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a nationwide Danish cohort study**

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Published in:
Scandinavian Journal of Rheumatology

DOI:
10.1080/03009742.2019.1616324

Publication date:
2020

Document version:
Accepted manuscript

Citation for published version (APA):
Nygaard, A., Møller Ljungdalh, P., Iachina, M., Nikolov, T. N., & Schiøttz-Christensen, B. (2020). Incidence of ankylosing spondylitis and spondyloarthritis in 2000–2013: a nationwide Danish cohort study. *Scandinavian Journal of Rheumatology*, 49(1), 21-27. <https://doi.org/10.1080/03009742.2019.1616324>

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Title: “Incidence of ankylosing spondylitis and spondyloarthritis in 2000-2013: A nationwide Danish cohort study”

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Category: Full length article

Short title (running head): “Incidence of AS and SpA in Denmark”

Keywords: Incidence, Spondyloarthritis, Ankylosing Spondylitis, Epidemiology, Denmark

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Abstract:

Objective: To describe the incidence of ankylosing spondylitis (AS) and spondyloarthritis (SpA) in the Danish population in 2000 to 2013, at both national and regional level, and to investigate any trends in incidence over time.

Methods: From the Danish National Patient Registry (NPR), we identified patients diagnosed with AS (ICD10:M45) or SpA (ICD10:M46) in the time period 1st January 2000 to 31st December 2013. Patients without a relevant contact in NPR at 12-24 months after initial diagnosis were excluded. Incidence rate ratios were calculated using the background population of men and women aged 18-45 years in 2000 to 2013 as comparator, and variations in incidence between time periods and the five Danish regions were evaluated.

Results: In total 3042 incident cases were identified (AS: 1849, SpA: 1193). AS incidence increased from 476 in 2000-2004 to 660 in 2010-2013, and the incidence rate ratio (IRR) increased from 1.49 (CI: 1.33-1.67) in 2005-9 to 1.74 (CI: 1.53-1.97) in 2010-2013. SpA incidence increased from 156 in 2000-2004 to 707 in 2010-2013, where the IRR increased from 2.45 (CI: 2.03-2.94) in 2005-9 to 6.31 (CI: 5.27-7.55) in 2010-2013. The incidence of both AS and SpA increased in all five Danish regions.

Conclusion: The incidence of both AS and SpA in Denmark increased from 2000 to 2013. However, the proportion of patients diagnosed with SpA rather than AS was significantly higher in 2010-2013. This might be due to increased awareness of SpA and new treatment options, but possibly also misclassification of patients with SpA.

Introduction

Axial spondyloarthritis is a group of inflammatory rheumatic conditions characterized by back pain due to inflammation in the sacroiliac joints and spine. The several subgroups of this condition include ankylosing spondylitis (AS), psoriatic arthritis, reactive arthritis, enteropathic spondyloarthritis, and undifferentiated spondyloarthritis (SpA) (1). Depending on the degree of structural damage in the sacroiliac joints, axial spondyloarthritis can be divided into non-radiographic axial spondyloarthritis (nr ax-SpA) and radiographic axial spondyloarthritis (ax-SpA), which includes AS (2).

The diagnosis of AS and SpA currently relies on the Modified New York criteria from 1984 and the Assessment of SpondyloArthritis International Society criteria (ASAS) with the imaging arm from 2009 (3). The few published studies on the incidence of axial spondyloarthritis show great variation, from 0.4 to 15 per 100,000 (4). When including only studies using the Modified New York criteria for AS, the incidence declines to 1.5 to 7.3 per 100,000 (5-16).

A possible explanation of the variation in AS incidence across studies using the same diagnostic criteria could be the differences in prevalence of HLA-B27 among the study populations (5).

Previous studies have shown a high prevalence of HLA-B27 in Scandinavian populations, and this was correlated to high incidence of AS reported in studies from Norway (5) and Finland (6).

Few studies have reported variation in incidence over time. One study found no significant variation in AS incidence in an American population from 1935-1989 (7), and a more recent study with 86 AS patients was unable to detect significant variation in incidence from 1980-2009 (8).

Before the introduction of biological agents, the treatment of spondyloarthritis relied on physical therapy and NSAIDs (non-steroidal anti-inflammatory drugs). In 2005 the first tumor necrosis

factor (TNF) alfa inhibitor, Remicade (Infliximab), was approved for treatment of AS patients in Denmark (17). Because anti-TNF alfa treatment is extremely expensive, it is relevant to evaluate the incidence of AS and SpA in the Danish population.

The purpose of this study was to describe the incidence of ankylosing spondylitis (AS) and spondyloarthritis (SpA) in the Danish population in 2000 to 2013, at both national and regional level, and to investigate any trends in incidence over time. To evaluate potential effects of the introduction of anti-TNF alfa treatment in 2005 and the implementation of the ASAS criteria in 2009, the incident cases were clustered into three time periods: i) 2000-2004, ii) 2005-2009, and iii) 2010-2013.

Methods

This study was a population-based nationwide cohort study using data from Danish health registries. The Danish health care system is tax-funded and provides free and equal access to health care for all citizens. The various national registries can be linked by applying the unique civil registration number (CPR number) that is assigned to Danish citizens at birth or immigration. The Danish National Patient Registry (NPR) was used to identify relevant cases.

NPR contains records of all discharges from Danish hospitals since its establishment in 1977. As of 1994, the NPR also contains registrations of all outpatient visits. The administrative data includes information such as CPR number, the patient's municipality, which hospital the patient was in contact with, and the dates and times of the given activity. The registry also contains clinical data on principal, secondary, and referral diagnoses based on the 10th version of the International Classification of Diseases (ICD-10) (18)(19). For the current analysis, we defined a relevant visit as

the registration of an activity at an inpatient or outpatient hospital visit combined with a relevant diagnosis.

Statistics Denmark collects and publishes national statistics (20). We used data from Statistics Denmark to provide information about the national background population and for each of the five regions of Denmark.

Study population

The study population comprised all patients seen at a Danish hospital in the period January 1st 2000 to December 31st 2013 who were aged 18-45 years, had a principal or secondary diagnosis of AS (ICD10:M45) or SpA (ICD10:M46), and had a valid Danish CPR number. Patients with a prior diagnosis of AS or SpA before the inclusion period started in 2000 were excluded. 434 patients had both a M46 and M45 diagnose registered in the NPR. In these cases the M46 diagnose were overruled and the patients were registered with M45 in the present study.

Patients with a relevant diagnosis but without a relevant clinical contact registered in NPR were excluded from the study. The guidelines from the Danish Society of Rheumatology state that patients with suspected axial spondyloarthritis should be followed at a rheumatology clinic at least once within the first six months after initial diagnosis and subsequently every six or twelve months (21). Thus we only included patients with at least one relevant contact in NPR within the first 12 months and at least one relevant contact in the 12-24 months after initial diagnosis.

Outcome

The primary outcome was the incidence of AS and SpA in Denmark in the time period 2000-2013. Secondary outcome was potential regional variation between the five regions of Denmark.

The incidences of AS and SpA were estimated by dividing the number of cases by the number of person-years for each disease. This resulted in an annual incidence per 100,000.

Statistical analysis

STATA software version 14 was used for data analysis.

Background population data obtained from Statistics Denmark were used to calculate AS and SpA incidence rates per 100,000 among men and women aged 18-45. The incidence rates were calculated nationwide, by gender, time periods, and region and then for each of the five Danish regions by gender and time periods. We also calculated the incidence rate of MRI scans nationwide and by gender. Between-group comparisons for continuous and categorical demographic variables were performed with independent sample t-test and Pearson Chi-square test respectively. A p-value <0.05 was considered statistically significant.

Differences in the incidence rate ratio (IRR) of AS and SpA between time periods and regions were tested using Poisson regression analysis.

Results

National level

The background population of men and women aged 18-45 years in 2000 to 2013 gave a total of 28,495,047 person-years.

In total, 3042 (AS: 1849 (60.8%), SpA: 1193 (39.2%)) patients from all five Danish regions were diagnosed with AS or SpA and had a least one relevant clinical contact in NPR at 12-24 months (Figure 1). Information about place of residence was unavailable for 26 patients. Mean patient age for AS was 33.6 years (SD: 7.00) and for SpA 32.7 years (SD: 7.29)

Males were overrepresented in the whole group (1.724, 56.7%) and specifically in the AS group (1.234, 63.3%). Females were overrepresented in the SpA group (703, 58.9%) (Table 1).

Figure 2 presents the incidence and trends over time in AS and SpA per 100,000 for males and females in the period 2000-2013. The incidence of SpA increased significantly from 2005 to 2010 and from 2010 to 2013 for both males and females ($p < 0.001$).

This is also reflected in Table 1, where the IRR for AS increased from 1.49 (CI: 1.33-1.67) in 2005-9 to 1.74 (CI: 1.53-1.97) in 2010-2013. The IRR for SpA increased from 2.45 (CI: 2.03-2.94) in 2005-9 to 6.31 (CI: 5.27-7.55) in 2010-2013.

The use of MRI in patients suspected for having spondyloarthritis has increased substantially since 2000. In 2013, 94.3% of females with AS and 98.1% with SpA had an MRI of the sacroiliac joints as part of their examination leading to an AS or SpA diagnosis in 2000-2013. Similarly, 95% of males with AS and 98.5% with SpA had MRI prior to final diagnosis (Figure 3).

Regional level

There were no statistically significant differences in the incidence of AS and SpA between the five regions of Denmark. All regions showed an increasing incidence of AS and SpA (Figure 4).

The distribution of AS and SpA differed across the five regions of Denmark (Figure 1). Region 1 had a higher proportion of AS cases (69.5%) than SpA (30.5%), while Region 2 had the most even distribution, with 52.1% AS cases and 47.9% SpA cases.

Males were overrepresented for AS and women for SpA in all regions of Denmark, although the proportions varied across regions. The greatest variation in AS was seen in Region 3 with 60.4% males and 39.6% females compared to Region 5 with 51.6% males and 48.4% females.

Discussion

This is the first Danish study to explore the incidence of AS and SpA over time. Our results show an overall increase in incidence of both AS and SpA from 2000 to 2013 and a change in distribution towards an increased proportion of SpA.

It is standard procedure in Denmark that a patient with suspected AS or SpA is evaluated by an experienced medical assistant or a specialist in rheumatology before the final diagnosis is verified (21). There is an unequal distribution of rheumatology experts in the five Danish regions, ranging from 2.1 per 100,000 citizens in region 5 to 7.6 per 100,000 citizens in region 1 (22). To assess whether this inequality influenced the diagnosis of AS and SpA, we investigated incidence trends in the five regions.

The significant increase in incidence of AS and SpA over time was seen in all of the five Danish regions, with no significant differences in incidence rates between the regions. However, we found interregional differences in the proportions of patients with AS and SpA. Region 1 had the highest percentage of AS cases (69.5%) while in Region 2, the distribution of AS and SpA cases was almost equal. The reason for this difference is not clear, as rheumatologists in all regions diagnose and treat patients with spondyloarthritis according to the national guidelines (21).

Males were overrepresented among all the cases and in the AS group, which is in line with previous literature regarding the epidemiology of spondyloarthritis (23).

The increased incidence of AS and SpA may partly be due to the new opportunities for medical treatment that have increased awareness of the AS and SpA diagnoses among general practitioners and other medical specialists. This could have led to an increasing number of referrals of patients for rheumatological evaluation and thereby increased AS/SPA incidence registered in the national databases. The introduction of the TNF alfa inhibitors in 2005 and 2006 in Denmark could thus

explain the increased incidence of AS and SpA from this time period (17). However, a recent study has shown a non-significant trend of decline in the incidence rate of AS patients starting first line biological DMARD treatment from 2010 to 2016 among Scandinavian countries including Denmark (24).

The diagnosis of AS currently relies on the Modified New York criteria from 1984 (3), which are based on radiographic changes of the sacroiliac joints at X-ray. As MRI examination detects inflammatory changes at an early stage, some of those patients will eventually fulfill the criteria for AS and will thereby change from a SpA to an AS diagnosis. In the present study 14% had both a M46 and M45 diagnose in NPR from 2000-2013. This is in line with data from the Swedish NPR in a previous study (25).

Previous studies have failed to show a significant increase in AS diagnosis over time (7)(8). We thus believe that the findings in the present study reflect changes in awareness and diagnostic practice rather than an actual increase of AS patients in the Danish population.

Besides the above-mentioned increased attention to the spondyloarthritis diagnoses, the implementation in 2009 of the ASAS classification criteria including the imaging arm could have contributed to the significant increase in SpA incidence from 2000-2013. Increased use of MRI in the evaluation of patients with inflammatory symptoms could overestimate SpA incidence if the MRI changes are overemphasized by the clinician. Previous studies have shown an increased probability of MRI changes to be detected in patients with unspecified low back pain (26). This means that some patients may be diagnosed with an inflammatory condition at an earlier stage, when X-rays of the sacroiliac joints do not yet show structural changes.

In recent years there has been increased awareness of patients who present with low back or pelvic pain and MRI signs of sacroiliac inflammation and their risk of being misclassified as having SpA

according to the ASAS criteria for spondyloarthritis. To prevent such misclassification, the Danish Society of Rheumatology has suggested a mandatory expert evaluation of each patient with suspected SpA before final diagnosis is given (27). This may result in a stabilizing or reduction in the incidence of SpA in the future.

Strengths and limitations

The current study was register-based, and cases were identified exclusively using the ICD-10 codes in the NPR. This meant that no clinical or imaging results prior to the registration were evaluated, and thus the final diagnosis was not validated. The validation of the ICD-10 codes for AS and SpA has been evaluated in a previous study (25). Based on high positive predictive values (PPV) for fulfilling different sets of SpA/AS criteria it was concluded, that the validity of AS/SpA diagnosis in the Swedish NPR was sufficient to be used for further studies. We believe, that the validity of diagnosis of AS and SpA in the Danish NPR would reflect the results from the Swedish study due to the fact that the Danish and Swedish population and Healthcare system is similar in many respects. The present study only included patients with a relevant hospital contact registered in the patient registry at 12-24 months after initial diagnosis. This approach reduced the risk of false positive diagnoses, but could have underestimated the incident cases.

We believe however, that the vast majority of Danish patients diagnosed with AS or SpA are followed every 6-12 months after initial diagnosis. Patients diagnosed and treated in private practice were not included in this study, which may also have led to underestimates of AS and SpA.

However the proportion of patients with AS or SpA in private practice is relatively small compared to out-clinic patients at the hospitals. In a previous study it is stated that only 5% of patients with a rheumatological disease are treated in private care (25). Furthermore, patients with severe disease activity and inadequate response to NSAID and psychical training must be referred to the hospital

in order to receive biological treatment. In view of the above, we do not believe that the proportion of patients treated in private care contributes to the incident cases of spondyloarthritis substantially. In the present study only patients up to 45 years were included according to the ASAS criteria for diagnosing spondyloarthritis. It is possible that this method has excluded some potential incident cases due to prolonged delay in the final diagnose of spondyloarthritis as suggested in a Swedish prevalence study of AS patients (28). However, the proportion of incidents cases of AS/SpA after the age of 45 is considered limited.

This study contributes with new knowledge and insight about the incidence and time trends of AS and SpA in the Danish population. Clustering the data into three time periods has given a more detailed view and suggests possible factors (such as new medical treatments and change in classification criteria) that could have influenced the epidemiology of the diseases.

In conclusion, this study has shown an increased incidence of AS and SpA at both national and regional levels from 2000-2013 in the Danish population. Future trend studies would be useful to investigate whether new insights into MRI changes in inflammatory disease and possible overestimation of spondyloarthritis will influence the incidence of AS and SpA.

Ethics and consent

The Region of Southern Denmark was the data controller for this project, and it is included in their records of personal data processing activities (file no. 16/1586). Additional approvals or consents were not needed for scientific research based exclusively on national register data. The data processing was conducted according to EU and Danish legislation on processing of sensitive personal information, as well as internal regulations from the Region of Southern Denmark. Analyses were run on pseudonymized data, and the results presented in this manuscript do not enable identification of single data subjects.

Conflicts of interest

The authors declare no conflicts of interest.

Funding

The study was supported by the Program for Clinical Research Infrastructure (PROCRIN) established by the Lundbeck Foundation and the Novo Nordisk Foundation.

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Figure 1: Distribution of patients in the five Danish regions with an AS (M45) or SpA (M46) diagnose in Danish National Patient Registry (NPR)

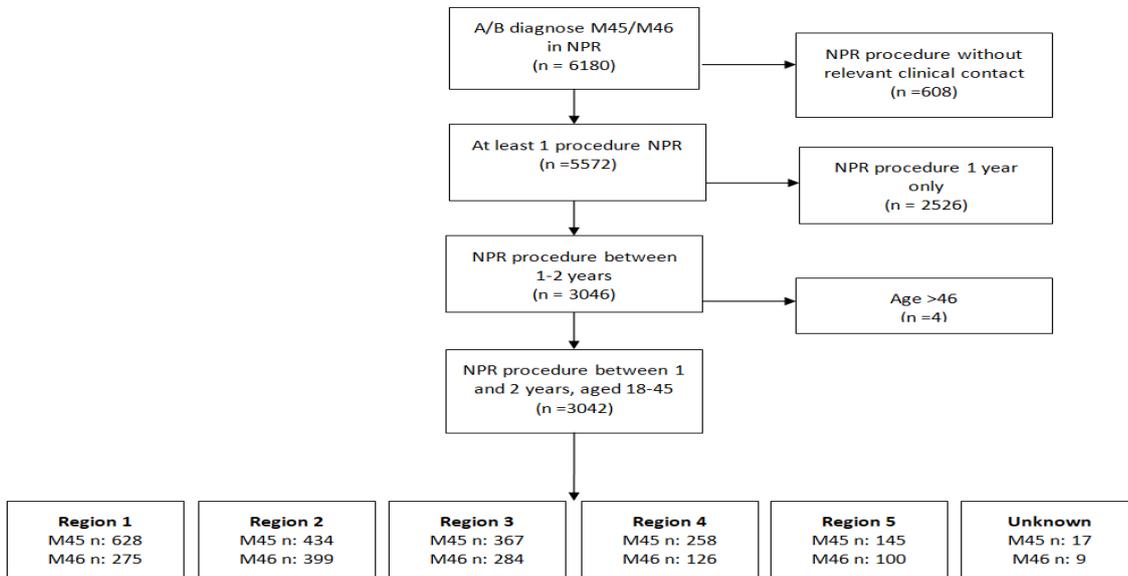


Figure 2: Incidence per 100,000 of SpA and AS for males and females in 2000 to 2013

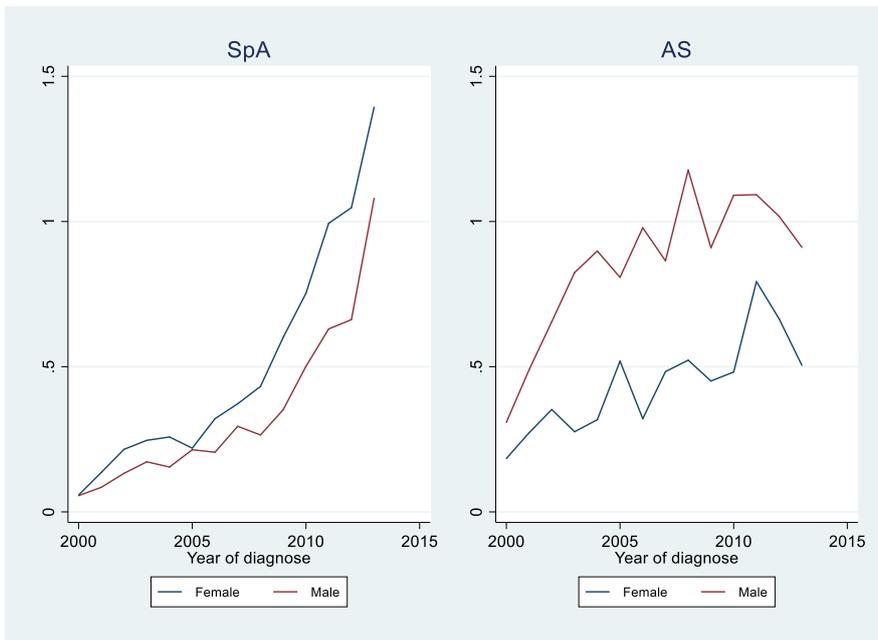


Figure 3: Percentage of patients receiving an MRI as a part of AS/SpA diagnose 2000-2013

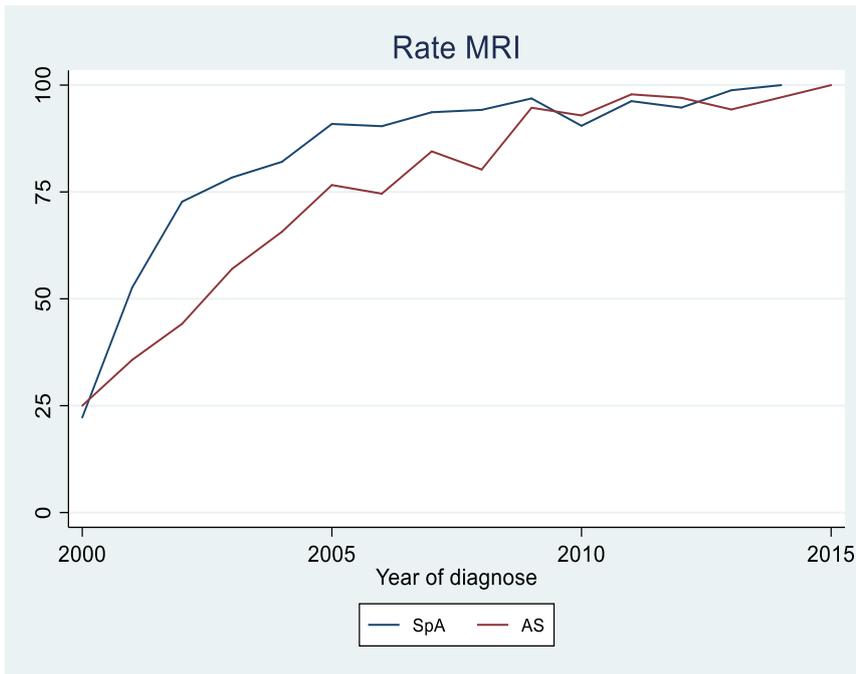


Figure 4: Incidence per 100,000 of SpA and AS for males and females in the five Danish regions in 2000 to 2013

