

# Risk of Myocardial Infarction in Patients With Psoriasis

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**P**SORIASIS IS A COMMON, chronic, immune-mediated disease that affects about 2% to 3% of the adult population.<sup>1,2</sup>

Approximately 6% to 11% of patients with psoriasis also have an associated inflammatory arthropathy (psoriatic arthritis).<sup>3,4</sup> The extent of body surface area affected by psoriasis is variable, ranging from limited disease (<2% body surface area) in approximately 80% of patients to more extensive skin involvement in approximately 20% of patients.<sup>5</sup> Psoriasis has serious impacts on health-related quality of life, even in patients with limited body surface area involvement.<sup>6</sup>

The pathophysiology of psoriasis is characterized by an increase in antigen presentation, T-cell activation, and T-helper cell type 1 (T<sub>H</sub>1) cytokines, resulting in thick scaly red plaques and in some patients, arthritis.<sup>7,8</sup> Psoriasis is also associated with markers of systemic inflammation, such as increased C-reactive protein levels.<sup>9-11</sup> The immunological abnormalities that lead to the development of psoriasis suggest that these patients may be at increased risk for other diseases associated with an inflammatory state. For example, increasing evidence suggests that a T<sub>H</sub>1 immune response, including activated T cells, antigen presenting cells, cytokines, and markers of systemic inflammation such as C-reactive protein, are

**Context** Psoriasis is the most common T-helper cell type 1 (T<sub>H</sub>1) immunological disease. Evidence has linked T<sub>H</sub>1 diseases to myocardial infarction (MI). Psoriasis has been associated with cardiovascular diseases, but has only been investigated in hospital-based studies that did not control for major cardiovascular risk factors.

**Objective** To determine if within a population-based cohort psoriasis is an independent risk factor for MI when controlling for major cardiovascular risk factors.

**Design, Setting, and Patients** A prospective, population-based cohort study in the United Kingdom of patients with psoriasis aged 20 to 90 years, comparing outcomes among patients with and without a diagnosis of psoriasis. Data were collected by general practitioners as part of the patient's medical record and stored in the General Practice Research Database between 1987 and 2002, with a mean follow-up of 5.4 years. Adjustments were made for hypertension, diabetes, history of myocardial infarction, hyperlipidemia, age, sex, smoking, and body mass index. Patients with psoriasis were classified as severe if they ever received a systemic therapy. Up to 5 controls without psoriasis were randomly selected from the same practices and start dates as the patients with psoriasis. A total of 556 995 control patients and patients with mild (n=127 139) and severe psoriasis (n=3837) were identified.

**Main Outcome Measure** Incident MI.

**Results** There were 11 194 MIs (2.0%) within the control population and 2319 (1.8%) and 112 (2.9%) MIs within the mild and severe psoriasis groups, respectively. The incidences per 1000 person-years for control patients and patients with mild and severe psoriasis were 3.58 (95% confidence interval [CI], 3.52-3.65), 4.04 (95% CI, 3.88-4.21), and 5.13 (95% CI, 4.22-6.17), respectively. Patients with psoriasis had an increased adjusted relative risk (RR) for MI that varied by age. For example, for a 30-year-old patient with mild or severe psoriasis, the adjusted RR of having an MI is 1.29 (95% CI, 1.14-1.46) and 3.10 (95% CI, 1.98-4.86), respectively. For a 60-year-old patient with mild or severe psoriasis, the adjusted RR of having an MI is 1.08 (95% CI, 1.03-1.13) and 1.36 (95% CI, 1.13-1.64), respectively.

**Conclusions** Psoriasis may confer an independent risk of MI. The RR was greatest in young patients with severe psoriasis.

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important to the development of atherosclerosis and ultimately, myocardial infarction (MI).<sup>12,13</sup> The observation that other T<sub>H</sub>1-mediated diseases, such as rheumatoid arthritis, are associated with an increased risk of MI supports the theory that T<sub>H</sub>1-mediated diseases predispose patients to MI.<sup>14-16</sup>

Several hospital-based studies have indicated that psoriasis is associated with a higher prevalence of cardiovascular diseases, including MI.<sup>17-21</sup> These studies did not control for any poten-

tially associated risk factors for MI and therefore it is unclear if psoriasis itself, or comorbidities and behaviors associated with psoriasis, explain this association. The goal of our study was to examine a broadly representative popu-

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lation-based cohort to determine the risk of MI in patients with psoriasis.

## METHODS

### Study Design

More than 1500 general practitioners in the United Kingdom, who were unaware of the hypothesis to be tested, collected data prospectively in this population-based cohort study between 1987 and 2002. Data were collected as part of the patient's electronic medical record and were maintained in the General Practice Research Database (GPRD). The GPRD contains data on more than 8 million persons with more than 35 million years of follow-up time and is broadly representative of the UK population.<sup>22</sup> General practitioners receive specific training, financial inducements, and penalties to ensure data accuracy. The GPRD has been used extensively for epidemiological studies. In the UK health care system, all of the patients' care is coordinated by the general practitioner. The ability of the GPRD to capture data from specialists, and validly identify psoriasis, MI, and the covariates used for this study, has been demonstrated previously.<sup>23-29</sup>

The study population consisted of all patients with psoriasis aged 20 to 90 years who had at least 1 day of observation time. Each patient with psoriasis was matched to up to 5 control patients (as available, based on matching criteria) who did not have diagnostic codes consistent with psoriasis, who were observed in the same practice, and who had a date of observation in the practice (the latest of either the date when the patient registered with the practice or the date when the practice was designated "up to standard") within 60 days. Therefore, we ensured that those patients with and without psoriasis were followed up by the same practices during similar time periods. For control patients, observation start time was the latest of the patient registration and up to standard dates. For patients with psoriasis, observation start time was the latest of the patient registration, up to standard, and psoriasis diagnosis dates. Practices are desig-

nated up to standard when audits demonstrate that at least 95% of relevant patient encounters are recorded and data are determined to be of suitable quality for epidemiological research. For all patients, follow-up time ended (ie, patients were censored) when they developed an MI, died, transferred out of the practice, or the practice was no longer up to standard, whichever came first.

### Study Groups

Diseases are classified in the GPRD by using Oxford Medical Information System (OXMIS) and Read codes. The OXMIS and Read codes are diagnostic codes that general practitioners use as part of the patient's electronic medical record. Patients were classified as having psoriasis if they ever received a diagnostic code for psoriasis. Patients with psoriasis were defined as having severe disease if they received a code consistent with severe disease (eg, treatment with psoralen or phototherapy, methotrexate, azathioprine, cyclosporine, etretinate, acitretin, hydroxyurea, or mycophenolate), as determined by the British National Formulary and the opinion of 2 dermatologists (D.J.M. and J.M.G.). The treatment codes were selected without any knowledge of whether or not the patients with psoriasis ever had an MI. Patients with psoriasis were classified as having mild disease if the patients never received a code consistent with severe disease. Patients were classified as controls if they never received a diagnostic code consistent with psoriasis.

### Measurement of Covariates

Patients were classified as having diabetes mellitus, hyperlipidemia, hypertension, or being a current smoker if they ever received a code for these conditions during the time that the practice was considered up to standard. Patients were determined to have a history of MI if they ever received a code for MI on or before their start date. Age was determined at the maximum of the patient registration and up to standard dates. Body mass index was deter-

mined based on the recorded height and weight that occurred closest to the start date and calculated as weight in kilograms divided by height in meters squared.

### Outcome Measure

Patients were classified as having an acute MI if they received a medical code consistent with this diagnosis after the start date and on or before the end date.

### Statistical Analyses

The sample size was determined by including the maximum eligible number of patients with psoriasis eligible based on the age criteria. We randomly selected and matched up to 5 control patients, as additional matching yields minimal statistical power. All eligible controls were not included to allow for analyses to be performed using standard hardware and software given the massive size of the database. Data were summarized descriptively. Associations between the presence of psoriasis and various covariates were tested by using the Fisher exact test for categorical variables and *t* test for continuous variables. All statistical tests were 2-tailed.

The rates of MI in the mild and severe psoriasis groups were compared with the rate of MI in the control population by using an unadjusted Cox proportional hazards regression model. Patients who died without MI were considered censored for the primary analysis; we also conducted sensitivity analyses considering the composite outcome of the earlier of MI and death. The rates were then adjusted for age, sex, and the presence of diabetes, hyperlipidemia, hypertension, or current smoking. Body mass index was not included in the primary model as it was recorded in only 61% of patients, but was included in a sensitivity analysis. We also assessed interactions between age and psoriasis and sex and psoriasis on the risk of MI. Each dichotomous variable in the model was checked for proportionality while adjusting for the other covariates in the model by examining diagnostic log-log survival plots.

We performed a sensitivity analysis in which patients had to have at least 6 months of follow-up time and could not have had an MI in the first 6 months to ensure the capture of incident, not prevalent, MIs. Additional sensitivity analyses were performed to ensure that all patients were actively followed up. First, we altered the end date such that it was defined as the earliest date at which the patient experienced MI, or received a last prescription or diagnosis; and second, we restricted the population to only include patients observed at least once per year by the general practitioners. One other sensitivity analysis was performed to demonstrate that the association of psoriasis with MI was not affected by the reason for censoring.

All statistical analyses were performed by using Stata version 8.2 (Stata-Corp LP, College Station, Tex). All P values are 2-sided and P<.05 was considered statistically significant.

**Protection of Study Subjects**

Data were stripped of personally identifiable information. The study was approved by the Office of Regulatory Affairs of the University of Pennsylvania, Philadelphia, and by the Scientific and Ethical Advisory Group of the Medicines Control Agency, United Kingdom. The requirement of informed consent was waived as the study included only anonymized data.

**RESULTS**

We identified 130 976 patients with psoriasis and 556 995 corresponding control patients, followed up for a mean of 5.4 years (TABLE 1). Patients with psoriasis were less likely to be censored by transferring out of the practice than were control patients. Among patients with psoriasis, 3837 (2.9%) were classified as having severe disease based on having received systemic treatment. The frequency of oral treatment for psoriasis was similar to that reported in other population-based studies from the United Kingdom.<sup>30</sup> The majority of patients classified with severe psoriasis received

**Table 1.** Characteristics of Study Groups\*

Characteristics	Study Group			P Value	
	Control (n = 556 995)	Mild Psoriasis (n = 127 139)	Severe Psoriasis (n = 3837)	Mild Psoriasis vs Control	Severe Psoriasis vs Control
Sex					
Male	261 023 (46.86)	61 100 (48.06)	1869 (48.71)	<.001	.01
Female	295 972 (53.14)	66 039 (51.85)	1968 (51.29)		
Age, y					
Mean	45.72	46.35	49.75	<.001	<.001
Median (IQR)	42 (30-60)	44 (31-60)	49 (36-63)		
Diabetes mellitus					
Yes	18 239 (3.27)	5478 (4.31)	270 (7.04)	<.001	.001
No	538 756 (96.73)	121 661 (95.69)	3567 (92.96)		
History of MI					
Yes	7780 (1.4)	2261 (1.78)	76 (1.98)	<.001	.002
No	549 215 (98.6)	124 878 (98.22)	3761 (98.02)		
Hyperlipidemia					
Yes	18 534 (3.33)	5822 (4.58)	227 (5.92)	<.001	<.001
No	538 461(96.67)	121 317 (95.42)	3610 (94.08)		
Hypertension					
Yes	66 366 (11.92)	18 521 (14.57)	762 (19.86)	<.001	<.001
No	490 629 (88.08)	108 618 (85.43)	3075 (80.14)		
Smoking†					
Yes	118 729 (21.32)	35 551 (27.96)	1150 (29.97)	<.001	<.001
No	438 266 (78.68)	91 588 (72.04)	2687 (70.03)		
Mean BMI‡	25.27	25.77	26.55	<.001	<.001
Reason for end of study					
Death	38 017 (6.83)	7033 (5.53)	304 (7.92)	<.001	<.001
End of up to standard	365 709 (65.66)	94 595 (74.40)	3091 (80.56)		
Transfer out	153 269 (27.52)	25 511 (20.07)	442 (11.52)		

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); IQR, interquartile range; MI, myocardial infarction.

\*Data are presented as number (percentage) unless otherwise indicated. Because of rounding, percentages may not all total 100.

†Defined as current or never.

‡Data for BMI were available for 61% of the patients.

methotrexate (TABLE 2). Documentation of psoralen and phototherapy use was low, because these therapies are restricted to specialists and are not well captured by the GPRD.

Patients with psoriasis were more likely to be men and older; however, the distribution of these variables was similar between patients with psoriasis and controls. Consistent with previous studies,<sup>19,20,31,32</sup> patients with psoriasis were more likely to have diabetes, hyperlipidemia, hypertension, a history of MI, have a higher body mass index, and be a current smoker.

The incidence rates of MI are shown in TABLE 3. Patients with psoriasis had a higher incidence of MI compared with control patients, with patients who had severe psoriasis having the highest rate. TABLE 4 provides the haz-

**Table 2.** Systemic Therapies Received by Patients With Severe Psoriasis (n = 3837)\*

Systemic Therapy	No. of Patients With Severe Psoriasis (%)
Methotrexate	2262 (58.95)
Azathioprine	629 (16.39)
Psoralen	622 (16.21)
Cyclosporine	394 (10.27)
Etretinate or acitretin	346 (9.02)
Hydroxyurea	222 (5.79)
Mycophenolate mofetil	9 (0.23)

\*Percentages do not add up to 100 because patients could have received more than 1 systemic therapy.

ard ratios for all of the factors in the adjusted model. As expected, all of the usual risk factors result in increased risk of MI in this population. Examination of log-log plots for each of the variables in our model demonstrated that assumptions of proportional hazards were met.

The increased relative risk of having an MI adjusted for potentially confounding variables was similar in men and women. However, there was effect modification by age on the relative risk of patients with psoriasis developing an MI (Table 4). The highest relative risk

for patients with psoriasis having an MI occurred in younger patients, and the relative risk was attenuated in older patients (FIGURE). For example, for a 30-year-old patient with mild or severe psoriasis, the relative risk of having an MI is 1.29 (95% confidence interval [CI],

1.14-1.46) and 3.10 (95% CI, 1.98-4.86), respectively. However, for a 60-year-old patient with mild or severe psoriasis, the relative risk of having an MI is 1.08 (95% CI, 1.03-1.13) and 1.36 (95% CI, 1.13-1.64), respectively. However, the attributable and excess risk of MI due to psoriasis, when controlling for major cardiovascular risk factors, increases as patients with psoriasis age due to the fact that the baseline risk of MI increases with age (Table 3).

We performed a series of sensitivity analyses (TABLE 5) to further ensure the validity of our results. Similar results were found in analyses that excluded MIs occurring within the first 6 months of follow-up to ensure capture of incident, not prevalent MI; or that required the last prescription or diagnosis be used as the end date to ensure that all patients were actively followed up and censored for the same reason; or that were restricted to patients who were observed at least once per year by the general practitioners to further ensure active follow-up. Additional sensitivity analyses demonstrated no evidence of confounding by body mass index when the models were limited to patients with a recorded height and weight. We also performed 2 additional analyses in the severe group. In the first model, we excluded patients ever treated with methotrexate and, in a second model, we excluded patients ever treated with oral retinoids or cyclosporine. The relative risk of MI in patients with severe psoriasis remained increased in both of these models and was statistically similar to our primary analysis. Finally, an increase in the adjusted relative risk for patients with psoriasis persisted in a model that included a composite end point of MI or death due to any cause.

**COMMENT**

Our study results suggest that psoriasis is an independent risk factor for MI. The risk of MI associated with psoriasis is greatest in young patients with severe psoriasis, is attenuated with age, and remains increased even after controlling for traditional cardiovascular

**Table 3.** Incidence of MI in Patients With Psoriasis Compared With Control Patients\*

Variable	Study Group		
	Control	Mild Psoriasis	Severe Psoriasis
Follow-up time, y			
Mean	5.61	4.51	5.70
Median (IQR)	5.21 (2.17-9.14)	3.80 (1.64-7.14)	5.37 (2.66-8.90)
No. of person-years	3 123 004	573 787	21 845
No. of new MI cases (%)	11 194 (2.0)	2319 (1.8)	112 (2.9)
Incidence per 1000 person-years (95% CI)	3.58 (3.52-3.65)	4.04 (3.88-4.21)	5.13 (4.22-6.17)
Aged 30-40 y			
Attributable risk	NA	1.068 per 10 000 person-years	7.222 per 10 000 person-years
Excess risk	NA	1 MI per 9365 patients per year	1 MI per 1385 patients per year
Aged 40-50 y			
Attributable risk	NA	2.743 per 10 000 person-years	16.060 per 10 000 person-years
Excess risk	NA	1 MI per 3646 patients per year	1 MI per 623 patients per year
Aged 50-60 y			
Attributable risk	NA	4.658 per 10 000 person-years	23.250 per 10 000 person-years
Excess risk	NA	1 MI per 2147 patients per year	1 MI per 430 patients per year

Abbreviations: CI, confidence interval; IQR, interquartile range; MI, myocardial infarction; NA, not applicable.  
 \*Attributable risk and excess risk were calculated based on the adjusted relative risk of MI in patients with psoriasis, which varies by age as shown in Table 4 and the Figure. Relative risk was adjusted for psoriasis (unadjusted), psoriasis, age, age × psoriasis (interaction term), diabetes, history of MI, hyperlipidemia, hypertension, sex, and smoking.

**Table 4.** Univariable and Multivariable Cox Proportional Hazard Regression Models of the Risk of MI in Patients With Mild and Severe Psoriasis Compared With Control Patients\*

Covariate	Model Hazard Ratio (95% CI)†	
	Mild Psoriasis	Severe Psoriasis
Psoriasis (unadjusted)	1.11 (1.07-1.17)	1.43 (1.18-1.72)
Psoriasis	1.54 (1.24-1.91)‡	7.08 (3.06-16.36)‡
Age per year	1.077 (1.076-1.079)	1.077 (1.076-1.078)
Age × psoriasis (interaction term)	0.994 (0.991-0.997)	0.97 (0.96-0.99)
Diabetes	1.61 (1.53-1.70)	1.62 (1.53-1.71)
History of MI	3.24 (3.07-3.41)	3.31 (3.13-3.51)
Hyperlipidemia	3.08 (2.93-3.23)	3.18 (3.02-3.36)
Hypertension	1.11 (1.07-1.16)	1.12 (1.07-1.17)
Male sex	2.12 (2.04-2.19)	2.14 (2.05-2.22)
Smoking	1.15 (1.10-1.20)	1.16 (1.11-1.21)

Abbreviations: CI, confidence interval; MI, myocardial infarction.  
 \*Body mass index was not included in the primary model because it was available for only 61% of the patients.  
 †P < .001 for all comparisons.  
 ‡The point estimate of the hazard ratio for MI due to mild or severe psoriasis is not directly interpretable as this hazard ratio was modified by age (ie, age × psoriasis interaction term was significant). Age was categorized in years. See the Figure for adjusted hazard ratio of MI in patients with mild and severe psoriasis based on age.

risk factors. The findings demonstrate a dose-response effect, given that patients classified as severe had a higher risk of MI than patients with mild psoriasis, consistent with the hypothesis that greater immune activity in psoriasis is related to a higher risk of MI.

The reason for the higher risk ratio of MI in younger patients with psoriasis may relate to the observation that psoriasis is a heterogeneous disease. For example, it has been hypothesized that those persons with earlier onset disease (before age 40 years) have more severe disease and a stronger association with human leukocyte antigen (HLA)-Cw6 than patients with onset of psoriasis after age 40 years.<sup>33,34</sup> Additionally, because most patients with psoriasis develop the disease before age 40 years (approximately 75%), there may be a survivorship effect in which after decades of psoriasis, those patients predisposed to MI would less likely be available in the older age groups of our study due to the mortality associated with MI.

Our study advances the literature establishing the association of psoriasis and MI in that it is a broadly representative population-based study, which controlled for major risk factors that are

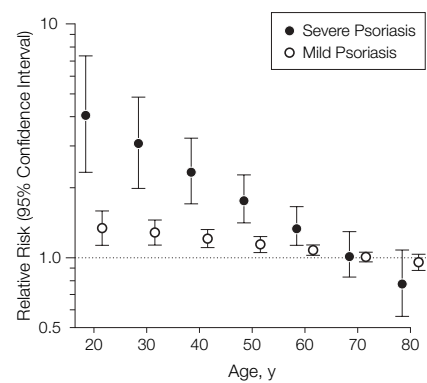
typically measured in epidemiological studies of cardiovascular disease. Our study also has the advantage of being large enough to allow for detailed analyses, which have yielded novel findings. The study is broadly representative of patients with psoriasis. The magnitude of association between severe psoriasis and MI in those patients younger than 50 years is similar to the magnitude of association for other major cardiac risk factors.

Observational studies may be limited by bias and confounding. Selection bias is unlikely to explain the results described herein as the patients with psoriasis and control patients were identified and included from the same well-defined source population. Information (ascertainment) bias is unlikely to explain the results as patients with psoriasis and control patients had information collected in the same manner (by general practitioners matched by practice) and the results were robust to multiple sensitivity analyses. Control patients were more likely to be censored by transferring out of the practice; however, the results were similar in sensitivity analyses in which patients were censored at the time of their last prescription or diagnosis to ensure

that all patients were actively followed up and censored for the same reason. Because MI is a major objective medical event, it is very unlikely that documentation of MI in the electronic medical record would vary between patients with psoriasis and those observed by general practitioners for diagnoses other than psoriasis.

The results also persisted when controlling for the major risk factors for MI. However, it is possible that unknown

**Figure.** Adjusted Relative Risk of Myocardial Infarction in Patients With Psoriasis Based on Patient Age



Adjusted relative risk is shown on a log scale.

**Table 5.** Sensitivity Analyses Hazard Ratio Point Estimates for Patients Aged 30 and 60 Years

	Hazard Ratio (95% CI)			
	Mild Psoriasis		Severe Psoriasis	
	Age 30 Years	Age 60 Years	Age 30 Years	Age 60 Years
Primary analysis	1.29 (1.14-1.46)	1.08 (1.03-1.13)	3.10 (1.98-4.86)	1.36 (1.13-1.64)
At least 6 mo of follow-up (to ensure capture of incident, not prevalent MIs)	1.27 (1.12-1.45)	1.08 (1.03-1.14)	2.11 (1.95-4.94)	1.45 (1.20-1.76)
Last prescription or diagnosis as end date (to ensure that patients are actively followed up and censored for the same reason)	1.28 (1.13-1.44)	1.07 (1.02-1.13)	2.90 (1.86-4.54)	1.32 (1.09-1.59)
Inclusion of patients observed ≥1 time/y by the general practitioner (to ensure that patients are actively followed up)	1.20 (1.06-1.36)	1.04 (0.99-1.09)	2.82 (1.81-4.40)	1.29 (1.07-1.56)
Primary model but also adjusting for BMI (excludes approximately 40% of patients for whom there was no BMI)	1.36 (1.17-1.58)	1.07 (1.01-1.13)	2.65 (1.53-4.59)	1.56 (1.25-1.93)
Primary model excluding approximately 40% of patients for whom there was no BMI; in this model, BMI was not included	1.37 (1.18-1.59)	1.08 (1.02-1.14)	2.70 (1.56-4.66)	1.58 (1.27-1.96)
Exclusion of patients treated with methotrexate	NA	NA	4.12 (2.24-7.58)	1.45 (1.11-1.91)
Exclusion of patients treated with oral retinoids or cyclosporine*	NA	NA	2.06 (1.16-3.67)	1.28 (1.03-1.58)
Composite end point of MI or death	1.44 (1.34-1.55)	1.20 (1.17-1.24)	2.08 (1.54-2.82)	1.42 (1.27-1.58)

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); CI, confidence interval; MI, myocardial infarction; NA, not applicable. \*Age × psoriasis interaction term was of borderline statistical significance ( $P = .06$ ).

or unmeasured confounding variables may explain some of the observed association. For example, recent literature has found modest associations between obesity, smoking, stress, and psoriasis when evaluating patients from referral centers or hospitals.<sup>31,35,36</sup> Information on body mass index was available for approximately 61% of patients, and patients with psoriasis had increases in body mass index compared with control patients. Other population-based studies have not found a significant association between psoriasis and body mass index.<sup>37</sup> In our study, we did not find any evidence of confounding by body mass index in the patients (>410 000) who had this information recorded. Furthermore, we measured smoking status as current or never and therefore could not determine if history of smoking or number of cigarettes smoked introduced any potential confounding.

Additionally, we defined severe psoriasis based on a history of having received systemic therapies and therefore cannot differentiate between the impact of psoriasis severity and systemic therapy on the risk of MI. The most commonly used systemic therapy was methotrexate, which recently has been shown to lower the incidence of cardiovascular outcomes, and therefore it is possible that our algorithm classifying severe psoriasis may underestimate the independent risk of MI in patients with severe psoriasis.<sup>38</sup> Oral retinoids and cyclosporine may induce certain cardiovascular risk factors, such as hypertension and hyperlipidemia, in some patients; however, these variables were measured in our analysis and would be unlikely to alter MI risk in an independent manner.<sup>39,40</sup> Furthermore, the findings in the severe group were robust to sensitivity analyses that excluded patients treated with methotrexate or cyclosporine and oral retinoids. We also did not directly assess psoriasis activity in our mild psoriasis group; therefore, it is possible that the risk of MI in those patients we classified as having mild disease varies based on psoriasis activity (eg, extent of skin

involvement). Finally, we did not examine if having psoriatic arthritis and the possible use of nonsteroidal anti-inflammatory drugs in addition to skin psoriasis further altered the risk of having an MI.

The results add to the growing evidence linking T<sub>H</sub>1 diseases to atherosclerosis and coronary artery disease. Psoriasis is the most prevalent T<sub>H</sub>1 autoimmune disease. The immune abnormalities in psoriasis are profound, leading to an estimated 20 billion T cells infiltrating the skin of a patient with severe psoriasis as well as profound increases in dendritic cells, T<sub>H</sub>1 cytokines (eg, TNF- $\alpha$ , interferon), and chemokines.<sup>7</sup> Other T<sub>H</sub>1 diseases, such as rheumatoid arthritis, have also been shown to be an independent risk factor for acute MI and multivessel coronary artery disease, when adjusting for coronary risk factors, such as diabetes, hyperlipidemia, hypertension, and smoking.<sup>14-16</sup> Additional studies have indicated that the severity of rheumatoid arthritis, measured by markers of systemic inflammation, is associated with an increased risk of cardiovascular death, even when controlling for traditional cardiovascular risk factors and comorbidities.<sup>16</sup> The exact mechanism by which T<sub>H</sub>1-mediated diseases such as psoriasis and rheumatoid arthritis predispose a patient to cardiovascular disease is unclear, but may be due to the common immunological pathways that function abnormally in these diseases. Furthermore, it is possible that the link between psoriasis and MI may be mediated by other factors beyond inflammation, such as psychological stress, sedentary lifestyle, or possibly poor compliance with management of cardiovascular risk factors.

Our findings are novel and therefore it is important that additional studies be performed to confirm these results and determine their therapeutic implications. In particular, it is important to determine the impact of clinical markers of psoriasis activity, such as body surface area, as well as biomarkers of systemic inflammation (eg, C-reactive protein) on the risk of

MI in patients with psoriasis. In the meantime, as part of good medical care, patients with psoriasis should be encouraged to aggressively address their modifiable cardiovascular risk factors.

**Author Contributions:** Dr Gelfand had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

**Study concept and design:** Gelfand, Neimann, Margolis.  
**Acquisition of data:** Gelfand, Neimann, Wang.

**Analysis and interpretation of data:** Gelfand, Neimann, Shin, Margolis, Troxel.

**Drafting of the manuscript:** Gelfand, Neimann, Shin, Margolis.

**Critical revision of the manuscript for important intellectual content:** Gelfand, Neimann, Shin, Wang, Margolis, Troxel.

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**Study supervision:** Gelfand, Margolis, Troxel.

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## REFERENCES

- Gelfand JM, Weinstein R, Porter SB, Neimann AL, Berlin JA, Margolis DJ. Prevalence and treatment of psoriasis in the United Kingdom: a population-based study. *Arch Dermatol*. 2005;141:1537-1541.
- Stern RS, Nijsten T, Feldman SR, Margolis DJ, Rolstad T. Psoriasis is common, carries a substantial burden even when not extensive, and is associated with widespread treatment dissatisfaction. *J Invest Dermatol Symp Proc*. 2004;9:136-139.
- Gelfand JM, Gladman DD, Mease PJ, et al. Epidemiology of psoriatic arthritis in the population of the United States. *J Am Acad Dermatol*. 2005;53:573.
- Shbeeb M, Uramoto KM, Gibson LE, O'Fallon WM, Gabriel SE. The epidemiology of psoriatic arthritis in Olmsted County, Minnesota, USA, 1982-1991. *J Rheumatol*. 2000;27:1247-1250.

5. Gelfand JM, Feldman SR, Stern RS, Thomas J, Rolstad T, Margolis DJ. Determinants of quality of life in patients with psoriasis: a study from the US population. *J Am Acad Dermatol*. 2004;51:704-708.
6. Rapp SR, Feldman SR, Exum ML, Fleischer AB Jr, Reboussin DM. Psoriasis causes as much disability as other major medical diseases. *J Am Acad Dermatol*. 1999;41:401-407.
7. Krueger JG, Bowcock A. Psoriasis pathophysiology: current concepts of pathogenesis. *Ann Rheum Dis*. 2005;64(suppl 2):ii30-ii36.
8. Schon MP, Boehncke WH. Psoriasis. *N Engl J Med*. 2005;352:1899-1912.
9. Rocha-Pereira P, Santos-Silva A, Rebelo I, Figueiredo A, Quintanilha A, Teixeira F. The inflammatory response in mild and in severe psoriasis. *Br J Dermatol*. 2004;150:917-928.
10. Chodorowska G, Wojnowska D, Juskiewicz-Borowiec M. C-reactive protein and alpha2-macroglobulin plasma activity in medium-severe and severe psoriasis. *J Eur Acad Dermatol Venereol*. 2004;18:180-183.
11. Vanizor Kural B, Orem A, Cimsit G, Uydu HA, Yandi YE, Alver A. Plasma homocysteine and its relationships with atherothrombotic markers in psoriatic patients. *Clin Chim Acta*. 2003;332:23-30.
12. Hansson GK. Inflammation, atherosclerosis, and coronary artery disease. *N Engl J Med*. 2005;352:1685-1695.
13. Ford ES, Giles WH. Serum C-reactive protein and fibrinogen concentrations and self-reported angina pectoris and myocardial infarction: findings from National Health and Nutrition Examination Survey III. *J Clin Epidemiol*. 2000;53:95-102.
14. Warrington KJ, Kent PD, Frye RL, et al. Rheumatoid arthritis is an independent risk factor for multi-vessel coronary artery disease: a case control study. *Arthritis Res Ther*. 2005;7:R984-R991.
15. Maradit-Kremers H, Crowson CS, Nicola PJ, et al. Increased unrecognized coronary heart disease and sudden deaths in rheumatoid arthritis: a population-based cohort study. *Arthritis Rheum*. 2005;52:402-411.
16. Maradit-Kremers H, Nicola PJ, Crowson CS, Ballman KV, Gabriel SE. Cardiovascular death in rheumatoid arthritis: a population-based study. *Arthritis Rheum*. 2005;52:722-732.
17. McDonald CJ, Calabresi P. Complication of psoriasis. *JAMA*. 1973;224:629.
18. McDonald CJ, Calabresi P. Occlusive vascular disease in psoriatic patients. *N Engl J Med*. 1973;288:912.
19. Ena P, Madeddu P, Glorioso N, Cerimele D, Rappelli A. High prevalence of cardiovascular diseases and enhanced activity of the renin-angiotensin system in psoriatic patients. *Acta Cardiol*. 1985;40:199-205.
20. Henseler T, Christophers E. Disease concomitance in psoriasis. *J Am Acad Dermatol*. 1995;32:982-986.
21. Mallbris L, Akre O, Granath F, et al. Increased risk for cardiovascular mortality in psoriasis inpatients but not in outpatients. *Eur J Epidemiol*. 2004;19:225-230.
22. Gelfand JM, Dattani H, Margolis DJ. The UK General Practice Research Database. In: Strom BL, ed. *Pharmacoepidemiology*. Vol 4. New York, NY: John Wiley & Sons; 2005:337-346.
23. Gelfand JM, Berlin J, Van Voorhees A, Margolis DJ. Lymphoma rates are low but increased in patients with psoriasis: results from a population-based cohort study in the United Kingdom. *Arch Dermatol*. 2003;139:1425-1429.
24. Gelfand JM, Wang X, Qing L, et al. Epidemiology and treatment patterns of psoriasis in the General Practice Research Database (GPRD) [abstract]. *Pharmacoepidemiol Drug Saf*. 2005;14:S23.
25. Lewis JD, Brensinger C. Agreement between GPRD smoking data: a survey of general practitioners and a population-based survey. *Pharmacoepidemiol Drug Saf*. 2004;13:437-441.
26. Jick H, Jick SS, Derby LE. Validation of information recorded on general practitioner based computerised data resource in the United Kingdom. *BMJ*. 1991;302:766-768.
27. Jick SS, Kaye JA, Vasilakis-Scaramozza C, et al. Validity of the general practice research database. *Pharmacotherapy*. 2003;23:686-689.
28. Walley T, Mantgani A. The UK General Practice Research Database. *Lancet*. 1997;350:1097-1099.
29. Jick H, Derby LE, Gurewich V, Vasilakis C. The risk of myocardial infarction associated with antihypertensive drug treatment in persons with uncomplicated essential hypertension. *Pharmacotherapy*. 1996;16:321-326.
30. Nevitt GJ, Hutchinson PE. Psoriasis in the community: prevalence, severity and patients' beliefs and attitudes towards the disease. *Br J Dermatol*. 1996;135:533-537.
31. Naldi L, Chatenoud L, Linder D, et al. Cigarette smoking, body mass index, and stressful life events as risk factors for psoriasis: results from an Italian case-control study. *J Invest Dermatol*. 2005;125:61-67.
32. Neimann AL, Shin DB, Wang X, Margolis DJ, Troxel AB, Gelfand JM. Prevalence of cardiovascular risk factors in patients with psoriasis [published online ahead of print September 26, 2006]. *J Am Acad Dermatol*. doi:10.1016/j.jaad.2006.08.040. Accessed September 26, 2006.
33. Henseler T, Christophers E. Psoriasis of early and late onset: characterization of two types of psoriasis vulgaris. *J Am Acad Dermatol*. 1985;13:450-456.
34. Langley RG, Krueger GG, Griffiths CE. Psoriasis: epidemiology, clinical features, and quality of life. *Ann Rheum Dis*. 2005;64(suppl 2):ii18-ii23.
35. Herron MD, Hinckley M, Hoffman MS, et al. Impact of obesity and smoking on psoriasis presentation and management. *Arch Dermatol*. 2005;141:1527-1534.
36. Fortes C, Mastroeni S, Leffondre K, et al. Relationship between smoking and the clinical severity of psoriasis. *Arch Dermatol*. 2005;141:1580-1584.
37. McGowan JW, Pearce DJ, Chen J, Richmond D, Balkrishnan R, Feldman SR. The skinny on psoriasis and obesity. *Arch Dermatol*. 2005;141:1601-1602.
38. Prodanowich S, Ma F, Taylor JR, Pezon C, Fasihi T, Kirsner RS. Methotrexate reduces incidence of vascular diseases in veterans with psoriasis or rheumatoid arthritis. *J Am Acad Dermatol*. 2005;52:262-267.
39. Lebwohl M, Drake L, Menter A, et al. Consensus conference: acitretin in combination with UVB or PUVA in the treatment of psoriasis. *J Am Acad Dermatol*. 2001;45:544-553.
40. Lebwohl M, Ellis C, Gottlieb A, et al. Cyclosporine consensus conference: with emphasis on the treatment of psoriasis. *J Am Acad Dermatol*. 1998;39:464-475.