Risk of hospitalization and death due to infection in people with psoriasis: a population-based cohort study using the Clinical Practice Research Datalink

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Summary

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Background Psoriasis is associated with risk factors for serious infections, but the independent relationship between psoriasis and serious infection is as yet unclear.

Objectives To determine whether people with psoriasis have a higher risk of hospitalization due to any infection, respiratory infections, soft-tissue and skin infections, or a higher risk of death due to infection.

Methods We conducted a cohort study of people (≥ 18 years) with psoriasis using the UK Clinical Practice Research Datalink (CPRD GOLD) linked to Hospital Episode Statistics (HES) and Office for National Statistics (ONS) mortality records between 1 April 2003 and 31 December 2016, and matched with up to six comparators on age, sex and general practice. Hospitalization was ascertained from HES records; death was ascertained from ONS mortality records. Stratified Cox proportional hazard models were estimated, with stepwise adjustment in different models for potential confounders or mediators between psoriasis and serious infection.

Results There were 69 315 people with psoriasis and 338 620 comparators who were followed up for a median (interquartile range) of 4·9 (5·9) and 5·1 (6·3) years, respectively. People with psoriasis had a higher incidence rate of serious infection [20·5 per 1000 person-years, 95% confidence interval (CI) 20·0–21·0, n = 7631] compared with those without psoriasis (16·1 per 1000 person-years, 95% CI 15·9–16·3, n = 30 761). The fully adjusted hazard ratio for the association between psoriasis and serious infection was 1·36 (95% CI 1·31–1·40), with similar results across the other outcomes.

Conclusions Psoriasis is associated with a small increase in the risk of serious infection. Further research is needed to understand how psoriasis predisposes to a higher risk of infection.

> **What is already known about this topic?**
>
> - Several studies have shown that people with psoriasis have a higher risk of hospitalization due to infection, but these studies are limited by residual confounding for lifestyle factors or underestimation of the true incidence of hospital admissions from primary care electronic health records.

What does this study add?

- Using a large primary care database linked with secondary care Hospital Episode Statistics, we found that, after adjusting for potential confounders and mediators, the hazard ratio for the association between psoriasis and the development of serious infection was 1·36 (95% confidence interval 1·31–1·40).
- In summary, we show that having psoriasis is independently associated with a small but increased risk of serious infection.

Psoriasis is a chronic and debilitating disease leading to significant morbidity. An important concern of patients with psoriasis and healthcare professionals is whether psoriasis is associated with serious infections, defined as infections that lead to hospitalization and are therefore associated with significant morbidity and/or mortality.

A significant contributor to the ill health of patients with psoriasis is the association with multiple comorbid conditions. The causal direction of the relationships between psoriasis and these conditions is complex and incompletely understood, but associations between psoriasis and potential risk factors such as obesity, high alcohol intake and smoking have been recognized in multiple observational studies.[1–4] However, there is uncertainty over whether having psoriasis predisposes to a higher risk of serious infection independent of these other factors. Studies that have investigated the relationship between psoriasis and serious infection have been limited thus far by a lack of adjustment for lifestyle factors[5] and potential misclassification by trying to determine hospital admissions using primary care electronic health records.[6,7]

Our aim in this study was to investigate the risk of hospitalization and death due to infection in patients with psoriasis in a large population-based UK cohort of primary care patients with linked hospital and mortality records.

Methods

Study design and setting

We performed a cohort study using data from the UK Clinical Practice Research Datalink (CPRD GOLD). The CPRD GOLD is a primary care database of prospectively collected anonymized medical records, covering patient information from general practices in the UK. Clinical events, including diagnoses, are coded using Read codes.[8] We utilized the data from a subset of general practices from England that were eligible for linkage to the national Hospital Episode Statistics (HES), Office for National Statistics (ONS) mortality records and Index of Multiple Deprivation 2010 (IMD) data.[9] The IMD is calculated based on the postcode of the place of residence of the individual, and is an area-level index of deprivation. In the linked data, diagnoses are coded using International Classification of Diseases, 10th revision (ICD-10) codes and procedures are coded using the Office of Population Censuses and Surveys Classification of Interventions and Procedures codes.

Study population

Adults (≥ 18 years) with psoriasis who had linked HES, ONS and IMD data and had been registered with their practice for at least 1 year prior to the first coded diagnosis of psoriasis in the study window from the CPRD were eligible for this study. Incident density sampling was used to identify up to six comparators matched by exact age, sex and general practice on index date to each patient with psoriasis. Comparators had to have had a consultation with the general practice within 6 months before or after the index date of the people with psoriasis to whom they were matched to be included. The study period was between 1 April 2003 and 31 December 2016. All individuals were followed up from the index date to the earliest date out of the outcome of interest, end of the study period, last date of data collection from the practice, date on which the patient transferred out from the practice, or the date of death (Figure 1).

Exclusion

Individuals with a history of hospitalization due to infection prior to the index date were identified using the main outcome codes from the linked HES data and were excluded from analysis. We also excluded individuals with a diagnosis of human immunodeficiency virus infection prior to the index date.

Definition of severe and active psoriasis

Two stratification methods were used to identify people who had severe psoriasis, and people who had predominantly active psoriasis. Individuals were defined as having severe psoriasis from the timepoint when they received a systemic treatment (acitretin, etretinate, ciclosporin, hydroxycarbamide, methotrexate and fumaric acid esters), phototherapy or a biologic therapy (etanercept, adalimumab, infliximab, ustekinumab, secukinumab and efalizumab) until the end of follow-up time using data from primary care records; i.e. as a time-varying covariate.
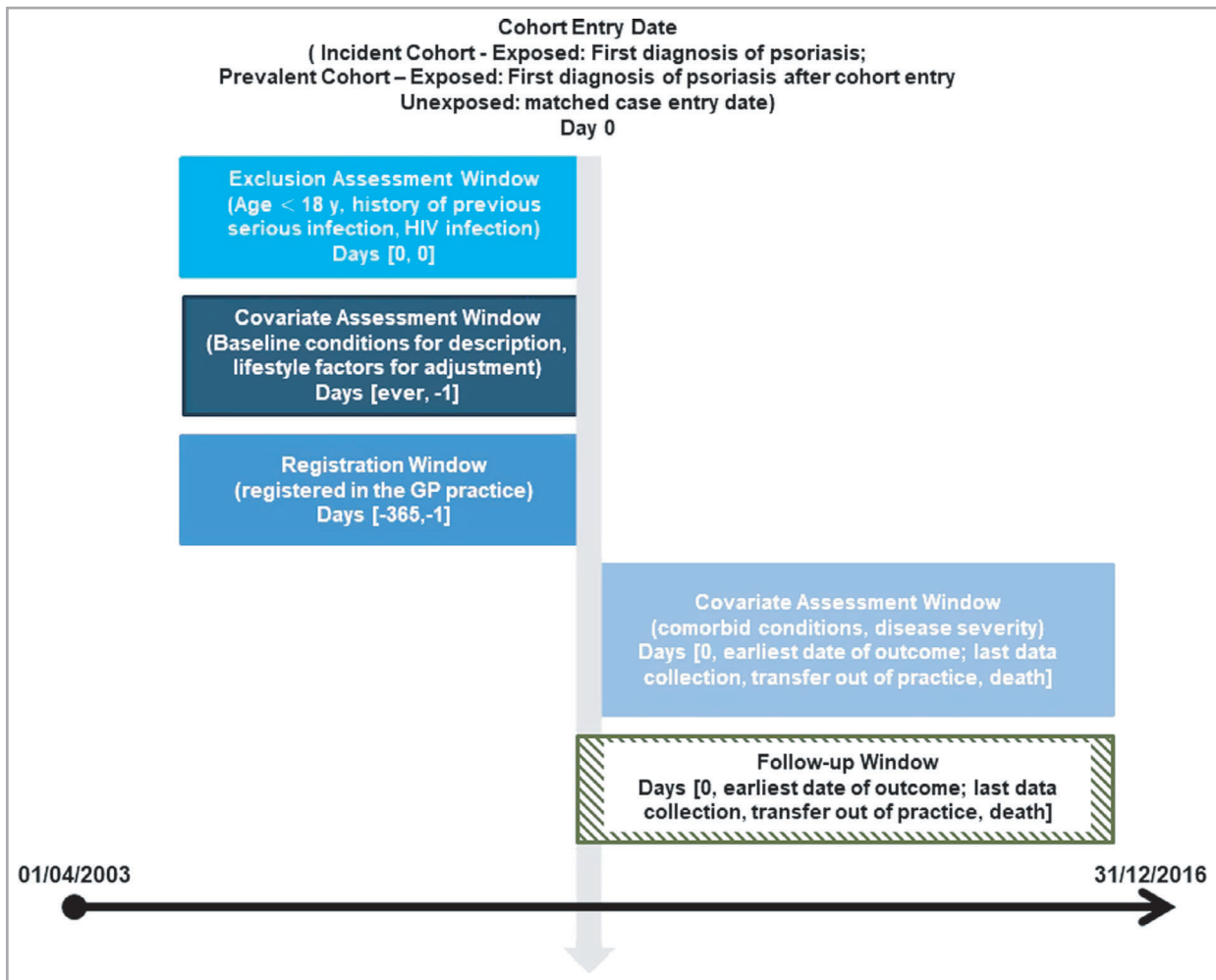
Fig 1. Graphical depiction of cohort study design, describing the setting, relevant dates of cohort entry, follow-up, covariate assessment and exit of the cohort.

Similar to a recent publication about atopic eczema,[10] individuals were classified to have active psoriasis at the latest of two CPRD or HES psoriasis records of either diagnoses or treatment appearing within a period of 1 year. Active psoriasis was assumed to last for 1 year, and prolonged for another year if another psoriasis entry was recorded before the year ended. People with psoriasis were then categorized into those who had no active psoriasis during follow-up, those who had active psoriasis for less than 50% of follow-up, and those who had active psoriasis for at least 50% of follow-up.

A sensitivity analysis was performed to improve the identification of people with severe psoriasis. Using data from the linked outpatient HES records, we improved the classification of phototherapy using the linked HES phototherapy records. We further defined severe psoriasis as people with psoriasis consulting a dermatologist in secondary care more than twice in 1 year, with the definition of severe psoriasis starting from the timepoint of the second consultation.

Identification of outcomes

The primary outcome of hospitalization due to infection and the secondary outcomes of hospitalization due to respiratory and skin/soft-tissue infections were identified using linked data from HES, with any code in any episode. Death due to infection was identified from the primary cause of death listed in the ONS mortality records. The list of infections is provided in Table S1 (see Supporting Information). To test for potential unmeasured confounding, we included a negative control outcome, namely hospitalization due to transport accident. This outcome was chosen as there was little biological plausibility for this to be associated with psoriasis, and we were able to control for confounding from alcohol between psoriasis and transport accidents. This outcome was identified from the linked HES data. All ICD-10 codes for the outcomes are listed in Table S1 (see Supporting Information) and are listed via the Clinical Codes repository[11] at https://clinicalcodes.rss.mhs.man.ac.uk.

Covariates

We developed a directed acyclic graph to identify covariates that might be potential confounders, mediators or colliders (Figure S1; see Supporting Information). We identified two tiers of covariates to adjust for in the analysis. The first tier included covariates that are plausible potential confounders. These included age, IMD status, body mass index (BMI), alcohol intake and smoking status. Age was mean-centred and modelled as a cubic term to account for nonlinearity. BMI was determined using the mibmi command in Stata,[12] and the closest BMI to the index date was taken. BMI readings taken more than 5 years before or after the index date were classed as missing. Alcohol intake was established using an existing algorithm[13] where the most recent record prior to or recorded on the index date was used. Smoking status was also established using an existing algorithm using information closest to the index date,[14] and separated into current, former and never smokers.

The second tier included covariates that were comorbid conditions that could be confounders or mediators for the relationship between infection and psoriasis. These included other immune-mediated inflammatory diseases (IMID, a composite covariate representing rheumatological conditions, inflammatory bowel disease and multiple sclerosis), diabetes and chronic obstructive pulmonary disease (COPD). Diabetes, IMIDs and COPD were included as time-varying covariates.

Statistical analyses

We estimated incidence rates of the primary and secondary outcomes for the psoriasis and comparison cohorts. We used Cox proportional hazards regression, stratified by matched set, to obtain hazard ratios (HRs) and 95% confidence intervals

(CIs) to investigate the association between psoriasis and the primary and secondary outcomes. We tested for potential effect modification for age and sex with psoriasis. If this test was significant, we explored the impact of effect modification in separate stratified models, and also included an interaction term to account for this in the multivariable regression models. We also tested for the proportionality assumption for the effect of having psoriasis on serious infection using log–log plots and comparisons between Kaplan–Meier observed survival curves and Cox predicted curves.

We performed several models sequentially including the different aforementioned groups of covariates to estimate the potential association; and to understand the effect of each group of covariates between the relationship of the exposure and the outcome. To investigate the effect of missing data, we performed multiple imputations of 20 datasets in the primary analyses, and complete case analysis was performed as a sensitivity analysis. Table 1 shows the other different sensitivity analyses that were conducted. We also calculated absolute risk differences for 5 years and 10 years after diagnosis using the nonparametric baseline survival and the estimated linear predictor from the Cox model.

This study was approved by the Independent Scientific Advisory Committee (ISAC) for Medicines and Healthcare Products Regulatory Agency database research (ISAC approval 18_012R). Analyses were performed using Stata version 15 (StataCorp, College Station, TX, USA). This study is reported according to the RECORD guidelines.[15]

Results

A total of 69 315 people with psoriasis and 338 620 comparison individuals were eligible for inclusion in the study

Table 1 Sensitivity analyses

Sensitivity analysis	Justification
The primary analysis was repeated in restricted psoriasis cohorts of mild or severe psoriasis. As this is a time-varying covariate, follow-up for mild psoriasis would be censored if the patient developed severe psoriasis when mild psoriasis cohort was restricted for	To investigate whether the risk of serious infection associated with psoriasis varies with severity of psoriasis or if it is associated with systemic therapies for psoriasis
The primary analysis was repeated on an incident psoriasis cohort	To limit the impact of left-censorship, especially because covariates measured at entry will precede onset of psoriasis for this subgroup and therefore will not be on the causal pathway between psoriasis and infection
The overall cohort was restricted to those having average mean consultations over one, three and five per year during follow-up	To investigate the potential impact of detection bias
The secondary outcome was substituted by hospitalization due to lower respiratory tract infection, and two analyses performed, one with the outcome obtained from Read codes and one from ICD-10 codes	To investigate whether misclassification could be introduced if primary care health records were used to determine infection, assuming that hospital ICD-10 codes are the gold-standard way of measuring hospitalization. Read codes from a recent study on serious infection risk in patients with psoriasis were used,[6] determining the outcomes from cases which led to hospitalization within 30 days

ICD, International Classification of Diseases.

Table 2 Comparison of characteristics at baseline for psoriasis and comparison cohorts

Baseline characteristics	Comparison cohort (n = 338 620)	Psoriasis cohort (n = 69 315)
Age (years), median (IQR)	49·0 (27·0)	48·0 (28·0)
Male, n (%)	154 159 (45·5)	33 522 (48·4)
Body mass index (kg m^{-2}) categories, n (%)		
Underweight, < 18·5	5285 (1·6)	949 (1·4)
Normal, 18·5–24·9	94 061 (27·8)	18 136 (26·2)
Overweight, 25·0–29·9	91 810 (27·1)	19 688 (28·4)
Obese, ≥ 30·0	67 100 (19·8)	16 820 (24·3)
Missing	80 364 (23·7)	13 722 (19·8)
Alcohol intake, n (%)		
Nondrinker	29 565 (8·7)	5552 (8·0)
Light drinker	47 899 (14·1)	9291 (13·4)
Former drinker	26 415 (7·8)	5700 (8·2)
Moderate drinker	129 963 (38·4)	25 736 (37·1)
Heavy drinker	44 761 (13·2)	11 471 (16·5)
Missing	60 017 (17·7)	11 565 (16·7)
Smoking status, n (%)		
Never smoker	137 263 (40·5)	22 773 (32·9)
Ex-smoker	101 915 (30·1)	23 378 (33·7)
Current smoker	92 008 (27·2)	22 506 (32·5)
Missing	7434 (2·2)	658 (0·9)
Index of multiple deprivation score quintile, n (%)		
1 (least deprived)	82 762 (24·4)	16 273 (23·5)
2	78 559 (23·2)	15 454 (22·3)
3	67 463 (19·9)	13 944 (20·1)
4	61 620 (18·2)	13 101 (18·9)
5 (most deprived)	47 938 (14·2)	10 485 (15·1)
Missing	278 (0·1)	58 (0·1)
Comorbidities at baseline, n (%)		
COPD	6909 (2·0)	2397 (3·5)
Diabetes	18 433 (5·4)	4132 (6·0)
Immune-mediated inflammatory diseases, n (%)		
All	5891 (1·7)	2935 (4·2)
Inflammatory bowel disease	628 (0·2)	807 (1·2)
Multiple sclerosis	0 (0·0)	170 (0·2)
Rheumatological diseases	5284 (1·6)	1963 (2·8)
Disease characteristics at baseline, n (%)		
Severe psoriasis	–	2324 (3·4)
No active psoriasis	–	11 841 (17·1)
Active psoriasis < 50% F/U	–	15 456 (22·3)
Active psoriasis ≥ 50% F/U	–	42 018 (60·6)

COPD, chronic obstructive pulmonary disease; F/U, follow-up; IQR, interquartile range.

(Figure S2; see Supporting Information). At cohort entry, the median age and interquartile range (IQR) for the psoriasis and comparison cohorts were 49·0 (27·0) and 48·0 (28·0), respectively (Table 2). There was a higher prevalence of obese individuals in the psoriasis cohort (24·3%) compared with the comparison cohort (19·8%). There was also a higher prevalence of heavy drinkers (16·5%) and current smokers (32·5%) in the psoriasis cohort compared with the comparison cohort (13·2% and 27·2%, respectively; Table 2). Similarly, there was a higher prevalence of all included comorbidities at baseline in the psoriasis cohort compared with those without psoriasis. Within the psoriasis cohort, 2324 individuals (3·4%) had severe psoriasis at baseline. Most individuals (82·9%) in the psoriasis cohort had active psoriasis over their follow-up period (Table 2).

Overall, 7631 (11·0%) of the psoriasis cohort and 30 761 (9·1%) of the comparison cohort developed an infection requiring hospitalization within a median (IQR) of 4·9 (5·9) and 5·1 (6·3) years of follow-up, respectively. The crude incidence rate of hospitalization due to any infection was 20·5 per 1000 person-years (95% CI 20·0–21·0) in the psoriasis cohort compared with 16·1 per 1000 person-years (95% CI 15·9–16·3) in those without psoriasis. Similarly, there were higher crude incidence rates for hospitalization due to respiratory infections, soft-tissue and skin infections, and death due to any infection in the psoriasis cohort compared with the comparison cohort (Table 3). The incidence rate of infection requiring hospitalization was similar between the prevalent and incident psoriasis subgroups. However, the incidence rate of infections requiring hospitalization was higher during the

Table 3 Event count and incidence rates of primary and secondary outcomes in the psoriasis and comparison cohorts

Characteristics	Comparison cohort	Psoriasis cohort
Patients per cohort, n	338 620	69 315
Follow-up (median, IQR) years	5·1 (6·3)	4·9 (5·9)
Median survival time (95% CI), years	16·2 (16·0–16·4)	13·7 (13·7–13·7)
Person-years	1 911 456	372 353
Hospitalization due to any infection[a]		
N (%)	30 761 (9·1%)	7631 (11·0%)
Incidence rate per 1000 person-years (95% CI)	16·1 (15·9–16·3)	20·5 (20·0–21·0)
Hospitalization due to respiratory infections[a]		
N (%)	11 626 (3·4%)	2791 (4·0%)
Incidence rate per 1000 person-years (95% CI)	6·1 (6·0–6·2)	7·4 (7·1–7·7)
Hospitalization due to soft-tissue and skin infections[a]		
N (%)	3818 (1·1%)	1167 (1·7%)
Incidence rate per 1000 person-years (95% CI)	2·0 (1·9–2·1)	3·1 (2·9–3·3)
Death due to any infection		
N (%)	2656 (0·8%)	613 (0·9%)
Incidence rate per 1000 person-years (95% CI)	1·4 (1·3–1·4)	1·6 (1·5–1·7)

CI, confidence interval; IQR, interquartile range. [a]First hospitalization due to infection event.

BMI categories show a higher risk of serious infection in the underweight category (HR 2·07, 95% CI 0·83–5·15) (data not shown), while there was an increasing risk of serious infection with increasing age categories defined by quintiles (Table S3; see Supporting Information). The log–log plot did not indicate a violation to the proportionality assumption.

The fully adjusted HR for comorbid conditions and lifestyle factor covariates was 1·36 (95% 1·31–1·40, Table 4). There were similar findings across the secondary outcomes, with the highest adjusted HR found for skin and soft-tissue infections (HR 1·56, 95% CI 1·43–1·70). The HR for the negative control outcome was not significantly raised in the unadjusted analysis (HR 1·09, 95% 0·96–1·24) and the adjusted analysis (HR 1·14, 95% CI 1·00–1·31, Table 4). The complete case models yielded similar results with higher effect estimates for the control outcome (HR 1·30, 95% CI 1·09–1·55, Table S4; see Supporting Information).

There was a higher unadjusted HR for serious infection in the incident psoriasis cohort (HR 1·56, 95% CI 1·51–1·61) compared with the prevalent psoriasis cohort (HR 1·28, 95% CI 1·23–1·32), but little difference in the effect estimates after adjustment (Table S5; see Supporting Information). The unadjusted and adjusted HRs for serious infection were also similar between mild and severe psoriasis exposure time with the sensitivity analysis including outpatient HES information to enhance severity definition yielding little difference in the estimated outcomes. There appeared to be a dose–response relationship with increasing serious infection risk with increased activity of psoriasis (Table S5; see Supporting Information). The sensitivity analysis investigating the effect of restricting to different number of average consultations per year found attenuated effect estimates for serious infection (Table S6; see Supporting Information).

When exploring the benefit of using linked HES records to ascertain infection outcomes rather than primary care records, we found an overall incidence rate for serious lower respiratory tract infections (LRTIs) of 2·2 (95% CI 2·1–2·2) per 1000 person-years using Read codes to ascertain LRTI hospitalizations and 3·2 (95% CI 3·1–3·3) using ICD-10 codes to ascertain LRTI hospitalizations. The use of Read codes also introduced differential misclassification leading to a change in

severe psoriasis exposure time compared with those in the mild psoriasis exposure time, and higher during the active psoriasis exposure time compared with people with nonactive psoriasis exposure time (Table S2; see Supporting Information).

The unadjusted HR for hospitalizations due to any infection was 1·46 (95% 1·42–1·50) (Table 4). There was evidence of variation of the risk of infection by age (P < 0·001, Table S3; see Supporting Information). The stratified unadjusted HRs for

Table 4 Hazard ratios (95% confidence intervals) for primary and secondary outcomes comparing the people with psoriasis with the comparison cohort (multiple imputation analysis)

Analysis	Unadjusted	Model 1[a]	Model 2[b]
Hospitalizations due to any infection	1·46 (1·42–1·50)	1·36 (1·31–1·41)	1·36 (1·31–1·40)
Hospitalization due to respiratory infections	1·44 (1·38–1·51)	1·37 (1·29–1·46)	1·35 (1·27–1·44)
Hospitalization due to skin and soft-tissue infections	1·68 (1·56–1·81)	1·55 (1·42–1·69)	1·56 (1·43–1·70)
Death due to infection	1·30 (1·18–1·43)	1·40 (1·14–1·71)	1·33 (1·08–1·63)
Control outcome: hospitalization due to transport accidents	1·09 (0·96–1·24)	1·14 (1·00–1·30)	1·14 (1·00–1·31)

[a]Adjusted for age (mean-centred and modelled as a cubic term), Index of Multiple Deprivation, body mass index, alcohol intake, smoking status, interaction term between psoriasis and age; missing data imputed. [b]Covariates adjusted in Model 1 + diabetes, chronic obstructive pulmonary disease, other immune-mediated inflammatory diseases; missing data imputed.

the relative risk with a small overestimate of the effect of psoriasis on the risk of serious infection with a HR of 1·40 (95% CI 1·23–1·59) compared with using ICD-10 codes (HR 1·33, 95% 1·21–1·47, Table S7; see Supporting Information).

Discussion

We found that people with psoriasis had an increased risk of hospitalization due to any infection. Hospitalizations due to respiratory infections, soft-tissue and skin infections were also increased. We also identified that people with psoriasis had a higher risk of death due to any infection compared with people without psoriasis. The elevated risk was attenuated but persisted after adjustment for potential confounders and mediators. We did not find a dose–response relationship between severity of psoriasis and serious infection, but we found that having active psoriasis for over half of the follow-up period was associated with the highest risk of serious infection.

The use of linked HES data to ascertain the primary and secondary outcome helps to avoid outcome misclassification and is a major strength of this study. HES data are used for monitoring of secondary care activity and activity-based payment, and as such are highly robust. Forty-four per cent of all hospitalizations recorded in HES, using people with diabetes as an exemplar,[7] were not captured in the CPRD within ± 30 days. We found that the use of primary care data alone to ascertain hospitalization outcome for LRTI would have underestimated the incidence rate by 31% (Table S7; see Supporting Information). The use of outpatient HES data, especially including data on phototherapy, also helps avoid misclassification of disease severity. We were able to include lifestyle factors and BMI from the rich primary care data in the CPRD, enabling us to adjust for these important potential confounders and/or mediators. The CPRD is representative of the general population of the UK.[16]

There is potential for exposure, comorbidity and disease severity misclassification, as these definitions are not predefined but rather extracted through the use of coding algorithms, and we lack quantitative measures of disease severity. Specifically, capture of systemic medication use for the treatment of psoriasis is low and likely to introduce misclassification. However, the use of validated coding algorithms, for example to ascertain people with psoriasis[17] and the comorbidities,[12,18] reduces the risk of misclassification. There are missing data for some of the covariates, and we may not be able to account for this adequately if the data were not missing at random. Our analysis focusing on psoriasis activity across the follow-up period should be interpreted with care as those with a shorter or longer duration of follow-up might be more likely to have active disease for the majority of the follow-up and these analyses are not time-updated.

There is also potential for residual confounding and detection bias. The sensitivity analysis restricting for increasing average mean consultations throughout follow-up, which may be a proxy for either unmeasured confounding through multimorbidity or an increased propensity for seeking healthcare consultations, found a persistent but attenuated elevated risk of serious infection in people with psoriasis. Similarly, we found an elevated risk of death due to infection in people with psoriasis, suggesting that detection bias does not fully explain the association between psoriasis and infection. Contrary to the other studies, we did not find a dose–response relationship between psoriasis severity, modelled as a time-varying covariate, and infection. As psoriasis severity is defined by exposure to systemic treatments, it is surprising that the exposure time with the addition of systemic treatments in people with psoriasis was not associated with an increased risk for serious infection, suggesting that there was misclassification for this variable.

There are similarities between our findings and two earlier observational studies that have also investigated the relative risk of hospitalization due to infection in large population cohorts of people with and without psoriasis. A Dutch population-based cohort from the PHARMO Record Linkage System of 25 742 people with psoriasis found an incidence rate of serious infection of 9·1 per 1000 person-years in the psoriasis cohort, and crude and adjusted HRs of 2·08 (95% CI 1·96–2·22) and 1·58 (95% CI 1·48–1·68), respectively.[5] A key limitation of this study was the lack of data on lifestyle factors such as BMI, smoking and alcohol. A recently published study used data from The Health Improvement Network (THIN) in the UK, a similar primary care electronic medical records database to the CPRD.[6] This reported a crude incidence rate of serious infection of 7·9 per 1000 person-years in a cohort of 199 700 people with psoriasis. The study found a crude and adjusted HR of 1·14 (95% CI 1·12–1·16) and 1·21 (95% CI 1·18–1·23), respectively. An important limitation in this study was the use of primary care data only to ascertain hospitalization due to infection, which may explain the lower incidence rates.

In terms of the implications for patients and clinicians, there is an increased risk of serious infection associated with having psoriasis. This increased risk is consistent across the two most common site-specific infections – respiratory and soft-tissue/skin infections. We also found an increased risk of death due to infection in people with psoriasis. The absolute risk difference in probability of serious infection between people with psoriasis and the comparison group is low at 0·77% (95% CI 0·69–0·86%) at 5 years and 3·12% (95% CI 2·77–3·47%) at 10 years (Table S8; see Supporting Information). Patients should therefore be counselled that any increased risk of serious infection independently associated with having psoriasis is small.

The mechanism by which psoriasis predisposes to infection is unclear. Although there are higher levels of antimicrobial peptides such as β-defensin in plaques of psoriasis, we found a higher risk of cellulitis and soft-tissue infections in people with psoriasis. A maladaptive immune response to skin microbiota in psoriasis may explain these findings, with people with psoriasis more likely to be colonized with *Staphylococcus aureus* than healthy controls.[19] The skew towards an excessive inflammatory cytokine milieu in psoriasis, in particular tumour necrosis factor-α and interleukin 17,[20] can also be

associated with the inflammation and tissue damage seen in bacterial[21] and viral infections, and may be the reason for the higher associated morbidity and severity of infections in our cohort of people with psoriasis. Excessive levels of pro-inflammatory cytokines can lead to dysregulation of the immune response and induce pathological inflammatory changes associated with septic shock.[22,23]

In conclusion, people with psoriasis have a small but increased risk of serious infection compared with people without psoriasis. People with psoriasis should not be unduly concerned about the risk of serious infection associated with the disease, because the absolute risks are small. There was no evidence that psoriasis had a protective effect against skin and soft-tissue infections. Future research should consider mechanistic work to understand how psoriasis predisposes to a higher risk of infection.

Acknowledgments

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Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's website:

Table S1 Code list to define exposure and primary, secondary and control outcomes.

Table S2 Event count and incidence rates of primary outcome in the categories tested in the sensitivity analyses.

Table S3 Unadjusted univariable hazard ratios (95% confidence intervals) for the effect of psoriasis and risk of serious infection stratified by age quintiles.

Table S4 Hazard ratios (95% confidence intervals) for primary and secondary outcomes comparing the patients with psoriasis with the comparison cohort (complete case analysis).

Table S5 Hazard ratios (95% confidence intervals) for primary outcome in the categories tested in the sensitivity analyses, compared against the comparison cohort.

Table S6 Sensitivity analysis investigating the impact of frequent general practitioner consultations throughout follow-up on the effect estimates.

Table S7 Comparison of the incidence rate of lower respiratory tract infection and the adjusted model outcome between using Read codes in primary care health records and ICD-10 in inpatient Hospital Episode Statistics records.

Table S8 Calculation of absolute risk difference between cases and controls based on Model 3.

Fig S1. Directed acyclic graph showing the assumed relationships between psoriasis, the outcome of serious infection, and potential confounders, mediators and colliders.

Fig S2. Flowchart showing the selection of participants from Clinical Practice Research Datalink into this cohort study.