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

Z.Z.N. Yiu 1,2, R. Parisi 3, M. Lunt, R.B. Warren, C.E.M. Griffiths, S.M. Langan and D.M. Ashcroft

1Dermatology Centre, Salford Royal NHS Foundation Trust, NIHR Manchester Biomedical Research Centre, 2Division of Informatics, Imaging & Data Sciences, School of Health Sciences, 3Centre for Epidemiology Versus Arthritis, Centre for Musculoskeletal Research, School of Biological Sciences and 4Centre for Pharmacoepidemiology and Drug Safety, School of Health Sciences, University of Manchester, Manchester Academic Health Science Centre, Manchester, UK
5Faculty of Epidemiology, and Population Health, London School of Hygiene and Tropical Medicine, London, UK
6Centre for Science and Public Health Research, School of Health and Related Research, University of Manchester, Manchester, UK

Correspondence
Email: zenna.yiu@manchester.ac.uk

Accepted for publication
23 March 2020

Funding sources
Z.Z.N.Y. is supported by a National Institute for Health Research (NIHR) Academic Clinical Lectureship at the University of Manchester to perform this study. The views expressed are those of the author and not necessarily those of the National Health Service, the NIHR or the Department of Health. C.E.M.G., R.B.W and D.M.A. are funded in part by the Medical Research Council (MRC) (grant No. MR/L011808/1) and the NIHR Manchester Biomedical Research Centre. C.E.M.G. is an NIHR Emeritus Senior Investigator. S.M.L. is supported by a Wellcome Senior Fellowship.

Conflicts of interest
Z.Z.N.Y. and R.P have no relevant conflicts of interest. R.B.W. has been a paid consultant and/or clinical trial investigator and/or received department research funds from AbbVie, Almirall, AstraZeneca, BMS, BI, Celgene, Novartis, Eli Lilly, Sanofi, Janssen, UCB. C.E.M.G. has received honoraria and/or research grants from AbbVie, Almirall, Amgen, BMS, Celgene, Galderma, LEO.

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
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. 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 and potential misclassification by trying to determine hospital admissions using primary care electronic health records.

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. 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. 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.

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.

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.
Similar to a recent publication about atopic eczema, 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 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 non-linearity. 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 algorithm13 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.
Risk of serious infection associated with psoriasis, Yiu et al.

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 (31-9)                 |
| Ex-smoker                                | 101 915 (30-1)                  | 23 378 (33-7)                 |
| Current smoker                           | 92 008 (27-2)                   | 22 506 (33-5)                 |
| 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 (23-3)                 |
| 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 (34·4%) 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 infectiona  | 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 infectionsa | 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 infectionsa | N (%) | 30 761 (9·1%) | 46 (0·8%) |
| 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. aFirst hospitalization due to infection event.

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 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 ascertain infection outcomes rather than primary care records, with the stratified unadjusted and adjusted HRs for serious infection being similar 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).

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

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 1a | Model 2b |
|----------|------------|----------|----------|
| 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) |

aAdjusted 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. bCovariates 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, 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.

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 and the comorbidities, 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. 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. 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. The skew towards an excessive inflammatory cytokine milieu in psoriasis, in particular tumour necrosis factor-α and interleukin 17, can also be
associated with the inflammation and tissue damage seen in bacterial\textsuperscript{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.\textsuperscript{12,23}

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

This study is based in part on data from the Clinical Practice Research Datalink (CPRD) obtained under license from the UK Medicines and Healthcare Products Regulatory Agency. The data is provided by patients and collected by the National Health Service as part of their care and support. The Office for National Statistics (ONS) is the provider of the ONS data contained within the CPRD data. Hospital Episode Data and the ONS data, © 2019, are re-used with the permission of The Health & Social Care Information Centre. All rights reserved.

The study was approved by the independent scientific advisory committee for CPRD research (Independent Scientific Advisory Committee approval 18_012R). The interpretation and conclusions contained in this study are those of the authors alone.

Z.Z.N.Y. had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

We are grateful to Dr Kathryn Mansfield for her helpful analysis in identifying and classifying covariates in the directed acyclic graph.

References

1. Naldi L, Chatenoud L, Linder D et al. Cigarette smoking, body mass index, and stressful life events as risk factors for psoriasis: results from an Italian case–control study. J Invest Dermatol 2005; 125:61–7.
2. Armstrong AW, Harskamp CT, Armstrong EJ. The association between psoriasis and obesity: a systematic review and meta-analysis of observational studies. Nutr Diabetes 2012; 2:e54.
3. Budu-Aggye A, Brumpton B, Tyrell J et al. Evidence of a causal relationship between body mass index and psoriasis: a Mendelian randomization study. PLOS Med 2019; 16:e1002739.
4. Poikolainen K, Reunala T, Karvonen J et al. Alcohol intake: a risk factor for psoriasis in young and middle aged men? BMJ 1990; 300:780–3.
5. Wakkee M, de Vries E, van den Haak P, Nijsten T. Increased risk of infectious disease requiring hospitalization among patients with psoriasis: a population-based cohort. J Am Acad Dermatol 2011; 65:1135–44.

6. Takeshita J, Shin DB, Ogdie A, Gelfand JM. Risk of serious infection, opportunistic infection, and herpes zoster among patients with psoriasis in the United Kingdom. J Invest Dermatol 2018; 138:1726–35.
7. Saine ME, Carbonari DM, Newcomb CW et al. Concordance of hospitalizations between Clinical Practice Research Datalink and linked Hospital Episode Statistics among patients treated with oral antidiabetic therapies. Pharmacoepidemiol Drug Saf 2019; 28:1328–35.
8. Chisholm J. The Read clinical classification. BMJ 1990; 300:1092.
9. Padmanabhan S, Carty L, Cameron E et al. Approach to record linkage of primary care data from Clinical Practice Research Datalink to other health-related patient data: overview and implications. Eur J Epidemiol 2019; 34:91–9.
10. Silverwood RJ, Forbes HJ, Abuabara K et al. Severe and predominantly active atopic eczema in adulthood and long term risk of cardiovascular disease: population based cohort study. BMJ 2018; 361:k1786.
11. Springate DA, Kontopantelis E, Ashcroft DM et al. ClinicalCodes: an online clinical codes repository to improve the validity and reproducibility of research using electronic medical records. PLOS ONE 2014; 9:e99825.
12. Kontopantelis E, Parisi R, Springate DA, Reeves D. Longitudinal multiple imputation approaches for body mass index or other variables with very low individual-level variability: the mimi command in Stata. BMC Res Notes 2017; 10:41.
13. Parisi R, Webb RT, Carr MJ et al. Alcohol-related mortality in patients with psoriasis: a population-based cohort study. JAMA Dermatol 2017; 153:1156–62.
14. Parisi R, Butter MK, Lust M et al. Psoriasis and the risk of major cardiovascular events: cohort study using the Clinical Practice Research Datalink. J Invest Dermatol 2015; 135:2189–97.
15. Benchimol EI, Smeeth L, Guttmann A et al.; RECORD Working Committee. The Reporting of studies Conducted using Observational Routinely-collected health Data (RECORD) statement. PLOS Med 2015; 12:e1001885.
16. Herrett E, Gallagher AM, Bhaskaran K et al. Data resource profile: Clinical Practice Research Datalink (CPRD). Int J Epidemiol 2015; 44:827–36.
17. Seminara NM, Abuabara K, Shin DB et al. Validity of The Health Improvement Network (THIN) for the study of psoriasis. Br J Dermatol 2011; 164:602–9.
18. Quint JK, Mullerova H, DiSantostefano RL et al. Validation of chronic obstructive pulmonary disease recording in the Clinical Practice Research Datalink (CPRD-GOLD). BMJ Open 2014; 4:e005540.
19. Ng CY, Huang YH, Chu CF et al. Risks for Staphylococcus aureus colonization in patients with psoriasis: a systematic review and meta-analysis. Br J Dermatol 2017; 177:967–77.
20. Das S, Khader S. Yin and yang of interleukin-17 in host immunity to infection. F1000Res 2017; 6:741.
21. Bordon J, Aliberti S, Fernandez-Botran R et al. Understanding the roles of cytokines and neutrophil activity and neutrophil apoptosis in the protective versus deleterious inflammatory response in pneumonia. Int J Infect Dis 2013; 17:e76–83.
22. Bosmann M, Ward PA. Therapeutic potential of targeting IL-17 and IL-23 in sepsis. Clin Transl Med 2012; 1:4.
23. Ulloa L, Tracey KJ. The ‘cytokine profile’: a code for sepsis. Trends Mol Med 2005; 11:56–63.

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.
Powerpoint S1 Journal Club Slide Set.
Video S1 Author video.