



Autonomic dysfunction and cardiovascular risk in psoriatic arthritis

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Abstract

Psoriatic arthritis (PsA) is an inflammatory disease with a high prevalence of cardiovascular (CV) events due to traditional cardiovascular risk factors and increased systemic inflammation. In this review, our objectives were to (i) evaluate the cardiovascular events and risk factors and (ii) investigate the relationship between autonomic dysfunction and CV diseases in PsA. A systematic review of the literature was done on the Medline/PubMed, Scopus, and the Directory of Open Access Journals databases between January 2017 and July 2022. After screening and exclusions, 73 studies were included for the final review. Patients with PsA have a greater risk of CV diseases and increased traditional CV risk factors, including hypertension, diabetes mellitus, obesity, metabolic syndrome, and dyslipidemia. Although autonomic dysfunction is more common in PsA than in the general population, its relationship with increased CV diseases in these patients is still unclear. Limitations in explaining CV risk in these patient groups complicate patient assessment as cardiovascular risk factors are linked to the morbidity and mortality of PsA, and it is essential to improve an optimal screening and management strategy for CV disease. All CV risk scoring systems cannot fully assess the CV risk in these patients, so in addition to scoring systems, carotid ultrasound evaluation may be a part of the CV evaluation.

Key Points

- Psoriatic arthritis is associated with an increased risk of cardiovascular disease due to traditional cardiovascular risk factors, increased systemic inflammation, and autonomic system dysfunction, although not fully demonstrated.
- The autonomic nervous system is crucial in regulating cardiovascular disease through its effect on the heart, blood vessels, and kidneys. Although the relationship between autonomic dysfunction and cardiovascular diseases has been shown, this relationship is still unclear in PsA.

Keywords Autonomic nervous system · Cardiovascular abnormality · Dysautonomia · Psoriatic arthritis

Introduction

Psoriatic arthritis (PsA) is a chronic inflammatory disease of the spondyloarthritis group characterized by various clinical

features, including synovitis, axial disease, enthesitis, and dactylitis. Although PsA is a rare disease, recent studies based on CASPAR criteria show that up to 30% of patients with psoriasis develop PsA, and its prevalence is estimated to be between 10 and 100 cases per 10,000 [1]. As musculoskeletal manifestations are the most common manifestations, patients with PsA can often suffer from extraarticular involvements such as uveitis, inflammatory bowel disease, and psoriasis leading to increased morbidity [2]. Moreover, these patients may develop other coexisting conditions and, recently, an increasing recognition regarding comorbidities. In a large, prospective study, the prevalence of comorbidity was high, with 42% of patients having three or more comorbid conditions [3]. Compared to the non-psoriatic population, patients with PsA have a 43% higher risk of cardiovascular (CV) disease, with a higher risk of myocardial infarction (MI) (68%), cerebrovascular diseases (22%), and heart failure (31%). Insulin resistance, diabetes mellitus (DM), dyslipidemia, obesity, hypertension (HT), and

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metabolic syndrome (MetS) are the risk factors associated with CV disease risk in these patients [4]. Traditional risk factors cannot fully explain these increased CV events, with inflammation and maybe autonomic dysfunction contributing to this increased risk [5, 6]. Although the cause of the increased risk has not been determined in all detail, patients with PsA have more CV diseases than the healthy population and even several inflammatory rheumatic diseases [7–9].

Psoriatic arthritis is one of the inflammatory diseases in which CV mortality and risk are the most important among rheumatic diseases, and the underlying mechanism is still unclear. A thorough understanding of the relationship between PsA and CV comorbidities can aid early modification of risk factors, minimize the impact of CV comorbidities, and improve long-term outcomes for patients. This review will focus on (i) cardiovascular diseases, (ii) their risk factors, and (iii) autonomic dysfunction in patients with PsA.

Search strategy

A systematic review of the literature was done on the Medline/PubMed, Scopus, and the Directory of Open Access Journals (DOAJ) databases from January 2017 to July 2022, in line with the recommendations of Gasparyan AY et al. [10]. Keywords for the search were “psoriatic arthritis” in combination with “cardiovascular risk,” “cardiovascular disease,” “coronary heart disease,” “coronary artery disease,” “atherosclerosis,” “obesity,” “smoking,” “hypertension,” “diabetes,” “dyslipidemia,” “autonomic dysfunction,” and “heart rate variability.”

This article is based on previous studies and contains no new studies with human participants or animals performed by any authors.

Study inclusion and exclusion criteria

The flowchart (Fig. 1) and the study’s methodology were generated per the PRISMA guidelines. One researcher (HG) searched. Two independent researchers (HG and SAK) screened the titles and abstracts of selected papers, and the potentially eligible papers were retrieved. In the studies that could not be decided and in which there was disagreement, a collective decision was made with all researchers. Articles fulfilling the following criteria were included: (1) trials, observational studies, letters, case reports, and meta-analyses that reported the CV risks and diseases in adult patients with PsA; (2) studies published between January 2017 and July 2022; and (3) studies written in English with full text available. The exclusion criteria were as follows: repeated papers, meeting abstracts, posters, review articles written

in languages other than English, and articles not directly related to the subject. The most relevant articles were hand selected.

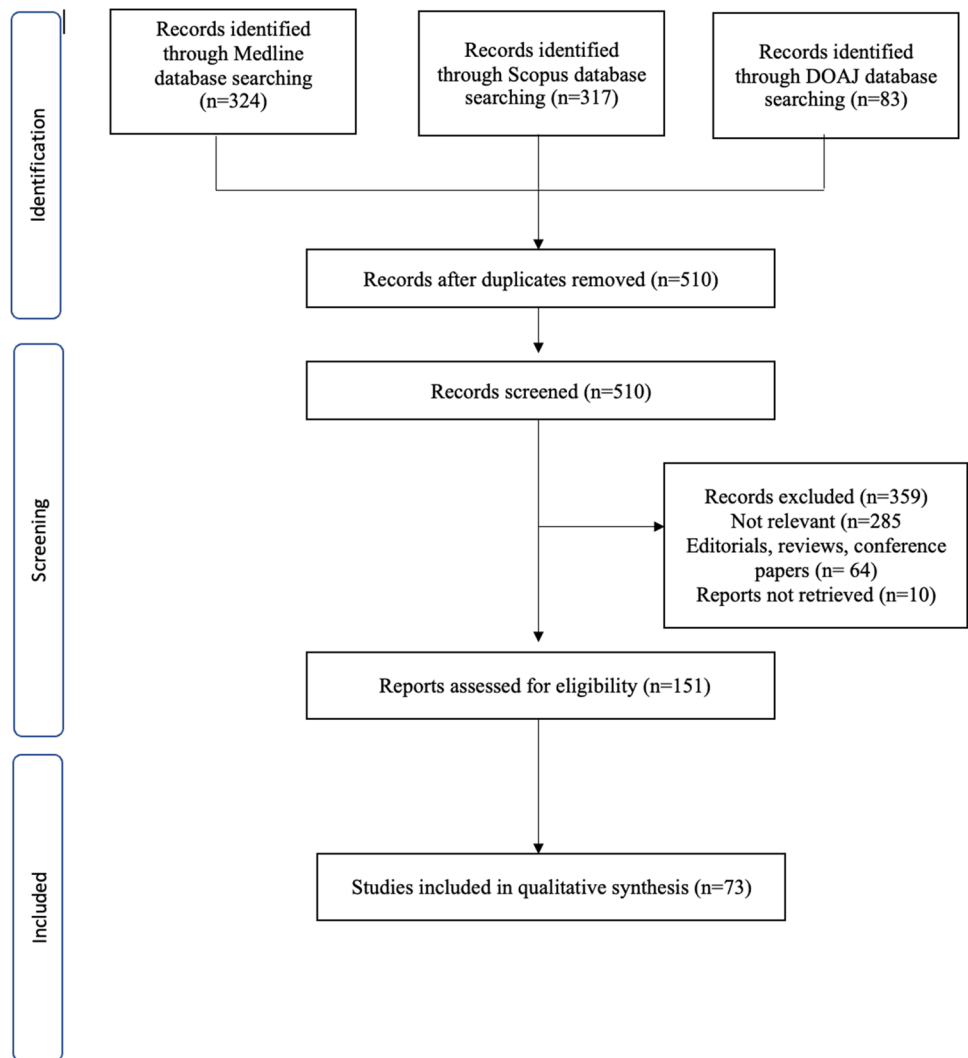
Results

Study selection

After an initial screening of titles and abstracts, 724 relevant articles were reached. Two independent investigators (HHG and SAK) read and reviewed the articles. Of the 724 studies identified, 437 were excluded because they did not address PsA and CV risk. Two hundred fourteen articles were duplicated. Finally, when we read the full texts of the remaining articles, we included 73 studies in our analysis.

Cardiovascular events

The most common and essential comorbidities accompanying PsA are those of a cardiometabolic nature. Therefore, in the last decade, numerous observational and epidemiological studies evaluated the prevalence of CV events in patients with PsA [5, 11–15]. A Swiss study comparing the risk of major CV events in a large cohort of rheumatoid arthritis (RA), PsA, and axial spondyloarthritis (axSpA) reported similar incidence and prevalence of major adverse cardiovascular events (MACE) [5]. A population-based cohort study by Charlton R. et al. [12] showed an increase in CV disease, cerebrovascular disease, ischaemic heart disease, and peripheral vascular disease in patients with PsA than in the general population. Similar to this cohort study, Polachek et al. reported a 43% and 22% increase in CV and cerebrovascular morbidity in PsA compared to the general population [4]. There was no significant difference between PsA and psoriasis for any CV outcomes. A population-based cohort study showed that CV disease, ischaemic heart disease, and peripheral vascular disease were higher in PsA than in the general population but not in psoriasis [12]. In the follow-up of 155 patients in 1550 patient-year, 21 patients had CV events (1.35 events per 100 patients/years): 8 cases of myocardial infarction or unstable angina pectoris, 3 cases of stable angina pectoris, 2 cases of transient ischemic attack, 4 cases of peripheral artery disease, and 4 cases of heart failure. In this study, during the follow-up, no fatal event occurred [13]. A Denmark nationwide cohort study investigated the risk of MI was not increased in mild psoriasis (HR 1.02; 95% CI:0.96–1.09), while the risk was slightly increased in severe psoriasis (HR 1.21; 95% CI: 1.07–1.37). In this study, 158 MI developed in patients with PsA in 38,832 follow-up years, and the overall risk of MI was slightly increased as severe psoriasis (HR 1.22; 95% CI:1.05–1.43) [16]. Another consequence of these cohort

Fig. 1 Study selection flow diagram

data is that increased disease duration is associated with MI risk [17]. Although the risk of MI and coronary artery diseases increased, MI-related mortality was lower than in patients without PsA. This may be related to awareness of CV diseases, early diagnosis, and early intervention in inflammatory conditions [18]. Despite increased CV events, all-cause mortality from CV disease in patients with PSA was not raised in most studies [19, 20].

Rheumatoid arthritis is one of the most researched diseases on this subject, and studies have compared CV events in RA and PsA. A case–control study by Degboe et al. reported that all CV events were more common in PsA than in RA and controls. Still, specific CV events were similar, including stroke and MI. Cardiovascular risk scoring according to SCORE, SCORE-PsA equation applying the 1.5 factor recommended by EULAR for RA patients and QRISK2 were higher in PsA than controls [15]. In a prospective cohort with PsA, AS, undifferentiated SpA (uSpA), and the general population followed for an average of 5 years, acute

coronary syndrome, stroke, and venous thromboembolism (VTE) were increased in all patient groups than in the general population [14]. Standardized acute coronary syndrome incidence rates were 4.3, 5.4, and 4.7 events per 1000 person-years at risk compared to 3.2 in the general population in AS, PsA, and uSpA. These rates were 5.4, 5.9, and 5.7 versus 4.7 in the general population for stroke. For VTE, it was 3.6, 3.2, and 3.5 compared to the general population ratio of 2.2 [14]. MI risk is also increased due to increased CV risk factors in inflammatory arthritis. In a meta-analysis in patients with arthritis, MI risk was significantly increased in RA (pooled RR: 1.69, 95% CI: 1.50 to 1.90), gout (pooled RR: 1.47, 95% CI: 1.24 to 1.73), PsA (pooled RR: 1.41, 95% CI: 1.17 to 1.69), osteoarthritis (OA) (pooled RR: 1.31, 95% CI: 1.01 to 1.71), and AS (pooled RR: 1.24, 95% CI: 0.93 to 1.65) [21]. Coronary artery calcifications are more common in these patients [22].

Although different results are seen regarding the increased burden and thrombosis risk from inflammatory diseases,

extensive cohort studies show that the risk is not as significant in PsA as in RA [23–25]. A population-based cohort assessing VTE risk in psoriasis, PsA, and RA patients was followed for 20 years. The risk of VTE, deep venous thrombosis (DVT), and pulmonary embolism (PE) was determined. While severe psoriasis and PsA using a DMARD had an elevated (but not statistically significant) risk for VTE and DVT, substantial risk for PE was observed [23]. Similarly, in a retrospective cohort of newly diagnosed 5275 PsA patients, VTE was seen in 1.2% of PsA patients during follow-up, while it was seen in 0.8% of patients in the control group [$p=0.023$, crude HR = 1.40 (95% CI: 1.05–1.87)]. In multivariate analysis, following adjustment for multiple covariates, this relation did not remain statistically significant [$p=0.16$, adjusted HR = 1.27 (95% CI: 0.91–1.80)]. Another essential feature of this study is older age and previous history of VTE as predictors of VTE [25]. On the other hand, the VTE risk is increased in various inflammatory rheumatic diseases such as RA, Chron's disease, and ulcerative colitis, but not in PsA [22]. With all these study results, in the future, further assessment of thrombosis risk in patients with PsA is an important research area.

Cardiovascular risk factors in PsA

The increased risk of CV disease in patients with PsA has been proposed to depend on expanded atherosclerotic conditions due to inflammation and traditional cardiovascular risk factors. One of the most important discoveries in recent history is that the conventional CV risk factors of patients with PsA are higher than in the general population. Table 1 represents the CV events and risk factors in PsA. In a multicenter study of 2254 patients, including psoriasis and PsA, 87.6% had at least one CV risk factor, 70.6% had more than one, 52.9% more than two, 35.4% had more than three, and 16.7% more than four risk factors. These risk factors were overweight or obesity (75.3%), central obesity (54.3%), dyslipidemia (49.4%), HT (45.1%), smoking (17.3%), and DM (13.3%), in order of frequency. Along with these CV risks, this may also result in an increased risk of major adverse CV events [26]. A cross-sectional study by Yagensky et al. reported that the prevalence of CV risk factors is 1.77 per patient, with PsA patients showing the highest number of CV risk factors (1.68 ± 0.13 for RA, 1.7 ± 0.13 for SpA, 2.04 ± 0.16 for PsA, and 1.78 ± 0.34 for non-inflammatory rheumatic disease) [8].

According to the data from the Australian Rheumatology Association, traditional cardiovascular risk factors, including HT [adjusted OR 1.7 (95% CI: 1.4–2.1), hyperlipidemia [2.0 (1.6–2.5)], DM [2.2 (1.6–3.0)], and ischemic heart disease [2.0 (1.3–2.9)] were found to be higher in PsA compared to RA. An increased risk in this study may be

related to the fact that the rate of patients with ischemic heart disease in PsA patients is higher than in RA [9]. In another study by Jefri et al., only obesity and DM were higher in RA patients compared to the healthy population. In contrast, all CV risk factors, such as HT, DM, hyperlipidemia, and obesity, were higher in PsA [27]. In a large cohort of gout, PsA, RA, and AS patients from Sweden, the most common CV risk factor was HT, while it was most common in gout patients (64.6%), followed by RA (43.4%), PsA (40.5%), and AS (29.3%), respectively. Women with PsA had more obesity and HT than women with RA and AS and more DM and hyperlipidemia than women with AS [28].

Different results were observed regarding the factors associated with increased risks. In a cross-sectional and retrospective study including 240 PsA patients, CV events were more prevalent than controls (OR 1.68, 95% CI: 1.02–2.76). The distribution of CVD was as follows: 15 ischemic heart disease events, 15 cerebrovascular disease events, and 11 ischemic peripheral vascular disease events. Age of onset of psoriasis > 40 years (OR 3.4, 95% CI: 1.1–10.0), a high number of swollen joints during evolution (OR 2.9, 95% CI: 1.1–8.0), HT (OR 5.3, 95% CI: 1.6–17.6), and dyslipidemia (OR 2.6, 95% CI: 1.0–7.2) were the independent CV disease-associated factors [29]. Interestingly, a study from India found sarcopenia and the presence of any traditional CV comorbidity were associated with high CV risk. Intramuscular fats and ectopic adipose tissue deposition predisposing to sarcopenia induce high CV risk [30]. High disease activity and carotid plaque are the other risk factors for CV events [11, 31–33]. In addition to those already mentioned, complements are also suspected to be one of these factors. The relationship of the complement system with CV risk factors and disease activity was investigated on the basis that complement component 3 originates from adipose tissue other than immune system cells. Serum levels of complement C3 were significantly elevated in patients with PsA, RA, and SpA compared to healthy controls, and obesity, DM, hyperlipidemia, atherogenic and ApoB/ApoA risks, and insulin resistance were more common in these patients [34]. Figure 2 represents the factors associated with increased cardiovascular disease in patients with PsA.

Autonomic dysfunction

Traditional cardiovascular risk factors typically fail to explain increased CV risk in PsA, where high chronic systemic inflammation is the other most important part. Recently, as studies on inflammation and CV risk have increased, the role of inflammation has been clarified, first with endothelial dysfunction and then with the development of atherosclerosis. However, the effect of chronic inflammation was not limited to only endothelial dysfunction. Studies show that chronic systemic inflammation

Table 1 Studies of the frequency of cardiovascular events and risk factors in psoriatic arthritis

Study	Type of publication	Psoriatic arthritis patients, <i>n</i>	Controls, <i>n</i>	Prevalence of CV events and risk factors
PolacheK et al. Canada [4]	Meta-analysis	32,973	GP	MI OR 1.68 (95% CI: 1.31–2.15), Cerebrovascular events OR 1.22 (95% CI: 1.05–1.41), HF OR 1.32 (95% CI: 1.11–1.57) Non-lethal MACE (2.86%)
Lauper K et al. Switzerland [5]	Retrospective and prospective cohort	805	RA (<i>n</i> = 3164), AxSpA (<i>n</i> = 1487)	DM OR: 1.35 (1.17–1.56), hypertension OR: 1.6 (1.66–1.97), HT OR: 1.81, CAD OR: 1.39 (1.66–1.97), hyperuricemia OR: 1.61 (1.39–1.86), MetS OR: 1.58 (1.32–1.88)
Haque N et al. Belgium [7]	Cross-sectional	262	Non-PsA SpA (<i>n</i> = 256)	HT (38.2%), hyperlipidemia (25.3%), ischaemic heart disease (7.6%), DM (12.9%), stroke (1.4%)
Sinnathurai P et al. Australia [9]	Cohort	490	RA (<i>n</i> = 3609)	DM (12.8%), high blood pressure (27.1%), obesity (32.1%), dyslipidemia (23.6%), and hyperuricemia (7.1%)
Lorenzo A et al. Spain [11]	Cross-sectional	140	-	Current smoking (23.7%), hyperlipidemia (15.4%), HT (28.4%), DM (6.1%), cerebrovascular disease (1.2%), ischaemic heart disease (4.6%), peripheral vascular disease (1.0%)
Charlton R. et al. United Kingdom [12]	Cohort	6783	GP (<i>n</i> = 27,132), PsO (<i>n</i> = 27,132)	Acute coronary syndrome HR 1.76 (1.59–1.95), stroke HR 1.34 (1.22–1.48), VTE HR 1.46 (1.29–1.65)
Bengtsson K. et al. United Kingdom [14]	Prospective cohort	16,063	AS (<i>n</i> = 6448), uSpA (<i>n</i> = 5190), GP (<i>n</i> = 266,435)	HT (34.4%), DM (12.1%), dyslipidemia (25.1%), current smoking (24.2%)
Degboé Y et al. Italy [15]	Case-control	207	GP (<i>n</i> = 414)	DM (7.2%), HT (21.2%)
Egeberg A et al. Denmark [16]	Retrospective cohort	8149	GP (<i>n</i> = 4,300,085)	The overall risk of MI was (HR 1.22; 95% CI: 1.05–1.43), and the first-time MI risk (HR 1.23; 95% CI: 1.04–1.47)
Ogdie A et al. USA [19]	Longitudinal cohort	8809	RA (<i>n</i> = 43,320), controls (<i>n</i> = 82,590)	DM 6.6%, hyperlipidemia 8.5%, HT 21.3%, MI 2.3%, stroke 1.2%, peripheral vascular disease 1%, atrial fibrillation 1.5%, current smoking 21.5%
Tinggaard AB et al. Denmark [22]	Cross-sectional cohort	370	PsO (<i>n</i> = 1356)	Dyslipidemia 41.4%, DM 10.3%, obstructive coronary artery disease 16.7% and OR 1.14 (95% CI: 0.98–1.33)

Table 1 (continued)

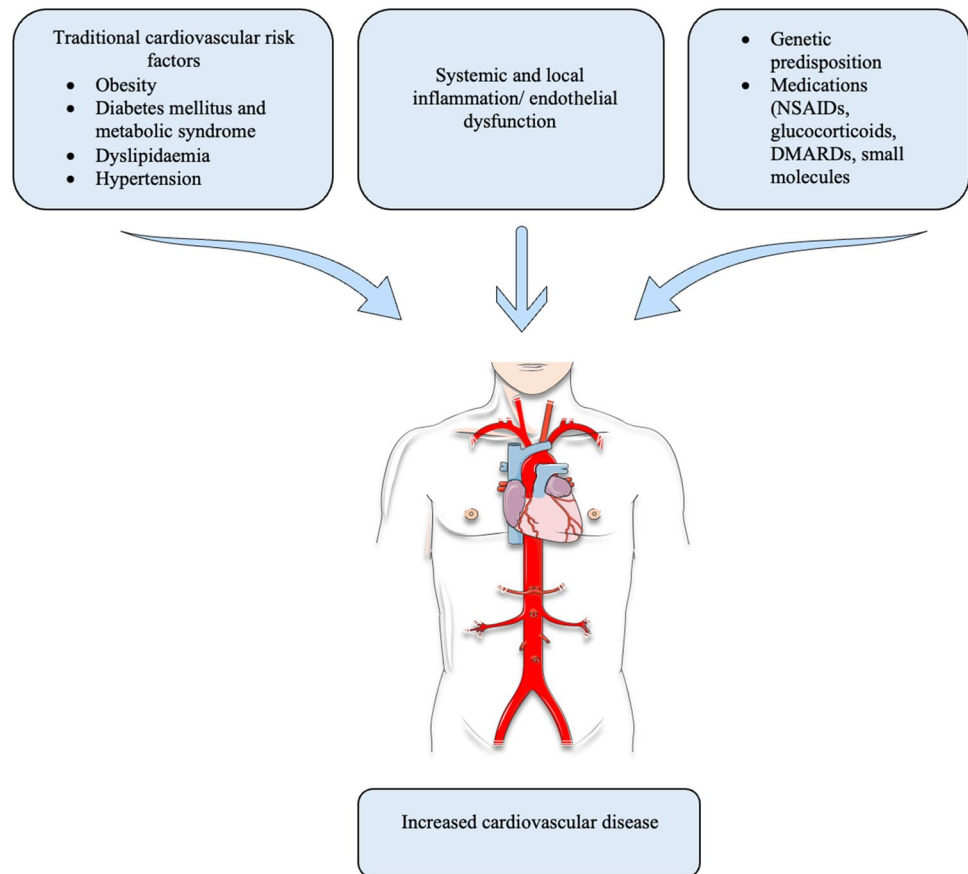
Study	Type of publication	Psoriatic arthritis patients, <i>n</i>	Controls, <i>n</i>	Prevalence of CV events and risk factors
Ogdie A et al. USA [23]	Prospective cohort	12 084	RA (<i>n</i> = 51,762), PsO (<i>n</i> = 194,288), controls (<i>n</i> = 1,225,571)	Fully adjusted VTE HR for PsA-No DMARD 1.07 (0.88–1.29), PsA-DMARD 1.10 (0.92–1.31) Fully adjusted DVT HR for PsA-No DMARD 1.07 (0.87–1.31), PsA-DMARD 1.02 (0.83–1.24) Fully adjusted PE HR for PsA-No DMARD 1.24 (0.85–1.84), PsA-DMARD 1.41 (1.00–2.03) Adjusted VTE HR 1.20 (0.96, 1.52), PE 1.08 (0.75, 1.55), DVT 1.34 (1.01, 1.77)
Galloway J et al. United Kingdom [24]	Retrospective cohort	6297	Ulcerative colitis (<i>n</i> = 14,182), Chron's (<i>n</i> = 9489, RA (23 410), controls (<i>n</i> = 213,512)	Tobacco use 42.2%, DM 33.8% HT 30.1%, AF 3.0%, vascular disease 3.7% VTE HR 1.4 (95% CI:1.05–1.87)
Gazitt T et al. Israel [25]	Retrospective cohort	5275	Control (<i>n</i> = 21,011)	Overweight or obesity (75.3%), central obesity (54.3%), dyslipidemia (49.4), HT (45.1%), smoking (17.3%), DM (13.3%)
Eder L et al. Canada [26]	Cross-sectional	1327	PsO (<i>n</i> = 927)	HT 22.4%, DM 7.8%, hyperlipidemia 9.9%, heart failure 1.9%
Jafri K et al. USA [27]	Cross-sectional and longitudinal	12,548	RA (<i>n</i> = 53,215), controls (<i>n</i> = 389,269)	Obesity 23%, smoking current 11.9%, HT 40.5%, DM 10.3%, hyperlipidemia 17.3%
Landgren AJ et al. Sweden [28]	Cross-sectional	699	Gout (<i>n</i> = 868) RA (<i>n</i> = 742), AS (<i>n</i> = 587)	Hypertension (OR 2.4, 95% CI:1.6–2.7) DM (OR 2.8, 95% CI:1.7–4.3)
Queiro R et al. Spain [29]	Cross-sectional retrospective	340	Controls (<i>n</i> = 600)	Obesity (OR 2.1, 95% CI:1.5–2.8), Tobacco use (OR 1.4 95% CI:1.0–1.8)
Kavadichanda C et al. India [30]	Cross-sectional	56	Non-PsA SpA	DM 10.7%, HT 7.1%, MetS 28.6%, smoking 12.5%
Kibari A et al. Israel [43]	Retrospective case-control	3161	Controls (<i>n</i> = 31,610)	Obesity 34.5%, DM 27.9%, hyperlipidemia 64%, HT 45.6%, tobacco use 28.6%
Kaine J et al. USA [44]	Retrospective observational cohort	14,898	Controls (<i>n</i> = 35,037)	HT 42.3%, hyperlipidemia 33.8%, coronary artery disease 6.6%, cerebrovascular disease 3.1%, peripheral vascular disease 2.8%, DM 15.9%, smoking 5.5%, obesity 9%
Cooksey R et al. United Kingdom [45]	Retrospective cohort	2128	RA (<i>n</i> = 8650), PsO (<i>n</i> = 24,630), controls (<i>n</i> = 1,187,706)	Ever smoking 46.7%, hyperlipidemia 12.6%, DM 13.1%, HT 33.3%, ischemic heart disease 14.5%
Nissen CB et al. Denmark [46]	Cross-sectional	170	AS (<i>n</i> = 116), RA (<i>n</i> = 836)	HT 30.7%, CVD 14.1%, DM 7.7%
Özkul Ö et al. Turkey [47]	Cross-sectional	55	PsO (<i>n</i> = 50), RA (<i>n</i> = 50)	Obesity 40%, MetS 29.1%, HT 20%

Table 1 (continued)

Study	Type of publication	Psoriatic arthritis patients, <i>n</i>	Controls, <i>n</i>	Prevalence of CV events and risk factors
Queiro R et al. Spain [48]	Retrospective cross-sectional	290	PsO (<i>n</i> = 310), control (<i>n</i> = 600)	DM 12%, HT 29%, dyslipidemia 28%, obesity 27.6%, and tobacco use 27.2%
Wang Q et al. China [49]	Case-control	171	PsO (<i>n</i> = 342)	Smoking 26.3%, coronary artery disease 4.1%, HT 24.6%, dyslipidemia 26.9%, DM 14%
Anyfanti P et al. Greece [50]	Cross-sectional	51	RA (<i>n</i> = 244), OA(<i>n</i> = 90), SpA(<i>n</i> = 67), SLE (<i>n</i> = 65)	HT 57.8%
Queiro R et al. Spain [51]	Cross-sectional	290	PsO (<i>n</i> = 310)	HT 24%, dyslipidaemia 28%, obesity 27.6%, tobacco use 27.2%
Toussirof E et al. France [52]	Cross-sectional	52	PsO (<i>n</i> = 52), GP (<i>n</i> = 92)	Obesity 21.2%, HT 28.8%, DM 7.7%, Dyslipidemia 17.3%, current smoking 15.4%
Landgren AJ et al. Sweden [53]	Cross-sectional	692	GP (<i>n</i> = 7559)	Obesity 28.6%, HT 40.3%, DM 10.5%
Fernández-Carballido C et al. Spain [58]	Cross-sectional	721	AS (<i>n</i> = 738)	HT 29.5%, obesity 29.1%, current smoker 21.8%, MI 1.5%, congestive heart failure 1% peripheral vascular disease 1%, DM 8.5%, cerebrovascular disease 0%
Patel P et al. Canada [63]	Cross-sectional	164	PsO (<i>n</i> = 103)	CV disease 7.3%, HT 44.5%, DM 17.7%, hypercholesterolemia 39.6
Queiro R et al. Spain [64]	Retrospective cross-sectional	340	Controls (<i>n</i> = 600)	DM 13.8%, OR 2.8, 95% CI:1.7–4.3, HT 36%, OR 2.4, 95% CI: 1.6–2.7, obesity 26%, OR 2.1, 95% CI: 1.5–2.8, tobacco use 26%, OR 1.4, 95% CI: 1.0–1.8
Rahmatpour Rokni G et al. Iranian [66]	Cross-sectional	48	PsO (<i>n</i> = 48), controls (<i>n</i> = 48)	MetS 58.3%
Adeodato Ramos LM et al. Brazil [67]	Cross-sectional	76	Controls (<i>n</i> = 76)	MetS 53.9%
Queiro R et al. Spain [68]	Cross-sectional retrospective	290	PsO (<i>n</i> = 310)	Hyperlipidemia 28.3% OR 2.5, (95% CI: 1.7, 3.3)
Fragoulis GE et al. Greece [81]	Cross-sectional	215	RA (<i>n</i> = 215), DM (<i>n</i> = 215)	Smoking 35.4%, hyperlipidemia 47.0%, HT 28.8%, obesity 29.4%, coronary artery disease 4.7%, stroke 3.7%, MACEs 5.6%

RA rheumatoid arthritis, PsO psoriasis, AS ankylosing spondylitis, SpA spondyloarthritis, SLE systemic lupus erythematosus, GP general population, DM diabetes mellitus, HT hypertension, MI myocardial infarction, CV cardiovascular, VTE venous thromboembolism, DVT deep venous thrombosis, PE pulmonary embolism, HF heart failure, MACE major adverse cardiovascular events, MetS metabolic syndrome

Fig. 2 Factors associated with increased cardiovascular diseases in psoriatic arthritis



affects the heart's autonomic system by causing a decrease in heart rate variability, which is the best marker of cardiac autonomic function and a predictor for morbidity and outcomes after MI and stroke [6, 35, 36]. Elevations in pro-inflammatory cytokines increase sympathetic activity and reduce cardiovagal baroreflex sensitivity and heart rate variability, resulting in autonomic dysfunction. Consequently, it plays a critical role in regulating cardiovascular disease through its effect on the heart, peripheral vascular, and kidneys. The autonomic nervous system is the part of the peripheral nervous system consisting of sympathetic, parasympathetic, and enteric nerves. Their function regulates the automatic physiologic processes, including heart rate, blood pressure, respiration, digestion, and sexual functions [37]. Although the autonomic system has been evaluated in many rheumatic diseases, studies on PsA are insufficient. The first study on this subject demonstrated that patients with PsA have decreased heart rate variability than healthy controls independently from the cardiovascular risk factors. Disease activity parameters and acute phase reactants levels were negatively correlated with heart rate variability parameters. The most likely explanation for decreased heart rate variability in PsA is the presence of systemic inflammation. Indeed, persistent systemic inflammation affects heart rate variability, most likely through reduced

parasympathetic regulation. Still, the exact mechanisms of the relationship between inflammation and autonomous regulation of heart rate variability are thus far not entirely clear [36]. One of the most detailed studies on inflammation and CV disease evaluated systemic inflammation, carotid stenosis, and autonomic dysfunction. The carotid bulb, containing peripheral baro- and chemoreceptors, is the major site of autonomic regulation and the primary site of choice for the arteriosclerotic process. Carotid arteriosclerosis interacts with carotid baro- and chemoreceptors and results in autonomic dysfunction, i.e., causes sympathetic hyperactivity and decreased vagal tone. In this study, low-grade systemic inflammation, as assessed by elevated hs-CRP levels, was associated with the severity of the carotid arteriosclerotic process. Increased hs-CRP levels were related to the carotid stenosis-associated reduction of vagal tone but not to the systemic burden of arteriosclerotic disease, including coronary and peripheral artery disease and other vascular risk factors [38].

Autonomic dysfunction is a risk factor for CV events, and parasympathetic autonomic dysfunction is linked to crucial features of inflammatory joint disease, including PsA, such as inflammation, physical inactivity, and pain. Heart rate variability measures the heart-rate variation and estimates the cardiac autonomic function. In a meta-analysis from Norway, RA and

SpA patients have cardiac parasympathetic autonomic dysfunction, which is related to inflammation [6].

Nowadays, the standard gold test for the autonomic system is the Ewing battery test which objectively measures heart rate variability and blood pressure response to orthostasis. However, this test is time-consuming and may only be performed in some centers. A study using the COMPASS-31 test, which evaluates autonomic functions through symptom questioning and investigates the relationship between autonomic dysfunction and CV risk, were performed in patients with PsA. In the patient group in which DM patients were excluded due to the known influence of diabetes on the autonomic system, 16.9% had HT, 37.3% had obesity, 34% had smoking, 19.8% had MetS, and 41.7% had dyslipidemia. All COMPASS-31 scores (orthostatic, vasomotor, secretomotor, gastrointestinal, bladder, and pupillomotor) were higher in patients with PsA than in healthy populations, suggesting an increased risk of autonomic dysfunction in PsA. However, this study had no relationship between autonomic system symptoms and CV disease risk [39]. The fact that COMPASS-31 provides a subjective evaluation and is not a standard gold test may not have clearly shown the relationship with CV diseases in this study. In the future, there is a need for studies in which objective evaluation is done for the autonomic system together with subjective tests, and its relationship with CV diseases can be seen more clearly.

Brock et al. evaluated autonomic system measures, disease activity, and cytokines by applying transcutaneous vagal stimulation to PsA and AS patient groups and demonstrated the first-time anti-inflammatory effect of short-term transcutaneous vagal nerve stimulation. The Ankylosing Spondylitis Disease Activity Score (ASDAS) assessed disease activity, and CRP values were significantly decreased in PsA after vagus stimulation. The vagal anti-inflammatory effects emerge primarily from cholinergic activation of nicotinic receptors on macrophages and immune cells in the spleen, inhibiting the production of pro-inflammatory cytokines and promoting the production of anti-inflammatory cytokines. Treatment with electrical vagal stimulation and nicotinic receptor agonists reduces systemic inflammation. Consequently, vagal stimulation modulates immune responses by neuroimmune interaction and may be considered vagal stimulation as a promising add-on therapy to existing pharmaceutical interventions in PsA [38, 40].

Smoking

Studies with a wide range of smoking prevalence in PsA often show similar rates to the general population [41–46]. The rate of smoking in PsA (31%) was less than in psoriasis (40%) and higher than in RA (14%) [47]. Like this study, tobacco use (34.5% vs. 27.2%, OR 1.4 95% CI: 1.0–2.0, $p < 0.05$) was more prevalent among psoriasis than in PsA. Obesity was also more prevalent in PsA, suggesting both may be risk factors for psoriatic disease [48]. Similarly to

these results, former smoking was associated with early-onset psoriasis but not PsA [49].

Hypertension

Comorbidities are highly prevalent in patients with PsA, especially cardiometabolic ones. Many studies suggest that HT is the most common CV risk factor. The prevalence of HT is between 7.1 and 57.8%, with some differences in study design and definition of HT [9, 11, 12, 15, 16, 27, 28, 45–54]. In a meta-analysis of 150,677 patients, HT (34.2%) was the most common comorbidity, followed by MetS (28.8%), obesity (27.4%), hyperlipidemia (24.2%), and any CVD (19.4%) [55].

The frequency of HT was higher in RA (38%) than in psoriasis (16%) and PsA (20%) ($p = 0.011$) [47]. In a study using various HT definitions, HT was found to be 57.8% in PsA according to the 2018 ESC/ESH guideline, while it was found to be 80% according to the ACC/AHA guideline. The difference in the rates of HT was due to the cut-offs used in the definitions. According to the 2018 ESC/ESH guideline, the cut-off for HT is 140/90 mmHg and 130/80 mmHg, according to the 2017 ACC/AHA guideline. In this study, HT prevalence was similar between male and female patients [50]. In a patient population combining psoriasis and PsA patients, hypertension was seen in 24% of patients, and later-onset of psoriasis and high BMI were shown as predictors of HT [51]. In another study, younger age (≤ 50 years of age: OR 2.59 (95% CI 1.87, 3.58)) and disease status (psoriasis vs. PsA OR 1.36 (95% CI 1.05, 1.78)) were the independent predictors of undertreatment of HT [26].

Obesity

Obesity is frequently seen in psoriasis and PsA, and it has been revealed that adipokines released from obesity-related adipose tissue may be a risk factor for developing the disease [52, 53]. Visceral adiposity-associated adipose inflammation may play a role in the pathogenesis of CV disease and contribute to the development of PsA [56]. In addition, TH17-derived cytokines have a critical role in the pathogenesis of obesity and inflammatory disease, especially PsA [48]. Even though obesity is a risk factor for the development of PsA in psoriasis [57]. The prevalence of obesity in patient groups of different ethnicities varies between 21.2 and 40% [13, 47, 48, 52, 58–61]. Furthermore, obesity was more common both in psoriasis (36.5% vs. 22%, OR 2.1 95% CI: 1.5–2.8, $p < 0.01$) and PsA (27.6% vs. 22%, OR 1.4 95% CI: 1.0–1.9, $p < 0.05$) than the control group [48]. In a study comparing PsA and AS patients from Spain, PsA patients had a higher body mass index. Obesity was associated with physical functions such as HT and triglycerides in the bivariate analysis [58]. In the ASAS-Per-SpA study, the highest mean body mass index

scores among other SpA groups were in PsA patients [62]. When overweight patients were distinguished from obese, 42% of patients with PsA were found to be overweight, and 30% were obese. Their body mass index scores were similar to RA. Being overweight and obese were the most prevalent CV risk factors, followed by smoking and HT [13]. In a multicenter study, 37.1% of patients were obese, and obese patients had more peripheral arthritis, hip pain, worse quality of life, function, disability, and increased disease activity [59]. In a study of 5275 patients, while the rate of obese patients in PsA was 33.5%, it was found to be 25.8% in the healthy population ($p < 0.001$) [25]. In addition to being a CV risk factor, obesity is a prognostic factor for poorer treatment outcomes [60]. The rate of MDA increased from 28 to 45%, with 7% weight loss in a patient group that was followed for 24 months. Weight loss was also associated with improved serum lipids, glucose and urate levels, and blood pressure [61].

Obesity is usually defined by the World Health Organization using body mass index, but body mass index gives an approximate percentage of fat. Waist circumference is also a valid measure for abdominal/android obesity and is strongly associated with CV complications. Regarding visceral obesity, psoriasis patients had a higher visceral fat mass than controls, but no difference was observed between PsA and controls [52].

Diabetes mellitus and metabolic syndrome

Mets is one such established CVD risk factor. In a study of SpA patients, MetS was seen in 9.92% of the PsA group while in 4.68% of the non-psoriatic SpA group. Mean waist circumference and triglyceride levels, MetS components, were significantly higher in these patients. Mets components were similar, including mean blood pressure and HDL cholesterol [7]. The risk of DM was found to be significantly higher in the PsA than in the general population and psoriasis [adjusted RR 1.40 (95% CI: 1.15–1.70) and 1.53 (95% CI: 1.19–1.97), respectively]. The authors of this study suggest that this increase in DM in PsA than psoriasis is linked to the additional inflammatory burden associated with arthritis in combination with higher levels of obesity, unknown genetic factors, diet, and exercise influence [12]. Similar to these results, another cohort saw DM in 9.7% psoriasis and 17.7% PsA [63]. Queiro et al. reported a higher prevalence of DM than in healthy populations and also late-onset psoriasis (OR 8.2, 95% CI: 1.9–12.4, $p = 0.002$) and HT (OR 7.5, 95% CI: 1.5–13.3, $p = 0.008$) were the associated factors for predicting DM [64]. DM's prevalence varies from 6.1 to 33.8% depending on the studies and patient populations [11, 12, 15, 16, 22, 25, 26, 43–46, 53, 58, 63].

A meta-analysis by Loganathan et al. has indicated a higher prevalence of MetS in patients with PsA compared

to psoriasis and RA. Subgroup analyses of these MetS components showed that central obesity was the most common in patients with a rate of 62.1%, followed by HT (50.2%), reduced HDL (36.6%), hyper-triglyceridemia (35.6%), impaired fasting glucose (25.8%), and DM (20.6%) [65]. Similarly, other studies show that MetS is higher in PsA than in psoriasis and healthy controls [66, 67]. Conversely, MetS showed no difference among PsA, RA, and controls in another study involving fewer patients [47].

Except for psoriasis, RA, and other SpA types, the rate of DM was found to be higher in PsA compared to the healthy population (33.8% vs. 26.2%, $p < 0.001$) [25]. Last, the DM incidence was 7–8% in PsA patients while 3–4% in the healthy population [16, 52].

Dyslipidemia

The prevalence of hyperlipidemia is substantial in PsA and higher than in the general population and psoriasis alone [26, 52, 63, 68]. The prevalence of dyslipidemia was between 9.9 and 64% in PsA, which may be attributed to the different patient populations and various definitions of dyslipidemia [26, 27, 30].

When the factors investigated were associated with hyperlipidemia, arthritis onset age above 40 years (OR 2.3), male sex (OR 1.9), low educational level (OR 1.9), oligoarthritis during follow-up (OR 2.2), DM (OR 4.1), obesity (OR 3.5), systemic treatment (OR 0.7), and ischaemic heart disease (OR 8.7) were the significant factors in the unadjusted model. However, age (OR 1.07, 95% CI 1.04, 1.11, $p < 0.001$) and systemic therapy (OR 0.40, 95% CI 0.17, 0.89, $p = 0.026$) were the most significant factors in the fully adjusted model. Thus for every ten years of increase in age, the frequency of HL increased by 7%, while patients exposed to systemic synthetic and/or biological DMARD treatments reduced the prevalence of this finding by 60% [68].

In a multicenter study from Canada, the USA, and Israel, dyslipidemia was present in 49.4% of patients with the most common CV risk factor. However, 35.8% did not have a previous diagnosis of dyslipidemia. Also, patient's adherence to treatment was poor, with only 34.4% of patients receiving treatment. Considering the patients who were not treated, although there was an indication for treatment, it was shown that being under 50 was a risk factor [26]. These studies report that patients with PsA have insufficient education and awareness about CV risk by inflammatory disease [69].

Systemic inflammation

Traditional cardiovascular risk factors cannot precisely explain increased cardiovascular morbidity and mortality in patients with PsA, and chronic increased inflammation, a

non-traditional risk factor, may act as an independent risk factor [70]. The effect of systemic inflammation on CV events is essential in many diseases, including PsA. In a study comparing RA, PsA, and axSpA patients, major MACEs were not different, suggesting that inflammation drives the increased risk of CV disease rather than a particular condition [5].

Carotid plaques were more common in the presence of nail involvement in PsA, and it was thought that nail involvement might be associated with severe skin involvement and systemic inflammation [71]. Similarly, patients with lower disease activity and minimal disease activity showed less carotid plaque and lower carotid intima thickness, demonstrating that systemic inflammation was a significant risk factor [11, 32].

Atherosclerosis

In recent years, there have been publications on subclinical atherosclerosis in PsA. These studies frequently use carotid artery intima-media thickness, plaques in the carotid, and the ankle-brachial index for subclinical atherosclerosis [11, 32, 33, 72–75]. In a study from Turkey to evaluate the impact of rheumatologic disease on endothelial dysfunction and subclinical atherosclerosis, PsA, RA, and healthy controls without previous CV disease or traditional risk factors were included. The percentage of brachial artery flow-mediated dilatation, a non-invasive indicator of endothelial dysfunction, was lower in PsA and RA patients than in healthy controls. These findings indicate that endothelial function is impaired in patients with PsA and RA. This study also confirmed the relationship between atherosclerosis pathogenesis and inflammation, showing that CRP levels and carotid intima-media thickness were positively correlated. Chronic immune-mediated inflammatory diseases were considered predisposing factors for the development of early atherosclerosis [33]. In a prospective study evaluating the effect of controlling increased inflammation and achieving low disease activity on atherosclerosis, patients with low disease activity according to the Psoriatic Arthritis Disease Activity Score (PASDAS) and Minimal Disease Activity (MDA) were more likely to have less plaque progression and change in mean intima-media thickness over 2 years. There was no difference between the patients with and without low disease activity, according to the Disease Activity Index for Psoriatic Arthritis (DAPSA). In multivariate analysis, achieving MDA had a protective effect on the progression of plaque, intima-media thickness, and total plaque area. The decrease in atherosclerosis associated with low disease activity in PASDAS and MDA may be related to the increased inflammation of components such as dactylitis and enthesitis in these scales [32]. Similarly to these results, the ankle-brachial index was lower in PsA than in healthy controls indicating subclinical atherosclerosis [72].

In a study evaluating CV risk factors and carotid plaques, age [OR 1.08 (1.03–1.13), $p < 0.001$], smoking [OR 4.26

(1.44–12.65), $p = 0.01$], enthesitis [OR 3.76 (1.36–10.40), $p = 0.01$], and erosive disease [OR 5.23 (1.33–20.50), $p = 0.02$] were factors associated with subclinical atherosclerosis [11]. On the other hand, only age was associated with subclinical atherosclerosis in patients with different kinds of arthritis, including PsA [73].

Cardiovascular risk scoring in PsA

CV risk scoring and risk score calculation are the cornerstones in predicting adverse CV events in all patients. Moreover, risk calculation plays an essential role in patient-specific treatment guidelines. Still, current risk-scoring tools have some limitations in rheumatic patients as they are designed for the general population. While these general scores include age, gender, blood pressure, lipid profiles, smoking status, and diabetes, they do not include factors that play an essential role in CV diseases for rheumatological diseases. Among these, CRP, which reflects inflammation and has a critical role in PsA and other inflammatory disorders, is not included in these scores.

Additionally, corticosteroids, nonsteroidal anti-inflammatory drugs, and factors such as obesity in PsA may also increase the CV risk. Thus, almost all the risk scoring systems do not account for systemic inflammation except Reynolds risk score, which includes high-sensitivity CRP. For this reason, EULAR recommended multiplying traditional risk scores such as the Framingham risk score by 1.5, first in RA and then in PsA and AS [76]. However, there is still suspense in this regard. In a large Italian cohort comparing the five CV risk scoring system in the PsA, all scores underestimated the CV risk. In all scores, most patients with CV events were in the low or low-intermediate risk group. As a result of the study, the cut-offs of these scoring systems should be determined specifically for these patient groups [13]. In another study that evaluated CV risk scores but also compared them with RA and the general population, four CV risk scores (Framingham, Regicor, Dorica, and Score) were similar between RA and PsA, and there was also a good concordance between Framingham and Dorica ($k = 0.709$; $p < 0.001$) [77]. Although all these risk-scoring systems are compatible, they cannot fully assess the CV risk in patients in the inflammatory group. For this reason, in many studies, in addition to these scoring, carotid ultrasound evaluation may be a part of the CV evaluation, as all these CV risk scoring systems underestimate the risk [78–80].

Conclusion

PsA is associated with an increased risk of cardiovascular disease due to traditional CV risk factors, increased systemic inflammation, and probably autonomic system dysfunction,

although not fully demonstrated. However, limitations in explaining CV risk in these patient groups complicate patient assessment as cardiovascular risk factors are linked to the morbidity and mortality of PsA. Improving an optimal screening and management strategy for CV disease is essential.

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Declarations

Disclosures None.

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