Increasing proportion of female patients with ankylosing spondylitis: a population-based study of trends in the incidence and prevalence of AS

Nisha N Haroon, J Michael Paterson, Ping Li, Nigil Haroon

ABSTRACT

Objective: With the introduction of MRI in diagnosis and tumour necrosis factor inhibitors for treatment, the field of ankylosing spondylitis (AS) has undergone significant changes. We carried out a population-based study of the trends in incidence and prevalence of AS over the past 15 years.

Methods: This is a retrospective analysis of provincial health administrative databases. Residents of Ontario, Canada aged 15 years or older diagnosed with AS between 1995 and 2010 were included in the study. Trends in prevalence and incidence of male and female patients with AS were separately analysed.

Results: We identified 24,976 Ontarians with AS. The prevalence of AS in Ontario has nearly tripled over the past two decades. The proportion of women with new diagnosis of AS is increasing, a trend that began around the year 2003. A higher proportion of male compared with female patients with AS were diagnosed at an earlier age.

INTRODUCTION

Axial spondyloarthritis (AxSpA) is characterised by chronic inflammation of the spine and affects millions of people. Spondyloarthritis (SpA) has been classified into axial (AxSpA) and peripheral SpA depending on the major clinical presentation. Ankylosing spondylitis (AS) is the prototype AxSpA with characteristic radiographic changes in the sacroiliac joints. The disease starts predominantly in young adults and in addition to chronic pain and disability, it causes significant morbidity and risk of mortality. AS poses a huge financial burden to the healthcare and public welfare systems by costing billions of dollars on treatment, disability and loss of productivity. The prevalence of AxSpA has been reported to be as high as that of rheumatoid arthritis, with estimates ranging from 1.0% to 1.4%. The prevalence of AS is increasing, a trend that began around the year 2003. A higher proportion of male compared with female patients with AS were diagnosed at an earlier age.

Strengths and limitations of this study

- This is the largest population-based epidemiological study on the incidence and prevalence of ankylosing spondylitis (AS).
- With the introduction of MRI in diagnosis and tumour necrosis factor inhibitors for treatment, the field of AS has undergone significant changes. Increasing awareness and early diagnosis has changed the epidemiological characteristics of AS. This study provides up-to-date data on changing trends in the incidence and prevalence of AS.
- The effect of HLA-B27 on the incidence and prevalence of AS could not be studied.
- Some patients with AS could have been misdiagnosed as chronic back pain and wrongly classified.
- The diagnosis of AS was not based on the modified New York criteria but on a diagnostic algorithm including physicians’ billing codes.

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Prepublication history and additional material is available. To view please visit the journal (http://dx.doi.org/10.1136/bmjopen-2014-006634).

Received 15 September 2014
Revised 10 November 2014
Accepted 26 November 2014

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Results: We identified 24,976 Ontarians with AS. The prevalence of AS in Ontario has nearly tripled over the past two decades. The proportion of women with new diagnosis of AS is increasing, a trend that began around the year 2003. A higher proportion of male compared with female patients with AS were diagnosed at an earlier age.

Conclusions: The prevalence of AS in Ontario has nearly tripled over the past two decades. The proportion of women with new diagnosis of AS is increasing, a trend that began around the year 2003. A higher proportion of male compared with female patients with AS are diagnosed at an earlier age.

INTRODUCTION

Axial spondyloarthritis (AxSpA) is characterised by chronic inflammation of the spine and affects millions of people. Spondyloarthritis (SpA) has been classified into axial (AxSpA) and peripheral SpA depending on the major clinical presentation. Ankylosing spondylitis (AS) is the prototype AxSpA with characteristic radiographic changes in the sacroiliac joints. The disease starts predominantly in young adults and in addition to chronic pain and disability, it causes significant morbidity and risk of mortality. AS poses a huge financial burden to the healthcare and public welfare systems by costing billions of dollars on treatment, disability and loss of productivity. The prevalence of AxSpA has been reported to be as high as that of rheumatoid arthritis, with estimates ranging from 1.0% to 1.4%. The prevalence of AS is increasing, a trend that began around the year 2003. A higher proportion of male compared with female patients with AS were diagnosed at an earlier age.
Documenting disease trends may improve our understanding of the pathogenesis of disease and aid in the planning of health services. Two major developments in the detection and treatment of AxSpA have been the introduction of MRI for early diagnosis and the approval of tumour necrosis factor-α inhibitor (TNFi) therapy for treatment.20 The existence of a window of opportunity in the treatment of AxSpA is being increasingly recognised,21 22 leading to mounting pressure for early diagnosis and increasing demand for up-to-date data on disease incidence and prevalence. Given the relatively low prevalence of AS, validated administrative databases represent a valuable resource for studying AS. Accordingly, we used Ontario’s population-based administrative data to estimate the incidence and prevalence of AS between 1995 and 2010.

METHODS
Study setting and data sources
We conducted a population-based cohort study to assess trends in the incidence and prevalence of AS using provincial health administrative data in Ontario, Canada. Ontario, Canada’s most populous province, is home to over 13.5 million residents who receive health services under a publicly funded universal health insurance system. Ontario’s provincial health administrative databases carry details of each resident’s healthcare utilisation. The databases are held securely in a linked, de-identified form and analysed at the Institute for Clinical Evaluative Sciences (ICES, http://www.ices.on.ca). The core data sets used for this study were: the Ontario Health Insurance Plan (OHIP) Registered Persons Data Base (RPDB), which contains demographic, place of residence and vital status information regarding all persons eligible to receive insured health services; the OHIP Claims History Database, which captures information regarding physician services,23 and the Canadian Institute for Health Information (CIHI) Discharge Abstract Database (DAD), which contains diagnostic and procedural information regarding all acute hospital admissions.24

AS definition
Ontario residents aged 15 years or older were included in the study. Patients with AS were identified as those who had at least two OHIP physician service claims with an International Classification of Diseases, Ninth Revision (ICD-9) diagnosis code of 720 over a period of 2 years, with at least one claim by a rheumatologist; or at least one CIHI-DAD record with an ICD-9 code of 720 or ICD-10 code of M45.25

Statistical analysis
We estimated the annual crude as well as age, sex and geographic location—standardised incidence and prevalence of AS among Ontarians aged 15 years or older from 1995 to 2010 (the years of data available at ICES). Among those who satisfied our criteria for AS (above), disease onset was defined as the date of first contact with the healthcare system for which a diagnosis of AS was provided. The annual incident population at risk was estimated as the Statistics Canada Census population estimate minus the number of prevalent AS cases in the preceding year. Prevalent cases were carried forward each year, and persons who died or emigrated were excluded from the numerator and the denominator. The administrative data were available only from 1991 onward and all prevalent cases would appear as incident cases during the early years of the study. Hence we report incidence from 1995 onward with 1991 onward and all prevalent cases would appear as incident cases during the early years of the study. Hence we report incidence from 1995 onward with 1991–1994 as a 36-month look-back period. All rates were age and sex standardised using the 1991 Ontario population as the standard population. To compare incidence and prevalence rates, the goodness of fit $\chi^2$ test was used and unless otherwise specified all tests were performed with 1° of freedom. All analyses were performed at the Institute for Clinical Evaluative Sciences using SAS V.9.3 (SAS Institute, Cary, North Carolina, USA).

RESULTS
Prevalence of AS
In 1995, 8.7 million Ontarians were aged 15 years or older. This number reached 11 million by the year 2010. The number of patients with AS more than tripled over the study period, from 6930 in 1995 to 24 976 in 2010, approximately 55% men. Data on prevalence rates stratified by age and gender are shown in table 1. The overall standardised prevalence increased nearly threefold over the study period, from 79/100 000 in 1995 to 213/100 000 in 2010 (figure 1).

Incidence of AS
The annual incidence of AS remained relatively stable over the 15-year study period (figure 2). From 1995 to 2010 the standardised incidence rates varied between 14 and 16 per 100 000 population. In 2010, the standardised incidence was 15/100 000 population.

Sex differences in epidemiological trends of AS
The prevalence increased by approximately twofold among men (from 101/100 000 in 1995 to 238/100 000 in 2010) and over threefold among women (from 59/100 000 in 1995 to 190/100 000 in 2010). Although men had greater prevalence of AS throughout the study, the male/female ratio decreased significantly over time from 1.70 in 1995 to 1.40 by 2000 ($\chi^2$: 91.01; p<0.0001), 1.30 by 2005 ($\chi^2$: 300.65; p<0.0001) and 1.21 by 2010 ($\chi^2$: 609.02; p<0.0001). There were 4315 male patients with AS in 1995, which increased to 13 660 by 2010. The number of female patients with AS increased from 2615 in 1995 to 11 316 by 2010. The male:female ratio of prevalent AS cases decreased in all age groups with time (figure 3A). The decline in the male/female prevalence ratio was most pronounced in patients with AS above
<table>
<thead>
<tr>
<th>Year</th>
<th>AS/Population</th>
<th>Prevalence* (CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1995</td>
<td>75/1,051,635</td>
<td>0.072 (0.069 to 0.075)</td>
</tr>
<tr>
<td>2000</td>
<td>87/1,125,592</td>
<td>0.077 (0.073 to 0.081)</td>
</tr>
<tr>
<td>2005</td>
<td>100/1,302,150</td>
<td>0.077 (0.073 to 0.082)</td>
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</table>

DISCUSSION

We report data from a large population-based study on incidence and prevalence of AS in North America. This is the largest epidemiological study on AS including close to 25,000 patients over a period of 15 years. Our results suggest that AS prevalence trends remain steady and continue to affect a large number of people in North America. The incidence and prevalence of AS in women have increased at greater rates than for men, resulting in shifting gender ratios.

Very few studies have reported incidence of AS from North America (table 2). The incidence reported by our study is the highest estimate when compared with all other studies (table 2) and this is reflected in the high prevalence of AS in North America. In 1992, a population-based study from USA reported an annual incidence of 7.3/100,000 population.17 A systematic review published in 2014 reported continent-specific prevalence rates for AS with the highest prevalence in North America.10 The authors reported a prevalence of 65 years of age with ratio decreasing from 2.1 in 1995 to 1.3 in 2010 (figure 3A). There were 2679 male patients with AS and 2649 female patients with AS above the age of 65 in 2010.

There was a clear changing trend in the incidence of AS in women (figure 2). The most striking difference in incidence of AS between men and women was observed between 2003 and 2006 (figure 2). The absolute male:female ratio in newly diagnosed patients with AS was 1.03 in 2010 compared with 1.30 in 1995 (χ²: 23.3; p<0.0001). To correct for the differences in the sex-stratified population at risk, the change in incidence rates in males and females was studied. There was an overall decrease in the difference between male and female incidence rates over the years (figure 3B). The incidence of AS in males was not significantly different in 1995 and 2010 (χ²: 1.3; p=0.25) but the AS incidence rate in females was significantly higher in 2010 compared with 1995 (χ²: 33.39; p<0.0001). A greater proportion of male compared with female patients with AS entered the cohort at an earlier age (figure 3C). Among male patients with AS, 50.8% were diagnosed in the 15–45 age group compared with 44.2% of female patients with AS. The trend in male:female incidence rates over time show more female patients than male patients with AS being diagnosed in the 45–65 age group from 2005 onwards (figure 3D). The male:female incidence ratios were stable overall in the 15–45 age group, but the ratio dropped in the >65 age group up to 2002 and then started to rise again. In the sex-specific AS incidence rates stratified by age group, the striking patterns that emerge include a drop in incident male patients with AS above 65 years of age in the initial period of follow-up and steady increase in incident female patients with AS in the 15–45 and 45–65 year age groups (see online supplementary figure S1).
31.9/10 000 population in North America. However, the rates were calculated based on pooled estimates from just two studies showing that there have been no systematic efforts in this regard. Another population-based study from Quebec, Canada, presented data on the prevalence of AS between 1996 and 2006. The reported incidence and prevalence rates were 11.5/100 000 person years and 140/100 000 population, respectively. The diagnosis was established on the basis of one physician claim based on the diagnostic code of AS (ICD-9 code: 720.0). The incidence and prevalence estimates of our study are higher than the Quebec study despite using more stringent criteria for diagnosis of AS. We defined AS based on two physician billing claims for the ICD-9 code 720 over 2 years, with at least one claim by a rheumatologist or at least one hospitalisation record.

The population of Ontario is very diverse in terms of ethnicity and genetic background. Our extensive literature review reveals a clear need to conduct large population-based studies in Europe and Asia to obtain true estimates of the disease burden. Though there have been similar studies in the past, these attempts were based on cross-sectional studies or rates calculated from hospital or clinic records and such estimates may be less accurate. There is growing concern about the financial and medical burden imposed on society by changing diagnostic and treatment paradigms of AxSpA. Of major concern is the potential overutilisation of MRI in the diagnosis of AxSpA and inappropriate use of TNFi for treating patients with mechanical back pain. There is immense interest in understanding the effect of these changing trends on the overall diagnosis and prevalence of AxSpA.

It has been well understood for some time that all patients with AxSpA may not have classic X-ray changes of AS. Classification criteria for AxSpA that include the entity non-radiographic axial SpA (nr-AxSpA) were established recently with the first TNFi trial in nr-AxSpA published in 2008. Classic sacroiliac joint changes seen in AS are not seen in patients with nr-AxSpA. It has been argued that nr-AxSpA is a distinct entity and should not be considered early AS. Except for higher C-reactive protein (CRP) and slightly better responses to TNFi in AS, the burden of disease appears to be similar.
in AS and nr-AxSpA. A distinct difference between the two groups is the greater proportion of women in nr-AxSpA. A sharp drop in incidence of AS in males above 65 years was noted from 1995 to 2002, with no significant decrease in female AS incidence in the same age group (see online supplementary figure S1). In the early part of the study some prevalent cases could have been identified wrongly as incident cases. However, a 36-month look-back period was included in the design to reduce this possibility. Earlier diagnosis of AS in males could have resulted in this shift in age group of incident cases but this was not reflected in an increase in the proportion of patients with AS diagnosed in the younger age groups (see online supplementary figures S1 and S2). Earlier diagnosis and longer survival could have resulted in the increase in prevalence of AS despite stable incidence rates. It is well known that diagnostic delays are higher in female patients with AS. A higher proportion of male patients in our study were diagnosed in the 15–45 year age group and this remained stable throughout the follow-up period (see online supplementary figure S2). The increase in female patients with AS seen from early 2000 onwards was reflected in an increasing proportion of female patients with AS being diagnosed in the 45–65 year age group. Our study is not designed to answer whether this reflects later onset of disease or delay in diagnosis of female patients with AS. Increased awareness of SpA in early 2000 could have led to the diagnosis of female patients with AS who were symptomatic for several years.

Figure 3  Sex bias in the incidence and prevalence of ankylosing spondylitis (AS). (A) The male:female prevalence ratio in each age group has been plotted to show changes over time. In all age groups the male:female prevalence ratio decreased with time. (B) The difference between male and female annual incidence of AS is decreasing progressively. (C) The proportion of total AS cases diagnosed in the different age groups, stratified by sex. Males have a greater proportion of patients diagnosed in the 15–45 year age group compared with females who have similar proportion of patients being diagnosed in the 15–45 and 45–65 year age groups. (D) The time trend of male:female ratio of incident AS cases in the different age groups from 1995 to 2010.
This is a health database-based study, one limitation is that the data can only provide information on patients who had access to healthcare providers. We could not study the effect of HLA-B27 on the incidence and prevalence of AS due to the lack of availability of these data from the ICES databases. In addition, some patients with AS could have been misdiagnosed as chronic back pain and wrongly classified. The diagnosis of AS was not based on the modified New York criteria but on a diagnostic algorithm including physicians’ billing codes. Physicians might have used the same code to identify patients with other forms of SpA including nr-axSpA. Diagnostic algorithms utilising health administrative data and the ICD-9 code-based definition have been validated. But the ICD-9 code 720 for AS has been validated only in the Veterans Affairs healthcare system in the USA. The use of one ICD-9 code of 720 has high sensitivity (91%) and specificity (99%) for identifying individuals with AS. Compared with the Quebec study that used this algorithm, we used a much stricter algorithm with two billing codes that has 100% specificity for a diagnosis of AS. The sensitivity of this algorithm is, however, lower at 82%, and the prevalence and incidence values in this study could be an underestimate.

The main strength of our study is that it provides the best and updated estimates of prevalence and incidence of AS based on a large number of patients from Canada. Most prior studies have defined AS based on hospital-based records. Our definition of AS from administrative databases, as aforementioned, is reliable and based on validated algorithms. Further, we could eliminate reporting and selection biases due to the population-based study design. Population-based studies in addition help capture larger sample sizes and allow better generalisability of results. Utilising data from health administrative databases ensured that few participants were lost to follow-up. The large sample size provided sufficient statistical power to study the temporal changes in incidence and prevalence as well as gender effects.

**CONCLUSIONS**

AS continues to affect millions of people in North America. The prevalence of AS steadily increased from 1995 to 2010. Increasing awareness of the disease with more diagnosis of women with AS could be affecting the gender ratio of AS cohorts over time.

**Table 2** Comparison of various studies that assessed the incidence and prevalence of ankylosing spondylitis

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Country</th>
<th>Design</th>
<th>N</th>
<th>Incidence (%)</th>
<th>Prevalence (%)</th>
</tr>
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<tr>
<td>Current study</td>
<td>2014</td>
<td>Canada</td>
<td>Population</td>
<td>24976</td>
<td>0.015</td>
<td>0.21</td>
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<tr>
<td>Koko et al</td>
<td>2014</td>
<td>Albania</td>
<td>Hospital</td>
<td>54</td>
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<td>0.061</td>
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<tr>
<td>Kassimos et al</td>
<td>2014</td>
<td>Greece</td>
<td>Military</td>
<td>285</td>
<td>No data</td>
<td>0.08*</td>
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<tr>
<td>Peláez-Ballestas et al</td>
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<td>Mexico</td>
<td>House survey</td>
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<td>0.1</td>
</tr>
<tr>
<td>Cakir</td>
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<td>Turkey</td>
<td>House survey</td>
<td>96</td>
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<td>0.12</td>
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<td>Szabo et al</td>
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<td>Population</td>
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<td>0.14</td>
</tr>
<tr>
<td>Haglund et al</td>
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<td>Population</td>
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<td>0.09</td>
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<tr>
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<td>Iceland</td>
<td>Hospital</td>
<td>256</td>
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<td>0.10</td>
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<td>Onen et al</td>
<td>2008</td>
<td>Turkey</td>
<td>Survey</td>
<td>31</td>
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<td>0.49</td>
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<tr>
<td>De Angelis et al</td>
<td>2007</td>
<td>Italy</td>
<td>Population</td>
<td>8</td>
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<td>Bakland et al</td>
<td>2005</td>
<td>Norway</td>
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<td>France</td>
<td>Survey</td>
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<td>1998</td>
<td>Germany</td>
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<td>No data</td>
<td>0.86</td>
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<td>Taiwan</td>
<td>Population</td>
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<td>0.19</td>
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<td>USA</td>
<td>Population</td>
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<td>0.007</td>
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<td>1985</td>
<td>Norway</td>
<td>Survey</td>
<td>27</td>
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<tr>
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<td>1979</td>
<td>USA</td>
<td>Hospital</td>
<td>102</td>
<td>0.01</td>
<td>0.13</td>
</tr>
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*In males.
Funding This study was supported by the Arthritis Center of Excellence located at the Toronto Western Hospital and the Institute for Clinical Evaluative Sciences (ICES), a non-profit research institute funded by the Ontario Ministry of Health and Long-Term Care (MOHLTC).

Competing interests None.

Ethics approval This study was approved by the Research Ethics Board at Sunnybrook Health Sciences Centre in Toronto, Ontario, Canada.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement No additional data are available.

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BMJ Open 2014 4:
doi: 10.1136/bmjopen-2014-006634

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