Obesity in Early Adulthood as a Risk Factor for Psoriatic Arthritis

Razieh Soltani-Arabshahi, MD; Bob Wong, PhD; Bing-Jian Feng, PhD; David E. Goldgar, PhD; Kristina Callis Duffin, MD; Gerald G. Krueger, MD

Objective: To study whether obesity increases the risk of psoriatic arthritis (PsA), given that obesity is a risk factor for psoriasis and is associated with more severe disease.

Design: Case series. We used Cox regression analysis to study the relationship between obesity and PsA while controlling for age at psoriasis onset, current body mass index (BMI), sex, family history of psoriasis, worst-ever body surface area (BSA) involvement, Koebner phenomenon, and nail involvement.

Setting: Dermatology clinics at the University of Utah School of Medicine.

Patients: Volunteer sample of patients with dermatologist-diagnosed psoriasis enrolled in the Utah Psoriasis Initiative from November 2002 to October 2008 (943 subjects; 50.2% women, 49.8% men).

Main Outcome Measures: Physician diagnosis of PsA from self-report questionnaire.

Results: In our subjects, we found that BMI at age 18 years was predictive of PsA (odds ratio [OR], 1.06) (P < .01) over and above control variables. Other variables that were predictors of PsA included younger age at psoriasis onset (odds ratio [OR], 0.98) (P < .01), female sex (OR, 1.43) (P = .01), higher worst-ever BSA involvement with psoriasis (OR, 1.01) (P = .04), Koebner phenomenon (OR, 1.59) (P < .01), and nail involvement (OR, 1.76) (P < .01). Current BMI and family history of psoriasis were not significant predictors of PsA.

Conclusions: This study suggests that obesity at age 18 years increases the risk of developing PsA. Adiposity is associated with higher levels of inflammatory cytokines known to be associated with psoriasis. This inflammatory milieu could increase the risk of PsA in predisposed subjects. Prevention and early treatment of obesity may decrease the risk of PsA.

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Obesity has emerged as a significant risk factor for psoriasis. Several case-control studies have shown that patients with psoriasis have a higher prevalence of overweight and obesity than the general population, the odds ratios (ORs) ranging from 1.6 to 2.05.¹⁻⁴ Patients with a higher body mass index (BMI) (calculated as weight in kilograms divided by height in meters squared) have a higher risk of developing psoriasis. According to a nested case-control study of the United Kingdom General Practice Research Database,³ the OR for psoriasis is 1.11 in overweight patients and 1.38 in obese patients compared with patients with BMIs ranging from 20 to 25. In etanercept trials, 46% of 3700 subjects with moderate to severe psoriasis were obese vs 31% of all adults in the United States.⁶ The average BMI in phase 2 and 3 clinical trials on biologic agents involving more than 10 000 patients with moderate to severe psoriasis was 30.6, which is in the obese category.⁶ Obese patients with psoriasis are more likely to have more severe disease, a finding supported by data showing a significant association between extent of psoriasis and BMI.⁷ It has also been shown that a BMI higher than 25 is one of the factors associated with failure to improve at 5-year follow-up, regardless of therapy type.⁹

Psoriatic arthritis (PsA) affects 6% to 42% of patients with psoriasis.¹⁰ Some studies have shown the affected patients to have more extensive skin psoriasis lesions,¹¹⁻¹³ although PsA can affect patients with very limited or no skin involvement as well.¹¹⁻¹⁴ Psoriatic arthritis shares some clinical features with rheumatoid arthritis (RA), both leading to joint destruction and significant morbidity.¹⁵ For some time it has been appreciated that RA is as-

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Author Affiliations:
Department of Dermatology (Drs Soltani-Arabshahi, Feng, Goldgar, Callis Duffin, and Krueger) and College of Nursing (Dr Wong), University of Utah School of Medicine, Salt Lake City.

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Table 1. Demographic Features of the Study Population

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Valuea</th>
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<tbody>
<tr>
<td>Men</td>
<td>470/943 (49.8)</td>
</tr>
<tr>
<td>Women</td>
<td>473/943 (50.2)</td>
</tr>
<tr>
<td>Age at enrollment, mean (SD), y</td>
<td>47.89 (16.69)</td>
</tr>
<tr>
<td>Age at onset of psoriasis, mean (SD), y</td>
<td>27.17 (16.54)</td>
</tr>
<tr>
<td>Positive family history of psoriasis</td>
<td>593/941 (63)</td>
</tr>
<tr>
<td>Worst-ever BSA, mean (SD)</td>
<td>22.13 (27.82)</td>
</tr>
<tr>
<td>Worst-ever BSA &lt;5%</td>
<td>314/899 (34.9)</td>
</tr>
<tr>
<td>Worst-ever BSA 5%–10%</td>
<td>166/899 (18.5)</td>
</tr>
<tr>
<td>Worst-ever BSA &gt;10%</td>
<td>419/899 (46.6)</td>
</tr>
<tr>
<td>Psoriatic arthritis</td>
<td>250/929 (26.9)</td>
</tr>
<tr>
<td>Age at onset of PsA, mean (SD), y</td>
<td>37.09 (14.66)</td>
</tr>
<tr>
<td>BMI at enrollment, mean (SD)</td>
<td>28.91 (7.08)</td>
</tr>
<tr>
<td>BMI at enrollment &lt;25</td>
<td>282/908 (31.1)</td>
</tr>
<tr>
<td>BMI at enrollment 25 to &lt;30</td>
<td>304/908 (33.5)</td>
</tr>
<tr>
<td>BMI at enrollment ≥30</td>
<td>322/908 (35.5)</td>
</tr>
<tr>
<td>BMI at age 18 y, mean (SD)</td>
<td>22.32 (4.18)</td>
</tr>
<tr>
<td>BMI at age 18 y &lt;25</td>
<td>728/800 (80.9)</td>
</tr>
<tr>
<td>BMI at age 18 y 25 to &lt;30</td>
<td>127/000 (14.1)</td>
</tr>
<tr>
<td>BMI at age 18 y ≥30</td>
<td>450/000 (50)</td>
</tr>
<tr>
<td>Smoking</td>
<td>345/943 (36.6)</td>
</tr>
<tr>
<td>Nail involvement</td>
<td>561/943 (59.5)</td>
</tr>
<tr>
<td>Koebner phenomenon</td>
<td>383/943 (40.6)</td>
</tr>
</tbody>
</table>

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); BSA, affected body surface area; PsA, psoriatic arthritis.
aUnless otherwise indicated, data are reported as number of patients in the reported category/number of patients overall (percentage).

DESCRIPTION OF THE STUDY PATIENTS

Patients enrolled in the Utah Psoriasis Initiative (UPI) from November 2002 to October 2008 (943 subjects; 50.2% women, 49.8% men) were included in the study (Table 1). Psoriatic arthritis was present in 250 patients with psoriasis (26.5%) (Figure 1). The mean (SD) age at the onset of psoriasis was 27.17 (16.54) years, and for PsA, 37.09 (14.66) years, with the risk increasing linearly over time. Psoriasis preceded PsA in 78.9% of the patients; PsA and psoriasis appeared at the same time in 11.2%; and PsA preceded psoriasis in 9.9%. All 3 groups were included in the study.

VARIABLES AFFECTING RISK OF DEVELOPING PsA

In the first block, variables that were predictors of PsA included younger age at psoriasis onset (OR, 0.98)
(P < .01), female sex (OR, 1.45) (P = .01), higher worst-ever body surface area involvement with psoriasis (OR, 1.01) (P = .04), Koebner phenomenon (OR, 1.59) (P < .01), and nail involvement (OR, 1.76) (P < .01). Current BMI and family history of psoriasis were not significant predictors of PsA (Table 2).

In the second block, BMI at age 18 years and BMI at enrollment were introduced into the model. Higher reported BMI at age 18 years was associated with increased risk of PsA (OR, 1.06) (P < .01) independent of the control variables mentioned in the first block, while current BMI was not associated with the risk of PsA (OR, 0.99) (P = .20).

At age 18 years, 14.1% of patients were considered overweight, and 5% were considered obese based on their retrospective self-reported height and weight. At the time of enrollment (mean [SD] patient age, 47.89 [16.69] years), 33.5% were overweight and 35.5% were obese. To illustrate the effect of obesity on PsA, Kaplan-Meier curves were developed for 3 categories of BMI at age 18 years (normal, overweight, and obese). Figure 2 shows the obese group having an earlier onset of PsA, followed by the overweight group, and finally the normal BMI group. Twenty percent of the overweight or obese group developed PsA by age 35 years. In the normal BMI group, 20% of the subjects developed PsA by age 48 years (χ² = 14.36, P < .01).

PHENOTYPIC CHARACTERISTICS OF OVERWEIGHT AND OBESITY IN PATIENTS WITH PSORIASIS

Our research group previously showed that patients with psoriasis in the UPI who had a higher BMI also had a larger BSA covered with psoriasis.19 Severe psoriasis was defined a worst-ever BSA of 10% or more. These facts, in addition to the finding that obesity was a risk factor for PsA over and above other clinical features such as nail disease and higher BSA, prompted an assessment of the clinical characteristics associated with higher BMI in our cohort (Table 3). Female patients enrolled in the UPI tended to have a normal BMI at age 18 years, and male patients tend to report BMIs in the overweight or obese category at age 18 years (P < .01). There was no significant association between BMI at age 18 years and family history of psoriasis. Patients who were overweight or obese at age 18 years were more likely to report severe psoriasis (56.8% for obese vs 46.6% for overweight vs 38.7% for normal weight) (P = .02). The reported frequency of Koebner phenomenon tended to increase in overweight and obese patients, although the increase was not statistically significant (P = .36). Also, plaque thickness and plaque size tended to increase with BMI at age 18 years, but the difference did not reach statistical significance (P = .28 for thickness and P = .12 for size).

In the present study, we have built models that include clinical risk factors for development of PsA in patients with psoriasis. According to our first model, patients with younger age at onset of psoriasis, more severe psoriasis, nail lesions, and positive Koebner phenomenon are more prone to develop PsA. While some studies have pro-

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Table 2. Hierarchical Cox Regression Model Predicting Time to Developing PsA

<table>
<thead>
<tr>
<th>Analysis Characteristic</th>
<th>OR (95% CI)</th>
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<tbody>
<tr>
<td>Block 1 (χ² change, 85.15)&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Age at psoriasis onset</td>
<td>0.98&lt;sup&gt;a&lt;/sup&gt; (0.96-0.98)</td>
</tr>
<tr>
<td>Family history of psoriasis</td>
<td>0.84 (0.62-1.15)</td>
</tr>
<tr>
<td>Female sex</td>
<td>1.45&lt;sup&gt;b&lt;/sup&gt; (1.09-1.94)</td>
</tr>
<tr>
<td>Severity, worst-ever BSA</td>
<td>1.01&lt;sup&gt;b&lt;/sup&gt; (1.00-1.01)</td>
</tr>
<tr>
<td>Nail involvement</td>
<td>1.76&lt;sup&gt;c&lt;/sup&gt; (1.25-2.47)</td>
</tr>
<tr>
<td>Koebner phenomenon</td>
<td>1.59&lt;sup&gt;c&lt;/sup&gt; (1.17-2.14)</td>
</tr>
<tr>
<td>Block 2 (χ² change, 8.72)&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>BMI at age 18 y</td>
<td>1.06&lt;sup&gt;c&lt;/sup&gt; (1.02-1.10)</td>
</tr>
<tr>
<td>BMI today</td>
<td>0.99 (0.96-1.01)</td>
</tr>
</tbody>
</table>

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); BSA, affected body surface area; CI, confidence interval; OR, odds ratio; PsA, psoriatic arthritis.

<sup>a</sup>P < .001.  
<sup>b</sup>P < .05.  
<sup>c</sup>P < .01.

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Figure 1. Time-to-event curve for development of psoriatic arthritis (PsA) in the study population.

Figure 2. Time-to-event curve for development of psoriatic arthritis (PsA) based on body mass index (BMI) (calculated as weight in kilograms divided by height in meters squared) at age 18 years in the study population.
posed a positive correlation between the severity of skin disease and the risk of PsA, others have not found any association between skin lesions and activity, severity, and functional status of the arthritis.21 Psoriatic nail lesions are seen more frequently in patients with PsA, the frequency being 40% to 45% in uncomplicated forms of psoriasis, and more frequently in patients with PsA, the frequency being 40% to 45% in uncomplicated forms of psoriasis and 87% in PsA.15 The observed association between Koebner phenomenon and PsA in our study could be explained by the microtrauma theory, which proposes that the ligament and tendon insertion points are subject to repeated microtrauma and that this contributes to development of PsA.22 Microtrauma theory could be the equivalent of Koebner phenomenon in the skin. Similarly, microtrauma to the nail unit could lead to psoriatic nail changes. Patients with active disease are more prone to showing a positive isomorphic response in the skin (Koebner phenomenon), nail (psoriatic nail changes), and joints (PsA).

We found a significant association between lower age at onset of psoriasis and risk of developing PsA, similar to the known association between lower age at psoriasis onset and severity of disease. Patients with a younger age at onset of psoriasis may have a different burden of genes or different types of triggers that put them at increased risk for PsA. Furthermore, a lower age at onset of psoriasis means that the autoimmune inflammatory cascade driving psoriasis has been in effect for a longer period and could push the genetically predisposed patient to be at an increased risk for PsA.

The present study suggests that increased BMI in early adulthood increases the risk of PsA in patients with psoriasis and is independent of other risk factors. Each unit increase in BMI at age 18 years was associated with a 5.3% increase in the risk of PsA. Thus, patients who report having been obese at age 18 years are 3 times more likely to develop PsA in the course of their psoriasis than patients with normal BMI at age 18 years. These results coincide with findings of a previous study showing that patients with PsA are more likely to have a BMI higher than 25 than controls (72.5% vs 53.6%) (P < .01).23 Obese patients are at especially higher risk for PsA if they have other risk factors, including early onset of psoriasis, nail involvement, and positive Koebner phenomenon. These data support a growing concept that patients more prone to PsA might benefit from more frequent and meticulous screening measures for early detection and treatment of PsA, ie, before the development of irreversible joint destruction.

Previously, our group19 reported that the prevalence of obesity in the UPI is higher than in the general population in Utah. This retrospective patient-reported assessment of body image before and after development of psoriasis suggested that obesity usually followed, rather than preceded, psoriasis, implying that psoriatic inflammation contributed to the obese state. However, the Nurses’ Health Study II (NHSII),24 which prospectively examined the relationships between BMI, weight change, waist circumference, hip circumference, waist-hip ratio, and incident psoriasis in 78,626 women over a 14-year period, found a graded positive association between BMI measured at multiple time points and the risk of incident psoriasis, which suggests that obesity is a risk factor for future development of psoriasis.

The design of our study did not allow us to confirm a causal relationship between obesity and PsA. Furthermore, if a causal relationship exists, the direction is not known. The same dilemma remains to be solved regarding the association between obesity and psoriasis.

In one possible sequence, PsA might predispose patients to obesity. Patients might reduce their physical activity because of social embarrassment and depression caused by PsA and/or the associated joint pain. Our group19 previously showed that obese patients in the UPI were less likely than nonobese patients to engage in physical activity at least 2 or 3 times a week for more than 30 minutes at.
a time. Obese patients were more likely to report that arthritis impeded their physical activity. Also, patients with PsA in the UPI had a higher prevalence of mood disturbances, especially depression, than patients with no evidence of arthritis (prevalence of depression, 26.6% vs 18.7%) (P = .02), and the presence of depression or other mood disturbances could decrease physical activity and fitness. In this sequence of events, PsA would precede obesity.

In the other sequence, obesity would precede PsA. In the present study, the mean (SD) age at onset of PsA was 37.09 (14.66), and the association with obesity was focused on BMI at age 18 years, ie, 2 decades before the mean age at onset of PsA. This sequence suggests that at least in some cases, obesity preceded PsA and might have acted as a predisposing factor to the condition.

A very plausible link between obesity and PsA is the chronic inflammatory state in obese subjects. It has been repeatedly observed that expansion of adipose tissue during weight gain is associated with recruitment of inflammatory macrophages through chemokines such as CC-chemokines ligand 2 (CCL2). Adipocytes and recruited macrophages produce cytokines such as tumor necrosis factor (TNF) and interleukin 6 (IL-6) and adipokines such as adiponectin, leptin, and resistin, which are thought to be associated with obesity, insulin resistance, and related inflammatory disorders. 1,25 Adiponectin is primarily anti-inflammatory, and leptin and resistin are proinflammatory. 26 The effect of leptin on naive and adaptive immunity could potentially be responsible for worsening of psoriasis. Leptin acts on naive T cells, increasing their IL-2 secretion and proliferation. It also increases interferon-γ production by memory T cells. 27 More interestingly, leptin inhibits the proliferation of regulatory T cells, which were recently found to be defective in function in psoriasis. 28 In case-control studies, serum leptin levels 29-31 and tissue leptin and leptin receptor expression 29 were significantly higher in patients with severe psoriasis than in those with mild to moderate psoriasis and controls. Serum leptin levels showed a positive correlation with the Psoriasis Area Severity Index (PASI). 29 In vitro, leptin and resistin could induce CXCL8 and TNF production by blood monocytes, both of which are implicated in the pathogenesis of psoriasis. In addition, leptin could induce IL-1β and IL-1 receptor antagonist production and secretion of amphiregulin, which in ex vivo–cultured lesional psoriasis skin upregulates epidermal proliferation. 32 Serum levels of adiponectin are lower in patients with psoriasis than in controls and inversely correlate with PASI score. 33 These observations argue for obesity and its associated inflammatory cytokines as adding to genetic susceptibility factors, perhaps increasing the probability of expression of both psoriasis and PsA.

Psoriatic arthritis has several features in common with RA. Both diseases are associated with an increased cardiovascular risk. 33,34 However, there are important differences between PsA and RA. Although RA is also associated with increased prevalence of cardiovascular risk factors including obesity, severe disease is associated with lower BMI. 18,19 In psoriasis, however, severe disease is associated with higher BMI.

A possible link between obesity and psoriasis and/or PsA could be driven by a genetic variation that predisposes the patients to both conditions. Several recent genome-wide association studies have revealed an association of genes (eg, FTO, INSIG2, MTRMR9, MCR4, SLC6A14, GAD2, ENPP1) with obesity. It is not known whether these genetic variations are seen more frequently in patients with psoriasis. A small study of 109 patients with psoriasis and 125 healthy controls did not show any association between G-2548A polymorphism of the leptin gene and psoriasis in a Turkish population. 35 Further studies are needed to investigate a genetic relationship between obesity and psoriasis and/or PsA.

There are several limitations to our study. First, the diagnosis of PsA in all participants was self-reported as having been diagnosed by a rheumatologist. We did not have a rheumatologist independently confirm the diagnosis; however, all patients were seen by dermatologists trained in assessing PsA, and equivocal cases were excluded from the study. Second, no data were collected on disease severity, joints affected, or subclassification of PsA. Furthermore, BMI at age 18 years was based on self-reported height and weight data and was not directly measured in the study. Patients might have underestimated or overestimated their weight at age 18 years. However, we believe that this bias nondifferentially affects patients with and without PsA and is unlikely to have distorted the association between PsA and BMI.

In summary, the present findings suggest that the presence of obesity at age 18 years increases the risk of developing PsA later in life. This increased risk is over and above other risk factors for PsA, including younger age at onset of psoriasis, having more severe psoriasis based on the worst-ever BSA involved, Koebner phenomenon, and nail involvement. Evaluation of additional sample sets in an attempt to replicate these results is imperative for strong conclusions to be drawn. Prospectively enrolled databases of patients with psoriatic disease with detailed clinical information, including rheumatologic examination, are needed to confirm these data.

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Correspondence: Razieh Soltani-Arabshahi, MD, Department of Dermatology, 4A330, University of Utah School of Medicine, 30 North 1900 East, Salt Lake City, UT 84132 (razi.soltani@hsc.utah.edu).

Author Contributions: Drs Soltani-Arabshahi, Wong, Callis Duffin, and Krueger had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Soltani-Arabshahi and Wong. Acquisition of data: Soltani-Arabshahi and Wong. Analysis and interpretation of data: Soltani-Arabshahi, Wong, Feng, Goldgar, Callis Duffin, and Krueger. Drafting of the manuscript: Soltani-Arabshahi and Wong. Critical revision of the manuscript for important intellectual content: Soltani-Arabshahi, Wong, Feng, Goldgar, Callis Duffin, and Krueger.

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