

Incidence and prevalence of axial spondyloarthritis: methodologic challenges and gaps in the literature

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Abstract

Objective

The incidence and prevalence of axial spondyloarthritis (axSpA), including ankylosing spondylitis (AS) and non-radiographic (nr-)axSpA, have been investigated in multiple populations, though there is a paucity of population-level data. Here, we identify population-based studies in AS and nr-axSpA, and describe the methodologic challenges in conducting these, outlining potential reasons for disparate incidence and prevalence estimates.

Methods

PubMed and Embase were searched for population-based studies providing incidence and prevalence rates, published in English from 1 Jan 2000–30 Jun 2015. Extracted information included incidence/prevalence rates, geographical population, study design, data source, case definition, age/gender, and classification criteria used.

Results

Of 2,148 articles identified, 19, from 15 countries, fulfilled eligibility criteria. Incidence rates per 100,000 patient-years were reported in 4 AS studies and varied from 0.4 (Iceland) to 15.0 (Canada). Reported AS prevalence rates per 100,000 persons also showed considerable variation (16 studies: 6.5 [Japan] to 540.0 [Turkey]). Only 3 axSpA and no nr-axSpA prevalence rates were reported. Considerable variation was seen in the methodology used to estimate incidence and prevalence rates, e.g. screening method, study design, and classification criteria. Although the prevalence of AS is known to vary by HLA-B27 status, only 4 studies reported this genetic marker.

Conclusion

There is an unmet need for future studies to use consistent methodology, capture all relevant information (including HLA-B27 positivity), and investigate under-reported populations (e.g. nr-axSpA; southern hemisphere countries) to estimate the population burden of axSpA. Future studies should aim to address data gaps to provide accurate incidence/prevalence estimates for the global axSpA population.

Key words

spondylarthropathies, ankylosing spondylitis, epidemiology, prevalence, incidence

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Introduction

The spondyloarthritides (SpA) are chronic inflammatory rheumatic diseases that include axial spondyloarthritis (axSpA, including patients with ankylosing spondylitis [AS] and non-radiographic axSpA [nr-axSpA]), and peripheral spondyloarthritis (including psoriatic arthritis, reactive arthritis, and arthritis associated with inflammatory bowel disease [IBD]) (1). These diseases share common symptomology, including inflammatory back pain, inflammation of the entheses (enthesitis), digits (dactylitis), and extra-articular disease manifestations such as uveitis (inflammation of the uvea), psoriasis and IBD (2).

AxSpA is characterised predominantly by inflammatory back pain and involvement of the spine and sacroiliac joints, and includes patients with definite radiographic sacroiliitis observed via x-ray and meeting the modified New York (mNY) criteria, classified as having AS, (3) and those without definite sacroiliitis detectable by conventional radiography and not meeting mNY criteria, classified as having nr-axSpA (4). Patients with nr-axSpA can have inflammation of their sacroiliac joints, as observed by magnetic resonance imaging (MRI), and may go on to develop radiographic damage visible via x-rays, thus progressing to a diagnosis of AS. However, not all patients will experience this progression (5, 6).

The definitions of the axSpA sub-populations above are currently aligned with the Assessment of SpondyloArthritis international Society (ASAS) classification criteria for axSpA and the mNY criteria for AS (3, 7). However, definitions of, and classification criteria for, axSpA have changed considerably over time (Table I).

The burden of disease is similar between AS and nr-axSpA patients, despite differences in the presence or absence of definitive radiographic changes. Both are associated with a decrease in patient health-related quality of life (8, 9) and work productivity (10), as well as a similar burden in terms of pain, fatigue and morning stiffness (11). An increased mortality in patients with AS has also been observed (12), though data for nr-axSpA are not currently

available. Selective biologic therapies can effectively treat axSpA, reducing disease burden and improving patient quality of life (8, 13-15). Given these factors, it is important to understand the incidence and prevalence of axSpA worldwide, including both AS and nr-axSpA, as prevalence information is of great benefit to healthcare organisations and government agencies in supporting their planning for the provision of care to axSpA patients.

A recent systematic literature review conducted by Stolwijk *et al.* (16) investigated reported prevalence rates of SpA, including axSpA and AS well as other rheumatologic conditions. The study found large differences in the prevalence and incidence estimates in the published literature. However, the reasons underlying this variability were not addressed. There are significant challenges in obtaining comparative population data, and to our knowledge there have been no studies that examine the factors affecting incidence and prevalence estimates, nor provide guidance on evaluation of population-based published literature.

Here, we conduct a focused analysis including only population-based studies. We identify publications reporting the incidence or prevalence of axSpA (including AS and nr-axSpA) at the population level, and present and compare these rates to investigate how various factors affect the reported rates, in order to better understand differences in published reports. In addition, gaps in the literature are discussed to direct further research efforts.

Materials and methods

Search strategy and review methodology

A systematic literature review was carried out in line with PRISMA guidelines to identify population-based studies of the incidence and prevalence of axSpA (17). Searches were performed using the online databases PubMed and Embase. Database searching considered all articles published between 1st January 2000 and 30th June 2015. Search terms included those for ankylosing spondylitis, axial spondyloarthritis, incidence, and prevalence, and aimed to identify

Table I. Classification criteria for axial spondyloarthritis or ankylosing spondylitis.

Criteria	Requirements for classification	Radiological criterion	Clinical criteria
<i>Ankylosing spondylitis</i>			
Rome (42) (1961)	Definite AS: Sacroiliitis plus 1 clinical criterion	Sacroiliitis: • Bilateral grade 2 or higher	<ul style="list-style-type: none"> • Low back pain/stiffness >3 months (improves with exercise but not relieved by rest) • Pain/stiffness in thoracic region • Limited motion in the lumbar spine • Limited chest expansion • History/evidence of uveitis/iritis
New York (1966)	Definite AS: Sacroiliitis (bilateral grade 3-4) plus 1 clinical criterion Sacroiliitis (unilateral grade 3-4, or bilateral grade 2) plus clinical criterion I Sacroiliitis (unilateral grade 3-4, or bilateral grade 2) plus clinical criterion II and III	Sacroiliitis: • Bilateral grade 3-4 • Unilateral grade 3-4 or bilateral grade 2	I. Limitation of lumbar spine motion (in all 3 planes, anterior flexion, lateral flexion, and extension) II. History/presence of pain at the dorso-lumbar junction or in the lumbar spine III. Limitation of chest expansion to ≤ 1 inch (2.5 cm) or less, measured at the level of the 4 th intercostal space
Modified New York (3) (1984)	Definite AS: Sacroiliitis plus 1 clinical criterion	Sacroiliitis: • Bilateral grade ≥ 2 • Unilateral grade 3-4	<ul style="list-style-type: none"> • Low back pain/stiffness >3 months (improves with exercise but not relieved by rest) • Limitation of lumbar spine motion (both sagittal and frontal planes) • Limitation of chest expansion relative to age/gender norms
<i>Axial spondyloarthritis</i>			
ASAS (7) (2009)	Axial spondyloarthritis: <ul style="list-style-type: none"> • Back pain >3 months • Age at onset <45 years, and: • Sacroiliitis on imaging plus ≥ 1 clinical criteria, or • HLA-B27 plus ≥ 2 clinical criteria Non-radiographic axSpA: <ul style="list-style-type: none"> • Fulfil ASAS criteria without definite radiographic sacroiliitis 	Sacroiliitis • Active inflammation on MRI highly suggestive of sacroiliitis • Definite radiographic sacroiliitis (according to mNY criteria)	<ul style="list-style-type: none"> • Inflammatory back pain • Arthritis • Enthesitis (heel) • Uveitis • Dactylitis • Psoriasis • Crohn disease • Good response to NSAIDs • Family history of SpA • HLA-B27 • Elevated C-reactive protein level

mNY: modified New York; nr-axSpA: non-radiographic axial spondyloarthritis; axSpA: axial spondyloarthritis.

all reports of either incidence or prevalence in these patient populations. Full search terms are shown in Supplementary Table I.

Eligible articles reported population-based incidence or prevalence rate (or provided sufficient data such that one could be calculated). Studies using randomly selected populations were included only when the authors then extrapolated the results to the total population. Cohort or cross-sectional studies that started with high-risk patients or reported on populations with multiple rheumatologic conditions as one rate were excluded.

Initially, the titles and abstracts of all identified articles were reviewed against eligibility criteria, and any potentially relevant articles identified (articles of uncertain eligibility were included at

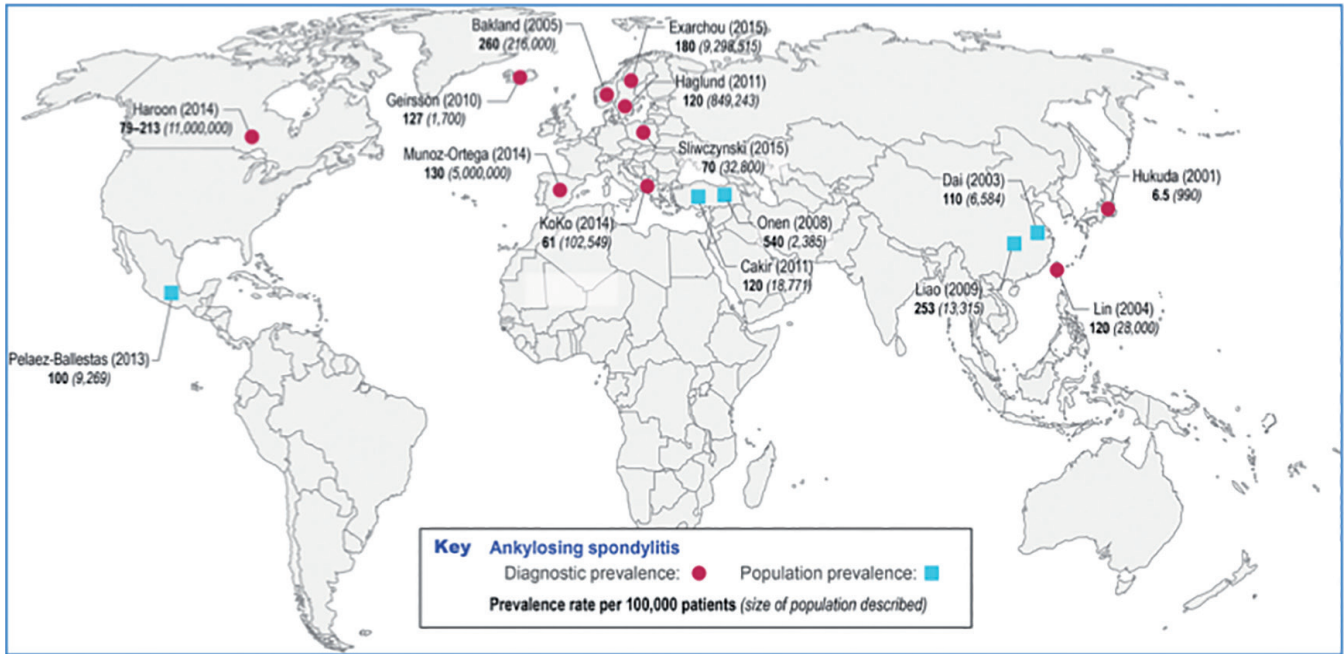
this stage). Full-texts for all potentially relevant articles were obtained and assessed for inclusion against the eligibility criteria. At the full-text stage, only articles that were definitely relevant (*i.e.* met eligibility criteria) were included. Identified articles were assessed against the eligibility criteria by two reviewers. Following the literature review, information was extracted from all included full-text publications. Where available, the reported incidence and prevalence rates were extracted. Other study information extracted included the article reference, year(s) covered by the study, geographical population, study design (*e.g.* cross-sectional, retrospective, cohort, etc.), data source (*e.g.* questionnaire, rheumatology clinic records, ICD codes, etc.), case definition, classification criteria used to define the popula-

tion of interest, age and gender information, and strengths and limitations of the analyses.

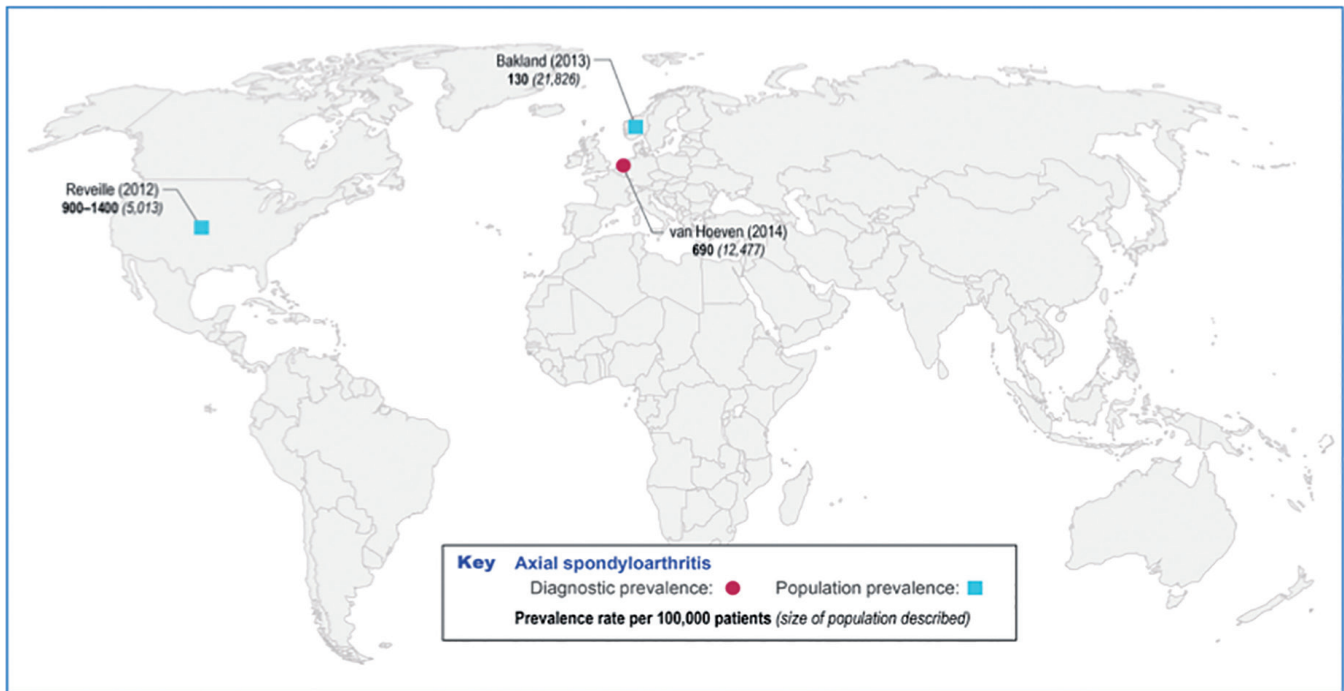
Results

Included articles and reported incidence and prevalence estimates

The initial literature review identified 14,735 articles using the AS search terms, and 1,260 using the axSpA search terms. Of these, 1,868 and 280, respectively, remained following the application of the incidence/prevalence search terms. This gave a total of 2,148 articles, the abstracts of which were reviewed against eligibility criteria. Of these, 2,004 articles were discarded at the title/abstract stage, and full-texts assessed for 144 papers. Following the full-text review, 18 articles from 14 countries (Fig. 1) fulfilled eligibility



A. Studies reporting prevalence rates for ankylosing spondylitis.



B. Studies reporting prevalence rates for axial spondyloarthritis.

Fig. 1. Geographical location and size of identified studies, including those reporting diagnostic and population prevalence. Hukuda 2001 used randomly selected populations from which the authors extrapolated the results to the total population. Data shown here are the total population.

criteria. The majority of articles excluded at the title/abstract stage and the full-text stage were excluded as they were not population-based studies, or did not report incidence or prevalence rates.

Incidence rates

Of the 18 identified articles, incidence

rates for AS were reported in 4 articles, in 2 cross-sectional (18, 19) and 2 retrospective cohort studies (20, 21) (Table II), ranging from 0.44 per 100,000 patient years (PY) in Iceland (18) to 15/100,000 PY in Ontario, Canada (21) (Table II). Three of the studies reported crude estimates (0.44–7.27/100,000

PY) (18-20), one reported an age and sex adjusted definition (14.00–15.00/100,000 PY) (21). There was no geographical overlap in the studies, making comparison difficult. The use of a cross-sectional study for estimating incidence rates has limitations because true capture of person-

Table II. Reported incidence rates of ankylosing spondylitis from identified studies

Author (Year)	Study year/period	Population	Study design	Data source and case ascertainment method	Classification criteria	Incidence rate, per 100,000 patient years (crude/adjusted)
Bakland (2005) (20)	1960–1993	Norway: Tromso and Finnmark Counties	Retrospective cohort	Cases identified as patients with an ICD code of 720 or M45 from the database of a single regional rheumatology department serving all of Northern Norway	Modified New York	7.26 (crude)
Geirsson (2010) (18)	1947–2005	Iceland	Cross-sectional study	Cases for patients aged ≥ 18 identified from i) a database for an ongoing genetic study of inflammatory bowel disease (rheumatologist diagnosed); ii) an electronic registry of patients admitted to 2 hospitals with rheumatology specialist services with ICD-10 codes of M45, M45.5, M45.9, M46, or M46.9; iii) personal calls to all private rheumatology services in Iceland (rheumatologist diagnosed). Reported prevalence shows data combined from all sources	New York	Annual incidence for 1947–2005 ranged from 0.44–5.48 (crude)
Haroon (2014) (21)	1995–2010	Canada: Ontario	Retrospective cohort	Cases identified from administrative health databases: i) ≥ 2 Ontario Health Insurance physician service claims with an ICD-9 code of 720 over 2 years with ≥ 1 claim by a rheumatologist; ii) ≥ 1 CIHI-DAD (Canadian Institute for Health Information – Discharge Abstract Database) record with an ICD-9 code of 720 or an ICD-10 code of M451	Study Specific Case Definition	14.00 (1995) 15.00 (2006) (age- and sex-adjusted)
KoKo (2014) (19)	1995–2010	Albania: Gjirokaster	Cross-sectional study	Cases attained from hospitals, GPs, clinics, and work disability database. Patients presented bilateral sacroiliitis grade >2 or universal sacroiliitis grade >3 , and one of the following: (i) pain in the lower back for ≥ 3 months; (ii) limited movement of the lumbar spine; and (iii) a reduction in chest opening cases confirmed by a rheumatologist	Modified New York	6.00 (crude)

time is not feasible. Additionally, assumptions about whether the population is in a steady state must be made in order to calculate the estimated incidence rates and often these characteristics are unknown. For example, Geirsson *et al.* (18) included prevalent AS cases when calculating the incidence, giving an inaccurate estimate.

No articles reported incidence rates for nr-axSpA or the whole axSpA population.

Prevalence rates

Prevalence rates for AS were reported in 15 articles and for axSpA in 3 articles (Table III and Table IV). No article reported prevalence rates for nr-axSpA. AS prevalence rates varied greatly from 6.5/100,000 persons in the population of Japan (22) to 540/100,000 in Turkey (23) (Table III). The reported prevalence rate in Japan was particu-

larly low, with only 4 other reported prevalence rates below 100/100,000 persons: 61/100,000 in Southern Albania (19), 70/100,000 in Poland (24), and 79/100,000 in Ontario, Canada (this study reported a range, from 79/100,000 in 1995 to 213/100,000 in 2010) (21). The majority of reported prevalence rates were between 100 and 200 per 100,000 persons, with 8 reported prevalence rates in this category. A further 3 articles reported prevalence rates greater than 200 per 100,000 persons (20, 23, 25). These studies represented the regions of Norway (Tromso and Finnmark Counties), China (the Han population) and Turkey (the adult, urban population), with prevalence rates of 260, 253 and 540 per 100,000 persons, respectively.

In the overall axSpA population, prevalence rates were reported in 3 studies and again varied widely (Table IV).

The lowest reported prevalence rate was 130/100,000 persons in Norway, the second was 690/100,000 persons in the Netherlands, and the highest estimates were from the US where rates of 900/100,000 and 1,400/100,000 persons were reported (Table IV).

Causes of variability in prevalence estimates

Geographic variability

The 19 articles identified here report studies carried out in 15 different countries all from the northern hemisphere (Fig. 1). In articles reporting AS prevalence rate, 3 countries were investigated in more than one study: China, Sweden, and Turkey. Prevalence rates varied in Turkey (with rates of 120 and 540 per 100,000 persons in the Çakir (26) and Onen (23) studies, respectively) and China (with rates of 110 and 253 per 100,000 persons in the Dai (27)

Table III. Reported prevalence rates of ankylosing spondylitis from identified studies.

Author (Year)	Study year/period	Population	Study design	Data source and case ascertainment method	AS criteria	Prevalence rate, per 100,000 persons (crude/adjusted)
<i>Ankylosing Spondylitis</i> Bakland (2005) (20)	1960–1993	Norway: Tromso and Finnmark Counties	Retrospective cohort	Adult cases with an ICD diagnosis code of 720 or M45 from the database of a single regional rheumatology department serving all of Northern Norway	Modified New York	260 (crude)
Çakir (2011) (26)	2000	Turkey: Havsa study	Cross-sectional survey	Cases (all ages) identified in a door-to-door questionnaire of 17 villages within the Havsa region of Turkey. Case confirmation performed at local health center and/or hospital clinic. Adjusted to the general population distribution of Turkey using direct standardisation	Rome	120 (age- and sex-adjusted)
Dai (2003) (27)	1997–1998	China: Shanghai	Cross-sectional survey	Cases identified in a door-to-door questionnaire from a random sample of 4 of the 13 communities within Shanghai. Clinical follow-up for case ascertainment by a team consisting of a rheumatologist and 2 other physicians. Adjusted according to the standard Chinese population	Modified New York	110 (age- and sex-adjusted)
Exarchou (2015) (29)	2009	Sweden	Cross-sectional study	Cases for patients aged 16–64 living in Sweden in 2009 identified from the population register as having ≥1 ICD diagnosis of AS (codes not provided) by any clinical department between 1967 and 2009	Study Specific case Definition	180 (crude)
Geirsson (2010) (18)	2005	Iceland	Cross-sectional study	Cases for patients aged ≥18 identified from i) a database for an ongoing genetic study of inflammatory bowel disease (rheumatologist diagnosed); ii) an electronic registry of patients admitted to 2 hospitals with rheumatology specialist services with ICD-10 codes of M45, M45.5, M45.9, M46, or M46.9; iii) personal calls to all private rheumatology services in Iceland (rheumatologist diagnosed). Reported prevalence shows data combined from all sources	New York	127 (crude)
Haglund (2011) (28)	2003–2007	Sweden: South	Cross-sectional study	Patients identified from population register aged ≥15 during the study period with an AS ICD-10 diagnosis (M45). Prevalence standardised to European standard population	Not reported	120 (crude)
Haroon (2014) (21)	1995–2010	Canada: Ontario	Retrospective cohort	Cases identified from administrative health databases: i) ≥2 Ontario Health Insurance physician service claims with an ICD-9 code of 720 over 2 years with ≥1 claim by a rheumatologist; ii) ≥1 CIHI-DAD (Canadian Institute for Health Information – Discharge Abstract Database) record with an ICD-9 code of 720 or an ICD-10 code of M451	Not reported	From 79 (95% CI 78–81) in 1995 to 213 (95% CI 211–216) in 2010 (age- and sex-adjusted)
Hukuda (2001) (22)	1990–1996	Japan	Cross-sectional study	Cases identified from a survey of medical records at clinics and hospitals by physicians during 2 time periods; medical records assessed using a questionnaire from the Japan AS society. SpA patients identified using Modified New York or Rome criteria or by ordinary, clinical, or roentgenographic features. Radiographic exam of the sacroiliac joint and whole spinal column was mandatory and that of appendicular skeleton was performed as appropriate. Data extrapolated to entire Japanese population	Modified New York or Rome	6.5 (crude)

Author (Year)	Study year/ period	Population	Study design	Data source and case ascertainment method	AS criteria	Prevalence rate, per 100,000 persons (crude/adjusted)
KoKo (2014) (19)	1995–2010	Albania: Gjirokaster	Cross-sectional study	Cases attained from hospitals, GPs, clinics, and work disability database. Patients presented bilateral sacroiliitis grade >2 or universal sacroiliitis grade >3, and one of the following: (i) pain in the lower back for ≥3 months; (ii) limited movement of the lumbar spine; and (iii) a reduction in chest opening cases confirmed by a rheumatologist	Modified New York	61 (crude)
Liao (2009) (25)	2006	China: Han population	Cross-sectional survey	Cases identified using a face to face questionnaire of 12 questions with confirmation by a rheumatologist based on clinical features, family history, x-ray results, and HLA-B27 tests	Modified New York	253 (crude)
Lin (2004) (40)	2001	Taiwan	Cross-sectional study	National health insurance records of patients aged 18–45 had received a principal diagnosis of AS ICD-9 code 720.0 in an ambulatory medical care visit between 1 st January and 31 st December 2001 and received ≥1 other visit during this time period with a principal diagnosis of AS (total of at least 2 visits with primary diagnosis)	Study Specific Case Definition	120 (crude)
Munoz-Ortega (2014) (36)	2006 Catalonia	Spain:	Cross-sectional study	Cases identified on electronic health care professional medical records with an ICD-10 code of M45	Study Specific Case Definition	130 (crude)
Onen (2008) (23)	2000	Turkey: adult urban population	Cross-sectional survey	Cases identified by a screening telephone interview (3 questions) with a follow-up examination (detailed medical history and complete physical examination) at a hospital. Pelvic x-rays of sacroiliac joints were taken when patients had ≥1 of the following clinical features: inflammatory back pain, asymmetric oligoarthritis, limited chest expansion, limited lumbar spinal movements. Data standardised to Turkish census population	Modified New York	540 (age- and sex-adjusted)
Pelaez-Ballestas (2013) (31)		Mexico: Cuajimalpa	Cross-sectional survey	Cases identified via a door to door questionnaire (COPCORD stage 1 questionnaire) assessing fulfilment of the Berlin criteria for inflammatory back pain, with subsequent confirmation by a rheumatologist (clinical history, physical examination, HLA-B27 and CRP tests, and pelvic x-rays)	Modified New York	100 (crude)
Sliwczynski (2015) ²⁴	2013	Poland	Cross-sectional study	Cases identified as ICD-10 codes of M45 as a main or co-existing diagnosis from the National Health Fund (national payer database)	Study Specific case definition	70 (crude)

COPCORD: Community Oriented Programme for Control of Rheumatic Diseases; CI: Confidence Interval.

and Liao (25) studies, respectively), but were more similar in Sweden (with rates of 120 and 180 per 100,000 persons in the Haglund (28) and Exarchou (29) studies, respectively). The high variability reported in the Turkish and Chinese studies may be due to the different regions included in the reports, whereas the Swedish estimates used the full population.

Many reports focused solely on a specific region within a country, limiting the generalisability of findings. Only 7 articles claimed to report prevalence for the entire population (23, 25–27, 30–32). A geographical focus on specific countries, rather than populations, also ignores a key factor that affects the geographical distribution of AS: the close relationship between this disease

and a genetic variation of the HLA-B gene, HLA-B27 (33, 34). The prevalence of HLA-B27 is unequally distributed around the world and is more common in certain populations (35); therefore differences in the prevalence of AS between regions may represent differences in the prevalence of HLA-B27 positivity. However, only 5 of the included studies reported both the prev-

Table IV. Reported prevalence rates of axial spondyloarthritis from identified studies.

Author (Year)	Study year/period	Population	Study design	Data source and case ascertainment method	AxSpA criteria/case definition	Prevalence rate, per 100,000 persons (Crude/Adjusted)
<i>Axial spondyloarthritis</i>						
Reveille (2012) (32)	2009–2010	United States	Cross-sectional study	A representative sample from NHANES was assessed for fulfilment of ESSG and Amor criteria	ESSG and Amor criteria ¹	Amor: 900 ESSG: 1400 (crude)
Bakland (2013) (30)	1986–1987	Tromsø, Norway	Retrospective cohort	Patients with low back pain were recruited from a population survey in Norway and given a full follow-up medical examination by a rheumatologist, including HLA-B27 testing, and x-rays of their SI joints	ASAS	Undiagnosed axSpA: 130 Total axSpA: 530 ² (crude)
van Hooft (2014) (41)	Jan–Jul 2010	Netherlands	Prospective cohort	Surveys of health care professionals in the Netherlands identified patients with ICD-9 codes consistent with chronic low back pain. Identified patients were then given a follow-up medical examination and interview, including a HLA-B27 and CRP tests and x-ray/MRI assessment	ASAS	690 (crude)

¹The ESSG and Amor criteria were used, supplemented by a questionnaire as not all ESSG/Amor items were collected. Patients were also required to have chronic low back pain for a diagnosis of axSpA.

²Authors state a total prevalence of undiagnosed axSpA of 130 per 100,000 persons. This value was then combined with the author's previous data (showing a prevalence of established radiographic axSpA of 400 per 100,000 persons) to give the total axSpA prevalence as 530 per 100,000 persons.

presence of AS and or HLA B27 (18, 20, 22, 25, 36), and none of the 3 studies in the overall axSpA population reported the prevalence of HLA-B27 in these populations, preventing any assessment of the association of these factors. Of the studies that did report data on HLA-B27, 64–93% of patients with a diagnosis of AS were positive for the HLA-B27 gene (18, 20, 22, 25, 36). A number of other genetic factors have also been identified to be associated with AS and axSpA, and as such may impact the geographical differences in the prevalence of these diseases (37–39).

Population screening vs. diagnostic prevalence

Two different methodologies were employed for estimating population-based prevalence; those using diagnosis codes or descriptors among patients who came to medical attention (diagnostic prevalence), and those screening the broader population for cases of disease (population prevalence).

Of the 18 studies identified, 11 studies reported diagnostic-based estimates (18–22, 24, 28, 29, 36, 40, 41), and 7 screened a population (23, 25–27, 30–32). Of those reporting diagnostic estimates, only 4 were from countries with universal healthcare where the full popu-

lation can be identified in a database, and had utilised the full population register (21, 24, 28, 29). Other studies which reported diagnostic prevalence identified cases from a specialty clinic that served the population of that area (18, 20, 22), or sourced data from a specific geographic region only (19, 21, 28, 36). Additionally, amongst studies making diagnostic-based estimates, not all used the same definition of disease, making the estimates difficult to compare even within this subgroup.

Among the 15 studies reporting AS prevalence rates, 5 studies across 3 countries made use of questionnaires to initially identify or screen possible AS patients (23, 25–27, 31) (with prevalence rates ranging from 100/100,000 persons to 540/100,000 persons), for whom classification was then confirmed during clinical follow-up. These studies differed in the specific questionnaire used and in the method by which this was administered (3 door-to-door, 1 face-to-face, 1 via telephone). Clinical follow-up was most commonly performed by a rheumatologist, though details on the procedures were inconsistently reported. A lower mean estimate was seen in studies using diagnostic prevalence (110.4 per 100,000 persons) compared to those reporting popula-

tion prevalence (224.6 per 100,000 persons). Given that in almost any population a number of patients with the disease of interest will remain undiagnosed, diagnostic prevalence would be expected to underestimate the true disease prevalence.

Cross-sectional vs. cohort study design

Among the 15 studies reporting AS prevalence rates, 13 studies were cross-sectional (18, 19, 22–29, 31, 36, 40) and 2 were retrospective cohort studies (20, 21). In the case of axSpA prevalence rates, these were calculated in 1 cross-sectional study (32) and 2 cohort studies (one prospective (41) and one retrospective (30)). Variation was seen in the time period included in the studies, ranging from 1 through to 33 years. With a longer duration, any trends or changes over time in prevalence will not be captured, affecting the accuracy of the estimate. Additionally, the dates captured varied from 1960 to 2010, further complicating the comparison of different study estimates.

Classification criteria vs. case definition

Prior to publication of the ASAS criteria in 2009, AS was the main focus

of classification criteria as the prototypical disease state, with first the Rome criteria in 1961 seeking to define the population (42), followed by the New York criteria in 1966, and the mNY criteria published in 1984 (3). All 3 required definite sacroiliitis as demonstrated by x-ray for a positive classification, and thus did not capture patients in the early stages of the disease, which is now termed nr-axSpA. Two other sets of criteria, the Amor (43) and European Spondyloarthropathy Study Group (ESSG) (44) criteria, were also developed, and apply to the overall SpA population, rather than focusing on axSpA patients specifically. The 2009 ASAS criteria for axSpA allow for the classification of nr-axSpA patients in addition to AS patients. Criteria include either HLA-B27 positivity or inflammatory changes in the sacroiliac (SI) joints, as assessed by MRI, along with the presence of clinical features of SpA (7). The classification criteria used to define the AS population in different studies may impact the reported prevalence rates. Of the studies identified here that reported the classification criteria used (rather than a study-specific case definition), only 1 considered the Rome criteria (reporting an AS prevalence rate of 120/100,000 persons) and 1 the New York criteria (127/100,000 persons). The other 6 studies used the mNY criteria (ranging from 61/100,000 persons to 540/100,000 persons) (Table III).

Given the low number of studies using criteria other than the mNY criteria, it is difficult to draw any conclusions from these data. Where multiple studies investigated similar geographical regions, variation was observed between studies using different classification criteria, with the mNY criteria giving a higher prevalence rate (540/100,000) in Turkey than the Rome criteria (120/100,000), even though the mNY classification has stricter radiologic criteria than the Rome classification.

For the overall axSpA population, 2 studies (30, 41) reported prevalence rates using the ASAS classification criteria for axSpA (estimates of 530 and 690 per 100,000 persons), whilst the

third study (32) used the ESSG and Amor criteria for SpA (estimates of 900 per 100,000 persons using the Amor criteria and 1,400 per 100,000 persons using the ESSG criteria), with the additional requirement of inflammatory back pain to narrow down these criteria to an axSpA population. Although there are only 3 studies that report a prevalence for axSpA, the two studies in the Nordic countries used the same criteria (ASAS) and reported prevalence rates much less disparate than seen in the AS literature.

Given the differences between these classification criteria, comparing estimates of prevalence across studies of axSpA is difficult as they are dependent on the case definitions used. In particular, because nr-axSpA patients were not clearly defined prior to the ASAS criteria, these patients could have been misclassified, leading to potential overestimation of AS if nr-axSpA patients were erroneously included in the AS definition, or an underestimation of axSpA if nr-axSpA patients were excluded altogether.

Nine of the 15 studies made use of a database to identify cases and estimate prevalence; these 9 studies covered 8 countries (with prevalence rates ranging from 61/100,000 persons in Albania (19) to 260/100,000 persons in Norway) (20). Case definitions in the 9 studies were not consistent and included definitions requiring either ICD-9 or ICD-10 codes, sometimes in isolation and sometimes with secondary assessment (the Çakir study (26) combined cases from a registry of patients with ICD-10 codes with a database of inflammatory bowel disease patients and individual calls to private rheumatology services), across a range of time periods (from a 1 year period through to a 42-year period). Where reported, the majority of studies assessed the records of adults from the relevant databases, though the criteria used varied at the lower age bracket from ≥ 15 to ≥ 18 and at the upper age bracket from 45 to 64.

Crude vs. adjusted rates

The majority of the reported prevalence and incidence rates were crude rates. However, adjusted rates were found for

AS in 6 studies (4 reporting prevalence rate and 2 reporting incidence rate). These rates were adjusted for age and sex in 5 cases, and age alone in 1 case. High variability was seen in the prevalence rates calculated by both methods: AS adjusted prevalence rates ranged from 79/100,000 in Ontario, Canada to 540/100,000 in Turkey, crude rates ranged from 6.5/100,000 persons in Japan to 260/100,000 persons in Norway. Further description of the methods by which estimates were adjusted (*i.e.* direct standardisation, etc.) were not included in these studies making it difficult to accurately compare rates that were adjusted by the same variables.

Discussion

In this study we identified reports of the incidence or prevalence of axSpA at the population level, and outlined the challenges in estimating these rates and comparing them across studies. The systematic literature review revealed a paucity of data describing population-based epidemiology of axSpA, especially in the nr-axSpA population, for which no reported rates were identified. The absence of population-based prevalence estimates for nr-axSpA may be due to the historical lack of classification criteria for this population, and the difficulty in diagnosis.

The information collected here demonstrates the variability of reported incidence and prevalence rates. Reports of the incidence of AS ranged from 0.4 per 100,000 PY in Iceland (18), to 15 per 100,000 PY in Ontario, Canada (21), whilst prevalence ranged from 6.5 per 100,000 persons in Japan (22), to 540.0 per 100,000 persons in Turkey (23). Limited data were reported for the overall axSpA population (3 prevalence rates) (30, 32, 41).

Lack of standardisation in disease criteria across studies result in differing magnitudes of disease misclassification. Given the small number of population-based studies identified, and lack of uniformity in disease definitions, the extent and direction of the bias would be difficult to quantify and adjust for in reported estimates. The 3 studies reporting prevalence rates for axSpA showed significant differences

in study design and methodology, making comparisons difficult. The study reported by Bakland *et al.* (20) may have included undiagnosed SpA patients in its estimates, whilst that reported by Reveille *et al.* (32) did not use the ASAS classification criteria, but rather a combination of the ESSG and Armor criteria, along with presence of axial pain. These different methodologies may limit the accuracy of the estimates, further emphasising the need for more rigorous population based studies to examine this question.

Until there is a better understanding of nr-axSpA, and a consensus in the rheumatology community regarding its diagnosis, it will be difficult to capture this patient population. Refining the classification criteria for nr-axSpA diagnosis should be a priority for the community as the first step in acquiring prevalence and incidence data for the diseases.

Studies in nr-axSpA are also limited by the need to use x-rays to confirm the absence of radiographic damage of the sacroiliac joints, given the concerns associated with exposing the general public to x-rays for the purpose of screening alone. Study designs need to take these concerns into consideration.

One might consider a strategy of screening for inflammatory back pain among symptomatic – but otherwise unselected – young people in a community, which would then lead to selected x-ray and/or MRI testing to diagnose AS and nr-axSpA. However, the back pain experienced by several patients with axSpA may not have the typical characteristics associated with ‘inflammatory’ back pain, and hence such patients would be missed. An alternative option is pre-emptive genotyping, routinely performed at some medical centers or in certain communities as part of precision medicine programs for pharmacogenetic purposes, which might identify asymptomatic individuals who are HLA-B27 positive (45). Such individuals could then be referred for MRI and/or x-rays on the basis of the genotyping result alone, or due to them having some combination of HLA-B27 positivity and other clinical features. However, this approach would miss the

substantial proportion of patients who are HLA-B27 negative, and the screening and downstream imaging would be associated with high costs.

Differences across the reported rates can partially be attributed due to variation in the geographical populations assessed (in terms of ethnicity and other underlying risk factors, such as HLA-B27 positivity), lack of standardisation or adjustment of reported rates and the quality of available data. However, the considerable variation identified here is suggestive of issues in consistency of methodology, rather than biologic and geographical variation. Unfortunately, for the majority of countries/regions there was only one report showing incidence/prevalence rates, prohibiting direct comparison of the data and identification of the reasons underlying variability in rates. Where two studies were available for the same country, prevalence rates varied in Turkey (23, 26) and China (25, 27), but were more similar in Sweden (28, 29). This may be because the studies in Turkey and China used different methodologies, whilst those in Sweden were both diagnostic prevalence estimates based on ICD codes from population registers. For the 2 studies in Turkey, it is notable that Çakir 2011 (26) (120/100,000) included children in their analyses, which may have affected the reported prevalence rate given that the peak prevalence of AS occurs in the 35–54 age group.

As mentioned previously, the geographical distribution of AS may be affected by HLA-B27 positivity in different geographical populations (34). Of the 15 reports identified, HLA-B27 information was only included in 5, (18, 20, 22, 25, 36) preventing comparison of the prevalence of AS and its association with HLA-B27. Future studies should aim to capture this information to allow investigation of HLA-B27 positivity (and other associated genes) and AS prevalence across geographical regions.

Finally, the geographical distribution of identified articles (Fig. 1) shows a clear bias for studies performed in the northern hemisphere, and highlighting the unmet need for studies consider-

ing the prevalence of axSpA in Africa, Australasia and South America.

One optimal study design for producing accurate prevalence and incidence rates might be a large, randomly selected population-based survey to screen for patients at “high risk” of having AS for further diagnostic testing and definitive diagnosis. The population-based survey approach has been used to effectively screen for individuals with inflammatory back pain within the general population (46), and for those with axSpA among patients with inflammatory bowel disease (47). Studies on the overall axSpA spectrum should employ screening methodologies that ensure differentiation between axial and peripheral SpA, and exclude other clinical conditions with symptoms that overlap with axSpA, with physicians using the same classification criteria and validated algorithms, where necessary. In general, recruiting patients through registries is not recommended because of the associated recruitment bias, and because this would only provide a diagnostic prevalence of the disease, not the population prevalence. However, for countries where computerised universal healthcare is available, such as Sweden, population studies using patient registries are acceptable, since they allow the general population to be sampled and the denominator is known.

A population-based survey would have the additional advantage that it can be used to gain a better understanding of the patient journey, to characterise those in the early stages of their disease, *i.e.* those that may progress to AS. However, the limitations of large, randomly selected population-based surveys include a likely low response rate, the expense and the follow-up with additional testing.

At present, there are significant gaps in the literature. No data are currently available regarding the prevalence or incidence of nr-axSpA, leaving the burden of disease unknown and prohibiting assessment of disease progression to AS. Moreover, where data are available, eg. for the AS population, a lack of consistent methodology complicates the interpretation of these rates. Many of the studies identified here show dif-

ferences in more than one factor contributing to variability (e.g. geographic variability, classification criteria, use of crude vs. adjusted rates). This discordance makes it difficult to directly compare rates across studies. Future agreements on the methodology used for these types of studies would improve the comparison across studies and, ultimately, the generalisability of findings. Identification of these literature gaps will direct future efforts to target these areas and move the field forward towards the provision of more accurate and concise incidence and prevalence estimates for the global axSpA population. The results of this review will hopefully motivate future studies looking at population based incidence and prevalence, particularly in nr-axSpA. Additionally, these data provide a foundation for research related to the axSpA patients' journey.

Supplementary data

Search terms

- MeSH terms were used to search for articles relevant to AS Search Strategy (MeSH terms for AS and axSpA and prevalence):
 - Spondyloarthritis Ankylopoietica
 - Ankylosing Spondylarthritis
 - Ankylosing Spondylarthritis
 - Spondylarthritis, Ankylosing
 - Ankylosing Spondylitis
 - Spondylarthritis Ankylopoietica
 - Bechterew Disease
 - Bechterew's Disease
 - Bechterews Disease
 - Marie-Struempell Disease
 - Marie Struempell Disease
 - Rheumatoid Spondylitis
 - Spondylitis, Rheumatoid
 - Spondylitis Ankylopoietica
 - Ankylosing Spondyloarthritis
 - Ankylosing Spondyloarthritis
 - Spondyloarthritis, Ankylosing
 - Spondylarthritis
 - Spinal Arthritis
 - Spinal Arthritis
- Prevalence
 - Health Care Category
 - Environment and Public Health
 - Public Health
 - Epidemiologic Methods
 - Data Collection
 - Vital Statistics
 - Morbidity
 - Incidence
 - Prevalence

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References

1. OLIVIERI I, VAN TUBERGEN A, SALVARANI C *et al.*: Seronegative spondyloarthritis. *Best Pract Res Clin Rheumatol* 2002; 16: 723-39.
2. STOLWIJK C, BOONEN A, VAN TUBERGEN A *et al.*: Epidemiology of spondyloarthritis. *Rheum Dis Clin North Am* 2012; 38: 441-76.
3. LINDEN SVD, VALKENBURG HA, CATS A: Evaluation of diagnostic criteria for ankylosing spondylitis. *Arthritis Rheum* 1984; 27: 361-8.
4. RUDWALEIT M, LANDEWÉ R, VAN DER HEIJDE D *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* 2009; 68: 770-6.
5. WANG R, GABRIEL SE, WARD MM: Progression of patients with non-radiographic axial spondyloarthritis to ankylosing spondylitis: a population-based cohort study. *Arthritis Rheum* 2015.
6. WALLMAN JK, KAPETANOVIC MC, PETERSON IF *et al.*: Comparison of non-radiographic axial spondyloarthritis and ankylosing spondylitis patients baseline characteristics, treatment adherence, and development of clinical variables during three years of anti-TNF therapy in clinical practice. *Arthritis Res Ther* 2015; 17: 1-11.
7. RUDWALEIT M, VAN DER HEIJDE D, LANDEWÉ R *et al.*: The development of Assessment of SpondyloArthritis international Society classification criteria for axial spondyloarthritis (part II): validation and final selection. *Ann Rheum Dis* 2009; 68: 777-83.
8. SIEPER J, KIVITZ A, VAN TUBERGEN A *et al.*: Impact of certolizumab pegol on patient-reported outcomes in patients with axial spondyloarthritis. *Arthritis Care Res* 2015; 67: 1475-80.
9. KILTZ U, BARALIAKOS X, KARAKOSTAS P *et al.*: Do patients with non-radiographic axial spondylarthritis differ from patients with ankylosing spondylitis? *Arthritis Care Res* 2012; 64: 1415-22.
10. VAN DER HEIJDE D, PURCARU O, KAVANAUUGH A: FRI0439 High economic burden of axial spondyloarthritis related to paid work and household productivity at baseline in the rapid-axspa study: differences and similarities between ankylosing spondylitis and non-radiographic axial spondyloarthritis. *Ann Rheum Dis* 2013; 72: A523-A524.
11. RUDWALEIT M, HAIBEL H, BARALIAKOS X *et al.*: The early disease stage in axial spondylarthritis: results from the German Spondyloarthritis Inception Cohort. *Arthritis Rheum* 2009; 60: 717-27.
12. HAROON NN, PATERSON JM, LI P *et al.*: Patients With ankylosing spondylitis have increased cardiovascular and cerebrovascular mortality: a population-based study. *Ann Intern Med* 2015; 163: 409-16.
13. VAN DER HEIJDE D, KIVITZ A, SCHIFF MH *et al.*: Efficacy and safety of adalimumab in patients with ankylosing spondylitis: Results of a multicenter, randomized, double-blind, placebo-controlled trial. *Arthritis Rheum* 2006; 54: 2136-46.
14. SIEPER J, VAN DER HEIJDE D, DOUGADOS M *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* 2013; 72: 815-22.
15. SONG I-H, WEISS A, HERMANN K-GA *et al.*: Similar response rates in patients with ankylosing spondylitis and non-radiographic axial spondyloarthritis after 1 year of treatment with etanercept: results from the ESTHER trial. *Ann Rheum Dis* 2013; 72: 823-5.
16. STOLWIJK C, VAN ONNA M, BOONEN A *et al.*: The global prevalence of spondyloarthritis: A systematic review and meta-regression analysis. *Arthritis Care Res* 2015.
17. MOHER D, LIBERATI A, TETZLAFF J *et al.*: Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Ann Intern Med* 2009; 151: 264-9.
18. GEIRSSON AJ, EYJOLFSDOTTIR H, BJORNSDOTTIR G *et al.*: Prevalence and clinical characteristics of ankylosing spondylitis in Iceland-a nationwide study. *Clin Exp Rheumatol* 2010; 28: 333-40.
19. KOKO V, NDREPEPA A, SKËNDERAJ S *et al.*: An epidemiological study on ankylosing spondylitis in southern Albania. *Materia socio-medica* 2014; 26: 26.
20. BAKLAND G, NOSSENT HC, GRAN JT: Incidence and prevalence of ankylosing spondylitis in Northern Norway. *Arthritis Care Research* 2005; 53: 850-5.
21. HAROON NN, PATERSON JM, LI P *et al.*: Increasing proportion of female patients with ankylosing spondylitis: a population-based study of trends in the incidence and prevalence of AS. *BMJ open* 2014; 4: e006634.
22. HUKUDA S, MINAMI M, SAITO T *et al.*: Spondyloarthropathies in Japan: nationwide questionnaire survey performed by the Japan Ankylosing Spondylitis Society. *J Rheumatol* 2001; 28: 554-9.
23. ONEN F, AKAR S, BIRLIK M *et al.*: Prevalence of ankylosing spondylitis and related spondyloarthritis in an urban area of Izmir, Turkey. *J Rheumatol* 2008; 35: 305-9.
24. ŚLIWCZYŃSKI A, RACIBORSKI F, KŁAK A *et al.*: Prevalence of ankylosing spondylitis in Poland and costs generated by AS patients in the public healthcare system. *Rheumatology Int* 2015; 1-7.
25. LIAO Z, PAN Y, HUANG J *et al.*: An epidemiological survey of low back pain and axial spondyloarthritis in a Chinese Han population. *Scand J Rheumatol* 2009; 38: 455-9.
26. ÇAKIR N, PAMUK ÖN, DERVIŞ E *et al.*: The prevalences of some rheumatic diseases in western Turkey: Havsa study. *Rheumatology Int* 2012; 32: 895-908.

27. DAI S-M, HAN X-H, ZHAO D-B *et al.*: Prevalence of rheumatic symptoms, rheumatoid arthritis, ankylosing spondylitis, and gout in Shanghai, China: a COPCORD study. *J Rheumatol* 2003; 30: 2245-51.
28. HAGLUND E, BREMANDER A, PETERSSON IF *et al.*: Prevalence of spondyloarthritis and its subtypes in southern Sweden. *Ann Rheum Dis* 2011; 70: 943-8.
29. EXARCHOU S, LINDSTRÖM U, ASKLING J *et al.*: The prevalence of clinically diagnosed ankylosing spondylitis and its clinical manifestations: a nationwide register study. *Arthritis Res Ther* 2015; 17: 118.
30. BAKLAND G, ALSING R, SINGH K *et al.*: Assessment of SpondyloArthritis International Society criteria for axial spondyloarthritis in chronic back pain patients with a high prevalence of HLA-B27. *Arthritis Care Res* 2013; 65: 448-53.
31. PELÁEZ-BALLESTAS I, NAVARRO-ZARZA JE, JULIAN B *et al.*: A community-based study on the prevalence of spondyloarthritis and inflammatory back pain in Mexicans. *J Clin Rheumatol* 2013; 19: 57-61.
32. REVEILLE JD, WITTER JP, WEISMAN MH: Prevalence of axial spondylarthritis in the United States: Estimates from a cross-sectional survey. *Arthritis Care Res* 2012; 64: 905-10.
33. BROWN MA, KENNA T, WORDSWORTH BP: Genetics of ankylosing spondylitis [mdash] insights into pathogenesis. *Nat Rev Rheumatol* 2015.
34. CAULI A, DESSOLE G, FIORILLO M *et al.*: Increased level of HLA-B27 expression in ankylosing spondylitis patients compared with healthy HLA-B27 - positive subjects: a possible further susceptibility factor for the development of disease. *Rheumatology* 2002; 41: 1375-9.
35. SHEEHAN NJ: HLA-B27: what's new? *Rheumatology* 2010; 49: 621-31.
36. MUÑOZ-ORTEGO J, VESTERGAARD P, RUBIO JB *et al.*: Ankylosing spondylitis is associated with an increased risk of vertebral and nonvertebral clinical fractures: a population-based cohort study. *J Bone Miner Res* 2014; 29: 1770-6.
37. ROBINSON PC, BROWN MA: The genetics of ankylosing spondylitis and axial spondyloarthritis. *Rheum Dis Clin North Am* 2012; 38: 539-53.
38. ROBINSON PC, BROWN MA: Genetics of ankylosing spondylitis. *Mol Immunol* 2014; 57: 2-11.
39. TSUI FW, TSUI HW, AKRAM A *et al.*: The genetic basis of ankylosing spondylitis: new insights into disease pathogenesis. *Appl Clin Genet* 2014; 7: 105.
40. LIN C-W, HUANG Y-P, CHIU Y-H *et al.*: Increased risk of ischemic stroke in young patients with ankylosing spondylitis: a population based longitudinal follow-up study. *PloS one* 2014; 9: e94027.
41. VAN HOEVEN L, LUIME J, HAN H *et al.*: Identifying axial spondyloarthritis in Dutch primary care patients, ages 20-45 years, with chronic low back pain. *Arthritis Care Res (Hoboken)* 2014; 66: 446-53.
42. MOLL J, WRIGHT V: New York clinical criteria for ankylosing spondylitis. A statistical evaluation. *Ann Rheum Dis* 1973; 32: 354.
43. AMOR B, DOUGADOS M, MIJIYAWA M: [Criteria of the classification of spondylarthropathies]. *Rev Rhum Mal Osteoartic* 1990; 57: 85-9.
44. DOUGADOS M, LINDEN SVD, JUHLIN R *et al.*: The European Spondylarthropathy Study Group preliminary criteria for the classification of spondylarthropathy. *Arthritis Rheum* 1991; 34: 1218-27.
45. ABUL-HUSN NS, OWUSU OBENG A, SANDERSON SC *et al.*: Implementation and utilization of genetic testing in personalized medicine. *Pharmgenomics Pers Med* 2014; 7: 227-40.
46. SOLMAZ D, GUNDUZ O, AKAR S *et al.*: Telephone interview strategy can be used for screening inflammatory back pain in the community. *Int J Rheum Dis* 2015.
47. ALNAQBI KA, TOUMA Z, PASSALENT L *et al.*: Development, sensibility, and reliability of the Toronto Axial Spondyloarthritis Questionnaire in inflammatory bowel disease. *J Rheumatol* 2013; 40: 1726-35.