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The epidemiology of psoriatic arthritis: A literature review

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A B S T R A C T

Psoriatic arthritis (PsA) is a chronic, progressive musculoskeletal disease that affects 0.1%–1% of the general population and ~20% of patients with psoriasis. Significant differences exist in epidemiological estimates between studies, likely related to methodological and geographic differences. While most studies show an increase in prevalence over recent years, the underdiagnosis of PsA persists. Studies suggest that a complex interaction of multiple factors is involved in the development of PsA in patients with psoriasis and a single factor may not be able to effectively define at-risk patients with PsA. Modification of some risk factors such as weight loss may help in the prevention of the disease and improved outcomes.

Introduction

Psoriatic arthritis (PsA) is a chronic, progressive inflammatory disease that affects the skin, joints, and entheses. Once thought to be a benign disorder, it is now well established as a systemic inflammatory disease and can lead to serious joint damage and disability [1]. It usually occurs in patients with psoriasis, although in 10%–15% of patients, arthritis occurs before psoriasis [2,3] and in many cases,

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psoriasis and arthritis appear within the same time period [4]. Data on the epidemiology of PsA among the general population and patients with psoriasis are contradictory due to differences in the geographic location, target population, methodologies, and definition of PsA used in the studies [5]. Similarly, it is important to identify patients at increased risk of development of PsA and associated factors. In this review, we will discuss the epidemiology of PsA, which includes its incidence, prevalence, risk factors, and mortality.

Prevalence and incidence of PsA

Prevalence and incidence of PsA in the general population

The reported prevalence of PsA ranges from 0.1% to 1% in the general population around the world [6,7]. A 2018 systematic review and meta-analysis found the prevalence of PsA was 133 (95% CI,107–164) per 100,000 people (or 0.13%) in the general population [8]. High heterogeneity was observed between the included studies in the review, related in part to variability in the geographic region and case definition of PsA. Significant variability in the prevalence of PsA has been observed across studies from different geographic regions. The estimated prevalence of PsA was 1 and 670 per 100,000 in Japan [9] and Norway [10], respectively. Moreover, the prevalence also varies between different countries within a subcontinent. For example, in Europe, the prevalence was 20 and 670 per 100,000 in Sweden and Norway, respectively [10,11]. The prevalence was much lower in Asia: 0.1, 2, and 4 per 100,000 in Japan [9], China [12], and Taiwan [13], respectively (Table 1). The reported lower prevalence in Asia could be due to underdiagnoses [35]. However, differences in estimates between studies are also possibly related to factors such as genetic background, environmental factors (climate and infections), lifestyle (smoking, alcohol intake, and obesity), and dietary habits (Mediterranean diet and fish oil consumption) [36].

Methodological differences also exist between studies. In particular, the case definition of PsA varies by study. While the development of ClASsification of Psoriatic ARthritis (CASPAR) criteria in 2006 has allowed for some uniformity [37], only a few studies have used CASPAR criteria [10,12,22,23,36] as this requires physical examination of the patient (often by a rheumatologist). Other studies used different classification criteria that include diagnostic coding algorithms, diagnosis of psoriasis plus arthritis, and older criteria such as the European Spondyloarthropathy Study Group, Moll and Wright, and Vasey and Espinoza, which have shown inadequate sensitivity and specificity for PsA [8,38]. Among the various methods for case ascertainment, the lowest estimates were derived from studies using International Classification of Disease (ICD) codes to identify PsA cases, the highest prevalence was described in studies where self-reported diagnoses of PsA were used [6,39]. These factors make it difficult to compare or combine results from these studies.

There is relatively limited data on the incidence of PsA in the general population. The above-mentioned meta-analysis reported an incidence of 8.26 (95% CI, 41–167) per 100,000 in the general population [8]. The incidence of PsA is approximately 6.0–8.0 per 100,000 in most European countries [15,17,20,21,23]. However, similar to the prevalence estimates, reported incidence varies widely with the geographic location. The incidence of PsA was 0.1 and 43.1 per 100,000 in Japan [9] and Norway [10], respectively. The incidence (per 100,000) was lower in Greece (3.02) [18] and Czech-republic (3.60) [24] and higher in Israel (10.9) [30], Canada [13,35,36](29), Finland (23.10) [19], and Norway (43.10) [10].

Time trends in the incidence and prevalence of PsA in the general population

Most studies examining trends of PsA prevalence show an increase in prevalence over recent years [13,30,40]. While a higher male prevalence was reported in Norway [21] and Argentina [25], female predominance was noted in Denmark [27] and the Czech Republic [24]. Introduction of CASPAR criteria in 2006, increased awareness and recognition of PsA, and increased use of advanced imaging (e.g., ultrasound and magnetic resonance imaging) could have most likely contributed. Alternatively, a true increase in disease expression is possible. While the proportion of male and female patients with PsA

Table 1
Incidence of psoriatic arthritis in the general population.

Author, Year of publication	Study period	Geographic area	Study Design (data source)	Population	PsA case definition	Number of cases/ total number of patients	Incidence (95% CI) - per 100,000	M/F Ratio
Kaipiainen-Seppänen, 1996 [14]	1990	Finland	Retrospective (The nationwide sickness insurance scheme)	16+	Arthritis + psoriasis	65/1 million	6.1 (4.6,7.6)	1.3 (37/28)
Kaipiainen-Seppänen, 2000 [15]	1995	Finland	Retrospective	16+	Arthritis + psoriasis	74/1 million	6.8 (5.4, 8.6)	1.2 (40/34)
Shbeeb, 2000 [16]	1982–1991	Olmsted County, MN, USA	Retrospective (Rochester Epidemiology Project)	16+	Psoriasis + Arthritis	66	6.59 (4.99, 8.19)	0.9 (32/34)
Hukuda, 2001 [9]	1985–1996	Japan	Retrospective (Nationwide Hospital and Clinics)	16+	Psoriasis + Arthritis	126/101,100,000	0.06	NR
Söderlin, 2002 [17]	1999–2000	Sweden	Prospective (Växjö Central Hospital)	16+	Psoriasis + Arthritis	11/132,000	8 (4,15)	0.4 (3/8)
Alamanos, 2003 [18]	1982–2001	Northwest Greece	Retrospective (Ioannina University Hospital and the Ioannina General Hospital, and from patients referred to private rheumatologists)	16+	ESSG	221/488,435	1.96 (0.47, 3.45) 1982–1991 3.76 (2.32, 5.26) 1992–2001 3.02 (1.55, 4.49) Mean annual	0.9 (108/113)
Savolainen, 2003 [19]	2000	Finland	Prospective (the Municipal Hospital, or the University Hospital)	16+	Peripheral arthritis with psoriasis, excluding RF-positive polyarthritis or spondylitis with psoriasis	16/69,600	23.1 (13.2, 37.5)	0.6 (6/10)
Pedersen, 2008 [20]	1994–2002	Denmark	Cross-sectional study population-based study (Danish Twin Registry)	20+	M&W and CASPAR	54/21,293 (M&W) 50/21,293 (CASPAR)	6 (3,11)	1.1 (26/24)
Nossent, 2009 [21]	1978–1996	Norway	Retrospective Observational study (The Department of Rheumatology at the University Hospital of northern Norway)	16+	ICD-9/Moll and Wright	232/177,640	6.9 (3.5, 11.7)	1.4 (135/97)
Wilson, 2009 [22]	1970–1999	Olmsted County, MN, USA	Longitudinal, retrospective, population-based cohort study from REP.	18+	CASPAR	147/124,277	7.2 (6, 8.4)	1.6 (90/57)

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Table 1 (*continued*)

Author, Year of publication	Study period	Geographic area	Study Design (data source)	Population	PsA case definition	Number of cases/ total number of patients	Incidence (95% CI) - per 100,000	M/F Ratio
Soriano, 2011 [23]	2000–2006	Argentina	Retrospective (University Hospital-based Health Management Organization)	18+	CASPAR	35/138,288	6.26 (4.2, 8.3)	1.9 (23/12)
Hanova, 2010 [24]	2002–2003	Czech Republic	Prospective Population-based study (state hospitals and private practices)	16+	Vasey and Espinoza criteria	7/154,374	4.6 (1.8, 9.4) >16 3.6 (1.4, 7.6) age standardized IR	1.3 (4/3)
Hoff, 2013 [25]	2000–2008	Norway	Retrospective (NordTrøndelag Health Study III)	20+	CASPAR	188/50,806	35.9 (30.2, 41.6).	0.9 (NR)
Dönmez, 2015 [26]	2000–2012	Turkey	Retrospective (Trakya University Medical Faculty)	16+	CASPAR	172/616,000	2.8 (NR)	0.7 (2/3)
Egeberg, 2017 [27]	1997–2011	Denmark	Retrospective (Danish National Patient Register)	20+	ICD-8 and ICD-10	12,719/5.7 million	7.3 in 1997 to a maximum of 27.3 in 2010.	0.8 (NR)
De Socio, 2017 [28]	2014–2016	Italy	Retrospective (Rheumatology Outpatient Clinic of Campobasso)	18+	CASPAR	19/50,000	22.59	1.1 (10/9)
Sewerin, 2018 [29]	2009–2012	Germany	Retrospective (Statutory health insurance data)	NR	ICD codes	127,000–156,000/ 65 million	Male: 13.81–14.88 (2009), 11.59 –12.54 (2010), 9.59 –10.39 (2011), 9.84 –10.49 (2012). Female: 18.12 –19.14 (2009), 5.23 –16.14 (2010), 12.03–12.80 (2011), 11.76 –12.38 (2012)	0.8 (2009) 0.8 (2010) 0.8 (2011) 0.9 (2012)
Eder, 2018 [30]	2006–2015	Israel	Retrospective Population-based cohort study (Clalit Health Services)	18+	ICD-9	322/2,931,119	10.9 (9.8, 12.3)	NR
Wei, 2018 [13]	2000–2013	Taiwan	Taiwan National Health Insurance Research Database	16+	ICD-9	20/79,4016 (2006) to 68/83,504 (2012)	2.45 (1.36–3.54) to 8.10 (6.09–10.11)	1.75 (2001) and 1.20 (2013)
Eder, 2019 [31]	2008–2015	Ontario, Canada	Retrospective population-based cohort study (Ontario Health administrative databases)	20+	ICD-9 &10	11,441/10.9 million	13 to 15	NR

Hocevar, 2019 [32]	2014–2016	Slovenia	Retrospective (University Medical Center Ljubljana)	18+	CASPAR	115/704,342	5.4 (4.5, 6.5)	0.9 (57/58)
Muilu, 2019 [33]	2000–2014	Finland	Retrospective (Social Insurance Institution)	18+	ICD-10	6702/58,405	9 (2000–2004) 11 (2005–2009) 13 (2010–2014)	1.1 (12/11)
Pina Vegas, 2020 [34]	2015–2018	France	Retrospective (National hospital discharge database)	18+	ICD-10	NR	8.4	NR

Legend: PsA - psoriatic arthritis, M/F - male to female, F/U - follow up, PsA - psoriatic arthritis, NR - not reported, HICDA - Hospital Adaptation of International Classification of Diseases, CASPAR - the Classification of Psoriatic Arthritis, ICD - International Classification of Diseases, ESSG - European Spondylarthropathy Study Group criteria, M&W - Moll and Wright criteria, RF - rheumatoid factor, and REP - Rochester Epidemiology Project (medical records linkage system).

has been traditionally regarded as being mostly equal, slight variations in the sex proportion have been reported between studies.

Fewer studies that have examined trends in incidence over time show disparate results. Studies from the US (1970–1999 from Olmsted County, MN) [22], Denmark (1997–2011) [27], and Taiwan (2000–2013) [13] report increase in incidence. Other studies from Ontario, Canada (2008–2015) [40], and Israel (2006–2015) [30] show relatively stable incidence over time.

The data on sex ratio over time also appears disparate. While higher incidence in men was observed in the Olmsted County, US (1970–1999) [22], Norway (1978–1996) [21], Argentina (2000–2006) [23], and the Czech Republic (2002–2003) (27); Denmark (1998–2010) [27] and Taiwan [13] noted an increase in female predominance. Both sexes had a similar increase in incidence over time (2006–2015) in Israel [30]. Differences in study periods, geographic regions, and disease characteristics might have accounted for the disparate results.

Prevalence and incidence of PsA among patients with psoriasis

Similar wide variability in the prevalence of PsA is observed in patients with psoriasis. Alinaghi et al. reported a pooled PsA prevalence of 19.7% (95% CI 18.5%–20.9%) in patients with psoriasis in a 2019 systematic review and meta-analysis [41]. The prevalence of PsA was 21.6% in adult patients with psoriasis, and much lower in children and/or adolescents with psoriasis at 3.3%. Interestingly, a dose-response effect was also noted with the prevalence of PsA being higher in patients with moderate to severe psoriasis than that of mild psoriasis (24.6% vs.15.8%). The prevalence of PsA in psoriasis patients varied slightly between different subcontinents: 22.7% in Europe, 21.5% in South America, 19.5% in North America, 15.5% in Africa, and 14.0% in Asia [41].

There are fewer studies on the incidence of PsA among patients with psoriasis. The incidence of PsA in patients with psoriasis ranged from 0.27 to 2.7 per 100 person-years with the lowest estimates in Olmsted County, US (1970–1999) [42] and highest from The UK Health Improvement Network (THIN) database (1995–2010) [43] (Table 2).

Prevalence of PsA as a subset of spondyloarthritis

Only a few studies have reported the prevalence of PsA among patients with spondyloarthritis (SpA). While many studies show that PsA is the most common type of SpA, the estimated proportion of PsA in SpA differs between studies based on the study design, the definition of SpA, and geographic area. In two different studies from Finland, one from a referral-based rheumatology clinic (SpA defined by clinical and radiographic features) and the other from a nationwide insurance record, PsA was the most common form of SpA (44.4% and 37%, respectively) [15,19]. Similarly, PsA was the most prevalent SpA (42%) followed by AS (37%) in a cross-sectional population-based study of 2155 subjects from central Italy [48]. In another study from Skåne County Health Care Register, Sweden, PsA accounted for 54% of SpA cases, followed by AS (21.4%), and undifferentiated SpA (17.8%). In the study, SpA and its subtypes were defined based on ICD-10 codes [49]. Similarly, PsA was also the most common subtype of SpA (60.2%) in a prospective, multicenter cohort of SpA in Argentina (RESPONDIA-Argentina). In this study, SpA was defined based on the European Spondyloarthropathy Study Group (ESSG) criteria and subtypes were based on physician diagnosis [50]. However, in a similar study from Brazil of 1036 patients with SpA using the RESPONDIA protocol, AS was the most common subtype (72.3%), followed by PsA (13.7%) [51]. A nationwide telephone survey in France also found that AS (48%) was the most prevalent form of SpA, followed by PsA (41%). Rheumatologists confirmed the diagnosis of SpA in 29 patients among 9395 telephone interviewees, and all of them except one fulfilled the ESSG criteria [52]. Similarly, in a nationwide survey study from Japan, AS (68.3%) was the most frequent subtype followed by PsA (12.7%). The diagnosis of SpA was made by physicians based on clinical and radiographic features [9].

Table 2
Incidence of psoriatic arthritis among patients with psoriasis.

Author, Year of publication	Study period	Geographic area	Study Design (data source)	Population	PsA case definition	Number of cases/ total number of patients	Incidence (95% CI) as % of patients with psoriasis	M/F Ratio
Shbeeb, 2000 [16]	1982–1991	Minnesota, USA	Retrospective (Rochester Epidemiology Project)	16+	Psoriasis + Arthritis	66/1056	NR	0.9 (32/34)
Christophers, 2010 [44]	2006	UK, Italy, France, Spain, and Germany	Cross-sectional observational study (Patient Record Form)	NR	Psoriasis + Arthritis	19/1434	7.4	2.2 (68.3/31.7)
Wilson, 2009 [42]	1970–1999	Rochester, USA	Longitudinal, retrospective, population-based cohort study. (Rochester Epidemiology Project medical records linkage system in Olmsted County, Minnesota).	18+	CASPAR.	97/1633	Cumulative incidence of PsA following psoriasis incidence: 5 yr- 1.7% (1.0, 2.3%) 10 yr- 3.1% (2.2, 4.1%) 20 yr- 5.1% (3.7, 6.6%)	1.6 (6.4/3.9)
Eder, 2011 [45]	2006–2008	Toronto, Canada	Prospective longitudinal cohort study (The Toronto Psoriasis Cohort)	NR	Psoriasis + Arthritis	10/313	1.87 (0.71, 3.03)	0.7 (4/6)
Eder, 2016 [46]	2006–2014	Canada	A Prospective Cohort Study (The Toronto Psoriasis Cohort)	NR	CASPAR	51/464	2.7 (2.1, 3.6).	1.83 (33/18)
Elnady, 2019 [47]	NR	Saudi Arabia	Multicenter case-control study followed by prospective cohort study (two tertiary Saudi medical centers)	18+	CASPAR	9/104	4.3 (NR)	0.8 (4/5)

Legend: PsA - psoriatic arthritis, M/F - male to female, PsA - psoriatic arthritis, NR - not reported, HICDA - Hospital Adaptation of International Classification of Diseases, and CASPAR - the Classification of Psoriatic Arthritis.

Underdiagnosis and misclassification of PsA

Studies examining the prevalence of PsA in patients with psoriasis suggest that underdiagnosis is common in PsA and many patients are not diagnosed with PsA despite having the disease [5]. A 2015 systematic review showed that the prevalence of undiagnosed PsA among patients with psoriasis was 15.5% (95% CI 11.5%–19.5%) among the 12 studies included [53]. Studies from the last decade show a high prevalence of undiagnosed PsA ranging from 4.2% (Germany) to 33.6% (US) [54]. The absence of a gold standard diagnostic test for PsA and its heterogeneous manifestations make the diagnosis of PsA challenging. Moreover, patients with psoriasis often have other reasons for joint pain, such as osteoarthritis, fibromyalgia, and gout. These factors may lead to misclassification in studies using diagnostic codes. Similarly, clinic and population-based cohorts may also suffer from misclassification as a result of underdiagnosis of PsA [5]. The incidence and prevalence of PsA should therefore be interpreted in light of the potential for misclassification.

Clinical risk factors, predictors of PsA

PsA usually occurs in patients with psoriasis in the majority of patients (85%–90%) [2,3]. In most cases, there is a latency of several years before the development of arthritis, which provides an opportunity to study the risk factors for PsA. Studies suggest that a complex interaction of multiple factors is involved in this transition and a single factor may not be able to effectively define at-risk patients with PsA. Among these factors, it is important to sort out risk factors and predictors [55]. They are essentially distinguished by study design, temporality, and biological plausibility (Bradford Hill criteria) [56]. While risk factor implies causality and etiological relationship in the development of the disease, a predictor does not necessarily have to be causal but suggests that patients with this factor are more likely to develop the disease. Despite their differences, both risk factors and predictors could help identify patients likely to develop PsA [57].

It is also important to interpret the study results in the context of the study design. While longitudinal cohort studies are the ideal study design for studying risk factors occurring before the development of the outcome, they are often expensive, requiring a large number of patients and a long follow-up time. Because of their convenient design, many case-control and cross-sectional studies have described factors associated with PsA. However, several factors have to be considered while these studies are interpreted. The selection of controls is important and they should be from the same population, recall bias should be taken into account, and temporal association cannot be determined as a predictor may have temporally occurred *after* disease onset but prior to the diagnosis of PsA [58].

Psoriasis-related factors

Certain psoriasis-related factors such as psoriasis severity, nail lesions, and the involvement of certain body sites have been associated with the development of PsA [54,55]. It is unclear whether these factors are risk factors or predictors, and this has been an area of active investigation. Several studies have reported a higher prevalence of severe psoriasis in patients with PsA than that of patients with psoriasis only. A retrospective cohort study also showed an increased risk of PsA with a higher number of psoriasis sites involved (HR of 2.24 and 95% CI 1.23–4.08, for PsA in psoriasis patients with $\geq$3 affected sites) [42]. Another case-control study also showed higher odds of PsA in patients with BSA >75% (OR = 2.52 and 95% CI 1.33–4.75) [59]. Two other case-control studies, however, did not show an association [60,61]. Rouzaud et al. showed a possible association of PASI score in psoriasis and PsA in a meta-analysis of six cross-sectional studies (mean difference 3.39 and 95% CI 0.94–5.83) [62]. A few factors could explain this association. Severe skin involvement could be associated with higher systemic inflammation, ultimately leading to the development of synovio-entheseal inflammation [55]. However, detection bias cannot be ruled out as patients seeking care from a specialist are mostly those with severe psoriasis. Moreover, severe psoriasis only occurs in a minority of patients with psoriasis (~15%) and therefore would not be a sensitive marker [63].

Studies suggest that certain types of psoriasis such as nail, scalp, and inverse psoriasis are associated with the development of PsA. The prevalence of nail dystrophy is higher in patients with PsA (41–93%)

than that of patients with psoriasis only (15%–50%) [5]. In a 2014 meta-analysis, nail lesions were associated with PsA (OR 2.92 and 95% CI 2.34–3.64), particularly onycholysis (OR 2.38 and 95% CI 1.74–3.26) [62]. A more recent prospective cohort study showed that nail pitting was associated with the development of PsA (RR 2.5 and 95% CI 1.37–4.49) [46]. Nail lesions were associated with distal interphalangeal joint involvement in several cross-sectional studies [62]. It is postulated that nail involvement represents a form of enthesitis with inflammation of the nail bed or nail matrix [64]. A prospective study found that almost all psoriasis patients with subclinical enthesitis on ultrasonography had concomitant nail lesions [65].

Some studies have shown an association of psoriasis at specific locations with PsA. A retrospective cohort study from the Olmsted County, MN, USA including 1593 psoriasis patients with a mean follow-up of 13.1 (SD 8.8) years showed a higher risk of developing PsA in patients with scalp lesions (HR 3.89 and 95% CI 2.18–6.94) and intergluteal/perianal lesions (HR 2.35 and 95% CI 1.32–4.19) [42]. Among other cross-sectional studies, the prevalence of scalp lesions was also higher in patients with PsA than that of patients with psoriasis [35,66]. Three other cross-sectional studies, however, did not show an association with psoriasis at any specific locations [44,67,68]. Besides the association of inverse psoriasis with PsA in one cohort study [42], an association of specific types of psoriasis with PsA has not been described [62].

The association of duration of psoriasis with PsA has shown conflicting results. Out of six cross-sectional studies in a 2014 meta-analysis [62], only two cross-sectional studies showed an association of a longer duration of psoriasis with PsA [35,44].

Finally, non-specific musculoskeletal symptoms such as arthralgia, fatigue, and stiffness in the prodromal phase of PsA are important factors associated with the development of PsA [69,70]. They might signify early synovio-entheseal inflammation, underscoring the importance of collecting patient-reported outcomes in psoriasis.

Family history of PsA

Individuals with a family history of psoriasis or PsA have an increased risk of PsA [54]. Moreover, psoriasis patients with a history of PsA have a significantly increased risk to develop PsA [55]. A case-control study showed that the odds of PsA was increased in psoriasis patients with a family history of PsA (OR 20.5 and 95% CI, 2.49–169.10) [59] and the recurrence risk ratio (λ) is approximately 40 times higher in those with a history of PsA in a first-degree relative [71–73]. The λ seems to be significantly higher than other autoimmune diseases such as RA, SLE, and even psoriasis [55]. Considering this strong association, screening for family history of PsA among patients with psoriasis has been proposed in dermatology guidelines [74]. Moreover, this population of psoriasis patients with a first-degree relative with PsA provides a unique resource to study the clinical, demographic, and molecular differences in those that progress to develop PsA as compared to those that do not [55].

Environmental factors

Environmental factors such as physical/emotional stress or trauma and infections are thought to play a role in the development of PsA in genetically predisposed individuals. Eder et al. in a case-control study of 159 subjects in each group, showed that lifting heavy loads (OR 2.8 and 95% CI 1.51–5.05), injuries (OR 2.1 and 95% CI 1.11–4.01), and infections requiring antibiotics (OR 1.7 and 95% CI 1.00–2.77) were associated with the development of PsA [60]. Physical trauma is a well-described trigger of PsA. Injury/trauma in patients with psoriasis can lead to the development of new psoriasis plaques at those sites, which is referred to as a Koebner phenomenon. Disease expression in PsA is also postulated to be related to abnormal responses to physical stress on the joints ("deep Koebner" response). In a proof of concept study, mechanical loading was avoided with tail suspension (hind limb unloading) in experimental $TNF^{\Delta ARE}$ mouse models in which chronic, deregulated TNF production leads to arthritis and a Crohn's-like ileitis. Significantly lower inflammatory arthritis, Achilles enthesitis, and new bone formation were noted when compared with weight-bearing controls [75]. Several prospective studies have described an association of trauma in psoriasis patients with the development of PsA [76–78]. A matched cohort study from the UK THIN database showed that physical trauma

(manually reviewed trauma codes) in patients with psoriasis was associated with an increased risk of PsA when compared with controls (HR 1.32 and 95% CI 1.13–1.54). In the study, while bone and joint trauma were associated with an increased risk of PsA (HR 1.46, 95% CI 1.04–2.04 and HR-1.50, 95% CI 1.19–1.90, respectively), nerve and skin trauma were not [78]. Similarly, a case-control study showed that injuries that require a medical consultation (OR 2.53 and 95% CI 1.1–6.0) were associated with PsA as compared to patients with psoriasis only [79]. The same study also showed an association of recent shifting houses (OR 2.3 and 95% CI 1.2–4.4) with PsA. The association of psychological stress with the onset of PsA, other autoimmune diseases, and psoriasis has been described in several studies [80–82]. However, studying the association with emotional stress is challenging and would require long-term standardized assessment of stress. Similarly, infections have been long studied as triggers for autoimmune diseases. Association of infections with the development of arthritis is seen in reactive arthritis, which is a form of SpA. Infections such as diarrhea and those that require hospitalization have been reportedly associated with PsA [60]. Similarly, both psoriasis and PsA were found to be more common in patients infected with human immunodeficiency virus (HIV) than in controls in early studies of HIV. In those studies, psoriasis and PsA often occurred right before the development of opportunistic infections in HIV [83]. However, most of the data on these environmental risk factors come from case-control and longitudinal cohort studies, which will be required to better address these potential risk factors.

Smoking

Smoking is a risk factor for psoriasis; however, the association of smoking with the development of PsA has shown conflicting results. Most studies have shown an inverse association of smoking with the development of PsA [45,79,84], except Nurses' Health Study II that showed a positive association of smoking with PsA in female patients with psoriasis [85]. The inverse relationship could be secondary to "collider bias," where an intermediate condition (psoriasis) is related to both the exposure (smoking) and the outcome (PsA) [86]. Smoking may increase the risk of PsA indirectly by increasing the risk of psoriasis and also have a direct effect on the risk of PsA in the general population, leading to spurious results in case-control studies. Therefore, while studying the association of smoking with PsA, it is important to account for psoriasis (causal intermediate variable) [86]. The distribution of different PsA subgroups may also have led to disparate results. In a prospective cohort study from PsART (Psoriatic Arthritis Registry of Turkey), smoking was found to be a risk factor for axial PsA, but not other PsA subtypes [87].

Alcohol

Similarly, studying the association of alcohol with PsA can be challenging as consumption can change over time and a nonlinear relationship (J-shaped dose-effect curve) has been described in other studies such as psoriasis and RA [55]. Data from the Nurses' Health Study showed that women with the highest level of alcohol intake had a substantially elevated risk of PsA (HR 4.45 and 95% CI 2.07–9.59), but the risk was lower among moderate drinkers (HR 0.69 and 95% CI 0.49–0.99) than that of non-drinkers at baseline. Also, this association was not significant among patients with psoriasis [88].

Comorbidities

Several comorbidities such as obesity, hyperlipidemia, depression, thyroid disease, and uveitis, have been associated with an increased risk to develop PsA (Table 3) [55]. Association of obesity with the development of PsA has been described in four large cohort studies [43,92,93,95], three of them showing a dose-effect of BMI [43,93,95]. Moreover, a recent study showed that BMI reduction after gastric bypass surgery was associated with a lower risk to develop psoriasis and PsA [96]. Another study by Maglio et al. also showed a protective effect of bariatric surgery on psoriasis, but no reduction in the risk of PsA [97]. Furthermore, Green et al. showed that patients with psoriasis who lost weight were less likely to develop PsA [94]. Studies showing improvement in disease activity and treatment response in PsA following weight loss also indirectly support the association of obesity with PsA [98].

Table 3
Clinical risk factors/predictors of psoriatic arthritis (only cohort and case-control studies).

Author Year	Study design	Reference group	Predictor	Effect size (95% CI)
Comorbidities				
Wu 2014 (89)	Cohort Study	General Population	Hypercholesterolemia*	HR 1.6 (1.14-2.24)
Egeberg 2015 (90)	Cohort Study	General Population	Uveitis*	IRR 3.77 (2.66-5.34)
Eder 2016 (46)	Cohort Study	Psoriasis	Uveitis ever (TV)*	RR 31.5 (5.06-195.8)
Eder 2016 (46)	Cohort Study	Psoriasis	Thyroid disease (TV)	RR 2.27 (1.04-4.95)
Lewinson 2017 (91)	Cohort Study	Psoriasis	Depression*	HR 1.41 (1.10-1.80)
Obesity				
Soltani- Arabshahi 2010 (92)	Case Control	Psoriasis	BMI (continuous) at age 18 yrs old	OR 1.06 (1.02-1.10)
Li 2012 (93)	Cohort Study	General Population	BMI ≥ 35.0 vs normal (BMI <25) * (TV)	RR 6.46 (4.11-10.16)
Li 2012 (93)	Cohort Study	General Population	BMI at age 18 years, ≥ 30.0 vs normal (<25)*	RR 3.55 (1.75-7.23)
Li 2012 (93)	Cohort Study	General Population	BMI 30.0- 34.9 vs normal (<25) (TV)*	RR 3.12 (1.90-5.11)
Love 2012	Cohort Study	General Population	BMI ≥ 35.0 vs normal (<25)*	RR 1.96 (1.68-2.29)
Li 2012 (93)	Cohort Study	General Population	BMI at age 18 years, 23.0- 24.9 vs normal (21-22.9)*	RR 1.93 (1.11-3.37)
Li 2012 (93)	Cohort Study	General Population	BMI 25.0- 29.9 vs normal (<25)* (TV)	RR 1.83 (1.15-2.89)
Love 2012 (43)	Cohort Study	General Population	BMI 30.0- 34.9 vs normal (<25)*	RR 1.57 (1.38-1.80)
Love 2012 (43)	Cohort Study	General Population	BMI 25.0-29.9 vs normal (<25)*	RR 1.17 (1.04-1.31)
Li 2012 (93)	Cohort Study	Psoriasis	BMI ≥ 35.0 vs normal (<25)*(TV)	RR 2.98 (1.86-4.78)

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Table 3 (*continued*)

Li 2012 (93)	Cohort Study	Psoriasis	BMI 30.0 - 34.9 vs normal (<25)* (TV)	RR 1.9 (1.13-3.18)
Li 2012 (93)	Cohort Study	Psoriasis	BMI 25.0 - 29.9 vs normal (<25)* (TV)	RR 1.8 (1.12-2.88)
Love 2012 (43)	Cohort Study	Psoriasis	BMI ≥ 35.0 vs normal (<25)*	RR 1.48 (1.20-1.81)
Love 2012 (43)	Cohort Study	Psoriasis	BMI 30.0 - 34.9 vs normal (<25)*	RR 1.22 (1.02-1.47)
Eder 2017 (69)	Case Control	Psoriasis	Obese (BMI ≥30) vs normal (BMI 18-25)*	OR 2.2 (1.47-3.25)
Eder 2017 (69)	Case Control	Psoriasis	Obese (BMI >30) vs not obese (BMI <30)*	OR 1.77 (1.23-2.56)
Lewinson 2017 (91)	Cohort Study	Psoriasis	Obese (BMI >30) vs not obese (BMI ≤30)*	HR 1.61 (1.40-1.86)
Thomsen 2021 (95)	Cohort Study	General Population	BMI ≥30.0 vs. normal (18.5-24.9)*	HR 2.46 (1.65-3.68)
Thomsen 2021 (95)	Cohort Study	General Population	Waist circumference: women ≥ 81 cm men ≥ 95 cm vs. women < 81 cm men < 95 cm	HR 1.75 (1.30-2.35)
Green 2020 (94)	Cohort Study	General Population	BMI 25.0-29.9 vs normal (<25)*	OR 1.76 (1.41–2.19)
Green 2020 (94)	Cohort Study	General Population	BMIs of 30.0-34.9 vs normal (<25)*	OR 2.04 (1.60–2.60)
Green 2020 (94)	Cohort Study	General Population	BMIs of ≥35.0 vs normal (<25)*	OR 2.42 (1.85–3.16)
Smoking				
Li 2012 (85)	Cohort Study	General Population	Current Smokers*	RR 3.12 (2.07-4.69)
Li 2012 (85)	Cohort Study	Psoriasis	Current smoker vs nonsmoker *	RR 1.62 (1.00-2.63)
Eder 2012 (84)	Case Control	Psoriasis	Current smoker vs nonsmokers*	OR 0.57 (0.41-0.81)

Lewinson 2017 (91)	Cohort Study	Psoriasis	Smoking status*	HR 0.87 (0.80-0.94)
Nguyen 2018 (86)	Cohort Study	General Population	Current smoker vs nonsmoker*	HR 1.27 (1.19-1.36)
Nguyen 2018 (86)	Cohort Study	General Population	Current smoker vs nonsmoker*	HR 1.23 (1.16-1.29)
Nguyen 2018 (86)	Cohort Study	Psoriasis	Current smoker vs nonsmoker*	HR 0.88 (0.83-0.94)
Alcohol status				
Green 2020 (94)	Cohort Study	General Population	Moderate drinker vs. nondrinker*	OR 1.57 (1.16-2.11)
Trauma				
Thorarensen 2017 (78)	Cohort Study	General Population	Joint Trauma*	HR 1.50 (1.19-1.90)
Thorarensen 2017 (78)	Cohort Study	General Population	Bone Trauma*	HR 1.46 (1.04-2.04)
Thorarensen 2017 (78)	Cohort Study	General Population	All Trauma*	HR 1.32 (1.13-1.54)
Nail				
Wilson 2009 (42)	Cohort Study	Psoriasis	Nail dystrophy*	HR 2.24 (1.26-3.98)
Soltani- Arabshahi 2010 (92)	Case Control	Psoriasis	Nail involvement	OR 1.76 (1.25-2.47)
Eder 2016 (46)	Cohort Study	Psoriasis	Nail pitting	RR 2.21 (1.24-3.92)
Psoriasis Duration				
Li 2012 (93)	Cohort Study	Psoriasis	Duration, years ≥25 *	RR 3.12 (1.96-4.97)
Li 2012 (93)	Cohort Study	Psoriasis	Duration, years ≥25*	RR 1.9 (1.09-3.33)
Li 2012 (93)	Cohort Study	Psoriasis	Duration, years <25*	RR 1.7 (1.19-2.42)
Eder 2012 (84)	Case Control	Psoriasis	Duration of psoriasis, 16-21 years vs ≤5 *	OR 0.46 (0.28-0.74)
Eder 2012 (84)	Case Control	Psoriasis	Duration of psoriasis, ≥21 years vs ≤5 *	OR 0.37 (0.26-0.53)

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Table 3 (*continued*)

Psoriasis Location				
Wilson 2009 (42)	Cohort Study	Psoriasis	Site of psoriasis, scalp*	HR 3.75 (2.09-6.71)
Wilson 2009 (42)	Cohort Study	Psoriasis	Site of psoriasis, intergluteal/perianal*	HR 1.95 (1.07-3.56)
Psoriasis Quality				
Soltani- Arabshahi 2010 (92)	Case Control	Psoriasis	Koebner phenomenon	OR 1.59 (1.17-2.14)
Psoriasis Severity				
Wilson 2009 (42)	Cohort Study	Psoriasis	No of affected sites ≥3 sites vs 1 site	HR 2.24 (1.23-4.08)
Wilson 2009 (42)	Cohort Study	Psoriasis	No of affected sites ≥3 sites vs 1 site	HR 2.24 (1.23-4.08)
Tey 2010 (59)	Case Control	Psoriasis	Severity of psoriasis (maximum BSA), 76-100%*	OR 2.52 (1.33-4.75)
Eder 2012 (84)	Case Control	Psoriasis	Severe psoriasis: yes vs no*	OR 2.07 (1.47-2.92)
Eder 2016 (46)	Cohort Study	Psoriasis	PASI score, >20 vs. <10*	RR 5.39 (1.64-17.7)
Patient-reported Outcomes				
Eder 2017 (58)	Cohort Study	Psoriasis	Arthralgia, Female (TV)*	HR 5.91 (2.46-14.2)
Eder 2017 (69)	Cohort Study	Psoriasis	Back stiffness (yes/no), (TV)*	HR 3.71 (1.95-7.02)
Eder 2017 (69)	Cohort Study	Psoriasis	Level of fatigue (mFSS >5), (TV)*	HR 3.09 (1.76-5.53)
Eder 2017 (69)	Cohort Study	Psoriasis	Level of stiffness (VAS >2), (TV)*	HR 3.06 (1.69-5.52)
Eder 2017 (69)	Cohort Study	Psoriasis	Level of pain (VAS >2), (TV)*	HR 2.66 (1.44-4.81)
Eder 2017 (69)	Cohort Study	Psoriasis	Morning joint stiffness (yes/no), (TV)*	HR 2.25 (1.55-3.25)
Eder 2017 (69)	Cohort Study	Psoriasis	Level of physical function (SF-36 PCS <46), (TV)*	HR 1.89 (1.06-3.42)
Eder 2017 (69)	Cohort Study	Psoriasis	Level of psychological distress (SF-36 MCS <42), (TV)*	HR 1.8 (1.01-3.22)
Rech 2020 (70)	Cohort Study	General Population	Acute rheumatism*	OR 2.93 (1.76-4.86)
Rech 2020 (70)	Cohort Study	General Population	Pain in unspecific joint*	OR 1.74 (1.01-2.99)

Legend: * indicates adjustment for other covariates - Adjusted effect sizes were included whenever possible. Colors represent the strength of the association, with red shades suggesting an increased risk and green shades suggesting a decreased risk of PsA in patients with the given predictor; darker shades represent an increased effect size. For many of the predictors measured, only two categories exist (the absence or presence of the predictor), and the reference group is simply the absence of the predictor; however, for predictors for which more than two categories were assessed (for example, smoking status can include current smoker, past smoker, and nonsmoker), the comparator category is included in the predictor column. BSA - body surface area, IRR - incidence rate ratio, mFSS - modified fatigue severity scale, PASI - psoriasis area and severity index, RR - relative risk, SF-36 MCS - short form 36 mental component scale, SF-36 PCS - short form 36 physical component scale, TV - time varying exposure, and VAS - visual analogue scale (Adapted from Scher et al. [42]).

However, misclassification of osteoarthritis as PsA could be partly responsible for the association of obesity and PsA seen in these studies [99].

While other metabolic factors such as hyperlipidemia and hyperuricemia have also been described as risk factors for PsA [89,100], it is unclear if these are independently associated with the development of PsA or related to concurrent obesity. A retrospective cohort study found that physician-diagnosed hypercholesterolemia, independent of obesity, was associated with the development of PsA (HR 1.58 and 95% CI 1.13–2.23) [89]. Meanwhile, the association of other comorbidities such as depression and thyroid disease is difficult to explain pathophysiologically, although plausible [46,91].

The role of extra-articular manifestations of psoriatic disease, such as uveitis and inflammatory bowel disease (IBD), in the development of PsA is complicated (Fig. 1). The risk of uveitis seems to be higher in PsA (IR 3.77 and 95% CI 2.66–5.34) than that of psoriasis only (IR for mild psoriasis: 1.59 and 95% CI 1.32–1.91; IR for severe psoriasis: 2.17, 95% CI 1.40–3.38) [90]. Similarly, the risk of IBD appears to be higher in PsA than that in psoriasis only [101,102]. We did not find any study that specifically examines IBD as a risk factor or predictor for PsA. Because of the increased prevalence of these extra-articular manifestations in PsA as compared to psoriasis, the presence of these factors may possibly help identify at-risk patients with psoriasis.

Mortality in PsA

Overall mortality in PsA

Studies on mortality in PsA from observational studies show evidence that is contradictory. Only a few prospective cohort and population-based studies have examined the mortality risk in PsA (Table 4). Earlier studies from the prospective University of Toronto PsA cohort showed a higher standardized mortality rate (SMR) from 1.4 to 1.6 [103,104]. While overall mortality was higher than the general population in nearly four decades of follow-up, the mortality risk decreased over time [103,104]. During the study periods, 1978–1986, 1987–1995, and 1996–2004, the SMRs were 1.89, 1.83, and 1.21, respectively. A more recent study (1978–2017) from the same cohort by Elalouf et al. showed no increase in overall mortality rate (SMR 0.92 and 95% CI 0.81–1.05) in PsA [112]. It is possible that increased recognition, early diagnosis, and better treatment may have improved the mortality in PsA over time.

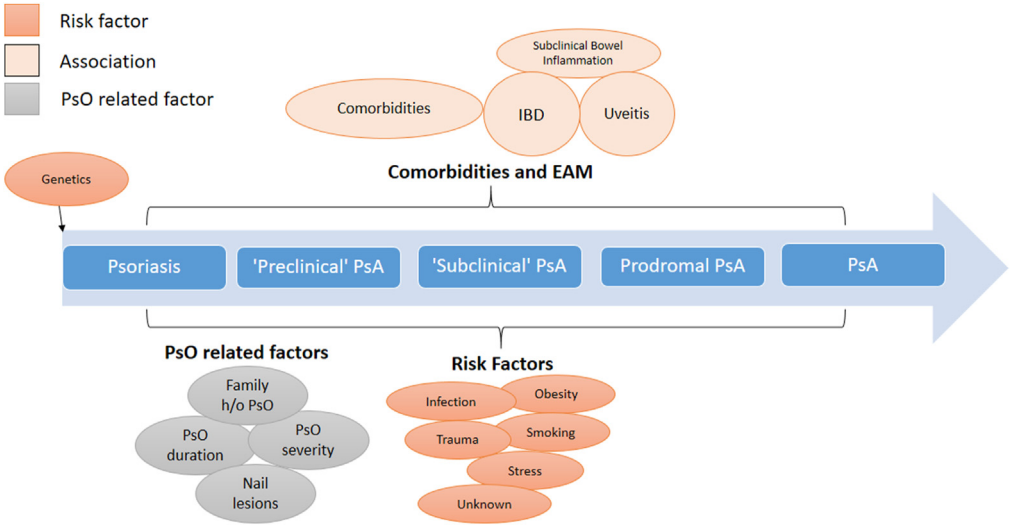

Fig. 1. The complex relationship of different variables with the development of psoriatic arthritis.

Table 4
Mortality of psoriatic arthritis – overall and cause-specific.

Author, Year	Years of observation	Geographic area	Study Design (data source)	Population	No. of PsA pts.	PsA case definition	Comparison group	Assessment of mortality/outcome definition	Mortality rate (95% CI)
All-cause (overall)									
Wong 1997 [103]	1978–1993	Canada	Prospective cohort (University of Toronto PsA clinic)	16+	428	Arthritis + psoriasis	General population of Ontario	Clinic's computerized database/ICD-9	SMR 1.62 (1.21 –2.12)
Ali 2007 [104]	1978–2004	Canada	Prospective cohort (University of Toronto PsA clinic)	43.7 ± 13.4	680	Arthritis + psoriasis	General population of Ontario	Death certificates	SMR 1.36 (1.12, 1.64)
Shbeeb 2000 [16]	1982–1991	US	Population-based, retrospective cohort (REP, Olmsted County, MN).	16+	66	Arthritis + psoriasis	General population of the Olmsted Country, USA	NR	No increased mortality SMR –NR
Alamanos 2003 [18]	1982–2001	Northwest Greece	Population-based, retrospective (Loannina Hospitals and patients referred to private rheumatologists)	16+	221	ESSG	General population of Greece	NR	4 deaths SMR not available
Wilson 2009 [22]	1970–1999	Minnesota, US	Population-based, retrospective cohort (REP, Olmsted County, MN).	18+	147	CASPAR	2000 US White population	NR	SMR 0.91 (0.58, 1.37)
Ahlehoff 2011 [105]	1997–2006	Denmark	Nationwide population-based cohort (Danish NPR)	18+	607	Arthritis + psoriasis	General population of Denmark	National Causes of Death Register/ICD-10	RR 1.74 (1.32, 2.30)
Buckley 2010 [106]	1985–2007	Bath, UK	Retrospective cohort, single-center (Royal National Hospital, Bath)	NR	453	Arthritis + psoriasis	General population of the UK	Death certificates from the Registry of Births, Marriages, and Deaths/NR	SMR 0.82 (0.58, 1.13)
Mok 2011 [107]	1999–2008	Hong Kong, China	Retrospective hospital registry (CDARS - outpatient clinics and inpatient admissions)	NR	778	ICD -9	General population of Hong Kong	Death Registry/ICD-9	SMR 1.59 (1.16, 2.03)
Ogdie 2014 [108]	1994–2010	UK	Population-based cohort study (THIN database)	18+	8706	Read code	General population of the UK	Specific codes recommended by Cegedim, the administrators of THIN	aHR 1.02 (0.92,1.12)
Juneblad 2016 [109]	1995–2011	Sweden	Retrospective cohort from Västerbotten County, Sweden	NR	464	Arthritis + psoriasis	General population of Sweden	National Causes of Death Register and the National Inpatient Care Register/ICD-10	SMR 1.22 (0.89, 1.63)

Lee 2017 [110]	2001–2012	Taiwan	Nationwide population-based, retrospective (National Health Insurance database)	18+	9572	Psoriasis identification algorithm (Arthritis + psoriasis)	General population of Taiwan	National Death Registry/ICD-10	SMR 1.47 (1.36, 1.58)
Skov 2019 [111]	1998–2014	Denmark	Nationwide population-based cohort (Danish NPR)	NR	9817	ICD-10	General population of Denmark	Civil Registration System/ICD-10	Death rate per 1000 −1.16 (0.96, 1.36) SHR 1.06, P = 0.19
Elalouf 2020 [112]	1978–2017	Canada	Prospective cohort (University of Toronto PsA clinic)	NR	1490	CASPAR	General population of Ontario	Death registry and death certificates (ICD-9 and ICD-10)	SMR 0.92 (0.80, 1.05) Age specific SMR 20-39: 3.36 (1.61,8.18) 40-59: 0.97 (0.68,1.34) 60-79: 0.88 (0.73,1.06) 80 +: 0.86 (0.66,1.10)
Cardiovascular									
Wong 1997 [103]	1978–1993	Toronto, Canada	Observational prospective cohort (University of Toronto PsA cohort Registry)	NR	428	Arthritis + psoriasis	General population of Ontario	ICD-9.	SMR 1.33 (0.77, 21.53)
Alamanos 2003 [18]	1982–2001	Northwest Greece	Population-based, retrospective (Ioannina University Hospital and the Ioannina General Hospital, and from patients referred to private rheumatologists)	16+	221	ESSG	General population of Greece	NR	2/4 (50%) CV deaths SMR not available
Ali 2007 [104]	1978–2004	Canada	Prospective cohort (University of Toronto PsA Clinic)	43.7 ± 13.4	680	Arthritis + psoriasis	General population of Ontario	Death certificates	SMR 0.25
Ahlehoff 2011 [105]	1997–2006	Denmark	Observational Studies (Psoriasis cohort from Danish National Patient Register)	18+	607	Arthritis + psoriasis	General population of Denmark	National Causes of Death Register/ICD-10	RR 1.84 (1.11, 3.06)
Juneblad 2016 [109]	1995–2011	Sweden	Retrospective cohort from Västerbotten County, Sweden	NR	464	Arthritis + psoriasis	General population of Sweden	National Causes of Death Register and the National Inpatient Care Register (ICD-10)	SMR 1.64 (1.02, 2.52)

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Table 4 (*continued*)

Author, Year	Years of observation	Geographic area	Study Design (data source)	Population	No. of PsA pts.	PsA case definition	Comparison group	Assessment of mortality/outcome definition	Mortality rate (95% CI)
Ogdie 2017 [113]	1994–2010	United Kingdom	Longitudinal cohort study (THIN database)	18+	8706	Read code	General population of the UK	specific codes recommended by Cegedim, the administrators of THIN	aHR 1.09 (0.91, 1.32)
Elalouf 2020 [112]	1978–2017	Canada	Prospective (University of Toronto Psoriatic Arthritis Clinic)	NR	1490	CASPAR	General population of Ontario	Death registry and death certificates (ICD-9 and ICD-10)	SMRs for: Atherosclerosis 1.01 (0.27, 2.58) CHF 2.57 (0.94, 5.59) MI 1.11 (0.74,1.58)
Renal									
Elalouf 2020 [112]	1978–2017	Canada	Prospective (University of Toronto Psoriatic Arthritis Clinic)	NR	1490	CASPAR	General population of Ontario	Death registry and death certificates (ICD-9 and ICD-10)	SMR 11.88 (7.53,17.8)
Respiratory									
Wong 1997 [103]	1978–1993	Toronto	Observational prospective cohort (University of Toronto PsA cohort Registry)	NR	428	Arthritis + psoriasis	General population of Ontario	ICD-9	SMR 5.05 (2.40, 9.33)
Alamanos 2003 [18]	1982–2001	Northwest Greece	Retrospective (Ioannina University Hospital and the Ioannina General Hospital, and from patients referred to private rheumatologists)	16+	221	ESSG	General population of Greece	NR	1/4 deaths from Miliary TB
Ali 2007 [104]	1978–2004	Canada	Prospective cohort (University of Toronto PsA Clinic)	43.7 ± 13.4	680	Arthritis + psoriasis	General population of Ontario	Death certificates	SMR 0.1
Ogdie 2017 [113]	1994–2010	United Kingdom	Longitudinal cohort study (THIN database)	18+	8706	Read code	General population of the UK	Specific codes recommended by Cegedim, the administrators of THIN	aHR 0.97 (0.79 −1.20)
Elalouf 2020 [112]	1978–2017	Canada	Prospective (University of Toronto Psoriatic Arthritis Clinic)	NR	1490	CASPAR	General population of Ontario	Death registry and death certificates (ICD-9 and ICD-10)	SMR 98.5 (36.1, 214.4) SMR 2.46 (1.27, 4.31) Pneumonia

Malignancy									
Wong 1997 [103]	1978–1993	Toronto	Observational prospective cohort (University of Toronto PsA cohort Registry)	NR	428	Arthritis + psoriasis	General population of Ontario	ICD-9	SMR 0.73 (0.31, 1.46)
Ali (2007) [104]	1978–2004	Canada	Prospective cohort (University of Toronto PsA Clinic)	43.7 ± 13.4	680	Arthritis + psoriasis	General population of Ontario	Death certificates	SMR 0.24
Ogdie 2017 [113]	1994–2010	United Kingdom	Longitudinal cohort study (THIN database)	18+	8706	Read code	General population of the UK	Specific codes recommended by Cegedim, the administrators of THIN	aHR 1.03 (0.86, 1.25)
Juneblad 2016 [109]	1995–2011	Sweden	Registry (PsA cohort from a Västerbotten County, Sweden)	NR	464	Arthritis + psoriasis	General population of Sweden	National Causes of Death Register and the National Inpatient Care Register (ICD-10)	SMR 1.13 (0.62, 1.89)
Elalouf 2020 [112]	1978–2017	Canada	Prospective (University of Toronto Psoriatic Arthritis Clinic)	NR	1490	CASPAR	General population of Ontario	Death registry and death certificates (ICD-9 and ICD-10)	SMR 0.97 (0.72,1.28)
Injuries/poisoning/suicide									
Wong 1997 [103]	1978–1993	Toronto	Observational prospective cohort (University of Toronto PsA cohort Registry)	NR	428	Arthritis + psoriasis	General population of Ontario	ICD-9	SMR 3.54 (1.40, 7.31)
Alamanos 2003 [18]	1982–2001	Northwest Greece	Retrospective (Ioannina University Hospital and the Ioannina General Hospital, and from patients referred to private rheumatologists)	16+	221	ESSG	General population of Greece	NR	1 death (25%) SMR 0.25
Ali 2007 [104]	1978–2004	Canada	Prospective cohort (University of Toronto PsA Clinic)	43.7 ± 13.4	680	Arthritis + psoriasis	General population of Ontario	Death certificates	1.36 (1.12, 1.64)
Elalouf 2020 [112]	1978–2017	Canada	Prospective (University of Toronto Psoriatic Arthritis Clinic)	NR	1490	CASPAR	General population of Ontario	Death registry and death certificates (ICD-9 and ICD-10)	SMR 0.82 (0.4,1.4)
Ogdie 2014 [108]	1994–2010	United Kingdom	Longitudinal cohort study (THIN database)	18+	8706	Read code	General population of the UK	Specific codes recommended by Cegedim, the administrators of THIN	aHR for suicide 3.03 (1.56, 5.90)

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Table 4 (*continued*)

Author, Year	Years of observation	Geographic area	Study Design (data source)	Population	No. of PsA pts.	PsA case definition	Comparison group	Assessment of mortality/outcome definition	Mortality rate (95% CI)
Infections									
Ogdie 2017 [113]	1994–2010	United Kingdom	Longitudinal cohort study (THIN database)	18+	8706	Read code	General population of the UK	specific codes recommended by Cegedim, the administrators of THIN	aHR 1.05 (0.79, 1.39)
Elalouf 2020 [112]	1978–2017	Canada	Prospective (University of Toronto Psoriatic Arthritis Clinic)	NR	1490	CASPAR	General population of Ontario	Death registry and death certificates (ICD-9 and ICD-10)	SMR 5.32 (2.13, 10.96)
CNS									
Elalouf 2020 [112]	1978–2017	Canada	Prospective (University of Toronto Psoriatic Arthritis Clinic)	NR	1490	CASPAR	General population of Ontario	Death registry and death certificates (ICD-9 and ICD-10)	SMRs for Alzheimer's 0.43 (0.01, 2.44) CVA 0.38 (0.10, 0.97)
Other causes									
Wong 1997 [103]	1978–1993	Toronto	Observational prospective cohort (University of Toronto PsA cohort Registry)	NR	428	Arthritis + psoriasis	General population of Ontario	ICD-9	SMR 6.59 (2.07,15.52)
Ali 2007 [104]	1978–2004	Canada	Prospective cohort (University of Toronto PsA Clinic)	43.7 ± 13.4	680	Arthritis + psoriasis	General population of Ontario	Death certificates	SMR 0.05

Legend: PsA-psoriatic arthritis, CASPAR-the Classification of Psoriatic Arthritis, ICD- International Classification of Diseases, ESSG- European Spondylarthropathy Study Group criteria, REP-Rochester Epidemiology Project, THIN- The Health Improvement Network, CDARS- Clinical Data Analysis and Reporting System, THIN- The Health Improvement Network, NPR- National Patient Register, HR-hazard ratio, aHR-adjusted HR, and SHR-standardized HR.

Population-based studies that examine the mortality of PsA from different periods show disparate results (Table 4). Two different studies from a record linkage system in Olmsted County, Minnesota, USA, did not show an increase in mortality in patients with PsA [16,22]. Wilson et al. reported an SMR of 0.91 (CI 0.58–1.37) over 13.6 years mean follow-up in 147 patients with PsA from 1970 to 2000 [22]. Among the other population-based studies [16,18,42,105,108,110,111], only studies from Denmark [105] and Taiwan [110] showed increased mortality (RR 1.74, 95% CI 1.32–2.30 and SMR 1.47, 95% CI 1.36–1.58). A more recent study from the same Denmark National Patient Registry (1998–2014) showed a higher mortality rate than that of controls only in patients with psoriasis and not PsA [111]. Therefore, data from Denmark and the University of Toronto cohort likely suggest that mortality rates in PsA have improved over time. Other recent studies, published after 2010, also do not show higher mortality in PsA [108,109,111,112], except the study from the Taiwan National Health Insurance database [110].

Most studies reported age- and sex-adjusted SMRs that compare mortality in PsA to the census statistics. Two large population-based studies by Ogdie et al. [108] and Ahlehoff et al. [105] reported aHR and RR, respectively using internal comparators, again with discordant results. Ogdie et al. conducted a large population-based study from the UK THIN database, which compared mortality in patients with PsA (n = 8706), psoriasis (n = 138,424), and RA (n = 41,742) to matched controls (n = 81,573). There was no increased risk of mortality in PsA than that of population controls in the study after the adjustment for age and sex (HR 1.06 and 95% CI 0.80–1.10) or among DMARD users vs. non-users. In contrast, the Danish nationwide cohort study (1997–2006) by Ahlehoff et al. showed higher all-cause mortality in PsA than that of population controls (RR 1.74 and 95% CI 1.32–2.30) after the adjustment for age, sex, socioeconomic status, calendar year, comorbidities, and medications [105].

The discrepancies in the SMRs reported between different studies could be due to different reasons: in the study design – clinic or hospital-based cohort vs. population-based study and SMRs vs. internal controls. Control population based on regional data as compared to national estimates and the method of ascertaining deaths. In general, studies from specialty clinics and hospital-based studies might include patients with more severe disease leading to selection bias. A large proportion of patients in the general population have mild disease and are likely never seen by a specialist. The severity of PsA may be associated with increased mortality as seen in psoriasis [114]; however, this has not been clearly demonstrated in PsA. Population-based cohort studies might provide estimates closer to true mortality rates. Similarly, estimates from an internal comparison group might better approximate the true effect as compared to SMR, which could underestimate the risk [115].

Most studies reported age- and sex-adjusted mortality rates. Variability in mortality rates among male and female patients has been described in some studies [112,116]. Fagerli et al. reported significantly higher mortality in male patients (SMR 1.75 and 95% CI 1.11–2.63) but not in female patients (SMR 1.36 and 95% CI 0.81–2.15) [116]. In another study from the University of Toronto cohort, sex-specific SMR was significantly higher in female patients (SMR 1.08, 95% CI 0.89–1.30) but not in male patients (SMR 0.80 and 95% CI 0.66–0.97). In the same study, age-specific mortality rates were high (SMR 3.36 and 95% CI 1.61–6.18) for 20–39 years of age although overall mortality and mortality in older age groups (40+ years of age) was not increased [112]. Therefore, It might be important to examine age-specific mortality rates even if the overall mortality is not different from the general population.

Cause-specific mortality in PsA

Increased cause-specific mortality has been reported in PsA, specifically cardiovascular (CV) mortality. In a 2013 systematic review by Horreau et al. that includes four observational studies [103,105–107], they did not find an increase in CV mortality among patients with PsA [117]. Three recent studies following this review have shown contradictory results. A large population-based cohort study from the UK THIN database did not show increased CV mortality (HR 1.09 and 0.91–1.32) in patients with PsA as compared to matched controls. Similarly, cause-specific mortality rates for

atherosclerosis (SMR 1.01 and 95% CI 0.27–2.58), congestive heart failure (SMR 2.57, 95% CI 0.94–5.59), or myocardial infarction (SMR 1.11 and 95% CI 0.74–1.58) were not increased in a study from the University of Toronto PsA cohort [112]. Juneblad et al. used a retrospective PsA cohort from Västerbotten County, Sweden, found higher CV mortality in patients with PsA than that of the general population of Sweden (SMR 1.64 and 95% CI 1.02–2.52), although overall mortality was not increased in PsA (SMR 1.22 and 95% CI 0.89–1.63).

Beyond CV causes, increased mortality from respiratory diseases was reported in the University of Toronto cohort [103,112]. Increased mortality from respiratory diseases was reported in a study (1978–1993) by Wong et al. (SMR 5.05 and 95% CI 2.40–9.33) [103] and a more recent study (1978–2017) from the same cohort (SMR 98.5 and 95% CI 36.1–214.4) [112]. However, the study from the UK THIN database did not show an increase in respiratory disease-specific mortality (HR 0.97 and 95% CI 0.79–1.20) [113]. Although an increased risk of malignancies such as non-melanoma skin cancer has been observed in PsA [118], studies to date have not reported an increase in malignancy-related mortality in PsA [103,104,109,112,113]. Interestingly, an increased risk of suicide and poisoning-related death has been reported in PsA cohorts from the University of Toronto (SMR 3.54 and 95% CI 1.40–7.31) [103] and UK THIN database (HR for suicide 3.03 and 95% CI 1.56–5.90) [113].

Factors associated with mortality in PsA

Few studies have examined predictors of mortality in PsA. Gladman et al. reported that radiographic damage (RR 3.88 and 95% CI 1.32–11.35) and high ESR (RR 3.77 and 95% CI 1.31–10.83) were associated with mortality in PsA [119]. A recent study from the same cohort also reported the association of high acute phase reactants with (HR 1.56 and 95% CI 1.14–2.13); however, the association with radiographic damage was not significant. In the study, the presence of heart disease (HR 1.67 and 95% CI 1.12–2.49) and malignancy (HR 1.79 and 95% CI 1.22–2.61) was also associated with mortality in PsA [112].

Impact of therapy on mortality in PsA

The impact of treatment of PsA on mortality is not clear unlike in patients with RA, where methotrexate and TNFi have been shown to improve mortality [120,121]. While we did not find any studies that specifically examined the association of therapy in PsA with mortality (overall or cause-specific), some observational studies have indirectly examined this association in their multivariate model. Prior medication use was not significantly associated with mortality in PsA (RR 1.83 and 95% CI 0.93–3.60) in the University of Toronto cohort (1978–1993) [119]. Similarly, data from the UK THIN PsA cohort (1994–2010) did not show an increase in mortality among both patients with PsA on DMARDs (HR 0.94 and 95% CI 0.80–1.10) and not on DMARDs (HR 1.06 and 95% CI 0.94–1.19) [108]. Drug registries provide some information with regard to the causes of death; however, it is hard to interpret these data in the absence of a control group [122]. While further prospective studies of longitudinal cohorts might provide some evidence, one must consider confounding by indication while interpreting the results.

Summary

In this review, we discuss the epidemiology of PsA in the general population and patients with psoriasis and explore the risk factors for PsA in patients with psoriasis. While most studies show an increase in prevalence over recent years, the underdiagnosis of PsA persists. A single factor may not be able to effectively define at-risk patients with PsA and complex interaction of multiple factors seem to play a role. While most studies show that the overall mortality in PsA is not higher than that of the general population, cause-specific mortality from CV comorbidities and psychiatric manifestations seem to be higher. Targeting modifiable risk factors such as obesity with weight loss and early screening and management of associated comorbidities may mitigate the risk of PsA development and improve outcomes.

Practice points

- The epidemiological studies in psoriatic arthritis (PsA) are affected by geographic (genetic background, environmental factors, lifestyle, and dietary habits) and methodological (case definition of PsA and study design) differences between studies.
- Underdiagnosis is common in PsA and many patients with psoriasis are not diagnosed with PsA despite having the disease.
- Using a combination of risk factors and predictors to identify patients with psoriasis at increased risk of developing PsA may help the clinicians reduce the risk of PsA by modifying some of these factors.

Research agenda

- Large, prospective studies are required to examine the interactions between different risk factors in the development of PsA and the potential risk reduction by the modification of these factors.
- Designing longitudinal studies to understand the complex relationship of cardiometabolic comorbidities in psoriatic disease, their trajectories, and their effect on disease outcomes could help devise strategies to better address them in the real-world setting.

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Declaration of competing interest

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