Axial spondyloarthritis: concept, construct, classification and implications for therapy

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Abstract | The axial spondyloarthritis (axSpA) disease concept has undergone substantial change from when the entity ankylosing spondylitis was defined by the modified New York criteria in 1984. Developments in imaging, therapy and genetics have all contributed to changing the concept of axSpA from one of erosions in the sacroiliac joints to a spectrum of disease with and without changes evident on plain radiographs. Changes to the previously held concept and construct of the disease have also necessitated new classification criteria. The use of MRI, primarily of the sacroiliac joints, has substantially altered the diagnosis and differential diagnosis of axSpA. Many in the axSpA community believe that the current classification criteria lack specificity, and the CLASSIC study is underway to examine this area. Although much about the evolving axSpA disease concept is universally agreed, there remains disagreement about operationalizing aspects of it, such as the requirement for the objective demonstration of axial inflammation for the classification of axSpA. New imaging technologies, biomarkers and genetics data will probably necessitate ongoing revision of axSpA classification criteria. Advances in our knowledge of the biology of axSpA will settle some differences in opinion as to how the disease concept is applied to the classification and diagnosis of patients.

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Axial spondyloarthritis (axSpA) is a disease commonly encountered in the field of rheumatology. The concept of axSpA — that is, the idea of what it is (BOX 1) — is the result of the recognition of the early phases of the disease historically termed ankylosing spondylitis (AS). Historically, in the era of the modified New York criteria, sacroiliac damage had to be evident on plain radiographs to fulfil the criteria for AS[1]. MRI, however, has since opened our eyes to an expanded disease spectrum. The recognition that inflammation is present in the spine and sacroiliac joints prior to the development of erosions revealed an earlier phase of axSpA in an objective way that was not possible previously. The construct of the disease, a type of operational definition, has thus had to evolve to include this expanded spectrum, as illustrated in FIG. 1. This new construct in turn led to the development of new classification criteria for axSpA to enable investigation of this neglected early part of the disease spectrum in a reproducible way. The process of constructing classification criteria highlighted the differing views of academics and clinicians around the world about what constitutes the construct of axSpA.

Despite some disagreement, there is much about the axSpA construct that is universally accepted. First, the concept of non-radiographic axSpA (nr-axSpA) has been introduced to complement the widely known and recognized disease entity AS. axSpA is now recognized as an umbrella term that encompasses both AS and nr-axSpA and a continuum from early or mild to late or severe disease. Information from imaging studies, primarily using MRI, is helping to characterize the range of changes seen in the axial skeleton in health and disease, as only in understanding the full spectrum of manifestations can we understand where 'normal' stops and 'disease' starts. In addition, in many areas in science and medicine we learn so much about the fundamentals of a phenomenon when the ability to influence it becomes available, as with new therapies. In this way, how axSpA responds to treatment and what this response means about its underlying biology has given fruitful insights into what the disease is and what it is not. This Review examines the theoretical basis for axSpA, the concept and the construct, and the resultant classification criteria that have been proposed. In addition, we discuss some of the issues identified in diagnosing and classifying axSpA, and further explore the nature of axSpA in the context of theories such as the philosophical concept of 'natural kinds' and latent class analysis of SpA. Fundamentally redefining a disease is

Key points

- The concept of axial spondyloarthritis (axSpA) has expanded from ankylosing spondylitis with evidence of erosions to a spectrum of disease encompassing non-radiographic axSpA and radiographic axSpA.
- The current classification criteria capture the entire spectrum of axSpA, but many in the field believe they lack specificity; the CLASSIC study is underway to further assess this issue.
- The concept of axSpA is largely agreed upon in the research community, but opinion still diverges about some aspects, for example, the demonstration of objective axial inflammation for axSpA classification.
- The current definition of a positive sacroiliac joint MRI scan lacks specificity for axSpA, as demonstrated in imaging studies of individuals with and without back pain and post-partum women.
- Concepts such as the theory of natural kinds and latent class analysis enable us to further examine the crucial features of the axSpA concept, with sacroiliitis being the core feature.
- Advances in our understanding of the biology of axSpA via novel imaging, genetic and biomarker studies will probably enable the resolution of many current issues in axSpA diagnosis and classification.

not a common occurrence, and in this Review we also explore how this considerable change has affected the recognition of axSpA in the clinic, the use of imaging and access to therapies. We conclude by discussing unanswered questions and potentially fruitful areas of further research.

Spondyloarthritis and axSpA

The SpA umbrella. Any discussion of axSpA must start with reviewing the overarching concept of spondyloarthritis (SpA) as a whole. SpA as a disease label has been applied to presentations of disease that include a wide range of individual elements[2] (FIG. 2). These elements include spinal inflammatory disease, with the pathological feature being a polyenthesitis of the vertebral column. In addition, peripheral inflammatory arthritis, peripheral enthesitis (for example, Achilles tendonitis), dactylitis, anterior uveitis, skin psoriasis, non-specific urethritis, conjunctivitis, aortitis and inflammatory bowel disease (IBD) are also recognizable elements that make up the constellation of features recognized as SpA. These features often, but not always, manifest in loosely defined groups, which historically have then attracted their own (sub)labels, including AS, psoriatic arthritis (PsA), enteropathic arthritis (IBD-associated arthritis) and reactive arthritis (formally referred to as Reiter syndrome[3]). The term 'undifferentiated SpA' has also been used when the constellation of features is more recognizable as SpA than as another entity, such as rheumatoid arthritis, but does not fall within one of the loosely defined (sub)groups, such as PsA[4,5]. At least initially, Behçet disease was also included in the schema of SpA owing to descriptions of polyarthritis, sacroiliitis and seronegativity in series of patients with Behçet disease[6]; however, this classification has not been widely adopted and genetic association studies have failed to find important shared genetic factors[6–8]. Historically, vital motivation for devising the SpA concept was to distinguish PsA from rheumatoid arthritis with coincident psoriasis by the absence of rheumatoid factor, which generated the terms 'seronegative arthritis' and 'seronegative SpA'[9].

However, one of the challenges of this historical (sub)grouping approach has been that patients with similar clinical features can fall into different groups because of a marked overlap of clinical features between the entities. However, some distinct clinical presentations exist that support a 'splitting' approach[10,11]. For example, dactylitis is more closely associated with PsA than with other forms of SpA, and urethritis and conjunctivitis are more closely associated with reactive arthritis. The problems inherent in lumping all spondyloarthropathies together as SpA or splitting SpA into subgroups such as PsA and AS has led to a movement to instead describe (or at least classify) SpA as either axSpA or peripheral SpA (pSpA). This phenotypic approach has some appeal because similar presentations attract the same label. For instance, PsA and enteropathic arthritis, which both manifest as lower limb inflammatory oligoarthritis, would both be referred to as peripheral SpA. As another example, AS and PsA with predominantly axial involvement would both be referred to as axSpA. However, this schema does not address the issue of which descriptor to use when patients have features that fit with both. Therefore, axSpA sits as a phenotypic description of a member of the SpA group with axial involvement. The best way in which to subdivide SpA remains unclear; some aspects of subdivision have demonstrable value but myriad issues arise when subdivision is attempted.

The concept and construct of axSpA. As explained in BOX 1, generally speaking, concepts are ideas that may or may not be solely theoretical, whereas constructs are built-up, operational structures that apply to real instances. The concept of axSpA is universally accepted in rheumatology, as evidenced by its inclusion in academic papers, textbooks and as a topic at clinical and academic meetings[12,13]. Also, doctors seeing patients with the constellation of symptoms that has come to be

Box 1 | **axSpA disease construct, concept, classification and diagnosis**[28,30,90,91]

Concept: a concept is an abstract idea, and can extend to include both known examples and unknown examples. The idea may or may not refer to something that exists in the real world. An example of a concept in the field of axial spondyloarthritis (axSpA) might be the presence of axSpA in the absence of objective signs such as elevated C-reactive protein or sacroiliac joint inflammation on MRI; this concept is an abstract idea that may or may not exist.

Construct: a construct is an abstract idea that contains conceptual elements. Constructs are more specific and less abstract than concepts. Constructs encompass actual cases, whereas concepts extend over both actual and possible cases. axSpA is itself a construct, which includes conceptual elements such as sacroiliac joint inflammation, spinal inflammation and associated features such as anterior uveitis.

Classification criteria: classification criteria provide a standardized definition of a disease to enable the identification of a homogeneous group of cases for research purposes. A set of classification criteria does not capture the whole spectrum of manifestations of a disease, but should be highly specific in order to minimize false-positive errors. An example in axSpA is the 2009 Assessment of SpondyloArthritis International Society (ASAS) classification criteria for axSpA[16].

Diagnostic criteria: diagnostic criteria are a set of signs, symptoms and tests for use in ordinary clinical practice to guide the care of individual patients. They should have near perfect positive and negative predictive value (which is rare). No diagnostic criteria exist for axSpA or SpA.

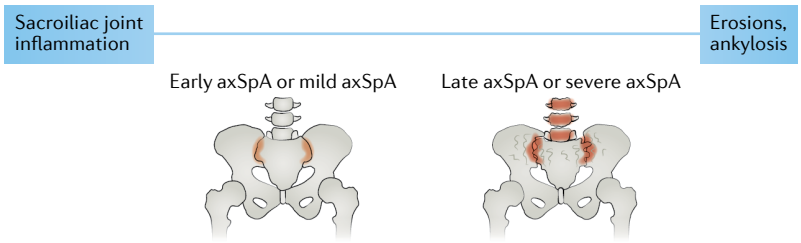

Fig. 1 | **The spectrum of axial spondyloarthritis.** In this illustration, the spectrum of axial spondyloarthritis (axSpA) is shown extending from early (or mild) disease, involving only inflammation in the sacroiliac joints, through to severe (or late) disease with erosive damage in the sacroiliac joints. This schematic is not meant to imply that early and mild disease, or late and severe disease, are synonymous, only that a similar spectrum concept exists.

known as axSpA is a universal experience. Although this manuscript is concerned with the concept and construct of axSpA, from an operational point of view axSpA is viewed as an inflammatory disorder of the axial spine and sacroiliac joints, and nr-axSpA is a subcategory of this disorder, in which plain radiographs of the pelvis do not show radiographic damage that meets the modified New York criteria for AS (grade 2 bilateral or grade 3 unilateral damage), whereas in radiographic axSpA (r-axSpA, or AS) these criteria are met[1].

There is also universal acceptance about the clinical features that constitute the construct (FIG. 2). These elements make up SpA as a whole, and the specific label axSpA is applied when axial involvement is predominantly present. From empirical evidence, however, when these disease elements are applied by clinicians in different settings to reach a diagnosis of axSpA, the resultant patient cohort is remarkably variable demographically, genetically and clinically (see the section below on classification criteria). This variability suggests that the elements of the construct are assigned different relative values by different clinicians when deciding on a diagnosis.

Diagnosis of axSpA

A diagnosis of axSpA is generally considered in the presence of chronic back pain with onset before the age of 45 years, although onset of axSpA after this age has also been described[14,15]. The back pain can be 'inflammatory' in nature (inflammatory back pain) but this is not a rule; in typical axSpA cohorts, 63–92% of patients have inflammatory back pain according to various classification criteria[16,17]. If features typically associated with axSpA are present (FIG. 2), imaging with plain radiography of the pelvis is commonly undertaken and if unequivocal radiographic sacroiliitis is apparent, then often the diagnosis of axSpA is made at this point. If the plain radiograph is normal or equivocal, as it often is because the changes are not advanced or bowel or soft tissue is overlying, then MRI of the sacroiliac joints is often ordered. In cases of axSpA, sacroiliac joint MRI often reveals bone marrow oedema and/or fatty lesions and sometimes structural changes such as erosions. The use of gadolinium contrast agent can also enable visualization of synovitis, capsulitis and enthesitis, although the additive value of using contrast-enhanced MRI for the diagnosis of axSpA has been shown to be negligible[18,19].

Research into the value of sacroiliac joint MRI for the diagnosis of axSpA has yielded a wide range of MRI sensitivity[20]. The only study to use a non-clinician diagnostic standard involved analysis of biopsy-obtained sacroiliac joint tissue, and in this study sacroiliac joint MRI was found to have a sensitivity of 38%[21]. However, sacroiliac joint biopsy has not been extensively studied and is not used clinically in the diagnosis of axSpA; thus, the value of this approach as the gold standard of underlying diagnosis is very uncertain. Lacking a positive sacroiliac joint on MRI the diagnosis might also be made, at least provisionally, on the basis of an elevated C-reactive protein (CRP) concentration (in the absence of any other explanation for this elevation). This point does, however, promote robust debate in the axSpA community. MRI can be repeated with the aim of demonstrating objective inflammatory sacroiliitis, as an elevated CRP concentration lacks specificity in this context[22,23]. However, it should be noted that the value of repeat MRI is largely limited to use in those who are male and/or HLA-B27 positive[22,24,25]. A CRP test can also be repeated following an initial normal result, as 'CRP positivity' varies over time in those with nr-axSpA and it is not uncommon for some individuals with AS to have universally normal CRP concentrations[26]. In the clinical diagnostic process, differential diagnoses are considered (TABLE 1) and alternative explanations for abnormal findings are also considered. For example, an elevated CRP concentration can be found in obese but otherwise healthy patients, and can also arise from other diseases, such as IBD[27].

Once a diagnosis is assigned, the diagnostic label is allocated. The field of rheumatology is currently in transition from using the labels 'AS' and 'nr-axSpA' to using the overall label axSpA with the sub-labels 'r-axSpA' and 'nr-axSpA'. The term AS is losing relevance as the emphasis is now shifting to considering axSpA as a continuum from non-radiographic to radiographic disease (FIG. 3). Notably, this whole label transition now underway is based on the long-held erroneous belief that a diagnosis of AS requires radiographic sacroiliitis. This was not the intention of the modified New York criteria for AS[1], which were called 'diagnostic criteria' but were intended to be applied to groups of patients rather than individuals (BOX 1). The science of criteria construction has developed considerably since the publication of the modified New York criteria in the 1980s. At that time, criteria intended for epidemiological studies such as surveys and prevalence estimates were called diagnostic criteria[1], whereas diagnostic criteria are now constructed for use in individual patients and classification criteria are constructed for groups of patients with a disease[28–30].

Imaging and the axSpA construct

A detailed discussion of imaging in axSpA is outside the scope of this article; an excellent contemporary review on the subject is available elsewhere[31]. The influence of imaging on the concept of axSpA has been to demonstrate the presence of inflammation in the absence of radiographically evident disease. This advance in imaging was arguably the stimulus to re-examine the concept of axSpA, which, as mentioned above, previously required radiographic evidence of damage in the

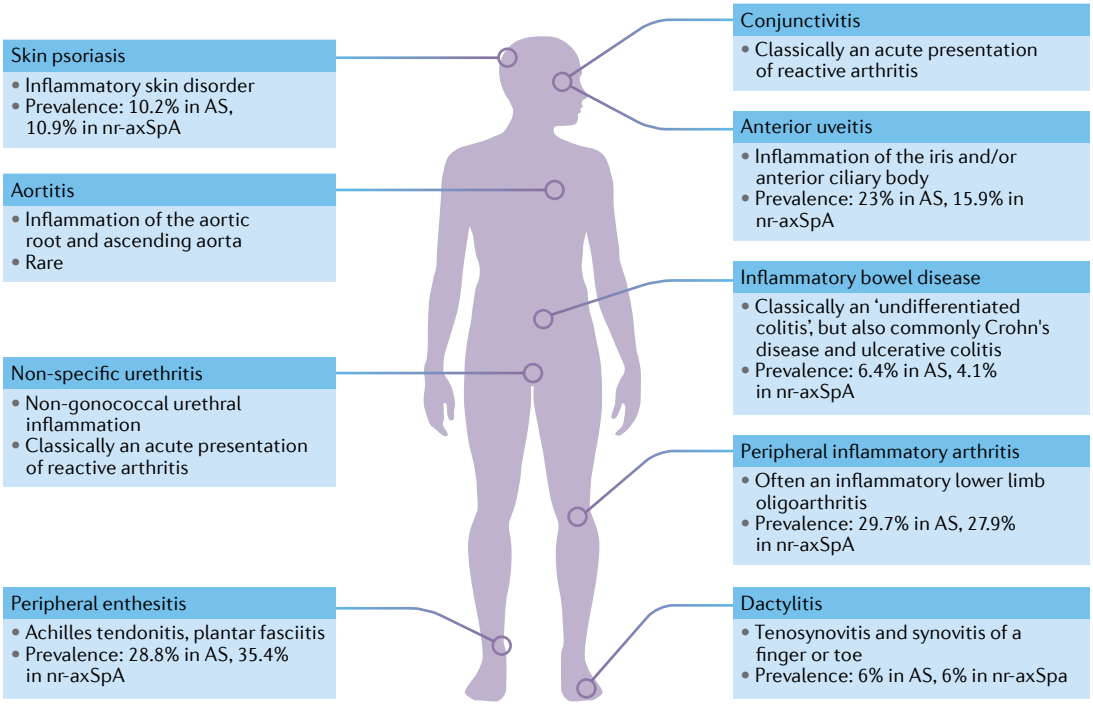

Fig. 2 | **Clinical features of axial spondyloarthritis in addition to axial disease.** The extra-axial features of axial spondyloarthritis (axSpA) are shown. Prevalence rates in ankylosing spondyloarthritis (AS) and non-radiographic axial spondyloarthritis (nr-axSpA) are from de Winter et al.[2].

sacroiliac joints. MRI has consequently improved the confidence of physicians in assigning a diagnosis of axSpA to patients who formerly in clinical practice would have had no objective signs of axial inflammation. This former lack of an objective test for sacroiliac joint inflammation probably contributed to long diagnostic delays in patients with axSpA[32], which were also caused by excessive weight being assigned to the absence of radiographic sacroiliitis and by difficulty with the interpretation of plain radiographs of the sacroiliac joints. The application of MRI has now highlighted that little weight should be given to negative plain radiography findings.

The use of MRI has enabled us to move to a state where axSpA can be more confidently identified at an earlier stage than when sacroiliac joint erosions is demonstrated on plain radiographs. This state, however, has introduced additional issues to be addressed. Significant and/or severe axSpA does not present a diagnostic conundrum; however, the use of sensitive imaging techniques has presented challenges such as identifying where normal variation stops and disease starts.

There remains a high degree of uncertainty about the implications of 'abnormal' findings on MRI. The issue now is to differentiate early or mild disease from normal variation in the population. Erosions on plain radiographs are highly specific for AS (or r-axSpA, to use the emerging terminology), but when this highly specific feature is not required for diagnosis or classification (because the concept of axSpA is now one of axial inflammation and does not require axial joint damage) then diagnostic certainty is reduced. This reduction in certainty is because the symptom of inflammatory back pain lacks specificity, inflammatory markers can commonly be normal and rates of 'abnormal' sacroiliac joint MRI scans are high in non-axSpA populations both with and without back pain[17,26,33–38] (TABLE 2).

The changing classification of axSpA

Historical and current classification. Classification criteria are a research tool that should promote homogeneity among groups of patients and should be applied to patients in whom a clinical diagnosis has already been made[30]. Criteria for classification should have a high specificity (>90%) in order to avoid misclassification (that is, the inclusion of patients who do not have the disease).

As the concept of AS–axSpA has changed considerably over the past few decades, so have the proposed classification criteria[1,16,39,40] (FIG. 4). Radiographic sacroiliitis has long been regarded as the hallmark of the disease, and was required to fulfil either the original or the modified New York criteria, thus reflecting the prevailing view of AS as a disease that causes radiographic damage evident on plain radiographs[1,16,39] (FIG. 4). In retrospect, the new, broader concept of axSpA first emerged in 1985. In a study of first-degree relatives of HLA-B27-positive patients with AS, the presence of "spondylitic disease without radiologic evidence of sacroiliitis" was reported in some of these first-degree relatives, many of whom were female[41]. Despite having some of the clinical features of SpA, these relatives did not fulfil the modified New York criteria[1].

The new concept is that only a proportion of patients with nr-axSpA will progress to r-axSpA (AS); the rest will continue to have nr-axSpA or the disease will spontaneously resolve (FIG. 3). Rates of progression from nr-axSpA to r-axSpA (AS) have been reported in

Table 1 | **Differential diagnosis of axial spondyloarthritis**

Diagnosis	Descriptor
Non-specific low back pain	Chronic back pain with normal or abnormal imaging
Diffuse idiopathic skeletal hyperostosis	Ligamentous calcifications and/or ossifications around the spine
Fracture	Fracture of the vertebral body, spinous process or transverse process and osteoporotic stress fracture
Degenerative arthritis	Back pain, and abnormal spinal imaging
Septic arthritis of the sacroiliac joint and/or spine	Back pain, elevated inflammatory markers and/or abnormal imaging
Crystal arthritis	Inflammatory crystal arthritis that can affect the spinal column
Osteitis condensans ilii	Back pain and abnormal sacroiliac joint imaging post-pregnancy

different cohorts as 1–12% over 2 years, 6–46% over 2–9 years and 26–59% over >10 years[42–51].

In recognition of the broadening concept of axSpA, the 2009 Assessment of SpondyloArthritis International Society (ASAS) classification criteria were developed for the full spectrum of axSpA[16,30]. However, these criteria are not sufficiently specific[16,52,53]: their sensitivity and specificity were reported as 82.9% and 84.4%, respectively[16,52]. Which features help to explain the low specificity of the current ASAS classification criteria for axSpA? It can be concluded that the lack of specificity of these criteria reflects the way they were derived. Briefly, the criteria were derived first by experts assessing 71 'paper patients' (theoretical case vignettes), most of which lacked radiographic sacroiliitis. An additional 649 cases were contributed by ASAS members from 25 centres in 16 countries; these patients had to have had back pain for >3 months with an onset prior to the age of 45. In their routine clinical work-up, 391 (60%) of the 649 patients were diagnosed with axSpA. Among these 391 patients, 52% were male, 66% were HLA-B27 positive, 62% had a normal CRP concentration and 30% met the modified New York criteria for AS. Of the remaining non-axSpA patients, 28% were HLA-B27 positive, three times the background population prevalence of HLA-B27 in white populations. The variance between contributing centres in HLA-B27 was not reported in these papers.

Of note, a subsequent study of genetic profiling[54] in a subset of the patient cohort used in developing the ASAS axSpA classification criteria provides some clues to understanding the low (84.4%) specificity of those criteria[16,52,54]. In this study, the patients, who were from nine centres in six countries, were classified according to the ASAS criteria for axSpA and, using the clinical data supplied, further classified according to the modified New York criteria for AS[1,54]. The results indicate that different centres had very different views on how to arrive at a clinical diagnosis, as evidenced by the differing prevalence of HLA-B27 between the centres (even within the same country), which might reflect either issues with recruiting into the cohort or differences between physicians in what they consider the axSpA construct to be. For example, the HLA-B27 prevalence ranged from 21% to 70%, the proportion of female patients from 5% to 71%, the proportion of patients with axSpA was between 37% and 90%, and the proportion of patients meeting the modified New York criteria ranged from 0% to 48%[54].

In the presence of a gold standard for a disease (for example, in gout, the clear demonstration of urate crystals in a sterile inflamed joint) one might expect a correct diagnosis in all cases, and classification criteria for that disease would have 100% specificity. However, the situation is quite different for a disease such as axSpA, with a broader concept of disease that newly includes the notion of non-radiographic disease, a condition for which there is no gold standard. In this context, the diagnosis can only be based on expert opinion, taking into consideration a plethora of clinical signs and symptoms, a few highly non-specific biomarkers (HLA-B27 and CRP concentration) and imaging results (MRI)[37]. Therefore, it seems very probable that the demonstrated heterogeneity in establishing a clinical diagnosis of axSpA on the basis of experts' opinions is responsible for the subsequent substantial lack of specificity of the ASAS classification criteria for axSpA.

Fundamental to some of the disagreements in the axSpA community is the idea that axSpA can be classified in the absence of objective signs of inflammation. Therefore, it is important to address the issues around the lack of specificity of sacroiliac joint MRI findings. Thus, for some the axSpA construct requires objective inflammation (and therefore it is definitely required for classification) and for others it does not.

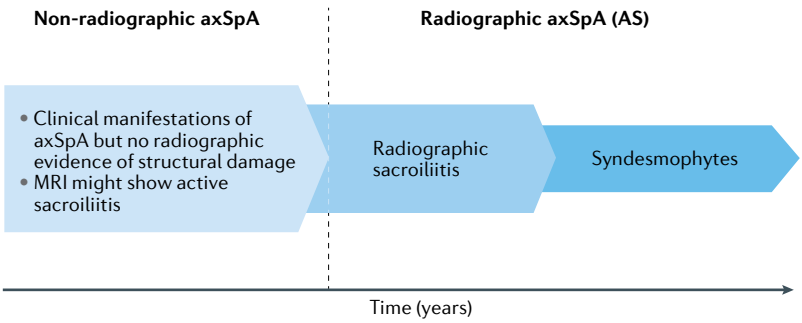

Fig. 3 | **The concept of axial spondyloarthritis.** The concept of axial spondyloarthritis (axSpA) now encompasses non-radiographic (nr-axSpA) and radiographic axSpA (or ankylosing spondylitis (AS)). The arbitrary division between these two entities is becoming less relevant clinically. The decreasing sizes of the three chevrons emphasizes that a decreasing proportion of patients progress to each subsequent stage. In other words, only some patients with nr-axSpA will develop radiographic axSpA (AS), whereas others might continue to have nr-axSpA, perhaps forever, or have a self-limiting disease course. This figure also illustrates that not all patients with radiographic sacroiliitis progress to form syndesmophytes and consequently spinal ankylosis. Adapted with permission from Rudwaleit et al.[30], Wiley.

Diseases as natural kinds. Thinking about SpA as a natural kind (BOX 2) might help to clarify the distinctions between the disorders included under the SpA umbrella and how to identify the cluster of properties that are characteristic of each disease kind. For example, radiographic ankylosis of the sacroiliac joints is a pathognomonic feature of AS, yet many people with AS do not and never will exhibit this degree of sacroiliitis and others who are diagnosed in the early stage of disease

do not manifest any degree of radiographic sacroiliitis[50]. Similarly, HLA-B27 is found in more people without SpA than with SpA but HLA-B27 positivity is considered to be a disposition towards certain modes of antigen presentation that can manifest in AS[8]. The precise label (AS or axSpA) is less important than the concept of the disease as a kind. On the other hand, the disposition to sacroiliac joint ankylosis is not especially necessary or sufficient for PsA, whereas the disposition towards psoriasis is much more important. The recognition that it is possible to fulfil the CASPAR classification criteria for PsA without actually having manifest psoriasis underscores the recognition that it is the disposition towards psoriasis, rather than its manifestation, that is most salient[55].

Latent class analysis. Latent class analysis is a modelling methodology that can be used to classify items. The basic tenet of this methodology is that unobserved (latent) categories (classes) in a system or model differ by observable characteristics[56]. Class membership can be estimated using assumptions of independence of the observable variables. The latent class analysis of patients with SpA within the DEvenir des Spondylarthropathies Indifférenciées Récentes (DESIR) and the SpondyloArthritis Caught Early (SPACE) cohorts provides some support for a dispositional perspective[57]. These cohorts include people with inflammatory back pain and clinically diagnosed axSpA (DESIR) and those with chronic low back pain with onset before age 45 years (SPACE). Latent class analysis of the SPACE cohort identified four clusters of individuals: those with axial disease, which was most strongly associated with imaging evidence of sacroiliitis and HLA-B27; those at risk of disease, which was most strongly associated with a family history

Table 2 | **Studies reporting positive MRI scans in populations with and without axSpA**

Study population	*n*	Sex	Back pain	Proportion with a positive MRI scan[a]	Study	Ref.
Healthy men	29	Male	No	0%	Seven et al. (2019)	33
Hospital cleaning staff	26	Female	No	4%	Seven et al. (2019)	33
Long-distance runners	23	Male and female	No	4%	Seven et al. (2019)	33
Individuals with chronic back pain	47	Male and female	Yes	6%	De Winter et al. (2018)	34
Individuals with lumbar disc herniation	25	Male and female	Yes	8%	Seven et al. (2019)	33
Runners	24	Male and female	No	13%	De Winter et al. (2019)	34
Participants in a community health study	793	Male and female	57%[b]	17%	Baraliakos et al. (2019)	35
Women without post-partum buttock and/or pelvic pain	14	Female	No	21%	Seven et al. (2019)	33
Individuals with chronic back pain	1,020	Male and female	Yes	21%	Arnbak et al. (2016)	89
Healthy individuals	47	Male and female	No	23%	De Winter et al. (2018)	34
Runners (post-running)	20	Male and female	NS	30%	Weber et al. (2018)	37
Runners (pre-running)	20	Male and female	NS	35%	Weber et al. (2018)	37
Military recruits (at baseline)	11	Male and female	No	41%	Varkas et al. (2018)	36
Women with post-partum buttock and/or pelvic pain	46	Female	Yes	41%	Seven et al. (2019)	33
Elite ice hockey players	22	Male	NS	41%	Weber et al. (2018)	37
Military recruits after 6 weeks' training	11	Male and female	No	50%	Varkas et al. (2018)	36
Individuals with axSpA	41	Male and female	Yes	56%	Seven et al. (2019)	33
Women with post-partum back pain	7	Female	Yes	57%	De Winter et al. (2018)	34
Post-partum women within 10 days of vaginal delivery	25	Female	31%	64%	Renson et al. (2020)	38
Individuals with axSpA	47	Male and female	Yes	92%	De Winter et al. (2018)	34

axSpA, axial spondyloarthritis; NRS, numeric rating scale; NS, not specified; SpA, spondyloarthritis. [a]According to the current Assessment of SpondyloArthritis International Society definition of a positive sacroiliac joint MRI for the classification of SpA[20]. [b]On a 0–10 NRS for back pain, of 0, 28% NRS between 1 and 3, and 29% NRS ≥4.

Rome criteria for AS (1961) (ref.[40])

Clinical criteria:

1. Low back pain and stiffness of >3 months' duration that is not relieved by rest.
2. Pain and stiffness in the thoracic region.
3. Limited motion in the lumbar spine.
4. Limited chest expansion.
5. History or evidence of iritis or its sequelae.

Radiological criterion:

6. X-ray showing bilateral sacroiliac changes characteristic of AS (this would exclude bilateral osteoarthrosis of sacroiliac joints).

Definite diagnosis of AS:
- Four of the five clinical criteria are fulfilled; or
- Radiological criterion plus one other criterion are fulfilled.

New York criteria for AS (1968) (ref.[39])

Clinical criteria:

1. Limitation of motion of the lumbar spine in all 3 planes (anterior flexion, lateral flexion, and extension)
2. A history of pain or the presence of pain at the dorsolumbar junction or in the lumbar spine.
3. Limitation of chest expansion to 1 inch (2.5cm) or less, measured at the level of the fourth intercostal space.

Definite AS:
- Grade 3–4 bilateral sacroiliitis associated with at least 1 clinical criterion; or
- Grade 3–4 unilateral or grade 2 bilateral sacroiliitis associated with clinical criterion 1 or with both clinical criteria 2 and 3.

Probable AS:
- Grade 3–4 bilateral sacroiliitis without any signs or symptoms satisfying the clinical criteria.

Modified New York criteria for AS (1984) (ref.[1])

Clinical criteria:

1. Low back pain and stiffness for more than 3 months, which improves with exercise but is not relieved by rest.
2. Limitation of motion of the lumbar spine in both the sagittal and frontal planes.
3. Limitation of chest expansion relative to normal values corrected for age and sex.

Radiological criterion:
- Grade 2–4 bilateral or grade 3–4 unilateral sacroiliitis.

Definite AS:
- Radiological criterion fulfilled in association with at least one clinical criterion.

Probable AS:
- Three clinical criteria are fulfilled; or
- Radiological criterion is fulfilled without any signs or symptoms satisfying the clinical criteria. (Other causes of sacroiliitis should be considered.)

ASAS criteria for axSpA (2009) (ref.[16])

Entry criterion:
- Back pain of ≥3 months' duration and age at onset <45 years.

Classification of axSpA by imaging arm:
- Sacroiliitis on imaging and at least one SpA feature.

Classification of axSpA by HLA-B27 arm:
- HLA-B27-positive plus two or more SpA features.

SpA features:
- Inflammatory back pain, arthritis, heel enthesitis, uveitis, dactylitis, psoriasis, Crohn's disease or ulcerative colitis, good response to NSAIDs, family history of SpA, HLA-B27, elevated CRP concentration.

Sacroiliitis on imaging:
- Active (acute) inflammation on MRI highly suggestive of sacroiliitis associated with SpA; or
- Definite radiographic sacroiliitis as per the modified New York criteria.

Fig. 4 | **Classification criteria for axSpA.** Proposed classification criteria for ankylosing spondylitis (AS) and axial spondyloarthritis (axSpA) have changed considerably over the past few decades, reflecting changes in the concept of the disease. ASAS, Assessment of SpondyloArthritis International Society; CRP, C-reactive protein.

of SpA and HLA-B27; those with no SpA; and those with back pain as well as peripheral arthritis and/or enthesitis. Furthermore, these phenotypes tended to remain stable over time in the DESIR cohort[57].

For the disease entity of AS–axSpA, it seems that the disposition towards sacroiliitis is crucial to the concept of this disease. Sacroiliitis is central to the modified New York criteria[1]. For the 2009 ASAS axSpA classification criteria, features contributing to the classification of axSpA included radiographic sacroiliitis, which had an odds ratio (OR) of 32.3, and active inflammation of sacroiliac joints on MRI, which had an OR of 66.7; by comparison, all other features had ORs of approximately 1–7 (REF.[16]). These ORs also suggest that clinicians feel that sacroiliitis is the crucial feature of the concept of axSpA.

Towards improving axSpA classification. A way forward for improving the specificity of classification criteria to approach 100% would be to develop new classification criteria, beginning with a thorough discussion among their developers with the aim of building consensus about the diagnosis using a wide variety of real patients. One should define the construct of the disease: which clinical and biologic dispositions characterize the disease to be classified and which features would be aberrant? This approach seems particularly important to consider in the context of a new, broadened disease concept in the absence of a gold standard. The consensus about the disease construct should of course be properly assessed by thorough appraisal of observer variation. Other issues to be addressed to improve specificity include the need for standardized diagnostic work-up and comparability across referral patterns, to avoid or reduce diagnostic bias.

One issue that has generated considerable debate is that, at its core, axSpA is defined by axial inflammation, more specifically sacroiliac joint inflammation. However, the ASAS 2009 criteria enable classification of axSpA without objective evidence of axial inflammation. For the purposes of diagnosis and the inherent pragmatism that it requires, this issue is not so important. However, to be true to the aim of classification criteria — that is, to assemble a homogeneous group of patients for clinical study — classification of axSpA without objective evidence of inflammation moves away from the accepted core concept of the disease. Newer imaging techniques and/or biomarkers might enable us to demonstrate sacroiliac joint inflammation in different ways, but at present the absence of objective evidence is a challenge to the long-held concept of axial inflammation.

The basic framework for classification criteria in rheumatology, which has generally been followed since the development of the 2010 ACR–EULAR rheumatoid arthritis criteria, consists of the following elements: a statement regarding to whom the criteria should be applied; specification of the elements or items of the criteria; determination of the relative weight of the individual elements, and a statement of how the elements of the criteria should be combined to arrive at a (usually) binary result (that is, the presence or absence of the health condition of interest); and determination of the accuracy of all the criteria. Overall accuracy is generally expressed as the proportion of people who have the health condition of interest who are also deemed to have the condition according to the criteria (sensitivity), and as the proportion of people do not have the health condition who are also deemed to not to have the condition

Box 2 | **Natural kinds**

In philosophy, 'natural kinds' refer to the idea that some objects can be classified and resemble each other in important ways[92]. The classical example of natural kinds in physical sciences are the chemical elements in the periodic table: each element is a natural kind. An understanding of what it is to be a natural kind might help with disease nosology and conceptualization of disease kinds, if it were the case that diseases are in fact natural kinds. Although that claim is not altogether settled, it is still potentially useful to consider spondyloarthritis conditions through this lens.

One important concept of natural kinds is the homeostatic property cluster (HPC) theory of kinds, which roughly holds that kind membership is about sharing a cluster of properties and that causal forces exist that explain the co-instantiation of these property clusters[93]. When applying the HPC concept of natural kinds to disease, a useful extension is to consider a key property of the kind to be a disposition, rather than a manifestation. For example, radiographic juxta-articular erosions are a characteristic manifestation of rheumatoid arthritis, but not all patients with rheumatoid arthritis exhibit this manifestation, especially in early-stage disease. The disposition towards erosive disease can be considered one of the cluster of properties that characterize rheumatoid arthritis. Similarly, acute anterior uveitis is characteristic of SpA diseases, but only occurs in a minority of cases[94]. Thus, a disposition towards developing acute anterior uveitis is a member of the HPC.

according to the criteria (specificity). Some of these elements can be derived from empirical data, but some rely greatly on expert knowledge and opinion.

To independently validate the 2009 ASAS criteria, the Classification of Axial SpondyloarthritiS Inception Cohort (CLASSIC) study has been established[58]. This multinational study will largely replicate the methods of the original ASAS classification study[16]. The CLASSIC study investigators aim to recruit 1,000 consecutive patients referred to a rheumatologist because of back pain for >3 months and who are <45 years of age[58]. If the specificity of the ASAS criteria is ≥90% and the sensitivity ≥75%, no further investigation of the criteria will reportedly be undertaken; however, if the criteria do not meet these thresholds then refinements will reportedly be made and tested[59]. The current ASAS criteria for axSpA were not derived using relative weighting of each element of the disease, and this technique might be one to consider to better align the construct of axSpA with the resultant classification criteria.

Therapy and the axSpA construct

In trying to clarify where normal variation ends and disease begins, the response of symptoms to effective therapies can potentially provide insight. Most patients with non-inflammatory causes of low back pain do not respond well to treatment with TNF inhibitors[60]; thus, it is possible that response to TNF inhibitors could be helpful in distinguishing normal variation on MRI from axSpA. In clinical trials of adalimumab, golimumab and etanercept, patients with axSpA with elevated CRP concentration and/or sacroiliitis on MRI at baseline responded better to treatment than those with a normal CRP concentration and/or no sacroiliitis on MRI[61–64].

Advisory bodies for single-payer systems such as The National Institute for Health and Care Excellence in the UK and the Pharmaceutical Benefits Advisory Committee in Australia have made increasingly rigorous assessments of applications to licence and fund new therapies for axSpA[65,66]. The FDA has also meticulously assessed applications to register biologics for the treatment of nr-axSpA, and after holding public hearings initially elected not to register the TNF inhibitors adalimumab and certolizumab pegol for this indication on the basis of the trial data presented[64,67,68]. Questions raised by the FDA and EMA when examining applications for the registration of biologics for nr-axSpA concerned the natural history of nr-axSpA, the rate of spontaneous remission and the potential for over-treatment with TNF inhibitors[67,69]. Although the response rates in patients without sacroiliitis on MRI and/or normal CRP concentration were lower than in those with objective signs of disease, they were not numerically similar to placebo. Is this observation a demonstration that the axSpA construct should apply in the absence of an elevated CRP concentration or an abnormal MRI? Is this mild disease, early disease or both, and what is the prognosis of this type of disease? These are questions that remain unanswered at present.

Another trial of certolizumab pegol in nr-axSpA has since been performed and in 2019 the FDA approved this agent for use in the treatment of nr-axSpA[70]. The issue around the registration of certolizumab had centred on how trial participants' plain pelvic radiographs were read in the RAPID-axSpA trial[68]. Initially, radiographs were read locally at each centre where patients were enrolled and managed. However, when this procedure was revised and radiographs were read centrally by a small group of expert readers, an appreciable proportion of patients had their films assessed as AS rather than nr-axSpA; as the reported cohort included a proportion of patients with AS[67] the FDA therefore felt that the outcome of the trial could not be relied upon as a good assessment of the efficacy of certolizumab in nr-axSpA. This incident is an example of the limitations of plain radiographs of the sacroiliac joints, the examination of which has very low inter-reader and intra-reader reliability, and which are increasingly seen as having little relevance to the wider concept of axSpA[31]. The reduced therapeutic response to TNF inhibitors in those who lack objective evidence of inflammation led regulators (such as the EMA and FDA) and agencies that make funding recommendations (for example, the Pharmaceutical Benefits Advisory Committee) to stipulate the presence of inflammation as a requirement for treatment with TNF inhibitors for nr-axSpA when the medications were first registered[65].

Consensus, disagreement and questions

We have moved to a new era in which it is broadly agreed that axial inflammation, and specifically sacroiliac joint inflammation, is a core element of the axSpA construct. However, there remains a divergence of opinion concerning individuals who have symptoms that could be attributed to axSpA but who lack MRI or CRP evidence of axial inflammation. That such patients could potentially fulfil the 2009 ASAS classification criteria for nr-axSpA has caused debate in the SpA community, as some do not believe that patients without objective evidence of inflammation should be included in the axSpA construct[53,67,71–74]. Therefore, the 2009 ASAS classification criteria are believed by some to lack specificity[53].

Owing to the absence of explicit diagnostic criteria for axSpA, classification criteria have, at times, been presented as an alternative. However, diagnosis is not their primary purpose. As mentioned above, the sensitivity and specificity of the 2009 ASAS axSpA criteria are 83% and 84%, respectively, which means that an appreciable proportion of axSpA cases are missed, or individuals without axSpA are included, when classification criteria are used directly in the clinic; classification criteria also do not exclude 'disease mimickers' or 'look-alikes'[30,59,75].

The unanswered questions in the field revolve firstly around the specificity and sensitivity of sacroiliac joint MRI. A growing body of evidence suggests that healthy individuals have a high rate of positive sacroiliac joint MRI (TABLE 2), as it is currently defined by ASAS[20]; in some subgroups, such as post-partum women, this rate can be as high as 64%[38]. Part of the issue could be the lack of familiarity of radiologists with axSpA imaging, or the scanning technique used, but more important is the lack of specificity of the ASAS definition of a positive sacroiliac joint MRI scan[20,76–80]. There is evidence that including structural or erosive change, in addition to evidence of inflammatory activity (bone marrow oedema), increases the specificity of the definition[81,82]. Progress in this area is already being made via proposed changes to imaging protocols[83]. Second, and linked to the first point, is the question of the value (or not) of scanning the spine in addition to the sacroiliac joints. To date, the conclusion has been that there is a limited role for this additional imaging; however, some evidence suggests that a proportion of patients have spine-limited disease that spares the sacroiliac joints[84–86]. Third, what is the natural history of nr-axSpA, including prognostic factors, rates of spontaneous remission and risk factors for progression? Finally, the role of other biomarkers such as genetics and the microbiome[87,88] requires better clarification. Research aimed at addressing these questions could provide clarity on prognosis and identify predictors of response to therapy, as well as potential new therapies.

Conclusions

Owing to advances in imaging techniques, the concept of axSpA has expanded to include axial inflammation that does not (or has not) caused erosive damage. This shift has enabled the recognition and treatment of disease in many people who previously would not have received a diagnosis of axSpA. It has also brought a new set of challenges, primarily distinguishing normal variation from early or mild disease; research to try to clarify this difficult issue is ongoing. The intensity of interest on the part of the public, industry and academia is encouraging, as axSpA has been blighted by long diagnostic delays and a lack of effective treatment since the disease has been recognized. This situation is starting to change, but there is certainly ample scope to improve further for the benefit of our patients.

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1. van der Linden, S., Valkenburg, H. A. & Cats, A. Evaluation of diagnostic criteria for ankylosing spondylitis. A proposal for modification of the New York criteria. *Arthritis Rheum.* **27**, 361–368 (1984).
2. de Winter, J. J. et al. Prevalence of peripheral and extra-articular disease in ankylosing spondylitis versus non-radiographic axial spondyloarthritis: a meta-analysis. *Arthritis Res. Ther.* **18**, 196 (2016).
3. Panush, R. S., Paraschiv, D. & Dorff, R. E. The tainted legacy of Hans Reiter. *Semin. Arthritis Rheum.* **32**, 231–236 (2003).
4. Dougados, M. et al. The European Spondylarthropathy Study Group preliminary criteria for the classification of spondylarthropathy. *Arthritis Rheum.* **34**, 1218–1227 (1991).
5. Zochling, J., Brandt, J. & Braun, J. The current concept of spondyloarthritis with special emphasis on undifferentiated spondyloarthritis. *Rheumatology* **44**, 1483–1491 (2005).
6. Moll, J. M. et al. Associations between ankylosing spondylitis, psoriatic arthritis, Reiter's disease, the intestinal arthropathies, and Behcet's syndrome. *Medicine* **53**, 343–364 (1974).
7. Kirino, Y. et al. Genome-wide association analysis identifies new susceptibility loci for Behcet's disease and epistasis between *HLA-B*51* and *ERAP1*. *Nat. Genet.* **45**, 202–207 (2013).
8. International Genetics of Ankylosing Spondylitis Consortium (IGAS). et al. Identification of multiple risk variants for ankylosing spondylitis through high-density genotyping of immune-related loci. *Nat. Genet.* **45**, 730–738 (2013).
9. Wright, V. & Moll, J. The Meaning of Seronegativity and Seropositivity, in Seronegative Polyarthritis. (Elsevier/North-Holland Biomedical Press, 1976).
10. Nash, P. et al. Seronegative spondyloarthropathies: to lump or split? *Ann. Rheum. Dis.* **64**, ii9–ii13 (2005).
11. Taylor, W. J. & Robinson, P. C. Classification criteria: peripheral spondyloarthropathy and psoriatic arthritis. *Curr. Rheumatol. Rep.* **15**, 317 (2013).
12. Sieper, J. & Poddubnyy, D. Axial spondyloarthritis. *Lancet* **390**, 73–84 (2017).
13. Taurog, J. D., Chhabra, A. & Colbert, R. A. Ankylosing spondylitis and axial spondyloarthritis. *N. Engl. J. Med.* **374**, 2563–2574 (2016).
14. Olivieri, I. et al. Spondyloarthritis with onset after age 45. *Curr. Rheumatol. Rep.* **15**, 374 (2013).
15. Toussirot, E. Late-onset ankylosing spondylitis and spondylarthritis: an update on clinical manifestations, differential diagnosis and pharmacological therapies. *Drugs Aging* **27**, 523–531 (2010).
16. Rudwaleit, M. et al. The development of Assessment of SpondyloArthritis International Society classification criteria for axial spondyloarthritis (part II): validation and final selection. *Ann. Rheum. Dis.* **68**, 777–783 (2009).
17. Poddubnyy, D. et al. Diagnostic accuracy of inflammatory back pain for axial spondyloarthritis in rheumatological care. *RMD Open* **4**, e000825 (2018).
18. Hermann, K. G. et al. Magnetic resonance imaging of inflammatory lesions in the spine in ankylosing spondylitis clinical trials: is paramagnetic contrast medium necessary? *J. Rheumatol.* **32**, 2056–2060 (2005).
19. de Hooge, M. et al. Magnetic resonance imaging of the sacroiliac joints in the early detection of spondyloarthritis: no added value of gadolinium compared with short tau inversion recovery sequence. *Rheumatology* **52**, 1220–1224 (2013).
20. Maksymowych, W. P. et al. MRI lesions in the sacroiliac joints of patients with spondyloarthritis: an update of definitions and validation by the ASAS MRI working group. *Ann. Rheum. Dis.* **78**, 1550–1558 (2019).
21. Gong, Y. et al. Ten years' experience with needle biopsy in the early diagnosis of sacroiliitis. *Arthritis Rheum.* **64**, 1399–1406 (2012).
22. Bakker, P. A. et al. Is it useful to repeat MRI of the sacroiliac joints after three months or one year in the diagnostic process of patients with chronic back pain suspected of axial spondyloarthritis? *Arthritis Rheumatol.* **71**, 382–391 (2019).
23. Sengupta, R. et al. Short-term repeat magnetic resonance imaging scans in suspected early axial spondyloarthritis are clinically relevant only in HLA-B27-positive male subjects. *J. Rheumatol.* **45**, 202–205 (2018).
24. Rusman, T. et al. Presence of active MRI lesions in patients suspected of non-radiographic axial spondyloarthritis with high disease activity and chance at conversion after a 6-month follow-up period. *Clin. Rheumatol.* **39**, 1521–1529 (2020).
25. van Onna, M. et al. HLA-B27 and gender independently determine the likelihood of a positive MRI of the sacroiliac joints in patients with early inflammatory back pain: a 2-year MRI follow-up study. *Ann. Rheum. Dis.* **70**, 1981–1985 (2011).
26. Landewe, R. et al. A single determination of C-reactive protein does not suffice to declare a patient with a diagnosis of axial spondyloarthritis 'CRP-negative'. *Arthritis Res. Ther.* **20**, 209 (2018).
27. Visser, M. et al. Elevated C-reactive protein levels in overweight and obese adults. *JAMA* **282**, 2131–2135 (1999).
28. Aggarwal, R. et al. Distinctions between diagnostic and classification criteria? *Arthritis Care Res.* **67**, 891–897 (2015).
29. Khan, M. A. & van der Linden, S. Axial spondyloarthritis: a better name for an old disease: a step toward uniform reporting. *ACR Open Rheumatol.* **1**, 336–339 (2019).
30. Rudwaleit, M., Khan, M. A. & Sieper, J. The challenge of diagnosis and classification in early ankylosing spondylitis: do we need new criteria? *Arthritis Rheum.* **52**, 1000–1008 (2005).
31. Maksymowych, W. P. The role of imaging in the diagnosis and management of axial spondyloarthritis. *Nat. Rev. Rheumatol.* **15**, 657–672 (2019).
32. Feldtkeller, E. et al. Age at disease onset and diagnosis delay in HLA-B27 negative vs. positive patients with ankylosing spondylitis. *Rheumatol. Int.* **23**, 61–66 (2003).
33. Seven, S. et al. Magnetic resonance imaging of lesions in the sacroiliac joints for differentiation of patients with axial spondyloarthritis from control subjects with or without pelvic or buttock pain: a prospective, cross-sectional study of 204 participants. *Arthritis Rheumatol.* **71**, 2034–2046 (2019).
34. de Winter, J. et al. Magnetic resonance imaging of the sacroiliac joints indicating sacroiliitis according to the Assessment of Spondyloarthritis International Society definition in healthy individuals, runners, and women with postpartum back pain. *Arthritis Rheumatol.* **70**, 1042–1048 (2018).
35. Baraliakos, X. et al. Frequency of MRI changes suggestive of axial spondyloarthritis in the axial

skeleton in a large population-based cohort of individuals aged <45 years. *Ann. Rheum. Dis.* **79**, 186–192 (2020).
36. Varkas, G. et al. Effect of mechanical stress on magnetic resonance imaging of the sacroiliac joints: assessment of military recruits by magnetic resonance imaging study. *Rheumatology* **57**, 508–513 (2018).
37. Weber, U. et al. Frequency and anatomic distribution of magnetic resonance imaging features in the sacroiliac joints of young athletes: exploring "background noise" toward a data-driven definition of sacroiliitis in early spondyloarthritis. *Arthritis Rheumatol.* **70**, 736–745 (2018).
38. Renson, T. et al. High prevalence of spondyloarthritis-like MRI lesions in postpartum women: a prospective analysis in relation to maternal, child and birth characteristics. *Ann. Rheum. Dis.* **79**, 929–934 (2020).
39. Bennett, P. & Wood, P. Population studies of the rheumatic diseases; Proceedings of the Third International Symposium, New York, June 5th–10th, 1966. (Excerpta Medica Foundation, 1968)
40. Kellgren, J., Jeffrey, M. & Ball, J. The epidemiology of chronic rheumatism. Vol. 1 (Blackwell Scientific Publications, 1963).
41. Khan, M. A. et al. Spondylitic disease without radiologic evidence of sacroiliitis in relatives of HLA-B27 positive ankylosing spondylitis patients. *Arthritis Rheum.* **28**, 40–43 (1985).
42. Sampaio-Barros, P. D. et al. Undifferentiated spondyloarthritis: a longterm followup. *J. Rheumatol.* **37**, 1195–1199 (2010).
43. Poddubnyy, D. et al. Rates and predictors of radiographic sacroiliitis progression over 2 years in patients with axial spondyloarthritis. *Ann. Rheum. Dis.* **70**, 1369–74 (2011).
44. Sany, J. et al. Unclassified HLA-B27 inflammatory rheumatic diseases: followup of 23 patients. *Arthritis Rheum.* **23**, 258–259 (1980).
45. Schattenkirchner, M. & Kruger, K. Natural course and prognosis of HLA-B27-positive oligoarthritis. *Clin. Rheumatol.* **6**, 83–86 (1987).
46. Mau, W. et al. Clinical features and prognosis of patients with possible ankylosing spondylitis. Results of a 10-year followup. *J. Rheumatol.* **15**, 1109–1114 (1988).
47. Oostveen, J. et al. Early detection of sacroiliitis on magnetic resonance imaging and subsequent development of sacroiliitis on plain radiography. A prospective, longitudinal study. *J. Rheumatol.* **26**, 1953–1958 (1999).
48. Bennett, A. N. et al. Severity of baseline magnetic resonance imaging-evident sacroiliitis and HLA-B27 status in early inflammatory back pain predict radiographically evident ankylosing spondylitis at eight years. *Arthritis Rheum.* **58**, 3413–3418 (2008).
49. Dougados, M. et al. Rate and predisposing factors for sacroiliac joint radiographic progression after a two-year follow-up period in recent-onset spondyloarthritis. *Arthritis Rheumatol.* **68**, 1904–1913 (2016).
50. Dougados, M. et al. Sacroiliac radiographic progression in recent onset axial spondyloarthritis: the 5-year data of the DESIR cohort. *Ann. Rheum. Dis.* **76**, 1823–1828 (2017).
51. Wang, R., Gabriel, S. E. & Ward, M. M. Progression of nonradiographic axial spondyloarthritis to ankylosing spondylitis: a population-based cohort study. *Arthritis Rheumatol.* **68**, 1415–1421 (2016).
52. Rudwaleit, M. et al. The development of Assessment of SpondyloArthritis international Society classification criteria for axial spondyloarthritis (part I): classification of paper patients by expert opinion including uncertainty appraisal. *Ann. Rheum. Dis.* **68**, 770–776 (2009).
53. van der Linden, S. et al. The ASAS criteria for axial spondyloarthritis: strengths, weaknesses, and proposals for a way forward. *Curr. Rheumatol. Rep.* **17**, 62 (2015).
54. Thomas, G. P. et al. Genetic diagnostic profiling in axial spondyloarthritis: a real world study. *Clin. Exp. Rheumatol.* **35**, 229–233 (2017).
55. Taylor, W. et al. Classification criteria for psoriatic arthritis: development of new criteria from a large international study. *Arthritis Rheum.* **54**, 2665–73 (2006).
56. Rindskopf, D. & Rindskopf, W. The value of latent class analysis in medical diagnosis. *Stat. Med.* **5**, 21–27 (1986).
57. Sepriano, A. et al. What is axial spondyloarthritis? A latent class and transition analysis in the SPACE and DESIR cohorts. *Ann. Rheum. Dis.* **79**, 324–331 (2020).
58. US National Library of Medicine. ClinicalTrials.gov. CLassification of axial spondyloarthritis inception cohort (CLASSIC). https://clinicaltrials.gov/ct2/show/NCT03993847 (2020).
59. Hayward, R. J. & Machado, P. M. Classification criteria in axial spondyloarthritis: what have we learned; where are we going? *Rheum. Dis. Clin. North Am.* **46**, 259–274 (2020).
60. Dimitroulas, T. et al. Biologic drugs as analgesics for the management of low back pain and sciatica. *Pain. Med.* **20**, 1678–1686 (2019).
61. Dougados, M. et al. Symptomatic efficacy of etanercept and its effects on objective signs of inflammation in early nonradiographic axial spondyloarthritis: a multicenter, randomized, double-blind, placebo-controlled trial. *Arthritis Rheumatol.* **66**, 2091–2102 (2014).
62. Brown, M. A. et al. Evaluation of the effect of baseline MRI sacroiliitis and C reactive protein status on etanercept treatment response in non-radiographic axial spondyloarthritis: a post hoc analysis of the EMBARK study. *Ann. Rheum. Dis.* **77**, 1091–1093 (2018).
63. Sieper, J. et al. A randomized, double-blind, placebo-controlled, sixteen-week study of subcutaneous golimumab in patients with active nonradiographic axial spondyloarthritis. *Arthritis Rheumatol.* **67**, 2702–2712 (2015).
64. Sieper, J. et al. Efficacy and safety of adalimumab in patients with non-radiographic axial spondyloarthritis: results of a randomised placebo-controlled trial (ABILITY-1). *Ann. Rheum. Dis.* **72**, 815–822 (2013).
65. Pharmaceutical Benefits Advisory Committee. Public summary document — November 2017 PBAC meeting. http://www.pbs.gov.au/industry/listing/elements/pbac-meetings/psd/2017-11/files/golimumab-nraxSpA-psd-november-2017.pdf (2017).
66. National Institute for Health and Care Excellence. Golimumab for treating non-radiographic axial spondyloarthritis. https://www.nice.org.uk/guidance/TA497 (2018)
67. Deodhar, A. et al. The concept of axial spondyloarthritis: joint statement of the spondyloarthritis research and treatment network and the Assessment of SpondyloArthritis international Society in response to the US Food and Drug Administration's comments and concerns. *Arthritis Rheumatol.* **66**, 2649–2656 (2014).
68. Landewe, R. et al. Efficacy of certolizumab pegol on signs and symptoms of axial spondyloarthritis including ankylosing spondylitis: 24-week results of a double-blind randomised placebo-controlled phase 3 study. *Ann. Rheum. Dis.* **73**, 39–47 (2014).
69. Sieper, J. Different approaches to drug approval by EMA and FDA — the example of non-radiographic axial spondyloarthritis [SP0108]. *Ann. Rheum. Dis.* **75**, 27 (2016).
70. Deodhar, A. et al. A fifty-two-week, randomized, placebo-controlled trial of certolizumab pegol in nonradiographic axial spondyloarthritis. *Arthritis Rheumatol.* **71**, 1101–1111 (2019).
71. Robinson, P. C. et al. Axial spondyloarthritis: a new disease entity, not necessarily early ankylosing spondylitis. *Ann. Rheum. Dis.* **72**, 162–164 (2013).
72. Akkoc, N. & Khan, M. A. Looking into the new ASAS classification criteria for axial spondyloarthritis through the other side of the glass. *Curr. Rheumatol. Rep.* **17**, 515 (2015).
73. Braun, J. et al. Classification and diagnosis of axial spondyloarthritis — what is the clinically relevant difference? *J. Rheumatol.* **42**, 31–38 (2015).
74. Robinson, P. C., Sengupta, R. & Siebert, S. Non-radiographic axial spondyloarthritis (nr-axSpA): advances in classification, imaging and therapy. *Rheumatol. Ther.* **6**, 165–177 (2019).
75. Proft, F. & Poddubnyy, D. Ankylosing spondylitis and axial spondyloarthritis: recent insights and impact of new classification criteria. *Ther. Adv. Musculoskelet. Dis.* **10**, 129–139 (2018).
76. Renson, T. et al. High prevalence of sacroiliac bone marrow edema on MRI in post partum women: a temporary phenomenom [abstract]. *Arthritis Rheumatol.* **71**, 597 (2019).
77. Lambert, R. G. et al. Defining active sacroiliitis on MRI for classification of axial spondyloarthritis: update by the ASAS MRI working group. *Ann. Rheum. Dis.* **75**, 1958–1963 (2016).
78. Lukas, C. et al. MRI for diagnosis of axial spondyloarthritis: major advance with critical limitations 'Not everything that glisters is gold (standard)'. *RMD Open* **4**, e000586 (2018).
79. van Tubergen, A. & Weber, U. Diagnosis and classification in spondyloarthritis: identifying a chameleon. *Nat. Rev. Rheumatol.* **8**, 253–261 (2012).
80. Bradbury, L. A. et al. Diffusion-weighted imaging is a sensitive and specific magnetic resonance sequence in the diagnosis of ankylosing spondylitis. *J. Rheumatol.* **45**, 771–778 (2018).
81. Weber, U. et al. Development and validation of a magnetic resonance imaging reference criterion for defining a positive sacroiliac joint magnetic resonance imaging finding in spondyloarthritis. *Arthritis Care Res.* **65**, 977–85 (2013).
82. Weber, U. et al. Assessment of structural lesions in sacroiliac joints enhances diagnostic utility of magnetic resonance imaging in early spondylarthritis. *Arthritis Care Res.* **62**, 1763–71 (2010).
83. Weber, U. et al. MRI of the sacroiliac joints in athletes: recognition of non-specific bone marrow oedema by semi-axial added to standard semi-coronal scans. *Rheumatology* **59**, 1381–1390 (2020).
84. van der Heijde, D. et al. Spinal inflammation in the absence of sacroiliac joint inflammation on magnetic resonance imaging in patients with active nonradiographic axial spondyloarthritis. *Arthritis Rheumatol.* **66**, 667–73 (2014).
85. Weber, U. et al. Does spinal MRI add incremental diagnostic value to MRI of the sacroiliac joints alone in patients with non-radiographic axial spondyloarthritis? *Ann. Rheum. Dis.* **74**, 985–92 (2015).
86. Weber, U. et al. Diagnostic utility of candidate definitions for demonstrating axial spondyloarthritis on magnetic resonance imaging of the spine. *Arthritis Rheumatol.* **67**, 924–33 (2015).
87. Costello, M. E. et al. Brief report: intestinal dysbiosis in ankylosing spondylitis. *Arthritis Rheumatol.* **67**, 686–691 (2015).
88. Costello, M. E. et al. The intestinal microbiome in human disease and how it relates to arthritis and spondyloarthritis. *Best Pract. Res. Clin. Rheumatol.* **29**, 202–212 (2015).
89. Arnbak, B. et al. Associations between spondyloarthritis features and magnetic resonance imaging findings: a cross-sectional analysis of 1,020 patients with persistent low back pain. *Arthritis Rheumatol.* **68**, 892–900 (2016).
90. Markus, K. A. Constructs, concepts and the worlds of possibility: connecting the measurement, manipulation, and meaning of variables. *Measurement* **6**, 54–77 (2008).
91. Taylor, W. & Fransen, J. Distinctions between diagnostic and classification criteria: comment on the article by Aggawal et al. *Arthritis Care Res.* **68**, 149–150 (2015).
92. Dragulinescu, S. Diseases as natural kinds. *Theor. Med. Bioeth.* **31**, 347–69 (2010).
93. Williams, N. E. Arthritis and nature's joints, in Carving Nature at its joints. in Natural Kinds in Metaphysics and Science (eds Campbell, J. K, O'Rourke, M. & Slater, M. H.) (MIT Press, 2011).
94. Robinson, P. C. et al. Genetic dissection of acute anterior uveitis reveals similarities and differences in associations observed with ankylosing spondylitis. *Arthritis Rheumatol.* **67**, 140–151 (2015).

Author contributions
All authors researched data for the article, made substantial contributions to discussion of the content, writing and review/editing of the manuscript before submission.

Competing interests
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