All-cause and cause-specific mortality in psoriasis: A systematic review and meta-analysis

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Background: An overview of mortality risk associated with psoriasis is lacking.

Objective: To perform a systematic review and meta-analysis of mortality risk in psoriasis.

Methods: We included studies reporting all-cause or cause-specific mortality risk estimates in psoriasis patients compared with general population or subjects free of psoriasis. We calculated pooled relative risks (RRs) and 95% confidence intervals (CIs).

Results: We included 12 studies. The pooled RRs for all-cause mortality were 1.21 (95% CI 1.14-1.28) in psoriasis, 1.13 (95% CI 1.09-1.16) in mild psoriasis, and 1.52 (95% CI 1.35-1.71) in severe psoriasis. The pooled RRs for cardiovascular mortality were 1.15 (95% CI 1.09-1.21) in psoriasis, 1.05 (95% CI 0.92-1.20) in mild psoriasis, and 1.38 (95% CI 1.09-1.74) in severe psoriasis. For noncardiovascular causes, mortality risk from liver disease, kidney disease, and infection was significantly increased in psoriasis, regardless of disease severity. The mortality risk in liver and kidney disease was the highest. There was also a significantly increased mortality risk associated with neoplasms in severe psoriasis patients and chronic lower respiratory disease in all and mild psoriasis patients.

Limitations: Although associations were consistent, their magnitude was heterogenous.

Conclusion: Psoriasis is associated with an increased risk for mortality from all causes (in a dose-response manner with disease severity) and from several specific causes. (J Am Acad Dermatol 2019;80:1332-43.)

Key words: cardiovascular disease; cause of death; infectious disease; kidney disease; liver disease; malignancy; mortality; psoriasis; respiratory disease; systematic review.

Psoriasis is a multisystemic, immunologically mediated disease that predominately involves the skin and joints. It affects ~2%-3% of people in the United States and Europe.[1,2] Psoriasis significantly impairs quality of life, affecting physical, emotional, and social well-being.[3] Indeed, psoriasis patients have an increased risk for depression, suicide, and anxiety.[4-6] In addition, unhealthy behaviors, such as smoking and excessive alcohol consumption, are more prevalent in psoriasis patients.[7,8]

Psoriasis has other important health implications beyond the skin. It is associated with several medical comorbidities, particularly in those with severe

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disease.[9,10] Comorbidities include metabolic syndrome and its components, cardiovascular disease, chronic obstructive pulmonary disease, liver and kidney disease, infection, and malignancy.[11-18] The pathophysiology underlying the association between psoriasis and these comorbidities is unclear. It might be a result of shared genetic basis, systemic inflammation, treatments for psoriasis, or increased prevalence of traditional risk factors such as smoking.[19]

Because of higher rates of comorbidities, psoriasis patients might be at increased risk for death. Several previous meta-analyses have found an increased cardiovascular mortality risk in patients with severe psoriasis,[12,20,21] but to our knowledge, there is no systematic review and meta-analysis on all-cause and cause-specific mortality risk in psoriasis. Data on mortality risk can inform prevention efforts and advance knowledge of disease pathophysiology. Therefore, we conducted a systematic review and meta-analysis of all-cause and cause-specific mortality risk in psoriasis patients.

CAPSULE SUMMARY

- Although psoriasis is associated with several comorbidities, mortality risk needs clarification.
- Psoriasis is associated with increased mortality risk from all-causes in a dose-response manner with disease severity and from several specific causes, such as cardiovascular, liver, kidney, and infectious disease. Thus, psoriasis patients should receive appropriate screening and preventative interventions.

MATERIALS AND METHODS

This systematic review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement.[22] Two authors independently participated in the literature search, study selection, data extraction, and quality assessment. Any disagreements were resolved by discussion.

Literature search

On July 17, 2018, we searched PubMed, Embase, and Web of Science databases without date restrictions. In brief, we included the terms "psoriasis," "mortality," and "cohort" in our search strategy. An example of the search used for PubMed is shown in Fig 1. We also searched references of related reviews and included articles.

Study selection

Titles and abstracts from the search were screened, and full texts of potential articles were reviewed. We included studies if they were published peer-reviewed English-language cohort articles; reported all-cause or cause-specific mortality risk estimates (relative risks [RRs], mortality rate ratios, odds ratios, standardized mortality ratios [SMRs], or hazard ratios with 95% confidence intervals [CIs]); and compared patients with psoriasis diagnoses with persons in the general population or persons from the same study setting without psoriasis. For cause-specific mortality, we examined cardiovascular disease, kidney disease, liver disease, respiratory disease, infection, and malignancy.

We excluded review articles, commentaries, and editorials. We also excluded studies that investigated only specific subgroups of psoriasis or comparison groups (eg, patients with psoriatic arthritis or depression). However, studies were eligible for inclusion if psoriasis patients were categorized as mild or severe. Patients were considered to have severe psoriasis if they had received a treatment for severe psoriasis, had >10% body surface area involvement, or had been hospitalized with psoriasis as the primary diagnosis.

Because of possible sample overlap, we compared studies with similar country of origin and data source. We included the study with the longest study period. In the United Kingdom, 8 studies presented overlapping data.[23-30] For all-cause mortality, we included the study by Ogdie et al (2014).[28] For cause-specific mortality and cardiovascular mortality, we included the studies by Abuabara et al (2010)[23] and Ogdie et al (2015),[29] respectively. Likewise, for 2 studies from Sweden,[31,32] we included the study by Svedbom et al (2015)[32] for cause-specific mortality and Mallbris et al (2003)[31] for cardiovascular mortality. For 2 studies conducted in the United States,[33,34] we included the study by Stern et al (2011).[33] For 2 studies conducted in Demark,[35,36] we excluded the study by Skov et al (2018)[35] because it included patients with a hospital-based psoriasis diagnosis that may or may not have been the primary diagnosis, a subgroup which might be at increased risk for mortality compared with all psoriasis patients.

Data extraction and assessment of study quality

Using a standardized data extraction form, we extracted information from each study on first

Abbreviations used:

CI: confidence interval
RR: relative risk
SMR: standardized mortality ratio

author, publication year, country, setting, study period, number of psoriasis patients, population of psoriasis patients (inpatient and/or outpatient), patient characteristics (age and sex), comparison group, ascertainment of psoriasis diagnosis and mortality, all-cause and cause-specific mortality estimates, and variables adjusted for.

We assessed study quality using a modified Newcastle-Ottawa Scale and judged studies as having low (7 points), medium (5-6 points), or high (≤4 points) risk for bias.[37,38] We also assessed study quality by including various study components in subgroup analyses.[39,40]

Statistical analyses

All statistical analyses were conducted using Stata version 13 (StataCorp LP, College Station, TX). Meta-analyses of mortality were performed for all causes and each type of cause. We calculated RRs with 95% CIs as the measure of association. SMRs, hazard ratios, mortality rate ratio, and odds ratios were considered comparable estimates of RRs.[39,40] We chose a random effects model and used the DerSimonian-Laird method[41] because of potential between-study heterogeneity. If a study provided multiple estimates for different psoriasis categories (such as mild and severe), we combined these estimates using a fixed effects model to derive an estimate for all psoriasis patients in that study.

To assess heterogeneity, we used the I^2 statistic and $\chi 2$ test. I^2 values of 25%, 50%, and 75% represented low, moderate, and high heterogeneity, respectively.[42] We conducted subgroup analyses by using univariate metaregression to identify potential sources of heterogeneity by study characteristics.[43] Subgroups were chosen a priori and included region (Europe vs other), baseline year (before 2000 vs after 2000), study period duration (≤10 years vs >10 years), comparison group (general population vs other), effect measure (SMR vs other), and variables adjusted for (basic vs additional).

We also conducted sensitivity analyses and assessed the influence of individual studies on the overall effect by omitting each study 1 at a time. Last, to assess potential publication bias, we visually inspected funnel plots and conducted Egger's linear regression test.[44] Subgroup analyses, influence analyses, and publication bias assessment were performed if ≥5 studies were available. All statistical tests were 2-sided, and a P value of <.05 was considered statistically significant.

RESULTS

Studies selected and characteristics

Fig 1 shows the study selection flowchart. After screening 569 articles by title and abstract, we assessed 48 full-text articles for eligibility. We ultimately included 12 studies.* Table I summarizes the main characteristics of the included studies. Studies were conducted in 7 countries: Taiwan, Argentina, Sweden, United States, Denmark, United Kingdom, and Finland. Study duration varied from 6-32 years. The mean age of psoriasis patients ranged from 43.6-67.9 years, and the percentage of female patients were 4.5%-54.5%.

Psoriasis and all-cause mortality

Table II and Fig 2 describe results for all-cause mortality. For 6 studies including 299,374 psoriasis patients, the pooled RR for all-cause mortality was 1.21 (95% CI 1.14-1.28, I^2 = 90.2%, P < .001). Univariate metaregression revealed significant heterogeneity by comparison population (P = .02). Studies with a general comparison population (RR 1.16, 95% CI 1.11-1.21) had a smaller (but still significant) effect than studies with other comparison populations, such as other patients in the medical center or on the same health plan (RR 1.73, 95% CI 1.40-2.13). For 4 studies including 265,292 patients with mild psoriasis, the pooled RR for all-cause mortality was 1.13 (95% CI 1.09-1.16, I^2 = 62.1%, P = .048). For 6 studies including 36,428 patients with severe psoriasis, the pooled RR for all-cause mortality was 1.52 (95% CI 1.35-1.71, I^2 = 93.4%, P < .001). Metaregression did not reveal significant heterogeneity. For each individual study, the RRs of all-cause mortality for all, mild, and severe psoriasis patients were significantly increased.

Psoriasis and cause-specific mortality

Tables II and III describe the results for cause-specific mortality. For 5 studies including 285,675 psoriasis patients, the pooled RR for cardiovascular mortality was 1.15 (95% CI 1.09-1.21, I^2 = 65.9%, P = .02). Metaregression did not reveal significant heterogeneity. For 3 studies including 188,223 patients with mild psoriasis, the pooled RR for cardiovascular mortality was 1.05 (95% CI 0.92-1.20,

*[23,28,29,31-33,36,45-49]

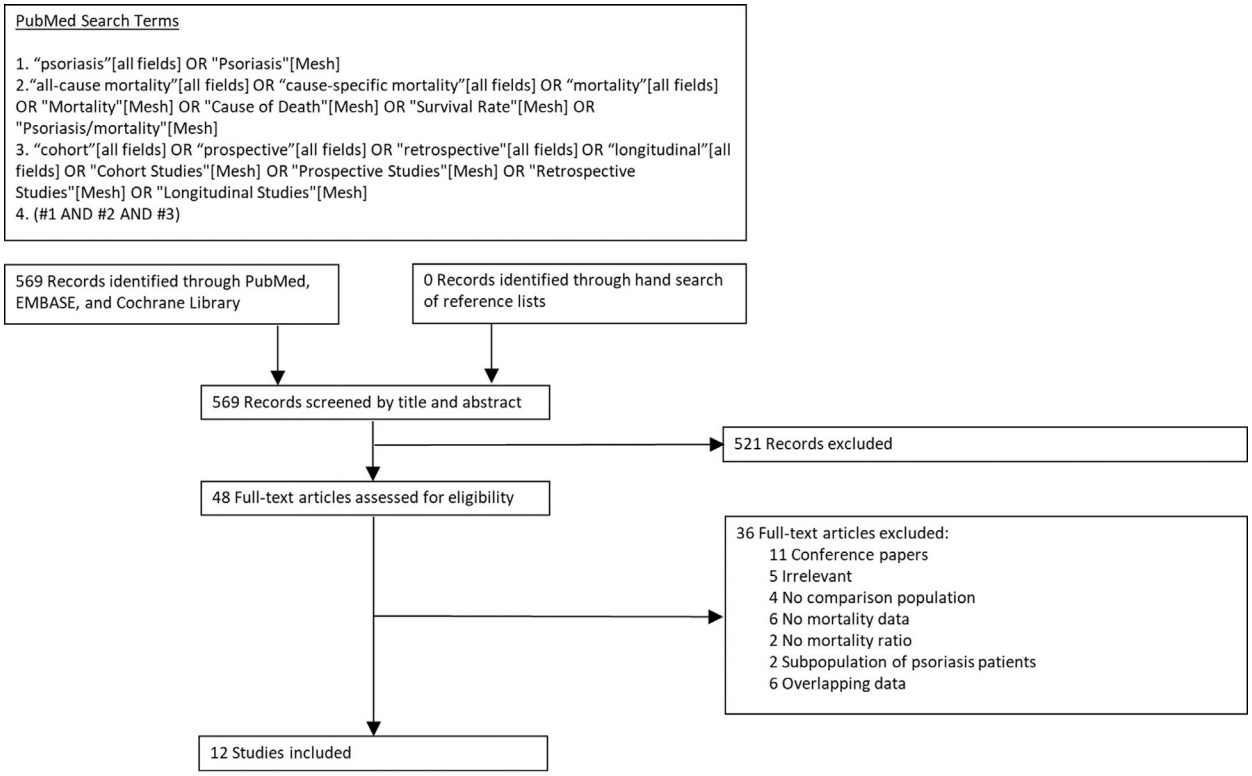

Fig 1. Flow diagram of studies selected for the systematic review. *MeSH*, Medical subject heading.

I^2 = 90.3%, $P < .001$). For 4 studies including 17,317 patients with severe psoriasis, the pooled RR for cardiovascular mortality was 1.38 (95% CI 1.09-1.74, I^2 = 91.0%, $P < .001$).

For noncardiovascular causes of death, the mortality risk in liver and kidney disease was highest. The RRs for mortality in kidney disease was 2.16 (95% CI 1.37-3.40) for all psoriasis patients, 2.20 (95% CI 1.36-3.56) for mild psoriasis patients, and 3.54 (95% CI 1.73-7.26) for severe psoriasis patients. One study by Stern et al (2011) reported a nonsignificantly increased risk for mortality (RR 1.25, 95% CI 0.50-2.58) associated with renal failure in severe psoriasis.[33] The RRs for mortality in liver disease was 2.31 (95% CI 1.61-3.31) for all psoriasis patients, 2.00 (95% CI 1.34-2.99) for patients with mild psoriasis, and 3.97 (95% CI 2.87-5.50) for patients with severe psoriasis.

The RR for mortality from infections was 1.24 (95% CI 1.14-1.36) for all psoriasis patients, 1.41 (95% CI 1.11-1.79) for patients with mild psoriasis, and 1.58 (95% CI 1.22-2.05) for patients with severe psoriasis. One study by Stern et al (2011) found a nonsignificantly increased risk for mortality associated with sepsis in severe psoriasis (RR 1.56, 95% CI 0.63-3.21).[33] Among severe psoriasis patients, there was a significantly increased mortality risk associated with neoplasms but not with malignancies. Last, risk for mortality was significantly increased in chronic lower respiratory disease for all and mild psoriasis patients but not severe psoriasis patients.

Sensitivity analyses, publication bias, and study quality

We performed sensitivity analyses, influence analyses, and publication bias assessment if ≥5 studies were available for a given analysis. In sensitivity analyses, replacing included studies with those excluded because of possible sample overlap had a negligible effect on the pooled estimate; our results remained significant (data not shown). For all-cause mortality in severe psoriasis, limiting the analysis to only studies involving both mild and severe psoriasis also had negligible effect on the pooled estimate (RR 1.63, 95% CI 1.51-1.78). In influence analyses, the pooled estimate also remained significant.

Because few studies were included in each analysis, visual inspection of the funnel plot was difficult to interpret. However, Egger's test showed no evidence of publication bias ($P > .05$). For study quality, we judged 7 studies to be at low risk for bias, 4 studies to be at medium risk for bias, and 1 study to be at high risk for bias.

Table I. Main characteristics of studies

Author, year, country	Setting	Study period (total years)	No. psoriasis patients	Psoriasis patient population	Psoriasis determination, severe disease definition	Comparison group	Assessment of mortality	Mean age, years	Sex, % female
Lee et al, 2017,[46] Taiwan	National Health Insurance database	2001-2012 (12)	80,167	Inpatients + outpatients	ICD-9 from database, severe: received a systemic therapy	General population	National Death Registry	47.8 mild, 45.9 severe	38.5 mild, 32.3 severe
Masson et al, 2016,[45] Argentina	Health insurance plan	2010-2015 (6)	1481	Inpatients + outpatients	Medical records	Persons without psoriasis in same plan	In-hospital or out-of-hospital death	Mean 55.3	54.5
Svedbom, 2015,[32] Sweden	Regional registers	2001-2010 (10)	39,074	Inpatients + outpatients	ICD-10 from registry, severe: hospitalized or received systematic therapy	General population	Causes of Death Register	49.1 mild 51.9 severe	53.2 mild, 48.8 severe
Ogdie et al, 2015,[29] UK	The Health Improvement Network in the UK	1994-2010 (17)	138,424	Inpatients + outpatients	Diagnostic code, severe: received disease-modifying antirheumatic drug	General population	Code noting death or transfer due to death	47.6 mild, 49.3 severe	51.3 mild, 49.2 severe
Ogdie et al, 2014,[28] UK	The Health Improvement Network in the UK	1994-2010 (17)	138,424	Inpatients + outpatients	Diagnostic code, severe: received disease-modifying antirheumatic drug	General population	Code noting death or transfer due to death	47.6	51.0
Maradit-Kremers et al, 2013,[47] USA	Cohort of Rochester Epidemiology Project	1979-2005 (27)	1344	Inpatients + outpatients	Medical records	General population	Death certificates	43.6	49.0
Stern et al, 2011,[33] USA	Clinical trial participants from several dermatology departments	1976-2005 (30)	1376	Inpatients + outpatients with severe psoriasis	Trial records, severe: body surface area involvement	General population	Interviews + National Death Index	46.0	35.0
Ahlehoff et al, 2011,[36] Denmark	Nationwide register	1997-2006 (10)	36,992	Inpatients + outpatients	ICD-8 and ICD-10 from register, severe: hospitalized	General population	Central Population Register and National Causes of Death Register	47.2 mild, 46.9 severe	50.6 mild, 48.4 severe
Abuabara et al, 2010,[23] UK	General Practice Research Database	1987-2002 (16)	3603	Inpatients + outpatients	Diagnostic code for psoriasis, severe: received a systemic therapy	General population	Code noting death	52.2 severe	51.4 severe
Prodanovich et al, 2009,[48] USA	Miami Veterans Administration Medical Center	1985-2006 (22)	3236	Outpatients	ICD-9 from medical records	Persons without psoriasis in same medical center	Medical records	67.9	4.5

Mallbris et al, 2003,[31] Sweden	National Inpatient Registry and Swedish Psoriasis Association	Mild: 1987-1998 (12); Severe: 1964-1995 (32)	28,748	Inpatients + outpatients	Mild: member of Swedish Psoriasis Association; Severe: hospitalized with ICD-7, ICD-8, and ICD-9	General population	Swedish Death Register	-	55.0 mild, 48.0 severe
Poikolainen et al, 1999,[49] Finland	National Hospital Discharge Register	1973-1995 (23)	5687	Inpatients	Severe: principle diagnosis of psoriasis in hospital discharge	General population	Cause of Death Register	-	44.9

ICD, International Classification of Diseases.

DISCUSSION

In this first systematic review of all-cause and cause-specific mortality risk in psoriasis, we found that psoriasis patients, especially those with severe disease, have increased risk for all-cause mortality compared with those without psoriasis. For cause-specific mortality, we found increased cardiovascular mortality risk in all and severe psoriasis patients but not in those with mild disease. Mortality risk in liver, kidney, and infectious disease was also significantly increased, regardless of disease severity. Last, there was an increased mortality risk associated with neoplasms in severe psoriasis and chronic lower respiratory disease in all and mild psoriasis.

An elevated risk for death has been well documented in chronic inflammatory diseases, such as inflammatory bowel disease, systemic lupus erythematosus, rheumatoid arthritis, and ankylosing spondylitis.[50-54] All studies in our analyses that categorized patients into mild or severe psoriasis found a dose-response relationship, with higher all-cause mortality risk for those with more severe disease, as did a nationwide Danish population study that examined only death rates.[55] Most studies used specific treatments or inpatient admission to define severe psoriasis. However, 2 studies did show higher mortality risk with increasing body surface area involvement,[27,33] which might be a more objective clinical severity measure.[56,57] Subgroup analyses indicated no difference in mortality risk between studies with a baseline year before and after 2000. Although tests of homogeneity have low power, a recent large population study found no change in the mortality gap between those with and without psoriasis over a 15-year period.[30]

The mechanisms underlying increased mortality risk in psoriasis patients are unclear. Excess death might be a result of systemic inflammation, adverse effects of treatments, comorbidities, or behavioral risk factors. Our subgroup analyses indicated no significant difference in mortality risk between studies that adjusted for age and sex and those that additionally adjusted for other factors. However, most of the latter studies did not account for all mortality risk factors, such as smoking or obesity. Nevertheless, a recent large population study found increased mortality risk in severe psoriasis even after adjusting for several major mortality risk factors.[27]

For cause-specific mortality, RR for mortality was highest in liver and kidney disease. But compared with RR, absolute and excess risk estimates are better indicators of public health impact. Several studies included in our review showed small absolute and excess risks in kidney and liver disease, with

Table II. Results for all-cause and cause-specific mortality

Author, year	Mortality measure	No. deaths	Psoriasis severity	RR (95% CI)	Adjustment	Additional comments
All-cause mortality						
Lee et al, 2017[46]	SMR	7198	All	1.14 (1.11-1.16)	Age, sex, calendar year	
			Mild	1.12 (1.09-1.15)		
			Severe	1.53 (1.45-1.60)		
Masson et al, 2016[45]	HR	107	All	1.48 (1.08-2.03)	Age, sex, hypertension, smoking, diabetes, dyslipidemia	
Svedbom et al, 2015[32]	HR	2302	All*	1.19 (1.14-1.24)	Age, sex, comorbidity	
		2007	Mild	1.15 (1.10-1.21)		
		295	Severe	1.56 (1.36-1.79)		
Ogdie et al, 2014[28]	HR	9021	All	1.10 (1.06-1.13)	Age, sex	
		8693	Mild	1.08 (1.04-1.12)		
		328	Severe	1.75 (1.56-1.95)		
Stern et al, 2011[33]	SMR	617	Severe	1.10 (1.02-1.2)	Age, sex, calendar year	
Ahlehoff et al, 2011[36]	MRR	-	All*	1.21 (1.17-1.25)	Age, sex, calendar year, concomitant medication, comorbidity, socioeconomic data	
		-	Mild	1.16 (1.11-1.20)		
		-	Severe	1.73 (1.54-1.94)		
Prodanovich et al, 2009[48]	OR	634	All	1.86 (1.56-2.21)	Age, sex, hypertension, diabetes, dyslipidemia, smoking, vascular disease	
Poikolainen et al, 1999[49]	SMR	1918	Severe*	1.59 (1.52-1.66)	Age, sex, calendar period	
Cardiovascular disease						
Lee et al, 2017[46]	SMR	1528	All	1.08 (1.02-1.13)	Age, sex, calendar year	
Ogdie et al, 2015[29]	HR	1695	All*	1.13 (1.03-1.23)	Age, sex, hypertension, diabetes, hyperlipidemia, smoking, cohort start year	
		1645	Mild	1.09 (1.00-1.20)		
		50	Severe	1.54 (1.15-2.05)		
Maradit-Kremers et al, 2013[47]	HR	77	All	1.04 (0.79-1.37)	Age, sex, calendar year	
Stern et al, 2011[33]	SMR	246	Severe	1.02 (0.90-1.16)	Age, sex, calendar year	
Ahlehoff et al, 2011[36]	RR	-	All*	1.18 (1.10-1.26)	Age, sex, calendar year, medication, comorbidity, socioeconomic data	
		-	Mild	1.14 (1.06-1.22)		
		-	Severe	1.57 (1.27-1.94)		
Mallbris et al, 2003[31]	SMR	2831	All*	1.20 (1.15-1.24)	Age, sex, calendar year	
		1302	Mild	0.94 (0.89-0.99)		
		1529	Severe	1.52 (1.44-1.60)		
Kidney disease						
Svedbom et al, 2015[32]	HR	29	All*	2.16 (1.37-3.40)	Age, sex, comorbidity	
		26	Mild	2.20 (1.36-3.56)		
		3	Severe	1.87 (0.48-7.28)		
Stern et al, 2011[33]	SMR	7	Severe	1.25 (0.50-2.58)	Age, sex, calendar year	Renal failure
Abuabara et al, 2010[23]	HR	18	Severe	4.37 (2.24-8.53)	Age, sex	

Liver disease						
Svedbom et al, 2015[32]	HR	51	All*	2.31 (1.61-3.31)	Age, sex, comorbidity	
		39	Mild	2.00 (1.34-2.99)		
		12	Severe	4.26 (1.87-9.73)		
Stern et al, 2011[33]	SMR	32	Severe	4.04 (2.76-5.70)	Age, sex, calendar year	
Abuabara et al, 2010[23]	HR	2	Severe	2.03 (0.37-11.12)	Age, sex	
Respiratory disease						
Lee et al, 2017[46]	SMR	444	All	1.09 (0.98-1.19)	Age, sex, calendar year	
Svedbom et al, 2015[32]	HR	98	All*	1.29 (1.02-1.63)	Age, sex, comorbidity	Chronic lower respiratory disease
		91	Mild	1.36 (1.07-1.74)		
		7	Severe	0.66 (0.28-1.58)		
Stern et al, 2011[33]	SMR	23	Severe	0.79 (0.50-1.19)	Age, sex, calendar year	
Abuabara et al, 2010[23]	HR	22	Severe	2.08 (1.24-3.48)	Age, sex	Chronic lower respiratory disease
Infection						
Lee et al, 2017[46]	SMR	710	All	1.22 (1.13-1.30)	Age, sex, calendar year	
Svedbom et al, 2015[32]	HR	102	All*	1.39 (1.10-1.74)	Age, sex, comorbidity	
		93	Mild	1.41 (1.11-1.79)		
		9	Severe	1.16 (0.54-2.46)		
Stern et al, 2011[33]	SMR	7	Severe	1.56 (0.63-3.21)	Age, sex, calendar year	Sepsis
Abuabara et al, 2010[23]	HR	71	Severe	1.65 (1.26-2.18)	Age, sex	
Malignancy						
Lee et al, 2017[46]	SMR	1831	All	1.03 (0.98-1.08)	Age, sex, calendar year	
Svedbom et al, 2015[32]	HR	624	All*	1.05 (0.97-1.15)	Age, sex, comorbidity	Neoplasms
		540	Mild	1.02 (0.93-1.12)		
		84	Severe	1.32 (1.03-1.69)		
Stern et al, 2011[33]	SMR	146	Severe	1.02 (0.86-1.20)	Age, sex, calendar year	
Abuabara et al, 2010[23]	HR	67	Severe	1.41 (1.07-1.86)	Age, sex	

CI, Confidence interval; *HR*, hazard ratio; *MMR*, mortality rate ratio; *OR*, odds ratio; *RR*, relative risk; *SMR*, standardized mortality ratio.
*Relevant categories combined by using a fixed-effects model to determine summary estimate for all psoriasis patients.

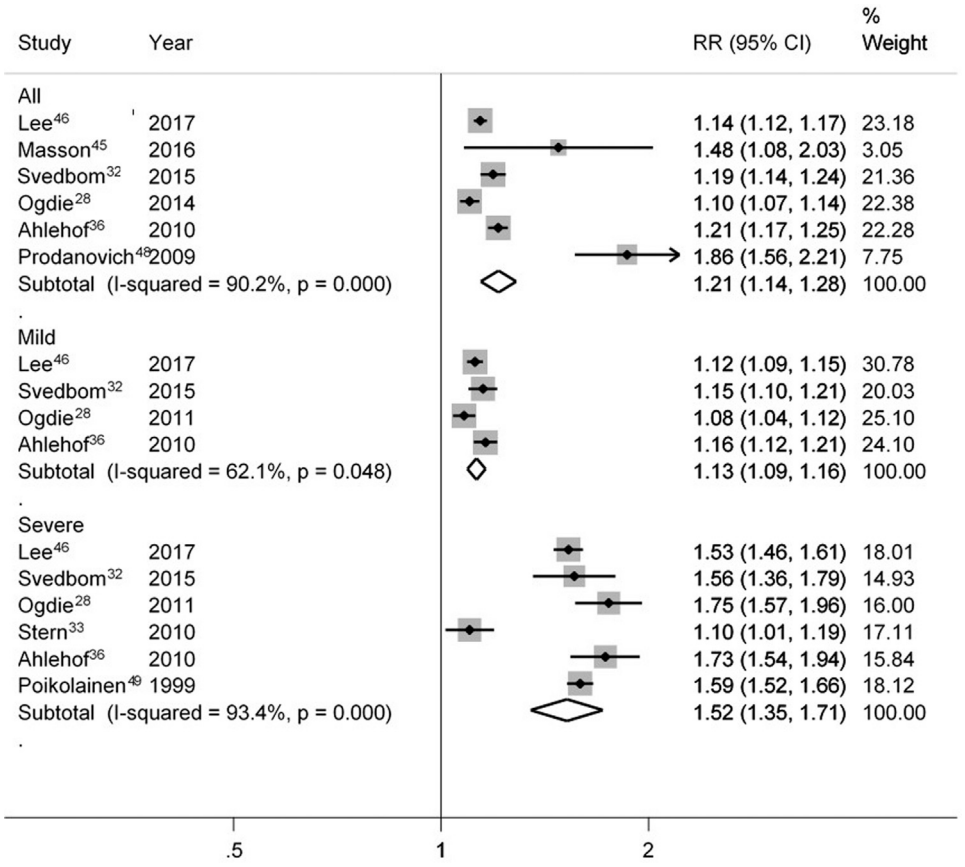

Fig 2. Forest plot for all-cause mortality in all, mild, and severe psoriasis patients. *CI*, Confidence interval; *RR*, relative risk.

cardiovascular disease, malignancy, and infection largely driving increases in all-cause mortality.[23,32,46] However, the strong association in kidney and liver disease should be investigated further.

The elevated risk for death from liver disease might be related to higher prevalence of nonalcoholic fatty liver disease and alcohol consumption in psoriasis patients, as well as use of systemic treatments, such as methotrexate.[8,13,58] In fact, 2 studies showed a 3.5−7-fold increased risk for mortality secondary to alcohol-related liver disease among severe psoriasis patients.[34,49] Another large population study confirmed alcoholic liver disease to be the most common cause of alcohol-related deaths in psoriasis patients.[59] For kidney disease, recent cohort studies have reported a positive association between psoriasis and glomerulonephritis, chronic kidney disease, and end-stage renal failure independent of traditional risk factors.[60-63] In these studies, the higher risk for kidney disease with increasing psoriasis severity aligns with our mortality findings.

For cardiovascular disease, our findings are consistent with previous meta-analyses showing an increased cardiovascular mortality risk in severe but not mild psoriasis.[12,20,21] These meta-analyses also reported a dose-response relationship between psoriasis severity and risk of myocardial infarction and stroke. One study of severe psoriasis indicated an increased risk for death associated with several specific cardiovascular diseases: ischemic heart disease, cerebrovascular disease, and pulmonary embolism.[31] However, another study found no increased risk for death associated with myocardial infarction.[33]

Our findings on infection-related mortality are similar to other cohort studies that have noted a positive association between psoriasis and both severe infection and hospitalized pneumonia.[64-66] There is also a concern for serious infections related to the adverse effects of biologic therapies, although 1 meta-analysis of randomized trials showed no increased risk for serious infection.[67] However, limitations included lack of statistical power and short follow-up of included trials. Nevertheless, another recent meta-analysis of prospective registries confirmed no increased risk for serious infection associated with anti−tumor necrosis factor biologic therapies compared with classic therapies.[68]

Table III. Meta-analysis for cause-specific mortality for all, mild, and severe psoriasis

Cause	No. studies	RR (95% CI)	I^2, %
Cardiovascular			
All	5	1.15 (1.09-1.21)	65.9
Mild	3	1.05 (0.92-1.20)	90.3
Severe	4	1.38 (1.09-1.74)	91.0
Kidney			
All	1	2.16 (1.37-3.40)	-
Mild	1	2.20 (1.36-3.56)	-
Severe	2	3.54 (1.73-7.26)	17.1
Renal failure			
Severe	1	1.25 (0.50-2.58)	-
Liver			
All	1	2.31 (1.61-3.31)	-
Mild	1	2.00 (1.34-2.99)	-
Severe	3	3.97 (2.87-5.50)	0
Respiratory			
All	1	1.09 (0.98-1.19)	-
Severe	1	0.79 (0.50-1.19)	-
Chronic lower respiratory disease			
All	1	1.29 (1.02-1.63)	-
Mild	1	1.36 (1.07-1.74)	-
Severe	2	1.24 (0.40-3.79)	80.0
Infection			
All	2	1.24 (1.14-1.36)	12.1
Mild	1	1.41 (1.11-1.79)	-
Severe	2	1.58 (1.22-2.05)	0
Sepsis			
Severe	1	1.56 (0.63-3.21)	-
Malignancy			
All	1	1.03 (0.98-1.08)	-
Severe	2	1.18 (0.86-1.61)	74.1
Neoplasms			
All	1	1.05 (0.97-1.15)	-
Mild	1	1.02 (0.93-1.12)	-
Severe	1	1.32 (1.03-1.69)	-

CI, Confidence interval; *RR*, relative risk.

Two included studies showed increased mortality from malignancies and neoplasms in severe psoriasis,[23,32] and 1 study found no elevated risk in severe psoriasis.[33] However, the latter study did note a significantly increased risk for death from nonmelanoma skin cancer. Given the increased risk for some cancers in psoriasis,[16] these findings warrant additional investigation. Also, with regards to respiratory-related mortality, further research is needed given the known association between psoriasis and both smoking and chronic obstructive pulmonary disease.[7,69]

Our study has several strengths. We assessed studies for risk for bias, performed several sensitivity analyses, and included a large number of patients in our all-cause and cardiovascular mortality analyses. Our study also has limitations. First, included studies were heterogeneous in several aspects, such as summary measures used, classification of cause-specific mortality, definition of severe psoriasis, length of follow-up, and confounder adjustment. However, point estimates for each study were qualitatively similar for all-cause analyses and most cause-specific analyses, and we also used a random effects model to address potential heterogeneity. Second, noncardiovascular cause-specific mortality analyses and subgroup analyses lacked statistical power because few studies were included. Thus, these findings should be interpreted with caution. Last, since mortality studies are typically only age- and sex-adjusted, we were unable to determine whether psoriasis is an independent risk factor for mortality.

Our findings suggest that psoriasis patients, particularly those with risk factors and severe disease, should receive appropriate screening and preventative interventions. Further studies are needed to assess the effect of psoriasis on mortality independent of mortality risk factors, to clarify cause-specific mortality in psoriasis patients, and to determine the mechanisms underlying excess mortality.

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