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ORIGINAL ARTICLE

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Psoriasis and the Risk of Major Cardiovascular Events: Cohort Study Using the Clinical Practice Research Datalink

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The association between psoriasis and risk of major cardiovascular (CV) events (myocardial infarction, acute coronary syndrome, unstable angina, and stroke) is unclear. A cohort study with 48,523 patients with psoriasis and 208,187 controls was conducted. During a median follow-up of 5.2 years, 1,257 patients with psoriasis (2.59%) had a major CV event, compared with 4,784 controls (2.30%). In the multivariable analysis, inflammatory arthritis hazard ratio (HR) 1.36 (1.18–1.58), diabetes HR 1.18 (1.06–1.31), chronic kidney disease HR 1.18 (1.07–1.31), hypertension HR 1.37 (1.29–1.45), transient ischemic attack HR 2.74 (2.41–3.12), atrial fibrillation HR 1.54 (1.36–1.73), valvular heart disease HR 1.23 (1.05–1.44), thromboembolism 1.32 (1.17–1.49), congestive heart failure HR 1.57 (1.39–1.78), depression HR 1.16 (1.01–1.34), current smoker HR 2.18 (2.03–2.33), age (year) HR 1.07 (1.07–1.07), and male gender HR 1.83 (1.69–1.98) were statistically significant for the risk of major CV events. The age- and gender-adjusted HRs of a major CV event for psoriasis were 1.10 (1.04–1.17) and for severe psoriasis 1.40 (1.07–1.84), whereas the fully adjusted HRs were attenuated to 1.02 (0.95–1.08) and 1.28 (0.96–1.69). In conclusion, neither psoriasis nor severe psoriasis were associated with the short-to-medium term (over 3–5 years) risk of major CV events after adjusting for known cardiovascular disease risk factors.

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INTRODUCTION

Psoriasis is a chronic skin disorder, now recognized as one of the most common immune-mediated diseases (Griffiths and Barker, 2007) with a prevalence between 0.91% and 8.5% in Western countries (Parisi *et al.*, 2013). The severity of psoriasis can range from a mild disease involving small body surface area to extensive skin involvement and, in many cases, has a major impact on people's quality of life (Rapp *et al.*, 1999; Gelfand *et al.*, 2004; Stern *et al.*, 2004). Psoriasis often coexists with other disorders, perhaps due to chronic inflammation (Griffiths and Barker, 2007), such as obesity (Naldi *et al.*, 2005; Setty *et al.*, 2007), hypertension, hyperlipidemia (Neimann *et al.*, 2006), and diabetes (Lee *et al.*, 2014), which are associated with an increased risk of cardiovascular disease (CVD). The main hypothesis for an association between psoriasis and CVD is that increased systemic inflammation, as occurs in psoriasis, exacerbates other chronic inflammatory diseases including atherosclerosis, which could lead to myocardial infarction (MI) or stroke (Griffiths and Barker, 2007; Boehncke *et al.*, 2011). The possible link between psoriasis and CVD is complex for several reasons: psoriasis is associated with unhealthy lifestyles (increased likelihood of smoking, little physical activity, and obesity; Nijsten and Wakkee, 2009); a higher prevalence of CVD risk factors (such as, diabetes, hypertension, and hyperlipidemia (Neimann *et al.*, 2006)); and therapies for psoriasis that may increase (e.g., ciclosporin (Nijsten and Wakkee, 2009)) or decrease (e.g., methotrexate (Westlake *et al.*, 2010)) the CVD risk; all aspects which may confound the association between the two disorders.

Conflicting evidence exists regarding the relationship between psoriasis and CVD. A number of studies have

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Abbreviations: ACS, acute coronary syndrome; BMI, body mass index; CPRD, Clinical Practice Research Datalink; CVD, cardiovascular disease; IMD, index of multiple deprivation; MI, myocardial infarction; ONS, Office for National Statistics

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suggested an increased risk of fatal and non-fatal CVD events in patients with psoriasis after controlling for several major CVD risk factors (Mallbris *et al.*, 2004; Gelfand *et al.*, 2006; Ludwig *et al.*, 2007; Kaye *et al.*, 2008; Gelfand *et al.*, 2009; Mehta *et al.*, 2010; Ahlehoff *et al.*, 2011, 2012; Lin *et al.*, 2011; Li *et al.*, 2012; Dregan *et al.*, 2014). In contrast, other studies have concluded that psoriasis is not an independent risk factor for CVD (Brauchli *et al.*, 2009; Wakkee *et al.*, 2010; Stern and Huibregtse, 2011; Dowlatshahi *et al.*, 2013). A recent systematic review of epidemiological studies suggested a possible association between severe psoriasis and CVD but acknowledged that the majority of studies failed to adequately adjust for important risk factors (Samarasekera *et al.*, 2013). Inflammatory arthritis, a common co-morbidity in patients with psoriasis and a recognized risk factor for CVD (Han *et al.*, 2006; Symmons and Gabriel, 2011; John and Kitas, 2012), has rarely been considered as a possible confounder. It is also important to note that, in many studies using electronic medical record databases, severe psoriasis is typically defined by exposure to systemic or biologic therapies, which may also be used to treat inflammatory arthritis. This raises the possibility of misclassification of severe psoriasis when not taking account of the presence of inflammatory arthritis. Furthermore, little consideration has been given in earlier studies to the time-varying nature for the development of risk factors or the severity of psoriasis.

Given these premises, a large population-based cohort study was undertaken in order to investigate whether psoriasis is independently associated with an increased risk of major cardiovascular (CV) events (MI, acute coronary syndrome (ACS), unstable angina, and stroke) when taking into account relevant CVD risk factors.

RESULTS

Between 1994 and 2009, 48,523 patients with psoriasis and 208,187 controls met the inclusion criteria. Table 1 summarizes the demographic characteristics of the included patients. Patients with psoriasis had a higher prevalence of the majority of risk factors compared with the control group at baseline (Table 1) and a higher prevalence of all time-varying risk factors at the end of follow-up except for atrial fibrillation, transient ischaemic attack, and congestive heart failure (Table 2). In particular, inflammatory arthritis was present in 2.39% of patients with psoriasis and 0.98% of the controls at baseline and in 4.69% of the patients with psoriasis and 1.38% of the controls by the end of follow-up. In addition, at baseline, there were 1.03% of patients with psoriasis receiving phototherapy, systemic, or biologic therapies, which increased to 4.29% patients by the end of follow-up. Of note, 50.62% of patients receiving systemic or biologic therapies also had a diagnosis of inflammatory arthritis by the end of follow-up. Methotrexate was the most commonly used systemic treatment used in patients with psoriasis (Table 3).

During a median follow-up of 5.2 years, 1,257 patients with psoriasis (2.59%) had a major CV event, compared with 4,784 controls (2.30%). The unadjusted incidence rate of a major CV event per 1,000 person-years was higher in the psoriasis group than the control group (4.13 per 1,000 person-years (95% confidence interval (CI): 3.91–4.36) and 3.87 per 1,000 person-years (95% CI: 3.76–3.98), respectively; Table 4). Investigating the assumption of proportionality by using Schoenfeld residuals revealed time-varying effects for hypertension, transient ischaemic attack, atrial fibrillation, and gender. However, allowing these variables to have different effects for the first 3 years of follow-up compared with the later follow-up removed the non-proportionality ($P=0.12$). The age-and gender-adjusted hazard ratio (HR) of major CV events associated with the presence of psoriasis was 1.10 (95% CI: 1.04–1.17), but this was attenuated and became nonsignificant in the multivariate model (HR 1.02 (95% CI: 0.95–1.08)). The presence of severe psoriasis was associated with an increased risk of major CV events in the age-and gender-adjusted analysis (HR 1.40 (95% CI: 1.07–1.84)), but in the fully adjusted model the HR was above 1 but not significant (HR 1.28 (95% CI: 0.96–1.69)). In the multivariate analysis, the following risk factors (inflammatory arthritis HR 1.36 (95% CI: 1.18–1.58); diabetes HR 1.18 (95% CI: 1.06–1.31); chronic kidney disease HR 1.18 (95% CI: 1.07–1.31); hypertension HR 1.37 (95% CI: 1.29–1.45); transient ischaemic attack HR 2.74 (95% CI: 2.41–3.12); atrial fibrillation HR 1.54 (95% CI: 1.36–1.73); valvular heart disease HR 1.23 (95% CI: 1.05–1.44); thromboembolism HR 1.32 (95% CI: 1.17–1.49); congestive heart failure HR 1.57 (95% CI: 1.39–1.78); depression HR 1.16 (95% CI: 1.01–1.34); current smoker HR 2.18 (95% CI: 2.03–2.33); age (year) HR 1.07 (95% CI: 1.07–1.07); and male gender HR 1.83 (95% CI: 1.69–1.98)) were significantly related to the risk of major CV events (Table 5), whereas hyperlipidemia was not (HR 1.04 (95% CI: 0.96–1.11)). A fully adjusted model with an interaction between psoriasis or severe psoriasis and age was fitted; however, the interaction terms were nonsignificant ($P=0.40$ or $P=0.25$, respectively) and for this reason were not included in the final model.

Results from sensitivity analyses did not change the main findings. Similar results were obtained when adjusting the model for different set of risk factors (Supplementary Table S1 online) or when including body mass index (BMI) and index of multiple deprivation (IMD) as additional risk factors in the multivariate model (Table 6). Likewise, results from the analyses of patients with at least one general practice visit per year, patients with at least 6-month follow-up, or results that took into account patients exposed to methotrexate, ciclosporin, or oral retinoids were consistent with the main findings (Table 6). Finally, a nested analysis including patients from the Clinical Practice Research Datalink (CPRD) linked to the Office for National Statistics (ONS) mortality data and patient-level socioeconomic status (IMD) also yielded similar results to the main findings (Table 6).

DISCUSSION

Our findings suggest that patients with psoriasis have an increased prevalence of comorbidities associated with CVD; however, neither psoriasis nor severe psoriasis was significantly associated with the short-to-medium term risk (over 3–5 years) of major CV events when taking into account other established risk factors for CVD. In particular, the risk of a

Table 1. Characteristics of patients at baseline

	Psoriasis patients	Controls	*P*-values
No.	48,523	208,187	
Demographics			
Men (%)	22,932 (47.26)	88,998 (42.75)	<0.001
Women (%)	25,591 (52.74)	119,189 (57.25)	
Median age (IQR)	47 (25)	48 (26)	<0.001
Comorbidities/covariates			
Severe psoriasis (%)	503 (1.03)	—	—
Inflammatory arthritis (%)	1,158 (2.39)	2,040 (0.98)	<0.001
Chronic kidney disease (%)	444 (0.92)	1,991 (0.96)	0.398
Hypertension (%)	7,467 (15.39)	31,079 (14.93)	0.011
Hyperlipidemia (%)	4,131 (8.51)	16,203 (7.78)	<0.001
Depression (baseline) (%)	2,096 (4.32)	7,113 (3.42)	<0.001
Smoking status			
Never-smoker (%)	15,551 (32.05)	79,214 (38.05)	<0.001
Ex-smoker (%)	12,948 (26.68)	52,656 (25.29)	
Current smoker (%)	15,379 (31.69)	52,435 (25.19)	
Unknown smoking status (%)	4,645 (9.57)	23,882 (11.47)	
Body mass index[1], mean ± SD	27.40 ± 5.63	26.73 ± 5.36	<0.001
<20—underweight (%)	1,966 (4.05)	9,503 (4.56)	<0.001
20–24.9—normal (%)	11,879 (24.48)	55,197 (26.51)	
25–29.9—overweight (%)	13,362 (27.54)	54,065 (25.97)	
30+—obese (%)	9,880 (20.36)	34,337 (16.49)	
Unknown BMI (%)	11,436 (23.57)	55,085 (26.46)	
IMD score[2](%)			
1	6,808 (14.03)	29,898 (14.36)	0.005
2	6,553 (13.50)	28,763 (13.82)	
3	5,605 (11.55)	23,789 (11.43)	
4	5,186 (10.69)	21,190 (10.18)	
5	4,083 (8.41)	17,309 (8.31)	
Unknown (%)	20,288 (41.81)	87,238 (41.90)	

Abbreviations: BMI, body mass index; IMD, index of multiple deprivation; IQR, interquartile range.
[1]BMI is calculated as weight in kilograms divided by height in meters squared.
[2]IMD is presented in quintiles with one being the most affluent area and five the most deprived.

major CV event was 36% higher in patients with psoriasis who also had inflammatory arthritis compared with those who did not.

Consistent with other studies, we found a higher prevalence of CVD risk factors in patients with psoriasis (Gelfand *et al.*, 2006; Neimann *et al.*, 2006; Kaye *et al.*, 2008). Our findings are in line with those reported by others who did not find an overall higher risk of MI associated with psoriasis (Brauchli *et al.*, 2009; Wakkee *et al.*, 2010). However, compared with those studies, our research has important strengths: (a) our sample size was large (Wakkee *et al.*, 2010); (b) psoriasis cases were identified on the bases of diagnosis and treatment received (Brauchli *et al.*, 2009); and (c) we accounted for important confounders including inflammatory arthritis (Brauchli *et al.*, 2009; Wakkee *et al.*, 2010).

Our findings are different from several previous studies exploring risk of major CV events. Ogdie *et al.* (2015), using The Health Improvement Network, reported an increased risk of major adverse CV events in patients with either mild or severe psoriasis. The cohort of patients with psoriasis identified by Ogdie *et al.* (2015) had possibly longer disease duration compared with patients identified in our cohort because of different study designs (prevalent versus incident cohort). However, a prevalent cohort is associated with the problem of left censoring. For instance, patients with the most severe psoriasis or CVD may have already died before cohort

Table 2. Characteristics of patients at the end of follow-up for time-varying covariates

	Psoriasis patients	Controls	*P*-values	Mild psoriasis patients	Controls	*P*-values	Severe psoriasis patients	Controls	*P*-values
No.	48,523	208,187		46,439	200,226		2,084	7,961	
Severe psoriasis (%)	2,084 (4.29)	—		—	—		2,084	—	
Inflammatory arthritis (%)	2,275 (4.69)	2,874 (1.38)	<0.001	1,220 (2.63)	2,737 (1.37)	<0.001	1,055 (50.62)	137 (1.72)	<0.001
Diabetes (%)	2,806 (5.78)	9,767 (4.69)	<0.001	2,618 (5.64)	9,305 (4.65)	<0.001	188 (9.02)	462 (5.80)	<0.001
Chronic kidney disease (%)	2,400 (4.95)	9,509 (4.57)	<0.001	2,241 (4.83)	9,146 (4.57)	0.017	159 (7.63)	363 (4.56)	<0.001
Hypertension (%)	12,140 (25.02)	48,596 (23.34)	<0.001	11,481 (24.72)	46,628 (23.29)	<0.001	659 (31.62)	1,968 (24.72)	<0.001
Hyperlipidemia (%)	6,232 (12.84)	23,239 (11.16)	<0.001	5,912 (12.73)	22,169 (11.07)	<0.001	320 (15.36)	1,070 (13.44)	0.024
Atrial fibrillation (%)	877 (1.81)	3,605 (1.73)	0.251	827 (1.78)	3,470 (1.73)	0.478	50 (2.40)	135 (1.70)	0.033
Transient ischaemic attack (%)	395 (0.81)	1,601 (0.77)	0.309	382 (0.82)	1,534 (0.77)	0.212	13 (0.62)	67 (0.84)	0.319
Congestive heart failure (%)	719 (1.48)	2,733 (1.31)	0.004	681 (1.47)	2,660 (1.33)	0.021	38 (1.82)	73 (0.92)	<0.001
Thromboembolism (%)	1,212 (2.50)	4,864 (2.34)	0.035	1,128 (2.43)	4,678 (2.34)	0.235	84 (4.03)	186 (2.34)	<0.001
Valvular heart disease (%)	587 (1.21)	2,352 (1.13)	0.136	559 (1.20)	2,249 (1.12)	0.141	28 (1.34)	103 (1.29)	0.859
Smoking status									
Never-smoker (%)	15,232 (31.39)	80,541 (38.69)	<0.001	14,563 (31.36)	77,484 (38.70)	<0.001	669 (32.10)	3,057 (38.40)	<0.001
Ex-smoker (%)	18,814 (38.77)	73,056 (35.09)		17,920 (38.59)	69,979 (34.95)		894 (42.90)	3,077 (38.65)	
Current smoker (%)	13,344 (27.50)	46,846 (22.50)		12,841 (27.65)	45,160 (22.55)		503 (24.14)	1,686 (21.18)	
Unknown smoking status (%)	1,133 (2.33)	7,744 (3.72)		1,115 (2.40)	7,603 (3.80)		18 (0.86)	141 (1.77)	

Table 3. Phototherapy, systemic, or biologic treatments received by patients with psoriasis

	Psoriasis patients
No.	2,084[1]
Methotrexate (%)	1,486 (71.31)
PUVA/Phototherapy (%)	404 (19.39)
Ciclosporin (%)	215 (10.32)
Oral retinoids (%)	128 (6.14)
Hydroxycarbamide (%)	49 (2.35)
Etanercept (%)	9 (0.43)
Adalimubab (%)	8 (0.38)
Fumaric Acid (%)	2 (0.1)
Infliximab (%)	1 (0.05)

[1]Percentages do not add up to 100% because patients could have received more than one treatment.

entry, and hence such studies only address the question as to what happens to patients who have already survived with their psoriasis. In contrast with our study, Dregan *et al.* (2014), using CPRD, reported an increased and significant risk of coronary heart disease in patients with severe psoriasis. However, they may have misclassified severe psoriasis on the basis of treatments received without considering co-morbid inflammatory arthritis. Ahlehoff *et al.* (2011), using a Danish nationwide database, suggested an increased risk of CVD in patients with severe psoriasis with and without psoriatic arthritis. However, patients with severe psoriasis were identified using hospitalization for psoriasis or psoriatic arthritis, which could be subject to potential surveillance bias (Ahlehoff *et al.*, 2011). Moreover, comorbidities were assigned using prescribed treatments rather than diagnostic codes, which could lead to potential misclassification. Other differences compared with previous studies include the wider range of risk factors examined in our analyses (Ahlehoff *et al.*, 2011; Dregan *et al.*, 2014; Ogdie *et al.*, 2015), modeling these to account for the development of new risk factors over time (Ahlehoff *et al.*, 2011; Dregan *et al.*, 2014; Ogdie *et al.*, 2015); and examining the severity of psoriasis as a time-varying covariate, so that patients with severe psoriasis become at risk when they start receiving phototherapy, systemic therapy, or biologic therapies (rather than identified as whether they have ever been exposed to systemic treatment and all time under observation classed as severe psoriasis; Dregan *et al.*, 2014).

Strengths and limitations of this study

Observational studies are susceptible to bias and confounding. In this study, possible selection bias, information bias, and detection bias, which occur, for example, when patients with a skin disease are more likely to be diagnosed with another disease while visiting their physician for their skin condition (Wakkee *et al.*, 2010), were minimized, as patients with and without psoriasis came from the same database; they were selected from the same general practice and during the same time-window, respectively. Furthermore, potential detection bias was examined via sensitivity analysis by

Table 4. Event rates and incidence rates of major cardiovascular events in patients with psoriasis and controls and by psoriasis severity

	Psoriasis patients	Controls	Mild psoriasis patients	Controls to mild psoriasis	Severe psoriasis patients	Controls to severe psoriasis
No.	48,523	208,187	48,020	206,000	2,084	7,961
Follow-up in years, median (IQR)	5.48 (5.55)	5.12 (5.32)	5.33 (4.28)	5.00 (5.30)	3.59 (4.23)	3.65 (4.36)
Person-years	304,442	1,237,895	295,283	1,202,902	9,159	34,992
Number of major CV events (%)	1,257 (2.59)	4,784 (2.30)	1,203 (2.51)	4,644 (2.25)	54 (2.59)	140 (1.76)
Incidence per 1,000 person-years (95% CI)	4.13 (3.91; 4.36)	3.87 (3.76; 3.98)	4.07 (3.85; 4.31)	3.86 (3.75; 3.97)	5.90 (4.52; 7.70)	4.00 (3.39; 4.72)

Abbreviations: CI, confidence interval; CV, cardiovascular; IQR, interquartile range.
Psoriasis severity was modeled as a time-varying covariate.

Table 5. Hazard ratios associated with psoriasis and potential confounding variables for the risk of incident major cardiovascular events in Cox regression models

	Age and gender adjusted HR (95% CI)	*P*-value	Multivariate HR (95% CI)	*P*-value
Psoriasis[1]	1.10 (1.04; 1.17)	0.002	1.02 (0.95; 1.08)	0.606
Severe psoriasis[1]	1.40 (1.07; 1.84)	0.015	1.28 (0.96; 1.69)	0.089
Inflammatory arthritis	1.48 (1.28; 1.70)	<0.001	1.36 (1.18; 1.58)	<0.001
Diabetes	1.31 (1.18; 1.45)	<0.001	1.18 (1.06; 1.31)	0.002
Chronic kidney disease	1.18 (1.18; 1.45)	0.001	1.18 (1.07; 1.31)	0.001
Hypertension	1.37 (1.30; 1.44)	<0.001	1.37 (1.29; 1.45)	<0.001
Hyperlipidemia	1.09 (1.01; 1.17)	0.020	1.04 (0.96; 1.11)	0.346
Transient ischaemic attack	3.21 (2.82; 3.65)	<0.001	2.74 (2.41; 3.12)	<0.001
Atrial fibrillation	1.85 (1.65; 2.07)	<0.001	1.54 (1.36; 1.73)	<0.001
Valvular heart disease	1.49 (1.28; 1.75)	<0.001	1.23 (1.05; 1.44)	0.012
Thromboembolism	1.38 (1.22; 1.56)	<0.001	1.32 (1.17; 1.49)	<0.001
Congestive heart failure	1.99 (1.77; 2.24)	<0.001	1.57 (1.39; 1.78)	<0.001
Depression	1.30 (1.13; 1.50)	<0.001	1.16 (1.01; 1.34)	0.037
Age	1.07 (1.07; 1.07)	<0.001	1.07 (1.07; 1.07)	<0.001
Male	1.87 (1.78; 1.97)	<0.001	1.83 (1.69; 1.98)	<0.001
Never smoker	Reference			
Ex-smoker	1.18 (1.11; 1.26)	<0.001	1.18 (1.10; 1.25)	<0.001
Current smoker	2.22 (2.07; 2.38)	<0.001	2.18 (2.03; 2.33)	<0.001
Unknown	1.34 (1.19; 1.51)	<0.001	1.23 (1.09; 1.40)	0.001
Calendar year	0.95 (0.94; 0.95)	<0.001	0.95 (0.94; 0.96)	<0.001

Abbreviations: CI, confidence interval; HR, Hazard ratio.
[1]The variable "psoriasis" identifies all patients with psoriasis, both mild and severe. The reference group for this variable is the group of controls (patients without psoriasis). The variable "severe psoriasis", which is modeled as a time-varying covariate, identifies patients who are (i) severe at baseline or (ii) patients who have mild psoriasis at baseline but develop severe psoriasis during follow-up. The variable "severe psoriasis" is entered into the model (both univariate and multivariate) together with the general variable "psoriasis". Therefore, when both variables "psoriasis" and "severe psoriasis" are included into the model, the variable "severe psoriasis" will identify patients with severe psoriasis against controls. Therefore, the reference population for the "severe psoriasis" variable is the group of controls.

selecting only patients who had at least one general practice visit per year. Our findings were consistent after multiple sensitivity and subgroup analyses. Several additional strengths can be identified in our study. First, important confounders, including traditional and non-traditional CVD risk factors, were taken into account in order to investigate the association between psoriasis and major CV events, in particular inflammatory arthritis. Second, we present a large

Table 6. Sensitivity analyses: adjusted hazard ratios associated with psoriasis for the risk of incident major cardiovascular events

	Fully adjusted model using multiple imputation	Fully adjusted model including BMI and IMD score using multiple imputation	Inclusion of patients with at least 1 GP visit per year[1]	Inclusion of patients with at least 6 months follow-up[2]	Fully adjusted model plus a covariate for patients on methotraxete	Fully adjusted model plus a covariate for patients on ciclosporin/oral retinoids	Linkage of patients from CPRD to ONS and IMD information[3]
	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
Psoriasis	1.02 (0.96; 1.08)	1.02 (0.95; 1.08)	1.02 (0.95; 1.09)	1.01 (0.94; 1.07)	1.02 (0.95; 1.08)	1.02 (0.95; 1.08)	1.02 (0.93; 1.11)
Severe psoriasis	1.29 (0.97; 1.70)	1.30 (0.98; 1.72)	1.32 (0.99; 1.76)	1.26 (0.95; 1.68)	1.33 (0.97; 1.82)	1.28 (0.95; 1.71)	1.10 (0.72; 1.68)

Abbreviations: BMI, body mass index; CI, confidence interval; CPRD, Clinical Practice Research Datalink; GP, general practice; HR, hazard ratio; IMD, index of multiple deprivation; ONS, office for national statistics.
[1]The analysis included 170,930 patients corresponding to 66.58% of the original sample. Fully adjusted model.
[2]The analysis included 245,111 patients corresponding to 95.48% of the original sample. Fully adjusted model.
[3]The analysis included 132,075 patients corresponding to 51.45% of the original sample. Fully adjusted model plus the IMD score.

population-based study representative of the UK. Third, only patients with at least a diagnostic code of psoriasis and a treatment for psoriasis were included in the cohort to minimize the risk of disease misclassification. Fourth, more advanced methodology was employed such as the use of the shared frailty model, which takes better account of the matched nature of the data and the use of time-varying covariates.

Some potential limitations also need to be taken into account. As this was an observational study, the risk of residual confounding should be considered. Given that CPRD is a primary care database, diagnoses of psoriasis were not necessarily confirmed by dermatologists; phototherapy, systemic therapy, or biologics were used as a surrogate to assess disease severity rather than more objective measures, such as the psoriasis area and the severity index or the body surface area covered by psoriasis. The group of patients having or developing severe psoriasis could be underpowered to investigate the end point of interest. Our duration of follow-up was on average over 5 years for patients with psoriasis and over 3 years for those who developed severe psoriasis while under observation. However, chronic inflammation may take longer to develop adverse CV outcomes, and, as such, future studies with longer follow-up are recommended.

Furthermore, because of the limited number of patients exposed to biologic treatments, it was not possible to investigate whether biologic therapy potentially reduces the risk of major CV events. Our study was specifically designed to investigate whether psoriasis is independently associated with the risk of major CV events, and in order to minimize the risk of bias we excluded patients from our cohort with a prior history of CVD or diabetes.

CONCLUSIONS AND IMPLICATIONS

Patients with psoriasis have an increased prevalence of CV risk factors and co-morbid conditions associated with CVD. However, neither psoriasis nor severe psoriasis was related to a short-to-medium term (over 3–5 years) risk of major CV events (MI, ACS, unstable angina, or stroke) after adjusting for important CV risk factors. The co-occurrence of inflammatory arthritis and psoriasis was an independent risk factor for major CV events. This implies that patients with psoriasis should be screened for traditional risk factors, and these should be treated according to local guidelines. Patients with inflammatory arthritis are at increased risk of CVD, and this may be an additional reason to minimize the patient's cumulative inflammatory burden.

MATERIALS AND METHODS

Study design

An inception cohort study was conducted using the CPRD. The CPRD comprises medical records from general practices in the UK holding the demographic and the medical history of patients including treatments, clinical events, test results, and referrals to hospitals. On September 2012, data were available for 652 practices and over 12 million patients. In CPRD, clinical diagnoses are recorded using hierarchical clinical Read codes (Robinson *et al.*, 1997). Numerous studies have demonstrated the validity of CPRD for observational research studies (Jick *et al.*, 1991; Herrett *et al.*, 2010), including studies on psoriasis (Gelfand *et al.*, 2003) and major CV events (Gulliford *et al.*, 2009; Khan *et al.*, 2010).

The protocol of this study was approved by the CPRD Independent Scientific Advisory Committee (protocol reference number 11_134A). The study is reported according to STROBE guidelines (Erik von *et al.*, 2007).

Study population

The study population included patients with a first diagnosis of psoriasis between 1 January 1994 and 31 December 2009, who were 20 years or older at the time of the diagnosis. A comparison group of up to 5 controls per psoriasis patient was selected. Patients from both cohorts did not have any history of CVD or diabetes before the index date (first diagnosis of psoriasis) or corresponding consulting date and, in order to capture incident not prevalent cases of psoriasis or major CV events, all patients had to have at least 2 years prior registration within their general practice before entry into the study cohort. The control group consisted of patients who never received a

diagnostic code for psoriasis. Controls were matched to psoriasis patients by age, gender, and general practice. We assigned control patients the same index date as the patients with psoriasis to whom they were matched. Person-time under observation for each patient was calculated from the corresponding index date up to the end of the study, which was the earliest date of the occurrence of a major CV event (MI, ACS, unstable angina, or stroke), transfer out of the practice, death date, end of follow-up (31 December 2011) or when the practice was no longer up to research data quality standards set by CPRD. Patient consent was not required; all patient data contained in CPRD is anonymised.

Definition of exposure

Patients with psoriasis were included if they had their first diagnostic code for psoriasis during 1 January 1994–31 December 2009 and received a recognized treatment for psoriasis (emollients, topical treatment, phototherapy, systemic therapy, or biologics (CG153 Psoriasis: NICE guideline; Samarasekera and Smith, 2014)). Patients were classified as having severe psoriasis once they had received a systemic treatment (acitretin, etretinate, ciclosporin, hydroxycarbamide, methotrexate, and fumaric acid), phototherapy, or a biologic therapy (etanercept, adalimumab, infliximab, ustekinumab, and efalizumab); alternatively they were classified as mild psoriasis.

Outcome of interest

The outcome of interest was fatal, and non-fatal incident major CV end point including MI, ACS, unstable angina, or stroke. In our main analysis, the combined CV end point was identified using Read codes in CPRD. In sensitivity analysis, we identified the combined CV end point in both CPRD and national mortality records (ONS) for those patients registered in practices that provided linked data between CPRD and ONS.

Covariates

The following covariates were included in the model and tested in age-and gender-adjusted or multivariate analyses to investigate the association between psoriasis and risk of major CV events. Presence of psoriasis, age, gender, depression, and calendar year were calculated at baseline, whereas other covariates such as having or developing severe psoriasis, inflammatory arthritis (which included both diagnostic codes for psoriatic arthritis or rheumatoid arthritis), diabetes, chronic kidney disease, hypertension, hyperlipidemia, atrial fibrillation, transient ischaemic attack, congestive heart failure, thromboembolism, valvular heart disease, and smoking status were modeled as time-varying covariates. Psoriasis was defined as severe from the date of the first exposure to phototherapy, systemic, or biologic treatment and was considered severe from that point forward in time. Smoking status, classified as current, former, never smoker, or unknown smoking status, allowed patients to switch from one smoking class to another during follow-up. Depression was modeled as a static variable rather than a time-varying covariate because it is not possible to reliably determine when a depressive episode has resolved in databases such as CPRD. Additional analyses controlling for BMI and socioeconomic status (measured by the IMD; Department for Communities and Local Government, 2010) were conducted as part of the sensitivity analyses because of the higher levels of missing data.

All code lists used for exposure, and outcome are available for download from www.clinicalcodes.org (Springate *et al.*, 2014).

Statistical analysis

Continuous variables were summarized as median and interquartile range. Characteristics at baseline and at the end of follow-up for time-varying covariates were summarized as proportions by the exposure group. Event rates for the study outcome and incidence rates of the combined CV end point per 1,000 person-years with 95% CIs were calculated for patients with and without psoriasis and by disease severity. Cox proportional hazard regression was used to estimate the age-and gender-adjusted HRs and 95% CIs for each variable, and Cox regression with a shared frailty model was used to estimate the adjusted HRs and 95% CIs. Schoenfeld residuals were used to test the assumption of proportionality for individual variables and the model overall. Three of the risk factors taken into account contained missing data (Table 1): smoking status, BMI, and the IMD score. Smoking status was included in the main analysis, and a category was introduced for the missing values. Because of the high proportion of missing data BMI and IMD score were included only in sensitivity analyses. For BMI, an algorithm based on interpolation was used for data cleaning and for imputation of values over time.

Multiple sensitivity analyses were performed on the initial cohort identified from CPRD in order to test the robustness of the results. Different set of risk factors were included in the fully adjusted model in order to investigate a more complex or parsimonious model.

Multiple imputation was examined in the sensitivity analyses to allow individuals with missing BMI and patient-level IMD to be included. An additional model was fitted including BMI and patient-level IMD information in the fully adjusted model in order to investigate possible confounding due to BMI or socioeconomic status. Other sensitivity analyses were as follows: (a) including only those patients with at least one general practice visit per year; (b) including only those patients with at least 6 months of follow-up; (c) testing for an interaction between the presence of psoriasis or severe psoriasis with age; and (d) additional adjustment for patients exposed to methotrexate or for patients exposed to ciclosporin or oral retinoids. Finally, a nested analysis was carried out to assess the robustness of the main findings to potential outcome misclassification. Approximately 70% of CPRD practices in England are linked to the ONS, which is a national register of births and deaths. Patients identified from CPRD practices linked to the ONS and who had index date (first diagnosis of psoriasis or corresponding consulting date) between 1 January 1998 and 31 December 2009 were identified and followed-up until 31 December 2011. As ONS uses the International Classification of Disease (ICD) coding system, the ICD-9/10 codes corresponding to the combined CV end points were used (www.clinicalcodes.org; Springate *et al.*, 2014). The outcome was the first event of fatal or non-fatal major CV events (MI, ACS, unstable angina, or stroke) recorded in CPRD or ONS.

All statistical analyses were performed using Stata v12 (StataCorp, College Station, TX).

CONFLICT OF INTEREST

Dr HSY reports serving on advisory boards for Abbvie/Abbott and Novartis, serving on an advisory board and acting as a speaker for Leo Pharma, acting as a speaker for Janssen and Stiefel, and consulting for Teva Pharmaceuticals. Prof CEMG reports receiving grants and speaker fees from Abbvie and Celgene, serving on advisory boards for Actelion, Novartis, Sandoz, UCB

Pharma, and Lilly, grant funding, speaker fees, and serving on advisory boards for Janssen and Pfizer, and grants funding from GSK-Stiefel and Leo Pharma. Prof DMA reports grant funding from Abbvie and serving on advisory boards for Pfizer and GSK. Prof DPMS reports grants from Arthritis Research UK and from the NIHR, during the conduct of the study. No other disclosures were reported. The funder was not involved in the design or the conduct of the study; collection, management, analysis, or interpretation of the data; or preparation of the manuscript. The funder approved the paper for submission for publication. The remaining authors state no conflict of interest.

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AUTHOR CONTRIBUTIONS

All authors were involved in the design of the study. MKR, DMA, DPMS, CEMG, and HSY screened the lists of medical and treatment codes. RP performed the statistical analyses supervised by DMA and ML. RP wrote the first draft of the manuscript supervised by DMA. All authors critically revised the final paper. RP had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

SUPPLEMENTARY MATERIAL

Supplementary material is linked to the online version of the paper at http://www.nature.com/jid

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