RISK OF HOSPITALISATION DUE TO INFECTION IN PATIENTS WITH PSORIASIS

A Prospective Cohort Study Using the United Kingdom Clinical Practice Research Datalink

Zenas ZN Yiu[1], Rosa Parisi[2], Mark Lunt[3], Richard B Warren[1], Christopher EM Griffiths[1], Sinéad M Langan[5,6], Darren M Ashcroft[4]

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

Email: zenas.yiu@manchester.ac.uk ***Twitter:*** @ZZNYiu ***Webpage:*** http://personalpages.manchester.ac.uk/staff/zenas.yiu

SUMMARY

We found that people with psoriasis had an increased risk of hospitalisation due to infection as compared to the general population after taking into account potential confounders and mediators. However, the absolute increase in risk is small.

BACKGROUND

1 Psoriasis is associated with potential risk factors for infection, such as obesity, high alcohol intake and smoking.

2 Patients with psoriasis and their clinicians are often concerned about the risk of serious infections, defined as infections that lead to hospitalisation.

3 Studies that have investigated this relationship thus far are limited by lack of adjustment for lifestyle factors and potential misclassification of outcome by the determination of hospital admissions using primary care records only.

AIM

To investigate the risk of hospitalisation due to infection overall; respiratory infections; skin / soft-tissue infections; and death due to infection in patients with psoriasis compared to matched comparison patients in a large population-based United Kingdom cohort of primary care patients with linked hospital and mortality records.

METHODS

Clinical Practice Research Datalink (CPRD GOLD):
Primary care database of anonymised medical records from general practices (GP) in the UK. Clinical events coded using Read codes.

- Subset of data in England eligible for linkage to the national Hospital Episode Statistics (HES), Office for National Statistics (ONS) mortality records and Index of Multiple Deprivation 2010 (IMD) used.

- Inclusion and exclusion criteria, along with the windows for assessment of covariates, registration, and follow-up are outlined in *Figure 1*. Each person with psoriasis matched with up to six comparators by age, sex, general practice on index date.

- Definition of severe psoriasis - from the timepoint when a person 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 from primary care records.

- We included phototherapy through linked HES records to avoid misclassification, and added the inclusion of the need to consult 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.

- The outcomes of hospitalisation due to infection and death due to infection were identified in HES and ONS data respectively. Negative control of hospitalisation due to transport accident from HES was used.

- We identified covariates that might be potential confounders, mediators or colliders (*Figure 2*). We fitted three stratified Cox proportional hazards models for each identified outcome - unadjusted, Model 1 and Model 2. *Model 1* - plausible potential confounders - age, IMD status, body mass index (BMI), alcohol intake, smoking status. *Model 2* + potential confounders or mediators: other immune-mediated inflammatory diseases, diabetes, chronic obstructive pulmonary disease (COPD).

- Missing data accounted for by 20 multiply imputed datasets.

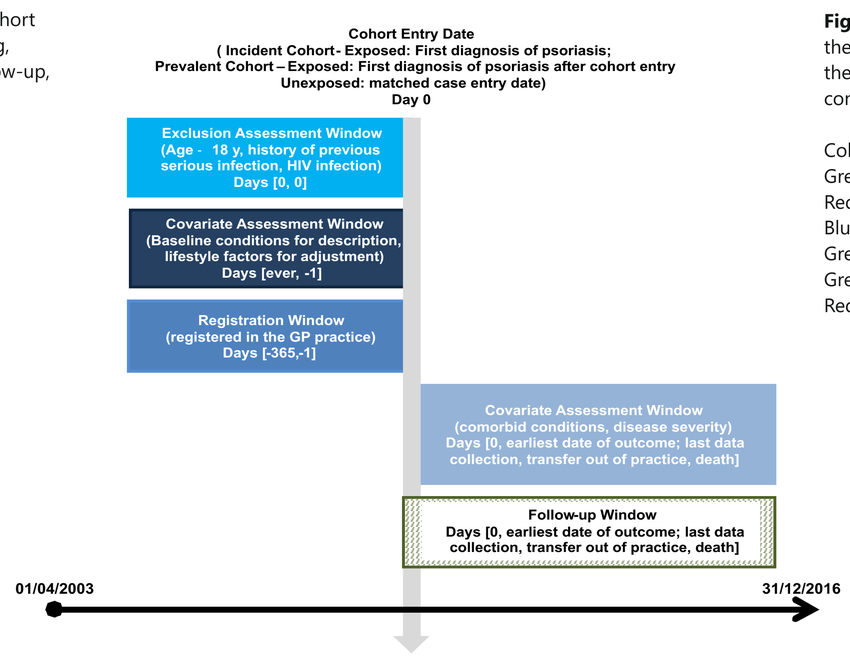
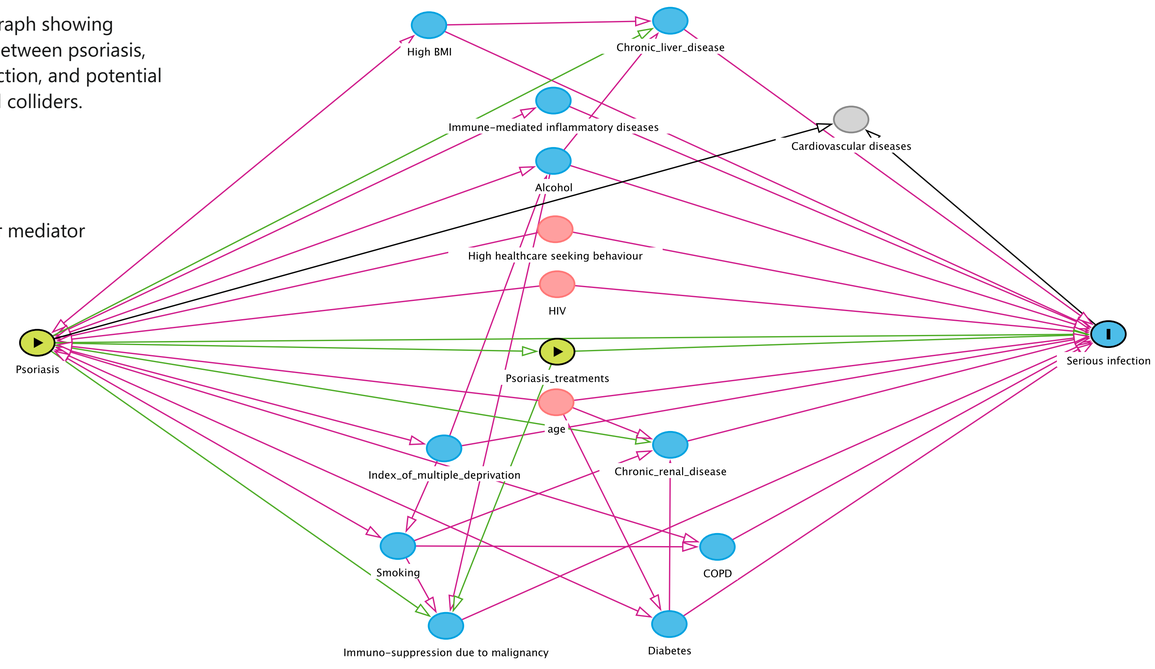


Figure 1: Graphical depiction of cohort study design, describing the setting, relevant dates of cohort entry, follow-up, covariate assessment and exit of the cohort.

Figure 2. Directed acyclic graph showing the assumed relationships between psoriasis, the outcome of serious infection, and potential confounders, mediators and colliders.

Coloured circle - variable
Green - exposure
Red - likely confounder
Blue - maybe confounder or mediator
Grey - collider
Green arrow - causal path
Red arrow - biasing path



RESULTS

Covariate	Comparison cohort	Psoriasis cohort
Patients per cohort, N	338,620	69,315
Follow-up (median, interquartile range) 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
Hospitalisation due to any infection		
N (%)	30,761 (9.1%)	7,631 (11.0%)
Incidence rate per 1000 person-years (95% CI)	16.1 (15.9-16.3)	20.5 (20.0-21.0)
Hospitalisation due to respiratory infection		
N (%)	11,626 (3.4%)	2,791 (4.0%)
Incidence rate per 1000 person-years (95% CI)	6.1 (6.0-6.2)	7.4 (7.1-7.7)
Hospitalisation due to soft-tissue infection		
N (%)	3,818 (1.1%)	1,167 (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 (%)	2,656 (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)

Table 1: Event count and incidence rates of primary and secondary outcomes in the psoriasis and comparison cohorts

Analysis	Unadjusted	Model 1	Model 2
Hospitalisation due to any infection	1.46 (1.42-1.50)	1.36 (1.31-1.41)	1.36 (1.31-1.40)
Stratified by Mild psoriasis	1.40 (1.36-1.44)	1.39 (1.33-1.46)	1.39 (1.34-1.44)
Severe psoriasis	1.47 (1.41-1.55)	1.27 (1.18-1.36)	1.26 (1.19-1.34)
Hospitalisation due to respiratory infections	1.44 (1.38-1.51)	1.37 (1.29-1.46	1.35 (1.27-1.44
Hospitalisation 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 - hospitalisation due to transport accidents	1.09 (0.96-1.24)	1.14 (1.00-1.30)	1.14 (1.00-1.31)

Table 2: Hazard ratios (95% confidence intervals) for primary and secondary outcomes comparing the people with psoriasis with the comparison cohort from Cox proportional hazards model. The absolute risk difference in probability of serious infection between people with psoriasis and the comparison group is low and translates to 0.77% (95% CI 0.69-0.86%) at 5 years and 3.12% (95% CI 2.77-3.47%) at 10 years.

Strengths and weaknesses of the study

✓ Use of linked HES data from secondary care to avoid outcome misclassification
✓ Large sample of UK people representative of the general population
✓ Accounted for potential confounding by lifestyle factors

✘ Potential for exposure, comorbidity, disease severity misclassification
✘ Residual confounding
✘ Potential detection bias

DISCUSSION

1 In the largest UK study to date investigating the risk of serious infection in patients with psoriasis, we found that people with psoriasis had a higher risk compared with age, sex and general practice matched patients. We also identified that people with psoriasis had a higher risk of death due to any infection compared to people without psoriasis.
2 We did not show a dose-dependent response with severity of psoriasis and the risk of serious infection.
3 There was no evidence that psoriasis had a protective effect against skin and soft-tissue infections.
4 Although the relative risk of serious infection in people with psoriasis is higher than people without psoriasis, the absolute risk difference is small. People with psoriasis therefore should not be unduly concerned about this risk.
5 Future research should consider mechanistic work to understand how psoriasis predisposes to a higher risk of infection.