Risk of Myocardial Infarction is Increased in Multiple Major Types of Arthritis: A Systematic Review and Meta-Analysis of Population-Based Studies

Orit Schieir[1], Cedomir Tosevski[2], Richard H Glazier[3], Sheilah Hogg-Johnson[4], Elizabeth M. Badley[1,5]

[1]Division of Epidemiology, University of Toronto Dalla Lana School of Public Health, [2] Rouge Valley Health System, [3]Institute for Clinical Evaluative Sciences, Centre for Research on Inner City Health, Li Ka Shing Knowledge Institute, St. Michael's Hospital, Department of Family and Community Medicine, St. Michael's Hospital, Department of Family and Community Medicine, University of Toronto, [4] Institute for Work and Health, [5]Division of Health Care & Outcomes Research, Toronto Western Research Institute, Toronto, Ontario, Canada.

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Orit Schieir, Cedomir Tosevski, Richard H Glazier,
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EXTENDED REPORT

Incident myocardial infarction associated with major types of arthritis in the general population: a systematic review and meta-analysis

Orit Schieir,[1] Cedomir Tosevski,[2] Richard H Glazier,[3] Sheilah Hogg-Johnson,[4] Elizabeth M Badley[1,5]

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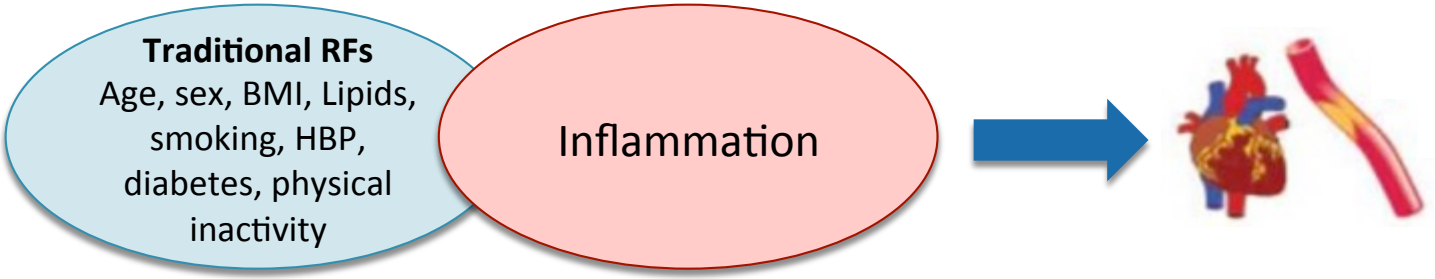
IHD Risk in Arthritis: What do we know?

Ischaemic heart disease (IHD) is a major contributor to chronic disease burden and is a leading cause of death worldwide[1]

> 50 years, several "traditional" heart disease risk factors identified[2]

More recently, inflammation has been shown to have pro-atherogenic effects leading to acute ischemic events[3,4]



Strongest most consistent evidence: RA and excess risk of MI[5]

[1]Moran et al. Circulation 2014; [2]Wong *Nat Rev Cardiol* 2014; *[3]Choy et al. Rhematology 2014; [4]Libby et al. Circulation 2002; Avina-Zubieta et al. Ann Rheum Dis 2012[4]*

IHD Risk in Arthritis: Study Gaps & Limitations

Far fewer studies in non- RA types of arthritis

Previous study/ SLR limitations:

- Focus on individual conditions (cannot compare risk across types)
- Variable study populations, sources for controls, designs, outcomes
- Minimal study inclusion criteria for control of confounding

Why does this matter?

Difficult for clinicians, patients and policy makers to get a clear sense of whether and to what extent IHD risk is increased across different arthritis populations and may result in missed opportunities for preventing or lowering risk particularly in non-RA types of arthritis

Objective

Undertake a systematic review and meta-analysis of best available evidence from population-based studies to quantify and compare risks for incident MI in 5 major types of arthritis (RA, AS, PsA, gout and OA)

Methods: Data Sources & Searches

Medline, EMBASE and CINAHL databases + manual searches

P	Adult general population
I/E	5 major types of arthritis (RA, PsA, AS, Gout, OA)
C	No arthritis
O	Incident AMI or ACS
S	Population-based cohort & case control

Limits: 1980-2015, English or French, RR & SE/CI adjusted for age & sex

Methods: Extraction, quality assessment, synthesis

Information extracted: Country, funding, study design, data source, sample size, FU, sample age range & percent female, exposure and outcome ascertainment, measures of association with SE / 95% CIs

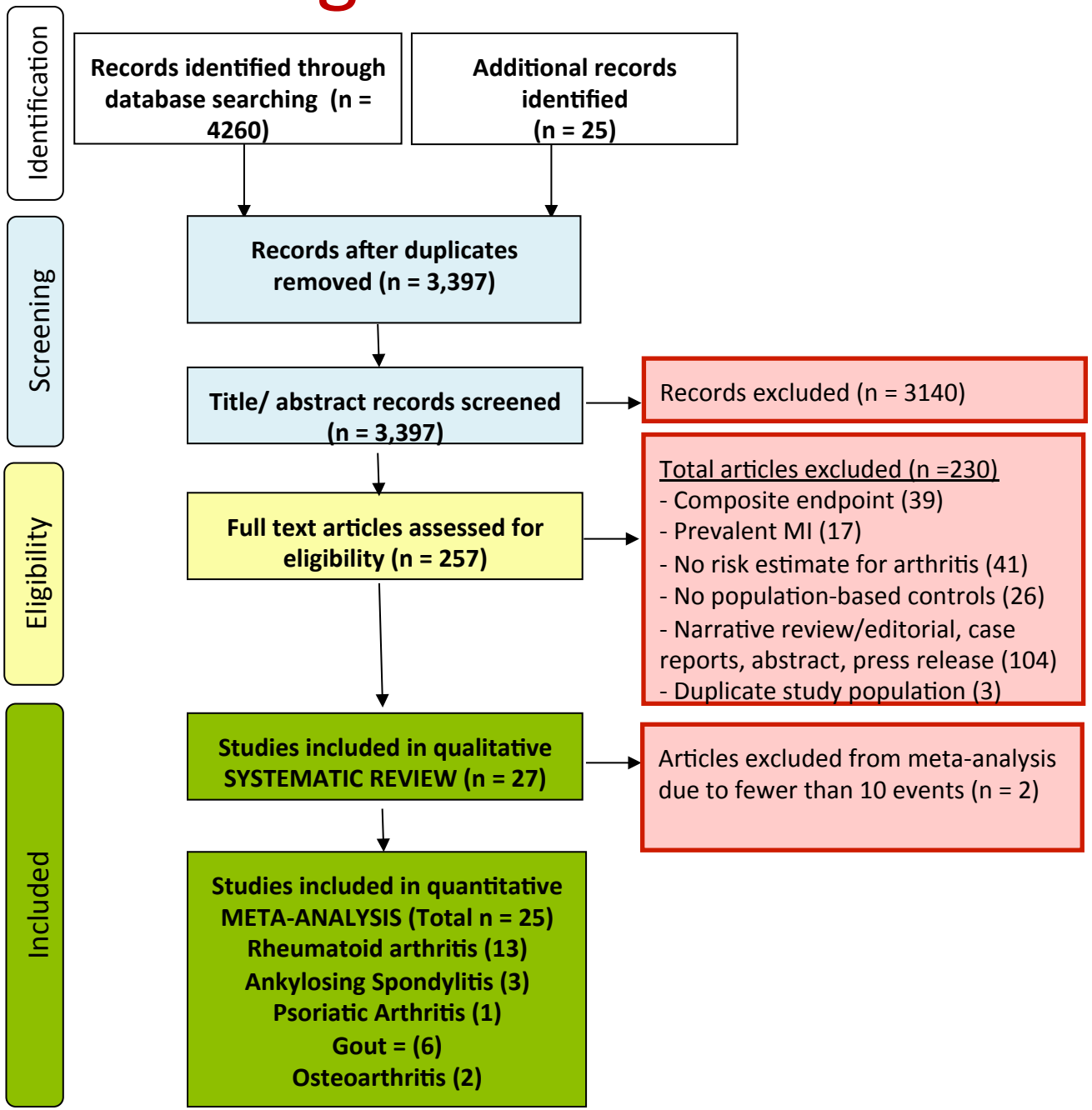
Quality assessment tool: Newcastle-Ottawa scale ranging from 0 (lowest) to 9 (highest)

Data Synthesis: Random-effects MA pooling studies with >10 events

- By type of arthritis
- Separately for studies with age/sex adjustment only vs. those also adjusted for 1+RFs

Univariate meta-regression: compare heterogeneity across arthritis

PRISMA Flow Diagram

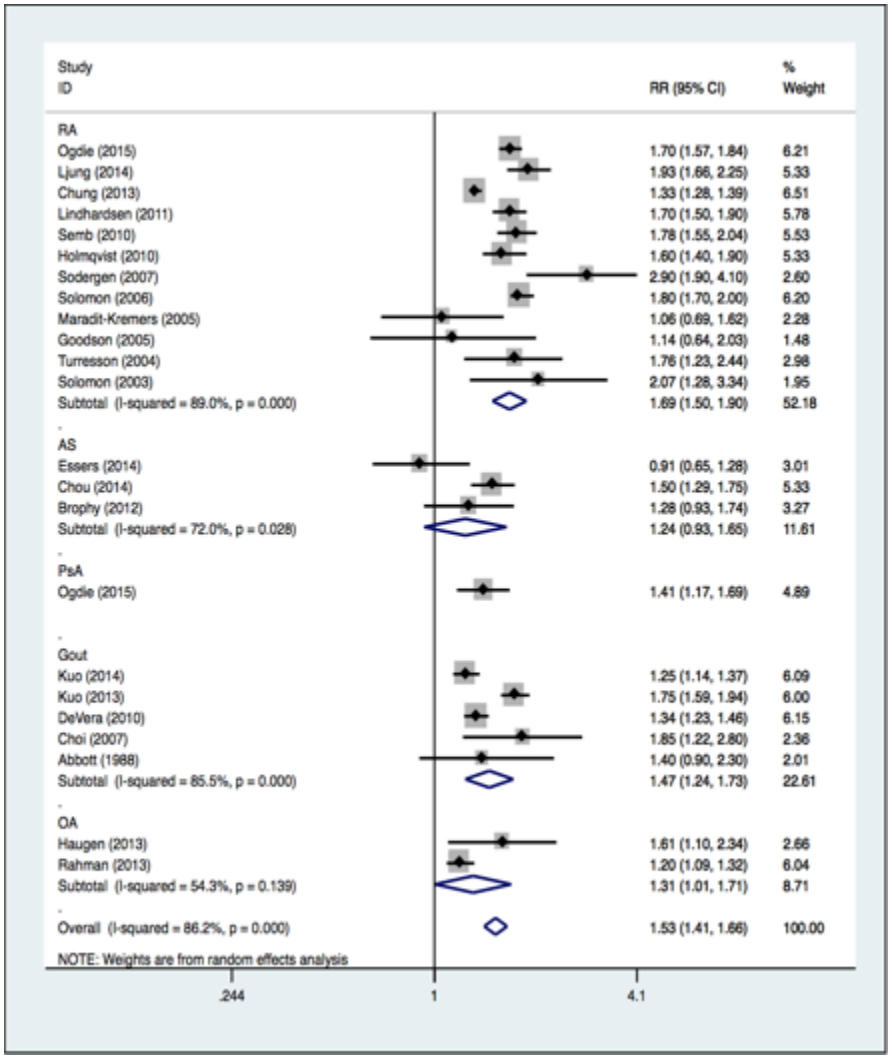


Results: Study Characteristics

- 26 cohort (9 prospective; 17 retrospective) and 1 case-control
- USA (8), UK (7), Sweden (5), Canada (3), China (3) and Denmark (1)
- All studies were of moderate to high quality (NOS range 6-9)
- 22/27 (82%) studies reported excess MI associated arthritis
- Traditional risk factors were more prevalent in all types of arthritis
- Included in meta-analysis: 6,466 incident MI; Arthritis N= 226,962

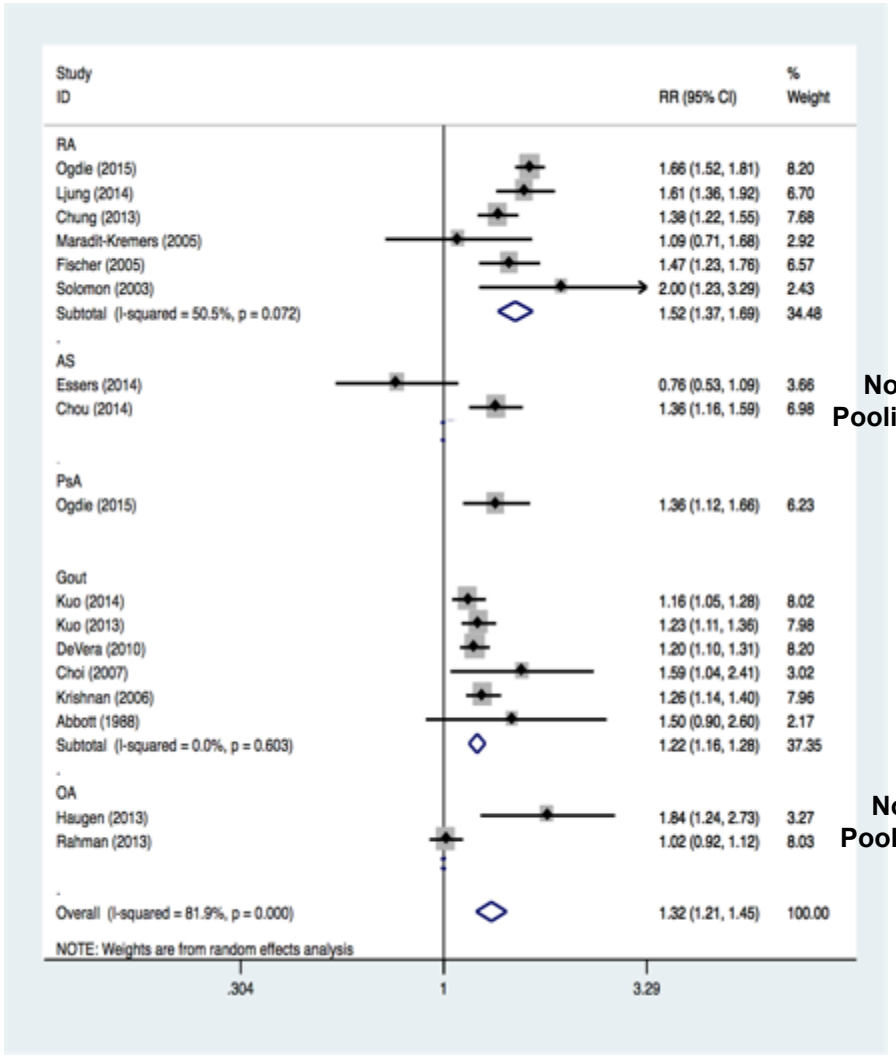
Results: Forest Plots of Population-Based Studies Estimating Risk of Incident Myocardial Infarction Associated with Major Types of Arthritis

A) Studies Adjusted for Age and Sex Only (N=23)



Age/Sex adjusted: Overall 50% increased risk of MI

B) Studies adjusted for Age, Sex and at least One Traditional Risk Factor[1] (N = 17)



RF adjusted: Overall 30% increased risk of MI

Results: Univariate Meta-Regression

How much does arthritis type drive differences in MI?

Studies Adjusted for Age and Sex Only (N=23)	OR	95% CI		p-value
Rheumatoid Arthritis		Reference		
Gout	0.87	0.70	1.09	0.20
Psoriatic Arthritis	0.84	0.55	1.27	0.38
Ankylosing Spondylitis	0.75	0.56	1.00	0.05
Osteoarthritis	0.78	0.56	1.08	0.12
Proportion of between-study variance explained				
Adjusted R-Squared	**20%**			
Knapp-Hartung joint test for all covariates	**p = 0.198**			

Studies Adjusted for 1+ RF (N=13*)	OR	95% CI		p-value
Rheumatoid arthritis		Reference		
Gout	**0.79**	**0.71**	**0.89**	**0.001**
Psoriatic Arthritis	0.89	0.68	1.15	0.33
Proportion of between-study variance explained				
Adjusted R-Squared	**90%**			
Knapp-Hartung joint test for all covariates	**0.004**			

* OA and AS omitted due to small number of studies & inconsistency across studies

Subgroup/other analyses

Subgroup analyses performed by: age, sex, inception vs. prevalent cohort, calendar period and geographic region

- **Age:** RRs tended to be highest in young, then middle-aged the older adults.
- **Sex:** MI-risk increased in M & F but point estimates consistently higher in women
- No other notable differences

Key Findings & Implications

1. MI Risk was consistently increased across major types of arthritis

   Much broader impact of arthritis on heart health

2. Traditional RF were more prevalent in all types of arthritis and consistently explained part of the added risk for MI in each type

3. Support for common mechanisms increasing MI risk across arthritis, though the relative contribution of direct vs. indirect effects may vary by type of arthritis.

   e.g. Direct contribution of systemic inflammation may be higher in RA than in gout, and conversely the role of traditional RF may be greater in gout.

Key findings/ implications

4. Results support the need for more integrated CV prevention strategies for arthritis to help mitigate heart disease risk
   - Canadian & European rheumatology CV guidelines do not include gout and OA though prevention strategies recommended for other types of arthritis may help reduce risk in gout and OA as well.

Limitations

- Few relevant studies were identified in PsA, AS and OA
- Only studies published in French or English were included
  - Though, no evidence of publication bias in funnel plots or egger test
- Differences in the types and proportions of patients being treated were not examined and could have contributed to heterogeneity
- Less than half of included studies tested for interactions by age and sex reported stratified results
- Over a third of studies did not adjust for conventional risk factors

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Table 3 Subgroup analyses of population-based studies estimating risk of incident myocardial infarction associated with major types of arthritis

Comparison	Studies adjusting for age and sex only		Studies adjusting for age, sex and at least one traditional risk factor*	
	n studies	Random-effects RR (95% CI)	n studies	Random-effects RR (95% CI)
Age				
<45	3	1.89 (1.69 to 2.12)	NA	
45–64	5	1.48 (1.28 to 1.71)		
65+	8	1.28 (1.19 to 1.38)		
Sex				
Female	10	1.59 (1.39 to 1.83)	6	1.35 (1.13 to 1.60)
Male	11	1.40 (1.26 to 1.57)	9	1.21 (1.11 to 1.32)
Cohort type				
Inception	13	1.45 (1.31 to 1.60)	10	1.31 (1.14 to 1.51)
Prevalent	10	1.64 (1.44 to 1.88)	7	1.33 (1.18 to 1.50)
Calendar period				
2005–2015	11	1.44 (1.30 to 1.60)	10	1.31 (1.15 to 1.48)
<2005	12	1.66 (1.48 to 1.86)	7	1.31 (1.19 to 1.44)
Region				
North America	8	1.48 (1.25 to 1.76)	8	1.27 (1.12 to 1.41)
Europe	12	1.57 (1.40 to 177)	6	1.34 (1.12 to 1.60)
Asia	3	1.51 (1.25 to 1.83)	3	1.31 (1.21 to 1.41)

*Traditional risk factors: smoking, obesity/body mass index, physical activity, hyperlipidaemia, diabetes and high blood pressure.
NA, not applicable; RR, relative risk.