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A STATEWIDE STUDY OF CARDIOVASCULAR OUTCOMES IN PATIENTS WITH ANKYLOSING SPONDYLITIS

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Abstract

Numerous studies have shown that ankylosing spondylitis is associated with an increased risk of cardiovascular disease including heart failure, acute myocardial infarction, stroke, transient ischemic attack, and cardiovascular mortality. This may be a direct result of inflammation or an indirect one from the use of anti-inflammatory drugs needed to treat ankylosing spondylitis, or from the coexistence of traditional risk factors. This is a retrospective case-control study of the occurrence of cardiovascular events in ankylosing spondylitis patients and matched controls. Data was obtained from the Myocardial Infarction Data Acquisition System, a statewide database containing hospitalizations for cardiovascular diseases in New Jersey. Two types of analyses were performed: unadjusted and adjusted for comorbidities. The odds ratio of developing heart failure in the ankylosing spondylitis group vs. matched controls was 1.59 (95% CI 1.44 - 1.76, $p < 0.001$) in the unadjusted model and 1.31 (95% CI 1.18 - 1.47, $p < 0.001$) after adjustment for hypertension, diabetes mellitus, acute kidney failure/chronic kidney disease, chronic liver disease, chronic obstructive pulmonary disease, and hyperlipidemia. Similarly, risks of myocardial infarction and cardiovascular mortality in ankylosing spondylitis patients were significantly higher in both, unadjusted and adjusted models while odds ratio for transient ischemic attack became non-significant after the adjustment.

Ankylosing spondylitis is associated with increased rates of the cardiovascular disease that are probably due of pathophysiologic changes attendant to the disease, as well as the presence of the comorbidities

Keywords: *Ankylosing spondylitis, cardiovascular disease, logistic regression*

Introduction

Axial spondylarthritis (axSpA) is an inflammatory arthritis of the spine which is associated with disabling chronic back pain typically before the age of 45. In advanced cases, it can lead to fusion of the spinal vertebrae and sacroiliac joints, and result in immobility [*Khan M.A. 2009; NIH 2022*]. SpA could include axial and peripheral involvements. Recently, axSpA without radiographic changes of sacroiliitis have been added to the spectrum of axSpA. Extraarticular manifestations of axSpA include anterior uveitis, psoriasis, inflammatory bowel disease, and cardiovascular disease [*El Maghraoui A., 2011; Taurog JD et al., 2016; Schieir O et al., 2017*]. The exact pathophysiology is not known but the genetic factors have been linked to development of the disease, in particular human leukocyte antigen (HLA) B27 surface protein coding allele [*Chen B et al., 2017; Colbert RA et al., 2014*] as well as environmental factors that may trigger an immune response leading to chronic inflammatory state and resulting in joint damage [*Smith JA 2015*]. Anky-

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losing spondylitis (AS) may be a major risk factor for cardiovascular diseases, either directly as a result of inflammation or indirectly due to prolonged use of anti-inflammatory drugs.

Bakland G. and co-authors (2011) examining 677 patients with ankylosing spondylitis followed at one hospital, reported a crude mortality of 14.5% inAS patients and standardized mortality rates that were significantly higher in males as compared to females. Cardiovascular disease was the most frequent cause of death. In a primary care database of all hospitalizations and death from myocardial infarction (MI) or stroke in Wales from 1999 to 2010, the authors found no significant effects of ankylosing spondylitis on MI and cerebrovascular disease. They found age- and gender-adjusted hazard ratios for MI of 1.28 (95% CI 0.93 - 1.74, p = 0.12) and for cerebrovascular disease of 1.0, (95% CI 0.73 - 1.39, p = 0.9) in ankylosing spondylitis patients as compared to controls [*Brophy S et al., 2012*]. In a retrospective cohort study of 8,616 patients with ankylosing spondylitis, Szabo S. and colleagues (2011) found increased age- and sex-standardized prevalence ratios for aortic valvular heart disease (1.58; 95% CI 1.31– 1.91), ischemic heart disease (1.37; 95% CI 1.31 - 1.44), congestive heart failure (1.34; 95% CI 1.26 - 1.42), cerebrovascular disease (1.25; 95% CI 1.15 - 1.35), and hospitalization for cardiovascular or cerebrovascular disease (1.31; 95% CI 1.22 - 1.41) as compared to the general population. In another retrospective cohort study of 21,473 patients with ankylosing spondylitis found that ankylosing spondylitis was associated with an increased adjusted hazard ratio for vascular death (1.36; 95% CI 1.13 - 1.65) [*Haroon NN et al., 2015*]. In a review of the risk of ischemic stroke in major rheumatic disorders Behrouz B. and co-authors (2014) reported that ankylosing spondylitis patients had a 25% higher risk of cerebrovascular disease. The risk was higher in patients aged 20-39. In the population-matched controls, risk ratios were approximately 2 for ankylosing spondylitis. Zoller B. and co-authors (2012) reported that ankylosing spondylitis was associated with increased risk of ischemic stroke with an overall standardized incidence ratio of 1.23, 95% CI 1.01 - 1.48 and for hemorrhagic stroke 2.72, 95% CI 1.96 - 3.67. Keller J. and colleagues (2014) using administrative claims data on 1479 ankylosing spondylitis patients and 5916 matched controls in the Taiwan National Health Insurance Data Base, reported that ankylosing spondylitis was associated with increased risk of stroke even after adjusting for covariates (HR = 2.3, 95% CI 1.9 - 2.8). The strengths, limitations, and contradictions of the studies described above were considered in the current study with an aimed to address these questions using another population-level database.

The purpose of this report is to examine the association between ankylosing spondylitis and cardiovascular outcomes using data from the Myocardial Infarction Data Acquisition System (MIDAS).

Materials and Methods

De-identified patient data obtained from MIDAS were used to conduct this retrospective study of ankylosing spondylitis patients and matched controls. MIDAS is a statewide database of all cardiovascular disease hospitalizations to nonfederal hospitals in New Jersey and includes information on patient demographics, comorbid conditions, procedures, and discharge status [*Kostis J et al., 2001; Kostis W et al., 2007; 2010*]. Long-term longitudinal follow-up is available for over 20 years. The information in MIDAS for vital status, age, gender and race is accurate above 98.8% [*Al Falluji N et al., 2002*].

The full MIDAS dataset contained more than 17 million records from more than 4.3 million cardiovascular patients admitted to New Jersey hospitals between January 1995 and December 2015. Totally 1,858 patients with ankylosing spondylitis diagnosis (ICD-9 code 720.0) were found in the dataset, 39 of whom were excluded for being discharged with ankylosing spondylitis and an additional diagnosis of an inflammatory spondylopathy, other inflammatory spondylopathies, spinal enthesopathy, sacroiliitis, or unspecified inflammatory spondylopathy (ICD-9 codes 720.81, 720.89, 720.1, 720.2 and 720.9). The remaining 1,819 ankylosing spondylitis patients were

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identified as cases for this study. Each ankylosing spondylitis patient was matched to three controls for birth year, gender, race, and ethnicity. Endpoints for this study included admission for heart failure (HF), acute myocardial infarction (AMI), stroke, transient ischemic attack (TIA) and cardiovascular (CV) mortality. Persons who visited an emergency room only but were not hospitalized were excluded from the analysis. This study was approved by the Rutgers Institutional Review Board and the Rowan University Institutional Review Board.

Statistical analyses were performed using R version 4.2.0 software [*R Project, 2022*]. Odds ratios (OR) of the outcomes comparing ankylosing spondylitis patients to controls were estimated using conditional logistic regression models by maximizing the conditional likelihood [*Gail MHL et al., 1981; Grambsch PM, 2000; CRAN, 2022*]. Two types of logistics regression models were constructed: unadjusted, with the main explanatory variable only (AS), and adjusted, with hypertension, diabetes mellitus (DM), acute kidney failure/ chronic kidney disease (AKF/CKD), chronic liver disease (CLD), chronic obstructive pulmonary disease (COPD), and hyperlipidemia as additional explanatory variables. Comorbidities and outcomes were defined using the International Classification of Disease 9th Revision (ICD-9) standard [*Medicode, 1996*]. The full list of annotated ICD-9 codes is in the Appendix Table 1.

Ratios of ORs for the different outcomes were calculated using the estimates obtained from the conditional logistic regression models. Since ORs are approximately log-normally distributed, log[OR] estimates and their corresponding standard errors were used to obtain the usual normal or t confidence intervals [*Mathieu S et al., 2010*].

Table 1:

Demographics of cases (AS) and controls (No AS) before and after matching.

Demographics	AS (n=1,819)	No AS, Unmatched (n=4,306,381)	No AS, Matched (n=5,457)
Birth Year±S.D.	1942±17	1944±20	1942±17
Female (%)	34.9	53.8	34.9
Race (%)			
White	83.3	72.7	83.3
Black	8.4	14.4	8.4
Other	8.2	12.9	8.2
Ethnicity (%)			
Hispanic	4.7	10.2	4.7
Non-Hispanic	82.6	77.9	82.6
Unknown	12.6	11.9	12.6

Results

The dataset contained 1,819 cases and over 4.3 million potential controls before matching. The matching was performed for each case, selecting 3 controls based on birth year, gender, race and ethnicity. The differences between the cases and controls are reported in Table 1. There was a lower proportion of white females among ankylosing spondylitis patients (34.9% in ankylosing spondylitis vs. 53.8% in unmatched non-AS patients) and the proportion of Hispanics in ankylosing spondylitis patients was less than half of that in non-AS patients in the unmatched population (4.7% and 10.2%, respectively). The differences in comorbidities between cases and controls before and after the matching are presented in Table 2.

Compared to controls, ankylosing spondylitis was associated with an increased incidence of heart failure,ransient ischemic attack, acute myo-

Table 2:

Distribution of cases (AS) and controls (No AS) by comorbidities before and after matching (% of N).

Comorbidities	AS (n=1,819)	No AS, Matched (n=5,457)	No AS, Unmatched (n=4,306,381)	Population (n=4,308,200)
HF	30.6	20.2	19.8	19.8
AMI	14.9	10.7	9.7	9.7
Stroke	7.0	6.3	5.9	5.9
TIA	6.1	4.5	4.3	4.3
Hypertension	84.0	75.0	74.4	74.4
DM	28.8	25.6	25.2	25.2
AKF/CKD	26.0	16.2	15.4	15.4
CLD	4.0	3.2	2.6	2.6
COPD	34.9	23.5	22.8	22.8
Hyperlipidemia	47.0	38.6	35.2	35.3

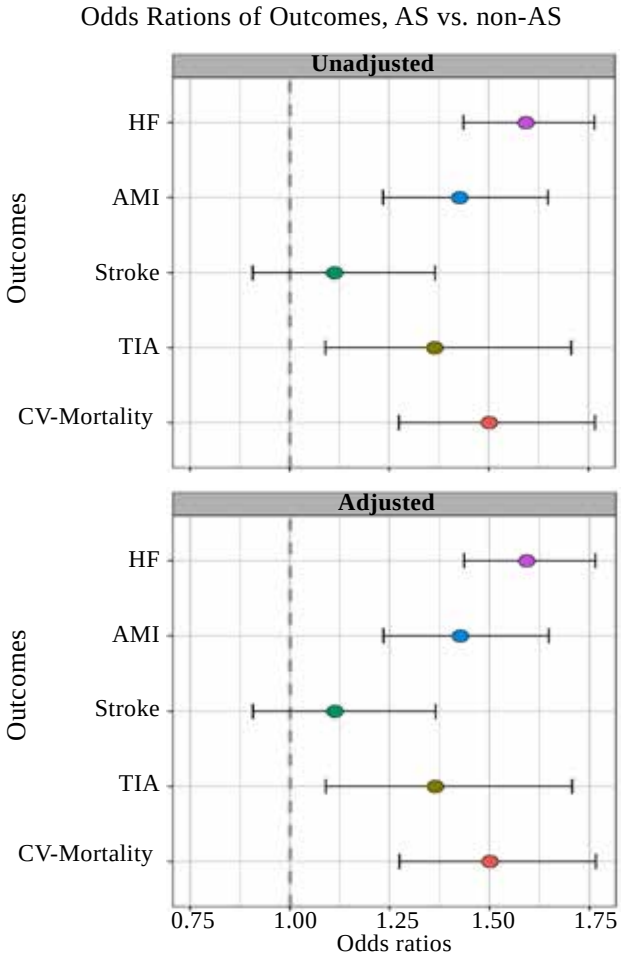

Figure 1. *Forest plot of odds ratios of outcomes in the unadjusted and adjusted models. Odds ratios for each outcome (HF, AMI, Stroke, TIA and CV Mortality) were estimated independently. On the right panel, odds rations were adjusted for Hypertension, DM, AKF/CKD, CLD, COPD and Hyperlipidemia.*

cardial infarction and cardiovascular mortality (Figure 1 and Appendix Table 2). The odds ratio of developing heart failure in the ankylosing spondylitispatients compared to the matched controls was statistically significantly above 1 in both, the unadjusted and the adjusted models (OR 1,59, 95% CI 1.44 - 1.76, $p < 0.001$, and OR 1.31, 95% CI 1.18 - 1.47, $p < 0.001$, respectively). Same trend was observed for acute myocardial infarction and cardiovascular mortality. The OR estimates for acute myocardial infarction were 1.43 (95% CI 1.23 – 1.65, $p < 0.001$), and 1.19 (95% CI 1.02 – 1.39, $p = 0.028$) in the unadjusted and the adjusted models respectively. The OR estimates for cardiovascular mortality were 1.50 (95% CI 1.27 – 1.77, $p < 0.001$), and 1.32 (95% CI 1.11 – 1.56, $p = 0.001$) in the unadjusted and the adjusted models respectively. The OR for transient ischemic attack

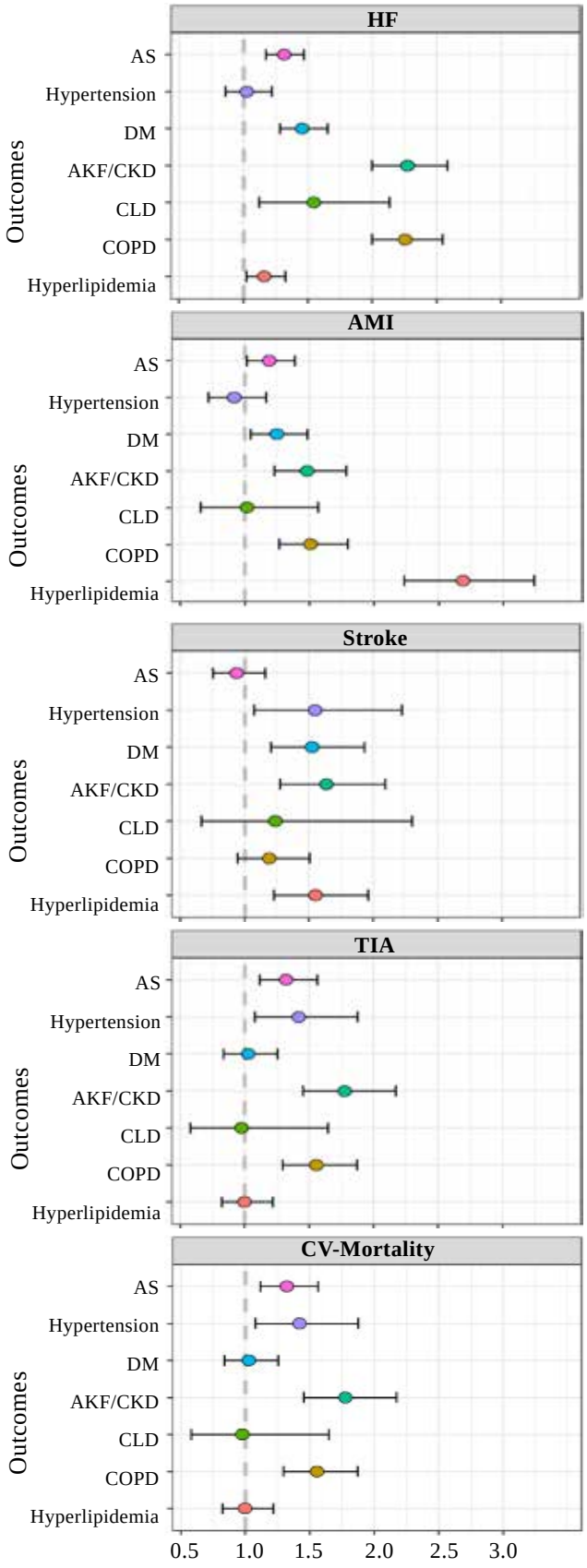

Figure 2. *Adjusted odds ratios of each outcome (HF, AMI, Stroke, TIA and CV Mortality) for AS vs. No AS (main effect) and selected comorbidities (Hypertension, DM, AKF/CKD, CLD, COPD and Hyperlipidemia)*

was significantly above 1 in the unadjusted mode (OR 1.36, 95% CI 1.09 – 1.71, p = 0.007) but not in the adjusted model (OR 1.16, 95% CI 0.91 – 1.47, p = 0.222). Ankylosing spondylitis was not significantly associated stroke in either model. The estimated effects of comorbidities on the outcomes are displayed in Figure 2 and in the Appendix Table 3.

Additionally, the ratios of the odds ratios were estimated. The odds ratio of heart failure in ankylosing spondylitis vs. non-AS patients was 1.44 times higher than the odds ratio of stroke in the unadjusted, and 1.40 times higher in the adjusted model. All other ratios of the odds ratios were not statistically significantly different from 1 (Figure 3 and Appendix Table 4).

DISCUSSION

These results indicate that ankylosing spondylitis is a significant risk factor for heart failure, acute myocardial infarction,ransient ischemic attack, and cardiovascular death. In addition, hypertension, DM, AKF/CKD, CLD, COPD and hyperlipidemia were major contributors to the increased risk of cardiovascular disease. Our findings are similar to those of Mathieu S. and co-authors (2010) who reported that based on epidemiological studies, ankylosing spondylitis is an independent risk factor for cardiovascular mortality. These authors reported that they could not determine if the increased risk was due to a direct effect of ankylosing spondylitis or to an increased prevalence of other risk factors in these patients. In a prospective nationwide study of 294,136 Swedish patients, including 6,448 ankylosing spondylitis patients, ankylosing spondylitis was associated with increased risk of acute coronary syndrome, stroke and venous thromboembolism compared to the general population [*Bengtsson K et al., 2017*]. Braun J and co-authors (2017) reported that heart failure may occur as a result of any inflammatory rheumatic disease and recommended regular reevaluation of cardiovascular risk factors in these patients. Castañeda S and colleagues (2016) reported that as compared to the general population, the standardized mortality ratios were higher in inflammatory rheumatic disease patients, including ankylosing spondylitis patients, and that the effect was primarily due to cardiovascular events. On the other hand, a study of 30,006 patient records from the British Clinical Research Datalink, conducted between 1987 and 2012 reported that there was no statistically significant association between ankylosing spondylitis and acute myocardial infarction or ischemic heart disease except for female patients in an age-adjusted model. However, this relationship was not statistically significant after adjustment for NSAID use [*Essers I et al., 2016*]. Bremander A. and co-authors (2011) published a study of 935 Southern Swedish ankylosing spondylitis patients comparing observed morbidity-rate ratios with the rates reported for the general population of the county of Skåne in southern Sweden. The estimated standardized morbidity-rate ratios were highest in patients with uveitis or inflammatory bowel disease. The rates for ischemic heart dis-

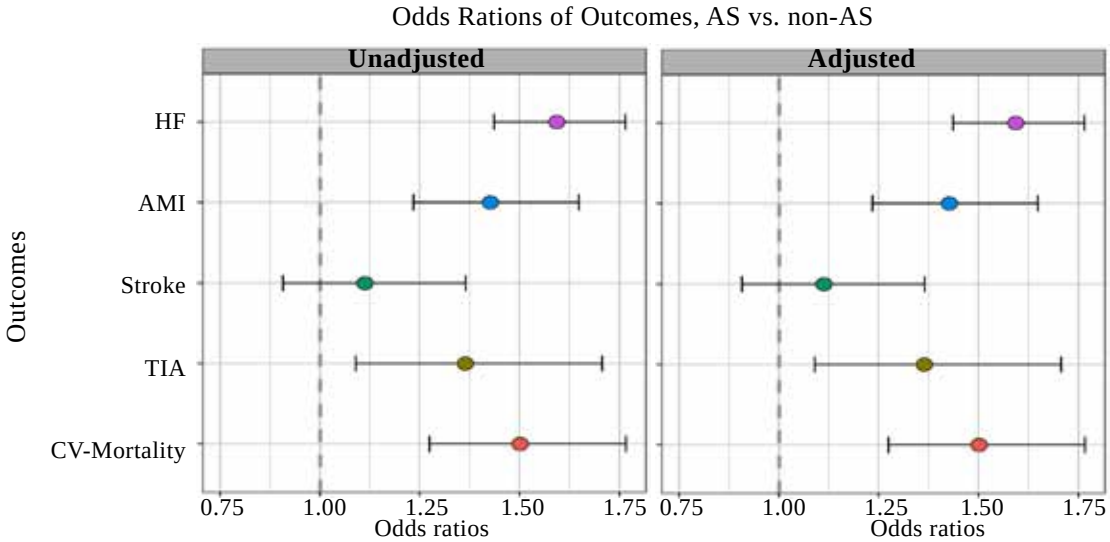

FIGURE 3. *Ratios of odds ratios of conditions associated with ankylosing spondylitis.*

ease, hypertension, and diabetes were significantly higher, although the rate for acute myocardial infarction separately was not statistically significant [*Bremander A et al., 2011*].

Patients with ankylosing spondylitis may develop cardiovascular disease (heart failure, stroke,ransient ischemic attack, and acute myocardial infarction) because of coexisting traditional risk factors and from complications of some treatments as well as from inflammatory cytokines (cyclooxygenase, tumor necrosis factor-alpha, and interleukin-17A) contributing to the pathophysiology of the disease. Heslinga SC and co-authors (2014) reported a higher incidence of left ventricular diastolic dysfunction that may lead to heart failure with preserved ejection fraction in a meta-analysis of ankylosing spondylitis patients compared to controls. This may be due to impaired microvascular function and low coronary blood flow reserve as has been observed in ankylosing spondylitis [*Caliskan M et al., 2008*]. In this study, decreased coronary flow reserve was correlated with hsCRP and TNF-alpha.

The association of ankylosing spondylitis with an increased risk of cardiovascular events may also be mediated by off-target effects of medical therapy used to treat ankylosing spondylitis. For example, treatment of ankylosing spondylitis with TNF inhibitors may lead to an increased risk of heart failure [*Wronski J, Fiedor P, 2019*]. The use of NSAIDs, in particular COX-2 inhibitors, has also been associated with an increased risk of cardiovascular events, and which have also been used in patients with ankylosing spondylitis [*Braun J et al., 2020*].

Our findings are congruent with previous reports [*Peters MJ et al., 2010; Park CJ et al., 2018*]. For example, Park and associates reported in a longitudinal study that acute myocardial infarction was about twice as common in patients with ankylosing spondylitis as compared to controls after adjusting for gender and age [*Park CJ et al., 2018*]. In addition, studies of markers for subclinical atheroma (endothelial dysfunction, arterial stiffness, and intima-media thickness) have shown earlier onset of arterial disease in patients with ankylosing spondylitis when compared to healthy controls [*Prati C. et al., 2019*].

In several previous studies, time to event analysis were performed for the ankylosing spondylitis and control groups and examined from the first diagnosis of ankylosing spondylitis. However, the timing of the first diagnosis of ankylosing spondylitis may be affected by patient characteristics, insurance type, and the criteria used for the diagnosis. For this reason, the association of cardiovascular outcomes with an ankylosing spondylitis diagnosis may not have a reliable temporal component.

A limitation of this study is that it is based on hospitalized patients and did not provide enough information to estimate the time of first ankylosing spondylitis diagnosis before the first hospitalization with cardiovascular disease. For this reason, we elected to report on all events occurring during the life of the patient in the ankylosing spondylitis and matched control groups. However, this study has significant strengths since it is derived from unbiased information on all hospitalizations in a given geographic area (New Jersey) with a clear definition of events and with longitudinal follow-up for over 20 years. Also, the findings of this study including the male predominance and the lower prevalence among Hispanics and Blacks are in agreement with previous reports [*de Winter JJ et al., 2016; Kopplin LJ et al., 2016*]. Another limitation is that the ankylosing spondylitis cohort could not be verified based on the Assessment of SpondyloArthritis International Society (ASAS) classification criteria [*Akkoc N, Khan MA, 2015*] since ICD-9 diagnoses codes do not provide the granularity for such assessment.

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APPENDIX

APPENDIX TABLE 1.

ICD-9 codes for outcomes and comorbidities.

Outcomes and Comorbidities	ICD-9
AMI	410.00; 410.01; 410.02; 410.10; 410.11; 410.12; 410.20; 410.21; 410.22; 410.30; 410.31; 410.32; 410.40; 410.41; 410.42; 410.50; 410.51; 410.52; 410.60; 410.61; 410.62; 410.70; 410.71; 410.72; 410.80; 410.81; 410.82; 410.90; 410.91; 410.92
AS	720.0
HF	428.1; 428.22; 428.32; 428.42; 428.9; 428.0; 428.20; 428.21; 428.23; 428.30; 428.31; 428.33; 428.40; 428.41; 428.43
AKF/CKD	584.5; 584.6; 584.7; 584.8; 584.9; 585.1; 585.2; 585.3; 585.4; 585.5; 585.6; 585.9
CLD	571.0; 571.1; 571.2; 571.3; 571.40; 571.41; 571.42; 571.49; 571.5; 571.6; 571.8; 571.9
COPD	490; 491.0; 491.1; 491.20; 491.21; 491.22; 491.8; 491.9; 492.0; 492.8; 493.00; 493.01; 493.02; 493.10; 493.11; 493.12; 493.20; 493.21; 493.22; 493.81; 493.82; 493.90; 493.91; 493.92; 494.0; 494.1; 495.0; 495.1; 495.2; 495.3; 495.4; 495.5; 495.6; 495.7; 495.8; 495.9; 496
DM	250.00; 250.01; 250.02; 250.03; 250.10; 250.11; 250.12; 250.13; 250.20; 250.21; 250.22; 250.23; 250.30; 250.31; 250.32; 250.33; 250.40; 250.41; 250.42; 250.43; 250.50; 250.51; 250.52; 250.53; 250.60; 250.61; 250.62; 250.63; 250.70; 250.71; 250.72; 250.73; 250.80; 250.81; 250.82; 250.83; 250.90; 250.91; 250.92; 250.93
Hypertension	401.0; 401.1; 401.9; 402.00; 402.01; 402.90; 402.91; 403.00; 403.01; 403.10; 403.11; 403.90; 403.91; 404.00; 404.01; 404.02; 404.03; 404.10; 404.11; 404.12; 404.13; 404.90; 404.91; 404.92; 404.93; 405.01; 405.09; 405.11; 405.19; 405.91; 405.99
Hyperlipidemia	272.0; 272.1; 272.2; 272.3; 272.4; 272.5; 272.6; 272.7; 272.8; 272.9
Other spondylitis and inflammatory spondylopathies (720.0 excluded)	720.1; 720.2; 720.81; 720.89; 720.9
Stroke	433.01; 433.11; 433.21; 433.31; 433.81; 433.91; 434.01; 434.11; 434.91
TIA	435.0; 435.1; 435.2; 435.3; 435.8; 435.9
Cardiovascular mortality (ICD-10) *	I00-I09, I11, I13, I20-I51, I60-I78

NOTES: (*) Source: http://www.health.state.ok.us/stats/Vital_Statistics/Death/039_causes.shtml

APPENDIX TABLE 2.

Figure 1 supplementary table. Unadjusted ORs.

Outcome	Odds Ratio	95%CI	p -Value
HF	1.59	(1.44, 1.76)	<0.001
AMI	1.43	(1.23, 1.65)	<0.001
Stroke	1.11	(0.91, 1.36)	0.304
TIA	1.36	(1.09, 1.71)	0.007
CV Mortality	1.50	(1.27, 1.77)	<0.001

APPENDIX TABLE 3.

Figure 2 supplementary table. Adjusted ORs for each outcome.

Outcome	AS	Hyper-tension	DM	AKF/CKD	CLD	COPD	Hyper-lipidemia
HF	1.31 (1.18; 1.47) p < 0.001	1.02 (0.86; 1.22) p = 0.793	1.45 (1.28; 1.65) p < 0.001	2.27 (2.00; 2.58) p < 0.001	1.54 (1.12; 2.13) p = 0.008	2.25 (2.00; 2.54) p < 0.001	1.16 (1.02; 1.32) p = 0.025
AMI	1.19 (1.02; 1.39) p = 0.028	0.92 (0.72; 1.17) p = 0.478	1.25 (1.05; 1.49) p = 0.014	1.48 (1.23; 1.79) p < 0.001	1.02 (0.66; 1.57) p = 0.944	1.51 (1.27; 1.8) p < 0.001	2.69 (2.23; 3.24) p < 0.001
Stroke	0.94 (0.76; 1.16) p = 0.565	1.55 (1.08; 2.22) p = 0.019	1.53 (1.21; 1.93) p < 0.001	1.64 (1.28; 2.1) p < 0.001	1.24 (0.67; 2.31) p = 0.499	1.19 (0.95; 1.51) p = 0.137	1.55 (1.23; 1.96) p < 0.001
TIA	1.16 (0.91; 1.47) p = 0.222	1.48 (1.00; 2.21) p = 0.05	1.25 (0.96; 1.63) p = 0.104	1.20 (0.89; 1.61) p = 0.237	1.66 (0.79; 3.46) p = 0.178	1.23 (0.94; 1.6) p = 0.132	2.23 (1.68; 2.94) p < 0.001
CV Mortality	1.32 (1.11; 1.56) p = 0.001	1.42 (1.08; 1.88) p = 0.013	1.03 (0.84; 1.26) p = 0.803	1.78 (1.45; 2.17) p < 0.001	0.98 (0.58; 1.65) p = 0.931	1.56 (1.29; 1.87) p < 0.001	1.00 (0.82; 1.22) p = 0.996

APPENDIX TABLE 4.

Figure 3 supplementary table. Ratios of odds ratios of outcomes in AS vs. No AS patients.

Ratio	Unadjusted	Adjusted
HF/AMI	1.12 (0.94, 1.34)	1.11 (0.92, 1.33)
HF/Stroke	1.44 (1.16, 1.79)	1.4 1.09, 1.78)
HF/TIA	1.17 (0.92, 1.5)	1.13 (0.86, 1.47)
HF/CV Mortality	1.07 (0.88, 1.29)	1.00 (0.81, 1.23)

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