

Original Investigation

Psoriasis Severity and the Prevalence of Major Medical Comorbidity

A Population-Based Study

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IMPORTANCE Despite the growing literature on comorbidity risks in psoriasis, there remains a critical knowledge gap on the degree to which objectively measured psoriasis severity may affect the prevalence of major medical comorbidity.

OBJECTIVE To examine the prevalence of major medical comorbidity in patients with mild, moderate, or severe psoriasis, classified objectively based on body surface area involvement, compared with that in patients without psoriasis.

DESIGN, SETTING, AND PARTICIPANTS Population-based cross-sectional study of patient data from United Kingdom-based electronic medical records; analysis included 9035 patients aged 25 to 64 years with psoriasis and 90 350 age- and practice-matched patients without psoriasis.

MAIN OUTCOMES AND MEASURES Prevalence of major medical comorbidity included in the Charlson comorbidity index.

RESULTS Among patients with psoriasis, 51.8%, 35.8%, and 12.4%, respectively, had mild, moderate, or severe disease based on body surface area criteria. The mean Charlson comorbidity index was increasingly higher in patients with mild (0.375 vs 0.347), moderate (0.398 vs 0.342), or severe psoriasis (0.450 vs 0.348) (each $P < .05$). Psoriasis overall was associated with higher prevalence of chronic pulmonary disease (adjusted odds ratio, 1.08; 95% CI, 1.02-1.15), diabetes mellitus (1.22; 1.11-1.35), diabetes with systemic complications (1.34; 1.11-1.62), mild liver disease (1.41; 1.12-1.76), myocardial infarction (1.34; 1.07-1.69), peptic ulcer disease (1.27; 1.03-1.58), peripheral vascular disease (1.38; 1.07-1.77), renal disease (1.28; 1.11-1.48), and rheumatologic disease (2.04; 1.71-2.42). Trend analysis revealed significant associations between psoriasis severity and each of the above comorbid diseases (each $P < .05$).

CONCLUSIONS AND RELEVANCE The burdens of overall medical comorbidity and of specific comorbid diseases increase with increasing disease severity among patients with psoriasis. Physicians should be aware of these associations in providing comprehensive care to patients with psoriasis, especially those presenting with more severe disease.

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Psoriasis is a common chronic inflammatory disease, mediated by type 1 and 17 helper T cells, which affects 2% to 3% of the general population.^{1,2} Although conventionally considered a disease limited to the skin and joints, increasing evidence suggests that psoriasis has far-reaching systemic effects.³⁻¹⁵ Research characterizing the risk of comorbidity in patients with psoriasis may advance our understanding of the natural history of psoriasis and improve clinical practice. In particular, the presence of comorbid diseases may affect psoriasis treatment choice and monitoring, as well as inform the provision of comprehensive care with proper health screening, evaluation, and management.^{16,17}

Multiple observational studies have demonstrated that patients with psoriasis, particularly those receiving systemic treatment or phototherapy, have higher incidences of myocardial infarction, stroke, diabetes mellitus, and cardiovascular mortality, independent of conventional risk factors for these outcomes.³⁻¹² Associations with other comorbid diseases, such as metabolic syndrome, chronic obstructive pulmonary disease, asthma, peptic ulcer disease, liver disease, renal failure, and rheumatoid arthritis, have also emerged.¹³⁻¹⁵

Despite the growing literature on psoriasis comorbidity, there is a critical knowledge gap on the degree to which psoriasis severity may affect the prevalence of comorbid diseases. Previous studies have relied on indirect measures of psoriasis severity, such as treatment use patterns, rather than direct and objective measures. Moreover, few epidemiologic investigations have been conducted using a validated comorbidity index for a wide array of major medical comorbid diseases that may confer prognostic information on mortality.¹³ Therefore, our objective was to examine the prevalence of major medical comorbid diseases in patients with mild, moderate, or severe psoriasis as assessed by objective measures of body surface area (BSA) involvement compared with that in patients without psoriasis in a broadly representative patient population.

Methods

Study Design

We conducted a population-based, cross-sectional study in The Health Improvement Network (THIN) to determine the prevalence of comorbid diseases in patients with psoriasis; THIN is an electronic medical records database of patient demographics, diagnostic, referral, and prescribing data from general practices using Vision software (In Practice Systems). The version of THIN used in this study included longitudinal data on 7.5 million registered patients from 415 general practices, with demographics broadly representative of the population in the United Kingdom. Most aspects of medical care in the United Kingdom, including specialist care, are coordinated by general practitioners (GPs) and captured in THIN as part of ongoing patient management. Studies have validated the accuracy of THIN data for epidemiologic research and for studying psoriasis in particular.^{18,19} This study was approved by the University of Pennsylvania Institutional Review Board and the Cambridgeshire Research Ethics Committee.

Study Cohort

Eligible case patients in the study cohort were identified with a validated algorithm¹⁹ from individuals aged 25 to 64 years with at least 1 psoriasis diagnostic Read code within the 2 years before survey administration. At the time of sampling, eligible patients needed to be registered with 1 of 228 practices (55% of THIN practices) that were actively responding to questionnaires through THIN's Additional Information Services. Eligible patients with psoriasis were randomly sampled within age categories, and questionnaires were mailed to their GPs to verify the presence of psoriasis and assess the extent of disease. Completed questionnaires were collected during the subsequent 12 months.

Patients were defined as having psoriasis if their diagnosis was confirmed in the questionnaire. The questionnaire also determined the severity of psoriasis, namely, mild (limited disease with $\leq 2\%$ BSA affected), moderate (scattered disease with 3%-10% BSA affected), and severe psoriasis (extensive disease with $>10\%$ BSA affected).^{2,20} The face and construct validity of this approach has been demonstrated in previous studies showing that nondermatologists rated degrees of skin involvement accurately and that patients categorized with higher BSA involvement are more likely to require frequent visits for psoriasis and require systemic therapy or phototherapy for psoriasis.^{19,21,22} Case patients with missing medical records were excluded. Ten patients with no history of psoriasis diagnostic codes ever (ie, control patients) were randomly matched to the patients with psoriasis based on age category and general practice. Controls were required to be alive and actively registered with at least 1 practice visit within 2 years before sampling.

Outcomes

Major medical comorbid disease burden was evaluated by means of the Charlson comorbidity index, a prognostic index designed to predict the risk of mortality attributable to comorbid diseases by measuring 17 major systemic comorbid diseases.²³ Read codes for defining diseases in the Charlson comorbidity index were translated by one of us (H.Y.) from validated *International Classification of Diseases, 10th Revision (ICD-10)* coding algorithms created by Quan et al.²⁴ This approach was previously used by Khan et al²⁵ to validate that the Charlson comorbidity index is a strong predictor of 5-year mortality in a UK general practice medical records database analogous to THIN. Our codes were cross-checked with those from Khan et al to ensure completeness in capturing diagnoses. Under this algorithm, psoriatic arthritis was not included under "rheumatologic disease" of the Charlson comorbidity index. Comorbid diseases were identified by the presence of diagnostic Read codes or recordings in the Additional Health Details part of the database. Assessment of comorbid diseases occurred from the patients' start date (defined as the latest of the Vision software or computerization in the practice and registration dates of the patient) to the end date (defined as earliest date of transfer out of the practice, death, or date of survey sampling). Cardiovascular comorbid diseases (cerebrovascular disease, myocardial infarction, and peripheral vascular disease) were aggregated and presented as a combined outcome.

Table 1. Demographic Characteristics in Patients With Psoriasis and Controls

Characteristic	Patients With Psoriasis (n = 9035)	Controls (n = 90 350)	P Value
Psoriasis severity, No. (%) ^a			
Mild (≤2% BSA)	4523 (51.8)	NA	.66
Moderate (3%-10% BSA)	3122 (35.8)	NA	
Severe (>10% BSA)	1081 (12.4)	NA	
Age, median (IQR), y	46 (37-55)	46 (36-55)	
Age group, No. (%)			
25-34 y	1838 (20.3)	18 375 (20.3)	.29
35-44 y	2316 (25.6)	23 162 (25.6)	
45-54 y	2514 (27.8)	25 849 (28.6)	
55-64 y	2367 (26.2)	22 964 (25.4)	
Sex, No. (%)			
Male	4569 (50.6)	42 548 (47.1)	<.001
Female	4466 (49.4)	47 802 (52.9)	
Follow-up duration, median (IQR), y	10.7 (4.7-16.2)	10.7 (4.7-16.2)	.98
Psoriatic arthritis diagnosis, No. (%)	630 (7.0)	4 (0.0)	<.001

Abbreviations: BSA, body surface area; IQR, interquartile range; NA, not applicable.

^a Psoriasis severity was determined in 8726 of 9035 patients (96.6%).

Sample Size

With 4500 mild, 3000 moderate, and 1000 severe psoriasis cases and a baseline comorbidity prevalence of 3%, we estimated that we had 80% power to detect increased comorbidity prevalence odds ratios (ORs) of 1.29, 1.36, and 1.70 for mild, moderate, and severe psoriasis, respectively, in 2-sided tests at a significance level of .05.

Statistical Analysis

Sample characteristics and Charlson comorbidity index scores were summarized descriptively. Characteristics of patients with or without psoriasis were compared by using the Wilcoxon rank sum test for continuous variables and either the χ^2 or Fisher exact test for categorical variables, as appropriate. The associations between psoriasis severity and comorbid diseases were modeled by using conditional logistic regression, with adjustment for age, sex, and years of follow-up. We did not consider interaction terms or nonlinear effects. The Benjamini-Hochberg procedure was used to adjust for multiple comparisons of 17 outcomes, with differences considered significant at $P < .05$ in 2-sided tests.

As a sensitivity analysis, we excluded patients with psoriatic arthritis to prohibit potential confounding from known independent association between psoriatic arthritis and psoriasis severity. To assess for detection bias, we also excluded all patients who, on average, had had less than 1 average annual visit to the GP. Statistical analyses were conducted with Stata software, version 12.1 (StataCorp).

Results

Patient Characteristics

Of 10 474 eligible patients with psoriasis codes sampled for survey mailing, 10 026 had surveys returned by their GPs (response rate, 95.7%), with confirmed psoriasis diagnoses

in 9056 (90.3%). After exclusion of 21 patients with missing medical records, 9035 patients (90.1%) were included in the analysis. Psoriasis severity was determined in 8726 patients (96.6%), among whom 4523 (51.8%) had mild, 3122 (35.8%) had moderate, and 1081 (12.4%) had severe psoriasis (Table 1). Compared with 90 350 matched controls, patients with psoriasis had similar median age and follow-up duration but were more often male. Systemic therapy and/or phototherapy use was recorded before assessment of disease severity in 137 (3.0%), 278 (8.9%), and 322 (29.8%) of the patients with mild, moderate, or severe psoriasis, respectively, and psoriatic arthritis was diagnosed in 172 (3.8%), 250 (8.0%), and 180 (16.7%).

Comorbidity Prevalence

Mean Charlson comorbidity index scores were higher in patients with psoriasis than in controls across all categories of psoriasis severity (Table 2; all $P < .05$). Trend analysis of Charlson index scores by disease severity (from 0 [no psoriasis] to 3 [severe psoriasis]) also showed significant associations (P for trend $< .001$). After adjustment for age, sex, and follow-up duration, patients with mild (OR, 1.11; 95% CI, 1.03-1.19), moderate (1.15; 1.05-1.25), or severe psoriasis (1.35; 1.16-1.56) had higher odds of having at least 1 major medical comorbid disease than patients without psoriasis (P for trend $< .001$).

Prevalence ORs for comorbid diseases included in the Charlson comorbidity index were individually analyzed (Table 3). After adjustment for age, sex, and follow-up duration, significant associations were found between psoriasis and the following prevalent comorbid diseases: chronic pulmonary disease (OR, 1.08; 95% CI, 1.02-1.15), diabetes (1.22; 1.11-1.35), diabetes with systemic complications (1.34; 1.11-1.62), mild liver disease (1.41; 1.12-1.76), myocardial infarction (1.34; 1.07-1.69), peptic ulcer disease (1.27; 1.03-1.58), peripheral vascular disease (1.38; 1.07-1.77), renal disease (1.28; 1.11-1.48), and rheumatologic disease (2.04; 1.71-2.42). Significant associa-

Table 2. Charlson Comorbidity Index Score by Psoriasis Severity

Index Score	Patients, No. (%)											
	Any Psoriasis			By Psoriasis Severity								
	Case Patients	Controls	P Value	Mild	Controls	P Value	Moderate	Controls	P Value	Severe	Controls	P Value
0	6679 (73.9)	69066 (76.4)	<.001 ^a	3376 (74.6)	34596 (76.5)	.02 ^a	2316 (74.2)	23911 (76.6)	.001 ^a	773 (71.5)	8274 (76.5)	
1	1658 (18.4)	15195 (16.8)		821 (18.2)	7639 (16.9)		570 (18.3)	5279 (16.9)		215 (19.9)	1796 (16.6)	
2	363 (4.0)	3628 (4.0)		177 (3.9)	1753 (3.9)		122 (3.9)	1244 (4.0)		44 (4.1)	445 (4.1)	<.001 ^a
3	218 (2.4)	1582 (1.8)		104 (2.3)	805 (1.8)		74 (2.4)	506 (1.6)		29 (2.7)	194 (1.8)	
≥4	117 (1.3)	879 (1.0)		45 (1.0)	437 (1.0)		40 (1.3)	280 (0.9)		20 (1.9)	101 (0.9)	
Mean index (SD)	0.40 (0.85)	0.35 (0.79)	<.001 ^b	0.38 (0.80)	0.35 (0.78)	.02 ^b	0.40 (0.88)	0.34 (0.77)	<.001 ^b	0.45 (0.92)	0.35 (0.79)	<.001 ^b

^a χ^2 Test.

^b t Test.

Table 3. Association Between Psoriasis Severity and Prevalent Comorbid Diseases^a

Comorbid Disease	Patients, No. (%)		OR for Psoriasis Overall (95% CI)	Adjusted P Value ^b	OR by Severity (95% CI)			Adjusted P Value for Trend ^{b,c}
	Case Patients	Controls			Mild	Moderate	Severe	
Cancer	142 (1.6)	1719 (1.9)	0.85 (0.71-1.02)	.11	0.91 (0.72-1.16)	0.83 (0.61-1.14)	0.66 (0.38-1.15)	.06
Cerebrovascular disease	98 (1.1)	844 (0.9)	1.17 (0.94-1.45)	.21	0.98 (0.71-1.35)	1.14 (0.80-1.64)	2.50 (1.46-4.26)	.03
Chronic pulmonary disease	1368 (15.1)	12877 (14.3)	1.08 (1.02-1.15)	.02	1.08 (0.99-1.18)	1.06 (0.95-1.18)	1.18 (0.98-1.40)	.03
Congestive heart failure	34 (0.4)	303 (0.3)	1.08 (0.75-1.56)	.71	0.93 (0.54-1.61)	0.77 (0.37-1.59)	2.98 (1.37-6.49)	.30
Dementia	7 (0.1)	47 (0.1)	1.32 (0.57-3.04)	.59	2.18 (0.77-6.11)	0.76 (0.17-3.41)	NA	.78
Diabetes mellitus	476 (5.3)	3844 (4.3)	1.22 (1.11-1.35)	<.001	1.14 (0.99-1.32)	1.22 (1.03-1.46)	1.32 (1.00-1.74)	.004
Diabetes with complications	130 (1.4)	944 (1.0)	1.34 (1.11-1.62)	.006	1.17 (0.89-1.54)	1.36 (0.97-1.89)	1.87 (1.16-2.99)	.003
Hemiplegia	7 (0.1)	100 (0.1)	0.70 (0.32-1.50)	.44	0.70 (0.25-1.93)	0.65 (0.15-2.76)	1.06 (0.13-8.43)	.53
Metastatic tumor	5 (0.1)	66 (0.1)	0.81 (0.32-2.08)	.67	0.65 (0.15-2.77)	1.27 (0.35-4.52)	NA	.78
Mild liver disease	88 (1.0)	616 (0.7)	1.41 (1.12-1.76)	.008	1.29 (0.93-1.79)	1.46 (0.97-2.18)	1.69 (0.96-2.97)	.007
Moderate to severe liver disease	4 (0.0)	43 (0.0)	0.91 (0.33-2.55)	.81	0.87 (0.21-3.72)	0.64 (0.08-4.84)	NA	.50
Myocardial infarction	95 (1.1)	693 (0.8)	1.34 (1.07-1.69)	.03	1.39 (1.01-1.91)	1.39 (0.93-2.07)	1.28 (0.68-2.44)	.03
Peptic ulcer disease	98 (1.1)	771 (0.9)	1.27 (1.03-1.58)	.04	1.18 (0.85-1.63)	1.54 (1.11-2.12)	1.08 (0.54-2.17)	.03
Peripheral vascular disease	75 (0.8)	554 (0.6)	1.38 (1.07-1.77)	.02	1.05 (0.71-1.55)	1.92 (1.29-2.85)	1.85 (0.95-3.61)	.003
Renal disease	251 (2.8)	2026 (2.2)	1.28 (1.11-1.48)	.005	0.97 (0.77-1.21)	1.41 (1.11-1.79)	1.83 (1.26-2.68)	<.001
Rheumatologic disease	161 (1.8)	845 (0.9)	2.04 (1.71-2.42)	<.001	2.01 (1.56-2.58)	1.85 (1.36-2.50)	2.89 (1.84-4.53)	<.001
Atherosclerotic outcomes ^d	250 (2.8)	1961 (2.2)	1.28 (1.11-1.47)	.004	1.14 (0.93-1.39)	1.39 (1.11-1.76)	1.81 (1.25-2.63)	<.001

Abbreviations: NA, not applicable owing to small numbers of detected cases; OR, odds ratio.

^a Models are conditioned on matching criteria and adjusted for age, sex, and years of follow-up; AIDS was not modeled because of its low detected prevalence.

^b P values corrected for multiple comparisons with the Benjamini-Hochberg procedure.

^c Trend analysis was conducted by coding psoriasis severity score as a linear variable (0 indicates no psoriasis; 1, mild; 2, moderate; and 3 severe).

^d Atherosclerotic outcomes were aggregated from cerebrovascular disease, myocardial infarction, and peripheral vascular disease.

tions were not observed between psoriasis and prevalence of cancer, metastatic tumor, or congestive heart failure.

Significant positive trends were demonstrated between psoriasis severity and increased comorbidity prevalence for each of the comorbid diseases listed above, with significantly higher prevalence among patients with psoriasis overall (each adjusted P for trend < .05). For example, strong dose-response relationships were demonstrated, with 22% and 32% increases in diabetes, 36% and 87% increases in diabetes with

complications, and 39% and 81% increases in aggregated atherosclerotic outcomes among patients with moderate or severe psoriasis, respectively, compared with controls. There was also a nonsignificant trend showing modest increases in prevalence of these outcomes in patients with mild psoriasis. There was a trend for an association between cerebrovascular disease and psoriasis severity (adjusted P for trend = .03), but its association with psoriasis overall was not significant (adjusted P = .21).

Sensitivity Analyses

After exclusion of patients with psoriatic arthritis, point estimates for most comorbidity associations remained similar, with a notable exception for rheumatologic disease. Its association with psoriasis overall was attenuated (OR, 1.29; 95% CI, 1.03-1.61), and its association with psoriasis severity was no longer significant (P for trend = .20). After exclusion of all patients who, on average, had less than 1 average annual visit to the GP, all point estimates for comorbidity associations also remained similar (data not shown).

Discussion

These results provided novel evidence supporting a positive dose-response relationship between objectively measured psoriasis severity and the burden of major medical comorbid diseases in a broadly representative patient sample. We demonstrated that psoriasis severity is associated with higher mean Charlson comorbidity index and higher odds of having at least 1 major medical comorbid disease. Given the prognostic significance of the Charlson comorbidity index in predicting short-term mortality,²⁵ the higher disease burden associated with more severe psoriasis may in part explain the excess mortality previously seen in patients with psoriasis receiving systemic therapy.^{10,26}

Although previous studies have suggested higher prevalence of comorbid diseases in patients with psoriasis, most relied on treatment with systemic therapies or phototherapy as a surrogate marker for moderate to severe disease.^{3-10,12-14} This approach may not accurately reflect psoriasis severity, because patients with severe psoriasis are often undertreated, and systemic treatments for psoriasis may themselves either increase or decrease the risk of developing comorbid conditions.^{20,27-29} Our results confirmed that patients with psoriasis have higher odds of numerous major systemic comorbid diseases, with a positive dose-response relationship demonstrated between objectively measured psoriasis severity and prevalence of specific comorbid diseases.

Dose-response trends were demonstrated between psoriasis severity and cardiovascular comorbid diseases, including myocardial infarction and peripheral vascular disease. Prior studies also have shown that moderate to severe psoriasis, estimated from treatment pattern and/or affected body sites as proxy measures, is an independent risk factor for cardiovascular disease.^{3,6,13} Shared inflammatory pathways between psoriasis and atherosclerosis, including the activation of inflammatory cells and the expression of proinflammatory cytokines, may link psoriasis with cardiovascular disease.³⁰⁻³³ Indeed, an experimental mouse model of psoriasis has shown that sustained cutaneous inflammation is sufficient for promoting vascular inflammation and thrombosis.³³ Of note, the association between cerebrovascular disease and psoriasis overall was not statistically significant, despite the presence of a significant trend with severity. This lack of association was found in 1 population-based study¹³ but contrasts with findings of other studies showing that patients with psoriasis had higher stroke incidence, independent of conventional risk factors.^{4,5} Given

the limited number of cases detected in our relatively young patient samples, the lack of association with cerebrovascular disease may be attributable to inadequate statistical power.

Strong dose-response relationships were seen between psoriasis severity and prevalent diabetes. In particular, a novel association was revealed with diabetes-associated systemic complications, including nephropathy, retinopathy, neuropathy, and vasculopathy. Higher risk of diabetes has been shown in patients with psoriasis, particularly those receiving systemic treatments, independent of obesity and other risk factors.^{7,12} Independent associations were also demonstrated between objectively measured psoriasis severity and metabolic syndrome components, including hyperglycemia.¹⁵ Diabetes, insulin resistance, and obesity have been linked to psoriatic inflammation through common cytokines and adipokines mediators.³¹ Overlapping disease susceptibility loci between psoriasis and both type 1 (ie, interferon induced with helicase C domain 1 gene [IFIH1] and tyrosine kinase 2 gene [TYK2]) and type 2 diabetes (ie, CDK5 regulatory subunit associated protein 1-like 1 gene [CDKAL1]) have been identified and lend additional biological plausibility.³² Given the higher burden of prevalent diabetes among patients with psoriasis, the newly identified association between psoriasis severity and risk of chronic diabetic complications warrants confirmation in future studies.

Psoriasis severity was also associated with mild liver disease, a category including chronic hepatitis, alcoholic liver disease, and nonalcoholic fatty liver disease. Previous studies have linked psoriasis with increased risk of nonalcoholic fatty liver disease independent of alcohol intake, obesity, and hepatotoxic medications^{34,35} but yielded inconsistent results concerning chronic hepatitis B and C risks.^{13,36-38} Subclinical hepatic inflammation noted on advanced imaging studies in patients with psoriasis also suggested potential mechanisms for liver dysfunction.³⁰ Our data did not reveal any association between psoriasis and moderate to severe liver disease, such as cirrhosis or liver failure, but the small number of detected cases prevented us from reaching firm conclusions.

We also detected higher prevalence of renal disease related to psoriasis severity. Psoriasis has been associated with microalbuminuria, a sign of subclinical glomerular dysfunction and a marker of cardiovascular risk, independent of risk factors such as hypertension and diabetes.³⁹⁻⁴³ Although higher mortality attributed to renal disease was demonstrated among patients with psoriasis, mixed results have been shown regarding the prevalence of renal failure in psoriasis.^{10,13,44} Potential confounding factors, such as hypertension, diabetes, and the use of nephrotoxic psoriasis treatments, should be scrutinized to assess whether psoriasis is independently associated with the development of chronic kidney disease.

Our data also provide further evidence to support previous associations between psoriasis and chronic obstructive pulmonary disease,^{45,46} peptic ulcer disease,¹³ and autoimmune rheumatologic diseases beyond psoriatic arthritis.⁴⁷ Future studies need to examine these associations with psoriasis severity after adjustment for disease-specific risk factors.

This study should be reviewed in light of its strengths and limitations. The major strength lies in its population-based

methods with a very high survey response rate for assessing psoriasis severity, minimizing selection bias and enhancing generalizability of the findings. Misclassification of psoriasis severity by GPs can be a potential source of error; however, it was previously demonstrated that untrained patients with psoriasis can reliably classify psoriasis severity using a similar approach.²² Although patients with severe disease that is well controlled by systemic therapy and/or phototherapy may be classified as having mild disease based on our methods, only a small proportion (3.0%) of patients with no more than 2% BSA involvement had a history of such treatment use. Moreover, such misclassification would probably bias our dose-response results toward the null. Because GPs may have determined psoriasis severity at any time up to 12 months after survey mailing, our cross-sectional design precluded the establishment of temporal relationships between psoriasis severity and comorbidity.

Detection bias cannot be excluded but is unlikely to account for our results, because our hypotheses were unknown to GPs who routinely cared for patients with psoriasis and controls, and our study findings were robust to the exclusion of patients with low levels of GP follow-up care. The lack of associa-

tion found between psoriasis and prevalent internal malignancy may also argue against the presence of detection bias. Our study may have been underpowered in detecting associations with comorbid diseases for which the overall prevalence in our sample is low. Finally, we did not evaluate the degree to which these associations are due primarily to psoriasis or to confounding factors, such as smoking, obesity, or treatment. Therefore, our results should be considered hypothesis generating and require confirmation in prospective studies.

In conclusion, our study demonstrated increases in major medical comorbid disease burden in patients with psoriasis according to objectively measured disease severity, which may have implications for the excess mortality risks from severe psoriasis. Moreover, dose-response relationships between psoriasis severity and prevalence of cardiovascular disease and diabetes were demonstrated and confirmed previous epidemiologic findings. Several less well-characterized comorbid associations were also recognized and might warrant further research. Physicians should be aware of these comorbid disease associations to provide comprehensive medical care to patients with psoriasis, especially those presenting with more severe disease.

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