# Risk of coronary artery disease in patients with ankylosing spondylitis: a systematic review and meta-analysis

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> **Objective:** To investigate the association between coronary artery disease (CAD) and ankylosing spondylitis (AS). **Methods:** We conducted a systematic review and meta-analysis of observational studies that reported relative risks, hazard ratios, standardized prevalence ratio or standardized incidence ratios with 95% confidence comparing CAD risk in patients with AS versus non-AS controls. Pooled risk ratios and 95% confidence intervals (CIs) were calculated using a random-effect, generic inverse variance of DerSimonian and Laird.

> **Results:** Out of 229 potentially relevant articles, ten studies (five retrospective cohort studies and five crosssectional studies) were identified and included in our data analysis. The overall pooled risk ratio of CAD in patients with AS was 1.41 (95% CI: 1.29-1.54). The pooled risk ratios for cross-sectional and cohort studies were 2.08 (95% CI: 1.28-3.40) and 1.36 (95% CI: 1.31-1.41), respectively. The statistical heterogeneity of this meta-analysis was moderate with an I<sup>2</sup> of 56%.

> **Conclusions:** Our study demonstrated a statistically significant increased CAD risk among patients with AS with 41% excess risk.

Keywords: Meta-analysis; epidemiology; ankylosing spondylitis (AS); venous thromboembolism

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# Introduction

Chronic inflammation is increasingly recognized as a nontraditional risk factor for coronary artery disease (CAD) as its association with accelerated atherosclerosis is well-established (1,2). Several studies have illustrated the deleterious effect of oxidative stress and inflammatory cytokines on endothelial function (3-6). Chronic inflammation has also been demonstrated to promote a hypercoagulable state as a result of excessive activation of the coagulation cascade as well as chronic inhibition of the anti-coagulation and fibrinolytic pathway (7,8). These factors may well serve as the elemental pathophysiology for the development of premature CAD. Moreover, an increased incidence of CAD has been observed in several autoimmune inflammatory disorders, such as rheumatoid arthritis, idiopathic inflammatory myositis, systemic sclerosis, primary biliary cirrhosis and systemic vasculitides (9-13).

Ankylosing spondylitis (AS), a form of seronegative spondyloarthritis (SpA), is a chronic systemic arthritis that primarily affects the sacroiliac joint and the axial skeleton. Characteristic clinical manifestation includes back pain and progressive stiffness of the spine though it can also involve the hips, shoulders and peripheral joints. Extraarticular manifestations, including uveitis, may also be seen in patients with AS and other forms of SpA. AS is typically a disease of young males, with a peak age of onset between 20 and 30 years and a male-to-female ratio of about 3 to 1, although there can be considerable geographical and ethnic variation (14,15).

In light of chronic inflammation, patients with AS may be at an increased risk of developing premature CAD. However, the data on CAD risk in these patients remain inconclusive owing to conflicting epidemiological studies. Thus, to further investigate this association, we conducted a

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systematic review and meta-analysis of observational studies that compared the risk of CAD in patients with AS versus non-AS controls.

# Methods

# Search strategy

Two investigators (P.U. and I.S.) independently searched published studies indexed in MEDLINE and EMBASE database from inception to July 2014 as well as the American College of Rheumatology annual conference abstract database from 2006-2013, using the search strategy described in Supplementary material. A manual search of references of selected retrieved articles was also performed.

## Inclusion criteria

The inclusion criteria were as follows: (I) epidemiological study (cross-sectional, case-control or cohort study) published as original study or conference abstract reporting CAD incidence or prevalence in patients with AS; (II) relative risk (RR), odds ratio (OR), hazard ratio (HR), standardized incidence ratio (SIR) or standardized prevalence ratio (SPR) with 95% confidence intervals (CIs) were provided; (III) non-AS participants and were used as a reference group for cohort study and cross-sectional study while participants without CAD were used for case-control study.

Study eligibility was independently appraised by each investigator noted above. Differing decisions were resolved by consensus with the senior investigator. Quality of the included cohort and case-control studies was independently evaluated by the two investigators using the Newcastle-Ottawa quality assessment scale which assessed each study in three areas including: (I) the selection of the study groups; (II) the comparability of the groups; (III) the ascertainment of the exposure or outcome of interest for case-control or cohort studies respectively (16). Adapted Newcastle-Ottawa quality assessment was used to appraise the quality of crosssectional studies (17).

## Data extraction

A standardized data collection form was used to extract the following information: title of the article, first author's last name, authors' affiliation, publication year, country where the study was conducted, year of publication, study size, study population, criteria used for the diagnosis of AS, definition and diagnosis of CAD, average duration of follow up, number of cases, number of controls, percentage of female and adjusted effect estimates with 95% CI. This data extraction was independently performed by the two investigators.

# Statistical analysis

Data analysis was performed using Review Manager 5.3 software from the Cochrane Collaboration. Adjusted point estimates and standard errors were extracted from individual studies and were combined by the generic inverse variance method of DerSimonian and Laird (18). We used a random-effect model rather than a fixed-effect model in light of the high likelihood of between study variance. The statistical heterogeneity was assessed by Cochran's Q test. This test was complemented with the I<sup>2</sup> statistic, which quantifies the proportion of total variation across studies that is due to heterogeneity rather than chance. A value of I<sup>2</sup> of 0% to 25% indicates insignificant heterogeneity, 26% to 50% low heterogeneity, 51% to 75% moderate heterogeneity, and 76% to 100% high heterogeneity (19).

# Results

Our search strategy yielded 229 potentially relevant studies. Two hundred and two studies were excluded based on abstract screening as they were clearly not cohort, casecontrol or cross-sectional studies or were not conducted in patients with AS, leaving 27 studies for full-length article review. Sixteen of them were excluded since they were descriptive studies without a control group and one study was excluded because they reported only the overall risk for cardiovascular disease (which included both CAD and cerebrovascular disease) but did not have a separate report on CAD (20). Ten studies [five retrospective cohort studies and five cross-sectional studies (21-30)] with 25,795 patients with AS met our eligibility criteria and were included in the meta-analysis. Figure 1 outlines our search methodology and literature review process. The detailed description and Newcastle-Ottawa quality assessment scale of the included studies are provided in Tables 1 and 2.

Our meta-analysis demonstrated a statistically significant increased CAD risk among patients with AS with a pooled risk ratio of 1.41 (95% CI: 1.29-1.54). Subgroup analysis revealed a statistically significant increased CAD risk for both types of study with pooled risk ratios of 1.36 (95% CI: 1.31-1.41) and 2.08 (95% CI: 1.28-3.40) for cohort and cross-sectional studies, respectively. The overall statistical



Figure 1 Outline of our search methodology. AS, ankylosing spondylitis.

heterogeneity was moderate with an I<sup>2</sup> of 56%. Most of the statistical heterogeneity came from cross-sectional studies as their I<sup>2</sup> was 78% while cohort studies had an I<sup>2</sup> of 0%. *Figure 2* demonstrates the forest plots of our findings.

## Sensitivity analysis

To confirm the robustness of our results, we performed jackknife sensitivity analysis by excluding one single study at a time (31). The results of this sensitivity analysis suggested that our results were robust as the pooled risk ratios remained significantly elevated, ranging from 1.37 to 1.48, with the corresponding 95% CI bounds remained more

than one.

We also performed a sensitivity analysis by excluding the studies with lower quality. We excluded the study by Berg *et al.* (24) and Kumar *et al.* (25) as their Newcastle-Ottawa scores were only five and four, respectively. The study by Peters *et al.* (23) was also excluded as the authors included only older patients (>50 years old) and, thus, a possibility of selection bias. The pooled effect was slightly reduced after the exclusion of these studies with a pooled risk ratio of 1.36 (95% CI: 1.31-1.41). Interestingly, the I<sup>2</sup> was dramatically reduced to 0% with this sensitivity analysis, suggesting that these lower quality studies were the main source of statistical heterogeneity.

Table 1 Main characteris	tics of cross-sectional studies	in the meta-analysis			
Characteristics	Sukenik <i>et al.</i> (21)	Han <i>et al</i> . (22)	Peters <i>et al.</i> (23)	Berg <i>et al.</i> (24)	Kumar <i>et al.</i> (25)
Country	Israel	USA	The Netherlands	Norway	USA
Study design	Cross-sectional	Cross-sectional	Cross-sectional	Cross-sectional	Cross-sectional
Year	1987	2006	2010	2011	2011
Cases	AS patients who presented to the study center in Beer Sheva, Israel	Cases were identified by using the PharMetrics Patient Centric Database which contains fully adjudicated medical service and prescription drug claim from health plan across USA. Data were selected for adults (age >17 years old), who were continuously enrolled from January 2001 through December 2002	AS patients age between 50-75 years old who were registered at the Jan van Breemen institute or VU medical center	AS patients who presented to the study center in Oslo, Norway, from 2008-2010	All patients diagnosed with AS at the VA medical center, Jackson, MS. Cases were identified by using the hospital database
Diagnosis of AS	Case must fulfil New York classification criteria	Diagnostic code from the database	Registry of the study center	Case must fulfil New York classification criteria	Diagnostic code from the database
Reference group	Sex and age matched, randomly selected from the same community	Sex, age and geographic matched, randomly selected from the same database	Patients between 50- 75 years old identified from the Netherlands Information Network of General Practice which are representative of the Dutch population	Randomly selected by Statistics Norway	Matched population from the American Heart Association data
Definition of CAD	MI	IHD	MI	N/A	N/A
Diagnosis of CAD	Chart review	Diagnostic code from the database	Diagnostic code from the database plus chart review for verification	Chart review	Chart review
Mean age for cases, Y	44.6	47.3	N/A	50.7	60.4
Woman, %	7.5	40.4	26.4	38.1	2.5
Number of cases	40	1,843	383	161	81
Number of control	40	7,372	75,333	134	N/A
Confounder adjusted	Age and sex	Age and sex	Age and sex	Age, sex and smoking	None
Quality assessment	Selection: 2 stars	Selection: 4 stars	Selection: 4 stars	Selection: 2 stars	Selection: 3 stars
(Newcastle-Ottawa scale)	Comparability: 1 star Outcome: 3 stars	Comparability: 2 stars Outcome: 3 stars	Comparability: 1 star Outcome: 2 stars	Comparability: 1 star Outcome: 2 stars	Comparability: 0 star Outcome: 1 star
Abbreviations: AS, anky	losing spondylitis; VA, veter	an affair; CAD, coronary artery disease;	MI, myocardial infarction; IH	ID, ischemic heart disease;	; N/A, not available.

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Table 2 Main characteristics of	cohort studies in the meta-analy	ysis			
Characteristics	Bremander <i>et al.</i> (26)	Szabo et al. (27)	Brophy <i>et al.</i> (28)	Zöller et al. (29)	Chou <i>et al.</i> (30)
Country	Sweden	Canada	Wales	Sweden	Taiwan
Study design	Retrospective cohort	Retrospective cohort	Retrospective cohort	Retrospective cohort	Retrospective cohort
Year	2011	2011	2012	2012	2014
Cases	All patients in Skane county who carried a diagnosed with AS at between January 1, 2004 to December 31, 2007. Cases were identified by using the Skane Health Care Register (SCHR) which essentially covered all medical care in the county	All patients in Quebec, Canada, who carried a diagnosed with AS at between January 1, 2004 to December 31, 2006. Cases were identified by using the Regie de l'Assurance Maladie du Quebec (RAMQ) which covered 99% of the population	All patients who carried a diagnosis of AS. Cases were identified by using the Health Information which contained the medical records of patients registered with 1 in 3 general practices (GP) in Wales	All patients who were hospitalized with a main diagnosis of AS (without previous or co-existing coronary artery disease) between 1964 and 2008. Cases were identified by using the Swedish national registry	All patients in Taiwan who were diagnosed with AS between 2000-2009. Cases were identified by using the National Health Insurance Research Database which covered 99% of the population
Diagnosis of AS	Diagnostic code from the database	Diagnostic code from the database	Diagnostic code from the database	Diagnostic code from the database	Diagnostic code from the database
Reference group	Using age- and sex- specific general population morbidity rates for IHD (data obtained from SCHR) as the comparator for the calculation of standardized morbidity ratio	Using age- and sex- specific general population morbidity rates for IHD (data obtained from RAMQ) as the comparator for the calculation of standardized prevalence ratio	Using age- and sex-specific general population morbidity rates for IHD (data obtained from the same database) as the comparator for the calculation of standardized incidence ratio	Using Swedish age- and sex-specific general population incidence rates for AMI, angina, and chronic coronary heart disease as the comparator for the calculation of standardized incidence ratio	Sex, age and index date- matched, randomly selected from the same database
Definition of CAD	AMI	ΠΗ	M	AMI, angina, and chronic coronary heart disease	Acute coronary syndrome
Diagnosis of CAD	Diagnostic code from the database	Diagnostic code from the database	Diagnostic code from hospital database which was linked with all GP records	Diagnostic code from the same database	Diagnostic code from the same database
Table 2 (continued)					

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Table 2 (continued)					
Characteristics	Bremander <i>et al.</i> (26)	Szabo et al. (27)	Brophy <i>et al.</i> (28)	Zöller <i>et al</i> . (29)	Chou <i>et al.</i> (30)
Follow-up	Until occurrence of CAD,	Until December 31, 2006	Until death, first record of MI	Until hospitalization for	Until emigration from the
	system, emgradou non use system, or December 31, 2007			from the system, or December 31. 2008	2009
Mean age of cases, Y	52.3	42.5	46.1	N/A	N/A
Woman, %	32.8	43.9	24.1	28.5	52.3
Number of cases	935	8,616	1,686	5,788	6,262
Number of control	761,210	50,699	1,206,621	N/A	25,048
Average range of follow up, Y	. 2.1	10.2	4.1	N/A	8.0
Confounder adjusted for	Age and sex.	Age and sex.	Age and sex.	Age, sex, socioeconomic status, obesity, alcohol, HTN, DM, CHF and renal disease.	Age, sex, DM, HTN, dyslipidemia and stroke.
Quality assessment (Newcastle-Ottawa scale)	Selection: 3 stars Comparability: 1 star Outcome: 3 stars	Selection: 3 stars Comparability: 1 star Outcome: 3 stars	Selection: 4 stars Comparability: 1 star Outcome: 3 stars	Selection: 4 stars Comparability: 1 star Outcome: 3 stars	Selection: 4 stars Comparability: 2 stars Outcome: 3 stars
Abbreviations: AS, ankylosi hypertension; DM, diabetes n	ng spondylitis; IHD, ischemic nellitus.	: heart disease; AMI, acut	e myocardial infarction; CAD	, coronary artery disease;	N/A, not available; HTN,

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Figure 2 Forest plot of all included studies.



Figure 3 Funnel plot of all included studies. RR, relative risk.

### Evaluation for publication bias

Evaluation for publication bias was performed using funnel plot as shown in *Figure 3*. The graph is asymmetric, suggesting that publication bias in favor of positive studies may be present.

## Discussion

Our study is the first systematic review and meta-analysis of observational studies assessing the risk of CAD among patients with AS. We are able to demonstrate a statistically significant association between AS and CAD with an overall 1.41-fold increased risk compared with non-AS participants.

This finding is not only of important from medical

standpoint, but also from socioeconomic perspective as patients with AS, typically young adults in their working age, are already vulnerable for a reduced productivity because of their musculoskeletal symptoms (32-34). Their capability to work might be further jeopardized because of the coronary artery complication, which certainly could cause more economic and psychological consequences.

The pathophysiology behind the association between AS and CAD is not well-described though an increasingly number of evidence are pointing toward the detrimental effect of chronic inflammation to the endothelial cell integrity. It has been demonstrated that endothelial dysfunction and direct endovascular injury from inflammatory cytokine, activated inflammatory cells and oxidative stress can accelerate the progression of atherosclerosis (3-6). Furthermore, chronic inflammation related to autoimmune disease has been linked to a thrombophilic state (7,8), another predisposing factor for the development of CAD.

In addition, other conventional cardiovascular risk factors, particularly metabolic syndrome and dyslipidemia, are more prevalent in patients with AS compared with healthy individuals (35) which, again, might be a direct consequence of the underlying inflammatory process (36) in conjunction with decreased functional capacity and physical activity secondary to their arthritis.

The adverse effect of non-steroidal anti-inflammatory drugs (NSAIDs), one of the most commonly use medications in patients with AS, on the cardiovascular system is also well-recognized (37-39). Use of NSAIDs

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might be another contributory cause of elevated CAD risk.

Even though most of the included studies are of high quality, there are some limitations and, thus, the results should be translated with caution.

First, most of the included studies were conducted using medical registry-based database and, thus, a possibility of coding inaccuracy for both AS and CAD. Second, statistical heterogeneity was present in this study, though the heterogeneity was significantly reduced after exclusion of lower quality studies. Third, this is a metaanalysis of observational studies which, at the best, can only demonstrate an association, not causality. Therefore, we cannot make a conclusion that AS itself versus other potential confounders, such as use of NSAIDs, causes the increased CAD risk. Furthermore, these studies were at risk of detection bias as the patients, because of their AS, exposed to more medical examinations and investigations and, thus, more likelihood of CAD detection (40).

# Conclusions

In conclusion, our meta-analysis demonstrated a statistically significant increased CAD risk among patients with AS with 41% excess risk. Physicians should be aware of this association, and an appropriate management for conventional cardiovascular risk factor modification should be incorporated to the routine care for these patients.

# Acknowledgements

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# **Supplementary**

Database: Ovid MEDLINE

- 1. exp Coronary Disease/
- 2. coronary disease\$.mp.
- 3. exp Coronary Artery Disease/
- 4. coronary arter\$ disease\$.mp.
- 5. exp Coronary Stenosis/
- 6. coronary stenos\$.mp.
- 7. coronary atheroscleros\$.mp.
- 8. (coronary adj3 disease\$).mp.
- 9. (coronary adj3 syndrome\$).mp.
- 10. cad.mp.
- 11. coronary arterioscleros\$.mp.
- 12. exp Myocardial Infarction/
- 13. myocardial infarct\$.mp.
- 14. exp Coronary Thrombosis/
- 15. coronary thrombos\$.mp.
- 16. exp Angina, Unstable/
- 17. unstable angina.mp.
- 18. (unstable adj3 angina).mp.
- 19. exp Angina, Stable/
- 20. stable angina.mp.
- 21. exp Angina Pectoris/
- 22. angina pectoris.mp.
- 23. acs.mp.
- 24. ami.mp.
- 25. exp Cardiovascular Diseases/
- 26. cardiovascular disease.mp.
- 27. or/1-26
- 28. Bechterew\$ Disease.mp.
- 29. Marie Struempell Disease.mp.
- 30. spondylarthr\$.mp.
- 31. exp Spondylarthritis/
- 32. exp Spondylarthropathies/
- 33. exp Spondylitis, Ankylosing/
- 34. ankylosing spondylitis.mp.
- 35. or/28-34
- 36. 27 and 35

# Database: EMBASE

- 1. exp Coronary Artery Disease/
- 2. exp Coronary Artery Atherosclerosis/
- 3. coronary arter\$ atheroscleros\$.mp.
- 4. exp Coronary Artery Obstruction/
- 5. coronary arter\$ obstruction\$.mp.
- 6. (coronary arter\$ adj5 stenos\$).mp.
- 7. coronary atheroscleros\$.mp.
- 8. coronary arterioscleros\$.mp.
- 9. (coronary adj3 disease\$).mp.
- 10. (coronary adj3 syndrome\$).mp
- 11. coronary arter\$ disease\$.mp.
- 12. exp Heart Infarction/
- 13. heart infarction.mp
- 14. exp Coronary Artery Thrombosis/
- 15. coronary thrombosis.mp.
- 16. exp Angina Pectoris/
- 17. angina pectoris.mp.
- 18. myocardial infarct\$.mp.
- 19. acs.mp.
- 20. ami.mp.
- 21. acute angina.mp.
- 22. (unstable adj3 angina).mp.
- 23. cad.mp.
- 24. or/1-23
- 25. exp Spondylarthropathies/
- 26. exp Spondylitis, Ankylosing/
- 27. ankylosing spondylitis.mp.
- 28. Bechterew\$ Disease.mp.
- 29. Marie Struempell Disease.mp.
- 30. spondylarthr\$.mp.
- 31. exp Spondylarthritis/
- 32. or/25-31
- 33. 24 and 32