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Risk of serious infection, opportunistic infection and herpes zoster among patients with psoriasis in the United Kingdom

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Abstract

The risk of infection among patients with psoriasis of varying severity in a broadly representative population remains poorly understood. Using The Health Improvement Network (THIN), an electronic medical records database representative of the general United Kingdom population, we performed a cohort study to determine the risks of serious infection, opportunistic infection, and herpes zoster among patients with versus without psoriasis and according to psoriasis severity. We identified 187,258 patients with mild, and 12,442 patients with moderate-to-severe psoriasis based on treatment patterns. Using Cox proportional hazards regression, the adjusted hazard ratios (95%

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PREVIOUS OR PLANNED MEETING PRESENTATION

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CONFLICT OF INTEREST

Dr. Takeshita receives a research grant (to the Trustees of the University of Pennsylvania) from Pfizer Inc. for work that is unrelated to this manuscript and received payment for continuing medical education work related to psoriasis that was supported indirectly by Eli Lilly and Novartis. Dr. Ogdie has served as a consultant for Bristol-Myers Squibb, Novartis, Pfizer Inc., and Takeda, receiving honoraria; and is a co-investigator on a research grant (to the Trustees of the University of Pennsylvania) from Pfizer Inc. Dr. Gelfand served as a consultant for Coherus (DSMB), Dermira, Janssen Biologics, Merck (DSMB), Novartis Corp, Regeneron, Sanofi, and Pfizer Inc., receiving honoraria; and received research grants (to the Trustees of the University of Pennsylvania) from Abbvie, Janssen, Novartis Corp, Regeneron, Sanofi, Celgene, and Pfizer Inc.; and received payment for continuing medical education work related to psoriasis that was supported indirectly by Eli Lilly and Abbvie. Dr. Gelfand is a co-patent holder of resiquimod for treatment of cutaneous T cell lymphoma.

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confidence intervals [CI]) for serious infection were 1.18 (1.16–1.21) and 1.63 (1.52–1.75) for the mild and moderate-to-severe psoriasis groups, respectively. Among a nested cohort of 8,569 psoriasis patients with disease severity classified by body surface area involvement, similar results were obtained with the exception of an attenuated but significantly increased risk of serious infection among the moderate-to-severe psoriasis group (1.27 [1.10–1.47]). Overall, the risks of opportunistic infection and herpes zoster were significantly increased only among the moderate-to-severe psoriasis group and were associated with immunosuppressive therapy. Our analyses suggest that psoriasis is associated with an increased risk of serious infection, and psoriasis severity is a predictor of serious infection risk.

INTRODUCTION

Psoriasis is a common, chronic, immune-mediated disease primarily of the skin that affects 2–4% of the general population.(Gelfand *et al.*, 2005; Kurd and Gelfand, 2009) Over the last decade, there have been major advances in our understanding of comorbid diseases associated with psoriasis, particularly cardiometabolic comorbidities.(Azfar *et al.*, 2012; Gelfand *et al.*, 2009; Gelfand *et al.*, 2006; Langan *et al.*, 2012; Mehta *et al.*, 2010; Wan *et al.*, 2013; Yeung *et al.*, 2013) However, despite being the second leading cause of death among psoriasis patients receiving therapies for moderate-to-severe disease,(Abuabara *et al.*, 2010) infection as a comorbidity of psoriasis remains poorly understood. With the development of several targeted biologic therapies that block key cytokines in the development of psoriasis such tumor necrosis factor (TNF), interleukin (IL)-12/23, and IL-17 in the last decade, much effort has been invested into the study of infection risk related to these newer therapies. However, little is known about the risk of infection among all patients with psoriasis and potentially attributable to the disease itself. Based on basic research that has identified increased expression of antimicrobial peptides in psoriasis skin lesions,(Hollox *et al.*, 2008) psoriasis has historically been considered to have protective mechanisms against infection. As there are few data that actually quantify and characterize the risks of various infections among patients with psoriasis, additional studies are necessary to better understand the potential association between psoriasis and infections. Thus, the aim of our study was to determine the risk of serious infection, opportunistic infection, and herpes zoster among patients with psoriasis using a large, population-based electronic medical record database in the United Kingdom, leveraging information on important confounders and direct measures of psoriasis severity that are not typically available in other large databases.

RESULTS

Study Cohort Baseline Characteristics

For our primary study using the full The Health Improvement Network (THIN) cohort, we identified 199,700 patients with psoriasis (187,258 with mild disease and 12,442 with moderate-to-severe disease based on receipt of phototherapy or systemic therapy) and 954,315 randomly-selected patients without psoriasis. Compared with patients without psoriasis, those with psoriasis were younger and were more likely to be current or past smokers (Table 1). Patients with moderate-to-severe psoriasis had higher body mass index (BMI), were more likely to be drinkers, and were more likely to have received systemic

corticosteroids than those without psoriasis. Most comorbidities were similarly prevalent among patients with and without psoriasis, reflective of psoriasis patients being generally younger. With regards to flu and pneumonia vaccinations, patients with mild psoriasis were less likely and patients with moderate-to-severe psoriasis were more likely to have received vaccinations than patients without psoriasis. Among patients with moderate-to-severe psoriasis, the majority were treated with methotrexate (69.5%) (Table S1).

In the Incident Health Outcomes and Psoriasis Events (iHOPE) cohort, we identified 8,569 patients with psoriasis (4,437 had mild disease defined by < 3% body surface area [BSA] involvement; 4,132 had moderate-to-severe disease defined by ≥ 3% BSA involvement, of whom 25.7% had > 10% BSA involved) and 83,540 matched patients without psoriasis (Table S2). Patients with psoriasis had higher BMI and were more likely to be current or past smokers. Comorbidities were similarly prevalent among patients with and without psoriasis, and patients with moderate-to-severe psoriasis were more likely to have received pneumonia vaccination than those without psoriasis.

Serious Infection

The incidence rates of serious infection derived from the full THIN cohort are summarized in Table 2. Patients with psoriasis had a higher incidence of serious infection than patients without psoriasis; the incidence rate was highest among patients with moderate-to-severe disease. The serious infections with the highest incidence rates among patients with psoriasis in descending order were lower respiratory tract, skin and soft tissue, and upper respiratory tract infections (Table 3). In multivariable analyses, psoriasis was associated with an increased risk of serious infection with adjusted hazard ratios (HRs) of 1.21 (95% confidence interval [CI], 1.18–1.23), 1.18 (1.16–1.21), and 1.63 (1.52–1.75) for the overall, mild, and moderate-to-severe psoriasis groups, respectively (Table 2). While effect modification by age and sex were each found to be statistically significant, differences among hazard ratios stratified by age and sex, respectively, were numerically small and, thus, not reported. The results were robust to multiple sensitivity analyses including an analysis that excluded patients who had received immunosuppressive psoriasis treatments (Table 4). The attributable risks of serious infection among all patients with psoriasis and those with mild and moderate-to-severe disease were 16.2, 14.4, and 49.5 per 10,000 person-years, respectively; the excess risks were one serious infection per 616, 693, and 201 patients with any, mild, and moderate-to-severe psoriasis, respectively, per year (data not shown).

In the iHOPE cohort, the adjusted HRs (95% CI) for serious infection were 1.21 (1.09–1.35), 1.16 (0.99–1.35), and 1.27 (1.10–1.47) among all patients with psoriasis and patients with mild and moderate-to-severe disease as defined by BSA involved by psoriasis, respectively (Table 2). A significant dose-dependent relationship between BSA involvement and serious infection was observed (P for trend = 0.005). When patients who had received immunosuppressive psoriasis treatments were excluded from the iHOPE analyses (N=557), the HRs for serious infection remained similar among all patients with psoriasis and those with mild and moderate-to-severe disease: 1.18 (1.05–1.32), 1.15 (0.99–1.34) and 1.21 (1.03–1.42), respectively (data not shown). Importantly, the risk of serious infection was

observed to be similar in both the full THIN and iHOPE cohorts with the exception of the moderate-to-severe psoriasis subgroup among whom the risk of serious infection was attenuated but still significantly elevated in the iHOPE versus full THIN cohort (Figure 1). Using the iHOPE cohort-derived HRs for serious infection, the attributable and excess risks of serious infection among all patients with psoriasis and those with mild and moderate-to-severe disease were 16.2, 12.2, and 20.4 per 10,000 person-years, respectively, and one serious infection per 617, 817, and 489 patients with any, mild, and moderate-to-severe psoriasis, respectively, per year (data not shown).

Opportunistic Infection

The incidence rates of opportunistic infection derived from the entire THIN cohort are summarized in Table 5. Opportunistic infection incidence rates were similar between patients with mild psoriasis and those without psoriasis. Patients receiving therapies for moderate-to-severe psoriasis had a higher incidence of opportunistic infection than all other groups with or without psoriasis. By far, the most common opportunistic infection among all groups was tuberculosis with incidence rates of 1.05, 0.94, and 3.00 per 10,000 person-years among all patients with psoriasis and those with mild and moderate-to-severe disease, respectively, versus 1.15 per 10,000 person-years among those without psoriasis (data not shown). In multivariable analyses, only patients with moderate-to-severe psoriasis had an increased risk of opportunistic infection (HR 1.57; 95% CI 1.06–2.34). Neither age nor sex was a significant effect modifier. In sensitivity analyses, the risk of opportunistic infection was substantially attenuated when patients who had received immunosuppressive psoriasis treatments were excluded (HR 1.17; 95% CI 0.44–3.12) (Table 4).

Herpes Zoster

The incidence rates of herpes zoster derived from the entire THIN cohort are summarized in Table 5. Incidence rates were the highest among patients receiving therapies for moderate-to-severe psoriasis. In multivariable analyses, patients with moderate-to-severe psoriasis had the greatest risk of herpes zoster (HR 1.17; 95% CI 1.06–1.30); mild psoriasis was also associated with a significant but small increased risk of herpes zoster (HR 1.07; 95% CI 1.05–1.10). Neither age nor sex was a significant effect modifier. In sensitivity analyses, exclusion of patients who had received immunosuppressive psoriasis treatments resulted in complete attenuation of the association between moderate-to-severe psoriasis and herpes zoster (HR 0.97; 95% CI 0.76–1.23) (Table 4).

DISCUSSION

Our population-based study in the UK demonstrates that psoriasis is associated with an increased risk of serious infection, independent of traditional risk factors for infection that are captured in routine medical practice. The risk of serious infection was greatest among patients with moderate-to-severe disease whether defined indirectly by treatment pattern in the full THIN cohort or directly by BSA involvement in the nested iHOPE cohort. While the serious infection risk among patients with moderate-to-severe psoriasis was attenuated in the iHOPE versus full THIN cohort, it remained significantly higher by 20–30% when psoriasis severity was defined by BSA involvement, even when those who had received

immunosuppressive therapies were excluded. Collectively, our findings support the idea that psoriasis severity, defined by either treatment pattern or affected BSA, is a predictor of serious infection risk beyond traditional risk factors for infection that are identifiable and collected in routine medical practice. In contrast, higher risks of opportunistic infections and herpes zoster were essentially limited to those patients receiving therapies for moderate-to-severe psoriasis and were entirely (or nearly entirely) associated with immunosuppressive therapies used to treat more severe psoriasis.

The pathophysiologic mechanisms for increased risk of serious infection among patients with psoriasis remain poorly understood. Underlying immune dysfunction characterized by TNF and IL-17 induced inflammation in patients with psoriasis may be hypothesized to alter psoriasis patients' infection risk profile. For example, several proinflammatory cytokines including TNF, IL-6, and IL-17 have been found to be elevated in the serum of patients with psoriasis compared to those without the disease.(Arican *et al.*, 2005; Suarez-Farinas *et al.*, 2012) Notably, in a single study of elderly individuals in the U.S., elevated levels of TNF and IL-6 prior to infection were associated with higher risk of pneumonia requiring hospitalization,(Yende *et al.*, 2005) suggesting that the altered serum cytokine profile of psoriasis patients may contribute to their risk of serious infection. Though such proinflammatory cytokines are known to be involved in the mediation of normal and protective systemic inflammatory responses to pathogens, overproduction of particular cytokines including TNF may also contribute to the promotion of bacterial invasion and initiation of pneumonia, in particular.(Cundell *et al.*, 1995; Mason *et al.*, 1997; White *et al.*, 1986)

Our findings add to the scant literature that exists regarding the association between psoriasis and infection and are consistent with smaller population-based studies in the Netherlands (Wakkee *et al.*, 2011) and Taiwan (Kao *et al.*, 2014) that also found increased risks of serious infection and hospitalized pneumonia, respectively, among patients with psoriasis. To our knowledge, ours is the first study to examine the risk of opportunistic infection and the second to evaluate the risk of herpes zoster across an entire cohort of patients with psoriasis regardless of treatment status. The novelty and a major strength of our study lies in its larger size and inclusion of risk factors for infection such as BMI, smoking and drinking status, and vaccination history that were not available in prior studies as well as use of a nested cohort of psoriasis patients with information on BSA involvement by psoriasis, thus allowing us to directly evaluate the effect of psoriasis severity on the serious infection outcome. Additional strengths of our study include the use of a large population-based psoriasis cohort with validly identified psoriasis diagnosis that is representative of the general population in the UK and, thus, likely generalizable to other Western countries.

Some limitations of our study include potential misclassification of psoriasis severity particularly in the full THIN cohort that used therapy as a surrogate measure of disease severity. In THIN, systemic medications for psoriasis are often prescribed by specialists or consultants and are not always recorded by general practitioners (GPs). Nevertheless, prior studies evaluating treatment patterns among patients with psoriatic disease in THIN indicate that the prevalence of oral systemic treatment in THIN approximates that of population-based estimates of moderate-to-severe psoriasis,(Ogdie *et al.*, 2014; Ogdie *et al.*, 2013)

suggesting that use of systemic therapy is a reasonable indicator of more severe psoriasis. While compared to our analysis in the full THIN cohort the risk of serious infection among those with ≥ 3% BSA affected by psoriasis in the nested iHOPE cohort was attenuated, it was still significantly increased and supported our primary finding in THIN that the risk of serious infection is greatest among those with moderate-to-severe disease. Notably, the association between serious infection and moderate-to-severe psoriasis in the iHOPE cohort was largely driven by the moderate psoriasis group. Thus, the true risk of serious infection among patients with moderate-to-severe psoriasis may be underestimated in the iHOPE cohort. Misclassification of the infection outcomes and hospitalizations is also possible, though likely to be non differential which, if anything, would bias our results towards the null. While we accounted for numerous potential confounders in our analyses (BMI, smoking and drinking status, vaccination history), which had not been included in prior studies, additional unmeasured or unknown confounders (e.g., ethnicity or region of origin as a risk factor for tuberculosis) may still exist. Lastly, ascertainment bias may be considered though this is unlikely to explain our results as patients with and without psoriasis had information collected in a similar manner, and our sensitivity analyses limiting the study population to those patients who had seen their GP at least once yearly yielded results similar to the primary analyses.

In conclusion, our findings suggest that psoriasis is associated with an increased risk of serious infection, and more severe psoriasis, whether defined by treatment pattern or by BSA involvement, is a predictor of greater serious infection risk. Considering that the incidence rates for upper and lower respiratory infections were among the highest of the infection types evaluated in patients with psoriasis, it is particularly relevant for GPs and dermatologists to ensure flu and pneumonia vaccination, especially among those who have more severe psoriasis or are receiving immunosuppressive therapy, consistent with the British Association of Dermatologists guidelines,(Smith *et al.*, 2017) Advisory Committee on Immunization Practices recommendations,(Kim *et al.*, 2015; Strikas *et al.*, 2015) and the National Psoriasis Foundation Medical Board's recommendations to vaccinate adult patients on systemic immunosuppressive therapy for psoriasis.(Wine-Lee *et al.*, 2013) Psoriasis patients with moderate-to-severe disease are also at increased risk of developing opportunistic infections and herpes zoster, but this risk appears to be limited to those patients receiving immunosuppressive therapies. Therefore, GPs and dermatologists should also consider herpes zoster vaccination with the new non-live vaccine for psoriasis patients who will be or are already receiving immunosuppressive therapies. Future studies will be important to further characterize the risk of various infections among patients with psoriasis, compare the risk of infection associated with psoriasis to that of other chronic diseases, and delineate the pathophysiologic mechanisms that contribute to the increased risk of infections associated with psoriasis and its therapies.

MATERIALS & METHODS

Study design and data source

We conducted a population-based cohort study using THIN, an electronic medical records database in the UK. We performed an additional cohort study only for the serious infection

outcome using the iHOPE cohort, which is a nested cohort of patients within THIN.(Langan *et al.*, 2012; Seminara *et al.*, 2011; Yeung *et al.*, 2013) THIN is broadly representative of the general UK population and contains information on medical diagnoses, treatment, and select laboratory data for over 12 million individuals covering 5.7% of the population. THIN has been widely used for epidemiologic research and has been validated for the study of psoriasis and other diagnoses.(Lewis *et al.*, 2007; Meropol and Metlay, 2012; Seminara *et al.*, 2011) In the UK, the majority of patients are registered with a GP who serves as the primary contact for all aspects of the patient's care and records data on diagnoses, prescriptions, and laboratory results in the electronic medical record. Data in this study were collected prospectively between 1994 and January 2014. This study was conducted according to the Declaration of Helsinki and reported according to the Strengthening the Reporting of Observational Studies in Epidemiology(von Elm *et al.*, 2007) statement. The study was granted exempt status by the University of Pennsylvania Institutional Review Board and approved by THIN's scientific review committee. Data were de-identified and, thus, patient consent was not possible/waived.

Study population and time of observation

THIN cohort—All patients with psoriasis aged 18–89 at the start date were included in the study. Diagnoses in THIN are recorded using the Read diagnostic code scheme,(Chisholm, 1990) and prescriptions are recorded using codes from the UK Prescription Pricing Authority.(Garcia Rodriguez and Perez Gutthann, 1998) Patients were identified to have psoriasis (i.e., exposed) if they had received at least one Read code for psoriasis, as previously validated in THIN.(Seminara *et al.*, 2011) Moderate-to-severe psoriasis was defined by the presence of a prescription code for therapies used to treat moderate-to-severe psoriasis (i.e., phototherapy including ultraviolet B or psoralen and ultraviolet A [PUVA], methotrexate, cyclosporine, oral retinoids, etanercept, infliximab, adalimumab, or ustekinumab).

Each patient with psoriasis was matched with up to five randomly-selected patients without psoriasis (i.e., unexposed with no history of a Read code for psoriasis) who were seen in the same practice and who had a date of observation within 180 days of the start date of the patient with psoriasis. We excluded patients with human immunodeficiency virus (HIV), malignancy (excluding non-melanoma skin cancer), or solid organ or liquid transplant prior to cohort entry (Figure S1A).

The start date for follow-up began on the latest of the following: date when the patient's practice began using THIN software, 180 days after patient registration in the practice, and date of psoriasis diagnosis for the exposed or the closest corresponding visit date for the unexposed. Censoring occurred when patients developed the outcome of interest, died, transferred out of THIN, or reached the end of the study.

Incident Health Outcomes and Psoriasis Events cohort (iHOPE)—The iHOPE cohort was created by randomly sampling patients in THIN who were alive and aged 25 to 64 years at the time of sampling, had received at least one Read code for psoriasis in the two years prior to sampling, and were registered in a practice with an Additional Information

Services (AIS) contract (i.e., an agreement to complete questionnaires in exchange for compensation). Surveys with face and content validity designed by experts in epidemiology, dermatology, and primary care were sent to GPs of the sampled psoriasis patients to verify their psoriasis diagnosis and classify their disease extent via the National Psoriasis Foundation classification system into mild (limited disease with < 3% BSA affected), moderate (scattered disease with 3 to 10% BSA affected), or severe (extensive disease with > 10% BSA affected). The exposed group consisted of patients with psoriasis Read codes whose psoriasis diagnosis and amount of skin involvement were verified by their GPs. Patients with moderate and severe psoriasis in the iHOPE cohort were combined into a single moderate-to-severe psoriasis group resulting in two disease severity categories (mild and moderate-to-severe) and, thus, enabling more direct comparisons with the mild and moderate-to-severe psoriasis groups that were identified by treatment pattern in the full THIN cohort. The unexposed comparison group was constructed by matching each psoriasis patient to up to 10 randomly-selected patients without psoriasis Read codes who were from the same practice, in the same age category, and alive and actively registered with at least one GP visit within two years prior to sampling. We excluded patients with HIV, malignancy (excluding non-melanoma skin cancer), or solid organ or liquid transplant prior to cohort entry (Figure S1B).

The start date for follow-up was defined by the GP survey sampling date (November 2008 to September 2010). Censoring occurred when patients developed the outcome (serious infection), died, transferred out of THIN, or reached the end of the study.

Outcome and covariate definitions

Three infection outcome categories were evaluated separately using the full THIN cohort: serious (i.e., hospitalized) infection, opportunistic infection, and herpes zoster. Only the serious infection outcome was also evaluated using the iHOPE cohort; the other infection outcomes were not common enough to assess reliably in the smaller iHOPE cohort. The serious infection outcome was defined by at least one Read code for a prespecified set of infections modified from Patkar et al.(Patkar *et al.*, 2009) followed by Read code for hospitalization within 30 days.(Meropol and Metlay, 2012) The opportunistic infection outcome was defined by at least one Read code for any of the following infections: actinomycosis/nocardia, aspergillosis, BK virus, cryptococcus, cytomegalovirus, mucormycosis, other mycoses (blastomycosis, coccidioidomycosis, histoplasmosis, and paracoccidioidomycosis), pneumocystis, progressive multifocal leukoencephalopathy, tuberculosis, and toxoplasmosis. The herpes zoster outcome was defined by at least one Read code for herpes zoster. Covariates assessed were potential confounders or risk factors for infection including age, sex, presence of comorbid disease including asthma/chronic obstructive pulmonary disease (COPD), cardiovascular disease (CVD), chronic kidney disease (CKD), congestive heart failure (CHF), dementia, depression, diabetes, inflammatory bowel disease (IBD), liver disease, osteoarthritis (OA), psoriatic arthritis (PsA), rheumatoid arthritis (RA), and systemic lupus erythematosus (SLE), inhaled or systemic corticosteroid use within 90 days of start date, infection or any hospitalization within 30 days of start date, flu and pneumonia vaccination status, smoking and drinking history, body mass index (BMI), and Townsend deprivation index. See Table S3 for variable

code lists. Patients were classified as having a comorbid disease if they had received a diagnostic code for any of the comorbid conditions of interest before the study start date. Smoking and drinking status, BMI, and Townsend deprivation index were determined from the data closest in time to the start date.

Statistical analysis

Patients with psoriasis (overall, mild, and moderate-to-severe) were compared to patients without psoriasis using standardized differences whereby a standardized difference ≥ 0.1 was considered to indicate a significant difference between groups.(Austin, 2009) Incidence rates of the various infection outcomes among patients with and without psoriasis were reported descriptively. Cox proportional hazards regression was used to compare the rates of infection in the overall, mild, and moderate-to-severe psoriasis groups to that in the unexposed group. A purposeful selection modeling approach was used to build the multivariable model.(Bursac *et al.*, 2008) All covariates with significant imbalance between exposed and unexposed groups were included in the multivariable model as potential confounders. Nonsignificant covariates ($P > 0.05$) were eliminated from the multivariable model if their removal did not change the hazard ratio estimates of the exposure variable by more than 10%. Effect modification by age and sex were also evaluated for each outcome. Log-log survival plots were examined to test the proportional hazards assumption.

We performed multiple sensitivity analyses to further assess the robustness of our primary analyses in the full THIN cohort as follows: i) multiple imputation for missing data; ii) limited analyses to only those patients who had been seen at least once yearly by their GP to minimize ascertainment bias; iii) excluded patients with IBD or RA, both of which have been suggested to be associated with increased risk of infection; iv) excluded patients with psoriatic arthritis to assess the relationship between skin-only disease and the outcomes; v) excluded patients with prior history of the infections of interest in order to assess incident infection risk; and vi) excluded patients who had received immunosuppressive psoriasis treatments (methotrexate, cyclosporine, any biologic) in an effort to minimize medication effects on the risk of infection. All statistical analyses were performed with Stata (Version 13, StataCorp, College Station, TX, USA). Statistical significance was determined by two sided P values at $P<0.05$.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

BMI	body mass index
BSA	body surface area
CHF	congestive heart failure
CI	confidence interval
CKD	chronic kidney disease
COPD	chronic obstructive pulmonary disease
CVD	cardiovascular disease
HR	hazard ratio
IBD	inflammatory bowel disease
iHOPE	Incident Health Outcomes and Psoriasis Events
OA	osteoarthritis
PsA	psoriatic arthritis
PUVA	psoralen and ultraviolet A
RA	rheumatoid arthritis
SLE	systemic lupus erythematosus
THIN	The Health Improvement Network

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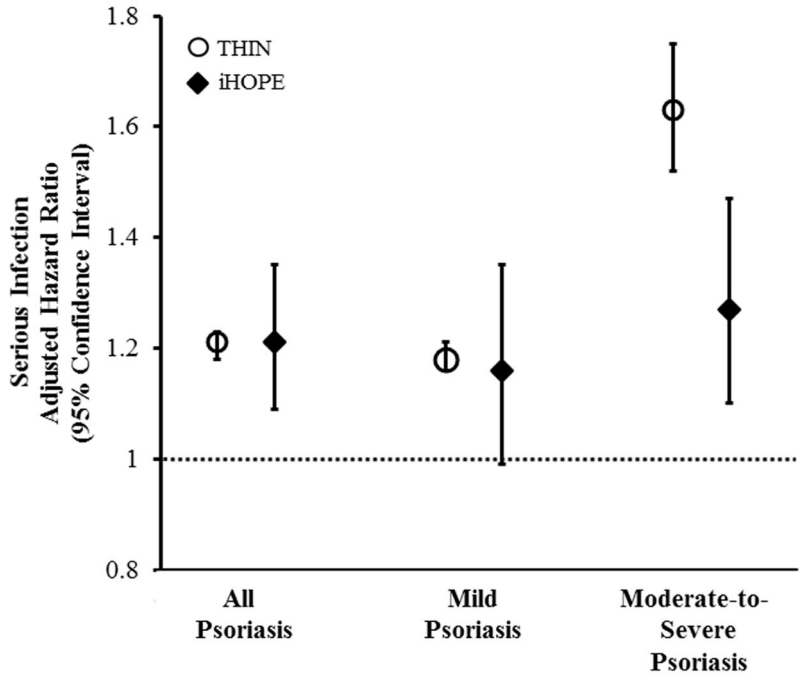

Figure 1. Adjusted Risk of Serious Infection by Psoriasis Severity: THIN Versus iHOPE Cohort
Moderate-to-severe psoriasis defined by receipt of phototherapy or systemic therapy in THIN cohort and ≥3% BSA in iHOPE cohort.

Table 1

Baseline Characteristics: THIN Cohort

Characteristic N (%)	No Psoriasis N=954,315	All Psoriasis N=199,700	Standardized Difference[a]	Mild Psoriasis N=187,258	Standardized Difference[a]	Moderate-to-Severe Psoriasis N=12,442	Standardized Difference[a]
Age							
mean (SD)	49.9 (17.6)	46.6 (17.4)	0.19	46.4 (17.5)	0.20	49.4 (15.1)	0.07
median (IQR)	49 (36, 63)	45 (32, 60)		45 (32, 60)		49 (38, 60)	
Male sex	422,290 (44.3)	96,701 (48.4)	0.08	90,643 (48.4)	0.08	6,058 (48.7)	0.10
Asthma/COPD	135,925 (14.2)	28,012 (14.0)	0.006	26,079 (13.9)	0.009	1,933 (15.5)	0.04
Cardiovascular Disease	92,571 (9.7)	16,628 (8.3)	0.05	15,486 (8.3)	0.05	1,142 (9.2)	0.04
Chronic Kidney Disease	21,534 (2.3)	3,487 (1.8)	0.04	3,131 (1.7)	0.04	356 (2.9)	0.05
Congestive Heart Failure	15,776 (1.7)	2,577 (1.3)	0.03	2,400 (1.3)	0.03	177 (1.4)	0.02
Dementia	5,017 (0.53)	1,177 (0.59)	0.009	1,137 (0.61)	0.01	40 (0.32)	0.03
Depression	159,551 (16.7)	34,472 (17.3)	0.01	31,828 (17.0)	0.007	2,644 (21.3)	0.12
Diabetes Types 1 and 2	61,194 (6.4)	11,817 (5.9)	0.02	10,678 (5.7)	0.03	1,139 (9.2)	0.11
Inflammatory Bowel Disease	11,005 (1.2)	2,663 (1.3)	0.02	2,400 (1.3)	0.01	263 (2.1)	0.07
Liver Disease	4,900 (0.51)	1,464 (0.73)	0.03	1,320 (0.70)	0.02	144 (1.2)	0.08
Osteoarthritis	110,495 (11.6)	20,450 (10.2)	0.04	18,616 (9.9)	0.05	1,834 (14.7)	0.10
Psoriatic Arthritis	0 (0)	10,078 (5.0)	NA	5,365 (2.9)	NA	4,715 (37.9)	NA
Rheumatoid Arthritis	263 (0.03)	3,063 (1.5)	0.17	1,495 (0.8)	0.12	1,568 (12.6)	0.53
Systemic Lupus Erythematosus	1,457 (0.15)	369 (0.18)	0.008	312 (0.17)	0.004	57 (0.46)	0.05
Inhaled Corticosteroids within 90 days prior to start date	40,612 (4.3)	7,677 (3.8)	0.02	7,120 (3.8)	0.02	557 (4.5)	0.009

Characteristic N (%)	No Psoriasis N=954,315	All Psoriasis N=199,700	Standardized Difference[a]	Mild Psoriasis N=187,258	Standardized Difference[a]	Moderate-to-Severe Psoriasis N=12,442	Standardized Difference[a]
Systemic Corticosteroids within90 days prior to start date	20,654 (2.2)	5,199 (2.6)	0.03	3,931 (2.1)	0.005	1,268 (10.2)	0.34
Flu Vaccine	290,414 (30.4)	51,485 (25.8)	0.10	46,630 (24.9)	0.12	4,855 (39.0)	0.18
Pneumonia Vaccine	141,187 (14.8)	24,000 (12.0)	0.08	21,566 (11.5)	0.10	2,434 (19.6)	0.13
Herpes Zoster Vaccine	121 (0.01)	15 (0.01)	0.005	13 (0.01)	0.006	2 (0.02)	0.004
Any hospitalization within 30 days prior to start date	15,110 (1.6)	1,760 (0.88)	0.06	1,444 (0.77)	0.08	316 (2.5)	0.08
Infection within 30 days prior to start date	45,826 (4.8)	5,870 (2.9)	0.10	5,567 (3.0)	0.10	303 (2.4)	0.10
History of opportunistic infection	9,696 (1.0)	1,658 (0.83)	0.02	1,539 (0.82)	0.02	119 (0.96)	0.009
History of herpes zoster	40,333 (4.2)	7,451 (3.7)	0.03	6,924 (3.7)	0.03	527 (4.2)	0.01
Smoking History							
None	457,358 (47.9)	77,739 (38.9)		72,903 (38.9)		4,836 (38.9)	
Current	208,690 (21.9)	57,717 (28.9)	0.20	54,417 (29.1)	0.20	3,300 (26.5)	0.33
Past	191,630 (20.1)	43,722 (21.9)		40,154 (21.4)		3,568 (28.7)	
Missing	*96,637 (10.1)*	*20,522 (10.3)*		*19,784 (10.6)*		*738 (5.9)*	
Drinking History							
None	108,057 (11.3)	20,901 (10.5)		19,524 (10.4)		1,377 (11.1)	
Some	609,093 (63.8)	129,754 (65.0)	0.03	121,476 (64.9)	0.04	8,278 (66.5)	0.19
A lot	39,820 (4.2)	7,883 (4.0)		7,064 (3.8)		819 (6.6)	
Missing	*197,345 (20.7)*	*41,162 (20.6)*		*39,194 (20.9)*		*1,968 (15.8)*	
Body Mass Index							
Underweight/Normal	343,611 (36.0)	67,717 (33.9)		64,177 (34.3)		3,540 (28.5)	
Overweight	261,401 (27.4)	54,246 (27.2)	0.06	50,593 (27.0)	0.05	3,653 (29.4)	0.31
Obese	158,487 (16.6)	36,798 (18.4)		33,424 (17.9)		3,374 (27.1)	

Characteristic N (%)	No Psoriasis N=954,315	All Psoriasis N=199,700	Standardized Difference[a]	Mild Psoriasis N=187,258	Standardized Difference[a]	Moderate-to-Severe Psoriasis N=12,442	Standardized Difference[a]
Missing	*190,816 (20.0)*	*40,939 (20.5)*		*39,064 (20.9)*		*1,875 (15.1)*	
Townsend Score							
1st Quintile	237,254 (24.9)	46,107 (23.1)		43,106 (23.0)		3,001 (24.1)	
2nd Quintile	200,546 (21.0)	40,474 (20.3)		37,855 (20.2)		2,619 (21.1)	
3rd Quintile	190,980 (20.0)	40,528 (20.3)	0.06	38,030 (20.3)	0.06	2,498 (20.1)	0.05
4th Quintile	168,753 (17.7)	36,405 (18.2)		34,225 (18.3)		2,180 (17.5)	
5th Quintile	117,224 (12.3)	26,442 (13.2)		24,844 (13.3)		1,598 (12.8)	
Missing	*39,558 (4.2)*	*9,744 (4.9)*		*9,198 (4.9)*		*546 (4.4)*	

IQR, interquartile range; SD, standard deviation; NA, not applicable

[a]Standardized difference ≥ 0.1 is considered to indicate meaningful imbalance between groups.(Austin, 2009)

Table 2

Incidence and Risk of Serious Infection

Full THIN Cohort	**No Psoriasis N=954,315**	**All Psoriasis N=199,700**	**Mild Psoriasis N=187,258**	**Moderate-to-Severe Psoriasis N=12,442**
Follow-up time (yrs)				
Mean (SD)	6.4 (4.7)	6.0 (4.7)	6.1 (4.7)	5.1 (4.0)
Median (IQR)	5.5 (2.3, 9.8)	5.0 (2.1, 9.4)	5.1 (2.1, 9.5)	4.2 (1.8, 7.5)
Number of person-years	6,096,846	1,207,499	1,143,873	63,625
Number (%) of serious infections	47,875 (5.0)	10,734 (5.4)	9,807 (5.2)	927 (7.5)
Incidence per 10,000 person years (95% CI)	78.5 (77.8, 79.2)	88.9 (87.2, 90.6)	85.7 (84.1, 87.4)	145.7 (136.6, 155.4)
Unadjusted hazard ratio (95% CI)	Reference	1.14 (1.12, 1.16)	1.10 (1.07, 1.12)	1.97 (1.84, 2.10)
Adjusted hazard ratio (95% CI)[a]	Reference	1.21 (1.18, 1.23)	1.18 (1.16, 1.21)	1.63 (1.52, 1.75)
iHOPE Cohort	**No Psoriasis** N=83,540	**All Psoriasis** N=8,569	**Mild Psoriasis** N=4,437	**Moderate-to-Severe Psoriasis** N=4,132
Follow-up time (yrs)				
Mean (SD)	4.1 (1.7)	4.2 (1.6)	4.2 (1.6)	4.2 (1.6)
Median (IQR)	4.4 (3.1, 5.6)	4.4 (3.3, 5.6)	4.4 (3.3, 5.6)	4.4 (3.3, 5.5)
Number of person-years	342,169	35,664	18,435	17,229
Number (%) of serious infections	2,588 (3.1)	371 (4.3)	180 (4.1)	191 (4.6)
Incidence per 10,000 person years (95% CI)	75.6 (72.8, 78.6)	104.0 (94.0, 115.2)	97.6 (84.4, 113.0)	110.9 (96.2, 127.8)
Unadjusted hazard ratio (95% CI)	Reference	1.38 (1.23, 1.53)	1.29 (1.11, 1.50)	1.47 (1.27, 1.70)
Adjusted hazard ratio (95% CI)[b]	Reference	1.21 (1.09, 1.35)	1.16 (0.99, 1.35)	1.27 (1.10, 1.47)

CI, confidence interval; IQR, interquartile range; SD, standard deviation; yrs, years

[a]Adjusted for age, sex, BMI, smoking and drinking status, asthma/COPD, CVD, CKD, CHF, dementia, depression, diabetes, IBD, liver disease, OA, RA, systemic corticosteroid use within 90 days prior to start date, flu and pneumonia vaccination status, hospitalization or infection within 30 days prior to start date, and Townsend score.

[b]Adjusted for age, sex, BMI, smoking status, asthma/COPD, CVD, CKD, CHF, dementia, depression, diabetes, IBD, liver disease, OA, systemic corticosteroid use within 90 days prior to start date, flu and pneumonia vaccination status, hospitalization or infection within 30 days prior to start date.

Table 3

Incidence Rates of Serious Infection Subtypes: THIN Cohort

Serious Infection Type	No Psoriasis N=954,315		All Psoriasis N=199,700		Mild Psoriasis N=187,258		Moderate-to-Severe Psoriasis N=12,442	
	N (%)	Rate[a] (95% CI)	N (%)	Rate[a] (95% CI)	N (%)	Rate[a] (95% CI)	N (%)	Rate[a] (95% CI)
Lower respiratory tract	16,156 (1.7)	26.1 (25.7, 26.5)	3,571 (1.8)	29.0 (28.1, 30.0)	3,244 (1.7)	27.8 (26.9, 28.8)	327 (2.6)	49.8 (44.7, 55.5)
Skin and soft tissue	7,426 (0.78)	11.9 (11.7, 12.2)	2,022 (1.0)	16.4 (15.7, 17.1)	1,817 (0.97)	15.5 (14.9, 16.3)	205 (1.6)	31.1 (27.1, 35.6)
Upper respiratory tract	8,631 (0.90)	13.9 (13.6, 14.2)	2,006 (1.0)	16.3 (15.6, 17.0)	1,817 (0.97)	15.6 (14.9, 16.3)	189 (1.5)	28.7 (24.9, 33.1)
Urinary tract	7,956 (0.83)	12.8 (12.5, 13.1)	1,581 (0.79)	12.8 (12.2, 13.4)	1,447 (0.77)	12.4 (11.7, 13.0)	134 (1.1)	20.2 (17.1, 24.0)
Conjunctivitis	1,491 (0.16)	2.4 (2.3, 2.5)	348 (0.17)	2.8 (2.5, 3.1)	325 (0.17)	2.8 (2.5, 3.1)	23 (0.18)	3.5 (2.3, 5.2)
Gastrointestinal	1,334 (0.14)	2.1 (2.0, 2.3)	312 (0.16)	2.5 (2.3, 2.8)	279 (0.15)	2.4 (2.1, 2.7)	33 (0.27)	5.0 (3.5, 7.0)
Sepsis	1,257 (0.13)	2.0 (1.9, 2.1)	305 (0.15)	2.5 (2.2, 2.8)	269 (0.14)	2.3 (2.0, 2.6)	36 (0.29)	5.4 (3.9, 7.5)
Cholecystitis/cholangitis	1,271 (0.13)	2.0 (1.9, 2.2)	253 (0.13)	2.0 (1.8, 2.3)	234 (0.12)	2.0 (1.8, 2.3)	19 (0.15)	2.9 (1.8, 4.5)
Abdominal abscess	177 (0.019)	0.28 (0.25, 0.33)	43 (0.022)	0.35 (0.26, 0.47)	42 (0.022)	0.36 (0.26, 0.48)	1 (0.008)	0.15 (0.02, 1.1)
Septic arthritis	128 (0.013)	0.20 (0.17, 0.24)	39 (0.020)	0.31 (0.23, 0.43)	31 (0.017)	0.26 (0.19, 0.38)	8 (0.064)	1.2 (0.60, 2.4)
Osteomyelitis	127 (0.013)	0.20 (0.17, 0.24)	35 (0.018)	0.28 (0.20, 0.39)	32 (0.017)	0.27 (0.19, 0.39)	3 (0.024)	0.45 (0.15, 1.4)
Breast abscess	108 (0.011)	0.17 (0.14, 0.21)	34 (0.017)	0.27 (0.20, 0.38)	31 (0.017)	0.26 (0.19, 0.38)	3 (0.024)	0.45 (0.15, 1.4)
Endocarditis	58 (0.006)	0.093 (0.072, 0.12)	12 (0.006)	0.097 (0.055, 0.17)	11 (0.006)	0.094 (0.052, 0.17)	1 (0.008)	0.15 (0.02, 1.07)
Prostate	38 (0.004)	0.061 (0.044, 0.084)	8 (0.004)	0.064 (0.032, 0.13)	7 (0.004)	0.060 (0.028, 0.13)	1 (0.008)	0.15 (0.021, 1.1)
Central nervous system	37 (0.004)	0.059 (0.043, 0.082)	8 (0.004)	0.064 (0.032, 0.13)	8 (0.004)	0.068 (0.034, 0.14)	0	0
Device-associated	6 (0.0006)	0.0096 (0.004, 0.021)	3 (0.0015)	0.024 (0.008, 0.075)	3 (0.0016)	0.026 (0.008, 0.079)	0	0
Central nervous system abscess	6 (0.0006)	0.0096 (0.004, 0.021)	2 (0.001)	0.016 (0.004, 0.064)	2 (0.001)	0.017 (0.004, 0.068)	0	0

CI, confidence interval

[a]Per 10,000 person-years

Table 4

Sensitivity Analyses for Serious Infection, Opportunistic Infection, and Herpes Zoster Outcomes: THIN Cohort

Sensitivity Analysis Model by Outcome	Number of Patients		All Psoriasis HR (95% CI)	Mild Psoriasis HR (95% CI)	Moderate-to-Severe Psoriasis HR (95% CI)
	No Psoriasis	Psoriasis			
Serious Infection					
Primary Model	954,315	199,700	1.21 (1.18, 1.23)	1.18 (1.16, 1.21)	1.63 (1.52, 1.75)
Multiple Imputation	954,315	199,700	1.20 (1.18, 1.23)	1.18 (1.15, 1.21)	1.63 (1.52, 1.75)
Exclude patients seen by GP less than once per year	909,728	192,303	1.20 (1.18, 1.23)	1.18 (1.15, 1.21)	1.61 (1.50, 1.73)
Exclude IBD and RA	943,052	194,047	1.21 (1.18, 1.23)	1.19 (1.16, 1.21)	1.64 (1.52, 1.76)
Exclude PsA	954,315	189,622	1.20 (1.17, 1.23)	1.18 (1.16, 1.21)	1.71 (1.57, 1.86)
Exclude patients with history of infection	366,203	89,312	1.25 (1.21, 1.30)	1.23 (1.18, 1.28)	1.73 (1.52, 1.98)
Exclude patients who had received immunosuppressive psoriasis treatments	951,676	190,055	1.19 (1.16, 1.22)	1.19 (1.16, 1.21)	1.56 (1.35, 1.82)
Opportunistic Infection					
Primary Model	954,315	199,700	0.91 (0.79, 1.04)	0.87 (0.75, 1.00)	1.57 (1.06, 2.34)
Multiple imputation	954,315	199,700	0.91 (0.79, 1.05)	0.87 (0.75, 1.00)	1.61 (1.08, 2.39)
Exclude patients seen by GP less than once per year	909,728	192,303	0.90 (0.79, 1.04)	0.86 (0.75, 1.00)	1.54 (1.03, 2.29)
Exclude IBD and RA	943,052	194,047	0.92 (0.80, 1.06)	0.89 (0.76, 1.03)	1.64 (1.06, 2.53)
Exclude PsA	954,315	189,622	0.91 (0.79, 1.04)	0.87 (0.75, 1.01)	1.66 (1.03, 2.68)
Exclude patients with history of opportunistic infection	944,619	198,042	0.92 (0.79, 1.06)	0.86 (0.74, 1.01)	1.76 (1.18, 2.65)
Exclude patients who had received immunosuppressive psoriasis treatments	951,676	190,055	0.88 (0.76, 1.02)	0.88 (0.76, 1.02)	1.17 (0.44, 3.12)
Herpes Zoster					
Primary Model	954,315	199,700	1.08 (1.05, 1.11)	1.07 (1.05, 1.10)	1.17 (1.06, 1.30)
Multiple imputation	954,315	199,700	1.08 (1.05, 1.11)	1.09 (1.06, 1.13)	1.20 (1.08, 1.33)
Exclude patients seen by GP less than once per year	909,728	192,303	1.08 (1.05, 1.11)	1.07 (1.04, 1.10)	1.16 (1.05, 1.28)
Exclude IBD and RA	943,052	194,047	1.08 (1.05, 1.11)	1.08 (1.05, 1.11)	1.12 (1.00, 1.26)
Exclude PsA	954,315	189,622	1.08 (1.05, 1.11)	1.08 (1.05, 1.11)	1.16 (1.02, 1.32)
Exclude patients with history of herpes zoster	913,982	192,249	1.07 (1.04, 1.10)	1.07 (1.04, 1.10)	1.19 (1.07, 1.32)
Exclude patients who had received immunosuppressive psoriasis treatments	951,676	190,055	1.08 (1.05, 1.11)	1.08 (1.05, 1.11)	0.97 (0.76, 1.23)

Table 5

Incidence and Risk of Opportunistic Infection and Herpes Zoster: THIN Cohort

Full THIN Cohort	No Psoriasis N=954,315	All Psoriasis N=199,700	Mild Psoriasis N=187,258	Moderate-to-Severe Psoriasis N=12,442
Opportunistic Infection				
Follow-up time (yrs)				
Mean (SD)	6.5 (4.8)	6.2 (4.7)	6.3 (4.8)	5.3 (4.1)
Median (IQR)	5.6 (2.4, 10.0)	5.3 (2.2, 9.7)	5.3 (2.2, 9.7)	4.4 (1.9, 7.9)
Number of person-years	6,240,165	1,239,794	1,173,285	66,509
Number (%) of opportunistic infections	1,329 (0.14)	236 (0.12)	211 (0.11)	25 (0.20)
Incidence per 10,000 person-years (95% CI)	2.13 (2.02, 2.25)	1.90 (1.68, 2.16)	1.80 (1.57, 2.06)	3.76 (2.54, 5.56)
Unadjusted hazard ratio (95% CI)	Reference	0.89 (0.78, 1.02)	0.84 (0.73, 0.97)	1.73 (1.16, 2.57)
Adjusted hazard ratio (95% CI)[a]	Reference	0.91 (0.79, 1.04)	0.87 (0.75, 1.00)	1.57 (1.06, 2.34)
Herpes Zoster				
Follow-up time (yrs)				
Mean (SD)	6.4 (4.7)	6.1 (4.7)	6.1 (4.7)	5.2 (4.1)
Median (IQR)	5.5 (2.3, 9.8)	5.0 (2.1, 9.4)	5.1 (2.1, 9.5)	4.2 (1.9, 7.7)
Number of person-years	6,084,648	1,209,265	1,144,308	64,957
Number (%) of herpes zoster cases	33,115 (3.5)	6,537 (3.3)	6,117 (3.3)	420 (3.4)
Incidence per 10,000 person years (95% CI)	54.4 (53.8, 55.0)	54.1 (52.8, 55.4)	53.5 (52.1, 54.8)	64.7 (58.8, 71.1)
Unadjusted hazard ratio (95% CI)	Reference	1.00 (0.97, 1.02)	0.98 (0.96, 1.01)	1.21 (1.10, 1.34)
Adjusted hazard ratio (95% CI)[b]	Reference	1.08 (1.05, 1.11)	1.07 (1.05, 1.10)	1.17 (1.06, 1.30)

CI, confidence interval; IQR, interquartile range; SD, standard deviation; yrs, years

[a]Adjusted for age, sex, BMI, smoking and drinking status, asthma/COPD, CVD, diabetes, IBD, inhaled and systemic corticosteroid use within 90 days prior to start date, hospitalization or infection within 30 days prior to start date, prior opportunistic infection, and Townsend score.

[b]Adjusted for age, sex, smoking status, asthma/COPD, CVD, dementia, depression, IBD, OA, RA, SLE, systemic corticosteroid use within 90 days prior to start date, infection within 30 days prior to start date, prior herpes zoster.