The Risk of Stroke in Patients with Psoriasis

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Psoriasis is a chronic Th-1 and Th-17 inflammatory disease. Chronic inflammation has also been associated with atherosclerosis and thrombosis. The purpose of this study was to determine the risk of stroke in patients with psoriasis. We conducted a population-based cohort study of patients seen by general practitioners participating in the General Practice Research Database in the United Kingdom, 1987–2002. Mild psoriasis was defined as any patient with a diagnostic code of psoriasis, but no history of systemic therapy. Severe psoriasis was defined as any patient with a diagnostic code of psoriasis and a history of systemic therapy consistent with severe psoriasis. The unexposed (control) population was composed of patients with no history of a psoriasis diagnostic code. When adjusting for major risk factors for stroke, both mild (hazard ratio (HR) 1.06, 95% confidence interval (CI) 1.0–1.1) and severe (1.43, 95% CI 1.1–1.9) psoriasis were independent risk factors for stroke. The excess risk of stroke attributable to psoriasis in patients with mild and severe disease was 1 in 4,115 per year and 1 in 530 per year, respectively. Patients with psoriasis, particularly if severe, have an increased risk of stroke that is not explained by major stroke risk factors identified in routine medical care.

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INTRODUCTION

Psoriasis is a chronic inflammatory disease of the skin and joints that affects about 1–3% of the general population (Gelfand *et al.*, 2005b; Kurd and Gelfand, 2009). It is associated with impairments in health-related quality of life even in mild cases, and with excess mortality in severe cases (Gelfand *et al.*, 2004, 2007). The cause of psoriasis remains unknown; however, its etiology involves a complex interaction between genetics and environmental exposures. Psoriasis is incurable, and once symptoms occur, the disease is characterized by a chronic course, with spontaneous, long-term remissions occurring in a minority of patients. Despite many treatment advances, the majority of patients with psoriasis, particularly if severe, have ongoing cutaneous pathology that persists for decades (Gelfand, 2007; Horn *et al.*, 2007; Nijsten *et al.*, 2007).

Psoriasis was earlier believed to affect only the skin, and in some patients, the joints; however, recent evidence suggests that chronic psoriasis may lead to other diseases in which inflammation is important (Azfar and Gelfand, 2008). For example, Th-1 chronic inflammation characteristic of the psoriasis phenotype is also central to the pathophysiology of other conditions, such as insulin resistance, atherosclerosis, and plaque rupture, leading to thrombotic events (Hirosumi *et al.*, 2002; Hansson, 2005). Recent epidemiological studies support the link between psoriasis and cardiovascular disease (Gelfand *et al.*, 2006; Ludwig *et al.*, 2007; Balci *et al.*, 2008). There is a paucity of data examining the risk of stroke in patients with psoriasis. For example, a recent study found a small increased risk of stroke in patients with psoriasis (hazard ratio (HR) 1.12, 95% confidence interval (CI) 1.00–1.25); however, this study did not make adjustments for confounding factors or psoriasis severity (Kaye *et al.*, 2008).

Stroke is a major cause of morbidity and mortality (Donnan *et al.*, 2008). The major common risk factors for stroke include diabetes, hypertension, and smoking (Donnan *et al.*, 2008), which also predispose to cardiovascular risk in general. Less common, but more specific, risk factors for stroke include transient ischemic attacks and atrial fibrillation (Donnan *et al.*, 2008). Most strokes (80%) are ischemic in nature, with the minority of strokes being hemorrhagic (Donnan *et al.*, 2008). Ischemic and hemorrhagic strokes share similar risk factors and can have similar clinical presentations. They can be differentiated on the basis of sophisticated imaging in the clinical setting, but are often difficult to differentiate in large population-based epidemiological studies. As with myocardial infarction, chronic inflammation is thought to play an important role in the pathogenesis of stroke (Ding *et al.*, 2008; McColl *et al.*, 2008). The purpose of this study was to

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Abbreviations: CI, confidence interval; GP, general practitioner; GPRD, General Practice Research Database; HR, hazard ratio; UTS, up-to-standard

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examine the risk of stroke in a broadly representative, population-based cohort of patients with psoriasis.

RESULTS

We identified 129,143 patients with mild psoriasis, 3,603 patients with severe psoriasis, and 496,666 and 14,330 matched controls, respectively (Table 1). Mild psoriasis patients were slightly younger than controls and severe psoriasis patients were slightly older than controls. Psoriasis patients, particularly if severe, were more likely to have established cardiovascular risk factors than patients without psoriasis. The majority of patients identified as having severe psoriasis were treated with methotrexate (Table 2).

The incidence of stroke in control subjects and psoriasis subjects is shown in Table 3. The unadjusted overall risk of stroke per 1,000 person-years was slightly lower in mild psoriasis patients (HR 3.7; 95% CI 3.5–3.8) compared with controls (4.05; 95% CI 4.0–4.1). The unadjusted overall risk of stroke per 1,000 person-years was higher in severe psoriasis patients (6.1; 95% CI 4.8–7.6) than in controls (4.4; 95% CI 3.8–5.0).

When adjusting for age and sex, both mild and severe psoriasis were associated with an increased risk of stroke (Table 4, HR 1.07, 95% CI 1.0–1.1, and 1.44, 95% CI 1.1–1.9, respectively). When adjusting for major risk factors for stroke (age, sex, diabetes, history of stroke or transient ischemic attack, hyperlipidemia, hypertension, smoking), both mild (HR 1.06, 95% CI 1.0–1.1) and severe (1.43, 95% CI 1.1, 1.9) psoriasis were independent risk factors for stroke. On the basis of these analyses, we estimate that each year there is approximately one excess stroke per 4,115 or 530 mild or severe psoriasis patients, respectively (that is, attributable risk). Obesity and atrial fibrillation were not included in the model, as their inclusion did not alter the association between psoriasis and stroke (see Table 5). In addition, on the basis of an external adjustment analysis, an unknown or unmeasured covariate with a prevalence of 20% in the control group would need to have a prevalence odds ratio of association with psoriasis of 2.67 and be associated with stroke with an odds ratio of 4.3 to render the association between severe psoriasis and stroke null. The results were robust to numerous sensitivity analyses as shown in Table 5.

DISCUSSION

The results of this study show that patients with severe psoriasis have a 44% increased risk of stroke, a potentially devastating comorbidity. The risk of stroke in patients with psoriasis was not explained by both common and rare major risk factors for stroke as identified in routine medical practice, suggesting that psoriasis may be an independent risk factor for stroke. Patients whom we classified as having mild psoriasis had a statistically significant increased risk of stroke; however, this association was very modest and of limited clinical significance for the individual patient. For example, on the basis of our data, a patient with mild psoriasis has an excess risk of stroke attributable to psoriasis of 1 in 4,115 per year, whereas a patient with severe psoriasis has an excess risk of stroke attributable to psoriasis of 1 in 530 per year.

The increased risk of stroke persisted in a variety of sensitivity analyses designed to insure that we were capturing incident, not prevalent, strokes, and that insured that all patients were seen regularly, minimizing the risk that information bias could explain the findings. Furthermore, the results persisted when excluding patients with psoriatic arthritis, restricting the severe group to patients treated with therapy specific to severe psoriasis (for example, oral retinoids), and when examining the risk based on different treatments that theoretically could increase (for example, cyclosporine, oral retinoids) or decrease (for example, methotrexate) the risk of stroke (Lebwohl and Ali 2001; Prodanowich *et al.*, 2005). Our findings are in agreement with recent studies that have found that psoriasis is an independent risk factor for cardiovascular disease in general (for example, Myocardial infarction and coronary artery disease) and cerebrovascular disease in particular (Gelfand *et al.*, 2006; Ludwig *et al.*, 2007; Balci *et al.*, 2008). Our study also extends the findings of earlier studies that observed an association between psoriasis and cerebrovascular disease or stroke, but did not account for psoriasis severity or confounding factors (Kaye *et al.*, 2008).

As with all studies, there are important limitations to consider. In database studies, there remains the possibility for misclassification of stroke because of coding errors or misdiagnosis. The overall incidence of stroke in our study was similar in the two control groups and is similar to rates of stroke reported using national statistics from England and Wales (Carroll, 2001). Although several studies have used General Practice Research Database (GPRD) to evaluate the epidemiology of stroke, a small validation study showed that, for 25 patients in the GPRD referred for a diagnostic code of stroke, there was a confirmation of stroke by the specialist in 64% of cases and a diagnosis of transient ischemic attack in 16% of cases, giving an overall agreement in the opinion of an acute cerebrovascular diagnosis of 80% (Gibbs *et al.*, 2001). If misdiagnosis of stroke were present, such errors would be expected to be non-differential misclassification and, therefore, would bias our results toward the null. Furthermore, it is difficult to differentiate between ischemic and hemorrhagic strokes in large population-based studies of medical record data, and therefore it cannot be determined directly how psoriasis influences the risk of various subtypes of strokes. As the majority of strokes are ischemic in nature, the results are likely driven by the association of psoriasis and ischemic stroke. The association between severe psoriasis and stroke was similar in a sensitivity analysis restricting the outcome of stroke to those who received therapy consistent with an ischemic etiology. Another potential limitation of our study is that we did not examine patients with exclusively incident (new onset) psoriasis. Therefore, we could not determine how the duration of psoriasis affects stroke risk, and it is possible that some bias toward null findings could be introduced through the depletion of susceptible patients (for example, some patients with psoriasis would have died from stroke before being captured in our study population). Ideally, an inception cohort study could be carried out; however, in diseases such as psoriasis, which may not come

Table 1. Characteristics of study groups

Characteristics	Mild group		Severe group	
	Control (*n*=496,666)	Psoriasis (*n*=129,143)	Control (*n*=14,330)	Psoriasis (*n*=3,603)
Sex				
Male	198,498 (40.0%)	61,956 (48.0%)	5,783 (40.4%)	1,750 (48.6%)
Female	298,168 (60.0%)	67,187 (52.0%)	8,547 (59.6%)	1,853 (51.4%)
		P<0.001		*P*<0.001
Age (y)				
Mean ± SD	46.1 ± 19.1	45.1 ± 17.8	49.7 ± 19.3	52.2 ± 16.7
Median (IQR)	43, 30, 61	42, 30, 59	48, 33, 65	52, 39, 66
		P<0.001		*P*<0.001
		Wilcoxon test		Wilcoxon test
Diabetes mellitus				
Yes	22,296 (4.5%)	5,858 (4.5%)	737 (5.1%)	270 (7.5%)
No	474,370 (95.5%)	123,285 (95.5%)	13,593 (94.9%)	3,333 (92.5%)
		P=0.470		*P*<0.001
History of stroke				
Yes	7,401 (1.5%)	1,648 (1.3%)	268 (1.9%)	89 (2.5%)
No	489,265 (98.5%)	127,495 (98.7%)	14,062 (98.1%)	3,514 (97.5%)
		P<0.001		*P*=0.023
History of TIA				
Yes	5637 (1.1%)	1254 (1.0%)	243 (1.7%)	68 (1.9%)
No	491,029 (98.9%)	127,889 (99.0%)	14,087 (98.3%)	3,535 (98.1%)
		P<0.001		*P*=0.432
History of stroke or TIA				
Yes	11,883 (2.4%)	2,655 (2.1%)	450 (3.1%)	140 (3.9%)
No	484,783 (97.6%)	126,488 (97.9%)	13,880 (96.9%)	3,463 (96.1%)
		P<0.001		*P*=0.028
Hyperlipidemia				
Yes	22,839 (4.6%)	6,775 (5.2%)	842 (5.9%)	250 (6.9%)
No	473,827 (95.4%)	122,368 (94.8%)	13,488 (94.1%)	3,353 (93.1%)
		P<0.001		*P*=0.019
Hypertension				
Yes	88,397 (17.8%)	22,829 (17.7%)	3,049 (21.3%)	858 (23.8%)
No	408,269 (82.2%)	106,314 (82.3%)	11,281 (78.7%)	2,745 (76.2%)
		P=0.313		*P*=0.001
Smoking				
Never	383,824 (77.3%)	96,944 (75.1%)	10,465 (73.0%)	2,488 (69.1%)
Current	19,839 (4.0%)	5,866 (4.5%)	755 (5.3%)	241 (6.7%)
Former	93,003 (18.7%)	26,333 (20.4%)	3,110 (21.7%)	874 (24.3%)
		P<0.001		*P*<0.001
BMI				
<25	166,470 (53.2%)	40,606 (49.6%)	5,057 (51.2%)	1,025 (42.1%)
⩾25 & <30	100,551 (32.1%)	27,701 (33.8%)	3,291 (33.3%)	860 (35.4%)
⩾30	45,977 (14.7%)	13,618 (16.6%)	1,522 (15.4%)	548 (22.5%)
		P<0.001		*P*<0.001

Table 1 Continued on the following page

Table 1. Continued

Characteristics	Mild group		Severe group	
	Control (*n*=496,666)	Psoriasis (*n*=129,143)	Control (*n*=14,330)	Psoriasis (*n*=3,603)
Reason for end of study				
Death	32,677 (6.6%)	7,302 (5.6%)	790 (5.5%)	297 (8.2%)
End of UTS	353,565 (71.2%)	95,275 (73.8%)	11,247 (78.5%)	2,860 (79.4%)
Transfer out	110,424 (22.2%)	26,566 (20.6%)	2,293 (16.0%)	446 (12.4%)
		P<0.001		*P*<0.001
Atrial fibrillation				
Yes	12,861 (2.6%)	3,046 (2.4%)	428 (3.0%)	99 (2.8%)
No	485,486 (97.4%)	126,117 (97.6%)	13,963 (97.0%)	3,505 (97.3%)
		P<0.001		*P*=0.507

BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); IQR, interquartile range, SD, standard deviation; TIA, transient ischemic attack; UTS, up-to-standard.
Data for BMI were available for 67% of the patients.
Unless noted otherwise, *P*-values are derived using Fisher exact test.

Table 2. Systemic therapies received by patients with severe psoriasis (*n*=3,603)[1]

Systemic therapy	Number of patients with severe psoriasis (%)
Methotrexate	2,114 (58.7%)
Psoralen	607 (16.9%)
Azathioprine	582 (16.2%)
Cyclosporine	390 (10.8%)
Etretinate or acetretin	333 (9.2%)
Hydroxyurea	208 (5.8%)
Mycophenolate mofetil	9 (0.3%)

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

to medical attention for many years; it is difficult to validly identify truly incident (new onset) cases in a medical records database setting. Furthermore, we did not directly determine the severity of psoriasis on the basis of the extent of skin disease, which may introduce misclassification of mild and severe psoriasis when using therapy as a marker of psoriasis phenotype. It is likely that our mild psoriasis group contains a small subset of patients with severe skin disease, as systemic therapies are used infrequently for psoriasis in the general population, and that our severe group contains a small subset of patients with mild skin disease despite the use of systemic therapy. This misclassification would result in an overestimation and underestimation of the risk of stroke in the mild and severe psoriasis patients, respectively. Moreover, the generalizability of our results to patients with severe psoriasis, who are not treated with the agents that we used to identify severe disease, needs to be determined in future studies. Finally, although our study suggests that psoriasis, particularly if severe, is an independent risk factor for stroke, it is possible that incomplete measurement of confounders or unknown confounding factors could explain some of the observed association. We did not adjust for alcohol in this analysis as validly measuring alcohol intake in any setting is challenging, the relationship between alcohol consumption and stroke is a complex "J-shaped" curve, and the relationship between stroke and alcohol intake is believed to be mediated by hypertension (which was adjusted for in our models) (Reynolds *et al.*, 2003; CDC, 2007). Analyzing our data using an external adjustment approach suggests that such an unknown or unmeasured confounder would have to be common in the general population, and have a strong association with psoriasis and a stronger association with stroke than the known stroke risk factors to render our findings null (Greenland, 1996).

This study adds to the growing literature suggesting that patients with psoriasis, particularly if disease is severe, are at increased risk of cardiovascular events that is not explained by traditional risk factors. Clinicians are advised to alert psoriasis patients, particularly if disease is severe, to have assessment and treatment of their cardiovascular risk factors as recommended by current guidelines (Friedewald *et al.*, 2008; Kimball *et al.*, 2008). More research is necessary to directly determine the mechanisms by which psoriasis may lead to adverse cardiovascular outcomes, as well as how psoriasis severity and treatment influence cardiovascular risk.

METHODS

Study population and data source

We conducted a cohort study using the GPRD, a medical records database in the United Kingdom that was established for epidemiological research in 1987 (Gelfand *et al.*, 2005a). The GPRD is representative of the UK population in terms of age, sex, and geographic distributions. Approximately 5% of the UK population is represented in the GPRD, and cumulative data are available for over 9 million patients with over 40 million person-years of follow-up time. In the United Kingdom, >99% of patients are registered with a General practitioner (GP) through the National Health Service, which coordinates all of the patient's medical care. Data on diagnoses and prescriptions are recorded by the GPs as part of the patient's electronic medical record. Patients with complex medical

Table 3. Incidence of stroke in patients with psoriasis compared with control patients

	Mild group		Severe group	
Variable	**Control (*n*=496,666)**	**Psoriasis (*n*=129,143)**	**Control (*n*=14,330)**	**Psoriasis (*n*=3,603)**
Follow-up time (y)				
Mean ± SD	4.2 ± 3.3	4.4 ± 3.3	3.4 ± 2.7	3.4 ± 2.7
Median (IQR)	3.5 (1.5, 6.6)	3.7 (1.6, 6.9)	2.6 (1.2, 5.0)	2.7 (1.2, 5.0)
Number of person-years	2,108,718	570,814.5	48,248.4	12,222.1
Number of new stroke cases (%)	8,535 (1.72%)	2,100 (1.63%)	212 (1.48%)	74 (2.05%)
Incidence per 1,000 person-years (95% CI)	4.05 (3.96, 4.13)	3.68 (3.52, 3.84)	4.39 (3.82, 5.03)	6.05 (4.76, 7.60)

CI, confidence interval; IQR, interquartile range; SD, standard deviation.

Table 4. Unadjusted and adjusted Cox proportional hazard regression models of the risk of stroke in patients mild and severe psoriasis compared with control patients

	Model hazard ratio (95% CI)	
Covariate	**Mild psoriasis**	**Severe psoriasis**
Unadjusted analysis		
Psoriasis	0.91 (0.86, 0.95)	1.38 (1.05, 1.80)
Adjusted for age and sex		
Psoriasis	1.07 (1.02, 1.12)	1.44 (1.10, 1.88)
Age per year	1.089 (1.087, 1.090)	1.09 (1.08, 1.10)
Sex (male)	1.27 (1.22, 1.32)	1.51 (1.20, 1.91)
Primary model (adjusted for major cardiovascular risk factors)[1]		
Psoriasis	1.06 (1.01, 1.11)	1.43 (1.10, 1.87)
Age per year	1.082 (1.081, 1.084)	1.08 (1.07, 1.09)
Diabetes	1.78 (1.69, 1.87)	1.60 (1.16, 2.19)
Hx of Stroke	4.26 (4.01, 4.51)	3.65 (2.57, 5.18)
Hx of TIA	2.01 (1.87, 2.16)	2.05 (1.40, 3.01)
Hyperlipidemia	1.12 (1.04, 1.20)	1.35 (0.92, 1.98)
Hypertension	1.49 (1.43, 1.55)	1.72 (1.35, 2.18)
Sex (male)	1.20 (1.16, 1.25)	1.42 (1.12, 1.80)
Smoking (current vs never)	0.97 (0.89, 1.06)	1.09 (0.71, 1.68)
Smoking (former vs never)	1.10 (1.03, 1.17)	1.24 (0.89, 1.73)

BMI, body mass index; CI, confidence interval; HR, hazard ratio; TIA, transient ischemic attack.
[1]BMI was not included in the primary analysis as these data are only available in about 65% of patients. BMI analyses are shown in Table 5. Atrial fibrillation was not included in the primary analysis as this is not a common stroke risk factor. Atrial fibrillation analyses are shown in Table 5. Interaction terms for sex and age were not statistically significant ($P > 0.05$).

conditions are seen by specialists (at the request of the GP) who may initiate a new treatment; however, patients are then referred back to the GP for chronic monitoring as necessary. Certain treatments, such as PUVA (psoralen plus UVA) and oral retinoids, are restricted to the dermatologists in the United Kingdom; however, GPs capture these treatments through their electronic medical record. The GPRD has been shown to capture information on diagnoses and treatments from specialists through the GP's electronic medical record (Jick *et al.*, 1991, 2003). GPs received specific training and were subject to inducements and penalties to ensure high-quality data. The data are also audited for completeness and a practice receives an up-to-standard (UTS) designation when at least 95% of the relevant prescriptions and diagnoses are captured electronically. Over 250 peer-reviewed scientific papers have been published using GPRD data (Gelfand *et al.*, 2005a). The GPRD has also been studied in numerous validation studies, including those of psoriasis and cardiovascular disease, to show that it captures these outcomes accurately (Gelfand *et al.*, 2003, 2005a, 2005b; Neimann *et al.*, 2006; Huerta *et al.*, 2007).

Time period and age eligibility. Data were used from 1987–2002 for patients who were age ⩾18 at the date their person-time began.

Definition of exposure

We defined mild psoriasis patients as those with a diagnostic code of psoriasis, but no history of systemic therapy at any time point. Severe psoriasis patients were defined as those with a diagnostic code of psoriasis and a history of systemic therapy consistent with severe psoriasis. Systemic therapy included phototherapy, PUVA, methotrexate, azathioprine, cyclosporine, oral retinoids (etretinate, acitretin), hydroxyurea, and mycophenolate mofetil. It is noted that during the time period that this study was conducted, biological therapies were not approved for use for psoriasis in the United Kingdom. The unexposed (control) population was composed of patients with no history of a psoriasis diagnostic code.

Sampling of exposed and unexposed cohorts

All patients defined as having mild or severe psoriasis (as defined above), who were ⩾age 18 at their index date and had at least 1 day of observation time, were included. For psoriasis patients, the index date was the first date on or after registration with the practice in which a psoriasis diagnosis was recorded. For patients with severe psoriasis, their index date was the first date on or after the first diagnosis of psoriasis in which the patient received a code for treatment consistent with severe disease. If psoriasis occurred before registration, then the registration date was the index date. For patients without psoriasis, their index date was the date of a medical record entry that was within 60 days of the psoriasis index date. Up to four control subjects who were ⩾age 18 at their index date were

Table 5. Sensitivity analysis hazard ratio point estimates

Covariate	Model hazard ratio (95% CI)	
	Mild psoriasis	Severe psoriasis
Primary analysis	1.06 (1.01, 1.11)	1.43 (1.10, 1.87)
At least 6 months of follow-up (to ensure capture of incident, not prevalent stroke)	1.07 (1.02, 1.13)	1.44 (1.08, 1.93)
Inclusion of patients with at least one GP visit per year	1.05 (1.002, 1.10)	1.40 (1.07, 1.83)
Primary model excluding patients with history of stroke or TIA (to ensure capture of incident, not prevalent stroke)	1.08 (1.02, 1.14)	1.39 (1.02, 1.89)
Primary model with BMI adjustment	1.03 (0.96, 1.10)	1.43 (1.02, 2.02)
Primary model excluding patients with no BMI captured	1.03 (0.96, 1.10)	1.41 (1.004, 1.99)
Primary model with atrial fibrillation adjustment	1.04 (0.99, 1.09)	1.46 (1.12, 1.91)
Primary model with exclusion of patients with psoriatic arthropathy	1.06 (1.01, 1.11)	1.50 (1.12, 2.00)
Primary model with exclusion of Methotrexate	NA	1.49 (1.01, 2.19)
Primary model with exclusion of oral retinoids or cyclosporine	NA	1.43 (1.07, 1.92)
Primary model with restriction of severe group to patients who have received a prescription for an oral retinoid	NA	1.45 (0.78, 2.67)
Primary model with restriction of stroke to patients who received a prescription code for anti-platelet, anti-coagulant, or thrombolytic therapy within 30 days of the stroke diagnosis.	0.99 (0.91, 1.09)	1.36 (0.80, 2.30)

BMI; body mass index; CI, confidence interval; GP, general practitioner; HR, hazard ratio; NA, not applicable; TIA, transient ischemic attack.

randomly selected for each psoriasis patient, matched on practice, date of registration in the practice, and psoriasis index date (corresponding to a medical record date of the control patient). The matching on dates occurred as follows: registration: ±90 days (if registration date ⩾1980, otherwise ±5 years), index date: ±60 days. The purpose of matching on practice, registration, and index dates was to ensure that patients with and without psoriasis were evaluated by similar physicians during the same time period to account for potential variations in medical practice and to allow for similar degrees of opportunity for GPs to identify medical conditions in psoriasis and non-psoriasis patients.

Person-time calculation. For mild psoriasis patients, follow-up started at the latest date when the patient first received a psoriasis code, registered in the practice, or the practice was deemed UTS. For severe psoriasis patients, follow-up started at the latest on the date when the patient could first be defined as having severe psoriasis (for example, received a treatment code consistent with severe disease), was registered with the practice, or the practice was deemed UTS. For unexposed subjects (controls), follow-up started at the latest date when the patient was registered in the practice, and the practice was deemed UTS. For all groups, follow-up ended at the earliest date of developing the outcome of interest (for example, stroke), death, transfer out of the practice, or end of UTS.

Outcome of interest. The outcome of interest was stroke occurring after the start date. Stroke was identified using diagnostic codes (READ or OXMIS) entered by the GP into the medical record. The use of diagnostic codes to identify stroke has been a well-accepted methodology in earlier GPRD studies (Gibbs *et al.*, 2001; Cleary *et al.*, 2004; Nightingale and Farmer, 2004; Souverein *et al.*, 2004; Mulnier *et al.*, 2006; Weiner *et al.*, 2007) (Tannen *et al.*, 2006). We defined any stroke code that occurred after the start date as an incident stroke, whereas any stroke code that occurred on or before the start date was defined as a prevalent (for example, history of) stroke.

Covariables of interest. Major epidemiological risk factors for stroke, including age, sex, hypertension, diabetes, hyperlipidemia, atrial fibrillation, body mass index, and smoking (current, former, non), were identified by the presence of diagnostic codes for the conditions or direct calculation from data in the medical record (for example, body mass index).

Analysis. The sample size was determined by including the maximum eligible number of patients with severe psoriasis on the basis of age criteria. We randomly selected up to four control subjects per patient with psoriasis, as additional matching yields minimal increases in statistical power. Data were summarized descriptively. Dichotomous variables were tested with Fisher's exact test and continuous variables were tested with a *t*-test. We fitted age- and sex-adjusted Cox models to determine the overall HR of stroke in psoriasis patients (Cox, 1972). When indicated by an association of psoriasis with stroke based on the Cox models, we fitted models with covariates for stroke included (described above) and models with age and sex interaction terms to determine whether the relative risk of stroke in psoriasis patients was different on the basis of sex or age characteristics. The primary model includes major cardiovascular risk factors. We did not include body mass index in the primary model as it is recorded in only about 65% of patients. Each dichotomous variable in the model was checked for proportionality while adjusting for the other covariates in the model by examining diagnostic log–log plots. A method of external adjustment was used to determine the degree to which our findings could be explained by an unknown or unmeasured confounder (Greenland, 1996). Multiple sensitivity analyses were carried out to test the underlying

assumptions of our primary analysis. All analyses were carried out using STATA 10.0.

Protection of human subjects

This study was approved by the University of Pennsylvania Institutional Review Board and by the Independent Scientific Advisory Committee of the Medicines and Healthcare Products Regulatory Agency of the United Kingdom Department of Health. The study was conducted in accordance with the Declaration of Helsinki.

Role of sponsors

The funding sources had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the manuscript.

CONFLICT OF INTEREST

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Study concept and design: Gelfand, Troxel, Kurd, Azfar. Acquisition of data: Gelfand, Wang, Shin, Kurd. Analysis and interpretation of data: Gelfand, Shin, Kurd, Troxel, Azfar. Drafting of the manuscript: Gelfand. Critical revision of the manuscript for important intellectual content: Gelfand, Shin, Troxel, Kurd, Wang, Dommasch, Azfar. Statistical analysis: Gelfand, Shin, Troxel, Wang. Obtained funding: Gelfand. Administrative, technical, or material support: Kurd, Wang, Dommasch. Shin Study supervision: Gelfand, Troxel.

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