ORIGINAL INVESTIGATION

Obesity, Waist Circumference, Weight Change, and the Risk of Psoriasis in Women

Nurses' Health Study II

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Background: Psoriasis is a common, chronic, inflammatory skin disorder. Higher adiposity may increase the risk of psoriasis, but, to our knowledge, no prospective data are available on this relationship.

Methods: We prospectively examined the relationships between body mass index (BMI [calculated as weight in kilograms divided by height in meters squared]), weight change, waist circumference, hip circumference, waist-hip ratio, and incident psoriasis in 78 626 women over a 14-year period (1991-2005) in the Nurses' Health Study II. The primary outcome was incident, self-reported, physician-diagnosed psoriasis.

Results: During the 14 years of follow-up, there were 892 self-reported incident cases of psoriasis. There was a graded positive association between BMI measured at multiple time points and the risk of incident psoriasis. When we analyzed BMI updated every 2 years, compared with a BMI of 21.0 through 22.9, the multivariate relative risks of psoriasis were 1.40 (95% confidence interval [CI], 1.13-1.73) for a BMI of 25.0 through 29.9; 1.48 (95% CI, 1.15-1.91) for a BMI of 30.0 through 34.9; and 2.69 (95% CI, 2.12-3.40) for a BMI of 35.0 or greater (P for trend, $<.001$). For BMI at the age of 18 years, the multivariate relative risk for the top BMI category (≥ 30.0) was 1.73 (95% CI, 1.24-2.41) and that for a lower BMI category (<21.0) was 0.76 (95% CI, 0.65-0.90) (P for trend, $<.001$). Weight gain from the age of 18 years, higher waist circumference, hip circumference, and waist-hip ratio were all associated with a higher risk of incident psoriasis (all P values for trend, $<.001$).

Conclusion: This large prospective study indicates that increased adiposity and weight gain are strong risk factors for incident psoriasis in women.

Arch Intern Med. 2007;167(15):1670-1675

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PSORIASIS IS A CHRONIC, INflammatory disease of the skin that affects approximately 2% of the population[1-4] and poses a lifelong burden for those affected.[3] A survey by the National Psoriasis Foundation found that 75% of patients with psoriasis reported a moderate to large negative impact of the disease on the quality of their life, with an alteration of everyday activities.[5] The negative impact of psoriasis may not be limited to its cutaneous or psychosocial manifestations. A recent large cohort study based on the General Practice Research Database in the United Kingdom found psoriasis to be an independent risk factor for myocardial infarction.[6] Higher adiposity may increase the risk of psoriasis, but, to our knowledge, no prospective data are available. Clinicians have observed the association between obesity and psoriasis for years; several recent studies have confirmed a cross-sectional association between the two.[7,8] For example, the prevalence of obesity in the patients with psoriasis in the Utah Psoriasis Initiative study was approximately twice that in the general population (34% vs 18%; $P<.001$).[7] An Italian case-control study found a similar association.[9] Overproduction of inflammatory cytokines such as tumor necrosis factor α (TNF-α), interleukin (IL)-1, IL-6, and IL-8 in adipose tissue is an important feature of obesity and may account for the pathogenesis of psoriasis.[4,10] The state of obesity was speculated to provide a chronic level of low-grade inflammation that not only may contribute to the risk of psoriasis but also may account for its severity.[10] Given the growing epidemic of obesity[11] in recent years and its associated negative health effects,[12,13] an accurate understanding of the impact of adiposity on psoriasis is important from the public health perspective as

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well as for comprehensive management of the condition. To address these issues, we prospectively evaluated the relationship between BMI (calculated as weight in kilograms divided by height in meters squared), weight change, waist circumference, hip circumference, waist-hip ratio, and incident psoriasis in a cohort of 78 626 women with no history of psoriasis.

METHODS

STUDY POPULATION

The Nurses' Health Study II is an ongoing longitudinal study of 116 608 female registered nurses from 15 US states who were between the ages of 25 and 42 years in 1989. The cohort is followed up with biennial questionnaires. The follow-up rate exceeds 90% for each 2-year period. In 2005, we asked participants if they had ever received a physician diagnosis of psoriasis and, if so, the date of the diagnosis. Of the 79 722 participants for whom we have data, 1096 with prevalent psoriasis that occurred before 1991 were excluded. We started follow-up in 1991 because it is the year for which we have corresponding information regarding smoking and alcohol status.

ASSESSMENT

Information on weight, height, and weight at the age of 18 years was obtained from the 1989 questionnaire. Participants then reported their current weight on the biennial mailed questionnaires. We analyzed the impact of BMI measured at multiple time points (age 18 years, baseline, and updated every 2 years during follow-up). Waist and hip circumference were reported in 1993. Weight change since the age of 18 years was calculated by subtracting the baseline or current weight (updated biennially) from the weight at age 18. The accuracy of self-reported anthropometric measures was evaluated among 140 Nurses' Health Study I participants by having trained technicians visit those participants twice.[14] After adjustment for age and within-person variability, the Pearson correlation coefficient between self-report and the average of the 2 technician measurements was 0.98 for weight, 0.91 for waist circumference, and 0.87 for hip circumference.[14]

The end point of the current study was a self-reported, physician diagnosis of incident psoriasis. The baseline and biennial follow-up questionnaires asked about smoking status and alcohol intake. The reproducibility and validity of this questionnaire for alcohol intake have been previously documented in the Nurses' Health Study cohort.[15]

STATISTICAL ANALYSIS

We computed person-time of follow-up for each participant from the return date of the 1991 questionnaire to the date of diagnosis of psoriasis or the end of the study period, whichever came first. We used Cox proportional hazards models to estimate the multivariate relative risk (RR) of incident psoriasis. We classified BMI at baseline and at each questionnaire cycle into 6 categories (<21.0, 21.0-22.9, 23.0-24.9, 25.0-29.9, 30.0-34.9, and ≥35.0). The World Health Organization classifies the last 3 categories as overweight, obesity class I, and obesity class II, respectively.[16] We combined the top 2 categories for BMI at the age of 18 years, as the number of subjects in these categories was small at that age. Weight change was analyzed in 5 categories (>−5 lb, −5.0 to +4.9 lb, +5.0 to +19.9 lb, +20.0 to +34.9 lb, and ≥ +35 lb). We categorized waist circumference into 5 categories (<31.0 in, 31.0-33.9 in, 34.0-36.9 in, 37.0-40 in, and >40.0 in). Hip circumference and waist-hip ratios were categorized in quintiles. Multivariate models were adjusted for age (continuous), smoking status (never, current, or past smokers), and alcohol intake (7 categories: none, 1-4 g/d, 5-9 g/d, 10-14 g/d, 15-29 g/d, 30-49 g/d, and ≥50 g/d). Weight change from the age of 18 years was also adjusted for weight at age 18; waist circumference, hip circumference, and waist-hip ratio were also adjusted for height. Linear trends in these adiposity measures were assessed in the models by using the median values for each category to minimize the influence of outliers. Examination of log-log survival curves for each of the variables in our model demonstrated that assumptions of proportional hazards were met. We explored potential interactions by age group (<30, 30-39, and ≥40 years) by testing the significance of interaction terms added to our final multivariate models. We calculated the population-attributable risk, an estimate of the percentage of psoriasis cases in this population that would theoretically not have occurred if the BMI had been lower than 25, assuming a causal relationship between BMI and incident psoriasis. For all RRs, we calculated 95% confidence intervals (CIs). All *P* values are 2-sided. All statistical analyses were performed using SAS software, version 9.1 (SAS Institute Inc, Cary, North Carolina).

The Partners Health Care System (Boston, Massachusetts) institutional review board approved this study. Return of a completed questionnaire was accepted by the institutional review board as implied informed consent.

RESULTS

BASELINE CHARACTERISTICS

We studied a total of 78 626 women for a combined follow-up time of 1 085 658 person-years, during which there were 892 newly diagnosed cases of psoriasis. The incidence rate of psoriasis was 82 per 100 000 person-years (95% CI, 77-89 per 100 000 person-years). The baseline characteristics of the cohort according to BMI are shown in **Table 1**. As expected, BMI, weight gain since age 18, waist and hip circumference, and waist-hip ratio varied in the same direction. With increasing category of BMI at baseline, women tended to be older and alcohol intake tended to decrease.

BMI AND INCIDENT PSORIASIS

We found a graded association between BMI measured at multiple time points (ie, updated every 2 years during follow-up, at baseline, and at age 18 years) and the risk of incident psoriasis (**Table 2**). When we analyzed BMI updated every 2 years, compared with women with a BMI of 21.0 to 22.9, the multivariate RRs of psoriasis were 1.40 (95% CI, 1.13-1.73) for a BMI of 25.0 to 29.9, 1.48 (95% CI, 1.15-1.91) for a BMI of 30.0 to 34.9, and 2.69 (95% CI, 2.12-3.40) for a BMI of 35.0 or greater (*P* for trend, <.001). At baseline, the corresponding multivariate RRs of psoriasis were 1.23 (95% CI 1.00-1.50), 1.73 (95% CI 1.36-2.20), and 2.23 (95% CI, 1.72-2.87) (*P* for trend, <.001). When we analyzed BMI at age 18 years, compared with a BMI of 21.0 to 22.9, the multivariate RR for a BMI of 30.0 or greater was 1.73 (95% CI, 1.24-2.41) (*P* for trend, <.001). Of note, there was no material difference in these multivariate RRs and RRs adjusted only

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Table 1. Baseline Characteristics According to BMI for Participants in Nurses' Health Study II in 1991[a]

Characteristic	BMI (Median)					
	<21.0 (19.9) (n = 20 124)	21.0-22.9 (22.0) (n = 18 577)	23.0-24.9 (23.9) (n = 13 823)	25.0-29.9 (26.6) (n = 15 786)	30.0-34.9 (31.9) (n = 6094)	≥35.0 (38.4) (n = 4095)
Age, y	34.9	35.5	35.9	36.1	36.5	36.8
Weight, lb	119.4	132.0	142.6	161.9	191.6	237.5
BMI at age 18 y	19.2	20.4	21.2	22.3	24.1	27.1
Weight gain since age 18 y, lb	3.5	9.8	16.6	28.7	47.9	76.3
Waist circumference, in	27.5	29.3	30.9	33.7	38.0	43.1
Hip circumference, in	36.3	38.1	39.5	42.0	45.8	51.3
Waist-hip ratio	0.76	0.77	0.78	0.81	0.83	0.84
Alcohol, g/d	3.7	3.6	3.3	2.8	2.0	1.6
Smoking status, %						
Never smoker	67.6	65.6	64.3	65.1	66.4	66.1
Previous smoker	20.8	23.3	24.0	22.5	21.9	22.8
Current smoker	11.4	11.0	11.5	12.3	11.6	11.0

Abbreviation: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared).
[a]Values are means unless otherwise noted.

Table 2. Relative Risk (RR) of Incident Psoriasis According to BMI Updated at Each Questionnaire, at Baseline, and at Age 18 Years

Variable	BMI						*P* Value for Trend
	Updated						
	<21.0	21.0-22.9	23-24.9	25.0-29.9	30.0-34.9	≥35.0	
Cases of psoriasis	97	133	142	237	115	156	. . .
Person-years	194 161	214 704	189 799	263 776	118 972	89 809	. . .
Multivariate RR (95% CI)[a]	0.81 (0.63-1.06)	1 [Reference]	1.19 (0.94-1.51)	1.40 (1.13-1.73)	1.48 (1.15-1.91)	2.69 (2.12-3.40)	<.001
	Baseline						
	<21.0	21.0-22.9	23.0-24.9	25.0-29.9	30.0-34.9	≥35.0	
Cases of psoriasis	159	184	158	194	105	90	. . .
Person-years	278 467	256 681	190 864	217 731	83 924	56 245	. . .
Multivariate RR (95% CI)[a]	0.80 (0.65-0.99)	1 [Reference]	1.14 (0.92-1.41)	1.23 (1.00-1.50)	1.73 (1.36-2.20)	2.23 (1.72-2.87)	<.001
	At Age 18 y						
	<21.0	21.0-22.9	23.0-24.9	25.0-29.9	≥30.0[b]		
No. of cases	433	225	107	77	42		. . .
Person-years	617 857	240 535	110 928	82 063	24 926		. . .
Multivariate RR (95% CI)[a]	0.76 (0.65-0.90)	1 [Reference]	1.02 (0.81-1.28)	0.97 (0.75-1.25)	1.73 (1.24-2.41)		<.001

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); CI, confidence interval.
[a]The multivariate adjusted model includes age, alcohol consumption, and smoking status.
[b]The number of women with a BMI of 35.0 or higher was insufficient to evaluate the category separately; therefore, this category was combined with a BMI of 30.0 to 34.9.

for age. Similarly, there was no difference in the RRs of the other adiposity measures evaluated in this study. The graded associations persisted across the age groups (<30 years, 30-39 years, and ≥40 years) and there was no significant interaction (*P* for interaction, >.20).

In contrast, a lower BMI (<21.0) was associated with a lower risk of incident psoriasis (Table 2). This inverse association was most apparent with BMI at the age of 18 years, the category with the largest person-time among the 3 BMI measures (multivariate RR for BMI <21.0 at age 18, 0.76 [95% CI, 0.65-0.90]). A graded inverse association was further observed within the lowest BMI category (multivariate RRs, 0.79 [95% CI, 0.67-0.94] for a BMI of 18.5-20.9 and 0.67 [95% CI, 0.53-0.85] for a BMI of <18.5 [underweight category according to the World Health Organization[16]]). A significant inverse association was also seen with a BMI of less than 21.0 at baseline (multivariate RR, 0.80 [95% CI, 0.65-0.99]) (Table 2).

WAIST AND HIP CIRCUMFERENCE, WAIST-HIP RATIO, AND INCIDENT PSORIASIS

There was a graded association between waist and hip circumference and the risk of incident psoriasis (**Table 3**). Compared with a waist circumference of less than 31 in, the multivariate RR of psoriasis for a waist circumference of greater than 40 in was 2.28 (95 CI%, 1.57-3.32; *P* for trend, <.001). A higher waist-hip ratio was associated with an increasing risk of incident psoriasis (*P* for trend, <.001), suggesting a larger contribution of waist circumference than hip circumference to the risk of incident psoriasis.

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Table 3. Relative Risk (RR) of Psoriasis According to Waist Circumference, Hip Circumference, and Waist-Hip Ratio

Variable	Waist Circumference, in					*P* Value for Trend
	<31.0	31.0-33.9	34.0-36.9	37.0-40.0	>40.0	
Cases of psoriasis	159	65	46	32	34	. . .
Person-years	274 153	83 540	48 435	30 875	24 809	. . .
Multivariate RR (95% CI)[a]	1 [Reference]	1.32 (0.99-1.77)	1.59 (1.14-2.21)	1.73 (1.18-2.53)	2.28 (1.57-3.32)	<.001
	Hip Circumference, Quintiles					
	≤36.0	36.1-37.9	38.0-39.4	39.5-42.0	>42.0	
Cases of psoriasis	51	47	66	70	100	. . .
Person-years	100 618	79 731	91 909	98 402	89 998	. . .
Multivariate RR (95% CI)[a]	1 [Reference]	1.18 (0.79-1.75)	1.45 (1.01-2.10)	1.42 (0.99-2.05)	2.22 (1.57-3.12)	<.001
	Waist-Hip Ratio, Quintiles					
	0.47-0.72	0.73-0.75	0.76-0.78	0.79-0.83	0.84-1.56	
Cases of psoriasis	60	53	55	74	92	. . .
Person-years	96 318	89 873	86 191	98 633	89 026	. . .
Multivariate RR (95% CI)[a]	1 [Reference]	0.94 (0.65-1.36)	1.01 (0.70-1.45)	1.16 (0.83-1.63)	1.57 (1.13-2.17)	<.001

Abbreviation: CI, confidence interval.
[a]The multivariate adjusted model included age, alcohol consumption, smoking status, and height.

Table 4. Relative Risk (RR) of Psoriasis According to Weight Change From the Age of 18 Years

Variable	Weight Change Between Age 18 y and Baseline, lb					*P* Value for Trend
	< –5.0	–5.0 to +4.9	+5.0 to + 19.9	+20.0 to +34.9	+35.0	
Cases of psoriasis	60	108	246	172	252	. . .
Person-years	83 970	150 591	355 229	214 957	214 811	. . .
Multivariate RR (95% CI)[a]	0.85 (0.61-1.17)	1 [Reference]	1.00 (0.80-1.25)	1.12 (0.88-1.43)	1.54 (1.22-1.94)	<.001
	Weight Change Between Age 18 y and Updated Follow-up, lb					
	< –5.0	–5.0 to +4.9	+5.0 to + 19.9	+20.0 to +34.9	+35.0	
Cases of psoriasis	37	64	197	178	398	. . .
Person-years	61 909	114 038	298 051	240 659	349 528	. . .
Multivariate RR (95% CI)[a]	0.91 (0.60-1.37)	1 [Reference]	1.24 (0.93-1.64)	1.35 (1.01-1.80)	1.88 (1.44-2.46)	<.001

Abbreviation: CI, confidence interval.
[a]The multivariate adjusted model included age, alcohol consumption, smoking status, and weight at the age of 18 years.

WEIGHT CHANGE AND INCIDENT PSORIASIS

As reflected in the person-year totals under weight-change categories in **Table 4**, most women experienced weight gain from the age of 18 years, whereas fewer than 10% of the women lost weight. There was a graded association between weight change since age 18 and the risk of psoriasis (Table 4). After adjustment for covariates and weight at age 18, compared with women who maintained weight (–5.0 to +4.9 lb), the RR of incident psoriasis for a weight gain of greater than or equal to 35 lb between age 18 and weight updated every 2 years was 1.88 (95% CI, 1.44-2.46; *P* for trend, <.001) (Table 4).

POPULATION-ATTRIBUTABLE RISK

In our cohort, 30% of the incident psoriasis cases were attributable to a BMI of 25.0 or greater (overweight). For women with a BMI of 30.0 or greater (obesity class I)[16] and a BMI of 35.0 or greater (obesity class II),[16] 50% and 63%, respectively, of psoriasis risk was attributable to excess weight.

COMMENT

Our objective was to prospectively evaluate the relationship between adiposity and incidence of psoriasis in a large prospective cohort of women. We found that multiple measures of adiposity, such as BMI, waist and hip circumference, and waist-hip ratio, along with change in adiposity as assessed by weight gain since the age of 18 years, were substantial risk factors for the development of incident psoriasis. The risk increased with increasing levels of adiposity, demonstrating a strong, consistent dose-response relationship. In contrast, a BMI of less than 21.0 was associated with a lower risk of incident psoria-

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sis, further supporting the link between adiposity and the risk of incident psoriasis. The current study provides the first prospective evidence that increased adiposity is a strong risk factor for incident psoriasis.

Previous cross-sectional studies and case-control studies have consistently suggested a significant link between increased adiposity and psoriasis. An inpatient series based on a Swedish population found that women with psoriasis had a higher prevalence of obesity ($P < .001$).[17] A recent case-control study involving 560 patients with newly diagnosed psoriasis and 690 controls found that the prevalence of psoriasis was approximately twice as high in individuals with a BMI of 30 or greater compared with a BMI of less than 26 (multivariate odds ratio, 1.9; 95% CI, 1.2-2.8).[9] Similarly, the prevalence of obesity in the patients with psoriasis enrolled in the Utah Psoriasis Initiative study was nearly twice as high as that in the general population (34% vs 18%; $P < .001$).[7] However, the patients with psoriasis who were enrolled in that hospital-based case series (median age at enrollment, 50 years) reported a normal median value of body image score at age 18 and at the onset of psoriasis (median age, 25 years) based on patients' retrospective recall. The case-series study design by its nature does not have an internal comparison group without psoriasis to allow a direct comparison between these adiposity variables at early ages and the risk of incident psoriasis. Because most individuals gain weight from their early adult years regardless of the presence of psoriasis, as also reflected in our data, it is critical to have an appropriate comparison group to accurately assess the role of adiposity in the early adult years. While previous cross-sectional studies left uncertainty regarding the temporal relationship between obesity and psoriasis,[7,18] our prospective longitudinal data indicate that increased adiposity precedes the occurrence of new cases of psoriasis. Furthermore, potential biased recall of adiposity was avoided in this study because the adiposity data were collected before the data on incident psoriasis.

The chronic, low-grade inflammatory state associated with adiposity may explain the increased risk of incident psoriasis among obese individuals. Overproduction of inflammatory cytokines such as TNF-α, IL-1, IL-6, and IL-8 in adipose tissue is an important feature of obesity and may account for the pathologic changes seen in psoriasis.[4,10] It has been observed that the white adipose tissue of obese rodents and humans is subject to macrophage infiltration and that the infiltrate increases in proportion to BMI and adipocyte hypertrophy.[19-21] These proinflammatory factors may play an important role in the pathogenesis of psoriasis. Also, the satiety hormone leptin has been shown to elicit multiple immunoregulatory effects, including the promotion of T-cell proliferation and the stimulation of TNF-α production in the adipose tissue. Therefore, leptin may serve as an additional link between obesity and risk of psoriasis.[10]

Conversely, weight loss may be an important target for prevention and management of psoriasis.[10,21] Weight loss may decrease the degree of obesity-induced inflammation by lowering the level of circulating inflammatory cytokines and macrophage infiltration in white adipose tissue depots.[22,23] For example, weight loss as a result of surgical intervention in obese subjects was associated with a reduction in the number and modified distribution of macrophages in the subcutaneous white adipose tissue.[23] Furthermore, weight loss as a result of lifestyle modifications was associated with a decrease in concentrations of TNF-α, IL-6, IL-8, C-reactive protein, and monocyte chemoattractant protein 1.[22] This reduction in the inflammatory components may be translated to a reduced risk and severity of psoriasis. Indeed, there are case reports of complete remission of severe psoriasis with the discontinuation of all psoriasis medications after substantial weight loss occurred as a result of gastric bypass surgery.[24,25] Notably, the patients involved did not experience any periods of remission in psoriasis for the entire disease duration (ie, 15 years[24] and 39 years[25]) before the surgery. Beyond the potential effect on psoriasis, reducing obesity would lead to a better overall clinical outcome in patients with psoriasis, who often suffer comorbidities related to their obese state.[10,26]

There are several strengths and limitations of our study. To our knowledge, it is the largest, prospective assessment of multiple markers of adiposity in relation to the risk of psoriasis. The measures of body size used were self-reported; however, these measures have been validated and their accuracy has been demonstrated.[14] While the onset of psoriasis was also self-reported, the data have not been validated. However, the consistency of the association with multiple different prior time points, including study baseline and age 18 years, argues for the validity of our findings. Similar to other population-based epidemiological studies of psoriasis, we did not clinically confirm the nurses' self-reported physician-diagnosis of psoriasis with an examination by a dermatologist.[3,27,28] A recent French study on a non–health professional population reported that the agreement between self-reported and dermatologists' diagnoses of psoriasis was moderate, although it was the second best among 5 common skin disorders.[29] While we expect the overall accuracy of self-reported physician-diagnosis of psoriasis to be higher among registered nurses, as was the case with other health data in our cohort, the corresponding accuracy against a dermatologist's examination is not available. However, when we also adjusted for comorbidities associated with increased adiposity, such as type 2 diabetes mellitus, hypertension, and cardiovascular disease, our results did not change materially. These data suggest that these comorbidities of obesity did not contribute to an increased ascertainment of psoriasis among obese women in our cohort. Nonetheless, it would be valuable to confirm these results using more specific case definitions of psoriasis as well as to evaluate outcomes of psoriasis subtypes. Our multivariate results were not adjusted for family history of psoriasis because this information was not available in our cohort. Although this variable and other factors such as stressful life events were found to be risk factors for psoriasis in a case-control study, these factors did not confound the relationship between obesity and the risk of psoriasis in that study.[9] Similarly, a family history of psoriasis was not associated with obesity in early life in the Utah Psoriasis Initiative study.[7]

The restriction to registered nurses in our cohort is both a strength and a limitation. The cohort of well-

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educated women minimizes the potential for confounding associated with socioeconomic status, and we were able to obtain high-quality data, with minimal loss to follow-up. Although the absolute rates of psoriasis and frequency of obesity may not be representative of a random sample of US women, the biological effects of adiposity should be similar. Our findings would be most directly generalizable to white women with no history of psoriasis. Furthermore, between the reported bimodal peaks of psoriasis onset time (23 and 55 years),[30] the age range of our cohort during the follow-up tended to overlap more with the second peak incidence cases. Therefore, our results may be more applicable to the later-onset cases of psoriasis.

In conclusion, this prospective study suggests that increased adiposity and weight gain are strong risk factors for incident psoriasis in women. Weight loss may be a potential target for the prevention and management of psoriasis.

Accepted for Publication: April 2, 2007.
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Financial Disclosure: None reported.
Funding/Support: This study was supported in part by grant 5 T32 AR007258-29 from the National Institutes of Health and by Nurses' Health Study II grant CA50385.
Additional Contributions: We thank the participants in the Nurses' Health Study II for their dedication and continued participation, the entire staff of the Nurses' Health Study II, and Rong Chen for her assistance with programming.

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