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

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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. Crude as well as age-standardised and sex-standardised incidence and prevalence of AS between 1995 and 2010 were calculated. Trends in prevalence and incidence of male and female patients with AS were separately analysed.

Results: We identified 24 976 Ontarians with AS. Age/sex-standardised AS prevalence increased from 79/100 000 in 1995 to 213/100 000 in 2010. Men had higher prevalence than women, but the male/female prevalence ratio decreased from 1.70 in 1995 to 1.21 by 2010. A higher proportion of male compared with female patients with AS were diagnosed in the 15–45 age group. Annual incidence rates revealed increasing diagnosis of AS among women after 2003.

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.

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.

INTRODUCTION

Axial spondyloarthritis (AxSpA) is characterised by chronic inflammation of the spine and affects millions of people.[1] Spondyloarthritis (SpA) has been classified into axial (AxSpA) and peripheral SpA depending on the major clinical presentation.[2 3] 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.[4] 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.[5 6] 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%.[7] Yet, until recently, AxSpA has received relatively less attention and is often overlooked in the initial stages due to the non-specific nature of the back pain.[8]

Large-scale studies of the incidence and prevalence of AS are scant. Studies examining epidemiological trends in AS have yielded variable results, some of which may be explained by differences in study design, geographic location, age, ethnicity, background prevalence of HLA-B27, genetic susceptibility and disease ascertainment.[9–13] Some authors have reported AS incidence rates, but these studies were mainly in Europe.[13–19]

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 1991–1994 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 χ^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 (χ^2: 91.01; p<0.0001), 1.30 by 2005 (χ^2: 300.65; p<0.0001) and 1.21 by 2010 (χ^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 1 Prevalence of ankylosing spondylitis (AS) by age group and sex

Year	1995		2000		2005		2010	
	AS/population	Standardised prevalence* (CI)	AS/population	Standardised prevalence* (CI)	AS /population	Standardised prevalence* (CI)	AS/population	Standardised prevalence* (CI)
Total								
15–44	3459/5 099 311	0.068 (0.066 to 0.070)	5386/5 263 168	0.103 (0.100 to 0.105)	6717/5 467 019	0.124 (0.121 to 0.127)	7575/5 487 687	0.139 (0.136 to 0.143)
45–64	2401/2 295 176	0.105 (0.100 to 0.109)	4849/2 665 183	0.184 (0.179 to 0.189)	8152/3 175 348	0.261 (0.256 to 0.267)	12 073/3 689 997	0.333 (0.327 to 0.339)
65+	1070/1 326 012	0.081 (0.076 to 0.086)	2231/1 462 216	0.153 (0.146 to 0.159)	3406/1 614 956	0.212 (0.204 to 0.219)	5328/1 839 008	0.290 (0.282 to 0.298)
All ages	6930/8 720 499	0.079 (0.078 to 0.081)	12 466/9 390 567	0.132 (0.129 to 0.134)	18 275/10 257 323	0.173 (0.171 to 0.176)	24 976/11 016 692	0.213 (0.211 to 0.216)
Men								
15–44	2238/2 557 571	0.088 (0.084 to 0.091)	3316/2 653 893	0.125 (0.121 to 0.130)	3984/2 757 931	0.145 (0.141 to 0.150)	4406/2 748 435	0.161 (0.157 to 0.166)
45–64	1431/1 135 902	0.126 (0.120 to 0.133)	2750/1 314 825	0.211 (0.203 to 0.219)	4533/1 570 141	0.292 (0.283 to 0.300)	6575/1 827 954	0.363 (0.355 to 0.372)
65+	646/559 780	0.115 (0.107 to 0.125)	1179/628 179	0.188 (0.177 to 0.199)	1725/698 783	0.248 (0.237 to 0.260)	2679/809 922	0.331 (0.319 to 0.344)
All ages	4315/4 253 253	0.101 (0.098 to 0.105)	7245/4 596 897	0.156 (0.153 to 0.160)	10 242/5 026 855	0.198 (0.194 to 0.202)	13 660/5 386 311	0.238 (0.234 to 0.242)
Women								
15–44	1221/2 541 740	0.048 (0.045 to 0.051)	2070/2 609 275	0.080 (0.077 to 0.084)	2733/2 709 088	0.102 (0.099 to 0.106)	3169/2 739 252	0.117 (0.113 to 0.121)
45–64	970/1 159 274	0.084 (0.078 to 0.089)	2099/1 350 358	0.158 (0.151 to 0.165)	3619/1 605 207	0.232 (0.224 to 0.239)	5498/1 862 043	0.303 (0.295 to 0.312)
65+	424/766 232	0.055 (0.050 to 0.061)	1052/834 037	0.127 (0.119 to 0.135)	1681/916 173	0.185 (0.176 to 0.194)	2649/1 029 086	0.260 (0.250 to 0.270)
All ages	2615/4 467 246	0.059 (0.056 to 0.061)	5221/4 793 670	0.108 (0.105 to 0.111)	8033/5 230 468	0.150 (0.147 to 0.153)	11 316/5 630 381	0.190 (0.186 to 0.194)

*Standardised for age, sex and geographic location.

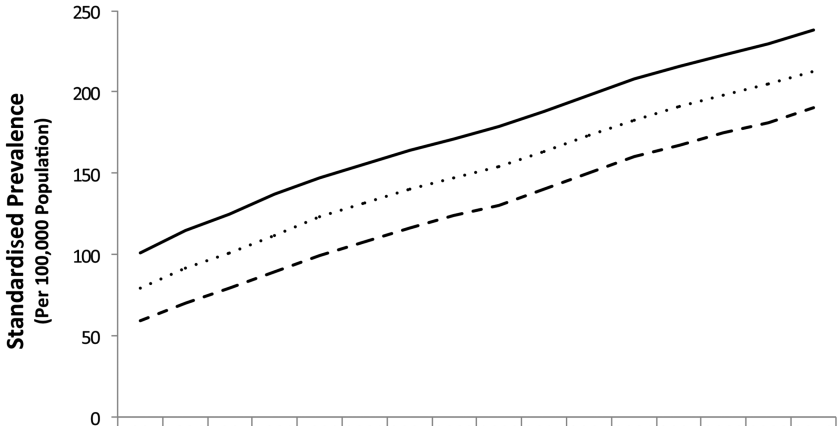
65 years of age with ratio decreasing from 2.1 in 1995 to 1.3 in 2010 (figure 3A). There were 2679 male patients with AS and 2649 female patients with AS above the age of 65 in 2010.

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 (χ^2: 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 (χ^2: 1.3; p=0.25) but the AS incidence rate in females was significantly higher in 2010 compared with 1995 (χ^2: 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).

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



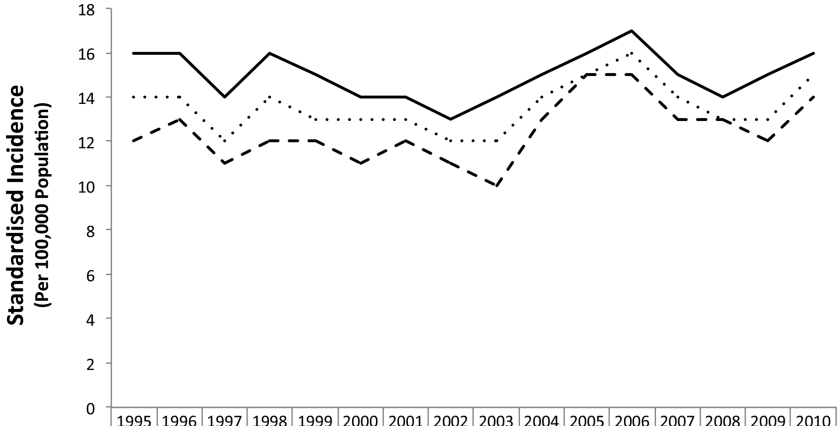
	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010
Overall	79	92	101	112	123	132	140	147	154	163	173	183	191	198	205	213
Male	101	115	125	137	147	156	164	171	179	188	198	208	216	223	230	238
Female	59	70	79	89	99	108	116	124	130	140	150	160	167	175	181	190

Figure 1 Trends in prevalence of ankylosing spondylitis (AS) in Ontario. Standardised prevalence of AS (per 100 000 population), adjusted for age, sex and geographic location. The graph shows the yearly trend in overall and sex-specific prevalence of AS from 1995 to 2010 in Ontario. The table below shows the overall as well as male- and female-specific prevalence of AS each year.

31.9/10 000 population in North America.[10] 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.[18] 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.[13–17 19] 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.[26 27] 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.[28] Except for higher C-reactive protein (CRP) and slightly better responses to TNFi in AS, the burden of disease appears to be similar



	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010
Overall	14	14	12	14	13	13	13	12	12	14	15	16	14	13	13	15
Male	16	16	14	16	15	14	14	13	14	15	16	17	15	14	15	16
Female	12	13	11	12	12	11	12	11	10	13	15	15	13	13	12	14

Figure 2 Trends in incidence of ankylosing spondylitis (AS) in Ontario. Standardised incidence rates of AS from 1995 to 2010 in Ontario with trends in males and females. Incidence rates were adjusted for age, sex and geographic location. The table below shows the overall as well as male- and female-specific incidence of AS each year.

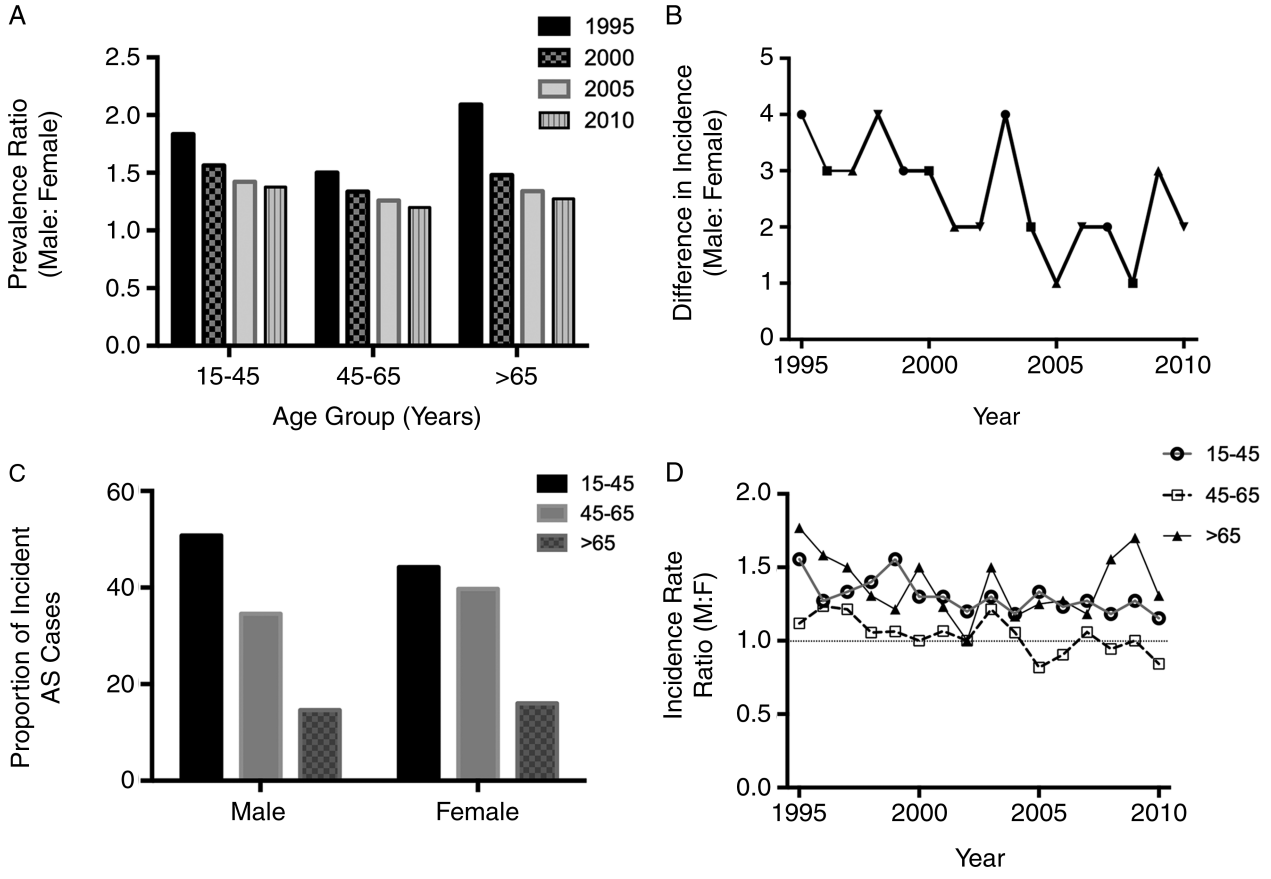


Figure 3 Sex bias in the incidence and prevalence of ankylosing spondylitis (AS). (A) The male:female prevalence ratio in each age group has been plotted to show changes over time. In all age groups the male:female prevalence ratio decreased with time. (B) The difference between male and female annual 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.

in AS and nr-AxSpA.[29] A distinct difference between the two groups is the greater proportion of women in nr-AxSpA cohorts. We tracked the sex ratio of new patients diagnosed with AS over time to study the impact of these changes in overall prevalence and incidence trends of AS. Our study shows that the epidemiological trend with more females diagnosed with AS started between 2000 and 2005 when TNFi were introduced for the treatment of AS. Between 2005 and 2010, when we would have seen the greatest impact of MRI, there were steady trends in the sex ratio. The impact of the new classification criteria and MRI for AxSpA would be clearer in a follow-up study including the period 2010–2015. The dramatic clinical response to TNFi could have resulted in increased awareness and changing perceptions of physicians towards AS. Our data thus do not support the notion that MRI use has resulted in changing gender ratios in the diagnosis of AS.

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.[30] 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.

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

Author	Year	Country	Design	N	Incidence (%)	Prevalence (%)
Current study	**2014**	**Canada**	**Population**	**24 976**	**0.015**	**0.21**
Koko *et al*[15]	2014	Albania	Hospital	54	0.006	0.061
Kassimos *et al*[31]	2014	Greece	Military	285	No data	0.08*
Peláez-Ballestas *et al*[32]	2013	Mexico	House survey	4	No data	0.1
Cakir[33]	2012	Turkey	House survey	96	No data	0.12
Szabo *et al*[18]	2011	Canada	Population	8045	0.01	0.14
Haglund *et al*[34]	2011	Sweden	Population	956	No data	0.12
Burgos-Vargas *et al*[35]	2011	Mexico	House survey	4059	No data	0.09
Hanova *et al*[13]	2010	Czech Republic	Population	185	0.006	0.09
Anagnostopoulos *et al*[36]	2010	Greece	Population	5	No data	0.29
Geirsson *et al*[37]	2010	Iceland	Hospital	256	No data	0.10
Onen *et al*[38]	2008	Turkey	Survey	31	No data	0.49
De Angelis *et al*[39]	2007	Italy	Population	8	No data	0.37
Bakland *et al*[14]	2005	Norway	Hospital	534	0.007	0.26
Alamanos *et al*[19]	2004	Greece	Hospital	113	0.002	0.03
Hukuda *et al*[40]	2001	Japan	Survey	676	0.0003	0.007
Saraux *et al*[41]	2001	France	Survey	14	No data	0.08
Kaipiainen-Seppänen *et al*[16]	2000	Finland	Reimbursement	11	0.007	0.15
Braun *et al*[11]	1998	Germany	Blood donors	9	No data	0.86
Chou *et al*[42]	1994	Taiwan	Population	17	No data	0.19
Carbone *et al*[17]	1992	USA	Population	158	0.007	
Gran *et al*[43]	1985	Norway	Survey	27	No data	1.4
Carter *et al*[9]	1979	USA	Hospital	102	0.01	0.13

*In males.

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[18 25 31] validated.[25] But the ICD-9 code 720 for AS has been validated only in the Veterans Affairs healthcare system in the USA.[25] The use of one ICD-9 code of 720 has high sensitivity (91%) and specificity (99%) for identifying individuals with AS.[25] 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.[18 25] The sensitivity of this algorithm is, however, lower at 82%, and the prevalence and incidence values in this study could be an underestimate.[25]

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.

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Contributors All authors were involved in the initial planning of the study. PL did all statistical analyses on data lodged in Institute for Clinical Evaluative Sciences, Toronto, Canada. NNH, NH and JMP were involved in the study design and protocol development. NNH wrote the draft manuscript, which was edited and approved by all authors.

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Competing interests None.

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

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