
Prevalence of cardiovascular risk factors in patients with psoriasis

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Background: Previous studies suggest that patients hospitalized for psoriasis have an increased frequency of a variety of cardiovascular comorbidities. Limited population-based data exist on this association, and few studies have determined which factors are independently associated with psoriasis.

Objective: We sought to determine whether the prevalence of the major cardiovascular risk factors was higher in mild and severe psoriasis than in patients without psoriasis.

Methods: We conducted a population-based study in the United Kingdom using the General Practice Research Database. Patients were classified as having severe psoriasis if they received a code for psoriasis as well as systemic therapy. Patients were defined as having mild psoriasis if they ever received a psoriasis code but no systemic therapy. Control subjects were selected from the same practices and start dates as psoriasis patients. Patients were classified as having risk factors if they received codes for diabetes, hypertension, hyperlipidemia, obesity, or smoking. Analyses were performed by using conditional logistic regression, and adjustments were made considering age, gender, person-years, and all cardiovascular risk factors.

Results: We identified 127,706 patients with mild psoriasis and 3854 with severe psoriasis. Respective prevalence rates of risk factors in those with severe psoriasis, mild psoriasis, and in controls were as follows: diabetes (7.1%, 4.4%, 3.3%), hypertension (20%, 14.7%, 11.9%), hyperlipidemia (6%, 4.7%, 3.3%), obesity (20.7%, 15.8%, 13.2%), and smoking (30.1%, 28%, 21.3%). Patients with mild psoriasis had a higher adjusted odds of diabetes (odds ratio [OR], 1.13; 95% confidence interval [CI], 1.08-1.18), hypertension (OR, 1.03; 95% CI, 1.01-1.06), hyperlipidemia (OR, 1.16; 95% CI, 1.12-1.21), obesity (OR, 1.27; 95% CI, 1.24-1.31), and smoking (OR, 1.31; 95% CI, 1.29-1.34) than controls. Patients with severe psoriasis had a higher adjusted odds of diabetes (OR, 1.62; 95% CI, 1.3-2.01), obesity (OR, 1.79; 95% CI, 1.55-2.05), and smoking (OR, 1.31; 95% CI, 1.17-1.47) than controls. Additionally, diabetes (OR, 1.39; 95% CI, 1.22-1.58) and obesity (OR, 1.47; 95% CI, 1.32-1.63) were more prevalent in those with severe psoriasis than with mild psoriasis.

Limitations: The study was cross-sectional and therefore the directionality of the associations could not be determined.

Conclusion: Multiple cardiovascular risk factors are associated with psoriasis. Cardiovascular risk factors that are key components of the metabolic syndrome are more strongly associated with severe psoriasis than with mild psoriasis. (*J Am Acad Dermatol* 2006;55:829-35.)

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Psoriasis is a common chronic immune-mediated disease that affects 1% to 3% of the population.¹⁻³ It affects people of all ages, and its incidence peaks in early adult life (20s) and then again in later adult life (50s and 60s).³⁻⁶ Clinical manifestations of psoriasis are heterogeneous, ranging from limited disease to very extensive disease. Presentations of the skin lesions vary throughout life, and there may be periods of remissions and exacerbations. The majority of patients (approximately 80%) have limited disease (eg, <2% body surface area [BSA]), whereas approximately 20% of patients have more extensive skin involvement (eg, >3%

Abbreviations used:

| | |
|-------------------|------------------------------------|
| BMI: | body mass index |
| BSA: | body surface area |
| CI: | confidence interval |
| CVD: | cardiovascular disease |
| GP: | general practitioner |
| GPRD: | General Practice Research Database |
| JNK: | c-Jun amino-terminal kinase |
| OR: | odds ratio |
| T _H 1: | type 1 helper T cells |
| TNF: | tumor necrosis factor |

BSA).⁷ Despite the fact that psoriasis carries minimal risk of mortality, it is associated with significant morbidity and has substantial economic costs to both patients and the health care system.⁸ The impact of psoriasis on quality of life may be significant even if relatively limited BSA is involved.⁹

The pathophysiology of psoriasis is characterized by increased antigen presentation, increased cutaneous T lymphocyte activity, and the up-regulation of type 1 helper T cytokines.¹⁰⁻¹² The etiology of psoriasis is unknown, but evolving evidence suggests psoriasis is a complex disorder caused by the interaction of multiple genes, the immune system, and environmental factors. Although few environmental factors have been definitively linked to chronic plaque psoriasis, recent evidence suggests that smoking and an elevated body mass index (BMI) may be risk factors for the development of psoriasis.¹³

Smoking and obesity are associated with psoriasis and are also established cardiovascular risk factors.¹⁴ In addition to smoking and obesity, several studies in the literature suggest a high prevalence of cardiovascular risk factors (eg, diabetes, hypertension, and hyperlipidemia) as well as cardiovascular disease (CVD) in psoriasis patients.¹⁵⁻²³ A major limitation of most of these studies is that they focus on highly selected psoriasis patients, such as those hospitalized for their disease. Since patients with multiple comorbidities (including smoking and alcohol use) are more likely to be hospitalized, these studies may have been limited by selection bias.²⁴ Additionally, none of these studies performed multivariable modeling to determine which cardiovascular risk factors may be independently associated with psoriasis.

The goal of our investigation was to perform a broadly representative population-based study to determine whether the prevalence of the major cardiovascular risk factors identified by the Framingham studies was higher in patients with mild and severe psoriasis than in patients without psoriasis. We also aimed to determine whether these risk factors were independently associated with both mild and severe psoriasis.

METHODS**Study design**

This was a cross-sectional (prevalence) study with data collected by general practitioners (GPs) in the United Kingdom (UK), who were participating in the General Practice Research Database (GPRD) between 1987 and 2002. GPs were unaware of the hypothesis to be tested. The data were collected as part of the patient's electronic medical record and are maintained in the GPRD. GPRD contains data on more than 9 million persons with more than 35 million person-years of follow-up time and is broadly representative of the UK population.²⁵ In the UK system of care, the GP is responsible for managing all aspects of a patient's care. GPs refer patients to specialists, and the information from the specialist is captured electronically by the GP.²⁶ GPs receive specific training, financial inducements, and penalties to ensure accuracy of the data. GPRD has been used extensively for epidemiologic studies. The validity of using the GPRD to study psoriasis and diseases associated with cardiovascular disease has been demonstrated previously.^{1,26-30}

Study population

The study population consisted of all psoriasis patients who had at least one day of observation time, as described previously.³¹ Each psoriasis patient was matched to up to 5 subjects (as available based on matching criteria) who did not have psoriasis, who were seen in the same practice, and who had a date of observation in the practice (the maximum of the date when the patient registered with the practice and the date when the practice was designated "up to standard") within 60 days. Practices are designated as being "up to standard" when audits demonstrate that at least 95% of relevant patient encounters are recorded and the data are determined to be of suitable quality for epidemiologic research. The matching was performed to ensure that patients were followed up in the same practice and time periods to minimize the impact of secular and geographic differences between those with and without psoriasis. The analyses were restricted to patients 20 to 90 years of age as cardiovascular risk factors are very rare in patients younger than 20 years, which diminished the number of eligible controls for this study.

Definition of prevalence

Prevalence is defined as the proportion of individuals in a population who have the disease of interest in a specified time period. Our definition of prevalence approximates lifetime prevalence as any

documentation of psoriasis or cardiovascular risk factors (diabetes, hypertension, hyperlipidemia, smoking, increased BMI) by the GP at the time the patient was registered in the practice would result in the patient being classified as having these diseases. In addition, documentation of these diseases could occur at any time that the patient was followed up in the practice over the 5 to 6 years of observation time.

Study time period

For all patients, observation start-time was the maximum of patient registration and “up-to-standard” dates. Follow-up time ended when patients died, transferred out of the practice, or the practice was no longer “up to standard” (whichever came earliest).

Definition of psoriasis

Diseases are classified in the GPRD using Oxford Medical Information System and Read codes. Oxford Medical Information System and Read codes are diagnostic codes that GPs 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 by the GP that has been validated in previous studies.^{1,28,29} For example, the epidemiology of psoriasis in GPRD is very similar to other population-based studies in the United Kingdom,³² and more than 90% of patients with a psoriasis diagnostic code receive psoriasis therapies.¹ Additionally, when directly querying a random sample of 100 GPs who had entered a diagnostic code of psoriasis, in approximately 90% of cases the GPs confirmed that psoriasis was still the diagnosis after 4 years of follow-up.²⁸ Psoriasis patients were defined as having “severe” disease if they received a treatment code consistent with severe disease (eg, psoralen, phototherapy, methotrexate, azathioprine, cyclosporine, etretinate, acitretin, hydroxyurea, mycophenolate) during the entire study time period. Treatments consistent with severe psoriasis were determined by the British National Formulary and the opinion of two dermatologists (D. J. M., J. M. G.). Psoriasis patients were classified as having “mild” disease if they received a code for psoriasis but never received a prescription code consistent with severe disease during the study period. Patients were classified as not having psoriasis (eg, control population) if they never received a diagnostic code consistent with psoriasis.

Definition of cardiovascular risk factors/comorbidities

Patients were classified as having a cardiovascular risk factor if they received a medical code consistent with diabetes, hypertension, hyperlipidemia, or current smoking at any time during the study period.

The BMI was determined by weight and height calculations or from documentation in the patient’s electronic medical record.

Statistical analysis

The data were summarized descriptively. The prevalence rates of cardiovascular risk factors in the psoriasis groups were first compared with those in the nonpsoriasis population using unadjusted conditional logistic regression modeling, which accounted for matching factors of practice and differences in observation time. The rates were then adjusted for age, sex, and person-years of observation to yield prevalence odds ratios. To test the independent association of individual cardiovascular risk factors with both mild and severe psoriasis, we also performed multivariable conditional logistic regression modeling, adjusting for each of the individual risk factors (diabetes, hypertension, hyperlipidemia, smoking, BMI) in addition to age, sex, and person-years. All statistical analyses were performed using Intercooled Stata 8.2 (Stata Corp, College Station, Tex).

Protection of study subjects

Data utilized for this study were stripped of personally identifiable information. The study was approved by the Office of Regulatory Affairs of the University of Pennsylvania and by the Scientific and Ethical Advisory Group of the Medicines Control Agency, United Kingdom. The study was conducted in concordance with the Declaration of Helsinki.

RESULTS

We identified 127,706 patients with mild psoriasis who were matched with 465,252 subjects without psoriasis and 3854 patients with severe psoriasis matched to 14,065 corresponding subjects without psoriasis (Table I). Psoriasis patients were slightly older than matched control patients and were more likely to be male than the controls. In addition, person-years of observation were slightly greater in both psoriasis groups compared with their respective control groups (Table I). Information on BMI was available for 61% of patients.

In unadjusted analyses, patients with mild and severe psoriasis were more likely to be current smokers and have diabetes, hypertension, hyperlipidemia, and increased BMI compared with controls (Table I). Patients with mild psoriasis had increased odds of having each of the cardiovascular risk factors that persisted (Table II) when adjusting for age, gender and person-years (diabetes: odds ratio [OR] 1.27, 95% confidence interval [CI] 1.23-1.31; hypertension: OR 1.16, 95% CI 1.14-1.18; hyperlipidemia:

Table I. Description of study groups

| Variable | Control—mild | Mild | Control—severe | Severe |
|---------------------------|-------------------|-------------------|--------------------|-------------------|
| No. (%) | 465,252 (78.46) | 127,706 (21.54) | 14,065 (78.49) | 3,854 (21.51) |
| Sex | | | | |
| Male | 218,269 (46.9) | 61,472 (48.1) | 6,555 (46.61) | 1,883 (48.86) |
| Female | 246,983 (53.1) | 66,234 (51.86) | 7,510 (53.39) | 1,971 (51.14) |
| Age (y) | | | | |
| Mean (median, 25th, 75th) | 45.7 (42, 30, 60) | 46.4 (44, 31, 60) | 46.34 (43, 31, 61) | 49.8 (49, 37, 63) |
| Person-years | 5.57 | 6.06 | 5.87 | 6.86 |
| Diabetes | 15,161 (3.26) | 5,564 (4.36) | 457 (3.25) | 272 (7.06) |
| Hyperlipidemia | 15,297 (3.29) | 6,024 (4.72) | 501 (3.56) | 232 (6.02) |
| Hypertension | 54,840 (11.79) | 18,718 (14.66) | 1,855 (13.19) | 769 (19.95) |
| Smoking | 98,337 (21.14) | 35,762 (28.00) | 3,157 (22.45) | 1,158 (30.05) |
| BMI 25-30* | 90,619 (32.88) | 29,759 (34.98) | 2,799 (33.38) | 994 (37.68) |
| BMI >30* | 36,117 (13.1) | 13,404 (15.75) | 1,093 (13.03) | 545 (20.66) |

BMI, Body mass index.

*BMI was available in 61% of patients.

Table II. Prevalence odds ratios of individual cardiovascular risk factors in mild and severe psoriasis versus controls

| Variable | Mild psoriasis model (95% CI)* | Severe psoriasis model (95% CI)* |
|------------------------|--------------------------------|----------------------------------|
| Diabetes | 1.27 (1.23-1.31) | 1.86 (1.58-2.19) |
| Hypertension | 1.16 (1.14-1.18) | 1.25 (1.13-1.39) |
| Lipids | 1.28 (1.24-1.33) | 1.31 (1.11-1.56) |
| Smoking | 1.40 (1.38-1.43) | 1.31 (1.20-1.44) |
| BMI 25-30 [†] | 1.12 (1.10-1.14) | 1.28 (1.15-1.43) |
| BMI >30 [†] | 1.29 (1.26-1.32) | 1.84 (1.60-2.11) |

BMI, Body mass index; CI, confidence interval.

*Model adjusted for age, sex, person-years.

[†]BMI was available in 61% of patients.

OR 1.28, 95% CI 1.24-1.33; smoking: OR 1.4, 95% CI 1.38-1.43; BMI 25-30: OR 1.12, 95% CI 1.10-1.14; BMI >30: OR 1.29, 95% CI 1.26-1.32). The OR of mild psoriasis after adjusting for age, gender, person-years, and each of the other comorbidities (Table III) remained statistically significantly elevated in patients with diabetes (OR 1.13, 95% CI 1.08-1.18), hypertension (OR 1.03, 95% CI 1.01-1.06), hyperlipidemia (OR 1.16, 95% CI 1.12-1.21), elevated BMI (BMI 25-30: OR 1.12, 95% CI 1.10-1.14; BMI >30: OR 1.27, 95% CI 1.24-1.31), and who were current smokers (OR 1.31, 95% CI 1.29-1.34); however, the magnitude of the association was small for hypertension. Similar results were obtained via sensitivity analysis in which we ensured that all patients were seen at least twice by GPs and that their end of observation time coincided with a GP visit (to ensure that all patients were actively followed up) (data not shown). Additionally, similar results were found

Table III. Prevalence odds ratios of individual cardiovascular risk factors in patients with mild and severe psoriasis versus controls

| Variable | Mild psoriasis model (95% CI)* | Severe psoriasis model (95% CI)* |
|--------------------------|--------------------------------|----------------------------------|
| Diabetes | 1.13 (1.08-1.18) | 1.62 (1.3-2.01) |
| Hypertension | 1.03 (1.01-1.06) | 1.00 (0.87-1.14) NS |
| Lipids | 1.16 (1.12-1.21) | 1.04 (0.84-1.28) NS |
| Smoking | 1.31 (1.29-1.34) | 1.31 (1.17-1.47) |
| BMI (25-30) [†] | 1.12 (1.1-1.14) | 1.27 (1.14-1.42) |
| BMI (>30) [†] | 1.27 (1.24-1.31) | 1.79 (1.55-2.05) |

BMI, Body mass index; CI, confidence interval; NS, not statistically significant.

*Model adjusted for age, sex, person-years, diabetes, hypertension, hyperlipidemia, smoking, and BMI.

[†]BMI data were available in 61% of patients.

when performing a sensitivity analysis in which we performed the multivariable model (except the BMI variable) in the entire patient sample (data not shown). Finally, similar results were found in a sensitivity analysis that included a history of myocardial infarction, indicating that the cardiovascular risk factors were not necessarily more likely to be identified in psoriasis patients because psoriasis is associated with CVD (eg, myocardial infarction) (data not shown).

In analysis of severe psoriasis, there was a statistically significant association (Table II) between each of the individual cardiovascular risk factors and severe psoriasis after adjusting for age, gender, and person-years (diabetes: OR 1.86, 95% CI 1.58-2.19; hypertension: OR 1.25, 95% CI 1.13-1.39; hyperlipidemia: OR 1.31, 95% CI 1.11-1.56; elevated BMI (BMI 25-30: OR 1.28, 95% CI 1.15-1.43; BMI >30: OR 1.84, 95% CI 1.60-2.11); current smokers: OR 1.31, 95% CI 1.20-1.44). This association persisted in the

case of diabetes, increased BMI, and current smoking after adjusting for age, gender, person-years, and all cardiovascular risk factors (Table III); however, the association was attenuated and no longer statistically significant in patients with hypertension (OR 1.00, 95% CI 0.87-1.14) and hyperlipidemia (OR 1.04, 95% CI 0.84-1.28). Similar results were obtained via sensitivity analyses that excluded patients treated with cyclosporine and oral retinoids (to ensure that therapies that have been associated with hypertension and hyperlipidemia did not solely account for reported associations between severe psoriasis and these comorbidities) (data not shown) and in which we assured that all patients were seen at least twice by GPs and that their end of observation time coincided with a GP visit (to ensure that all patients were actively followed up) (data not shown). Additionally, similar results were found in performing a sensitivity analysis in which we used the multivariable model (except the BMI variable) in the entire sample (data not shown). Finally, similar results were found in a sensitivity analysis that included a history of myocardial infarction, indicating that the cardiovascular risk factors were not necessarily more likely to be identified in severe psoriasis patients because severe psoriasis is associated with cardiovascular disease (eg, myocardial infarction) (data not shown).

The strongest associations with severe psoriasis in both adjusted analyses were with diabetes and obesity (BMI >30). In addition, these two diseases were more prevalent in patients with severe psoriasis than in those with mild psoriasis when adjusting for age, gender, and person-years (diabetes: OR 1.39, 95% CI 1.22-1.58; obesity: OR 1.47, 95% CI 1.32-1.63) (Table IV).

DISCUSSION

The results of this study suggest that diabetes, hypertension, hyperlipidemia, smoking, and increased BMI are associated with both mild and severe psoriasis. Additionally, these diseases are all independently associated with mild psoriasis; however, except for obesity and smoking, the association was negligible to modest for most of the cardiovascular risk factors and therefore unlikely to be of clinical significance. The association with severe psoriasis when controlling for traditional cardiovascular risk factors persists in the case of diabetes, smoking, and increased BMI (especially BMI >30 [obesity]), but in the case of hypertension and hyperlipidemia the association is attenuated, suggesting that these latter two diseases are not independently associated with severe psoriasis. In addition, patients with severe psoriasis were more likely to have each of the cardiovascular risk factors we studied compared with patients who had mild

Table IV. Prevalence odds ratios of individual cardiovascular risk factors in severe versus mild psoriasis

| Variable | Psoriasis model (95% CI)* |
|--------------------------|---------------------------|
| Diabetes | 1.39 (1.22-1.58) |
| Hypertension | 1.16 (1.07-1.26) |
| Hyperlipidemia | 1.06 (1.05-1.07) |
| Smoking | 1.07 (1.00-1.15) |
| BMI (25-30) [†] | 1.19 (1.09-1.30) |
| BMI (>30) [†] | 1.47 (1.32-1.63) |

BMI, Body mass index; CI, confidence interval.

*Model adjusted for age, sex, person-years.

[†]BMI data were available in 61% of patients.

psoriasis, with the magnitude of association being strongest for obesity, diabetes, and hypertension. These results suggest that psoriasis is associated with the complex disorder of metabolic syndrome, which incorporates hypertension, dyslipidemia, obesity, and impaired glucose tolerance, and that the association is stronger for severe psoriasis compared with mild psoriasis.³³

Similar to psoriasis, the metabolic syndrome is characterized by increases in the immunological activity of type 1 helper T cells (T_H1), which suggests the hypothesis that psoriasis may be associated with the metabolic syndrome because of shared inflammatory pathways.³⁴ For example, circulatory levels of tumor necrosis factor (TNF)- α , soluble TNF- α receptors, and in vitro TNF- α production have been shown to be elevated in patients with components of the metabolic syndrome, such as obesity and insulin resistance.^{34,35} TNF may lead to insulin resistance by inhibiting insulin-mediated tyrosine phosphorylation of the insulin receptor as well as insulin receptor substrate-1, key to downstream insulin signaling and glucose transportation to the cell surface.³⁶ Furthermore, TNF- α has also been shown to be a potent activator of c-Jun amino-terminal kinase (JNK), which stimulates activator protein-1, a major regulator of proinflammatory activity. Mouse models show that JNK activity is abnormally elevated in obesity and that the absence of the JNK1 molecule is associated with decreased adiposity, improved insulin sensitivity, and enhanced insulin receptor signaling.³⁷ Therefore it is possible that the association of the diseases which characterize the metabolic syndrome and psoriasis is explained by dysregulation of T_H1 pathways shared by these seemingly disparate diseases. Another explanation for the predisposition of psoriasis patients to develop metabolic syndrome may be that certain behaviors or the psychological impact of psoriasis itself (eg, poor eating habits, alcohol consumption, stress, decreased exercise due

to psoriasis symptoms or stigmatization) may lead to development of increased body weight and the metabolic syndrome. Lastly, the metabolic syndrome itself could predispose an individual to developing psoriasis as observed by a case-control study in which increased BMI (a precursor to the metabolic syndrome) was an independent risk factor for developing psoriasis (BMI 26-29: OR 1.6, 95% CI 1.1-2.1, BMI >30: OR 1.9, 95% CI 1.2-2.8 while controlling for age, sex, marital status, hospitalization, education level, smoking, and alcohol use).

Our study also confirms several previous reports that psoriasis is associated with smoking.³ Nicotine alters a wide range of immunological functions, including innate and adaptive immune responses.^{38,39} Nicotine can modulate the functional capacity of dendritic cells and can increase the secretion of proinflammatory T_H1 cytokines by dendritic cells.^{40,41} Studies support the hypothesis that nicotine alters the immune response by directly interacting with T cells and dendritic cells as well as indirectly through brain-immune interactions.⁴² Additionally, nicotinic cholinergic receptors have been demonstrated on keratinocytes that stimulate calcium influx and accelerate cell differentiation; they can also control keratinocyte adhesion and upward migration in the epidermis.⁴³ This suggests a biologic explanation for the association between smoking and psoriasis.

Our study advances the literature of the association of psoriasis and cardiovascular risk factors. To our knowledge, this study is the only broadly representative population-based study to date examining the prevalence of these combined cardiovascular risk factors with psoriasis. Additionally, our study examined patients with both mild and severe psoriasis and utilized multivariable modeling to determine which factors are independently associated with psoriasis. The study is broadly representative of all psoriasis patients; therefore the findings likely can be generalized to the general population of patients with psoriasis.

Observational studies may be limited by bias and confounding. Selection bias is unlikely to explain the results described herein because the psoriasis patients and control subjects were identified and included from the same well-defined source population. Information (ascertainment) bias is unlikely to explain the results because psoriasis patients and control subjects had information collected in the same manner (ie, by GPs matched by practice), and the results were robust to sensitivity analysis in which we ensured that all patients were actively followed up. Completeness of data may be an issue in epidemiologic studies. Information on BMI was available in our study for about 61% of patients,

which could affect generalizability. However, we thought this unlikely as our full multivariable analysis (adjusting for age, sex, person-years, and each of the cardiovascular risk factors except for BMI) in our entire study population was comparable to our analysis of only our population in which data on BMI were captured. Furthermore, we measured smoking status as "current" or "never" and therefore could not determine whether history of smoking or number of cigarettes smoked introduced any potential confounding. In addition, we defined severe psoriasis based on a history of having received systemic therapies; therefore we cannot differentiate between the impact of psoriasis severity and systemic therapy. The most commonly used systemic therapy was methotrexate, and to our knowledge methotrexate has no known association with diabetes, hypertension, hyperlipidemia, or smoking. Oral retinoids and cyclosporine may induce certain cardiovascular risk factors such as hypertension and hyperlipidemia in some patients; however, our findings in the severe psoriasis group were robust to sensitivity analyses, which excluded patients treated with cyclosporine and oral retinoids. We also did not directly assess psoriasis activity in our mild psoriasis group, which is likely heterogeneous; therefore it is possible that the association with cardiovascular risk factors in those we classified as having mild psoriasis varies on the basis of psoriasis activity (eg, extent of skin involvement). Finally, since the diagnosis of psoriasis was based on GP diagnosis, it is possible that some patients with mild psoriasis did not in fact have psoriasis. In the event that misclassification of psoriasis occurred, we believe this would bias our results toward the null, thus making our positive findings even stronger.

The findings of this study are important and add to the growing evidence that diabetes, hypertension, hyperlipidemia, smoking, and increased BMI are associated with psoriasis. In particular, the results of this study demonstrate that psoriasis is associated with key components of the metabolic syndrome and that this association is stronger in patients with severe psoriasis compared with those with mild psoriasis. This finding is important since those with as little as one or two metabolic syndrome risk factors are at increased risk for death caused by CVD.⁴⁴ Therefore, as part of good medical care, patients with psoriasis should be encouraged to identify and manage their modifiable cardiovascular risk factors.

REFERENCES

1. 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;141:1537-41.

2. 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;9:136-9.
3. Neimann AL, Porter SB, Gelfand JM. Epidemiology of psoriasis. *Expert Rev Dermatol* 2006;1:63-75.
4. Henseler T, Christophers E. Psoriasis of early and late onset: characterization of two types of psoriasis vulgaris. *J Am Acad Dermatol* 1985;13:450-6.
5. Langley RG, Krueger GG, Griffiths CE. Psoriasis: epidemiology, clinical features, and quality of life. *Ann Rheum Dis* 2005;64(Suppl 2):ii18-23; discussion ii24-5.
6. Smith AE, Kassab JY, Rowland Payne CM, Beer WE. Bimodality in age of onset of psoriasis, in both patients and their relatives. *Dermatology* 1993;186:181-6.
7. 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;51:704-8.
8. Javitz HS, Ward MM, Farber E, Nail L, Vallow SG. The direct cost of care for psoriasis and psoriatic arthritis in the United States. *J Am Acad Dermatol* 2002;46:850-60.
9. 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;41:401-7.
10. Krueger JG, Bowcock A. Psoriasis pathophysiology: current concepts of pathogenesis. *Ann Rheum Dis* 2005;64(Suppl 2):ii30-6.
11. Schon MP, Boehncke WH. Psoriasis. *N Engl J Med* 2005;352:1899-912.
12. Gaspari AA. Innate and adaptive immunity and the pathophysiology of psoriasis. *J Am Acad Dermatol* 2006;54(Suppl):S67-80.
13. Naldi L, Chatenoud L, Linder D, Belloni Fortina A, Peserico A, Virgili AR, 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;125:61-7.
14. Wilson PW, D'Agostino RB, Levy D, Belanger AM, Silbershatz H, Kannel WB. Prediction of coronary heart disease using risk factor categories. *Circulation* 1998;97:1837-47.
15. 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.
16. Lindegard B. Mortality and causes of death among psoriatics. *Dermatologica* 1989;179:91-2.
17. McDonald CJ. Cardiovascular disease in psoriasis. *J Invest Dermatol* 1989;92:646-7.
18. McDonald CJ, Calabresi P. Thromboembolic disorders associated with psoriasis. *Arch Dermatol* 1973;107:918.
19. McDonald CJ, Calabresi P. Complication of psoriasis. *JAMA* 1973;224:629.
20. McDonald CJ, Calabresi P. Occlusive vascular disease in psoriatic patients. *N Engl J Med* 1973;288:912.
21. Henseler T, Christophers E. Disease concomitance in psoriasis. *J Am Acad Dermatol* 1995;32:982-6.
22. Lindegard B. Diseases associated with psoriasis in a general population of 159,200 middle-aged, urban, native Swedes. *Dermatologica* 1986;172:298-304.
23. Mallbris L, Granath F, Hamsten A, Stahle M. Psoriasis is associated with lipid abnormalities at the onset of skin disease. *J Am Acad Dermatol* 2006;54:614-21.
24. Hennekens CH, Buring JE. Epidemiology in medicine. Philadelphia: Lippincott Williams & Wilkins; 1987.
25. Gelfand JM, Dattani H, Margolis DJ. The UK General Practice Research Database. In: Strom BL, editor. *Pharmacoepidemiology*. New York: John Wiley and Sons; 2005. pp. 337-46.
26. Jick H, Jick SS, Derby LE. Validation of information recorded on general practitioner based computerised data resource in the United Kingdom. *BMJ* 1991;302:766-8.
27. Walley T, Mantgani A. The UK General Practice Research Database. *Lancet* 1997;350:1097-9.
28. Gelfand JM, Wang X, Qing L, Neimann AL, Weinstein R, Margolis DJ, et al. Epidemiology and treatment patterns of psoriasis in the General Practice Research Database (GPRD). *Pharmacoepidemiol Drug Saf* 2005;14(Suppl):S23.
29. 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;139:1425-9.
30. Lewis JD, Brensinger C. Agreement between GPRD smoking data: a survey of general practitioners and a population-based survey. *Pharmacoepidemiol Drug Saf* 2004;13:437-41.
31. Gelfand JM, Shin DB, Neimann AL, Wang X, Margolis DJ, Troxel AB. The risk of lymphoma in patients with psoriasis. *J Invest Dermatol* doi:10.1038/sj.jid.5700410. Published online June 1, 2006.
32. Nevitt GJ, Hutchinson PE. Psoriasis in the community: prevalence, severity and patients' beliefs and attitudes towards the disease. *Br J Dermatol* 1996;135:533-7.
33. Grundy SM, Cleeman JI, Daniels SR, Donato KA, Eckel RH, Franklin BA, et al. Diagnosis and management of the metabolic syndrome: an American Heart Association/National Heart, Lung, and Blood Institute scientific statement. *Curr Opin Cardiol* 2006;21:1-6.
34. Wysocki J, Skoczynski S, Strozik A, Hochul B, Zygula M. [Metabolic or immunometabolic syndrome?] *Wiad Lek* 2005;58:124-7. Polish.
35. Elenkov IJ, Iezzoni DG, Daly A, Harris AG, Chrousos GP. Cytokine dysregulation, inflammation and well-being. *Neuroimmunomodulation* 2005;12:255-69.
36. Hotamisligil GS, Budavari A, Murray D, Spiegelman BM. Reduced tyrosine kinase activity of the insulin receptor in obesity-diabetes. Central role of tumor necrosis factor-alpha. *J Clin Invest* 1994;94:1543-9.
37. Hirosumi J, Tuncman G, Chang L, Gorgun CZ, Uysal KT, Maeda K, et al. A central role for JNK in obesity and insulin resistance. *Nature* 2002;420:333-6.
38. McAllister-Sistilli CG, Caggiula AR, Knopf S, Rose CA, Miller AL, Donny EC. The effects of nicotine on the immune system. *Psychoneuroendocrinology* 1998;23:175-87.
39. Sopori M. Effects of cigarette smoke on the immune system. *Nat Rev Immunol* 2002;2:372-7.
40. Aicher A, Heeschen C, Mohaupt M, Cooke JP, Zeiher AM, Dimmeler S. Nicotine strongly activates dendritic cell-mediated adaptive immunity: potential role for progression of atherosclerotic lesions. *Circulation* 2003;107:604-11.
41. Nouri-Shirazi M, Guinet E. Evidence for the immunosuppressive role of nicotine on human dendritic cell functions. *Immunology* 2003;109:365-73.
42. Sopori ML, Kozak W, Savage SM, Geng Y, Soszynski D, Kluger MJ, et al. Effect of nicotine on the immune system: possible regulation of immune responses by central and peripheral mechanisms. *Psychoneuroendocrinology* 1998;23:189-204.
43. Grando SA, Horton RM, Mauro TM, Kist DA, Lee TX, Dahl MV. Activation of keratinocyte nicotinic cholinergic receptors stimulates calcium influx and enhances cell differentiation. *J Invest Dermatol* 1996;107:412-8.
44. Malik S, Wong ND, Franklin SS, Kamath TV, L'Italien GJ, Pio JR, et al. Impact of the metabolic syndrome on mortality from coronary heart disease, cardiovascular disease, and all causes in United States adults. *Circulation* 2004;110:1245-50.