Psoriasis and metabolic syndrome: A systematic review and meta-analysis of observational studies

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Background: Increasing population-based studies have suggested a relationship between psoriasis and metabolic syndrome.

Objective: The objective of this study was to perform a systematic review and meta-analysis that synthesizes the epidemiologic associations between psoriasis and metabolic syndrome.

Methods: We searched for observational studies from MEDLINE, EMBASE, and Cochrane Central Register from Jan 1, 1980 to Jan 1, 2012. We applied the Meta-Analysis of Observational Studies in Epidemiology (MOOSE) guidelines in the conduct of this study.

Results: We identified 12 observational studies with a total of 1.4 million study participants fulfilling the inclusion criteria, among whom 41,853 were patients with psoriasis. Based on random-effects modeling of cross-sectional and case-controlled studies, the pooled odds ratio (OR) for metabolic syndrome among patients with psoriasis was 2.26 (95% confidence interval [CI] 1.70-3.01) compared with the general population. Visual inspection of a funnel plot and formal analysis with the Egger test suggested publication bias and absence of small studies in the published literature (P = .03). A dose-response relationship was also observed between psoriasis severity and prevalence of metabolic syndrome.

Limitations: No studies to date have assessed incidence of metabolic syndrome among patients with psoriasis.

Conclusions: Compared with the general population, psoriasis patients have higher prevalence of metabolic syndrome, and patients with more severe psoriasis have greater odds of metabolic syndrome than those with milder psoriasis. (J Am Acad Dermatol 2013;68:654-62.)

Key words: epidemiology; meta-analysis; metabolic syndrome; prevalence; psoriasis; risk factors; systematic review.

INTRODUCTION

Psoriasis is a chronic, inflammatory condition that affects approximately 1% to 3% of the general population.1,2 During the past 10 years, population studies have found that patients with psoriasis may have increased prevalence of cardiovascular risk factors and elevated risk for developing adverse cardiovascular outcomes.3-5 A number of recent population-based studies have also suggested a relationship between psoriasis and metabolic syndrome.

Abbreviations used:

AOR: adjusted odds ratio
CI: confidence interval
FFA: free fatty acid
NCEP ATP III: National Cholesterol Education Program Adult Treatment Panel III
OR: odds ratio

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Metabolic syndrome affects approximately 15% to 25% of the general population. Specifcally, it is a combination of disorders that, when occurring together, confer significantly elevated risk for development of subsequent cardiovascular disease that may be greater than the attributable risk of each component risk factor. Metabolic syndrome is thought to arise from insulin resistance and abnormal adipose tissue function.

Various organizations have proposed criteria for the diagnosis of metabolic syndrome, including the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III), the International Diabetes Foundation, the World Health Organization, and the European Group for the Study of Insulin Resistance. According to the updated NCEP ATP III from 2005, metabolic syndrome is diagnosed when a person has at least 3 of these 5 conditions: (1) fasting glucose 100 mg/dL or greater (or receiving drug therapy for hyperglycemia), (2) blood pressure 130/85 mm Hg or higher (or receiving drug therapy for hypertension), (3) triglycerides 150 mg/dL or higher (or receiving drug therapy for hypertriglyceridemia), (4) high-density lipoprotein-cholesterol complex (HDL-C) less than 40 mg/dL in men or less than 50 mg/dL in women (or receiving drug therapy for reduced HDL-C), and (5) waist circumference 102 cm (40 inches) or greater in men or 88 cm (35 inches) or greater in women; if Asian American, 90 cm (35 inches) or greater in men or 80 cm (32 inches) or greater in women.

Metabolic syndrome confers significant disease burden. For example, pooled data show that metabolic syndrome confers twice the risk for coronary artery disease, and it increases the risk of stroke, fatty liver disease, and certain types of malignancy. Recent literature suggests that psoriasis patients may have increased prevalence of metabolic syndrome. Current recommendations suggest that patients with psoriasis should be screened for metabolic syndrome, but the strength of this epidemiologic association has not previously been examined systematically. In this systematic review and meta-analysis, we aim to synthesize the literature on the association between psoriasis and metabolic syndrome from population-based studies.

**METHODS**

We performed the systematic review using MEDLINE, EMBASE, and Cochrane Central Register. We used the following search criteria: (“Psoriasis” [MeSH]) AND “Metabolic Syndrome” [MeSH], limiting our search to English-language and human-subjects studies published between Jan 1, 1980 and Jan 1, 2012. All abstracts were read to determine eligibility for inclusion in the meta-analysis. To be included, original studies needed to fulfill the following inclusion criteria: case-control, cross-sectional, cohort, or nested case-control design; evaluation of metabolic syndrome in conjunction with psoriasis; and analyses that compared psoriasis patients with control groups. Specifically, the studies had to evaluate the prevalence or incidence of metabolic syndrome as defined by physical examination, patient self-report, medical chart review, or medical billing codes.

The search yielded 53 results (Fig 1). We manually reviewed all abstracts and selected 38 full-text articles for further examination. After reading the full-length articles, we excluded the following articles because they did not fulfill inclusion criteria for systematic review: 11 articles were reviews; 5 were commentaries, letters, or case reports; 2 did not include a non-psoriasis control group; 2 focused exclusively on patients with psoriatic arthritis; 3 did not report measures of association between psoriasis and metabolic syndrome; 2 assessed only individual components of metabolic syndrome without overall assessment of metabolic syndrome; one did not include percentages or patient numbers. After these exclusions, 12 studies were included in the meta-analysis.

The Meta-Analysis of Observational Studies in Epidemiology (MOOSE) guidelines were used to guide analysis. Two reviewers (C.T.H. and A.W.A.) independently extracted the data and performed the systematic review, and any disagreements were appropriately addressed by discussion and agreement. For each study included, we recorded the study year, country in which the study population lived, setting in which the study took place, study design, numbers of case and control subjects, age, gender, whether the results were adjusted for...
comorbidities, data collection processes (prospective or retrospective), whether the results were a primary or secondary analysis of the publication, and whether psoriasis disease severity was assessed. To measure study quality, we used a previously validated 6-point scale, with values of 0 or 1 assigned to the following: study design, assessment of exposure, assessment of outcome, control for confounding, evidence of bias, and assessment of psoriasis severity. Studies with a score of 0 to 3 were categorized as lower quality, whereas studies with scores of 4 to 6 were categorized as higher quality.17

The included studies were either cross-sectional or case-control and all reported odds ratios (ORs). All studies reported prevalence of metabolic syndrome, and therefore the results are presented as pooled ORs. To estimate the pooled OR, we applied fixed-effects and random-effects models of DerSimonian and Laird. Study heterogeneity was assessed using the I² statistic. Because of significant study heterogeneity, reported pooled ORs are based on random-effects modeling.

Publication bias was assessed by using visual inspection of a funnel plot of the study size versus standard error, with formal statistical testing using the Begg adjusted rank correlation test.19,20

Observational studies may also differ significantly in study design, location, and outcome assessment. These variables may significantly impact the reported strength of association between exposure and outcome. Meta-regression is a method to examine the effect of these variables on the study findings. Pre-specified sources of heterogeneity included the following: study country, subject location (ambulatory or inpatient), multivariate adjustment for confounders, primary versus secondary analysis (ie, whether metabolic syndrome was the primary outcome of the paper or a secondary outcome), ascertainment of psoriasis disease severity, measure of outcome, and study quality (0 to 3 vs 4 to 6).

All analyses were performed using STATA Version 11.2 (STATA Corp, College Station, TX).

RESULTS

This systematic review and meta-analysis synthesized data from 12 studies with 1.4 million participants, among whom 41,853 were patients with
psoriasis (Table I).\textsuperscript{21-32} All studies were cross-sectional or case-control and assessed the prevalence of metabolic syndrome among patients with pre-existing psoriasis. Five of the 12 studies used the NCEP ATP III revised criteria to assess diagnosis of the metabolic syndrome, but the two largest studies used diagnostic codes where the treating physician had identified the patient as being diagnosed with the metabolic syndrome.\textsuperscript{22,27} The studies were conducted in diverse geographic locations, including the United States, Europe, Asia, India, and the Middle East.

Only 3 studies performed multivariate adjustment to adjust for other covariates (Table II).\textsuperscript{27-29} Covariate adjustment included age and gender; smoking status was variably included but did not alter the results. In these 3 studies, the reported adjusted ORs for metabolic syndrome ranged from 1.3 to 1.96. Meta-analysis of the 12 studies revealed significant between-study heterogeneity ($\Gamma^2 = 86\%$). Using random effects analysis to account for study heterogeneity, the pooled OR for metabolic syndrome was 2.26 (95\% CI, 1.70-3.01), as shown in Fig 2.

Because bias may exist with a tendency to not publish small studies that do not show an association between psoriasis and metabolic syndrome, we also assessed publication bias by graphically assessing the relationship between study size and the strength of reported association between psoriasis and the metabolic syndrome. A funnel plot revealed possible publication bias with an absence of smaller studies (Fig 3); formal testing with the Egger test confirmed bias ($P = .03$).

We also performed meta-regression analysis to investigate the possible association of study characteristics with the strength of the observed outcome. Stratification by study country, study quality, use of statistical adjustment, method of ascertainment, or whether the outcome was primary or secondary did not significantly affect the association between psoriasis and the metabolic syndrome (Table III).

Only 3 studies examined the association between metabolic syndrome and psoriasis severity; the other studies reported only pooled values for metabolic syndrome prevalence among patients with psoriasis without specifically stratifying by disease severity.\textsuperscript{21,27,31} The most comprehensive study examined the association between mild, moderate, and severe psoriasis and the prevalence of metabolic syndrome.\textsuperscript{27} After adjusting for covariates, there was a dose-response relationship between psoriasis

### Table I. Study population characteristics: Psoriasis and metabolic syndrome

<table>
<thead>
<tr>
<th>Study</th>
<th>Study setting</th>
<th>Study design</th>
<th>Total no. of patients</th>
<th>Mean age (y)</th>
</tr>
</thead>
<tbody>
<tr>
<td>*Sommer et al\textsuperscript{31} (2006)</td>
<td>Germany; inpatient (hospital charts)</td>
<td>Cross-sectional</td>
<td>1044 581</td>
<td>58.5 54.4</td>
</tr>
<tr>
<td>*Gisondi et al\textsuperscript{28} (2007)</td>
<td>Italy; outpatient (outpatient clinics)</td>
<td>Cross-sectional</td>
<td>334</td>
<td>63.8 62.1</td>
</tr>
<tr>
<td>Chen et al\textsuperscript{25} (2008)</td>
<td>Taiwan; outpatient (dermatology clinics)</td>
<td>Case-control</td>
<td>81 77</td>
<td>55.6 57.4</td>
</tr>
<tr>
<td>Chen et al\textsuperscript{24} (2009)</td>
<td>Taiwan; outpatient (dermatology clinics)</td>
<td>Case-control</td>
<td>37 40</td>
<td>56.0 58.9</td>
</tr>
<tr>
<td>*Al-Mutairi et al\textsuperscript{21} (2010)</td>
<td>Kuwait; outpatient (medical records)</td>
<td>Case-control</td>
<td>1835</td>
<td>52.7 52.3</td>
</tr>
<tr>
<td>*Augustin et al\textsuperscript{22} (2010)</td>
<td>Germany; outpatient (health insurance database)</td>
<td>Cross-sectional</td>
<td>1,310,090 33,981</td>
<td>NR NR</td>
</tr>
<tr>
<td>Bongiorno et al\textsuperscript{23} (2010)</td>
<td>Italy; outpatient (dermatology department)</td>
<td>Cross-sectional</td>
<td>348 400</td>
<td>47.6 47.6</td>
</tr>
<tr>
<td>*Nisa and Qazi\textsuperscript{30} (2010)</td>
<td>India; outpatient (dermatology department)</td>
<td>Case-control</td>
<td>150 150</td>
<td>36.3 37.3</td>
</tr>
<tr>
<td>*Takahashi et al\textsuperscript{32} (2010)</td>
<td>Japan; outpatient (dermatology clinic)</td>
<td>Case-control</td>
<td>154 151</td>
<td>57.2 53.1</td>
</tr>
<tr>
<td>*Love et al\textsuperscript{28} (2011)</td>
<td>United States; outpatient (NHANES)</td>
<td>Cross-sectional</td>
<td>2385 71</td>
<td>38.6 41.7</td>
</tr>
<tr>
<td>*Mebazaa et al\textsuperscript{29} (2011)</td>
<td>Tunisia; outpatient (dermatology clinic)</td>
<td>Case-control</td>
<td>216 164</td>
<td>48.6 46.3</td>
</tr>
<tr>
<td>*Langan et al\textsuperscript{27} (2012)</td>
<td>United Kingdom; outpatient (THIN database)</td>
<td>Case-control</td>
<td>40,650 4065</td>
<td>NR NR</td>
</tr>
</tbody>
</table>

NHANES, National Health and Nutrition Examination Survey; NR, not reported; Ps, psoriasis; pts, patients; THIN, The Health Improvement Network.

*Asterisk denotes that metabolic syndrome was the primary study outcome.
severity and metabolic syndrome, with adjusted ORs of 1.22, 1.56, and 1.98 for mild, moderate, and severe psoriasis, respectively.

**DISCUSSION**

To our knowledge, this is the largest systematic review and the first meta-analysis examining the relationship between psoriasis and metabolic syndrome with 41,853 psoriasis patients from more than 1.4 million total participants. From the pooled OR from the meta-analysis, we found that psoriasis patients had increased odds of metabolic syndrome compared with the general population and that metabolic syndrome has a high prevalence among patients with psoriasis.

Several possible biologic mechanisms may help explain the epidemiologic association between psoriasis and metabolic syndrome. Chronically elevated FFA along with increased TNF-α and IL-6 lead to increased glucose production in the liver, as well as reduced glucose uptake in the muscle. The combined dysfunction results in an overall state of impaired glucose tolerance. In addition to its effects on the liver and muscle, elevated FFA levels diminish insulin secretion by the pancreatic β-islet cells through enhancing the expression of uncoupling protein 2. While leptin may have anti-apoptotic properties on the β-islet cells, these anti-apoptotic properties may be diminished in an obese state seen in psoriasis patients.

Shared genetic risk loci may also account for at least part of the observed association. For example, **CDKAL1** is associated with both psoriasis and type 2 diabetes, whereas **PTPN22** is associated with psoriasis and type 1 diabetes, among other diseases. The consequences of altered adipokine function in psoriasis may also help explain the relationship

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<table>
<thead>
<tr>
<th>Study</th>
<th>Study period</th>
<th>Outcome ascertainment</th>
<th>No. of patients with metabolic syndrome in control group (%)</th>
<th>No. of patients with metabolic syndrome in psoriasis group (%)</th>
<th>Measure of association (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Sommer et al</em>&lt;sup&gt;31&lt;/sup&gt;</td>
<td>1996-2002</td>
<td>Manual chart review</td>
<td>11 (1.1)</td>
<td>25 (4.3)</td>
<td>OR 4.22 (2.06-8.65)</td>
</tr>
<tr>
<td><em>Gisondi et al</em>&lt;sup&gt;28&lt;/sup&gt;</td>
<td>NR</td>
<td>Clinical assessment; NCEP ATP III criteria</td>
<td>69 (20.6)</td>
<td>102 (30.1)</td>
<td>OR 1.65 (1.16-2.35)</td>
</tr>
<tr>
<td>Chen et al&lt;sup&gt;25&lt;/sup&gt;</td>
<td>2006-2007</td>
<td>Clinical assessment</td>
<td>13 (16.3)</td>
<td>10 (14.1)</td>
<td>OR 0.84 (0.31-2.26)</td>
</tr>
<tr>
<td>Chen et al&lt;sup&gt;24&lt;/sup&gt;</td>
<td>2006-2007</td>
<td>Clinical assessment</td>
<td>4 (10.8)</td>
<td>9 (22.5)</td>
<td>OR 2.40 (0.67-8.58)</td>
</tr>
<tr>
<td><em>Augustin et al</em>&lt;sup&gt;22&lt;/sup&gt;</td>
<td>2005</td>
<td>ICD-10</td>
<td>786 (0.1)</td>
<td>61 (0.2)</td>
<td>OR 2.86 (2.21-3.71)</td>
</tr>
<tr>
<td>Bongiorno et al&lt;sup&gt;23&lt;/sup&gt;</td>
<td>NR</td>
<td>Clinical assessment; NCEP ATP III criteria</td>
<td>32 (9.2)</td>
<td>103 (25.8)</td>
<td>OR 3.4 (2.23-5.24)</td>
</tr>
<tr>
<td><em>Nisa and Qazi</em>&lt;sup&gt;10&lt;/sup&gt;</td>
<td>2008-2009</td>
<td>Clinical assessment; NCEP ATP III criteria</td>
<td>9 (6.0)</td>
<td>42 (28.0)</td>
<td>OR 6.09 (NR)</td>
</tr>
<tr>
<td><em>Takahashi et al</em>&lt;sup&gt;32&lt;/sup&gt;</td>
<td>2006-2008</td>
<td>Manual chart review</td>
<td>25 (16.2)</td>
<td>38 (25.2)</td>
<td>OR 1.74 (0.99-3.05)</td>
</tr>
<tr>
<td><em>Love et al</em>&lt;sup&gt;28&lt;/sup&gt;</td>
<td>2003-2006</td>
<td>Clinical assessment; NCEP ATP III criteria</td>
<td>560 (23.5)</td>
<td>28 (39.9)</td>
<td>OR 2.16 (1.16-4.03)</td>
</tr>
<tr>
<td>Mebazaa et al&lt;sup&gt;29&lt;/sup&gt;</td>
<td>2008-2010</td>
<td>Clinical assessment; NCEP ATP III criteria</td>
<td>67 (31.0)</td>
<td>67 (40.9)</td>
<td>OR 1.39 (0.88-2.18)</td>
</tr>
<tr>
<td><em>Langan et al</em>&lt;sup&gt;27&lt;/sup&gt;</td>
<td>NR</td>
<td>Read codes (THIN database)</td>
<td>10,515 (25.9)</td>
<td>1389 (34.2)</td>
<td>OR 1.50 (1.40-1.61) Overall AOR 1.41 (1.31-1.51) Mild psoriasis: AOR 1.22 (1.11-1.35)</td>
</tr>
</tbody>
</table>

AOR, Adjusted odds ratio; CI, confidence interval; NCEP ATP III, National Cholesterol Education Program Adult Treatment Panel III; NR, not reported; OR, odds ratio; THIN, The Health Improvement Network.

*Asterisk denotes that metabolic syndrome was the primary study outcome.*
between psoriasis and metabolic syndrome. Whereas adiponectin and leptin dysfunction in psoriasis has been described relatively more frequently, other proinflammatory adipokines, such as resistin and visfatin, were also found to be up-regulated in psoriasis. Combined dysfunction of these adipokines may account for the development of diseases associated with atherosclerosis seen in patients with psoriasis.

The odds of metabolic syndrome were increased more than two-fold among patients with psoriasis when compared with matched controls or a cross-sectional comparator group. These findings support a strong strength of association between psoriasis and metabolic syndrome. Importantly, most studies also reported a high overall prevalence of metabolic syndrome among patients with psoriasis. With the exception of the studies by Sommer et al and Augustin et al, the reported prevalence of metabolic syndrome among patients with psoriasis ranged from 14% to 40% (see Table II). These findings suggest that metabolic syndrome is a common problem encountered in the clinical management of patients with psoriasis. With the increasing prevalence of obesity and diabetes among the general population, metabolic syndrome will likely become an even more common problem in the coming decade.

The studies identified in this meta-analysis had important sources of variability. First, the population studies were inconsistent in reporting measures of association for individual components of metabolic syndrome, thereby making the aggregate determination difficult regarding which component is most closely associated with psoriasis. Second, few studies examined psoriasis severity and its relationship with metabolic syndrome. In the most comprehensive study to date examining the association between mild, moderate, and severe psoriasis and the prevalence of metabolic syndrome, the authors found a robust dose-response relationship between psoriasis severity and prevalence of metabolic syndrome. This observation is supported by the translational data that T-helper inflammatory cytokines are increased in skin and sera of psoriasis patients, and

Fig 2. Meta-analysis of the prevalence of metabolic syndrome in the psoriasis patients.

Fig 3. Funnel plot of included studies. The absence of studies in the lower left corner suggests possible publication bias, with fewer small studies than expected located to the left of dashed line.
these inflammatory cytokines exert systemic effects on insulin regulation and lipid metabolism. Third, observational studies typically have differences in location, study design, and outcomes that may affect the strength of an observed association. When we assessed these variables using meta-regression, there was no statistically significant difference in outcomes based on each pre-specified variable. These findings suggest that the variability in study design did not significantly affect the findings of an association between psoriasis and metabolic syndrome.

This systematic review and meta-analysis needs to be interpreted in the context of the available primary studies. The methods for identifying metabolic syndrome differed among the studies. While 5 studies used the NCEP ATP III revised criteria to identify patients with metabolic syndrome, the two largest studies used diagnostic codes. The adjusted ORs were reported in only a minority of studies, whereas most studies presented unadjusted ORs for metabolic syndrome. Finally, graphical analysis with a funnel plot and formal testing with the Egger test suggested that smaller studies with a lack of reported association between psoriasis and metabolic syndrome might not have been published. This may have biased the results towards a stronger reported association between psoriasis and metabolic syndrome. Despite these limitations in primary studies, 11 of 12 studies found the same directionality in the association between psoriasis and metabolic syndrome.

In summary, this systematic review and meta-analysis found that psoriasis patients are more likely to have metabolic syndrome compared with the general population and that patients with psoriasis have a high overall prevalence of metabolic syndrome. There also appears to be a dose-response relationship between severity of psoriasis and prevalence of metabolic syndrome. These findings emphasize that patients with psoriasis should be screened for metabolic syndrome. Patients with metabolic syndrome should have intensive risk factor modification including lifestyle interventions, weight loss, and management of hypertension, diabetes, and hypercholesterolemia. More studies are needed to determine the mechanisms underlying the association between these two conditions and to learn the effect of psoriasis systemic therapies on metabolic syndrome.

REFERENCES


39. Coimbra S, Oliveira H, Reis F, Belo L, Rocha S, Quintanilha A, et al. Circulating levels of adiponectin, oxidized LDL and...