnosis* categories may have occurred (eg, transitions from *d-axSpA* at baseline to *most likely axSpA* at 2y) because of incomplete follow-up which per our analysis protocol made them ineligible for *d-axSpA* at 2y. Also, over-representation of the 2y-*d-non-axSpA* category may be the consequence of a substantial number of the recruited patients being excluded per protocol (absent or only one minor SpA feature, n=107 (19%)) and, therefore, having *d-non-axSpA* by default.

This study has several strengths, such as the large multicountry and multicentre population of patients with recent CBP (symptom duration<2y) suspected of *axSpA* but with unknown diagnosis at inclusion. That allowed for comparisons with 'concurrent' controls with *non-axSpA*, not possible in previous cohorts in which all patients have a known axSpA diagnosis (and longer symptom duration) at inclusion.[39 40] Moreover, unlike SPACE, most cohorts include patients with inflammatory back pain only, lacking a comparator.[39 40] Importantly, in SPACE, the same rigorous follow-up was applied over 2y in all patients with CBP (irrespective of the presence or absence of a clinical diagnosis of axSpA at baseline). Indeed, at each visit (3 months, 1 year and 2y), clinical, laboratory and imaging assessments (namely MRI) were repeated, resulting in a uniquely large amount of data. To avoid selection bias and increase the validity of our results, we deliberately refrained from using a 'per protocol' analysis of the cohort. Conversely, we included nearly all enrolled patients, using a comprehensive last observation carried forward approach for the diagnostic categorization. That was based not only on the LoC, but also (in)consistency of diagnosis in the last available visits, and the presence/absence of alternative diagnoses for the CBP. The LoC cut-off of≥7/<7 was chosen to obtain the highest specificity without losing sensitivity.[24 35] The gradient of HLA-B27 positivity decreasing throughout 2y-diagnosis categories (from *d-axSpA* to *d-non-axSpA*), and the high percentage of fulfilment of the ASAS classification criteria in *d-axSpA* patients (around 90%) further support the used cut-off. Notably, nearly 10% of patients received a high-confidence diagnosis of axSpA (*d-axSpA*) from rheumatologists after 2y, even though not fulfilling the ASAS classification criteria. This reinforces the validity of diagnostic decisions based on clinical judgement in our study.

Finally, SPACE is unique in including patients with axial symptom duration of at most 2y, which corresponds to the recent

ASAS definition of 'early axSpA' (for research purposes).[41] In the ASAS paper, it is stated 'this definition is aspirational, as we know that in clinical practice there is unfortunately still a long diagnostic delay and therefore it may initially not be feasible to include patients with ≤2y of symptom duration in research studies'.[41] Our data show that it is possible to recruit patients with true early axSpA fulfilling the ASAS definition.

In conclusion, nearly one-third of patients with CBP of less than 2y duration suspected of axSpA referred to the rheumatologist can be reliably diagnosed with *d-axSpA* at their first assessment. However, relevant diagnostic uncertainty remained in up to 30% of the patients after 2y. Of those, 25% received a most likely diagnosis, while only 5% had the highest diagnostic uncertainty (possible diagnosis). The yield of repeated assessments was modest for the new *d-axSpA* diagnosis over time, but MRI repetition can be worthwhile in HLA-B27 positive patients, especially if male. These results shed light into the definition of early axSpA and urge patients with CBP suspected of axSpA the prompt assessment by a rheumatologist.

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**Correction notice** This article has been corrected since it published Online First. The author equal contributor statement has been added.

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**Acknowledgements** The work on this manuscript was previously accepted to the EULAR Congress 2023 and ACR Convergence 2023 and published as conference abstracts in the correspondent supplement of Annals of Rheumatic Diseases and Arthritis & Rheumatology, respectively.

**Contributors** Study conception and design: DvdH. Acquisition of data: MvL, RAS, RBML, MvdS, KMF, IJB, MvO, SE, RR, FAvG. Dataset management: MLM, MvL, RAS. Analysis and interpretation of data: MLM, FAvG, DvdH, SR. Drafting the manuscript: MLM. All authors critically reviewed the manuscript for important intellectual contribution and approved the final version. Guarantors: MLM and FvG.

**Funding** MLM is supported by the Fundação para a Ciência e Tecnologia (FCT) grant SFRH/BD/143744/2019.

**Competing interests** MLM: none. SR: Research Grants—AbbVie, Galapagos, MSD, Novartis, Pfizer, UCB. Consultancy—AbbVie, Eli Lilly, Janssen, MSD, Novartis, Pfizer, Sanofi, UCB. MvL: none. RS: none. RBML: Consultancy—AbbVie, Eli-Lilly, Janssen, Galapagos, Gilead, Novartis, Pfizer, UCB. Director of Rheumatology Consultancy BVD. MvdS: Speaker—Janssen, Novartis, UCB. Consultancy—Abbvie, Eli Lilly, Novartis, UCB. Research Grants:Janssen, Novartis, UCB. KMF: none. IJB: none. MvO: none. SE: Consultancy—AbbVie, Janssen, Novartis, and UCB. RR: Consultancy: Abbvie, Eli-Lilly, Janssen, Novartis, Pfizer, UCB, Amgen. DvdH: Consultancy—AbbVie, ArgenX, Bayer, BMS, Cyxone, Eisai, Galapagos, Gilead, Glaxo-Smith-Kline, Janssen, Lilly, Novartis, Pfizer, Takeda, UCB Pharma. Director of Imaging Rheumatology bv. FAvG: Research Grants -Novartis. Consultancy—MSD, AbbVie, Novartis and BMS.

**Patient and public involvement** Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

**Patient consent for publication** Not applicable.

**Ethics approval** The SPACE study protocol was approved by the medical ethical committee of the Leiden University Medical Center (reference number P08.105), and the regional committee for medical and health research ethics in South-East Norway (reference number 2014/426). All participants provided written informed consent before enrolment, and coded data were used. Participants gave informed consent to participate in the study before taking part.

**Provenance and peer review** Not commissioned; externally peer reviewed.

**Data availability statement** Data are available upon reasonable request.



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