Review

Incidence of spondyloarthritis subtypes: a systematic review

Y. Alamanos[1], E. Pelechas[2], P.V. Voulgari[2], A.A. Drosos[2]

[1]Institute of Epidemiology, Preventive Medicine and Public Health, Corfu, Greece; [2]Division of Rheumatology, University of Ioannina Medical School, Greece.

Yannis Alamanos, MD, Assoc. Prof.
Eleftherios Pelechas, PhD, MSc, MAc
Paraskevi V. Voulgari, MD, Prof.
Alexandros A. Drosos, MD, FACR, Prof.

Please address correspondence to:
Alexandros A. Drosos,
University of Ioannina Medical School,
45110 Ioannina, Greece.
E-mail: adrosos@cc.uoi.gr

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ORCID:
Y. Alamanos: 0000-0001-5822-5702
E. Pelechas: 0000-0002-9383-5722
P.V. Voulgari: 0000-0002-5193-2284
A.A. Drosos: 0000-0002-2232-0326

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ABSTRACT

Objective. *Several epidemiologic studies of spondyloarthritis (SpA) and its subtypes have been reported during the last decades. The majority of these studies provided prevalence estimates and showed a considerable variation in the reported frequency of SpA subtypes. Most systematic reviews published in this field aimed to summarise the results of prevalence studies, however, incidence studies are important for an accurate picture of a disease occurrence in a defined population. We conducted a systematic review regarding the incidence of SpA subtypes on studies published during the last 25 years, to compare their methodology and summarise their results.*

Methods. *A systematic literature search of PubMed was performed to identify all published studies on the incidence of SpA subtypes between 1/1/1995 and 31/12/2019. Studies were considered eligible if the incidence of one or more SpA subtypes was measured in the general population, and met concrete inclusion criteria. Incidence rates (IR) were summarised using a random effect model.*

Results. *A total of 24 publications fulfilled the inclusion criteria. Most of them included results for two or more SpA subtypes. Sixteen studies presented the incidence of psoriatic arthritis, which gave an overall IR estimate of 9.7 cases per 100.000 person-years. Thirteen studies presented the incidence of ankylosing spondylitis with an overall IR estimate of 4.8, and eight studies presented reactive arthritis incidence with an overall IR estimate of 3.4. A small number of studies referred to the incidence of entero-pathic arthritis or undifferentiated spondyloarthritis.*

Conclusion. *Incidence studies of SpAs differ considerably in their methods, and result in a wide variation of the IRs for all SpA subtypes. Methodological differences may only partly explain the differences in disease occurrence observed among studies. More studies from different populations based on specific classification criteria are needed for a more accurate picture of SpA epidemiology.*

Introduction

Spondyloarthritis (SpA) represents a group of rheumatic diseases that comprises Psoriatic arthritis (PsA), ankylosing spondylitis (AS), reactive arthritis (ReA), entero-pathic arthritis (EA), and undifferentiated spondyloarthritis (uSpA). The first proposals for SpA classification criteria were Amor and the European Spondyloarthropathy Study Group (ESSG) criteria, published in the early nineties (1, 2). These criteria offered a basis for epidemiologic studies, although their validity and convenience were much debated. Other diagnostic and classification criteria have been proposed for specific SpA subtypes (3-6).

During the last decades, several incidence and prevalence studies of SpA subtypes have been reported, based on different methods of case recording and classification. These studies focused mainly on PsA and AS epidemiology (7, 8).

The majority of epidemiologic studies provided prevalence estimates and presented a considerable variation in the reported prevalence of SpA subtypes. As a consequence, systematic reviews published in this area aimed to summarise prevalence studies (9, 10), except for two systematic reviews of PsA incidence and prevalence studies (11, 12).

Incidence studies can present an accurate picture of a disease occurrence and offer the possibility to study important epidemiologic aspects, such as time trends and age at diagnosis. During the last decades, several incidence studies of SpA subtypes have been published

allowing an approach of their occurrence worldwide. In this study, we present a systematic review of incidence studies published during the last 25 years, to compare their methodology and summarise their results.

Methods

Search strategy

We conducted a systematic literature search of the electronic database PubMed including all articles published on one or more SpA subtype incidence in the general population, during the period between January 1995 and December 2019 (keywords: SpA and incidence, AS and incidence, PsA and incidence, ReA and incidence, EA and incidence, uSpA and incidence). The reference lists of relevant articles were also reviewed as well as all review articles concerning the epidemiology of SpA or specific subtypes of SpA. Two reviewers (AY, AAD) independently reviewed titles, abstracts, and full texts on eligibility criteria for inclusion. The search was limited to the English language.

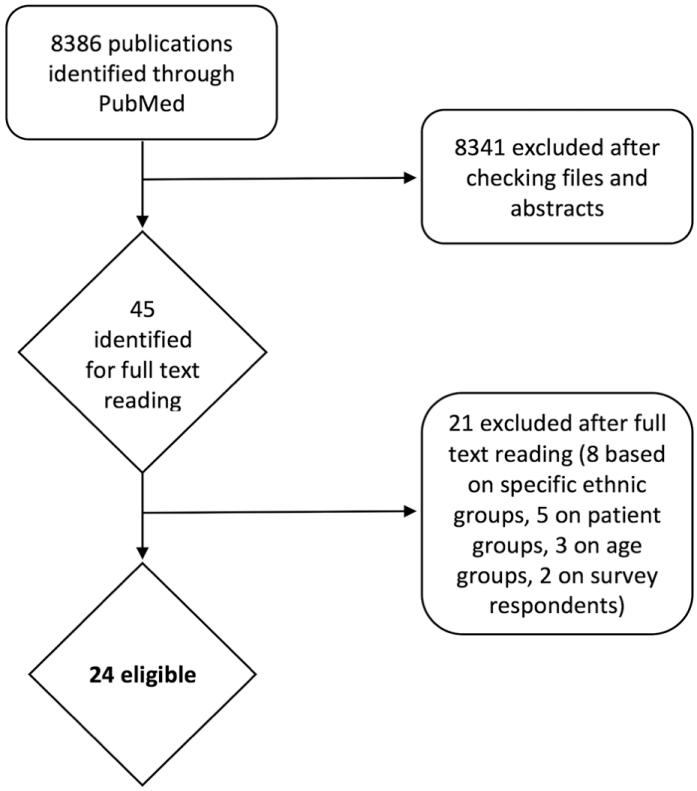
Inclusion criteria

Studies were considered eligible if they presented IR of one or more SpA subtypes based on original data for a precise general population. IR should include all newly diagnosed cases among inhabitants of a defined area during a defined period. The concrete statements of the study period, the study population, the methods of case ascertainment, and case definition were indispensable eligibility criteria. Studies focusing on specific groups, such as ethnic groups representing only a part of the general population, specific age groups, respondents of a survey, or patients groups were excluded.

Data extraction

From each study, we extracted data concerning IR, country, study period, study design, study population, criteria of case definition, methods of case ascertainment, male/female ratio, mean age at diagnosis, and time trends. IRs adjusted for age, and sex were preferred when available. We extracted the IRs as provided by the authors at each publication. When IR was not directly available, we tried to have an estimation based on data provided in the article concerning the number of cases and the person-years of the study. The female to male ratio was summarised with an incidence rate ratio (IRR: IR in men/IR in women). When the sex-specific IRs were not reported but the number of female and male patients was presented, the IRR was calculated using the assumption that the ratio of women to men in the general population was 1. The number of incident cases by sex was provided when available.

Fig. 1.



Study quality assessment

There is a lack of standardised quality criteria for systematic review and meta-analyses of descriptive epidemiological studies. In this systematic review, we attempted an evaluation of study quality based on the study design, the case identification method, and the completeness of the results. The study quality was considered "optimal" when the study design was prospective, the case definition was based on internationally accepted diagnostic criteria, and the results included the sex ratio as well as the age at diagnosis. The study quality was considered "good" when two of these criteria were completed, "moderate" when one criterion was completed, and "poor" when none criterion was met. The concrete definition of the study population or the clear statement of study design and methods of case ascertainment and case definition was not included in the quality assessment, because they were considered as indispensable eligibility criteria for the systematic review.

Statistical analysis

IR was defined as newly diagnosed cases in a defined period per 100.000 person-years. The overall rates and 95% CIs were calculated using a random-effect model. Overall IRR and mean age at diagnosis were calculated using a random-effects model as well. Heterogeneity of effects among studies was estimated using the I^2 test. Statistical analysis was done using Comprehensive meta-analysis software (https://www.meta-analysis.com). Forest plots were produced using the Distiller SR Forest Plot Generator from Evidence Partners. When two studies presented the incidence of a SpA subtype for two different periods, in the same population, using the same data sources and

Table I. Incidence studies of PsA.

Publication	Study period (year)	Country	Type of study Quality	Population	Case- definition (age)	Data source	Incidence rate [cases/10^5 persons years] (n)	m/f IRR (n)	Quality
Kaipiainen-Seppanen O. (1996)	1990	Finland	retrospective	16+	arthritis+psoriasis	Health Insurance records	6.1 (65)	1.3 (37/28)	Moderate
Kaipiainen-Seppanen O. (2000)	1995	Finland	retrospective	16+	arthritis+psoriasis	Health Insurance records	6.8 (74)	1.2 (40/34)	Moderate
Sheeb M (2000)	1982-1991	USA	retrospective	16+	arthritis+psoriasis	All health care providers medical records	6.6 (56)	0.9 (32/34)	Moderate
Hukuda S (2001)	1985-1996	Japan	retrospective	16+	arthritis+psoriasis	Hospitals and clinics medical records	0.06 (126)	--- (NA)	Poor
Soderlin MK (2002)	1999	Sweden	prospective	16+	arthritis+psoriasis	Hospital-+private re/logist	8.0 (11)	0.4 (3/8)	Moderate
Alamanos Y (2003)	1982-2001	Greece	retrospective	16+	EESG criteria	Hospital-+private re/logists	3.0 (221)	1.0 (108/113)	Good
Savolainen E. (2003)	2000	Finland	prospective	16+	arthritis+psoriasis	All physicians	23.1 (16)	0.7 (6/10)	Good
Nossent J (2009)	1978-1996	Norway	retrospective	16+	arthritis+psoriasis	Hospital medical records	6.9 (232)	1.5 (135/97)	Moderate
Wilson FC (2009)	1970-1999	USA	retrospective	18+	CASPAR criteria	All health care providers	7.2 (147)	1.6 (90/57)	Good
Hanova P (2010)	2002	Czeck Reb	prospective	16+	Vasey and Espinoza cr.	Hospital+ private re/logists	3.6 (7)	1.3 (4/3)	Optimal
Soriano E (2011)	2001-2005	Argentina	retrospective	18+	CASPAR criteria	Hospital medical records	6.3 (35)	2.8 (23/12)	Good
Hoff M (2013)	2000-2008	Norway	retrospective	20+	CASPAR criteria (+arthritis+psoriasis)	Hospital medical records +population based survey	35.9 (188)	0.9 (NA)	Moderate
Egeberg A. (2017)	1997-2011	Denmark	retrospective	20+	physician diagnosis	Nationwide Registry medical records	12.1 (NA)	0.8 (NA)	Moderate
Eder L (2019)	2008-2015	Canada	retrospective	20+	physician diagnosis	Health Insurance records	12.7 (11.441)	-- (NA)	Moderate
Hočevar A (2019)	2014-2016	Slovenia	retrospective	18+	CASPAR criteria	Hospital medical records	5.4 (115)	1.0 (57/58)	Good
Muilu P (2019)	2000-2014	Finland	retrospective	18+	physician diagnosis	Health Insurance records	11 (23)	1.1 (12/11)	Good

the same methods of case definition and case ascertainment, we included them as one study, using their pooled results.

Results

A total of 8386 publications were initially identified from the PubMed search. After checking titles and abstracts 8341 were excluded and after full-text readings, a total of 24 articles were finally included in the study (Fig. 1). We did not identify any additional papers based on hand searching /checking references. The incidence of all SpA or inflammatory joint diseases generally was reported in six studies (13-18), the incidence of PsA, AS and ReA in one study (19), of PsA only in nine studies (20-28), of AS only in seven studies (29-35), of ReA only in one study (36). All six studies reporting SpA incidence presented specific data for PsA and ReA, and five of them presented specific data for AS. The incidence of EA in the general population was reported in two studies (14, 17), and the incidence of uSpA was reported in five studies (13, 15-18).

Incidence of PsA

Table I presents the main characteristics of sixteen studies meeting the inclusion criteria and presenting PsA incidence (13-28). Two studies were carried out in the same Finish area, using the same methods of case ascertainment and case identification and are presented in Figure 2 as one study (13, 20). Two studies were carried out in the same area (Olmsted County Minnesota), using the same methods of case ascertainment and case identification, and the period of the larger study (24) includes the period of the first study (21). We included the results of the larger study. As a consequence, Figure 2 summarises the results of fourteen studies describing IRs for PsA, which gave an overall IR estimate of 9.9 cases per 100.000 person-years. Statistically significant heterogeneity was observed among stud-

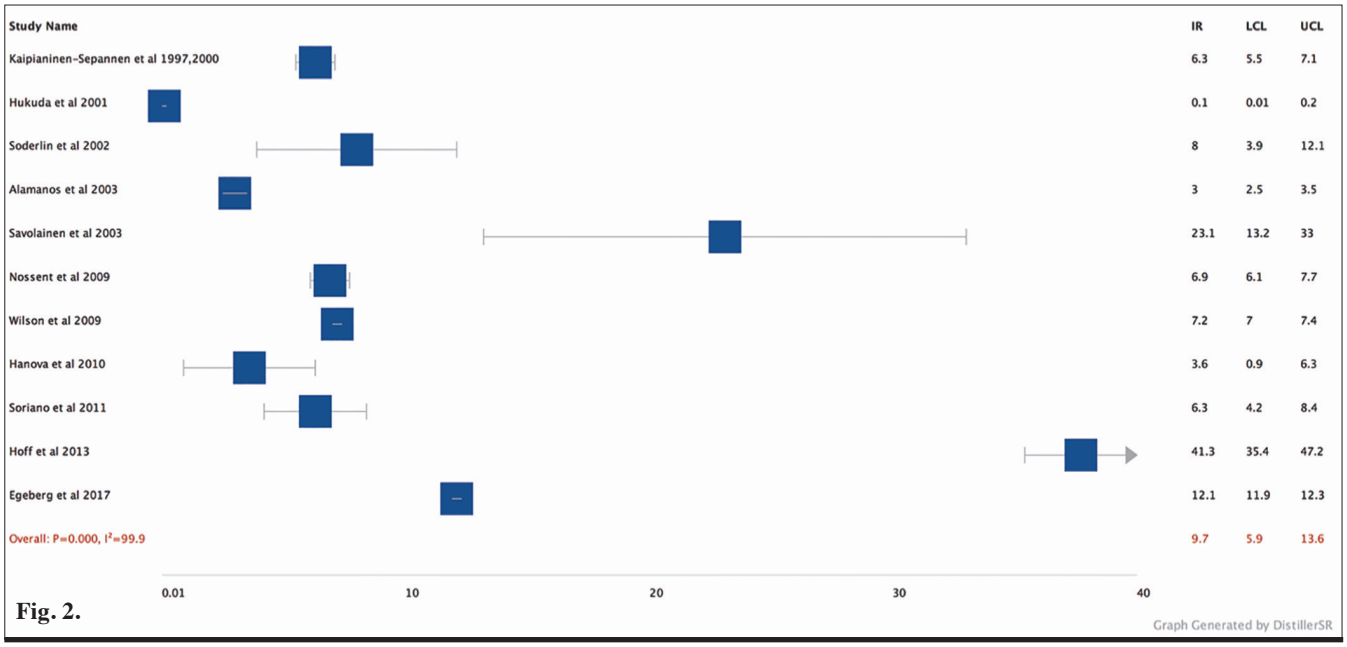


Fig. 2.

Table II. Incidence studies of AS.

Publication (year)	Study period	Country	Type of study	Population (age)	Case-definition	Data source	Incidence rate [cases/10^5 persons years] (n)	m/f IRR (n)	Quality
Kaipiainen-Seppanen O (1997)	1980,1985, 1990	Finland	retrospective	16+	clinical diagnosis	Health Insurance records	6.9 (219)	2.3 (153/66)	Moderate
Kaipiainen Seppanen O. (2000)	1995	Finland	retrospective	16+	clinical diagnosis	Health Insurance records	6.3 (68)	1.6 (42/26)	Moderate
Hukuda S (2001)	1985-1996	Japan	rerospective	16+	clinical diagnosis	Hospitals and clinics medical records	0.3 (676)	--- (NA)	Poor
Soderlin MK (2002)	1999	Sweden	prospective	16+	clinical diagnosis	Hospital-+private re/logist	1.5 (2)	--- (NA)	Moderate
Savolainen E (2003)	2000	Finland	prospective	16+	clinical diagnosis	All physicians	5.8 (4)	--- (4/0)	Good
Alamanos Y (2004)	1982-2001	Greece	retrospective	16+	mNY criteria	Hospital-+private re/logists medical records	1.5 (113)	4.8 (93/20)	Good
Bakland G 2005	1960-1993	Norway	retrospective	16+	mNY criteria	Hospital medical records	7.3 (534)	3.1 (404/130)	Good
Hanova P (2010)	2002	Czeck Reb	prospective	16+	mNY criteria	Hospital+ private r/logists	6.4 (13)	3.3 (10/3)	Optimal
Haroon N (2014)	1995-2010	Canada	retrospective	15+	clinical diagnosis	Health Insurance+Hospital medical records	15.0 (NA)	1.3 (NA)	Moderate
Koko V (2014)	2006-2010	Albania	retrospective	14+	mNY criteria	Hospital+physicians medical records	1,2 (54)	8 (48/6)	Good
Wright KA (2015)	1980-2009	USA	retrospective	18+	mNY criteria	All health care providers medical records	3.1 (86)	3.5 (67/19)	Good
Park JS (2018)	2010-2015	S. Korea	retrospective	Total	mNY criteria	Health Insurance records	6.3 (19.345)	2.1 (NA)	Good
Hočevar A (2019)	2014-2016	Slovenia	retrospective	18+	mNY criteria	Hospital medical records	2.9 (62)	2.5 (44/18)	Good

ies. Heterogeneity remains statistically significant after removing the two studies presenting the higher (26) and the lower (14) incidence. The male/female IRR varied between 0.4 and 2.8 and the overall estimate was 1.3 (95%CIs 1.0–1.5). The male/female ratio was not available for two studies (14, 28). Mean age at diagnosis was provided

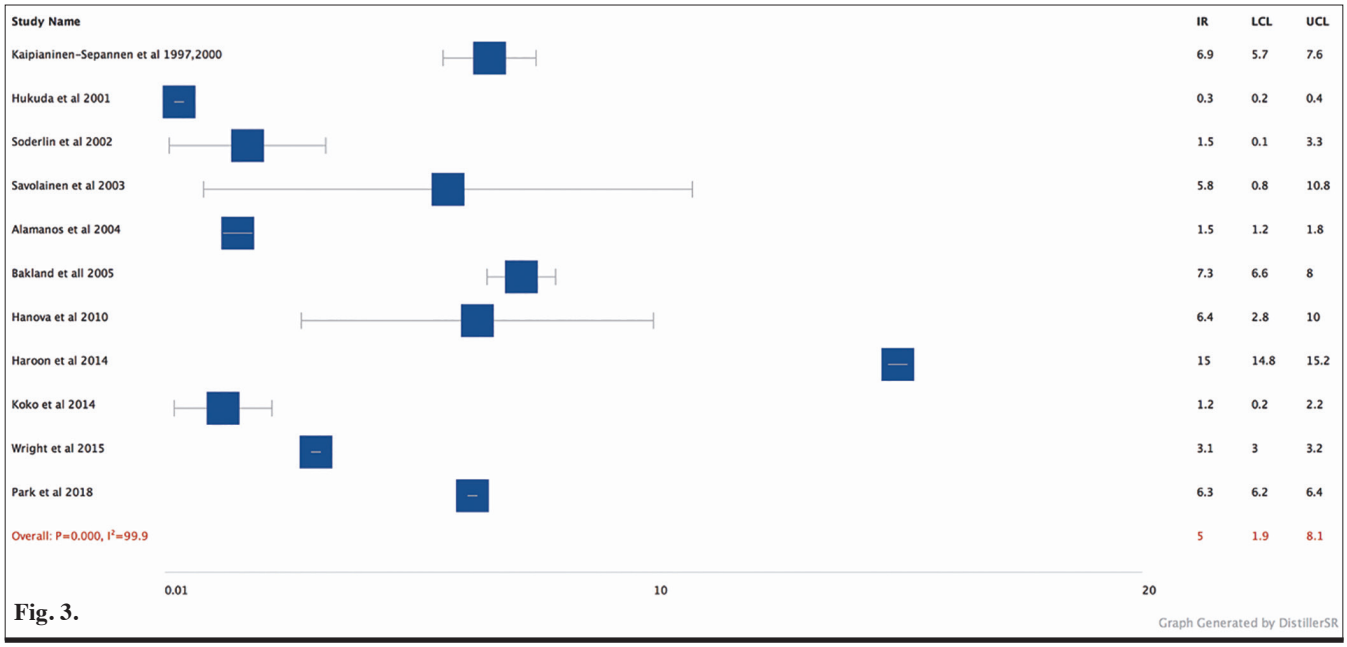


Fig. 3.

Table III. Incidence studies of ReA.

Publication (year)	Study period	Country	Type of study	Population (age)	Case-definition	Data source	Incidence rate [cases/10^5 persons years] (n)	m/f IRR (n)	Quality
Kaipiainen-Seppanen O (2000)	1995	Finland	retrospective	16+	clinical diagnosis	Health Insurance records	2.2 (24)	0.6 (9/15)	Moderate
Hukuda S (2001)	1985-1996	Japan	retrospective	16+	clinical diagnosis	Hospitals and clinics medical records	0.02 (40)	--- (NA)	Poor
Soderlin MK (2002)	1999	Sweden	prospective	16+	clinical diagnosis	Hospital- private practice	28.0 (37)	0.6 (14/23)	Moderate
Savolainen E (2003)	2000	Finland	prospective	16+	clinical diagnosis	All physicians	15.3 (7)	2.5 (5/2)	Good
Townes JM (2008)	2002-2004	USA	retrospective	Total	clinical diagnosis	Infections reported +telephone interviews	3.1 (575)	1.5 (230/345)	Poor
Hanova P (2010)	2002	Czeck Reb	prospective	16+	3rd International Workshop on Reactive Arthritis	Hospital- private practice	9.3 (17)	0.7 (7/10)	Optimal
Hočevar A (2019)	2014-2016	Slovenia	retrospective	18+	clinical diagnosis	Hospital medical records	1.0 (22)	0.8 (10/12)	Moderate
Muilu P (2019)	2000-2014	Finland	retrospective	18+	physician diagnosis	Health Insurance records	2.3 (5)	0.8 (2/3)	Moderate

in 7 studies and varied between 44 and 54 (overall estimation 49.7–95% CIs 38.1–61.3). Three studies did not present the mean age at diagnosis but provided incidence by age groups with a higher incidence in the age group 30–49 (21), 50–59 (25), and 55–64 (28).

Time trends of PsA were investigated in four studies (18, 27, 24, 28). In a Finish study, PsA incidence increased from 9 cases per 100.000 person-years between 2000–2004 to 13 between 2010 and 2014 (18). In a study from Denmark, the annual incidence of PsA presents a steady increase over 15 years (1997–2011), and the incidence at the end of the study was 3-fold higher than at the beginning (27). In the study from the USA the age- and sex-adjusted incidence of PsA per 100.000 person-years increased from 3.6 between 1970 and 1979 to 9.8 between 1990 and 2000 (24). In the Canadian study, standardised PsA IR presented a slight increase from13.0 cases per 100.000 person-years at 2008 to 14.0 at 2015 (28).

One study met all three quality criteria ("optimal"), six studies met two of them ("good"), eight studies met one criterion ("moderate"), and one study did not complete any quality criterion ("poor").

Incidence of AS

Table II presents the main characteristics of thirteen studies meeting the inclusion criteria and presenting AS

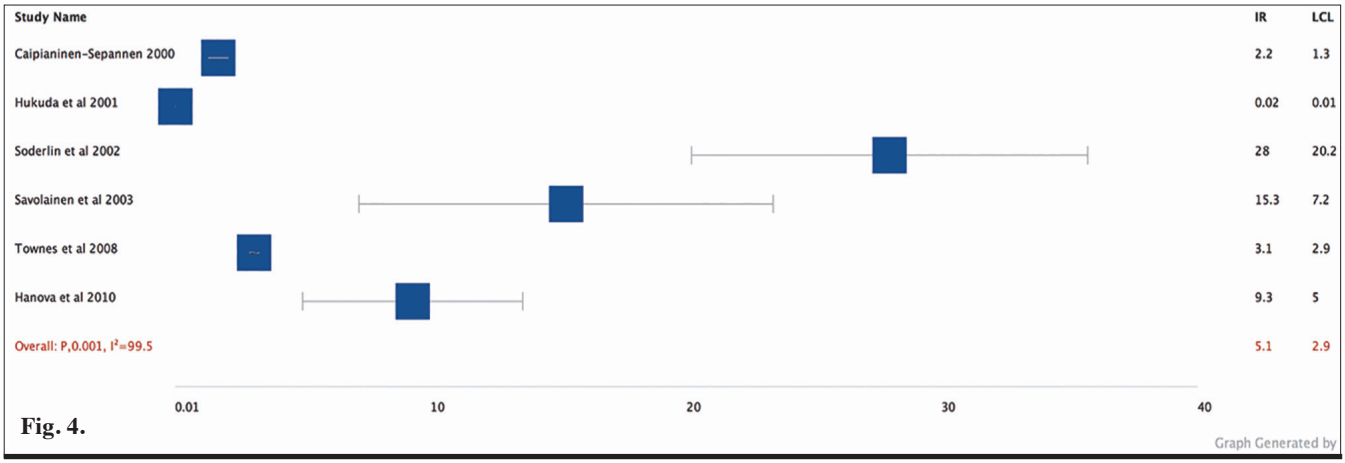


Fig. 4.

incidence (13-17, 19, 29-35). The two studies by Kaipianinen-Sepannen et al. were carried out in the same Finish area, using the same methods of case ascertainment and case identification and are presented in Figure 3 as one study (13, 29). So, Figure 3 summarises the results of twelve studies describing IRs for AS that gave an overall IR estimate of 4.8 cases per 100.000 person-years. Statistically significant heterogeneity was observed among studies. Heterogeneity remains statistically significant after removing the two studies presenting the higher (32) and the lower (14) incidence. The male/female IRR varied between 1.6 and 8 and the overall estimate was 3.0 (95%CIs 2.4–3.6). The male/female ratio was not available for two studies (14, 15), while for one study it could not be calculated because there was no female AS cases identified (16).

Mean age at diagnosis was provided in 7 studies and varied between 29.7 and 39.8 years (overall estimation 34.7–95% CIs 32.7–36.7).

Four studies investigated time trends of AS incidence (29, 31, 32, 34). In a study from a defined area of Finland, the annual incidence does not present any significant variation for the period 1980-1995 (IR 1980:6.6, 1985:6.9, 1990:7.3, 1995:6.3) (29). In a study from Northern Norway the IR was 10.6 per 100.000 person-years for the period 1971–1981, and 8.6 for the period 1982-1993 (31). In a Canadian study, the annual incidence of AS remained relatively stable over the 15-year study period (1995–2010), presenting a slight annual variation (32). In a study from the USA, although year-to-year fluctuations were noted, there was no significant change in the overall incidence of AS between 1980 and 2009 (34).

One study met all three quality criteria ("optimal"), seven studies met two of them ("good"), four studies met one criterion ("moderate"), and one study did not complete any quality criterion ("poor").

Incidence of ReA

Table III presents the main characteristics of eight studies meeting the inclusion criteria and presenting ReA incidence (13-19, 36). Figure 4 summarises the results of these eight studies that gave an overall IR estimate of 3.4 cases per 100.000 person-years. Statistically significant heterogeneity was observed among studies. Heterogeneity remains statistically significant after removing the two studies presenting the higher (15) and the lower (14) incidence. The male/female IRR varied between 0.6 and 2.5 and the overall estimate was 0.9 (95%CIs 0.5–1.3). The male/female ratio was not available for one study (14). Mean age at diagnosis was provided in 5 studies and varied between 38 and 42.5 (overall estimation 41.3–95% CIs 39.7–42.9). One study investigated time trends of ReA, which did not change significantly during the 15 years 2000–2014 in the Finish population (18).

One study met all three quality criteria ("optimal"), one study met two of them ("good"), four studies met one criterion ("moderate"), and two studies did not complete any quality criterion ("poor").

Incidence of other SpA subtypes

The incidence of EA in the general population was reported only in two studies and varied between 0.01 cases per 100.000 person-years in a Japanese study (14), and 0.6 cases per 100.000 persons-years in a Slovenian study (17). The incidence of uSpA was reported in five studies and varied significantly between them. It was found 11.7, 13.1, and 148.5 cases per 100.000 person-years in three Finish studies (13, 16, 18), 41cases per 100.000 person-years in a Swedish study (15), and 4.3 cases per 100.000 person-years in a Slovenian study (17).

Discussion

According to the results of this systematic review, the incidence studies of SpAs differ considerably in their methods, leading to a wide variation of IRs for all SpA subtypes. Methodological differences concern mainly the methods of study design, case identification, data source, and case recording, as well as the type of IRs. Some studies present age or age and sex-adjusted rates, while others present crude IRs. Adjusting methods for age differ as well or are not described in the articles.

We did not apply a precise age limit as an inclusion criterion. We considered the age limits applied by the authors of each study. The different age limits among studies may have a small impact on the incidence rates.

Methodological differences are related to the quality of the studies. A pooled risk estimate of a systematic review should be based on high-quality data and avoid variation due to methodolog-

ical differences. For this reason, we applied strict eligibility criteria concerning the clear statement of study methods. Besides, we attempted a quality assessment of the studies included. Assessment tools for systematic reviews and meta-analyses of descriptive epidemiological studies have been discussed. However, there is still al lack of standardised quality criteria for incidence studies (38-40). Therefore, we tried to evaluate the quality of studies included in the systematic review based on their design, the application of standardised classification criteria, and the completeness of their results. A vast majority of studies are retrospective, and most of them use case identification methods based on clinical diagnosis rather than specific classification criteria. Some studies do not provide data about sex ratio and age at diagnosis.

PsA is likely to present the highest incidence among SpA subtypes (9.9 cases per 100.000 person-years). The pooled results for sex ratios suggest a slightly higher incidence for men, and the peak age at diagnosis seems to be about 50 years. Four studies investigating time trends of PsA incidence indicate an increase in disease occurrence during the last decades.

The overall estimate of AS incidence is about 5 cases per 100.000 person-years. The pooled results suggest a male predominance in the disease occurrence and mean age at diagnosis between 30 and 40 years. Significant heterogeneity is observed among studies although modified New York criteria are systematically used for case identification in almost all studies published during the last 15 years (37). Four studies investigating time trends of AS incidence in defined areas of Finland, Norway, Canada, and the USA suggest a relatively steady occurrence of the disease.

The overall estimate of ReA incidence is 3.4 cases per 100.000 person-years. Analysis based on random effects indicates a statistically significant heterogeneity among studies. There is no sex predominance in the disease occurrence and the mean age at diagnosis is about 40 years.

Despite the limitations related to methodological differences among studies, the results of this systematic review suggest a significant geographical variation of SpA occurrence.

The study by Hukuda *et al*. indicates a very low occurrence of all types of SpA in the Japanese population compared to any other study worldwide (14). It is unlikely that such impressive differences may be related to methodological differences between studies and not to a significant variation of the disease occurrence. The low frequency of SpA, mainly of AS, in the Japanese population, has been attributed to the strong association with Human Leucocyte Antigen (HLA)-B27, which presents a significantly lower frequency in Japans than in Caucasians. AS and related SpA are strongly associated with HLA-B27. However, the association of HLA or other genetic factors with PsA remains uncertain. (7, 8, 41-43).

A wide variation of incidence has been observed even among studies carried out in European countries and the USA. Even studies from the same country present impressive differences (13, 16, 18, 23, 26). The age and sex distribution of cases present an important variation as well, suggesting a different epidemiologic profile of SpA subtypes among countries. It is difficult to interpret the different epidemiologic profiles observed among European and American populations.

Genetic, ethnic, environmental, and medical factors have been discussed as possibly associated with the occurrence and the manifestations of these diseases. Infectious agents, smoking, obesity, and dietary habits have been discussed and studied as potential risk factors associated with PsA and AS. An increase of PsA occurrence observed in different studies may be related to the above factors. However, their role remains still uncertain (7, 8, 43).

It should be pointed out that in the frame of this study we considered SpA as a group of rheumatic diseases including AS, PsA, EA, ReA, and uSpA. A decade ago, the Assessment of Spondyloarthritis International Society (ASAS) developed classification criteria for axial and peripheral SpA and incorporated the concept of non-radiographic axial SpA (5, 6). However, there are not published incidence studies of SpAs based on ASAS criteria, presenting the incidence of axial and peripheral SpA in the general population, except from a recent Slovenian study (17).

The relatively small number of incidence studies published, their methodological differences and the lack of studies for most areas of the world put important limitations in the understanding of SpA occurrence worldwide. Studies from different populations based on specific classification criteria are needed for a more accurate picture.

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