Published in final edited form as:

Rheum Dis Clin North Am. 2012 August ; 38(3): 441–476. doi:10.1016/j.rdc.2012.09.003.

Epidemiology of Spondyloarthritis

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Synopsis

Spondyloarthritis (SpA) represents a group of interrelated diseases with common clinical features and a close association with HLA-B27. Figures on the incidence and prevalence of diseases vary highly dependent on methodological differences between studies, the case definition used to classify disease and on the prevalence of HLA-B27 in the population studied. When summarizing the available literature, incidence rates of SpA are mainly based on the ESSG criteria and range between 0.48 and 63/100.000 while prevalence rates vary between 0.01 and 2.5%. For ankylosing spondylitis (AS), the most widely recognized representative of the SpA group of diseases, incidence rates of 0.44-7.3/100.000 and prevalence rates of 0.007-1.7% have been described in studies that were based on the (modified) New York criteria to classify cases. The incidence of psoriatic arthritis (PsA) varied from 3.6 up to 23.1/100.000 in different studies and prevalence between <0.1% and 0.4%, using a variety of classification criteria. The incidence of ReA has been estimated between 0.6 up to 28/100.000 in studies based on different source populations and different case definitions. The newly proposed criteria for axial SpA and peripheral SpA present an attractive new approach to facilitate classification of the SpA into two main subtypes and the

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axial SpA criteria allow earlier detection of patients with inflammatory back pain. It should be emphasized that these criteria were developed for use in a (specialized) clinical setting and not for large epidemiological studies.

Keywords

Spondyloarthritis; Ankylosing Spondylitis; Psoriatic arthritis; Reactive arthritis; Epidemiology; Incidence; Prevalence

Introduction

The term spondyloarthritis (SpA) refers to a disease (i.e. for which criteria have been developed) but also to a concept that represents a group of interrelated disorders. Classically these disorders comprise ankylosing spondylitis (AS), psoriatic arthritis (PsA), reactive arthritis (ReA), SpA related to inflammatory bowel disease (IBD-SpA) and undifferentiated SpA (uSpA). More recently a classification into an axial and peripheral disease has been proposed. Phenotypically, these diseases have several features in common including inflammatory back pain, peripheral arthritis (usually an oligoarthritis of the lower limbs), enthesitis, dactylitis, and extra-articular features such as uveitis, psoriasis and IBD. Genetically, the diseases are associated with the major histocompatibility complex class 1 antigen HLA-B27.

Epidemiology is the study of the distribution and the determinants of diseases in human populations. The epidemiology of a disease is the most important determinant of the burden of a disease in a population. This chapter will focus on the epidemiology of SpA all over the world by reviewing the literature on incidence and prevalence of the entire SpA group as well as the specific disorders belonging to SpA. However, it is important to consider first some challenges when determining the epidemiology of a disease. Firstly, the frequency of diseases reported in studies depends on criteria used for confirmation of the presence of a disease in the individual patients. For this purpose, classification criteria have been developed, and depending on the purpose and the methodological approach, they can have different test-characteristics. Secondly, numbers on prevalence and incidence may vary due to differences in study design, including the target population, sampling method and approach to assess the disease criteria. Therefore, these two aspects will be discussed first in the next paragraphs.

Importance of classification criteria and design for epidemiological studies

Classification criteria and their use in large epidemiological studies

In order to reliably estimate the prevalence of a disease, criteria are needed to identify homogenous groups of patients. In the last 50 years, major advances have been made in the recognition and classification of SpA as an entity and the specific disorders belonging to SpA. However, criteria developed for classification might not be useful for conducting epidemiological studies in the population but might be specifically designed for identification of patients attending specialized clinics and for inclusion in trials or observational studies. Classification criteria, in contrast to diagnostic criteria, are designed

for high specificity to avoid misclassification. As a result, they lack sensitivity at early or mild stages of disease, which might be a drawback in epidemiological studies, due to a possible underestimation of the incidence or prevalence of the disease and for diseases which are not frequent, large samples are needed to provide reliable estimates on incidence and prevalence. Secondly, classification criteria might include items, such as technical procedures (for instance, MRI), which might not be feasible for application in large population studies or items that require a specific physician diagnosis (for example, the presence of psoriasis).

Before classification criteria can be developed at all, disease have to be recognized as a 'morbus sui generis' by physicians. It was mainly in the 19th and beginning of the 20th century that that physicians raised the idea of SpA as a distinct disease. In the mid-nineteenth century, several cases of psoriasis in association with arthritis were published by Rayner, Cazenave, Devergre and Gilbert [1]. The name 'psoriasis arthritique' was first introduced in 1860 by skin physician Pierre Bazin. In the same century, the first cases of patients with inflammatory back pain and limited mobility of the spine (or ankylosis in post-mortem studies) were reported by Travers (1824) and Brody (1850) and later by Vladimir Bechterev (1893), Adolf Strümpel (1897) and Pierre Marie (1898). Several names were proposed to distinguish this disease from rheumatoid arthritis, yet the term 'rheumatoid spondylitis' was used for many years and only much later the term AS became widely accepted. In 1916, Hans Reiter contributed to the identification of the disease ReA for patients with arthritis, urethritis and conjunctivitis, although already in 1507 a patient was reported with arthritis in association with urethritis. Later in the 20th century, the association between ulcerative colitis and arthritis was first recognized (1930) and, in 1938, a patient with Crohn's disease was described who developed polyarthritis [1]. The ability to apply the RF-test more widely in the 1950s (after its discovery by Waaler and Rose in 1940 and 1948 respectively), helped to confirm that the entire group of disease described above were distinct from rheumatoid arthritis because they lacked rheumatoid factor and therefore the term 'seronegative variants of rheumatoid arthritis' was introduced. During the 1960s, Moll and Wright observed in family studies the striking association between sacroiliitis/AS and several other disorders such as PsA, ulcerative colitis, and arthritis related to Crohn's disease. In 1974, Moll and Wright established the concept of these disorders and chose as collective name the term 'spondarthritides' [2]. Remarkably, their observation was done without consideration of the HLA-B27 associations (which had only been described the preceding year) but resulted from clinical and radiological findings. The consideration of HLA-B27 in AS and other diseases in SpA, commencing during the 1970s, provided further confirmation of the concept [3].

Once the diseases were well established in clinical rheumatology, the need for classification criteria was recognized in order to be able to create homogenous groups of patients for clinical or population studies. Table 1 represents a chronological overview of the main criteria proposed and used in either clinical or epidemiological studies, with a brief description of the specific aim, methodological approach and description of items within the criteria that might hamper applicability in large epidemiological studies. In 1961, criteria were proposed to identify patients with AS for population surveys (Rome criteria) [4]. They required either the presence of four out of five clinical criteria or a sixth criterion

(radiographic sacroiliitis) plus one of the clinical criteria. The Rome criteria were based on expert opinion, but when evaluated later in a population study among American indigenous groups, the role of the radiographs was not found to be satisfactory [5]. This led to the revision of the Rome criteria into the New York criteria [6]. In New York, an expert committee agreed that for epidemiological purposes the diagnosis of AS should not be made without x-ray evidence of sacroiliitis, and therefore the presence of sacroiliitis was required for fulfillment of the criteria. Further, the clinical items were revised in an attempt to make them more objective. In an evaluation of the New York criteria, Moll and Wright found that the clinical criteria failed in terms of sensitivity and specificity [7]. Therefore, a modification was proposed in 1984, *the modified New York criteria* (mNY), in which an item for inflammatory back pain was added, but the radiographic criterion was kept [8]. Since then, the mNY criteria have been the most widely applied criteria in both clinical and epidemiological studies in AS. The main restriction of these criteria for use in epidemiological studies is that, although they perform well in established disease, they lack sensitivity in the early disease stage, in which radiographic damage is not yet visible, which could cause a delay up to 6-8 years in diagnosis [9].

For PsA, the first classification criteria were proposed in 1973 by Moll and Wright and required inflammatory arthritis, presence of psoriasis, and absence of rheumatoid factor [10]. These criteria discriminated poorly between psoriatic and rheumatoid arthritis. More sensitive criteria for clinical studies were proposed by Vasey and Espinoza, by McGonagle et al, and by Gladman, but none of them have been widely adopted nor validated at a satisfactory level [11]. Therefore, the CLASSification of Psoriatic Arthritis (CASPAR) criteria were developed in 2006 by the GRAPPA group [12]. The CASPAR criteria are easy to use and likely to perform well, although classifying early disease is the most important limitation of the criteria. Further, the sensitivity of the CASPAR criteria for use in epidemiological studies is not clear.

For ReA, despite several attempts, no universal validated classification or diagnostic criteria are available. Based on discussions at the 4th International Workshop on Reactive Arthritis in 1999, a consensus was achieved that the term ReA should be confined to patients, who present with clinical features typical of ReA, and in whom the preceding infection is caused by a microbe, which is commonly associated with ReA [13]. Further, preliminary, classification criteria for ReA were proposed but have never been validated. On the same line, no formal classification criteria for IBD-SpA or uSpA have been developed to our knowledge.

It was recognized that there also was a need for criteria to classify the whole spectrum of SpA, comprising the specified as well as unspecified forms of the disease. For this purpose, the European Spondyloarthritis Study Group (ESSG) and Amor criteria were developed in the early 1990s [14, 15]. They both cover the whole spectrum of SpA and include at the same time the axial and peripheral manifestations but also give weight to other features of the SpA concept not related to spinal or articular symptoms. The ESSG-criteria are easy to apply and therefore often used in epidemiological studies. However, it has been shown that these criteria sets lack sensitivity and specificity [16, 17]. Considering these drawbacks, efforts have been made in the last years to standardize and improve the making of an early

diagnosis, and new classification criteria have been established by the Assessment of SpondyloArthritis International Society (ASAS) [18, 19]. According to these new ASAS classification criteria, SpA is divided into predominantly axial involvement and predominantly peripheral manifestations. According to the ASAS axial SpA criteria, a patient suffering from chronic back pain with age at onset before 45 years can be classified as having axial SpA if sacroiliitis on imaging (radiographs or MRI) is present plus at least one SpA feature, or, in the absence of sacroiliitis on imaging, if HLA-B27 is positive plus at least two other SpA features. A patient can be classified as having peripheral SpA, if peripheral arthritis, enthesitis or dactylitis is present, plus at least one or two other SpA features. The advantage of the ASAS axial SpA criteria is the inclusion of MRI, which is able to show inflammation of the sacroiliac joints in an early stage of disease. The ASAS axial SpA criteria have shown to perform well, also in early stages of disease [19]. However, the inclusion of MRI and HLA-B27 testing make them infeasible for use in large epidemiologic studies. Power requirements to determine the prevalence of an uncommon disease hamper the application in large studies when MRI would be needed in a large proportion of patients. Not only are such exams expensive, but classification of abnormalities on MRI should have sufficient specificity to avoid overdiagnosis. However, also including plain X-rays in large population studies is a challenge, not in the least because ethical committees would raise objections against radiographs in healthy subjects.

Having elaborated on classification-criteria, we acknowledged that the ASAS criteria cannot simply be applied in large epidemiological (population) studies. Several alternative approaches can be seen in the literature. A two stage approach can be used, in which subjects are pre-screened by questionnaires and are invited for further exams in case of suspicion based on the (sensitive) screening question. In addition, other criteria such as ICD codes, insurance claims, or patients' reported physician made diagnoses have been used in epidemiological studies. All these alternative choices make assumptions with regard to accuracy of the diagnosis but none of them are accurate against true evaluation by classification criteria.

Quality of study design for prevalence and incidence studies

Decisions in policy and health care utilization are often influenced by prevalence and incidence of chronic diseases [20]. Therefore, studies on prevalence and incidence should be unbiased, high quality studies. However, these studies are always observational and this evidence is generally considered as low. Two sets of guidelines can be recognized when considering quality of (observational) studies. Firstly, guidelines can define how to conduct a study to the highest possible standards. For example, the initiative named Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) developed a checklist of 22 items, with recommendations about what should be included in a more accurate and complete description of observational studies [21]. Secondly, guidelines may define how to assess the risk of bias of individual studies when aggregating them in a systematic review. This is important, since a study may be performed to the highest possible standards, yet still has a high risk of bias. In 2006, Croft reported that the assessment of the quality or risk of bias of reviews on observational studies was rarely done and often incomplete because of lack of instruments and guidance, in particular for studies on incidence and prevalence (22).

Since then, much effort has been done to improve this shortcoming. Sanderson identified in a review 86 approaches to assess risk of bias in observational studies and concluded there was a need for more reliable tools (23). Shamlian et al reviewed tools to assess the quality and/or risk of bias of prevalence and incidence studies and reported the absence of agreement on type of items and way to score items, likely reflecting the need for extensive adaptations depending on the specific disease and population of interest (refer). In the same paper, they present a new checklist to assess the methodological and reporting quality of observational studies of incidence and prevalence that was mainly based on the review of existing instruments and expert knowledge (Delphi) [24]. Two aspects can be distinguished: (1) external validity, which is defined as the extent to which the results of a study can be generalized to the target population, and (2) internal validity, which is the extent to which the results of a study are correct for the subjects. When testing the tool, interrater agreement was poor and the authors recommended further testing of checklists. Recently, Hoy et al. developed another tool for risk of bias of prevalence studies [25]. This tool makes a distinction between assessing whether the research was conducted to the highest possible standards (methodological quality) and to which the results can be believed (risk of bias). The items in this risk of bias tool include the following questions (a ‘yes’-answer implicating a low risk of bias and a ‘no’-answer a high risk of bias):

External validity:

1. Was the target population a close representation of the general population?
2. Was the sampling frame a close representation of the target population?
3. Was some form of random selection used to select the sample?
4. Was the likelihood of non-response bias minimal?

Internal validity:

5. Were data collected directly from the subjects?
6. Was an acceptable case definition used?
7. Was the study instrument that measured the parameter of interest shown to have reliability and validity?
8. Was the same mode of data collection used for all subjects?
9. Was the length of the shortest prevalence period for the parameter of interest appropriate?
10. Were the numerator and denominator for the parameter of interest appropriate?

When interpreting studies on incidence and prevalence of SpA, these important questions were considered in the present review.

Literature review on prevalence and incidence SpA

Search strategy and appraisal

To be able to present a clear picture on the epidemiology of the SpA, an electronic search of PubMed was performed up to July 2012 using the following search terms: “spondyloarthritis”, “spondyloarthropathy”, “ankylosing spondylitis”, “psoriatic arthritis”, “reactive arthritis”, undifferentiated spondyloarthritis”, “incidence”, “prevalence”, and “epidemiology”. We limited our search to original articles and reviews published in English. Further, the reference lists of articles identified by the search strategy were searched. The search and selection of articles was done by one person mostly. Since this report did not have the intention to be a systematic review, no formal assessment or risk of bias was

performed but along the data extraction the main items for external and internal validity were checked and included in the tables (see tables 2-9).

Distribution HLA-B27 worldwide

It is well known that the prevalence of SpA and SpA related diseases show considerable differences among ethnic groups and populations. Partly this can be explained by differences in the prevalence of HLA-B27, with which the prevalence of SpA, and in particular AS, is roughly related. However, it should be noted there are very few studies on HLA-B27 prevalence that are truly population based or nationally representative. The prevalence of HLA-B27 is highest in the Pawaia tribe in Papua New Guinea (53%) [26], the Haida indigenous Americans on the Queen Charlotte Islands in Western Canada (50%) [27] and Chukotka Eskimos in Eastern Russia (40%) [28]. In Northern Scandinavian countries, HLA-B27 positivity is also reported to be common (15-25%) [29-31]. In the Western European population, the prevalence of HLA-B27 is estimated 4-13%, whereas HLA-B27 positivity is uncommon in the Arab countries (2-5%) [32] and Japan (1%) [33].

Overall, most patients with AS possess HLA-B27. Approximately 90% of the patients with AS of Germanic and northern European extraction are HLA-B27 positive. However, there are some racial differences. AS is virtually absent among South-American Indians, Australian Aborigines and African blacks [34]. Among blacks, the B27-negative AS forms a much greater proportion of AS patients (<60%) [35], probably because of the increased significance of non-B27 alleles. Also in the Middle East, the strength of the association is relatively weak compared with Western countries (25-75%) [36-38] and in sub-Saharan Africa the prevalence of HLA-B27 in patients with AS is reported to be very low. This was indirectly confirmed in a US multi-racial/ethnic study. National Health and Nutrition Examination Survey (NHANES)-2009 was the first nationally representative and population based prevalence of HLA-B27 in the US (6.1%), that was appropriately powered for whites (7.5%) and Mexican Americans (4.6%) but lacked power to guarantee the accuracy of the 1.1% frequency observed in African Americans [39]. The relation of HLA-B27 with other SpA subtypes is weaker compared to AS and is reported to be up to 70% in patients with ReA; 60-70% of patients with axial PsA; 25% of patients with peripheral PsA and up to 70% in patients with IBD-SpA [40, 41]. Different subtypes of HLA-B27 can be found throughout the world with different strengths of association with AS. HLA-B*2705 and B*2702 are the primary subtypes in Caucasians, B*2704 and B*2705 in Eastern Asia and B*2708 in Southern Asia [40]. Other subtypes (B*2706 and B*2709) were thought to be protective for the disease, although with both subtypes, AS cases have now been reported [41].

Incidence and prevalence of spondyloarthritis

Incidence—Only 4 studies reported the incidence of SpA as a disease entity which varied from 0.48 in Japan to 62.5/100.000 in Spain (Table 2). The low prevalence in Japan coincides with a very low prevalence of HLA-B27 (<0.5%). The study was based on a nationwide questionnaire survey in which physicians of institutes with possible SpA patients were asked to review the medical records [33]. SpA was classified based on clinical and radiographic features. The incidence was determined with the assumption that at least one-

tenth of the SpA population was recruited by the survey and was estimated not to exceed 0.48/100.000 person-years. The two most prevalent SpA subtypes were AS (68.3% of SpA) and PsA (12.7% of SpA). In a study from Finland, based on referrals to rheumatology outpatient clinics, the annual incidence of SpA was 52/100.000 person years [42], with PsA as most prevalent subtype (44.4%), followed by uSpA (25%). Another study from Finland, which used records of a nationwide insurance program, estimated an overall incidence of SpA of 19/100.000. This study only included patients who needed medical treatment for their condition [43]. Also in this study, PsA was the most frequent subtype (37%), followed by AS (32%).

In the last years, the importance of an early diagnosis of SpA has become clear and efforts have been made to diagnosis patients in an early stage. In a study from Spain, general practitioners in Madrid were asked and trained to refer all patients under 45 years with either inflammatory back pain or asymmetric arthritis of lower limbs with 3-24 months symptom duration to a specialized early arthritis clinic during 6 consecutive months [44]. Case definition was based on the ESSG criteria. The annual estimated incidence of SpA was 62.5/100.000, suggesting a high incidence of early SpA. However, ESSG criteria were used as gold standard, although it has been described that only 50% of the patients who fulfill the ESSG criteria are still classified as SpA five years later [16].

Prevalence—Sixteen studies reported data on the prevalence of SpA, which varied from 0.01% in Japan to 2.5 % in Alaska (Table 3). The highest prevalence of 2.5% in Alaskan Eskimos was based on combined ESSG and Amor criteria [45, 46]. However, most studies on prevalence of SpA are conducted in Europe. In a study from France prevalence of SpA was estimated to be 0.30% [47]. The study was based on a telephone survey in which a random sample of telephone numbers was selected and patients were asked if a diagnosis of SpA was ever made. Only patients with suspected SpA were called by a rheumatologist. This method probably underestimated the prevalence of SpA since only patients with a diagnosis were captured. Another telephone survey population study from France revealed a prevalence of 0.47%, which was nearly similar to the prevalence of rheumatoid arthritis in the same survey [48]. A study from Lithuania, using the same methodology as the study from France, estimated a SpA prevalence of 0.84% [49]. As indicated, not only the sensitivity of the initial screening question, but also possible bias in persons having or having not a telephone (possibly disfavoring persons of lower socio-economic status) should be taken into account when interpreting the figures. In a German study, 348 blood donors of which half were HLA-B27 positive were screened for SpA using the ESSG criteria and included the use of MRI for diagnosing early AS [50]. The estimated prevalence of SpA among the adult population was estimated at 1.9%, although this number was later adjusted to 1.73% (to adjust for selection bias when generalizing blood donors to the general population) [51]. However, it is doubtful if blood donors are a truly representative sample of the general population. In a Turkish population study 145 out of 2887 subjects who responded positively on a questionnaire were evaluated by a rheumatologist and showed a prevalence of 1.05% according to the ESSG criteria [50]. A comparable prevalence of SpA was reported in a study in central Italy (1.1%), despite the low HLA-B27 prevalence in Italy [51]. In this study, the most common form of SpA was PsA (38%) followed by AS (34%). A

population study in persons older than 50 years of age from the Azores, Portugal, estimated the overall prevalence of SpA according to the ESSG criteria at 1.6%, and remarkably only one in seven patients had a previous diagnosis of SpA [52]. In a population based epidemiological study in Greece, the estimated prevalence of SpA was 0.49% [55].

Recently, a prevalence study of SpA has been conducted in the USA. Both, ESSG (using 4 of 7 items) and Amor criteria (using 6 of 11 items) had been assessed in a representative sample of 5013 US adults aged 20-69 years along the 2009-2010 US National Health and Nutrition Examination Survey (NHANES). The overall age adjusted prevalence of SpA using the Amor criteria was 0.9% and when using the ESSG criteria 1.4% [56]. It should be noted that not all items required for the ESSG and Amor criteria could be assessed as it concerned a self-report questionnaire excluding items based on spinal mobility, laboratory assessment or radiography.

In most parts of Asia, the prevalence of SpA tends to be lower than in other countries in the world. A recent review from China estimated the prevalence between 0.49-0.93% [57]. However, a remarkably lower prevalence of SpA of 0.0095% was reported in the study from Japan [31]. In Thailand and Vietnam prevalences were estimated of 0.12% and 0.28% resp. [58, 59]. In the Middle-East, the prevalence of SpA is relatively low. A study from Iran estimated a prevalence of 0.23% and in Pakistan of 0.1%. It should be noted that the studies from China, Thailand, Vietnam, Iran and Pakistan were Community-Oriented Program for the Control of rheumatic disease (COPCORD) studies, which is a program to estimate the burden of pain, arthritis and disability in the community with the aim to improve musculoskeletal health. Providing accurate prevalence information is not the main focus of the program.

The limited number of studies that performed further subtyping suggested invariably that within patients with SpA a large proportion have undifferentiated SpA, a disease entity that cannot be classified further into AS, PsA or ReA. [46,48,50]

Phenotypic variations within SpA—Table 3 shows that data on gender diversity in the occurrence of SpA are conflicting. A recent English study in patients with SpA showed that female disease likewise was at least as severe as male disease [80]. In the same study, a slightly different phenotype was among sexes found. Women predominantly suffered from upper axial disease, together with stiffness, fatigue, and enthesitis. In contrast, men predominantly suffered from peripheral joint disease, whereas back pain was equally frequent in both sexes [80]. A study from Brazil found that female gender was more frequently associated with peripheral SpA, upper limb arthritis, dactylitis, psoriasis, nail involvement and family history of SpA, and male gender with pure axial involvement, radiographic sacroiliitis and positive HLA-B27. The number of painful and swollen joints was significantly higher in females [81].

Epidemiology of ankylosing spondylitis

Incidence—Eight studies addressed the incidence of AS, which varied from 0.44/100.000 persons in Iceland to 7.3/100.000 in US and Northern Norway (Table 4). Using data from the population-based Rochester epidemiology project, collected between 1935 and 1989, the

overall age- and sex-adjusted incidence rate in Minnesota was 7.3/100.000 person-years [60]. This incidence rate tended to decline between 1935 and 1989, but there was little change in the age at symptom onset or at diagnosis over the 55-year study period. A Finnish study using the nationwide sickness insurance scheme estimated the incidence of AS requiring antirheumatic medications at 6.9/100.000 with no change over time [61]. Studies from Norway and Czechoslovakia showed comparable incidences of AS of 7.3/100.000 and 6.4/100.000 respectively [62, 63]. The incidence in a study from Greece was found to be lower (1.5/100.000) [64]. The incidence in Japan was estimated at 0.48/100.000 [33].

Prevalence—Thirty –one studies reported on the prevalence of AS, which varied from < 0.01% in Japan to 1.8% in Norwegian Samis (Lapps) (Table 1). The highest prevalence of AS was found in a study in Haida indigenous Americans in Canada (6-10%), in line with the high HLA-B27 positivity among this population [27]. Another study in Alaskan Eskimos however, in whom the prevalence of HLA-B27 was also high (25-40%) reported a prevalence of only 0.4% [45, 46]. Most studies were conducted in Europe and prevalence of AS followed the geographic distribution of HLA-B27 with the highest prevalence of AS in Northern Norway. A study in Samis (Lapps) in whom the prevalence of HLA-B27 is 24%, reported a prevalence of 1.8% while an epidemiological survey among males and females in the young middle-aged population in Tromsø showed a prevalence of 1.1-1.4% [29,31. In contrast, a third study from Northern Norway, showed a prevalence of only 0.31% [62]. However, this study was hospital-based using medical record data and therefore only included patients with AS under care of a rheumatologist, likely representing the severe spectrum of the disease. In Central and Western Europe, population based studies from Czechoslovakia and Germany reported a relatively high prevalence of AS (0.9% and 0.86% resp.) [50, 63]. The prevalence of AS in the German blood donor study was later adjusted (for representativeness of blood donors for the general population) to 0.55% to account for sampling among blood donors [51]. According to a population-based study in Turkey the prevalence of AS in urban areas is 0.49% [52]. Lower prevalence rates of AS in Europe have been reported in population based studies from Greece (0.24%) [64]; a sample study of the Finish population 30 years of age (0.15%) [61]; and in studies from Hungary (0.23%) [65], and the Netherlands (0.24%) [66]. In an older study in the USA, the overall prevalence of AS in a mainly Caucasian population was reported to be 0.13% [67]. This study only included patients who sought medical care for their condition, and therefore the reported number is probably an underestimation. On the other hand, NHANES I (1971-1975) examined 6,913 participants between the ages of 25 and 74, obtaining pelvic radiographs in all but 2,010 of these individuals (the latter being women under the age of 50 years) [68]. The prevalence of severe or moderate radiographic sacroiliitis in men was 7.3 per 1000 in men (0.73%), and in women over 50 3.0 per 1000 (0.3%). How many had AS by modified New York criteria was not ascertained, as questions regarding inflammatory back pain (IBP) or measurements of spinal mobility were not done. The prevalence of AS in black Americans might be about one third of that in whites, although there is only indirect evidence for this [35]. Only a few studies reported on the prevalence of AS in Asia. The lowest prevalence of AS was found in Japan (0.0065%) [33]. The prevalence in Taiwan was somewhat higher: 0.19-0.54% [69]. In China, a recent review reported prevalence rates of AS ranging from 0.11-0.41% in different studies [55]. For the Middle East, limited available

data showed that AS is relatively uncommon in this part of the world. In Iraq a prevalence was reported of 0.07% [70] and in Iran of 0.14 [71]. For Australia, there is no evidence to support the occurrence of AS in the indigenous Australian Aborigines with pure ancestry, probably related to the very low frequency of HLA-B27 in this population [72]. Studies from Latin-America and Africa are scarce. A community-based COPCORD door-to-door study in 4059 subjects aged older than 18 years in Mexico, estimated a prevalence of AS of 0.02% [73]. AS is virtually absent in African blacks. In a study from Togo, there were only nine Togolese AS patients seen among all 2030 patients attending the rheumatology unit of a teaching hospital over a period of 27 months [74]. Also other studies from South-Africa and Zimbabwe showed that AS was extremely rare among African blacks [74, 75]. This can be expected due to the low prevalence of HLA-B27 in these populations. In addition, a study from Gambia found that the risk of developing AS was also small in HLA-B27 positive Gambians, compared to those of HLA-B27 negative Caucasians, suggesting a non-B27 protective factor reducing the prevalence of AS in this population [75].

HLA-B27 as risk for occurrence and phenotypic heterogeneity (severity) severity of AS

The prevalence of AS among persons carrying HLA-B27 varies substantially in epidemiological reports throughout the world. In the Netherlands, 2% of HLA-B27 positive subjects suffer from AS [10], but in northern Norway, 6.7% of HLA-B27+ may develop AS [29] and according to the blood donor study from Germany 6.4% [50]. Further, it has been shown that the risk of developing AS is much higher for HLA-B27+ first-degree relatives of HLA-B27+ AS patients (10-30%) [66].

The phenotype of the disease also differs among HLA B27+ and HLA B27- patients. In a large study of 1080 patient with AS, HLA-B27- patients were significantly older at disease onset [76]. The distribution in age and disease onset was significantly wider in B27- than in B27+ AS. The percentages with childhood disease did not differ significantly, whereas the percentage of late onset was significantly greater among B27- patients with AS. With respect to clinical manifestations, HLA-B27+ patients more frequently suffered from acute anterior uveitis than B27- patients [76]. Observations were conformed in some smaller studies [77,78].

Differences between male and female patients with AS

AS is traditionally considered as a predominantly male disease, with a commonly reported male:female ratio around 3:1. However, a study of 3000 members of the German Ankylosing Spondylitis Society, found a continuous increase in the percentage of females among patients diagnosed with AS in the last decades [79]. In 1960, only 10% of diagnosed AS patients were females increasing to 46% of the patients diagnosed since 1990. This suggests that the male predominance in AS may be, at least in part, an artifact induced by deficits in the diagnosis of AS among women many decades ago. In the same study it was shown that the age of disease onset was not significantly different between males and females, but there was a significantly longer delay in diagnosis among females. Moreover, a slower progression rate for spinal ankylosis was found in female patients, although they reported significantly more pain and need for drug therapy.

In a study from Mexico, it has been suggested that females have less severe disease, resulting in less disability [80]. A study with 769 patients with AS from the US (556 men, 213 women) showed no gender differences in cervical or lumbar radiographic severity [81].

Prevalence of extra-articular SpA features in AS

While the Rome and mNY criteria focused only on axial features to classify AS, extra-articular manifestations, including uveitis, psoriasis and inflammatory bowel disease, are also inherently part of the SpA concept since they occur much more frequently in patients with SpA/AS than would be expected from the general population. In the new ASAS axial SpA classification criteria, these features are now part of the classification. When summarizing the literature, the prevalence of uveitis was reported 33.2% (SD 0.8) in patients with a mean disease duration of 17.0 (SD 1.0) years [82]. The prevalence increased with longer disease duration. There are no exact data on the prevalence of psoriasis and IBD in AS, estimates vary for psoriasis from 10 to 25% and for IBD from 5 to 10% of patients [83]. In 236 AS patients included in the German Spondyloarthritis Inception cohort (GESPIC), psoriasis was present in 10.2% of AS patients and IBD in 2.6% patients [84]. Another cohort from France (DESIR) included 181 patients fulfilling the mNY criteria. IBD was present in 7.2% and psoriasis in 14.4% of patients [85].

Epidemiology of psoriatic arthritis

Incidence—The incidence of PsA reported in 7 studies varies from 0.1/100.000 in the Japan to 23.1/100.0000 in Finland (Table 6). The study reporting the lowest incidence in a study from Japan was based on a questionnaire sent to all medical institutions of the country potentially to be attended by patients with SpA [33]. Physicians at the institutes were asked to review the medical records. The incidence rates reported in several studies from Finland, Sweden, Czechoslovakia, Greece, Argentina and the USA were fairly uniform ranging from 3.0 to 8/100.000 [63, 86-90]. However, data from two Finnish studies were conflicting. In one study which examined all patients who were entitled under the nationwide sickness insurance scheme to receive medication for PsA, the annual incidence was 6/100.000 between 1990 and 1995 [86]. In a second study, the incidence was higher (23/100.000) [40]. In this study, information about the study was given through a local newspaper, and subjects attended one health center and two local hospitals for study. Classification was based on the presence of psoriasis and arthritis, excluding RF-positive polyarthritis or spondylitis with psoriasis. A study in the USA used the population-based data resources of the Rochester Epidemiology Project to identify all cases of inflammatory arthritis with a definite diagnosis of psoriasis between 1982 and 1991. The age- and sex- adjusted annual incidence rate was 6.6/100.000. A recent study in the same population, identified a population-based incidence cohort of subjects aged 18 years or over who fulfilled the CASPAR criteria between 1970 and 1999 and studied time trends of PsA incidence [91]. The overall age- and sex-adjusted incidence of PsA per 100.000 significantly increased from 3.6 between 1970 and 1979 to 9.8 between 1990 and 2000.

Prevalence—The prevalence of psoriatic arthritis is reported for 16 studies, and ranged between 0.02% in China and Mexico to 0.42% in Italy (Table 7). The majority of studies were performed in Europe and the USA [45, 62, 85, 88, 89, 90, 91]. Cross-sectional

population surveys that collect data directly from subjects reported a higher prevalence than retrospective studies which were based on medical record review. Most studies used the coexistence of psoriasis and arthritis, others the ESSG criteria. In a study from South-America (Argentina) based on the CASPAR criteria, the prevalence was 0.07% [88]. In a North-American study that used the CASPAR criteria (the Rochester epidemiology study), the point prevalence was 0.16% in 2000 [91]. In a study from Japan the prevalence was very low: 0.001% [31]. Studies from Africa, large parts of Asia and South-America are lacking.

Prevalence in patients with psoriasis

Among patients with psoriasis, the prevalence of PsA ranges between 6% and 42% in studies from Europe, USA and South-Africa, but figures are lower in Asian countries (1-9%) [94]. Some recent studies base the classification on the CASPAR criteria: in a study from the UK the prevalence was 13.8% among psoriasis patients [93] and a Chinese study found a prevalence of 5.8% [96]. Further, it is recognized that the underdiagnosis of PsA is probably high. In a study of 100 consecutive psoriasis patients without known PsA, the disease was diagnosed in 29% [97].

Epidemiology of IBD-SpA

Prevalence—Epidemiological studies of IBD-related SpA are scarce and present only data on prevalence. A prevalence of 0.09% was estimated in an Italian population study and of 0.02% in a Swedish study (Table 10). In patients with different forms of SpA about 60-70% have gut inflammation, which is mainly chronic inflammation discovered by endoscopy [98-100]. In 7% of SpA patients, this will develop to overt IBD [101].

Prevalence of SpA in patients with IBD—IBD has an estimated prevalence in the general population ranging from 0.01 to 0.5%, with highest numbers reported in studies from Western Europe and the USA [102]. Any spinal or articular SpA manifestation was found in 17 to 62% of patients. Peripheral arthritis has been reported in 5-28% of patients, predominantly in Crohn's disease. [103-109]. Twelve to 46% of patients with IBD fulfilled classification of SpA when applying the ESSG criteria and 2% to 10% of patients fulfilled the mNY criteria [103-108, 110-112]. Radiological evidence of sacroiliitis has been reported much more frequently: in 2% to 18% on plain X-rays and in 29% of patients on computed tomography (CT), of which only 3% were symptomatic [104, 105, 107, 110, 112, 113]. The frequency of HLA-B27 is generally not increased in the IBD population. The prevalence of HLA-B27 in a study in 406 patients with IBD from Norway was 13%, comparable with the general population in that area (10%), while in patients with c AS, the prevalence of HLA-B27 was 73% [110].

Epidemiology of reactive arthritis

Incidence—Six studies reported on the incidence of ReA and figures varied from 0.6-3.1/100.000 in Minnesota and Oregon, USA to 28/100.000 in South Sweden (Table 8). Most epidemiologic data of ReA are based on outbreak studies in which patients with joint symptoms during and after the infection are traced with questionnaire or other investigations. The large difference in criteria used, but more importantly in the population sampled, resulted in a wide variation in the estimate of the incidence of ReA which varies

between 0.6 and 28/100.000 subjects in population studies [116]. In a study from the USA, telephone interviews were performed of individuals with a confirmed infection of *Campylobacter*, *E. Coli*, *Salmonella*, *Shigella* and *Yersinia* and patients were asked for new onset rheumatologic symptoms [117]. Possible ReA patients were invited for physical examination. The estimated incidence of ReA was 0.6/100.000 subjects in the area of the outbreak when assuming that none of the non-responders would have SpA, up to 3.1/100.000 when assuming that the non-responders were equally likely to have ReA as the responders. In this study, no association between ReA and HLA-B27 was found. In a study from Czechoslovakia, patients with suspected symptoms of ReA were referred by their general physician to a rheumatologist. An age-standardized incidence of 9.3/100.000 subjects was found [63]. As the course of ReA may be self-limiting, not everyone with ReA might have sought help. Higher incidence rates (10-28/100.000) were found in studies from Scandinavian countries, where the prevalence of HLA-B27 is relatively high [42, 88, 118, 119]. The highest incidence of 28/100.000 was found in a study from Sweden, in which all suspected patients were referred from primary health care centers to a rheumatologist [88]. A recent review showed that, in outbreak studies, the occurrence of ReA after an infection of *Campylobacter* have been reported in 0.7-1.8% of patients; after a *Shigella* infection in 0-6.9% of patients; after a *Yersinia* infection in 0-21% of patients; and after a *Salmonella* infection in 0-29% of patients [116].

Prevalence—The prevalence of acute ReA arthritis has been estimated between 0.09% and 1.0%, depending on criteria used for diagnosis, racial/ethnic differences and the setting in which the study was undertaken (hospital series versus single-source outbreaks versus community-based series) (Table 9) [120]. Interestingly, no data are available from Scandinavian countries.

HLA-B27 in ReA—In contrast to the population based study from the USA, the risk of ReA in HLA-B27-positive patients has been reported in another study to be up to 50 times higher after the exposure of a triggering infection compared to HLA-B27-negative patients in hospital-based studies [121]. However, this number is possibly (partly) biased due to inclusion of the most severe cases in hospital based studies.

Epidemiology of undifferentiated SpA

No formal definition or classification criteria for USpA exists. Case definitions used comprise either incomplete forms of distinctly defined entities (“pre-radiographic phase of mNY AS”, “SpA not fulfilling all required ESSG or AMOR criteria”) or disease descriptions that fulfill ESSG or AMOR criteria but cannot be specified further into a specific SpA disease. There are few data on prevalence and incidence of uSpA. Limited data from Europe [48, 50] and Alaska [46] suggest that approximately 40% of patients with SpA have “undifferentiated” spondyloarthritis. Interestingly, some longitudinal studies are available in which patients with uSpA are followed prospectively. In a study from Brazil, 111 patients with uSpA fulfilling the ESSG and Amor criteria were followed up for 10 years. During the follow-up, 27 patients progressed to AS (24.3%) and 3 to PsA (2.7%), while 25 patients (22.5%) went into remission. HLA-B27 and buttock pain were independently associated with progression to AS [122].

Epidemiology and new classification criteria

Epidemiology of axial SpA

Axial SpA comprises AS and non-radiographic axial SpA. Epidemiological studies applying these criteria are not yet available and as indicated, these criteria were not developed for use in large population studies. However, there is an interesting report that applied the criteria in a general practitioner setting. In a study in Rotterdam, the Netherlands, 364 patients with chronic low back pain were identified from GP records. They underwent a complete history and physical examination by a rheumatologist, HLA-B27 was assessed and sacroiliac joints were imaged by conventional radiography and MRI. The overall point prevalence of axial SpA was 21.5% using the ASAS criteria, of which 67.5% were diagnosed by MRI and 15.5% were diagnosed by a positive HLA-B27 and two other SpA features. Of all patients, 6.6% fulfilled the mNY criteria for AS. In this study, three times as many patients were diagnosed as compared to the mNY criteria using conventional X-ray alone. Adding HLA-B27 increased the likelihood of diagnosis of SpA by 68%, and using X-rays increased the likelihood by 75% [129]

Summary

Data on prevalence and incidence of the SpA have become particularly important in the last years since more treatments have become available, making it necessary to gain insight whether or not patients have sought medical attention and to know what the impact on society would be in terms of health and costs when all patients would require a specific treatment approach. However, large variations in the population incidence and prevalence of SpA (as a disease entity) and its subtypes were seen when reviewing the existing literature. Partly, these variations could be attributed by the geographic distribution of HLA-B27, a main risk factor for SpA and explaining high figures for the Northern countries and low figures in the Japan and Middle Africa. However, also when concentrating on data from West-European countries and the USA, large differences remained. Not only differences in the way the target population was sampled, but also large differences in the approach to operationalize criteria to identify cases contributing to such differences. Overall, SpA as a disease is quite prevalent with figures in Western European countries between 0.3 and 2.5%. When subtyping SpA, undifferentiated SpA seems to make up about 40% of these cases. Prevalence of AS and PsA seem about similar in Western countries with figures up to 0.53 %. Although the prevalence of ReA and IBD-SpA seems somewhat lower it should also be realized there were fewer studies available and likely the case finding in epidemiological studies is even more challenging. Most recently, a new disease concept, called axial SpA has been developed including (besides AS) patients with non-radiological axial SpA and criteria for use in a clinical setting have been proposed. It will be particularly challenging to know whether this would be similar when cases are identified in unselected populations.

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Key points

- Data on incidence and prevalence become increasingly important not only for clinicians when trying to understand disease patterns but also for policy makers that need to be informed on budget of health impact of disease and their treatment at the population level. Hence the need for accurate data on incidence and prevalence.
- The variation in incidence and prevalence of SpA as a disease and the SpA subtypes varies highly and this cannot only be attributed to geographical variation in the prevalence of HLA-B27. As part of this variation likely will be explained by variation in quality and bias of the methodological approaches, the recently generic guidelines for performance of studies on incidence and prevalence could be adapted for use in the SpA
- A particular challenge will be to agree on a series of approaches with acceptable (low) risk of bias that could operationalize the present classification criteria (which are developed for use in a (specialized) clinical setting) for use in large epidemiological studies.
- While a large part of the SpA subtypes in epidemiological studies are as yet classified as ‘undifferentiated SpA’, this diagnosis will likely disappear with the acceptance of the new concepts and classification of axial- and peripheral SpA. The application of these criteria in epidemiological studies requires further consideration.
- Remarkably limited data are available on the prevalence of IBD related SpA and ReA. The new peripheral SpA criteria would likely encompass both entities, but the transient nature of ReA makes prevalence estimates especially challenging.

Table 1

Overview the most commonly used classification criteria for SpA and specific diseases of the SpA concept showing some relevant characteristics when considering large epidemiological studies.

Classification criteria, year of publication	Purpose	Method of development	Entry or required criteria (obliged)	Clinical criteria	Radiographic or laboratory criteria
Rome-criteria for AS, 1963 [4]	Population studies	Clinical experience of rheumatologists	-	- axial symptoms - limitation in mobility - extra-articular (uveitis)	- sacroiliitis (radiographic)
New York criteria for AS, 1966 [6]	Population studies	Clinical experience and results of a study of performance of Rome criteria	Radiographic sacroiliitis	- axial symptoms - limitation in mobility	- sacroiliitis (radiographic)
Modified New York criteria for AS, 1984 [8]	Diagnosis and clinical studies	Modification of NY criteria by experts based on results of study on Rome and NY criteria	Radiographic sacroiliitis	- Axial symptoms - Limitation in mobility	- sacroiliitis (radiographic)
Amor criteria for SpA, 1990 [14]	Clinical studies	A system of classification criteria was experimented in three studies.	-	- axial symptoms - peripheral - extra-articular	- sacroiliitis (radiographic) - HLA-B27
ESSG criteria for SpA, 1991 [15]	Clinical studies	Statistical testing of candidate variables in patients with SpA (expert's opinion) and controls, plus clinical reasoning	IBP or synovitis	- axial - peripheral - extra-articular	- sacroiliitis (radiographic)
Reactive arthritis, 2000 [13]	Clinical and epidemiological studies	Expert opinion	Arthritis and preceding enteritis or urethritis	-	- Evidence of triggering infection or persistent synovial infection
CASPAR criteria for PsA, 2006 [12]	Clinical studies	Statistical analysis of features in patients with PsA (based on expert's opinion) and control patients	Inflammatory articular disease	- Psoriasis - Dactylitis	- radiographic new bone formation hands - negative RF
ASAS axial SpA criteria, 2009 [19]	Clinical studies	Candidate criteria (by experts based on clinical reasoning) tested prospectively (expert's opinion). Final criteria based on statistical analysis and expert voting of candidate criteria.	>3 months back pain and age at onset <45 years	- Axial symptoms - Peripheral - Extra-articular	- sacroiliitis (radiographic or MRI) - HLA-B27 - CRP
ASAS peripheral SpA criteria, 2011 [18]	Clinical studies	Candidate criteria (by experts based on clinical reasoning) tested prospectively (expert's opinion). Final criteria based on statistical analysis and expert voting of candidate criteria.	Arthritis or enthesitis or dactylitis	- Axial - Peripheral - Extra-articular	- sacroiliitis (radiographic or MRI) - HLA-B27

Table 2

Summary of the studies on incidence of SpA

Author, year	Target population	Age	Sample	Method	Criteria	N sample	Response	Period	Incidence of SpA (/ 100,000)	Male:female
Hukuda, 2001[33]	Japan	>15	All patients with SpA seen at institutes	Questionnaires to clinics for medical record review	Clinical and radiographic features	134 institutes	70.9	1985-1996	0.48	4.5:3.0 : 1
Savolainen, 2003[42]	Kuopi, Finland	All	All referred patients	Examination by rheumatologist	Own study criteria	87,000	-	2000	52 *	-
Kauppiainen, 2000 [43]	5 districts of Finland	-	All patients receiving drug reimbursement	Finish sickness insurance scheme and hospital records	Own study criteria	1,000,000	-	1995	18.6 *	-
Munoz-Fernández, 2010 [44]	Madrid, Spain	<45	All patients visiting GPs in Madrid	Referral of possible early SpA patients to specialized unit	ESSG criteria	111,941	-	02/2006 07/2006-	62.5	1 : 1

* sum of prevalence of AS, PsA, ReA and uSpA

Table 3

Summary of studies on prevalence of SpA

	Target population	Age	Sample	Method	Criteria	N sample	Response	% male	Mean age	Prevalence of SpA (%; 95% CI)	Male:female
[45]	Tercera, Azores	>50	Random sample of osteoporosis survey	Interview + examination	ESSG	936	52	50	66.5	1.6 (0.8-2.7)	7:1
[47]	France	>18	Random sample of phone numbers	Phone screening question + phone rheumatologist interview (+ exam if needed)	Rheumatologists opinion	15219	65	-	-	0.30 (0.17-0.46)	1:1
[48]	Greece	>18	All residents in 7 areas + random sample 2 areas	Screening interview + examination	ESSG	10647	81.2	48.8	47	0.49 (0.38-0.60)	5.5:1
[49]	Marche-central Italy	>18	Random sample of subjects of GPs	Screening questionnaire+ examination	ESSG	3664	58.8	46.6	-	1.06 (0.78-1.38)	3.6:1
[50]	2 Lithuanian cities	>18	Random sample of phone numbers	Phone interview	Rheumatologists ascertainment	6543	65.1	25.5	-	0.84 (0.53-1.21)	1.3:1
[51]	Southern Sweden	>15	Health care registry	ICD-10 codes from health care register	ICD-10 code	849253	-	49	-	0.45 (0.44-0.47) (no ReA)	1:1
[52]	Izmir, Turkey	>20	Random selection of persons from 2 urban areas	Screening interview + examination	ESSG	2887	98 78 83	45.3	43.7	1.05 (0.70-1.50)	0.72:1
[53]	Berlin, Germany	-	HLA-B27+ and HLA-B27- blood donors	Screening questionnaires + examination	ESSG	348	85.3 71.4	67	38.5	1.9	3:1
[54]	USA	20-69	Representative sample of US adults	Interview + examination	Amor + ESSG (incomplete)	5013	-	48.4	-	Amor: 0.9 (0.7-1.1), ESSG: 1.4 (1.0-1.9)	0.5:1
[55]	Chukotka, Russia	>12	All residents of 2 settlements	Questionnaire + examination	ESSG/Amor	355	71.3%	44.2	-	2.5	-
[56]	Japan	>15	All patients with SpA seen at institutes	Questionnaires for medical record review	Clinical and roentgenographic features	134 institutes	70.9	-	-	0.0095	4.5-3: 1
[57]	North Pakistan	>15	Sample of three localities	Screening COPCORD questionnaire + examination	unclear	2090	95	-	-	0.10	-

Author, year	Target population	Age	Sample	Method	Criteria	N sample	Response	% male	Mean age	P Sp C
Minh Hoa, 2003 [59]	Urban Vietnam	>15	Total population of Trung Liet	Screening COPCORD questionnaire +examination	unclear	2119	86-94	-	0.	Stolwijk et al.
Davatchi, 2008 [71]	Teheran, Iran	>15	Sample of zip codes + adjacent houses	Screening COPCORD questionnaire +examination	unclear	10291	74.9	47.4	0.	
Liao, 2009 [127]	Dalang Town, China	>16	All residents of Dalang Town	Screening questionnaire + examination	ESSG	10921	88.8	52.1	0.	(.)
Boyer, 1994 [46]	Alaskan Eskimos	>20	2 populations enrolled in Alaska Area Native Health service	Review of records + further evaluation of possible SpA	ESSG/Amor	6749	89	-	2.	

Table 4

Summary of the studies on incidence of AS

Author, year	Target population	Age	Sample	Method	Criteria	N sample	Period	Incidence of AS (/ 100,000)	Male:female
Hanova, 2010 [63]	Czechoslovakia	>16	2 regions, all referred patients	Examination by rheumatologist	mNY	15,374	2002-2003	6.4 (4.5 – 14.4)	3.3: 1
Savolainen, 2003 [42]	Kuopi, Finland	All	All referred patients	Examination by rheumatologist	Study*	87,000	2000	5.8 (1.6 – 14.8)	4: 0
Kaipainen, 1997 [61]	Finland	>16	5 regions	Patients under nationwide sickness insurance to receive medication for AS	Specially reimbursed medication for AS	1,000,000	1980-1990	6.9 (6.0 – 7.8)	2.3:1
Alamanos, 2004 [63]	North-west Greece	>16	Patients referred to rheumatology clinics	Medical records review	mNY	488,435	1983-2002	1.5 (0.4 -2.5)	4.7: 1
Geirsson, 2010 [128]	Iceland	>18	AS patients seen by rheumatologists	Review of medical records + database genetic study, confirmation examination	mNY	220,441	1947-2005	0.44 to 5.48 (-)	1.9: 1
Bakland, 2005 [62]	Northern Norway	>16	Patients registered with AS at hospital	Medical records review	mNY	217,000	1960-1993	7.3 (5.3-9.2)	3.1:1
Carbone, 1992 [60]	Rochester, USA	-	AS patients registered in record system	Diagnosis from record system	mNY	18,000 – 69,000	1935-1989	7.3 (6.1-8.4)	4:1
Hukuda, 2001 [33]	Japan	>15	All AS patients seen at institutes	Questionnaires for medical record review	Clinical and roentgenographic features	134 institutes	70.9	0.48	-

Table 5

of studies on prevalence of AS

	Target population	Age	Sample	Method	Criteria	N sample	Response	% male	Mean age	Prevalence of AS (%; 95% CI)	Male:female
[1]	Czechoslovakia	>16	2 regions, all referred patients	Examination by rheumatologist	mNY	15.374	-	-	-	0.09 (0.08-0.11)	4.6: 1
	France	>18	Random sample of phone numbers	Phone screening question + phone rheumatologist interview (+ exam if needed)	Physician confirmation by phone or exam	15219	65	-	-	0.08 (0.03-0.15)	-
[63]	Finland	>30	Representative population sample	Examination	Specially reimbursed medication for AS	8000	90	-	-	0.15 (0.08-0.27)	2.7:1
[25]	Greece	>18	9 areas	Visiting households + interview	mNY	10647	81.2	48.8	47	0.24 (0.16-0.32)	6.1: 1
[66]	North-west Greece	>16	Patients referred to rheumatology clinics	Medical records review	mNY	488435	-	-	-	0.03 (0.03-0.03)	4.7: 1
[30]	Iceland	>18	AS patients seen by rheumatologists	Review of medical records + confirmation examination	mNY	220441	91.4	-	-	0.13 (0.11-0.14)	1.9:1
[55]	Marche, central Italy	>18	Random sample of subjects of GPs	Screening questionnaire, + examination	mNY	3664	58.8	46.6	-	0.37 (0.23-0.49)	-
[1983 [68]	Zoetermeer, Netherlands	>44	2 districts of the town	X-ray followed by examination	mNY	2957	NA	-	-	0.24	-
[1]	Norwegian Samis (Lapps)	20-64	Inhabitants 2 cities	Questionnaire + examination	NY	1723	78.2	53.7	-	1.8 (0.9-3.2)	2.7:1
[2]	Northern Norway	>16	A hospital-based AS patient registry	Medical records review	mNY	217.000	-	51	-	0.26	3.1:1
	Northern Norway	20-54	All inhabitants of Tromsø invited	Questionnaire + examination of random sample of positive responders	NY	21329	77.9 & 56	54.5	-	1.1 – 1.4	3.9-6.1: 1
[24]	Southern Sweden	>15	AS patients registered	ICD-10 codes from health care register	ICD-10 code	849253	-	49	-	0.12 (0.11-0.12)	2.1:1
	Izmir, Turkey	>20	Random selection of persons from 2 urban areas	Screening interview + examination	mNY	2887	98 78 83	45.3	43.7	0.49 (0.26-0.85)	1.2:1
	Berlin	-	HLA-B27+ and HLA-B27- blood donors	Screening questionnaires + examination	mNY	348	85.3 71.4	67	38.5	0.86	-
	Rochester, USA		AS patients registered	Medical record review	NY	33.000 – 52.000	-	-	-	0.13	3:1

Author, year	Target population	Age	Sample	Method	Criteria	N sample	Response	% male	Mean age
Maurer, 1979 [68]	USA	25-74	Complex multistage probability design	Questionnaire + X-ray (in women only 1h >50yrs)	X-ray sacroiliitis	6913	4903 (x rays available)		Stolwijk et al.
Boyer, 1994 [46]	Alaskan Eskimos	>20	2 populations enrolled in Alaska Area Native Health service	Review of records + further evaluation of possible SpA	NY	6749	89	-	-
Latin America									
Alvarez-Nemegyei, 2011 [73]	South-east Mexico	>18	Random sample of residents of Yucatán	Screening COPCORD questionnaire +examination	mNY	3195		38.2	42.7
Asia									
Hukuda, 2001 [33]	Japan population	>15	All patients seen at medical institutes	Questionnaires for medical record review	Either Rome or NY	134 institutes	70.9	-	-
Chou, 1994 [69]	Taiwan	>20	Random subjects from 3 areas	Screening questionnaire + examination	NY	8998	49	50.7	
Liao, 2009	Dalang Town, China	>16	All residents of Dalang Town	Screening questionnaire + examination	mNY	10921	88.8	52.1	-
Alexeeva, 1994	Chukotka, Russia		All residents of 2 settlements	Questionnaire + examination	NY	355	71.3%	44.2	-
Davatchi, 2008 [71]	Teheran, Iran	>15	Sample of zip codes + adjacent houses	Screening COPCORD questionnaire +examination	unclear	10291	74.9	47.4	-

Table 6

Summary of the studies on incidence of PsA

Author, year	Target population	Age	Sample	Method	Criteria	N sample	Period	Incidence of PsA (/100,000)	Male:female
Hukuda, 2001 [33]	Japan	>15	All AS patients seen at institutes	Questionnaires for medical record review	ESSG/Amor (clinical and radiographic)	134 institutes	70.9	0.1	-
Hanova, 2010 [63]	Czechoslovakia	>16	2 regions, all referred patients	Examination by rheumatologist	Vasey & Espinoza	15,374	2002-2003	3.6 (1.4-7.6)	1.3:1
Savolainen, 2003 [42]	Kuopi, Finland	All	All referred patients	Examination by rheumatologist	Own*	87,000	2000	23.1 (13.2-37.5)	1.6:1
Söderlin, 2002 [88]	South-Sweden	>16	All referred patients in Kronoberg County	Examination by rheumatologist	Psoriasis + arthritis, RF-	140,000	1999-2000	8 (4-15)	0.4:1
Shbeeb, 1999 [87]	Minnesota, USA	-	All medical records	Medical records review	Inflammatory arthritis + psoriasis	-	1982-1991	6.6 (5.0-8.2)	0.9:1
Wilson, 2009 [90]	Minnesota, USA	-	All Medical records	Medical record review	CASPAR	124277	1970-1999	7.2 (6.0-8.4)	1.7:1
Soriano, 2011 [90]	Buenos Aires, Argentina	>18	Members of a private health system insurance	Medical records review	CASPAR	138288	2000-2006	6.3 (4.2-8.3)	1.9: 1

Table 7

Summary of studies on prevalence of PsA

Author, year	Target population	Age	Sample	Method	Criteria	N sample	Response	% male	Mean age	Prevalence of PsA (%; 95% CI)	Male:female
Stolwijk et al., 2010 [63]	Czechoslovakia	>16	2 regions, all referred patients	Examination by rheumatologist	Vasey & Espinoza	15,374	-	-	-	0.05 (0.04-0.06)	0.85:1
Leclercq et al., 2005 [47]	France	>18	Random sample of phone numbers	Phone screening question + phone rheumatologist interview (+ exam if needed)	Physician diagnosis by phone or exam	15219	65	-	-	0.19 (0.09-0.35)	-
Antonopoulos et al., 2005 [123]	Greece	>18	9 areas	Visiting households for interview	ESSG + psoriasis	10647	81.2	48.8	47	0.17 (0.10-0.24)	4.8:1
Angelis et al., 2007 [53]	Marche, central Italy	>18	Random sample of subjects of GPs	Screening questionnaire+ examination)	mNY	3664	58.8	46.6	-	0.42 (0.31-0.61)	-
Englund et al., 2011 [124]	Southern Sweden	>15	All PsA patients registered	ICD-10 codes from health care register	ICD-10 code	849253	-	49	-	0.25 (0.24-0.26)	0.81:1
van der Maun et al., 1998 [50]	Berlin, Germany	-	HLA-B27+ and HLA-B27- blood donors	Screening questionnaires + examination	ESSG	348	85.3	67	38.5	0.29	-
Stolwijk et al., 2007 [93]	Reykjavik, Iceland	>18	Psoriasis database + hospital records for diagnosis of PsA	Confirming interview + examination	SwePsA	134253	-	-	-	0.14 (0.11-0.17)	0.57:1
Englund et al., 2005 [92]	Western Norway	>20	All PsA patients at rheumatology centers	ICD-codes 4 rheumatology centers	Psoriasis + arthritis or axial SpA	321454	-	-	-	0.20 (1.8-2.1)	1.7:1
North-America											
Stolwijk et al., 1999 [87]	Minnesota, USA	-	All PsA patients registered	Medical record review	Inflammatory arthritis + psoriasis	-	-	-	-	0.10 (0.08-0.12)	-
Stolwijk et al., 2009 [91]	Minnesota, USA	-	All PsA patients registered	Medical record review	CASPAR	124277	-	-	-	0.16 (0.13-0.19)	1.5:1
Stolwijk et al., 1994 [46]	Alaskan Eskimos	>20	2 populations enrolled in Alaska Area	Review of records + further evaluation of possible SpA	ESSG/AMor	6749	89	-	-	<0.1	-

Author, year	Target population	Age	Sample	Method	Criteria	N sample	Response	% male	Mean age	Prevalence PsA (% ^a , 95 CI)
			Native Health service Native Health service							
Latin-America										
Soriano, 2011 [90]	Buenos Aires, Argentina	>18	Members of a private health system insurance	Medical records review	CASPAR	138288	-	-	-	0.07 (0.06-0.08)
Alvarez-Nemegyei, 2011 [72]	South-east Mexico	>18	Random sample	Screening COPCORD questionnaire +examination	mNY	3195	-	38.2	42.7	0.02
Asia										
Hukuda, 2001 [33]	Japan population	>15	All patients seen at medical institutes	Questionnaires for medical record review	ESSG/Amor (clinical & radiographic features)	134 institutes	70.9	-	-	0.001
Liao, 2009 [127]	Dalang Town, China	>16	All residents of Dalang Town	Questionnaire + examination	ESSG	10921	88.8	52.1	-	0.02
Alexeeva, 1994 [125]	Chukotka, Russia		All residents of 2 settlements	Questionnaire + examination	Unclear	355	71.3%	44.2	-	0.3

Table 8
Summary of studies on prevalence of IBD related SpA

Author, year	Target population	Age	Sample	Method	Criteria	N sample	Response	% male	Mean age	Prevalence of IBD-SpA (%, 95% CI)
De Angelis,2007 [53]	Marche, central Italy	>18	Random sample of subjects of GPs	Screening questionnaire, + examination	ESSG+ IBD	3664	58.8	46.6	-	0.09 (0.04-0.16)
Haglund,2011 [124]	Southern Sweden	>15	All registered patients	ICD-10 codes from health care register	ICD-10 code	849253	-	49	-	0.02 (0.01-0.02)

Table 9

Summary of studies on incidence of ReA

Author, year	Target population	Age	Sample	Method	Criteria	N sample	Period	Incidence of ReA (/100,000)	Male:female
Söderlin, 2002 [88]	South-Sweden	>16	All referred patients in Kronoberg County	Examination by rheumatologist	Inflammatory joint disease preceded by infection	140,000	1999-2000	28 (20-39)	0.6:1
Hanova, 2010 [63]	Czechoslovakia	>16	2 regions, all referred patients	Examination by rheumatologist	Vasey & Espinoza	15,374	2002-2003	9.3 (5.5-14.8)	0.7:1
Townes, 2008 [117]	Minnesota and Oregon, USA	>1	Patients with culture infection reported to Foodnet	Screening telephone interview + examination	Inflammatory joint disease preceded by infection	6379	2002-2004	0.6-3.1	0.66:1
Savolainen, 2003 [42]	Kuopi, Finland	All	All referred patients	Examination by rheumatologist	Own *	87,000	2000	10 (4.1 – 20.8)	-
Isoniemi, 1987 [118]	Finland	>16	Referred patients in 29 counties surrounding Heinola	Examination	Peripheral synovitis preceded by GI or UG infection	260,000	1974-1975	27	0.75:1
Kvien, 1993 [119]	Oslo, Norway	18-60	All referred patients with suspected ReA	Examination by rheumatologist + follow-up	Arthritis with positive stool, culture or antibody titer	271,726	1988-1990	9.6	1:0.86

* Previous gastrointestinal or urogenital tract infection associated with peripheral synovitis or with inflammatory signs in sacroiliac, glenohumeral, or hip joints and positive stool culture or positive LCR test for *C. trachomatis* or elevated levels of antibodies against enteric bacteria associated with ReA

Table 10

Summary of studies on prevalence of ReA

Author, year	Target population	Age	Sample	Method	Criteria	N sample	Response %	% male	Mean age	Prevalence of ReA (%; 95% CI)	Male:female
Hanova, 2010 [63]	Czechoslava kia	>16	2 regions, all referred patients	Examination by rheumatologist	Third Intern workshop on ReA	15,374	-	-	-	0.09 (0.07-0.11)	1.2:1
Saraux, 2005 [47]	France	>18	Random sample of phone numbers	Phone screening question + phone rheumatologist interview (+ exam if needed)	Physician confirmation by phone or exam	15219	65	-	-	0.04 (0.01-0.07)	
De Angelis, 2007 [53]	Marche, central Italy	>18	Random sample of subjects of GPs	Screening questionnaire + examination	ESSG + prior UG or GI infection	3664	58.8	46.6	-	0.09 (0.04-0.16)	
Braun, 1998 [50]	Berlin	-	HLA-B27+ and HLA-B27- blood donors	Screening questionnaires + examination	ESSG	348	85.3	71.4	67	0.1	-
Alexeeva, 1994 [125]	Chukotka, Russia	-	All residents of 2 settlements	Questionnaire + examination	Unclear	355	71.3	44.2	-	0.6	-
Boyer, 1994 [46]	Alaskan Eskimos	>20	2 populations enrolled in Alaska Area Native Health service	Review of records + further evaluation of possible SpA	ESSG & Amor (Clinical & radiographic features)	6749	89	-	-	1.0	