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EPIDEMIOLOGY OF AXIAL SPONDYLOARTHRITIS: AN UPDATE

Runsheng Wang, MD, MHS and

Division of Rheumatology, Department of Medicine, Columbia University Medical Center, New York, NY

Michael M. Ward, MD, MPH

Intramural Research Program, National Institute of Arthritis and Musculoskeletal and Skin Diseases, National Institutes of Health, Bethesda, MD

Abstract

Purpose of review—To provide an update of the prevalence and incidence of axial spondyloarthritis in the general population and in patients with spondyloarthritis-related conditions, environmental risk factors for ankylosing spondylitis (AS), progression from non-radiographic axial spondyloarthritis to AS, mortality, and risks for cardiovascular events in patients with AS.

Recent findings—Increasingly, administrative health care data have been used to study disease frequency and outcomes. The prevalence of AS ranged from 9 to 30 per 10,000 persons, which are lower than previous estimates. Data on whether childhood infections influence the risk of AS were equivocal, while having been breast-fed may be protective. Progression of patients with non-radiographic axial spondyloarthritis to AS is slow, with estimates of 5.1% in five years and 19% in ten years. Risk of mortality is slightly increased in AS. Risks for cardiovascular events in AS were either not different from, or only slightly higher than in controls. No studies have examined these outcomes in the broader group of patients with axial spondyloarthritis.

Summary—Expanded use of administrative and registry data has facilitated studies of the epidemiology of AS, but lack of specific diagnostic codes limits use of these resources for studying axial spondyloarthritis in general.

Keywords

axial spondyloarthritis; ankylosing spondylitis; prevalence; mortality; cardiovascular disease

INTRODUCTION

Axial spondyloarthritis (SpA) is an umbrella term encompassing a number of inflammatory spine conditions, including ankylosing spondylitis (AS), non-radiographic axial SpA (nr-axSpA), SpA associated with inflammatory bowel disease, and undifferentiated SpA. Since

Address for correspondence: Dr. Michael Ward, NIAMS/NIH, Building 10 CRC, Room 4-1339, 10 Center Drive, Bethesda, MD 20892-1468. Telephone 301-496-7263; wardm1@mail.nih.gov.

CONFLICTS OF INTEREST

None.

the publication of the Assessment of SpondyloArthritis International Society (ASAS) classification criteria in 2009, several studies have investigated the prevalence and incidence of axial SpA in the general population and in patients with SpA-related conditions. We review studies of the progression of patients with nr-axSpA to AS. Environmental factors, particular early life events, have been investigated for potential influence on the risk of later development of AS. We review recent studies of mortality in AS, and examine evidence of the risk of cardiovascular events in these patients.

PREVALENCE AND INCIDENCE

Prevalence

Recent studies reported the prevalence of AS to range from 9 to 30 per 10,000 in the general population, depending on geographic area, study population or data source, case definition, and ascertainment methods (Table 1)[1–7]. Prevalences were higher in selected risk groups. For example, in a Canadian study, the prevalence of AS was three times higher in First Nations people, a group with a high prevalence of HLA-B27, than in non-First Nations people [2]. In a Scottish study, the prevalence was three times higher among patients under the care of rheumatologists compared to those identified from primary care practices [3].

Two studies of the prevalence of axial SpA expectedly reported higher prevalences than those for AS alone. In a U.S. study, Curtis *et al* [6] estimated the prevalence of SpA at 22.6 per 10,000. Among 18,757 employees of the French national utility company, 72 subjects self-reported SpA based on a medical questionnaire, and 32 subjects were classified with SpA after interview by a rheumatologist, pelvis radiographs, and HLA-B27 testing [7]. Seventy-five percent fulfilled ASAS axial SpA criteria, 25% fulfilled ASAS peripheral SpA criteria, and two-thirds had AS. The estimated SpA prevalence was 43 per 10,000.

In a systematic review and meta-analysis, Stolwijk *et al.* [8**] reported the global prevalence of axial SpA ranged from 20/10,000 in south-east Asia to 161/10,000 in Northern Arctic communities; the prevalence of AS varied from 2/10,000 in Sub-Saharan Africa to 35/10,000 in Northern Arctic communities. Heterogeneity in estimates was related to differences in the proportion of females, mean age of the sample, geographic area, year of data collection, case finding, and case ascertainment.

Incidence

The reported prevalence from these recent studies was substantially lower than what was previously known. Studies from the same geographic location with similar methodology would help inform whether the frequency of axial SpA has truly decreased over time. The incidence of AS in Olmsted County, Minnesota from 1935 to 1989 was estimated at 7.3 per 100,000. In the same population, the incidence of AS was 3.1 per 100,000 (95% CI 2.5 – 3.8) in 1980 to 2009 [9]. The authors attributed the decrease to increases in the local ethnic minority population. Whether these demographic changes fully explain the decline in AS incidence is unclear.

Study methods

Prevalence estimates may be affected by the ascertainment methods used in a study. Some studies used a two-step method, with an initial screening questionnaire followed by physician evaluation of screen-positive individuals. This method enhances accuracy, but can be limited in the number of participants included. Alternatively, population-based medical record linkage systems ensure near complete case ascertainment, but require substantial time and resources to establish. Increasingly, studies have used administrative data to identify cases with axial SpA or AS, which require validation of the diagnosis codes and search algorithms used to identify affected persons. Curtis *et al.* [6] investigated the prevalence of axial SpA and AS in Kaiser Permanente health plan members, and described the performance of this method. Among 5568 individuals with at least one ICD-9 diagnosis code for AS, 2295 individuals only had a single code by a primary care provider. AS was confirmed in only 2% of this group. Among four different search strategies, having two ICD-9 diagnoses of 720.X by rheumatologists had the highest positive predictive value at 81%, but sensitivity was only 67%.

Similarly, Dubreuil *et al.* [10] tested the validity of AS diagnosis codes in United Kingdom The Health Improvement Network using the general practitioner's diagnosis as the gold standard. They reported a positive predictive value of 88.6% for the presence of two AS diagnostic codes separated by at least seven days, and a positive predictive value of 85.7% for the presence of one AS diagnosis code in combination with a disease-modifying drug or biologic prescription.

Bioinformatics tools, such as natural language processing applied to electronic medical records, are being explored as a new tool to identify cases. Walsh *et al.* [11] reported the positive predictive values of these models for several SpA related concepts, including sacroiliitis, spondy* and HLA-B27 +, that ranged from 91.1% to 97.2%. Further studies are needed in this area.

PREVALENCE IN PATIENTS WITH RELATED CONDITIONS

Several studies examined the prevalence of AS in patients with related conditions, which may inform ways to improve referral and early diagnosis. Turina *et al.* [12] examined 51 first-degree relatives of patients with HLA-B27 positive AS, and 33% fulfilled criteria for SpA. More specifically, 57% had back pain, 6% had low-grade sacroiliitis, and 20% had sacroiliac bone marrow edema on imaging. The authors concluded that a substantial proportion of seemingly healthy relatives of AS patients had features of SpA.

Deodhar *et al.* [13] reported the proportion of patients with axial SpA among 751 patients with chronic back pain and either HLA-B27 positivity, inflammatory back pain, or sacroiliitis on imaging in the US. Of these, 348 fulfilled ASAS axial SpA criteria (238 with nr-axSpA and 108 with AS). The authors suggested among patients with chronic back pain with onset younger than 45 years, having one of these three SpA features was an effective way to identify those with possible axial SpA.

Thom *et al.* [14] examined the prevalence of inflammatory back pain and SpA in patients with psoriasis using data from 2009–2010 National Health and Nutrition Examination Survey (NHANES), and found higher frequencies of axial pain (31% versus 19%) and inflammatory back pain (9.0% versus 4.9%) in persons with psoriasis than in those without psoriasis. The prevalence of SpA by Amor or ESSG criteria was also significantly higher in the psoriasis group (14.3% versus 1.5%).

Chan *et al.* [15] reported the prevalence of sacroiliitis on computed tomography scans in patients with Crohn's disease, ulcerative colitis and controls as 15%, 16.9% and 5.6%. Among 49 patients with inflammatory bowel disease (IBD) who had sacroiliitis on scans, only five had been seen by a rheumatologist. In a meta-analysis of 71 studies on the prevalence of axial SpA in patients with IBD, the pooled prevalence of sacroiliitis was 10%, although its prevalence in the subset of population-based studies was only 3% [16*]. The pooled prevalence of AS was 3% overall, and 2% in population-based studies.

PROGRESSION OF NONRADIOGRAPHIC AXIAL SPONDYLOARTHRITIS

Since the development of axial SpA classification criteria, the relationship between nr-axSpA or undifferentiated SpA and AS has been of interest, particularly whether most patients with nr-axSpA progress to AS, and what are risk factors for progression.

We investigated these questions in a population-based study in Olmsted County, MN [17*]. Among 83 subjects who fulfilled ASAS criteria for axial SpA but did not have radiographic sacroiliitis, 19% progressed to AS after a mean follow up of 10.6 years. The probability that the condition remained as nonradiographic at 5, 10, 15 years was 93.6%, 82.7% and 73.6%. Subjects who were classified through the imaging arm had a significantly more frequent and more rapid progression than those classified through the clinical arm (28% vs. 17%, p=0.02).

Costantino *et al.* [18] reported a similar rate of progression in patients with axial SpA and having at least one SpA-affected relative. In 145 patients without radiographic sacroiliitis at inclusion, 27.3% developed radiographic sacroiliitis after 3 to 15 years, a result similar to our study. The Kaplan-Meier estimate of proportion of patients who progressed to radiographic sacroiliitis was 68.5% at 15 years of follow up, however, in the analysis, patients who lost to follow up were excluded from the number of patients at risk. Progression was associated with low-grade radiographic sacroiliitis at baseline, buttock pain, and absence of peripheral arthritis.

Dougados *et al.* [19] examined radiographic progression over two years in the Devenir des Spondyloarthropathies Indiffererenciees Recentes (DESIR) cohort, a prospective cohort of patients with early inflammatory back pain and high suspicion for axial SpA. Sixteen of 326 patients (4.9%) with nr-ax SpA progressed to AS. This was quite different from the GESPIC cohort [20], where 12% progressed to AS in two years. Current smoking, HLA-B27 positivity, and sacroiliac inflammation on imaging were the predictors for progression. In a follow up study of the DESIR cohort, net progression from nr-axSpA to AS over five years was 5.1% [21]. Inflammation on baseline sacroiliac joint MRI predicted the presence of

radiographic sacroiliitis at 5 years, both in HLA-B27 positive patients (OR 5.39 (95% CI 3.25 to 8.94)) and in HLA-B27 negative patients (OR 2.16 (95% CI 1.04 to 4.51)).

Xia *et al.* [22] conducted a systematic review and meta-analysis of 16 studies to assess the pooled rate of progression from undifferentiated SpA to AS. After 10 years, 40% of patients were projected to have progressed to AS.

Together, these findings suggest that only a small proportion of patients classified as nr-axSpA progress to AS, at least in the short-term.

ENVIRONMENTAL RISK FACTORS FOR THE DEVELOPMENT OF AS

AS is a highly heritable disease, and few studies have examined environmental risk factors. Three recent studies reported interesting observations suggesting that microbial exposures in childhood may play a role in the later development of AS.

Montoya *et al.* [23] investigated whether having been breast-fed was associated with the development of AS. Of 203 patients with AS, 57% were breast-fed, compared with 72% of 293 unaffected siblings, indicating that breast-feeding was protective (odds ratio 0.53; 95% CI 0.36, 0.77). The authors speculated that breast-feeding may have a protective effect on AS development in genetically susceptible patients by influencing the gut microbiota.

Lindstrom *et al.* [24] investigated whether childhood infections were associated with later development of AS in a case-control study in Sweden. Of the 2453 AS cases and 10257 age, sex and county matched controls, 17.4% of cases and 16.3% of controls had an infection-related hospitalization before age 17 years. AS was associated with slightly more respiratory tract infections (11.2% cases vs. 9.2% controls) but few cases of appendicitis (1.5% versus 2.5%). The authors suggested early childhood infections might be associated with the subsequent development of AS. In a related analysis of potential maternal and puerperal risk factors, birth by Caesarean section was not associated with the risk of AS, but having at least one older sibling, a surrogate for exposure to infections, was associated with a slight increased risk of AS [25].

MORTALITY AND CARDIOVASCULAR OUTCOMES

Mortality in AS

Recent information on mortality in AS is limited. Using the population-based Swedish National Patient Registry, Exarchou *et al.* [26] compared the mortality of persons with AS versus the general population. Over seven years, they observed 496 deaths in 8600 patients with AS, compared with 1533 deaths in 40460 matched controls, for a hazard ratio of 1.60 (95% CI 1.44 to 1.77). Less education, comorbidities, and history of hip replacement surgery were predictors of death.

In a population-based cohort study, Oza *et al.* [27**] examined the potential survival benefit of statin use in patients with AS. In a cohort of AS patients in a UK general practice database, they compared mortality between matched cohorts of 1108 statin initiators and 1108 non-initiators using 1-year cohort accrual blocks. Over five years, the mortality rate

was 16.5 per 1000 person-years among initiators and 23.8 per 1000 person-years among non-initiators (hazard ratio 0.63; 95% CI 0.46 to 0.85). The authors concluded that statin initiation was associated with a substantially lower risk of mortality in patients with AS.

Cardiovascular outcomes in AS

Studies on cardiovascular events in patients with AS have used different outcomes (Table 2) [28–31]. Overall, results point to a small increase in cardiovascular event risk compared to general population.

In a population-based cohort study using administrative health data from Ontario, Canada, Haroon *et al.* [28] reported an adjusted hazard ratio for cardiovascular and cerebrovascular death in AS of 1.36 (95% CI 1.13 to 1.65), compared to matched non-AS controls. Risk factors for vascular death included age, male sex, lower income, dementia, chronic kidney disease, peripheral vascular disease. Interestingly, among elderly patients with AS, use of nonselective nonsteroidal anti-inflammatory drugs and statins were protective for cardiovascular death.

In a population-based inception cohort of 86 patients with AS, Wright *et al.* [9] found a cumulative incidence of cardiovascular disease (including ischemic heart disease, myocardial infarction, angina, cardiovascular death, heart failure, peripheral arterial disease) of 15.8%, three times higher than the expected events predicted by the Framingham Risk Score. However, this study is limited by the small number of events.

Using Swedish population-based registries, Eriksson *et al.* [29] investigated the incidence of cardiovascular events in AS. Over 20,251 person-years of follow-up, the age and sex-adjusted relative risk for acute coronary syndromes was 1.3 (95% CI 1.0 to 1.7) compared with general population, and the relative risk for stroke was 1.5 (95% CI 1.2 to 1.8). Stroke risks were similarly elevated in AS and in patients with rheumatoid arthritis, whereas risks for acute coronary syndromes were only one-half as high in AS compared to rheumatoid arthritis.

Using claims data of Taiwan's National Health Insurance Research Database, Hung *et al.* [30] examined the incidence of cardiovascular disease (including hypertensive heart disease, coronary heart disease, congestive heart failure, cerebrovascular disease, and "other") in an incident cohort of 437 patients with AS aged 40 years or older, compared with 2685 non-AS patients. The hazard ratio for cardiovascular disease was 1.20 (95% CI 1.02 to 1.42). However, when isolating each condition, only the hazard ratio of "other" cardiovascular disease was statistically significant.

In contrast, using British Clinical Practice Research Datalink, Essers *et al.* [31] identified 3809 incident AS patients from 1987 to 2012, who were each matched to seven non-AS patients by age, sex, and practice. Risks were not significantly higher in AS, with an adjusted hazard ratio for ischemic heart disease of 1.20 (95% CI 0.97, 1.48) and for acute myocardial infarction of 0.91 (95% CI 0.65 to 1.28).

CONCLUSION

New information on the epidemiology of axial SpA includes a lower prevalence of axial SpA than previously reported, as well as a slightly increased risk for cardiovascular events and mortality. There has been an increase in studies using administrative and registry data to investigate these questions, for which sensitive and reliable methods are needed. Based on current data suggesting high predictive values of administrative health care codes for AS, use of these resources should be expanded. However, the lack of specific diagnostic codes means more work is needed before these methods can be used to study axial SpA in general.

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KEY POINTS

- Recent epidemiology studies indicate a lower prevalence and incidence of axial spondyloarthritis.
- Patients with ankylosing spondylitis have a slightly increased risk for mortality and a slightly increased risk for cardiovascular events, including vascular death.
- Current data suggested that using diagnostic codes for ankylosing spondylitis in administrative health data has high positive predictive value to identify these patients.

Table 1

Prevalence of axial spondyloarthritis and ankylosing spondylitis in general populations.

Reference	Years of Observation	Geographic area/Source data	Case definition	Ascertainment method	Number of cases/ total number of patients	Prevalence, per 10,000 (95% CI)
Exarchou *et al.* [1]	2009	Sweden/National Patient Registry	Clinical diagnosis of AS	Individuals with at least one registered AS diagnosis by ICD-9 codes by any clinical department (base definition) or by rheumatology/internal medicine (strict definition)	by base definition: 11030/5982237; by strict definition: 8538/5982237	by base definition: 18 by strict definition: 14
Barnabe *et al.* [2]	Mid-point of 2008–2009	Alberta, Canada/comprehensive provincial health databases	Clinical diagnosis of AS	Individuals with 2 or more ICD-9 or ICD-10 codes by any physician within 2 years; or 1 hospitalization discharge diagnosis; stratified by First Nation vs. non First Nation ethnicity	7685/NR	First Nations: 60 (50 – 60) non-First Nations: 20 (20 - 20)
Dean *et al.* [3]	2011	Scotland/Primary Care Clinical Informatics Unit Research electronic primary care database	Clinical diagnosis of AS	Individuals with Read Codes for AS (excluding juvenile AS)	1964/1469688	Primary Care: 13.4 (12.8 to 14.0)
	2010–2013	Scotland Registry for Ankylosing Spondylitis	Clinical diagnosis of AS	AS patients based on diagnosis by rheumatologists	1700/NR	Rheumatology: 4.7 (4.5 to 4.9)
Zeng *et al.*[4]	2012	Shantou, China/two randomly selected population	Clinical diagnosis of AS	Community-Oriented Program for the Control of Rheumatic Diseases methodology.	12/4056	30 (14 – 48)
Julian-Santiago *et al.*[5]	2012	Oaxaca, Mexico/two indigenous populations	Clinical diagnosis of AS	Community-Oriented Program for the Control of Rheumatic Diseases methodology.	1/1061	9 (0 – 50)
Curtis *et al.* [6]	1996 – 2009	California/Enrollees in Kaiser Permanente health plan	Clinical diagnosis of axial SpA and AS	Individuals with 1 or more inpatient or outpatient ICD-9 code for AS or another inflammatory spondyloarthropathies.	5568/NR	AS: 10.7 SpA: 22.6
Costantino *et al.* [7]	2010	France/population-based cohort	ASAS classification for axial and peripheral SpA	Two-step method	32/6556	43 (26 – 70)

AS: ankylosing spondylitis; SpA: spondyloarthritis; ICD: international Classification of Diseases; NR: not reported; CI: confidence interval.

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Table 2

Prevalence of cardiovascular and cerebrovascular events in patients with ankylosing spondylitis.

Author	Study Year	Study population	Outcomes	Patients/events (n/n)	Follow up (Patient-years, unless noted)	Hazard Ratio (95% CI)
Haroon *et al.* [28]	1995 to 2011	Ontario, Canada: AS: two diagnostic codes of AS over 2 years with one by rheumatologists C: age, sex, location of residence matched individuals	Vascular mortality	AS: 21,473/170 C: 86,606/594	AS: 166,920 C: 686,461	1.36 (1.13, 1.65)
Eriksson *et al.* [29]	2006 to 2011	Swedish National Patient Registry: AS: at least one diagnostic code for AS by internal medicine or rheumatology C: general population matched on birth year, sex, and residence	First acute coronary syndrome	AS: 4898/69 C: 22,315/216	AS: 20,251 C:91,601	1.3 (1.0, 1.7)
			First stroke	AS: 5248/65 C: 24,225/185	AS: 21,653 C:100,441	1.5 (1.1, 2.0)
Hung *et al.* [30]	2000 to 2005	Taiwan National Health Insurance Research Database: AS: one inpatient or two outpatient diagnosis of AS based diagnostic codes C: insured individuals matched on age and sex	Overall CVD: Hypertensive heart disease; coronary heart disease; heart failure; cerebrovascular disease, other.	AS: 537/176 C: 2685/780	AS: 3.71 years C: 4.21 years	1.20 (1.02, 1.42)
Essers *et al.* [31]	1987 to 2012	British Clinical Practice Research Databank: AS: inception cohort of patients with at least one recording of AS C: birth year, sex, time and practice location matched non-AS patients	First ischemic heart disease event	AS: 3809/102 C: 26,197/600	Overall: 6.6 years	1.20 (0.97, 1.48)
			First acute myocardial infarction	AS: 3809/38 C: 26,197/291		0.91 (0.65, 1.28)

AS: ankylosing spondylitis; C: comparator; CVD: cardiovascular disease; CI: confidence interval.