Acta Derm Venereol 2015; 95: 809–815

INVESTIGATIVE REPORT

Increased Cause-specific Mortality in Patients with Mild and Severe Psoriasis: A Population-based Swedish Register Study

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Several studies have shown excess risk for a number of comorbidities in patients with psoriasis compared with the general population, but data on cause-specific mortality in this patient population are limited. The aim of this study was to estimate the associations of psoriasis and 12 specific causes of death and all-cause mortality in patients with mild and severe psoriasis. The study was based on data from Swedish administrative registers and compared the risk of death in 39,074 patients with psoriasis with 154,775 sex-, age- and residency-matched referents using Cox proportional hazards models. In patients with mild and severe psoriasis, the strongest associations were observed for deaths due to kidney disease (hazard ratio [HR]=2.20, $p<0.01$) and liver disease (HR=4.26, $p<0.001$), respectively. Whilst cardiovascular disease was the main driver of excess mortality in absolute terms, the risks for other causes of death were also substantially elevated in patients with psoriasis compared with matched referents. ***Key words: Psoriasis; mortality; epidemiology.***

Accepted Mar 11, 2015; Epub ahead of print Mar 13, 2015

Acta Derm Venereol 2015; 95: 809–815.

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The clinical manifestations of psoriasis are not limited to the skin (1). The relative risk of comorbidities, including cardiovascular disease, cancer and chronic obstructive pulmonary disease, are increased in people with psoriasis (2). Severe psoriasis has been associated with excess mortality in a number of studies (3–6), whereas the evidence is more mixed for mild disease (3, 4, 6). Specific causes of death that have been reported to be elevated in psoriasis include cardiovascular disease (7–9), cancer (7, 8, 10) and liver disease (7, 10, 11).

Two studies have reported on a broad range of causes of death in patients with psoriasis compared with general reference populations. A UK study in patients with severe disease found that risks for 7 of 12 causes of deaths were elevated in patients with severe psoriasis (7). The highest increases in risk were reported for kidney disease and dementia. A recent nationwide Danish study reported rates for 9 causes of death in people with mild psoriasis, people with severe psoriasis, and people without psoriasis (12). Whilst no measures of relative risks were derived, patients with mild and severe psoriasis had statistically significantly higher death rates for all causes of death compared with those without psoriasis.

Sweden has high-quality registries on healthcare data. Healthcare providers are required to submit information for reimbursement purposes (13), therefore ensuring high-quality, and comprehensive reporting. Furthermore, there are nationwide registers that capture data on all medications dispensed at pharmacies (14), vital status (15), causes of death (16) and residency of inhabitants (15). Patient-level data in the registers can be linked using a 10-digit personal identification number unique to each Swedish citizen (17).

Existing evidence suggests that risks for numerous causes of death may be increased in people with psoriasis and further analyses are warranted. Data on increases in absolute and relative risks of specific causes of death may inform prevention efforts as well as discussions on aetiopathogenetic factors relevant to the disease and its course. The aim of this study was to estimate the association of psoriasis and cause-specific mortality.

METHODS

Data sources

The VEGA register and the Skåne Health Care Register (SHCR) are 2 regional databases established for reimbursement purposes with combined populations of approximately 2.8 million. The registers contain data on inpatient, specialist outpatient, and primary care, including dates, International Classification of Diseases, 10th revision (ICD-10) diagnoses, and procedure codes. The registers capture up to 10 ICD-10 codes for each contact. The primary diagnosis code denotes the medical condition or problem that is chiefly responsible for the contact. Additional codes describe relevant coexisting conditions. Both registers have previously been used in population-based health outcomes research (18–20) and SHCR has been shown to have high positive predictive value for psoriasis (21). Data from SHCR and VEGA were available from 1 January 2001 to 31 December 2010 and 1 January 2005 to 31 March 2011, respectively.

The Total Population Register (TPR) is a nationwide register with data on vital status, residency, and emigration and immigration status at any point in time for all permanent residents in Sweden since 1961 (15).

 doi: 10.2340/00015555-2095
 ISSN 0001-5555

The Causes of Death Register (CDR) includes all individuals who were registered in Sweden at the time of death. The register includes information on the date of death, and main (underlying) and up to 20 secondary causes of death based on death certificates. In 2006, death certificates for 99.3% of all deaths in Sweden were reviewed and incorporated into the CDR (16).

The Swedish Prescribed Drug Register (SPDR) is a nationwide register on prescriptions collected at any Swedish pharmacy since July 2005, including dates of prescription and dispatch, Anatomical Therapeutic Chemical (ATC)-code, package size, dosage, and prescription instructions (14). The SPDR is of high quality, with loss of information estimated at below 0.6%.

The study was approved by the Stockholm Ethical Review Board.

Study cohorts

Patients with a registered diagnosis of psoriasis (L40.x) were identified in the VEGA register and SHCR. For each patient with psoriasis, 4 individuals without psoriasis, but with similar age (± 1 year), same sex, and same residency (municipality), were identified. Individuals fulfilling the matching criteria were randomly drawn without replacement from the general population from December 31, the year before the corresponding patient's first registered diagnosis of psoriasis.

Patients and corresponding referents that fulfilled the following exclusion criteria were removed from the study cohorts: subjects with a reused Patient Identification Number (PIN); individuals who emigrated or died between matching and first registered date of diagnosis; and patient/referent pairs with first registered diagnosis after 31 December 2010. Furthermore, for the base case analysis, patients (and the corresponding referents) who did not have a registered primary diagnosis of psoriasis (but at least one secondary diagnosis) were excluded.

The study population was divided into 2 cohorts: patients with mild disease and patients with severe disease. Patients were classified as having severe psoriasis if the patient had been hospitalized with psoriasis as a primary diagnosis or had received at least one treatment for moderate to severe psoriasis (Table SI[1]). In order for patients to be classified as having severe psoriasis based on a filled prescription, the prescription had to be issued by a physician with a specialty other than rheumatology or gastroenterology. The reason for this requirement is that these medications are used also in the management of rheumatic diseases, Crohn's disease and ulcerative colitis. All patients not classified as having severe psoriasis were assigned to the mild cohort.

Follow-up time

The follow-up period for patients with mild disease and patients with severe disease (and corresponding referents) started at the date of the first registered diagnosis and the first date consistent with severe disease, respectively. Hence, follow-up started at the same date for patients and the corresponding referents. Patients with severe disease (and corresponding referents) did not contribute any follow-up time to the mild cohorts, reflecting that all patients who were classified as having severe psoriasis were alive at the date of first registered event consistent with severe disease. The follow-up period ended on 31 January 2010, or the date of death or emigration, whichever came first.

End-points and covariates

The end-points of interest were all-cause mortality and cause-specific mortality as reported in the CDR. The 15 leading causes of death in the USA (22) were collapsed into 8 groups and 4 additional categories (suicide, accidents, missing causes of death, and all other causes [defined as the residual mortality remaining after all specific causes of death had been accounted for]). The categories and the corresponding ICD codes are presented in Table SII[1].

Patient characteristics at the start date were described in terms of sex, age, years of follow-up and comorbidities. Comorbidities were identified based on ICD-10 codes in primary, specialist outpatient, or inpatient care up to 12 months prior to the start date. In addition to the 8 comorbidity groups, the Quan-Charlson Comorbidity Index (CCI) was derived (23). The index score is the sum of 19 predefined comorbidities that are assigned weights of 1, 2, 3, or 6, where a higher index score indicates a higher comorbidity burden.

Statistical methods

For baseline characteristics, comparisons among groups were conducted using *t*-tests for continuous variables and χ^2 tests for categorical variables. Absolute death rates were calculated as the number of deaths per 1,000 patient-years. The proportion of excess mortality attributable to a given cause of death was estimated by dividing the crude cause-specific excess mortality by crude all-cause excess mortality.

Cox proportional hazards models (24) were fit to estimate hazard ratios for each specific cause of death and all-cause mortality in patients and referents. For each cause of death, individuals were censored if they emigrated, died from other causes, or reached the study's end of follow-up. Hazard ratios (HRs) calculated in this manner assumes that competing risks do not exist. Nevertheless, this approach is recommended when the aim is to assess whether a factor (such as a disease) has biological relevance for an outcome with competing risks (such as death from a specific cause of death) and the results are valid for a population with similar characteristics regardless of the rate of competing risks (25). Furthermore, statistical significance of the HRs are reliable tests of association (26).

Models were fit for each cause of death, for patients with mild disease and patients with severe disease, and with and without comorbidity covariates. Hence, 52 models were fit in total: 13 causes of death (12 for specific causes of death and 1 for all-cause mortality), for 2 populations (patients with mild and severe disease and respective reference populations), with 2 sets of covariates (with and without comorbidities). All models included sex and age at the start date as independent variables.

In the models with comorbidity status as covariates, each model included a dichotomous comorbidity variable that took the value 1 if the subject had a diagnosis that was included in the group of ICD-10 codes that comprised the relevant cause of death groups (Table SII[1]). For example, in the models on deaths due to neoplasms, the comorbidity variable took the value 1 if at least one of the following ICD-10 diagnoses were present: C00–C97 and D00-D47. For accidents, suicide, and other causes of death, the CCI were included to control for comorbidity status instead of dummy variables for specific diagnoses. The reasons for this was that diagnoses codes for these events were infrequently used (accidents and suicide) or no relevant comorbidity group existed (other causes of death, and all-cause mortality). Comorbidities were elicited up to one year prior to the start date.

The proportional hazards assumption was investigated by graphical inspections of loess curves for Schoenfeld residuals and log(–log) plot of the survival distribution functions (27). Furthermore, interactions between the covariates in the model and time were included to explore the relationship between the regressors and follow-up time. The assumptions were found to be valid unless otherwise stated.

[1]https://doi.org/10.2340/00015555-2095

The software SAS (SAS for XP PRO, Release 9.2 TS2 M3, SAS Institute Inc. Cary, NC, USA) was used for statistical analyses.

Sensitivity analyses

Five sensitivity analyses on all-cause mortality were performed to assess whether the definitions of mild or severe psoriasis affected the base case results. For mild psoriasis the following 3 sensitivity analyses were performed: (*i*) patients with a non-primary psoriasis diagnosis were included in Cohort A; (*ii*) patients with diagnoses of pustular psoriasis or guttate psoriasis were excluded from Cohort A; (*iii*) referents without any registered healthcare visits were excluded from Cohort A1. For severe psoriasis, the following sensitivity analyses were performed: (*i*) patients who had a diagnosis of a rheumatic or gastrointestinal condition (relevant ICD-10 diagnoses are provided in Table SIII[1]) and received treatment with a traditional systemic or biologic therapy were excluded from Cohort B; and (*ii*) patients who were not hospitalized for psoriasis were excluded from Cohort B. Furthermore, unmeasured confounder analysis was used to assess the potential impact of unobserved variables on the association between outcome and exposure, where the models controlling for comorbidities indicated a positive significant association between psoriasis and mortality. The approach to unmeasured confounder analysis pursued in this study entails estimating the strength of an unmeasured confounder required to change the value of the HR to unity (no association) under assumptions on the prevalence of the risk factor in the patient and referent populations (28).

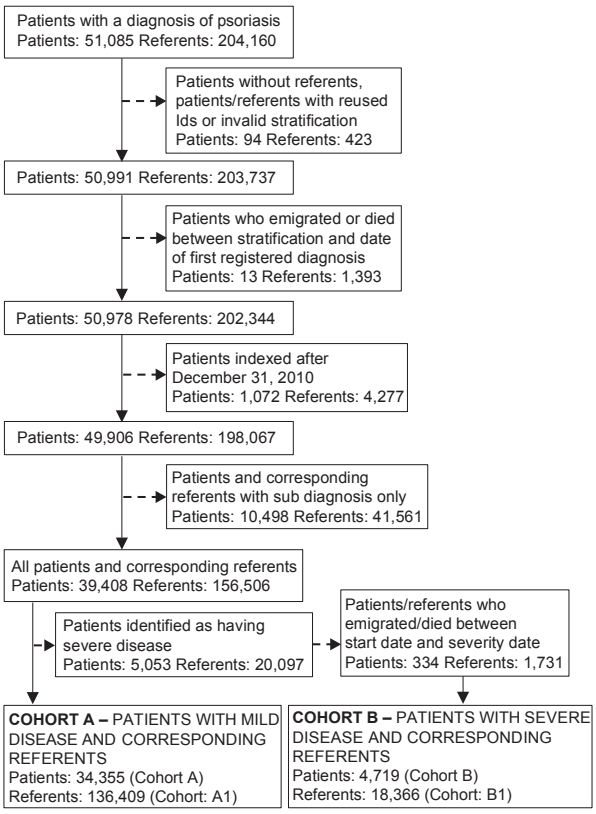

Fig. 1. Sequential sample selection of study subjects.

RESULTS

After application of exclusion criteria the study sample consisted of 39,074 patients with psoriasis and 154,775 age-, sex-, and residency-matched referents without psoriasis (Fig. 1). Approximately 12% of the patients with psoriasis were classified as having severe psoriasis.

Given the design of the study there were no statistically significant differences in age or sex between patients and referents in either the mild or severe cohorts (Table I). All comorbidity groups were more prevalent in both patients with mild disease and patients with severe disease compared with the corresponding referents ($p < 0.05$ for all comparisons). Furthermore, the overall comorbidity burden measured using the CCI was higher in both the patients with mild disease and patients with severe disease compared with corresponding referents ($p < 0.001$).

Crude all-cause mortality was higher in patients with mild disease and patients with severe disease compared with corresponding referents. Mortality was numerically higher for all specific causes of death except neurological disease in both patients with mild disease and patients with severe disease (Table II). Cardiovascular disease accounted for 48.3% of the increase in all-cause mortality in patients with mild psoriasis and 33.4% of the increase in patients with severe psoriasis. Patients with mild and severe psoriasis were on average 0.8 (76.3 vs. 77.2 $p < 0.01$) and 2.6 (76.6 vs. 74.0 $p < 0.01$) years younger than corresponding referents at time of death, respectively.

The diagnostic checks indicated that the proportional hazards assumption was not fulfilled given that the

Table I. *Baseline characteristics of the study population*

	Patients with mild disease			Patients with severe disease		
	Referents	Patients	*p*-value	Referents	Patients	*p*-value
Individuals, *n*	136,409	34,355		18,366	4,719	
Female, %	53.2	53.2	0.897	48.8	48.8	0.943
Age, years, mean ± SD	49.0 ± 19.3	49.1 ± 19.4	0.396	51.7 ± 15.8	51.9 ± 15.9	0.415
Years follow-up, mean ± SD	4.6 ± 2.8	4.6 ± 2.8	0.118	3.5 ± 2.0	3.4 ± 2.0	0.044
Comorbidities						
Charlson Comorbidity Index, mean ± SD	0.21 ± 0.95	0.26 ± 1.00	<0.001	0.25 ± 1.05	0.36 ± 1.09	<0.0001
Cardiovascular disease, %	6.6	8.3	<0.001	8.3	11.0	<0.0001
Neoplasm, %	3.9	4.7	<0.001	4.6	5.8	0.01
Diabetes mellitus, %	2.3	3.3	<0.001	3.1	5.1	<0.0001
Chronic lower respiratory disease, %	1.5	2.0	<0.001	1.6	2.1	0.01
Neurological disease, %	1.6	2.0	<0.001	1.9	2.3	0.05
Kidney disease, %	2.3	2.9	<0.001	2.8	3.5	0.01
Infection, %	4.2	7.6	<0.001	4.5	8.4	<0.0001
Liver disease, %	0.2	0.4	<0.001	0.3	0.5	0.052

Table II. *Number of deaths and crude mortality rates in the study population*

	Patients with mild disease					Patients with severe disease				
	Referents		Patients			Referents		Patients		
Cause of death	Deaths *n* (%)	Death rate[a]	Deaths *n* (%)	Death rate[a]	Excess rate[a]	Deaths *n* (%)	Death rate[a]	Deaths *n* (%)	Death rate[a]	Excess rate[a]
Cardiovascular disease	2,504 (36.5)	3.97	763 (38.0)	4.82	0.85*	257 (34.8)	4.03	101 (34.2)	6.28	2.25*
Neoplasm	2,026 (29.5)	3.21	540 (26.9)	3.41	0.19	238 (32.2)	3.73	84 (28.5)	5.22	1.49*
Diabetes mellitus	162 (2.4)	0.26	50 (2.5)	0.32	0.06	12 (1.6)	0.19	8 (2.7)	0.50	0.31**
Chronic lower respiratory disease	232 (3.4)	0.37	91 (4.5)	0.57	0.20*	25 (3.4)	0.39	7 (2.4)	0.44	0.04
Neurological disease	421 (6.1)	0.67	70 (3.5)	0.44	–0.23*	38 (5.1)	0.60	6 (2.0)	0.37	–0.22
Kidney disease	45 (0.7)	0.07	26 (1.3)	0.16	0.09*	7 (0.9)	0.11	3 (1.0)	0.19	0.08
Severe infection	252 (3.7)	0.40	93 (4.6)	0.59	0.19*	29 (3.9)	0.45	9 (3.1)	0.56	0.11
Liver disease	66 (1.0)	0.10	39 (1.9)	0.25	0.15*	11 (1.5)	0.17	12 (4.1)	0.75	0.57*
Suicide	84 (1.2)	0.13	27 (1.3)	0.17	0.04	12 (1.6)	0.19	3 (1.0)	0.19	0.00
Accidents	129 (1.9)	0.20	39 (1.9)	0.25	0.05	16 (2.2)	0.25	5 (1.7)	0.31	0.06
Other causes (Residual)	865 (12.6)	1.37	244 (12.2)	1.54	0.17	86 (11.6)	1.35	50 (16.9)	3.11	1.76*
Missing	82 (1.2)	0.13	25 (1.2)	0.16	0.03	8 (1.1)	0.13	7 (2.4)	0.44	0.31**
All-cause mortality	6,868 (100)	10.90	2,007 (100)	12.67	1.77*	739 (100)	11.58	295 (100)	18.33	6.76*

Comparisons conducted using a Cox model without controlling for comorbidities; [a]per 1,000 person years; *$p<0.01$; **$p<0.05$.

estimated HR for patients changed signs early in the follow-up for patients with mild disease. Therefore, models in which follow-up started one year after the initial start date were fit. In order to be included in the amended models, individuals had to survive the first year of follow-up. The results of the 2 sets of models were very similar, with the confidence intervals around the estimated HRs for each cause of death in the amended models covering the HR point estimates in the original models. Hence, the results of the original models are presented.

Controlling for comorbidity status at the start date attenuated the association between psoriasis and cause-specific mortality between 0.1% and 20.0% depending on mortality cause in patients with mild psoriasis and between 0.2% and 39.3% in patients with severe psoriasis. In patients with mild disease, the risks for all causes of death, except neurological disease and diabetes mellitus, were elevated. The associations were statistically significant at the 5% level for 6 causes of death: cardiovascular disease, chronic lower respiratory disease, kidney disease, severe infection, neurological disease, and liver disease. In patients with severe disease, the risks for 5 causes of death were statistically significantly elevated at the 5% level. Those were cardiovascular disease, cancer, liver disease, missing causes of death, and the composite group other causes of death (Fig. 2).

Five sensitivity analyses were performed to assess the findings from the main cohorts. The associations between psoriasis and all-cause mortality observed in the sensitivity analyses were similar to the associations observed in the main analyses (Table III).

The unmeasured confounder analysis showed that assuming a prevalence of the confounder of 20% in the psoriasis populations and 10% in the matched reference populations, the association between the confounder and the outcome that would force the associations between exposure and outcome to unity (no association) ranged from 1.5 to 12.0 in patients with mild psoriasis and 3.2 to 32.6 in patients with severe psoriasis depending on specific cause of death (Appendix S1[1]).

DISCUSSION

This study shows that both mild and severe psoriasis are associated with increased all-cause mortality and patients with mild and severe psoriasis die on average 0.8 and 2.6 years younger than age-, sex-, and residency-matched referents. The increases in all-cause mortality observed were largely driven by increased cardiovascular mortality, reflecting high absolute death rates in the total population. However, other causes of death were also elevated. In patients with mild disease, the estimated HRs when controlling for disease status at the start date were above 1.0 for all specific causes

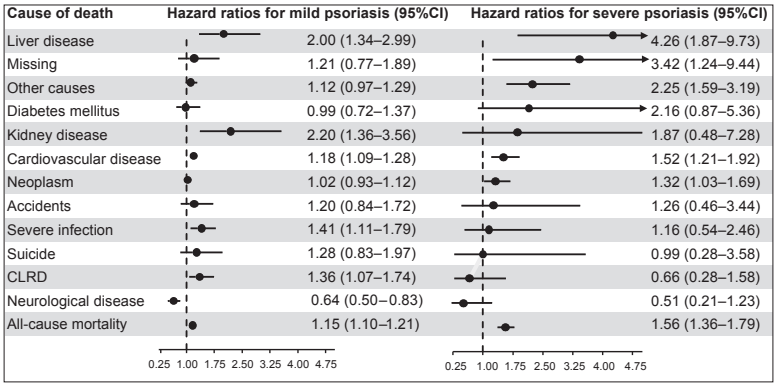

Fig. 2. Estimated hazard ratios for specific causes of death and all causes among patients with mild and severe disease compared with referents controlling for comorbidities.

Table III. *Sensitivity analyses of all-cause mortality*

Sensitivity analysis	Population	Hazard ratio (95% confidence interval)
Inclusion of patients with non-primary diagnosis	Mild psoriasis	1.21 (1.16–1.25)
Exclusion of patients with guttate of pustular diagnoses only	Mild psoriasis	1.14 (1.09–1.20)
Exclusion of referents with no registered healthcare visit	Mild psoriasis	1.14 (1.08–1.19)
Exclusion of all patients treated with systemics who had rheumatic or gastrointestinal disease	Severe psoriasis	1.79 (1.53–2.08)
Severe psoriasis classified as hospitalization with psoriasis as primary cause	Severe psoriasis	2.04 (1.64–2.52)

of death except neurological disease and diabetes mellitus; the associations were statistically significant for 6 of 12 specific causes of death and all-cause mortality. The strongest associations were observed for kidney disease (HR = 2.20, $p < 0.01$), and liver disease (HR = 2.00, $p < 0.001$). In patients with severe disease, when controlling for comorbidity status at the start date, the estimated HRs were above 1.0 for all specific causes of death except neurological disease, chronic lower respiratory disease and suicide. The associations were statistically significant for 5 of 12 specific causes of death and all-cause mortality. The strongest associations were observed for liver disease (HR = 4.26, $p < 0.001$), missing cause of death (HR = 3.42, $p = 0.02$), and other causes of death (HR = 2.25, $p < 0.001$).

In patients with mild disease, the association between psoriasis and death due to neurological disease was below 1 (HR 0.64, CI 0.50–0.83). Whilst the association between psoriasis and death due to neurological disease was similar in patients with severe psoriasis (HR 0.51, CI 0.21–1.23), it did not reach statistical significance, potentially due to insufficient sample size.

The results of this study support previous findings of elevated all-cause mortality in patients with severe psoriasis (3–6). Furthermore, previous associations between severe psoriasis and death due to cardiovascular disease (7–9), cancer (7, 8, 10) and liver disease (7, 10, 11) were confirmed. In contrast to previous analyses, this study controlled for the presence of the disease leading to death, strengthening the argument for a causal association between severe psoriasis and these causes of death. For patients with mild disease, a modest, but statistically significant, increase in all-cause mortality was found; a result that is in line with 2 of 3 previous studies (3, 4, 6). Whilst associations between psoriasis and liver disease (29) and psoriasis and kidney disease (30) have been observed previously, to our knowledge, findings of sizable and statistically significant associations between mild psoriasis and death due to liver disease and kidney disease have not been reported previously.

Psoriasis appeared to be inversely related to death due to neurological disease. This inverse association was not seen for severe patients in a UK study; on the contrary, Abuabara et al. (7) found a significant positive association between psoriasis and death due to dementia in patients with severe psoriasis. However, Stern & Huibregtse (10) reported no deaths due to dementia in a cohort of severe patients with psoriasis, although it is unclear whether this result is a true finding or a result of the data extraction (i.e. that deaths due to dementia were not identified in the study) (31).

The main strengths of this study are the following: The study design was population based, direct comparisons of patients with mild psoriasis and severe psoriasis to a reference population were conducted; comorbidity status at the start date was included in the regression models; patients were identified based on diagnoses rather than filled prescriptions; and the definition of severe psoriasis included both hospitalization and treatments.

The limitations of the study pertain to the nature of retrospective database analysis. For example, it is possible that some individuals did not seek care for their psoriasis or that psoriasis was not registered as a diagnosis, resulting in that those patients would have been omitted from the analysis or misclassified as referents. In this context, it may be interesting to note the higher risk of death in matched referents compared with patients observed in the period immediately after the first registered diagnosis. It is possible that seriously ill patients with psoriasis are not diagnosed with psoriasis, at least not as a primary diagnosis. This notion is supported by the slightly increased HR for all-cause mortality in the analysis when patients with only a secondary diagnosis were included in the analyses. Nevertheless, reflecting that secondary diagnoses are likely to be less certain than primary diagnoses and potentially result in misclassification bias, we elected to restrict the cohort to patients with at least one primary diagnosis. In this context it is important to note that the sensitivity and specificity of psoriasis diagnoses in VEGA or the SHCR have not been reported. However, the SHCR have high predictive value for psoriasis (21). Furthermore, given that retrospective data do not include clinical assessments; it was not possible to validate the classification of psoriasis into mild and severe using clinical measures such as the Psoriasis Assessment Severity Index (PASI). However, systemic treatment and hospitalizations with psoriasis as a primary diagnosis have been used to identify severe psoriasis in numerous studies (3–7, 9, 12).

Another limitation is that the SPDR does not contain data on indications for prescriptions. In the base case, we classified patients who were prescribed systemics or

biologics from a rheumatologist or gastroenterologist as patients with mild psoriasis. Hence, patients who were diagnosed with psoriasis but treated with systemics or biologics for another indication may have been misclassified as having severe psoriasis. However, in a sensitivity analysis all patients who were treated with systemics and biologics and had at least one primary diagnosis of relevant rheumatic or gastrointestinal disease were excluded from the severe population. The resulting point estimate for all-cause mortality increased compared with the base case, albeit with the base case point estimate covered by the confidence interval around the sensitivity point estimate. This implies that substantial misclassification bias for this reason is unlikely.

The rationale for measuring comorbidity status up to one year prior to the start date rather than during follow-up was to reduce the risk of interfering with the causal pathway between psoriasis and mortality. However, it should be noted that we did not identify an incident population, meaning that the problem may still remain. Furthermore, to the extent psoriasis and relevant comorbidities results from a common cause, controlling for comorbidities prior to the start date rather than during follow-up may inflate the estimated association between psoriasis and cause-specific and all-cause mortality.

The data underlying this analysis did not include important risk factors for mortality, such as smoking and obesity, potentially resulting in residual confounding. However, in patients with severe psoriasis an unmeasured confounder would have to be prevalent and carry a very high risk to nullify the findings. For example, for all-cause mortality, a risk factor prevalent in 10% of the referents would have to have a prevalence of 20% in patients with severe psoriasis and carry a HR of 3.6 to render the association between psoriasis and all-cause mortality insignificant; a highly unlikely scenario. This estimate can be compared with smoking, which has been associated with an HR for all-cause mortality of 1.3–1.8, depending on the number of cigarettes smoked per day (32).

We chose to highlight both the relative and the absolute excess risks for cause-specific mortality. Whilst absolute cause-specific death rates can inform prevention efforts on the population level, relative risks may highlight the importance of specific interventions in certain patients. Cardiovascular disease is the main driver of excess mortality in psoriasis on the population level. This result supports the notion that screening patients with psoriasis for cardiovascular risk factors may be appropriate. In addition, the results also highlight the importance of prevention efforts in patients susceptible to other diseases, such as liver disease.

In summary, this study shows that mild and severe psoriasis are associated with increased all-cause mortality. The increased all-cause mortality was primarily driven by cardiovascular disease. However, the risk for other specific causes of death, including liver and kidney disease, also appeared elevated in these patient populations, even when controlling for the presence of diagnoses of the relevant diseases at the start date. Furthermore, it is unlikely that the associations stem from unmeasured confounders. Further research is needed, preferably with more patients with severe disease, reducing the uncertainty for comparatively infrequent causes of death. A larger study may also facilitate stratification of deaths due to neurological disorders into several categories, providing more detail on the inverse relationship between psoriasis and deaths due to neurological disorders observed in this study. In addition, studies incorporating lifestyle factors and clinical measurements would be beneficial to better elucidate the relationship between psoriasis and cause-specific mortality.

ACKNOWLEDGEMENTS

This study was sponsored by Pfizer Inc. AS and JD are employees of OptumInsight, who were paid consultants to Pfizer in connection with the development of this manuscript.

Conflicts of interest. CM, JC and LM are employees and shareholders of Pfizer Inc; as employees of OptumInsight, JD and AS have provided consultancy services to numerous companies involved in the marketing of treatment for psoriasis; IP has received honoraria for educational lectures from Pfizer, Abbvie, UCB Pharma; MS has received honoraria for serving as advisor and for participating in symposia arranged by Abbvie, Novartis, Pfizer, Eli Lilly and Janssen-Cilag.

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