Risk of Incident Liver Disease in Patients with Psoriasis, Psoriatic Arthritis, and Rheumatoid Arthritis: A Population-Based Study

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Relatively little is known about the risk for incident liver disease in psoriasis (PsO), psoriatic arthritis (PsA), and rheumatoid arthritis (RA). We performed a cohort study among patients with PsO, PsA, or RA and matched controls in The Health Improvement Network from 1994 to 2014. Outcomes of interest were any liver disease, nonalcoholic fatty liver disease, and cirrhosis (any etiology). Among patients with PsO (N = 197,130), PsA (N = 12,308), RA (N = 54,251), and matched controls (N = 1,279,754), the adjusted hazard ratios for any liver disease were elevated among patients with PsO (without systemic therapy [ST] 1.37; with ST 1.97), PsA (without ST 1.38; with ST 1.67), and RA without an ST (1.49) but not elevated in patients with RA prescribed an ST (0.96). Incident nonalcoholic fatty liver disease was highest in patients with PsO prescribed an ST (2.23) and PsA with an ST (2.11). The risk of cirrhosis was highest among patients with PsO with an ST (2.62) and PsA without an ST (3.15). Additionally, the prevalence of liver disease and cirrhosis increased in a stepwise fashion with increasing body surface area affected by PsO (*P* for trend <0.001). More so than RA, PsO and PsA are associated with liver disease, particularly nonalcoholic fatty liver disease and cirrhosis, and this was true even among patients without ST exposure.

Journal of Investigative Dermatology (2018) **138,** 760–767; doi:10.1016/j.jid.2017.10.024

INTRODUCTION

Psoriasis (PsO) and psoriatic arthritis (PsA) have been associated with a number of metabolic comorbidities, in particular an increased incidence of diabetes and cardiovascular events. Furthermore, these diseases are associated with a high prevalence of obesity (Dubreuil et al., 2014; Ogdie et al., 2015a, 2015b). Similarly, PsO has been associated with a high *prevalence* of liver function test abnormalities and liver disease (Maybury et al., 2014; Ogdie et al., 2015a). Previous studies have reported an increased *prevalence* of liver disease, in particular fatty liver disease in patients with PsO (Abedini et al., 2015; Gisondi et al., 2009, 2016; Humphreys et al., 2017; Madanagobalane and Anandan, 2012; Miele et al., 2009; Tsai et al., 2011; van der Voort et al., 2014, 2016; Yang et al., 2011; Yeung et al., 2013). Among the factors associated with liver disease in patients with PsO, PsA had the strongest association (Miele et al., 2009). However, most of these studies have been mainly clinic based, focused on liver disease related to methotrexate use, and have not adjusted for other risk factors for liver disease including obesity and alcohol intake. Furthermore, few *longitudinal* studies have addressed the *incidence and risk for liver disease* in a broadly representative population of patients with PsO and PsA. In other words, does having PsO or PsA predispose a patient to *developing new* liver disease? The *incidence of liver disease* among patients with PsO and PsA compared with the general population is unknown. Relatively little is known about how the liver responds to chronic inflammation and how this may differ by the type or severity of inflammation. Furthermore, little is known about how skin disease severity, obesity, diabetes, and medication use play a role in the development of liver disease in patients with these diseases.

Liver injury in PsO has been postulated to result in part from cytokine release from skin-derived cells. This so-called hepato-dermal axis (Mantovani et al., 2016) postulates that psoriatic skin-derived lymphocytes and keratinocytes produce inflammatory cytokines such as IL-6, IL-17, and tumor necrosis factor-α that circulate systemically to the liver and induce an array of metabolic derangements that promote

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Abbreviations: aHR, adjusted hazard ratio; BMI, body mass index; CI, confidence interval; GP, general practitioner; HR, hazard ratio; iHOPE, Incident Health Outcomes and Psoriasis Event; NAFLD, nonalcoholic fatty liver disease; PsA, psoriatic arthritis; PsO, psoriasis; RA, rheumatoid arthritis; ST, systemic therapy; THIN, The Health Improvement Network

Received 24 May 2017; revised 13 October 2017; accepted 17 October 2017; accepted manuscript published online 02 November 2017; corrected proof published online 17 February 2018

Table 1. Characteristics of the study population at study entry

		Psoriasis		PsA		RA	
	Controls (N = 1,279,754)	No ST (N = 186,006)	ST (N = 11,124)	No ST (N = 5,786)	ST (N = 6,522)	No ST (N = 21,396)	ST (N = 32,855)
Age in years, mean (SD)	50.84 (17.98)	46.93 (17.76)	49.82 (15.60)	50.94 (14.96)	49.24 (13.69)	63.08 (16.46)	58.91 (14.58)
Female, N (%)	715,274 (55.9%)	96,030 (51.6%)	5,687 (51.1%)	2,886 (49.9%)	3,227 (49.5%)	15,070 (70.4%)	22,908 (69.7%)
Diabetes mellitus, N (%)	78,828 (6.16)	10,091 (5.43)	963 (8.66)	426 (7.36)	502 (7.70)	1,875 (8.76)	2,748 (8.36)
Hyperlipidemia, N (%)	117,205 (9.16)	14,678 (7.89)	1,216 (10.93)	561 (9.70)	644 (9.87)	2,240 (10.47)	3,563 (10.84)
Smoking							
Never, N (%)	616,327 (48.16)	72,717 (39.09)	4,202 (37.77)	2,528 (43.69)	3,067 (47.03)	9,637 (45.04)	14,006 (42.63)
Past, N (%)	270,148 (21.11)	52,995 (28.49)	3,027 (27.21)	1,308 (22.61)	1,231 (18.87)	4,291 (20.06)	7,256 (22.08)
Current, N (%)	259,985 (20.32)	40,652 (21.86)	3,233 (29.06)	1,394 (24.09)	1,802 (27.63)	4,543 (21.23)	8,986 (27.35)
Missing, N (%)	133,294 (10.42)	19,642 (10.56)	662 (5.95)	556 (9.61)	422 (6.47)	2,925 (13.67)	2,607 (7.93)
Alcohol consumption							
None, N (%)	145,932 (11.40)	19,386 (10.42)	1,227 (11.03)	675 (11.67)	715 (10.96)	3,735 (17.46)	5,355 (16.30)
Some, N (%)	812,057 (63.45)	120,659 (64.87)	7,407 (66.59)	3,838 (66.33)	4,367 (66.96)	11,768 (55.00)	19,737 (60.07)
A lot, N (%)	52,982 (4.14)	6,917 (3.72)	731 (6.57)	214 (3.70)	394 (6.04)	1,075 (5.02)	2,158 (6.57)
Missing, N (%)	268,783 (21.00)	39,044 (20.99)	1,759 (15.81)	1,059 (18.30)	1,046 (16.04)	4,818 (22.52)	5,605 (17.06)
BMI, mean (SD)	26.38 (5.45)	26.64 (5.58)	28.06 (6.08)	27.61 (5.62)	28.29 (5.99)	26.55 (5.53)	26.76 (5.53)
Oral steroids, N (%)	135,057 (10.55)	17,225 (9.26)	2,701 (24.28)	758 (13.10)	1,510 (23.15)	5,018 (23.45)	14,376 (43.76)
NSAIDs, N (%)	666,693 (52.10)	80,159 (43.09)	7,650 (68.77)	4,055 (70.08)	5,752 (88.19)	14,298 (66.83)	28,716 (87.40)
Cohort time in years, mean (SD)	6.50 (4.78)	6.21 (4.75)	5.31 (4.13)	6.12 (4.77)	5.83 (4.45)	5.71 (4.64)	6.13 (4.48)

Abbreviations: BMI, body mass index; NSAID, nonsteroidal anti-inflammatory drug; PsA, psoriatic arthritis; RA, rheumatoid arthritis; SD, standard deviation; ST, systemic therapy.

insulin resistance, a hallmark feature of nonalcoholic fatty liver disease pathogenesis (Carr et al., 2016). The converse may also be true in that the ensuing hepatic inflammation promotes keratinocyte proliferation and cutaneous inflammation (Mantovani et al., 2016). If such an axis exists, it is conceivable that patients with either longer duration of inflammation or increased PsO severity would have an increased risk of developing liver disease and propensity for developing cirrhosis, the most advanced form of liver disease.

In this longitudinal cohort study, we aimed to better understand the epidemiology of liver disease in patients with PsO and PsA. We used The Health Improvement Network (THIN), a population-based electronic medical records database, and the Incident Health Outcomes and Psoriasis Events (iHOPE) cohort (a nested study of patients with PsO in the THIN database with additional data regarding affected body surface area) to compare psoriatic patients with the general UK population. We additionally compared patients with PsO with those with rheumatoid arthritis (RA), as RA is another T helper type 1 and T helper type 17 immune-mediated systemic inflammatory disorder that has a spectrum of skin and joint manifestations as in PsO. The three disorders share many treatment approaches (e.g., methotrexate is a first-line therapy for all three diseases) and represent a spectrum of joint and skin inflammation (from skin only in PsO, joint only in RA, and both in PsA) (Coates et al., 2016). The objectives of this study were to (1) determine whether PsO, PsA, or RA is independently associated with an increased risk of developing liver disease compared with general population controls after accounting for medications, alcohol intake, and comorbidities such as obesity and metabolic syndrome and (2) determine whether PsO severity measured by body surface area (BSA), as a surrogate for inflammatory burden, is positively associated with liver disease (Dey et al., 2017; Rocha-Pereira et al., 2004). We hypothesized that PsO and PsA would be associated with an increased risk for liver disease compared with patients in the general population, and more specifically that these disorders would be associated with an increased risk for fatty liver disease and cirrhosis (Supplementary Figure S1 online).

RESULTS

Baseline characteristics

Baseline characteristics of the full THIN cohort are summarized in Table 1 (additional details in Supplementary Table S1 online). Patients with PsO (N = 197,130), PsA (N = 12,308), and RA (N = 54,251) were identified and matched to unexposed controls (N = 1,279,754). Patients with RA were more likely to be older, female, and suffer from more medical comorbidities. Compared with other groups, patients with PsA and PsO with a systemic therapy (ST) had higher body mass index (BMI). Among patients with PsO, PsA, and RA, 6%, 53%, and 61%, respectively, were prescribed an ST. Methotrexate was the most commonly prescribed ST. STs used are reported in Supplementary Table S2 online.

New diagnosis of any liver disease

The average follow-up time was approximately 6 years. The follow-up times, unadjusted incidence rates, and hazard ratios (HRs) for liver disease, cirrhosis, and nonalcoholic fatty liver disease (NAFLD) are shown in Table 2. The HRs and confidence intervals (CIs) are shown in Figure 1. In age and sex-adjusted Cox proportional hazard models, the risk of incident liver disease was higher for all disease categories compared with controls. Similarly, in the fully adjusted

Table 2. Incidence and risk of liver disease among patients with psoriasis, PsA, and RA

		Psoriasis		PsA		RA	
	Controls	No ST	ST	No ST	ST	No ST	ST
N	1,279,754	186,006	11,124	5,786	6,522	21,396	32,855
Mean cohort time (SD)	6.50 (4.78)	6.21 (4.75)	5.31 (4.13)	6.12 (4.77)	5.83 (4.45)	5.71 (4.64)	6.13 (4.48)
Person years (PY)	831,959.4	1,155,764.6	59,017.8	35,389.9	38,017.6	122,204.5	201,351.3
Any liver disease							
Liver disease cases, N (%)	8,140 (0.64)	1,593 (0.86)	132 (1.19)	64 (1.11)	70 (1.07)	189 (0.88)	227 (0.69)
Incidence per 10,000 PY	9.78	13.78	22.37	18.08	18.41	15.47	11.27
Unadjusted HR (95% CI)	Ref	1.41 (1.34–1.49)	2.35 (1.98–2.79)	1.85 (1.45–2.37)	1.91 (1.51–2.41)	1.60 (1.38–1.84)	1.17 (1.02–1.33)
Age/sex HR (95% CI)	Ref	1.40 (1.33–1.48)	2.32 (1.95–2.75)	1.80 (1.40–2.30)	1.87 (1.48–2.37)	1.60 (1.39–1.85)	1.19 (1.04–1.36)
Final model HR (95% CI)[1]		1.37 (1.29–1.45)	1.97 (1.63–2.38)	1.38 (1.02–1.86)	1.67 (1.29–2.15)	1.49 (1.26–1.76)	0.96 (0.83–1.12)
NAFLD							
NAFLD cases, N (%)	3,654 (0.28)	592 (0.32)	75 (0.67)	22 (0.38)	47 (0.72)	66 (0.31)	105 (0.32)
Incidence per 10,000 PY	4.37	5.11	12.67	6.20	12.34	5.38	5.20
Unadjusted HR (95% CI)	Ref	1.18 (1.08–1.28)	3.09 (2.46–3.88)	1.43 (0.94–2.17)	2.91 (2.19–3.89)	1.26 (0.99–1.60)	1.22 (1.01–1.49)
Age/sex HR (95% CI)	Ref	1.17 (1.07–1.27)	3.06 (2.44–3.85)	1.41 (0.93–2.14)	2.88 (2.16–3.84)	1.28 (1.00–1.63)	1.24 (1.02–1.51)
Final model HR (95% CI)[1]	Ref	1.18 (1.07–1.30)	2.23 (1.73–2.87)	1.02 (0.63–1.68)	2.11 (1.55–2.87)	1.20 (0.91–1.57)	0.92 (0.74–1.15)
Cirrhosis (any etiology)							
Cirrhosis cases, N (%)	1,364 (0.11)	293 (0.16)	25 (0.22)	18 (0.31)	9 (0.14)	55 (0.26)	52 (0.16)
Incidence per 10,000 PY	1.63	2.52	4.21	5.07	2.35	4.48	2.57
Unadjusted HR (95% CI)	Ref	1.55 (1.37–1.76)	2.66 (1.79–3.95)	3.11 (1.96–4.96)	1.46 (0.76–2.82)	2.77 (2.12–3.63)	1.60 (1.21–2.11)
Age/sex HR (95% CI)	Ref	1.64 (1.45–1.86)	2.76 (1.85–4.09)	3.06 (1.92–4.87)	1.54 (0.80–2.96)	2.22 (1.70–2.92)	1.42 (1.08–1.87)
Final model HR (95% CI)[1]	Ref	1.63 (1.41–1.88)	2.62 (1.72–4.01)	3.15 (1.89–5.24)	1.78 (0.92–3.45)	2.07 (1.50–2.86)	1.37 (1.02–1.86)

Abbreviations: CI, confidence interval; HR, hazard ratio; NAFLD, nonalcoholic fatty liver disease; PsA, psoriatic arthritis; RA, rheumatoid arthritis; SD, standard deviation; ST, systemic therapy.

[1]Final models adjusted for included age at start date, sex, smoking status, alcohol intake, body mass index category, and use of oral glucocorticoids and nonsteroidal anti-inflammatory drug in the baseline period. Diabetes was not statistically significant in the final model and did not change the HR when removed.

models, the risk of incident liver disease was significantly elevated compared with controls in all disease categories except the RA/ST group (adjusted HR [aHR] 0.96, 95% CI 0.83–1.12). Patients with PsO with an ST were associated with the highest risk (aHR 1.97, 95% CI 1.63–2.38) followed by patients with PsA prescribed an ST (aHR 1.67, 95% CI 1.29–2.15), patients with RA without an ST (aHR 1.49, 95% CI 1.26–1.76), those with PsA without an ST (aHR 1.38, 95% CI 1.02–1.86), and those with PsO without an ST (aHR 1.37, 95% CI 1.29–1.45). NAFLD was the most common subtype (37.85%) followed by alcoholic liver disease (18.53%), unknown causes (10.35%), viral etiologies (7.76%), biliary disease (4.33%), and autoimmune liver disease (0.60%). Ten percent of patients with liver disease were diagnosed with cirrhosis during the observational period. Subclassifications of new liver disease diagnoses are shown in Supplementary Table S3 online. We performed a series of sensitivity analyses to test the assumptions of the analyses performed (Supplementary Table S4 online). The sensitivity analyses did not substantially change the results of the primary models.

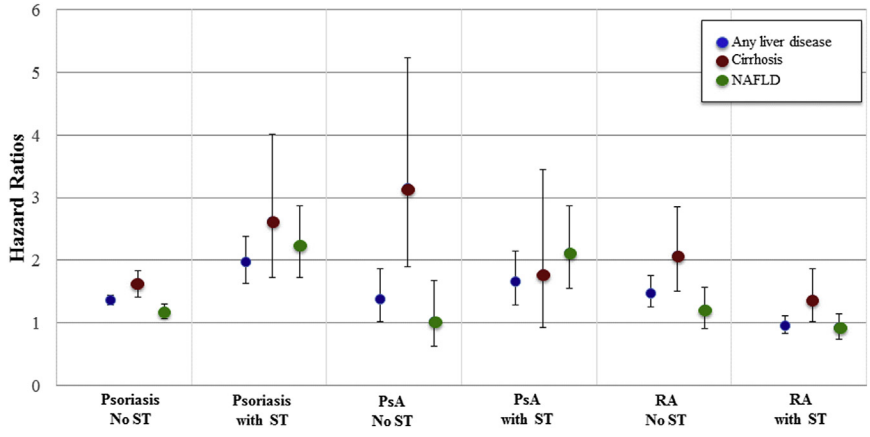

Figure 1. Risk of liver disease, cirrhosis, and NAFLD among patients with psoriasis, psoriatic arthritis, and rheumatoid arthritis (fully adjusted models). Hazard ratios and 95% confidence intervals are shown for any incident liver disease (blue), incident cirrhosis (red), and incident NAFLD (green), respectively, for each disease category. Models are adjusted for age, sex, smoking status, drinking, body mass index, oral glucocorticoid use, and nonsteroidal anti-inflammatory drug use in the baseline period. NAFLD, nonalcoholic fatty liver disease; PsA, psoriatic arthritis; RA, rheumatoid arthritis; ST, systemic therapy.

Table 3. Prevalence of liver disease among patients with psoriasis by body surface area in the iHOPE cohort

	Total (N)	Any liver disease			NAFLD			Cirrhosis (any etiology)		
		N (%)	Age/sex Adj OR (95% CI)	Age/sex/BMI Adj OR (95% CI)	N (%)	Age/sex Adj OR (95% CI)	Age/sex/BMI Adj OR (95% CI)	N (%)	Age/sex Adj OR (95% CI)	Age/sex/BMI Adj OR (95% CI)
Controls	87,596	2,145 (2.4%)	Ref	Ref	535 (0.6%)	Ref	Ref	198 (0.2%)	Ref	Ref
Mild PsO (≤2% BSA)	4,539	132 (2.9%)	1.18 (0.98–1.41)	1.13 (0.94–1.36)	37 (0.8%)	1.32 (0.94–1.84)	1.29 (0.92–1.81)	14 (0.3%)	1.33 (0.77–2.28)	1.31 (0.75–2.30)
Moderate PsO (3–10% BSA)	3,133	94 (3.0%)	1.22 (0.99–1.51)	1.19 (0.96–1.48)	28 (0.9%)	1.45 (0.99–2.13)	1.32 (0.89–1.97)	13 (0.4%)	1.83 (1.04–3.21)	1.82 (1.01–3.28)
Severe PsO (>10% BSA)	1,088	42 (3.9%)	1.62 (1.19–2.22)	1.67 (1.22–2.30)	9 (0.8%)	1.36 (0.70–2.64)	1.28 (0.66–2.48)	9 (0.8%)	3.83 (1.96–7.51)	4.21 (2.14–8.27)

The *P*-value for the trend for any liver disease and cirrhosis was <0.001.

Abbreviations: BMI, body mass index; BSA, body surface area; CI, confidence interval; iHOPE, Incident Health Outcomes and Psoriasis Events; NAFLD, nonalcoholic fatty liver disease; PsO, psoriasis; OR, odds ratio.

New diagnoses of NAFLD

Overall, there were relatively few new diagnoses of NAFLD (Table 2). However, these cases were disproportionately identified in patients with PsO with an ST and patients with PsA prescribed an ST. After adjusting for age, sex, BMI, smoking, and alcohol intake, oral glucocorticoids, and nonsteroidal anti-inflammatory drug use, patients with PsO with an ST and patients with PsA prescribed an ST had a substantially elevated risk of being diagnosed with NAFLD (Table 2, Figure 1).

New diagnoses of cirrhosis

In the unadjusted, age/sex adjusted, and fully adjusted models (Table 2), all disease categories were associated with an increased risk of being diagnosed with cirrhosis. This risk was statistically significant for all disease categories except among patients with PsA who were prescribed an ST. In the fully adjusted model, patients with PsA not prescribed an ST had the highest risk of cirrhosis relative to population controls (aHR 3.15, 95% CI 1.89–5.24), but this risk was also substantially elevated in patients with PsO with an ST (aHR 2.62, 95% CI 1.72–4.01) and patients with RA not prescribed an ST (aHR 2.07, 95% CI 1.50–2.86).

Prevalence of liver disease by objective measures of PsO severity

Demographics in the iHOPE cohort were similar to those for the full THIN cohort PsO population (Supplementary Table S5 online). Patients with mild (BSA ≤ 2%, N = 4,539), moderate (BSA 3–10%, N = 3,133), and severe (BSA > 10%, N = 1,088) PsO were matched to unexposed controls (N = 87,596). Among the patients with PsO, 268 cases of liver disease were identified (including 74 cases of NAFLD and 36 cases of cirrhosis). There was a higher prevalence of liver disease, cirrhosis, and NAFLD among all patients with PsO compared with controls (Table 3). There was a stepwise increase in the prevalence of any liver disease by PsO severity after adjusting for age, sex, and BMI: for mild, moderate, and severe PsO, odds ratio (95% CI) 1.13 (95% CI 0.94–1.36), 1.19 (95% CI 0.96–1.48), and 1.67, 95% CI 1.22–2.30), respectively (*P* for trend<0.001). Patients with moderate or severe PsO had a substantially elevated prevalence of cirrhosis (moderate PsO: odds ratio 1.82, 95% CI 1.01–3.28; severe PsO: odds ratio 4.21, 95% CI 2.14–8.27). The *P*-value for the trend was <0.001 for both liver disease and cirrhosis by PsO severity. The prevalence of NAFLD was elevated in patients with PsO but was not statistically significant in this smaller cohort.

DISCUSSION

In this population-based study, patients with inflammatory skin and/or joint disease had an elevated risk for new liver disease diagnoses, although patients with PsO with an ST had the highest risk and patients with RA who were prescribed an ST had the lowest risk. This increased incidence was independent of risk factors for liver diseases routinely captured in medical encounters. Overall, the lifetime prevalence of a diagnosis of liver disease in patients with PsO was 3–4% and, among patients without liver disease at baseline, the incidence over 5–6 years of follow-up was approximately 1%. NAFLD was the most common cause of incident liver

disease. Both NAFLD and cirrhosis were substantially elevated in PsO and PsA. To our knowledge, this is the first population-based study to simultaneously address the risk for incident liver disease in patients with these inflammatory diseases. Previous studies have also found an increased prevalence for NAFLD and liver disease, but none have examined incident disease or more serious outcomes such as cirrhosis, and most have not adjusted for other risk factors for liver disease (e.g., gender, BMI, alcohol intake, smoking status) (Abedini et al., 2015; Gisondi et al., 2009, 2016; Madanagobalane and Anandan, 2012; Miele et al., 2009; Rosenberg et al., 2007; van der Voort et al., 2014, 2016; Yang et al., 2011).

The results of this study support a particularly strong association between PsO and incident liver disease. This may thus support the presence of the hepato-dermal axis. Our findings also suggest an important role for systemic inflammation, which is known to be present in these three related but unique skin and joint diseases in the development of liver disease. Although systemic inflammation may play an important role in the development of liver disease, medications used to treat these inflammatory diseases can also cause liver toxicity. Methotrexate is the most commonly used ST for all three diseases. Previous publications have suggested that patients with PsO are more susceptible to methotrexate toxicity than patients with RA, but empiric data to support this hypothesis are scant (Kalb et al., 2009; Saporito and Menter, 2004; Walker et al., 1993; Whiting-O'Keefe et al., 1991; Yazici, 2010). Our results suggest that patients with PsO prescribed an ST are at an increased risk for liver disease, in particular NAFLD and cirrhosis, to a greater degree than patients with RA. After excluding patients prescribed methotrexate in a sensitivity analysis, the risk for liver disease remained increased in this PsO group but similar to the unexposed controls among patients with RA. Conversely, it may be that adequate control of inflammation reduces the risk of liver disease. We are unable to address this question in the current study as separating the effects of a medication from the reason for receiving a medication can be challenging (i.e., confounding by indication).

The strengths of this study include the use of a population-based approach and cohort study design, the large sample size, validated exposure definitions, examination of the outcome by levels of disease severity, and stable results across numerous sensitivity analyses. Because THIN is broadly representative of the United Kingdom, our results should be generalizable to the larger UK population and populations of similar developed nations. Furthermore, the use of the iHOPE subcohort, a population-based cohort with information on clinician-assessed BSA involvement by PsO, allowed for examination of the outcomes by objectively measured PsO severity. Likewise, the study should be interpreted in light of some limitations. First, the outcome definitions have not been formally validated against imaging diagnosis in THIN, although they tracked closely with another medical records database and have been used in several studies including studies in the Clinical Practice Research Datalink (Loomis et al., 2016; Ratib et al., 2014a, 2014b, 2015). We did not examine death from liver disease as an outcome, perhaps the most consequential outcome, though very rare and challenging to measure (Ogdie et al., 2017b). Because of the lack of reliable biomarkers for NAFLD diagnosis and staging (Carr et al., 2016), NAFLD may be inconsistently captured in clinical practice. Although there is potential for misclassification, it would likely affect all exposure groups to the same extent. However, patients with inflammatory diseases, particularly those who will receive or have received STs, may be more likely to have liver function tests evaluated and consequently receive a diagnosis for liver disease when compared with their healthy counterparts. Nevertheless, stronger associations were seen with PsO and this is unlikely to be explained by observation bias alone; however, patients with PsO, PsA, and RA may be screened with liver function tests differentially given previous reports of the higher incidence of liver disease in patients with PsO using methotrexate (Maybury et al., 2014). Our results were robust to several sensitivity analyses that addressed liver function testing. These included restriction to patients with liver function tests in the baseline period, in the follow-up period, and requiring patients to have at least annual visits with their general practitioner (GP), regardless of blood testing. Next, as the data used were derived from a medical record database, information on alcohol use may be incomplete and disease activity in patients with RA or PsA was not available. Thus, we were unable to directly draw conclusions between the degree of systemic inflammation and the risk of liver disease in these two groups. Furthermore, although we were able to directly address disease severity in patients with PsO within the iHOPE cohort, we did not have sufficient power to conduct longitudinal studies in this subgroup. In addition, we did not have sufficient knowledge of active and previous PsO therapies, in particular the biologics, to identify the impact of these therapies on the development of liver disease. Finally, we are unable to address whether patients who are likely to develop liver disease are "channeled" away from receiving an ST, thus making it appear as though the risk of liver disease is lower among patients with RA receiving a therapy (i.e., channeling bias). However, at baseline, patients with previous liver disease were excluded; furthermore, it is unclear why "channeling" may be different between patients with RA and those with PsO or PsA, suggesting a true interaction with therapy (or disease severity) and liver disease in PsO and PsA.

In conclusion, this population-based cohort study demonstrates that patients with inflammatory disorders, in particular patients with more severe PsO, have an elevated risk for serious liver disease. The findings also provide empirical support for the long-held expert opinion that patients with PsO may be more predisposed to liver disease than patients with RA. Elucidating the role of inflammation in liver disease, and conversely, the role the liver plays in perpetuating inflammation in PsO, PsA, and RA, may significantly advance our understanding of these inflammatory disorders. Risk factors for severe liver disease such as obesity, alcohol use, and hepatotoxic medications should be carefully considered in patients with PsO, particularly when systemic medications are indicated for more extensive skin or joint disease. Furthermore, physicians should counsel patients on the increased risk for liver disease and recommend weight loss and moderation of alcohol use, and possibly minimize

use of nonsteroidal anti-inflammatory drugs in combination with other hepatotoxic medications.

METHODS

Study design and data sources

A population-based cohort study was performed in THIN using data from 1994 to 2014. We additionally performed a nested cross-sectional study to assess the prevalence of liver disease in the iHOPE database, a nested subcohort of patients in THIN who have objective, GP-assessed PsO severity data expressed as percentage of BSA affected by PsO (Yeung et al., 2013). The two study cohorts are described below and in Supplementary Table S6 online. THIN is an electronic medical records database in the United Kingdom that includes patients from 562 general practices and contains data for more than 11 million individuals (Gladman et al., 2009). THIN database is broadly representative of the general UK population in terms of age, sex, geography, and medical diagnoses and has been used extensively in epidemiologic studies (Blak et al., 2011; Desai et al., 2012; Haynes et al., 2011; Lewis et al., 2007).

Study population

All patients in THIN between the ages of 18 and 89 years at the start date who had a diagnosis of PsO, PsA, or RA were included. Patients were required to have observation time in THIN after implementation of Vision software (software needed to extract data from the medical record into THIN). Patients with prior liver disease at baseline were excluded from the full cohort. Up to five unexposed controls were selected for each patient with PsO, PsA, and RA. Controls were matched on clinical practice and start date within the practice. Match date was either diagnosis date or 180 days after registration date, whichever was later. The "diagnosis" date for unexposed controls was defined as the first GP visit within 6 months of the date on which the matched exposed patients were diagnosed with their PsO, PsA, or RA. Ensuring that exposed and unexposed patients were followed by similar doctors during similar time periods minimizes bias. We have used this matching strategy in previous studies (Ogdie et al., 2014b, 2015b, 2017a, 2017b).

The iHOPE nested cohort included patients with PsO aged 25 to 64 years who were randomly sampled from THIN. Questionnaires were sent to the GP to ascertain the severity of PsO by BSA involvement, which was categorized as mild disease (≤2% BSA), moderate disease (3−10% BSA), or severe disease (>10% BSA). The start date for follow-up was defined by the GP survey sampling date (November 2008 to September 2010). Each patient in the cohort was assigned to up to 10 randomly selected living, age category-matched nonpsoriatic controls from the same practice with a visit to the GP within 2 years of sampling. Patients were then followed prospectively for the development of incident health outcomes (e.g., cardiovascular disease, incident PsA, etc.). This cohort has been previously described by Seminara et al. (2011) and Yeung et al. (2013). More information on the study populations and the cohort time is provided in Supplementary Table S6 online.

Exposure definitions

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 as having PsO, PsA, or RA if they had at least one read code for their respective disease. Read codes for these diagnoses have been previously validated within the same or analogous databases (Garcia Rodriguez and Perez Gutthann, 1998; Ogdie et al., 2014a; Rodriguez et al., 2009; Seminara et al., 2011; Watson et al., 2002, 2003). A priori we hypothesized an interaction between disease and prescriptions for STs (i.e., methotrexate, sulfasalazine, azathioprine, leflunomide, cyclosporine, mycophenolate, hydroxychloroquine, adalimumab, etanercept, infliximab, ustekinumab, golimumab, and certolizumab for patients with PsA or RA). Similarly, patients with PsO with a code for phototherapy (including UVB or psoralen and UVA), methotrexate, cyclosporine, oral retinoids, etanercept, infliximab, adalimumab, or ustekinumab were classified as PsO "prescribed a systemic therapy (ST)." In the United Kingdom, STs can be prescribed by consultants (specialists) but may be captured by GP records with the exception of the biological medications, which are rarely recorded in THIN (Ogdie et al., 2014a).

Outcomes: definitions of liver disease

The primary outcome of interest was a new code for any liver disease (i.e., NAFLD, cirrhosis, viral hepatitis, etc.). This definition excluded nonspecific liver function test abnormalities. We also did not examine death from liver disease as this is a challenging outcome to assess and requires manual review of the records and making assumptions of cause of death (Ogdie et al., 2017b). Additionally, as liver fibrosis is a pathologic description, we were not able to specifically assess for liver fibrosis. Secondary outcomes of interest were NAFLD and cirrhosis from any cause. Liver disease has previously been studied in THIN and similar databases; a list of Read diagnostic codes was created for each outcome and after review of existing code lists from these studies (Lo Re et al., 2009; Loomis et al., 2016; Noe et al., 2017; Ratib et al., 2014a, 2015). Liver function tests were available for a smaller portion of patients in THIN and were used in a sensitivity analysis described in Supplementary Table S4.

Covariates of interest

All covariates of interest were measured on or before start date and are listed in the Supplementary Methods online.

Statistical analyses

Statistical analyses were performed using STATA 13.0 (College Station, TX). Demographics and covariate distribution were descriptively reported by disease category (PsO, PsA, RA, control). Incidence was reported as the number of new outcomes divided by the total person years of follow-up after the start date for each category. Cox proportional hazards models were used to estimate the unadjusted, age- and sex-adjusted, and fully aHRs with 95% CIs. A purposeful selection modeling approach was used (Bursac et al., 2008). Covariates were initially included in the multivariable "full" model if they had a biologically plausible relationship to the exposure and outcome, or if they had a *P*-value of <0.05 when individually added to the age- and sex-adjusted Cox regression models. Covariates were then individually removed, starting with the highest *P*-value. If removal did not change the main effects >10% for any of the disease categories, the covariate was eliminated to create the most parsimonious model. We additionally examined the prevalence of liver disease within the iHOPE cohort stratified by PsO severity (mild, moderate, or severe) compared with matched controls. Prevalence was reported as the number of outcomes at any point during follow-up divided by the total number of patients for each disease category. Age- and sex-adjusted logistic regression models were used to compare the prevalence in each disease category with controls. We used a complete case analysis for the main analysis but examine the impact of missing data on alcohol

intake, smoking, and BMI in a sensitivity analysis. Several additional sensitivity analyses were conducted and are described in more detail in the Supplementary Methods.

Ethics approval

The study was approved by the University of Pennsylvania Institutional Review Board and the IMS/THIN Scientific Review Committee. De-identified datasets were used and thus patient consent was not possible/waived. STROBE guidelines were followed in reporting the results (von Elm et al., 2014).

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CONFLICT OF INTEREST

AO has served as a consultant for Novartis, Pfizer, BMS, Lilly, and Takeda; is a co-investigator on a research grant from Pfizer (PI: Gelfand). JT receives a research grant from Pfizer (unrelated to this study) and payment for continuing medical education work related to psoriasis that was supported indirectly by Eli Lilly. In the previous 12 months. JMG served as a consultant for Abbvie., Coherus, Janssen Biologics (formerly Centocor), Merck, Novartis, Valeant, and Pfizer, receiving honoraria; receives research grants (to the Trustees of the University of Pennsylvania) from Abbvie, Eli Lilly, Janssen, Novartis, Regeneron, Sanofi, and Pfizer; and received payment for continuing medical education work related to psoriasis that was supported indirectly by Lilly, and Abbvie. JMG is a co-patent holder of resiquimod for the treatment of cutaneous T-cell lymphoma. RMC is a co-investigator on a research grant from Intercept and a subinvestigator on a clinical trial from Audentes. ZCCF has received payment for continuing medical education work related to atopic dermatitis and is a PI for clinical trials sponsored by Regeneron, Vanda, and Tioga Pharmaceuticals.

ACKNOWLEDGMENTS

We thank Yihui Jiang and Suzette Baez Vanderbeek for administrative support. This study was supported in part by grants from the National Institute of Arthritis and Musculoskeletal and Skin Diseases K24-AR064310 (JMG), K23-AR063764 (AO), K23-AR068433 (JT), a Medical Dermatology Fellowship from The National Psoriasis Foundation (MHN), NIH Pharmacoepidemiology Training Grant T32-GM075766 (MHN), NIH Training Grant T32-AR007465-32 (SKG), Dermatology Foundation Career Development Award (JT), an unrestricted grant from Pfizer to the trustees of the University of Pennsylvania (JMG), an NIH grant K08-AA021424 (RMC), Robert Wood Johnson Foundation (RMC), Harold Amos Medical Faculty Development Award, 7158 (RMC), IDOM DRC Pilot Award P30 DK019525 (RMC) and in part by NIH P30-DK050306 and its pilot program (RMC), Health Resources and Services Administration: Grant number D34HP24459, Center of Excellence for Diversity in Health Education and Research (RMC), Perelman School of Medicine, University of Pennsylvania (RMC). Funding sources had no role in the design and conduct of the study; collection, management, analysis, and interpretation of data; preparation or approval of the manuscript; or decision to submit the manuscript for publication. Pfizer participated in reviewing the manuscript only. All other sponsors had no role in the review of the manuscript.

AUTHOR CONTRIBUTIONS

AO, JT, and JMG designed the study; AO and SKG wrote the first draft of the manuscript; DBS created the analytic dataset; and AO and SKG performed the analysis. All authors assisted in interpretation of the data and reviewed the final version of the manuscript.

SUPPLEMENTARY MATERIAL

Supplementary material is linked to the online version of the paper at www.jidonline.org, and at https://doi.org/10.1016/j.jid.2017.10.024.

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