Psoriatic arthritis and risk of overt cardiovascular disease: review of the evidence

Psoriatic arthritis (PsA) is a chronic inflammatory arthritis associated with psoriasis. Emerging evidence suggests that the systemic inflammation of PsA may lead to an increased likelihood of developing overt cardiovascular disease (CVD). It has been hypothesized that this systematic inflammation leads to insulin resistance, in turn triggering endothelial dysfunction and providing the basis for accelerated atherosclerosis. Ultimately, this results in major cardiovascular events such as myocardial infarction and stroke. However, there are a limited number of studies that have investigated the association between the onset of PsA and subsequent risk of overt CVD. Therefore, questions remain about the role of inflammation in the development of overt CVD. The purpose of this report is to review the literature on PsA and overt CVD, weigh the strength of existing evidence and discuss methodological challenges for future research.

Emerging evidence suggests that chronic inflammatory diseases such as rheumatoid arthritis (RA), systemic lupus erythematosus (SLE) and psoriasis have an elevated risk of cardiovascular morbidity and mortality compared to the general population [1–7]. Although fewer studies have examined the association between psoriatic arthritis (PsA) and cardiovascular manifestations, there is increasing awareness that the chronic inflammation of PsA may lead to an increased risk of cardiovascular disease (CVD) [1,7–12]. In addition, there is increasing interest in whether PsA adds additional risk for the development of CVD beyond that conferred by psoriasis alone [13,14]. Several pathogenetic aspects of chronic inflammation in psoriasis have been outlined in past reviews [9,15–18]. According to the ‘psoriatic march’ concept, psoriasis and its associated morbidities, such as obesity and metabolic syndrome [19–21] contribute to systematic inflammation, leading to insulin resistance, where the equilibrium between pro- and anti-atherogenic effects of insulin is shifted towards the former. This in turn triggers endothelial dysfunction, providing the basis for atherosclerosis and subsequently major cardiovascular events such as myocardial infarction (MI) and stroke. Other proposed mechanisms for PsA inflammation contributing a direct risk for CVD have included C-reactive protein, fibrinogen, homocysteine, dyslipidemia and plasminogen activator inhibitor [9,17,18]. Indeed, several subclinical studies using surrogate markers of atherosclerotic disease, for instance carotid intima-media wall thickness (IMT) and endothelial dysfunction, have shown accelerated atherosclerosis in PsA patients [17,22–26]. This observation has been made in patients without evident CVD and without conventional CVD risk factors, known to be elevated in psoriasis with and without arthritis [9,10,18,20,21,27,28]. Furthermore, at least two studies have reported that CVD is the major cause of death in PsA [29,30]. There is also some preliminary evidence that shows the favorable effect of anti-TNF treatment on cardiovascular disease risk in PsA [16,31], suggesting that control of the inflammatory process decreases occurrence of CVD manifestations. Taken together, this evidence has led to the establishment of guidelines emphasizing the need and importance of cardiovascular risk management in PsA [32]. Nevertheless, there are a limited number of empirical studies that have investigated the association between onset of PsA and subsequent risk of developing clinical or overt CVD. According to recent reviews [8,12], the role of systemic inflammation remains unclear. Does the inflammation of PsA act independently to increase the risk of developing overt CVD, or synergistically with conventional CVD risk factors? The purpose of this report is to review the current body of literature on PsA and overt CVD, weigh the strength of existing evidence, and discuss methodological challenges for future research. For the purpose of this review, clinical or overt cardiovascular disease was defined as myocardial infarction, angina, cerebrovascular disease, congestive heart failure, peripheral vascular disease.

KEYWORDS: cardiovascular disease • cardiovascular mortality • chronic inflammatory diseases • psoriatic arthritis

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and hypertension. The inclusion of hypertension was consistent with previous studies that have investigated the link between PsA and overt CVD [13,33–37]. Due to space constraints, this report did not review the subclinical studies or the conventional cardiovascular risk factor studies, with the exception of those that provide data on hypertension [26,38].

Method
In May 2012, an electronic literature review was conducted to identify published reports using Medline PubMed and Embase. All studies were restricted to those in humans and in the English language. Search terms combined inflammatory disease terms ("psoriasis" OR "psoriatic arthritis" OR "spondylarthropathies") AND cardiovascular disease terms ("cardiovascular disease" OR, "cardiovascular death" OR "cardiovascular mortality" OR "mortality" OR "myocardial infarction" OR "cerebrovascular disease" OR "stroke" OR "transient ischemic attack" OR "hypertension" OR "congestive heart failure" OR peripheral vascular disease" OR "angina").

Titles and abstracts from this initial search were reviewed to identify relevant papers. Exclusions included: reviews, editorials, nonclinical papers, nonadult population and clinical studies of psoriasis that did not provide data on the subgroup of psoriasis patients with arthritis. In addition, potentially relevant papers that did not include a comparison group [39–42] were excluded. Another potentially relevant study by Jamnitski et al. was also excluded [43]. Since the comparison group consisted of RA patients, this study was unable to determine whether the chronic systemic inflammation of PsA was associated with an increased risk of overt CVD compared with a population without chronic systemic inflammation. Additionally, we excluded a study that investigated the relationship between PsA and mitral valve prolapse, a condition not included in our definition of CVD [44]. Reference lists of reviews and relevant articles were also hand searched to identify additional articles.

Results
A total of ten studies were included in this review [13,14,26,30,33–38]. Eight studies examined the association between PsA and cardiovascular morbidity (Tables 1 & 2) and two investigated the link between PsA and cardiovascular mortality (Tables 3 & 4). Studies were conducted between 1978 and 2010 in Canada, USA, Denmark, Israel and Hong Kong. The number of PsA patients ranged from 47 to 3066. At study entry the mean (median) age of PsA samples ranged from mid-40s to early 50s, and the proportion of males ranged from 47.0 to 56.2%, with one exception. The study by Li et al. included women only (i.e., participants of the 1989 Nurses’ Health Study II) [33].

Morbidity studies
Six of the eight morbidity studies used a case–control design [26,34–38], one used a cross-sectional design, nested within a retrospective cohort study [13], and one used a retrospective cohort study design [35]. As shown in Table 1, studies varied in terms of ascertainment of PsA sample, diagnostic criteria, nature of comparison group, operational definition of cardiovascular disease and methods used to ascertain cardiovascular end points (e.g., administrative databases, medical charts and patient reports). However, all studies ascertained prevalent cases of PsA and prevalent cases of cardiovascular disease (Table 2), including the study by Li et al., where only nonfatal incident events were ascertained [33]. The assessment of conventional CVD risk factors varied across studies, with four (50%) considering age and gender only [13,26,34,38]. The study by Li et al. accounted for many conventional CVD risk factors, including age, BMI, ethnicity, family history, smoking, alcohol consumption and hyperlipidemia [33].

Hypertension
Of the eight morbidity studies, seven provided data on the association between PsA and prevalence of hypertension. The majority (71.4%) reported a significantly increased prevalence in PsA patients compared with the general population or comparison group (Table 2). Where available, the adjusted prevalence odds ratios (PORs) ranged from 1.3 to 2.1, with one exception. In the study by Khraiski et al., the PORs ranged from 4.8 to 17.9, varying by disease duration and gender (Table 2) [34]. One study controlled for the impact of surveillance bias (i.e., more intensive medical follow-up in PsA patients compared to the general population) and found that the age- and gender-standardized POR was reduced from 1.9 to 1.29, but remained statistically significant [18].

Two studies reported no association between PsA and prevalence of hypertension, after adjusting for age and gender [26,38]. The lack of statistical significance in the study by Kimhi et al. may be due to the relatively small number of PsA patients included in the age-matched analyses (n = 30, including four with hypertension) [26].
### Table 1. Characteristics of morbidity studies.

<table>
<thead>
<tr>
<th>Study year, country</th>
<th>Objectives</th>
<th>Design</th>
<th>Study period</th>
<th>PsA sample</th>
<th>Comparison group</th>
<th>Cardiovascular outcome</th>
<th>Confounders studied</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Li et al. (2012), USA</td>
<td>To make a prospective evaluation of the association between psoriasis and risk of incident nonfatal CVD</td>
<td>Retrospective cohort study, using data from the NHS II, started in 1989</td>
<td>1989–2009</td>
<td>NHS II respondents who reported being diagnosed with psoriasis prior to or in 2005 PsA confirmed using PASE questionnaire Excluded participants with a history of self-reported or confirmed CVD, diabetes, or cancer before 1991, or psoriasis subjects with unknown date of diagnosis</td>
<td>NHS II respondents without psoriasis</td>
<td>Participants’ report of newly diagnosed nonfatal MI or stroke, confirmed by medical records Diagnosis of MI based on WHO criteria, and diagnosis of stroke based on National Survey of Stroke, where possible</td>
<td>Age, BMI, smoking status, alcohol intake, physical activity, race, family history of stroke/MI, hypertension, hypercholesterolemia, current aspirin use, multivitamin use, postmenopausal hormone use, oral contraceptive use</td>
<td>[33]</td>
</tr>
<tr>
<td>Mok et al. (2011) Hong Kong</td>
<td>To compare the prevalence of atherosclerotic risk factors and the metabolic syndrome in patients with RA, AS and PsA</td>
<td>Case–control</td>
<td>2009</td>
<td>Met CASPAR diagnostic criteria, attended outpatient arthritis clinics at Pok Oi Hospital, aged ≥18 years</td>
<td>Hong Kong general population, ascertained from a community health survey</td>
<td>HTN defined as BP ≥130/85 mmHg or under treatment</td>
<td>Age, gender</td>
<td>[38]</td>
</tr>
<tr>
<td>Khrashi et al. (2011), Newfoundland and Labrador (Canada)</td>
<td>To describe comorbidities associated with early and established disease (duration &lt;2 years and ≥2 years, respectively)</td>
<td>Case–control</td>
<td>2010</td>
<td>Selected among psoriasis patients entered in ongoing cohort study between September 2008 and January 2010, met CASPAR criteria, aged ≥19 years</td>
<td>Newfoundland general population</td>
<td>HTN, angina, CAD, based on patient reports taken at NHS II enrolment</td>
<td>Age, gender</td>
<td>[34]</td>
</tr>
<tr>
<td>Gladman et al. (2009), Ontario (Canada)</td>
<td>To determine prevalence of CVD in comparison with the general population To examine risk factors of CVD relative to disease severity</td>
<td>Prevalence study nested within a retrospective cohort, using data from University of Toronto PsA clinic</td>
<td>1 January 1978–1 June 2004</td>
<td>PsA defined as rheumatologist-confirmed inflammatory arthritis associated with psoriasis Other inflammatory diseases excluded</td>
<td>Ontario general population, ascertained from the Canadian Community Health Survey</td>
<td>HTN, angina, MI, CVA, CHF, retrieved from clinical database, verified by hospital records, patient charts and primary care physicians</td>
<td>Age, gender</td>
<td>[13]</td>
</tr>
<tr>
<td>Tam et al. (2008) Hong Kong</td>
<td>To evaluate whether patients with PsA have an increased prevalence of CVD risk factors</td>
<td>Case–control</td>
<td>NR, presumably 2006–2007</td>
<td>Patients fulfilled Moll and Wright diagnostic criteria Recruited from the two regional HK hospitals</td>
<td>Healthy individuals from a broad spectrum of HK hospital staff, without prior history of overt CVD</td>
<td>HTN (SBP ≥140 mmHg or DBP ≥90 mmHg or use of antihypertensive drugs) Overt CVD (defined as MI, angina, CVA, TIA), retrieved from case notes</td>
<td>Ethnicity, age, gender, BMI</td>
<td>[35]</td>
</tr>
</tbody>
</table>

AS: Ankylosing spondylitis; BP: Blood pressure; CAD: Coronary artery disease; CASPAR: Classification criteria for psoriatic arthritis; CHF: Congestive heart failure; CVA: Cerebrovascular accident; CVD: Cardiovascular disease; DBP: Diastolic blood pressure; HTN: Hypertension; ICD-9: International Classification of Disease 9th Revision; IMT: Intima-media thickness; MI: Myocardial infarct; NHS: Nurses’ Health Study; NR: Not reported; PASE: Psoriatic Arthritis Screening and Evaluation; PsA: Psoriatic arthritis; RA: Rheumatoid arthritis; SBP: Systolic blood pressure; TIA: Transient ischemic attack.
<table>
<thead>
<tr>
<th>Study (year), country</th>
<th>Objectives</th>
<th>Design</th>
<th>Study period</th>
<th>PsA sample</th>
<th>Comparison group</th>
<th>Cardiovascular outcome</th>
<th>Confounders studied</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kondratiouk et al. (2008), CA, USA</td>
<td>To examine association between PsA and atherosclerotic thrombotic vascular conditions</td>
<td>Case–control</td>
<td>NR, presumably 2004–2007</td>
<td>Registered members of a comprehensive prepaid Northern California Health Plan, with ICD-9 diagnosis of PsA between 1995 and 2004</td>
<td>Registered members of same Health Plan as PsA cases, but without a PsA diagnosis or other rheumatic inflammatory condition</td>
<td>ICD-9 outpatient diagnosis of HTN, CAD, heart failure, cerebrovascular disease between 1995 and 2004</td>
<td>Age, gender, ethnicity, education, BMI, smoking status, alcohol intake</td>
<td>[36]</td>
</tr>
<tr>
<td>Kimhi et al. (2007), Israel</td>
<td>To identify vascular risk factors associated with PsA To examine IMT of the common carotid artery</td>
<td>Case–control</td>
<td>NR</td>
<td>Patients seen in department of rheumatology clinic (Tel Aviv Medical Center, Tel Aviv, Israel), presence of psoriasis confirmed by dermatologist, and the presence of a rheumatoid factor-negative inflammatory arthritis, aged ≥18 years Individuals with other joint diseases excluded</td>
<td>100 consecutive individuals undergoing routine check-up in outpatient departments (Tel Aviv Medical Center) Individuals with joint disease excluded</td>
<td>HTN, defined as SBP &gt;140 mmHg, DBP &gt;90 mmHg or use of anti-hypertensive agents</td>
<td>Age, gender</td>
<td>[26]</td>
</tr>
<tr>
<td>Han et al. (2006), USA</td>
<td>To compare the prevalence of CVD disease and risk factors in RA, AS and PsA</td>
<td>Case–control</td>
<td>2001–2002</td>
<td>Registered members of health plans across US, ICD-9 diagnosis of PsA, aged &gt;17 years</td>
<td>Drawn from same databases as PsA sample, same inclusion criteria, but no PsA</td>
<td>ICD-9 diagnosis of HTN, IHD, PVD, CHF, cerebrovascular disease</td>
<td>Age, gender, geographic region and previous length of time in health plan</td>
<td>[37]</td>
</tr>
</tbody>
</table>

AS: Ankylosing spondylitis; BP: Blood pressure; CAD: Coronary artery disease; CASPAR: Classification criteria for psoriatic arthritis; CHF: Congestive heart failure; CVA: Cerebrovascular accident; CVD: Cardiovascular disease; DBP: Diastolic blood pressure; HTN: Hypertension; ICD-9: International Classification of Disease 9th Revision; IMT: Intima-media thickness; MI: Myocardial infarct; NHS: Nurses’ Health Study; NR: Not reported; PASE: Psoriatic Arthritis Screening and Evaluation; PsA: Psoriatic arthritis; RA: Rheumatoid arthritis; SBP: Systolic blood pressure; TIA: Transient ischemic attack.
Table 2. Results for morbidity studies.

<table>
<thead>
<tr>
<th>Study (year)</th>
<th>Number of PsA patients</th>
<th>Male (%)</th>
<th>Age at study entry (years), mean (SD)</th>
<th>PsA duration (years), mean (SD)</th>
<th>Duration of follow-up (mean [SD] or person-years)</th>
<th>Number (%) of cardiovascular events</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Li et al. (2012)</td>
<td>NR</td>
<td>0</td>
<td>NR</td>
<td>NR</td>
<td>4213 person-years</td>
<td>MI 7 (-) Stroke 3 (-)</td>
<td>Multivariate-adjusted hazard ratio (95% CI) MI = 4.18 (1.96–8.90); stroke: 2.40 (0.77–7.51); combined MI and stroke: 3.47 (1.85–6.51)</td>
</tr>
<tr>
<td>Mok et al. (2011)</td>
<td>109</td>
<td>50</td>
<td>50.4 ± 10.6</td>
<td>3.6 ± 3.1</td>
<td>N/A</td>
<td>HTN 61 (56)</td>
<td>Prevalence of HTN not significantly different from controls (17%), once adjusted for age and gender (p = 0.48)</td>
</tr>
<tr>
<td>Khrashi et al. (2011)</td>
<td>165 (early: 57, established: 108)</td>
<td>51 (early: 38.6, established: 57.4)</td>
<td>Early 0.98 (-) Established 8 (-)</td>
<td>N/A</td>
<td>HTN 57 (34.5) (early = 15 [9.0], established = 42 [25.5]) Angina 3 (1.8) CAD 5 (3.0)</td>
<td>Age- and gender-standardized prevalence ratios: HTN: males early: 6.04 (1.20–10.88); established: 4.75 (2.56–6.95); females early: 14.35 (5.46–23.25); established: 17.86 (10.71–25.01) Standardized prevalence ratios for angina and CAD difficult to interpret due to small number of events</td>
<td></td>
</tr>
<tr>
<td>Gladman et al. (2009)</td>
<td>648</td>
<td>56.2</td>
<td>43.5 (-)</td>
<td>7.4 ± 8.3</td>
<td>8.3</td>
<td>HTN 206 (31.8) MI 50 (7.7) Angina 33 (5.1) CVA 8 (1.2) CHF 12 (1.9)</td>
<td>Age- and gender-standardized prevalence ratios: HTN: 1.90 (1.59–2.27); MI: 2.37 (1.73–3.80); angina 1.97 (1.24–3.12); CVA: 0.91 (0.34–2.43); CHF: 1.19 (0.50–2.86)</td>
</tr>
<tr>
<td>Tam et al. (2008)</td>
<td>102</td>
<td>47</td>
<td>48.7 ± 12.2</td>
<td>9.0 (range: 3.5–13.9)</td>
<td>N/A</td>
<td>HTN 50 (49.0) Overt CVD 0 (0)</td>
<td>Prevalence of HTN significantly higher than that observed in control group (19.5%), even after adjusting for age, gender, ethnicity and BMI</td>
</tr>
<tr>
<td>Kondratiouk et al. (2008)</td>
<td>99</td>
<td>50</td>
<td>NR</td>
<td>NR</td>
<td>N/A</td>
<td>HTN 44 (44.4) CAD 13 (13.1) Heart failure 11 (11.1) Cerebrovascular disease 5 (5.1)</td>
<td>Multivariate-adjusted odds ratios: HTN: 2.1 (1.3–3.2); CAD: 0.7 (0.4–1.3); heart failure: 2.0 (1.0–3.8); cerebrovascular disease: 0.8 (0.4–1.3)</td>
</tr>
<tr>
<td>Kimhi et al. (2007)</td>
<td>47</td>
<td>48</td>
<td>50 ± 13.5</td>
<td>12.1 ± 11</td>
<td>N/A</td>
<td>HTN 12 (25.5)</td>
<td>Prevalence of HTN significantly higher than that observed in controls (3%; p &lt; 0.0001), but no significant difference in subgroup analysis, comparing 30 age-matched PsA patients and controls</td>
</tr>
<tr>
<td>Han et al. (2006)</td>
<td>3066</td>
<td>49.1</td>
<td>49.7 ± 11.2</td>
<td>NR</td>
<td>N/A</td>
<td>HTN 874 (28.5) IHD 224 (7.3) Cerebrovascular disease 95 (3.1) PVD 89 (2.9) CHF 58 (1.9)</td>
<td>Age- and gender-standardized prevalence ratios: HTN: 1.3 (1.2–1.4); IHD: 1.3 (1.1–1.5); cerebrovascular disease: 1.3 (1.1–1.7); PVD: 1.6 (1.2–2.0); CHF: 1.5 (11.1–2.0)</td>
</tr>
</tbody>
</table>

CAD: Coronary artery disease; CHF: Congestive heart failure; CVA: Cerebrovascular accident; CVD: Cardiovascular disease; HTN: Hypertension; IHD: Ischemic heart disease; MI: Myocardial infarct; NR: Not reported; PsA: Psoriatic arthritis; PVD: Peripheral vascular disease; SD: Standard deviation.
Coronary artery disease

Five studies examined the association between PsA and coronary artery disease (CAD), variably defined as myocardial infarction (MI) or simply CAD or ischemic heart disease (IHD) (Table 2). Of these studies, two reported a significantly increased prevalence of CAD in PsA compared with the comparison population, after adjusting for age and gender (POR ranged from 1.3 to 2.57) [13,37]. The third study reported an increased incidence of nonfatal MI events in women, after adjusting for multiple traditional CVD risk factors (hazards ratio [HR] = 4.18 [95% CI: 1.96–8.90]) [33], although the number of nonfatal MIs was small (n = 7). The fourth study reported no association between PsA and CAD [36]. However, the wide 95% CI around the adjusted OR of 0.7 (95% CI: 0.4–1.3) suggested that the data were compatible with a ‘true’ increased or decreased prevalence of CAD, but the sample size was insufficient to have adequate statistical power (Table 2). Similarly, the fifth study reported inconclusive findings due to the small number of CAD events (n = 5) [34].

Two of these studies also reported on the prevalence of angina, with one reporting an increased prevalence, after adjusting for age and gender (POR = 1.97 [95% CI: 1.24–3.12]) [33]. The second study produced inconclusive results owing to the small number of events (n = 3) [34].

Cerebrovascular disease

Four studies provided data on the association between PsA and stroke events (Table 2). One reported a significantly increased prevalence of stroke events in PsA, after adjusting for age and gender (POR = 1.3 [1.1–1.7]) [37]. The second study found an increased incidence of nonfatal stroke events in women, once adjusting for multiple CVD risk factors (adjusted HR = 2.40 [95% CI: 0.77–7.51]), but did not achieve statistical significance, possibly owing to the small number of events (n = 3) and low statistical power [39]. The remaining two studies reported no significant association, but again the number of events was small in both studies (n = 8 and 5, respectively) and the 95% CI around the estimated parameter was wide, indicating low statistical power (Table 2) [13,36].

Congestive heart failure

Only three studies presented data on congestive heart failure (CHF) (Table 2). Two indicated a significant increase in the prevalence of CHF among PsA patients compared to the comparison population. Kondratiouil et al. reported a twofold increase in prevalence, after adjusting for a range of conventional cardiovascular risk factors [36]. Unfortunately, the time-dependent risk factors were measured 10 years prior to study entry. Han et al. found a 50% increase in prevalence after adjusting for age and gender [37]. The third study failed to report a significant association, again possibly due to low statistical power, as reflected in the wide confidence interval around the estimated POR of 1.19 (95% CI: 0.50–2.68) (Table 2) [13].

Finally, one study showed a 60% increase in prevalence of peripheral vascular disease in PsA patients compared with the control population, once adjusting for age and gender [37].

Mortality

Two studies provided data on the risk of cardiovascular mortality [14,30]. Both studies used a retrospective cohort design, relying on existing administrative or clinical databases for information on diagnosis, selected covariates and mortality end point, and enrolled PsA patients with established or severe disease (Table 3).

Using a hospital-based cohort of psoriasis patients, Ahlehof et al. reported a statistically significantly increase of 84% in cardiovascular mortality in the patients with PsA, compared with the general population, once adjusting for age, gender, comorbidity, concomitant medication and socioeconomic status (Table 4) [14]. It was also reported that this increased risk remained after accounting for baseline healthcare consumption and surveillance bias. There were insufficient numbers of MI, stroke and coronary revascularization events to calculate risk estimates by type of cardiovascular event in the subgroup of PsA patients. However, among patients with severe psoriasis (n = 2621), including the 607 with PsA, there was a statistically significant increase of 45, 71 and 77% in MI, stroke and coronary revascularization events, respectively.

In a specialty clinic-based cohort, Wong et al. also reported an increased risk of 33% in death due to cardiovascular disease compared with the general population, once adjusting for age and gender [30]. However, this difference did not achieve statistical significance, presumably due to low statistical power owing to the small number of observed/expected events [30]. This is reflected in the wide 95% CI around the estimated standard mortality ratio of 1.33 (95% CI: 0.72–21.53).
### Table 3. Characteristics of mortality studies.

<table>
<thead>
<tr>
<th>Study (year), country</th>
<th>Objectives</th>
<th>Design</th>
<th>Study period</th>
<th>PsA sample</th>
<th>Comparison group</th>
<th>Outcome</th>
<th>Confounders studied</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ahlehoff et al. (2010), Denmark</td>
<td>To investigate psoriasis-related risk of adverse cardiovascular events and mortality</td>
<td>Retrospective cohort, using individual-linkage of nationwide patient and vital status registers</td>
<td>1 January 1997–31 December 2006</td>
<td>First-time hospitalization for ICD-10 diagnostic code of PsA Included at time of third recorded PsA diagnosis (inpatient or outpatient) Excluded prevalent causes of psoriasis, diabetes, MI and stroke, and those &lt;18 years old on 1 January 1997</td>
<td>Danish general population</td>
<td>Obtained from national population and causes of death registries; ICD-10, all-cause mortality cardiovascular mortality (defined as MI, stroke and coronary revascularization), composite of MI, stroke, cardiovascular death</td>
<td>Age, gender, comorbidity, concomitant medication, socioeconomic status, calendar year</td>
<td>[14]</td>
</tr>
<tr>
<td>Wong et al. (1997), Ontario (Canada)</td>
<td>To investigate whether PsA is associated with an increased risk of mortality</td>
<td>Retrospective cohort, using data from PsA clinic, University of Toronto</td>
<td>1 January 1978–1 September 1994</td>
<td>PsA defined as rheumatologist-confirmed inflammatory arthritis associated with psoriasis. All patients followed at the University of Toronto PsA Clinic during study period. Other inflammatory diseases excluded</td>
<td>Ontario general population</td>
<td>Vital status determined through linkage with provincial cancer registry, follow-up interviews with patients and/or relatives, family physicians. Where possible death certificates were used to verify death and ICD-9 cause of death</td>
<td>Age, gender, calendar year</td>
<td>[30]</td>
</tr>
</tbody>
</table>

ICD-9: International Classification of Disease 9th Revision; ICD-10: International Classification of Disease 10th Revision; MI: Myocardial Infarct; PsA: Psoriatic arthritis.
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After a systematic search of the literature, we identified eight studies that examined the association between PsA and overt cardiovascular morbidity, defined here as hypertension, MI, angina, cerebrovascular disease, CHF and peripheral vascular disease. Data were sparse, with seven, five, four, three, two and one studies providing data on hypertension, CAD, cerebrovascular disease, CHF, angina and peripheral vascular disease, respectively. Only two studies examined the association between PsA and the risk of cardiovascular mortality.

Moreover, there was limited evidence to suggest that PsA increased the risk of developing overt CVD. The strongest body of evidence supported an association between PsA and prevalence of hypertension, with five of the seven studies showing an increased prevalence in PsA, compared with the general population. However, these studies failed to establish a clear temporal sequence between onset of PsA and subsequent risk of developing hypertension. Therefore, important questions remain unanswered: is the increased prevalence a result of PsA itself, or the result of coexisting comorbidities or conventional CVD risk factors, such as obesity and smoking, or the consequence of disease duration or related treatments, or simply the effect of selection and detection biases that operate in existing studies?

Similar questions remain about the link between onset of PsA and the major cardiac end points, namely CAD and stroke. Three of five studies showed an increased prevalence (not incidence) of CAD. Moreover, the two studies that found no evidence of an association between PsA and CAD suffered from low statistical power. The results for both stroke and CHF were also inconclusive owing to the small number of studies, the inability of positive studies to establish a clear temporal sequence between onset of PsA and subsequent risk, and the low statistical power of negative studies.

There was some evidence to suggest that PsA increased risk of CVD mortality. To our knowledge, only two studies have specifically reported on the association between PsA and cardiovascular mortality [14,30]. Both reported an increased risk (ranging from 33 to 84%) compared with the general population, although in one study the observed increased risk did not achieve statistical significance, presumably due to low statistical power [30]. Of note, both studies recruited PsA patients with more established or severe disease, and neither study adjusted for the...
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Future research in this area requires studies that are designed to address methodological limitations of existing research. As suggested by others [5,45,46], a prospective cohort design is likely the best suited, since it has many advantages over previously used cross-sectional (prevalence), case–control and retrospective cohort designs. By starting with an inception (early disease) cohort without overt cardiovascular disease, a prospective study is able not only to establish a clear temporal sequence between onset of PsA and risk of overt cardiovascular disease, but also to minimize the effect of potential selection biases imbedded in a prevalence cohort. In addition, there is a greater likelihood of obtaining an adequate sample size through a priori sample size (power) calculations, multisite collaborations, and long-term follow-up in order to observe an adequate number of events. Furthermore, data collection on the range of conventional cardiovascular risk factors is feasible, making it possible to account for their confounding or modifying influences in the analyses. It is also possible to ascertain prospectively all fatal and nonfatal incident CVD events, using the same assessment methods for both the PsA and non-PsA cohort members. This potentially reduces the effect of ascertainment biases inherent in existing studies. Plus the prospective follow-up allows for the ascertainment of incident events using reliable and valid methods. As noted by Kramer et al., the quality of the evidence is reduced for cardiac end points that are either difficult to define clinically or lack reliability when ascertained from administrative databases or from patient reports (e.g., angina, congestive heart failure) [9]. Nevertheless, there are major disadvantages of the prospective cohort design, in particular the enormous time, effort and costs that are required to assemble a sufficiently large cohort of both PsA and non-PsA members and to follow the cohort over an extended period, while ensuring minimum attrition and missing data. In addition, aggressive anti-inflammatory treatments in PsA patients may make it difficult to detect an elevated risk of overt CVD, if it truly exists.

Conclusion
There was limited evidence to suggest that PsA increased the risk of developing overt cardiovascular disease. Well-designed prospective studies with long-term follow-up are best suited to address this relationship, but pose considerable challenges, raising doubts about their feasibility. However, other recent reviews have indicated that patients with PsA have an increased prevalence of conventional CVD risk factors, as well as accelerated atherosclerosis, even in the absence of CVD risk factors [6,8,47]. Therefore, the clinical management of both conventional CVD risk factors and systemic inflammation is recommended to reduce the risk of cardiovascular manifestations in PsA patients [1,8,16,32].

Future perspective
Cardiovascular manifestations in PsA will continue to have major implications for patient management. Systemic anti-inflammatory treatment options should carefully consider

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### Executive summary

**Background**
- Psoriatic arthritis (PsA) is an inflammatory arthritis associated with psoriasis.
- There are questions about the contribution of the systemic inflammation to the subsequent development of overt cardiovascular disease (CVD).

**Method**
- Systematic literature search using Medline PubMed and Embase. Search terms combined inflammatory disease terms and CVD terms.

**Results**
- Overall data were sparse, with seven, five, four, three, two and one studies providing data on hypertension, coronary artery disease, cerebrovascular disease, congestive heart failure, angina and peripheral vascular disease, respectively.
- Results of positive studies were inconclusive owing to ambiguities about temporal sequence between PsA onset and risk of CVD and to prevalence-incidence bias, whereas negative studies suffered from low statistical power.
- Two studies examined the association between PsA and risk of cardiovascular mortality, and both reported an elevated risk in patients with more established or severe disease.

**Conclusion**
- There was limited evidence to suggest that PsA increased the risk of developing overt CVD.
- Future research requires study designs that are able to address methodological limitations of existing studies.
- Where feasible, a prospective cohort design is likely the best suited, since it has many advantages over the previously used cross-sectional (prevalence), case–control and retrospective cohort designs.
their potential effects on cardiovascular health. In addition, standard clinical practice will incorporate strategies to improve patients’ conventional CVD risk profile, such as smoking cessation counseling, dietary referral or counseling to promote healthy body weight and eating practices, and, where necessary, treatment of hypertension and hyperlipidemia. Additional randomized clinical trials are required to study the risks and benefits of aggressive systemic anti-inflammatory therapies on subclinical and clinical cardiovascular endpoints. Where feasible, the results of prospective cohort studies will help to clarify the causal (or noncausal) pathways linking chronic inflammation of PsA and overt cardiovascular disease.

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References
Papers of special note have been highlighted as:
* of interest

* Recent and interesting review of cardiovascular disease and conventional and nonconventional cardiovascular risk factors in psoriatic arthritis (PsA).
15. This mortality study was specifically designed to test the association between PsA and risk of cardiovascular mortality.
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* This study used data from the Nurses’ Health Study II, a large-scale, prospective study initiated in 1989. By doing this, it nicely illustrates the strengths and limitations of relying on data from a pre-existing cohort to test the association between PsA and cardiovascular risk.


* Provides a nice overview of existing prospective observational studies in psoriasis and PsA.