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Obesity and risk of incident psoriatic arthritis in US women

Wenqing Li, PhD[1], **Jiali Han, PhD**[1,2,3], and **Abrar A. Qureshi, MD, MPH**[1,2]

[1]Department of Dermatology, Brigham and Women's Hospital and Harvard Medical School

[2]Channing Laboratory, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School

[3]Department of Epidemiology, Harvard School of Public Health

Abstract

Objectives—Both overall and central obesity has been associated with risk of psoriasis from prospective study. Data on the association between obesity and psoriatic arthritis (PsA) have been very sparse and no evidence on obesity measures and risk of incident PsA is available now. We aimed to evaluate the association between obesity and risk of incident PsA in a large cohort of women.

Methods—A total of 89,049 participants were included from the Nurses Health Study II over a 14-year time period (1991–2005). Information on BMI, weight change, and measures of central obesity (waist circumference, hip circumference, and waist-hip ratio) was collected during the follow-up. Incidence of clinician-diagnosed PsA was ascertained and confirmed by supplementary questionnaires.

Results—We identified 146 incident PsA cases during 1,231,693 person-years' follow-up. Among total participants, BMI was monotonically associated with an increased risk of incident PsA. Compared with BMI less than 25.0, the relative risk (RR) was 1.83 for BMI 25.0 through 29.9 (95% confidence interval (CI): 1.15–2.89), 3.12 for BMI 30.0 through 34.9 (95% CI: 1.90–5.11), and 6.46 for BMI > 35.0 (95% CI: 4.11–10.16). There was a graded positive association between weight change from age 18, measures of central obesity, and risk of PsA (*P* for trend <0.001). The analysis among participants developing psoriasis during follow-up revealed a similar association (*P* for trend <0.01), indicating an increased risk of PsA associated with obesity among psoriatics.

Conclusion—In this study we provide further evidence linking obesity with risk of incident PsA among U.S. women.

Corresponding author: Abrar A. Qureshi, MD, MPH, Assistant Professor, Harvard Medical School, Department of Dermatology, Brigham and Women's Hospital, 45 Francis St, 221L, Boston, MA 02115. aqureshi@bics.bwh.harvard.edu.

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Participants consent Obtained.

Ethics approval The institutional review board of Partners Health Care System approved this study.

Keywords

obesity; weight change; psoriatic arthritis; epidemiology

INTRODUCTION

Psoriatic arthritis (PsA) is a well-recognized co-morbidity of psoriasis and an inflammatory musculoskeletal condition occurring in 0.25% of the US population[1, 2]. Previous reports indicate that PsA leads to impaired quality of life due to joint damage and deformity, as well as an increased mortality[1]. Despite this major impact, there is little understanding of PsA risk factors, which limits prevention and early detection efforts.

A link between obesity and psoriasis and arthritis has been reported. Increased adiposity and weight gain have been associated with risk of psoriasis in a prospective study[3]. Obesity is a significant risk factor for osteoarthritis at sites throughout the body, especially the knee[4, 5]. The reports on obesity and rheumatoid arthritis (RA) have been conflicting and one study only observed increased risk of anti-cyclic citrullinated peptides-negative RA associated with obesity[6–8]. Data on obesity and PsA were sparse and no prospective studies are available[9, 10]. One study observed a higher body mass index (BMI) and waist-hip ratio (WHR) between PsA and healthy controls[9]. The other reported BMI at age 18 as a risk factor for PsA compared with psoriatics[10]. This study did not indicate current BMI as a risk factor. No data on BMI, central obesity, weight change and risk of PsA in a prospective design is available although we have reported an association between visceral obesity and weight change correlated with psoriasis[3]. Given the differential cutaneous phenotypes between psoriasis and PsA, as well as the conflicting evidence on obesity and arthritis, the association between adiposity measurements and risk of PsA deserves further examination in a prospective setting.

In this study, we prospectively investigated the association between BMI (BMI updated biennially during the follow-up, and BMI at age 18), weight change, waist circumference, hip circumference, WHR and incidence of PsA both among all participants and among women with psoriasis from the Nurses' Health Study II (NHS II).

METHODS

Study cohort

NHS II is an ongoing longitudinal cohort of women established in 1989 when 116,430 female nurses aged 25–42 responded to a mailed questionnaire enquiring about their medical history and lifestyle practices. Biennially, updated information on lifestyle factors and medical history was collected by mailed questionnaires. The follow-up rate exceeds 90%.

Assessment of main exposure

In 1989, participants responded to questions on their height, weight, and weight at the age 18 years. Weight was further recorded biennially thereafter. BMI was calculated as weight in kilograms divided by the square of height in meters (kg/m^2). Weight change since age 18

was obtained by deducting the weight at age 18 from the current weight. We asked participants to measure waist (measured at the umbilicus) and hip circumference (measured at the largest circumference) to the nearest quarter of an inch in 1993. The validation of self-reported anthropometric measurements was evaluated among 140 NHS participants. 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[11].

Assessment of main outcome (PsA)

In 2005, we asked participants on physician-diagnosed psoriasis and the diagnosis date. Of the 97,476 responders, 2,529 reported ever being diagnosed with psoriasis; of these, 1,151 self-reported psoriatics occurred since 1991. Psoriasis self-reports were confirmed by using the Psoriasis Screening Tool (PST), which has 99% sensitivity and 94% specificity[12]. This questionnaire was mailed to 1886 participants who self-reported psoriasis and responded to the 2007 main questionnaire. A diagnosis was validated if adhering to the scoring algorithms based on multiple *a priori* hypotheses. 1637 (87%) responded and 1511 (92%) was confirmed.

We confirmed the diagnosis of PsA by using the Psoriatic Arthritis Screening and Evaluation (PASE) questionnaire, which includes both symptom and function scales [13, 14]. A total score of ≥47 has been shown to identify PsA with high accuracy[13, 14]. We observed a positive association between PASE score and 28-joint Disease Activity Score (DAS 28) (personal communication, Enrique Soriano). PASE also has good test-retest precision and is sensitive-to-change to therapy[13]. Furthermore, PASE can distinguish between symptoms of PsA and osteoarthritis[14].

Assessment of covariates

Biennially from 1989, the smoking status and intensity among current smokers was assessed. Data on alcohol intake were available every four years since 1991. Physical activity was asked in 1991, 1997, 2001, and 2005, and a good validity and reproducibility was found [15]. Depressive symptoms were assessed with the Mental Health Index-5 in 1993, 1997, and 2001 which has been shown valid for major depression[16]. Participants reported regular antidepressant medication use biennially from 1993. Menopausal status and postmenopausal hormone use, personal history of cancer, diabetes, cardiovascular disease, hypertension and hypercholesterolemia was collected biennially.

Statistical analysis

Two set of analyses were performed to evaluate the risk of PsA associated with obesity among total participants, as well as among those with psoriasis. For all the main analyses, of the 97,476 responders, we excluded participants who did not respond to the psoriasis question in 2005 (N=58), prevalent psoriasis or PsA in 1991 (N=1,376), those unable to pass the confirmation of self-reports (N=97) or without response to the PST or PASE questionnaire (N=467), PsA with missing diagnosis date (N=2), and participants with BMI less than 10 or missing (N=6,334). For the analysis among total participants, we excluded incident psoriatics without musculoskeletal phenotypes in the previous follow-up period

(N=93); therefore 89,049 participants remained. For the analysis among psoriatics, we excluded participants who did not develop psoriasis (N=88,586), 556 with confirmed psoriasis remained. Because we excluded self-reported psoriasis cases that were not validated in the main analysis, we also performed a sensitivity analysis by using all self-reports.

We calculated person-years from the return date of 1991 questionnaire to the psoriasis diagnosis date, or the end of follow-up (June 2005), whichever came first. Information on BMI was categorized as <25.0, 25.0–29.9, 30.0–34.9, or ≥35.0, and updated during the follow-up. The cutoffs were consistent with the classification of World Health Organization on overweight, obesity class I and obesity class II. Given the distribution of subjects, BMI at age 18 was classified as <21.0, 21.0–22.9, 23.0–24.9, 25.0–29.9, or ≥30.0. Weight change was classified as four categories (loss or increase of <20.0, 20.0–49.9, 50.0–99.9, or ≥100.0 lbs). We analyzed waist circumference, hip circumference, and WHR in tertiles. Cox proportional hazards analysis stratified by age and follow-up interval was performed to calculate the age and multivariate-adjusted relative risk (RR) and 95% confidence interval (CI). Multivariate models were adjusted for age (continuous), smoking (never, past, current with 1–14, 15–24, or ≥25 cig/d), vigorous physical activity (metabolic equivalent hours/wk, in quintiles) and alcohol intake (0, <4.9, 5.0–9.9, 10–14.9, 15–29.9, or ≥30.0 g/d). Linear trend tests were conducted by using the median in different categories. To evaluate the change of association, we performed association analyses between obesity and risk of PsA by including cases with PASE scores less than the first, second, third, and fourth quartile respectively.

As a sensitivity analysis, level of depressive symptoms (MHI-5 scores, 86–100, 76–85, 53–75, or 0–52) or anti-depressant medication use (never, past, or current), postmenopausal hormone use (premenopausal, never, or ever users), personal history of chronic diseases (yes or no, including cancer, diabetes, cardiovascular disease, hypertension and hypercholesterolemia) were concomitantly adjusted for. Another sensitivity analysis was performed in a case-control design to include all PsA and confirmed psoriatics before and after 1991. Analyses were carried out by using Statistical Analysis System software (SAS, version 9.2; SAS Institute Inc, Cary, NC). All *P* values were 2-tailed with the significance level set at $P < 0.05$. The study was approved by the institutional review board of Partners Health Care System. The participants' return of a completed questionnaire was accepted as informed consent of the present study.

RESULTS

Participants with higher BMI were more likely to be older and tended to have less alcohol intake and less physical activity. We observed an increase in weight at age 18, weight gain, waist and hip circumference, and waist-hip ratio, with increasing categories of BMI in 1991 (Table 1).

We documented 146 incident PsA cases during 1,231,693 person-years of follow-up. Risk of PsA was monotonically elevated with increasing BMI (*P* for trend <0.0001). Compared with BMI less than 25.0, the risk for BMI 25.0–29.9, 30.0–34.9, and ≥35.0 increased to 1.83

(95% CI: 1.15–2.89), 3.12 (95% CI: 1.90–5.11), and 6.46 (95% CI: 4.11–10.16) respectively (Table 2). There was a trend toward increased risk of PsA by weight change since age 18 and the RR of PsA by weight gain of 10 lbs was 1.17 (95% CI: 1.12–1.22). The positively graded association persisted when analyzing the central adiposity measures (*P* for trend <0.001). When one measure of central obesity (waist circumference, hip circumference, or WHR) was included in the model with BMI, its association remained significant except for WHR after adjusting for BMI (*P* for trend =0.064) (Table 2 and Online Supplementary Tables S1–2).

We repeated all the analyses by excluding participants without developing psoriasis to examine the risk of PsA among psoriatics (Table 3). Participants with BMI ≥35.0 were 2.98 times more likely to develop PsA (95% CI: 1.86–4.78, *P* for trend <0.0001). Similarly, risk of PsA among confirmed psoriasis was monotonically elevated with weight change (*P* for trend <0.0001), and measures of central obesity (*P* for trend all <0.01). We also evaluated the effect estimates by concomitantly adjusting for BMI and one measure of central obesity, BMI and WHR remained significant when cross-adjusting (Table 3 and Online Supplementary Tables S1–2). The effect values of BMI remained similar across analyses adjusting for measures of central obesity.

We compared the association between obesity and PsA with severity scores less than the first (49), second (53), third (58), and fourth (75) quartile both among the total participants and among psoriatics. We observed an elevation of RR when including PsA with the higher PASE scores (data not shown).

Stratified analysis by smoking or physical activity did not find any material differences. We performed secondary analyses by adjusting for the level of depressive symptomatology or anti-depressive medication use, post-menopausal hormone use and personal history of chronic diseases and no material change of the results was observed. Sensitivity analysis was carried out to examine the association between obesity and PsA among all self-reported psoriatics (data not shown). A case-control analysis was conducted to incorporate the information of prevalent cases (Online Supplementary Tables S3–4) and the association remains robust.

Discussion

We prospectively evaluated the association between measures of adiposity and risk of incident PsA in a well-established cohort of women. Our results indicated markedly accumulated risk of PsA, correlated with BMI, weight change since the early adulthood, waist and hip circumference, and WHR, both among total participants and among women with psoriasis. These associations existed in a dose-dependent fashion, highlighting the effect of adiposity in development of PsA.

The cutaneous and musuloskeletal effects of adiposity have received great interest recently. Obesity was demonstrated as an independent risk factor for psoriasis in our prospective study[3]. A cross-sectional study also pointed to the link particularly among those with severe psoriasis[17]. However, there is still lack of agreement on the severity of skin phenotypes

between psoriasis and PsA[1, 18, 19]. The adverse effect of obesity on risk of osteoarthritis has been published[4, 5]. Although obesity was found to be associated with increased risk of RA, several recent studies did not support this association, as reviewed by Stavropoulos-Kalinoglou A et al[6]. Interestingly, RA patients with high BMI have lower mortality than thinner patients [20]. Given the marked differences between PsA and other types of arthritis, addressing the role of obesity in PsA development was needed. Moreover, in this study, we were able to evaluate the correlation between obesity and PsA both among the total participants and among those with psoriasis.

In general, there are sparse data on the association between obesity and PsA. Tam et al observed a higher current BMI and WHR among PsA compared with healthy controls but failed to find a significant difference for waist circumference[9]. Soltani-Arabshahi et al suggested that BMI in early adulthood increased the risk of PsA, but did not observe an association between current BMI or other measures of obesity and PsA[10]. In addition, the study design left uncertainty regarding the temporal relationship and did not allow for causal inference. In our prospective analysis, BMI conveys a significantly increased risk of PsA in a dose-dependent manner. In contrary to a report on RA[20], the association was stronger in our study, when including more severe PsA, as defined by higher PASE scores. Weight gain from early adulthood and measures of central obesity also monotonically increased the risk. The effect was robust among never and ever smokers, those with more or less physical activity, comprehensively demonstrating the independent role of high adiposity in development of PsA.

Obesity at age 18 appears to be the only measure that became null when we performed the analyses among psoriasis cases, which did not replicate the observation among total participants and of a previous report[10]. On the other hand, weight gain from age 18 was robustly associated with risk of PsA with a beyond 10% elevated risk per 10 lbs weight increase. Weight change rather than weight at early adulthood may serve as a major relevant factor.

Anthropometric measures of abdominal obesity have been proposed as substantial indicators of health risk[21–23]. Our analysis showed similar trends in risk of PsA associated with waist circumference, hip circumference, and WHR. Cross-adjustment of BMI and measures of central obesity reached similar effect values of BMI, even some of which did not fulfill statistical significance possibly due to the increased standard error by co-linearity. Central obesity measures were greatly attenuated but still had residual effect on risk of PsA even after adjusting for BMI. Stratified analysis by BMI indicated especially for the non-obese participants (BMI <30 kg/m2), central obesity was significantly associated with risk of PsA.

Inflammation may be the key mechanism underlying our findings. Obesity in psoriasis has been associated with both decreased plasma levels of adiponectin and enhanced systemic inflammation and oxidative stress[24–28]. Adiposity can augment cytokines expression by the recruited inflammatory infiltrate, such as IL-6 and TNF-α, relevant to psoriasis pathophysiology [26–28]. The leptin and resistin overload may elicit the cutaneous pro-inflammatory changes in psoriasis [29]. Given PsA is a well recognized systemic inflammatory disorder, a fundamental pathological process that leads to PsA could be the

chronic inflammatory state induced by adiposity[1, 2]. Alternatively, obesity and PsA may share some still unknown common cause. Despite a statistical association, it is early to jump to a conclusion of a causal link. Obesity may serve as a surrogate endpoint for other risk factors of PsA although smoking or physical activity does not seem to modify the association. Another possible mechanism to explain this link is mental health disorders. Psoriasis has been associated with depression, which appears to be reciprocally correlated with obesity[30, 31]. We observed a higher percentage of participants with depression symptoms and anti-depressant medications use among the obese. However, sensitivity analyses accounting for depression did not materially change the results in this study, indicating that the role of obesity is independent of depression.

To our knowledge, this is the first prospective study on this topic. We observed a compelling association by employing multiple markers of obesity to probe into the risk of PsA. Because the anthropometric measures may change over time, using updated BMI and weight change overtime instead of only BMI at baseline allowed us to evaluate the harms of continuing gain in weight and also evaluate the benefits of weight loss. Our study was reasonably powered. A variety of sensitivity analyses were applied and the results did not differ appreciably, arguing for the robustness of the observations.

Our study also has retrospective characteristics and selection and information bias may be a concern. Survivorship bias would be a major concern on selection of participants given that the psoriasis question was asked in 2005. However, a cohort of younger women ensures our results were less likely to be greatly distorted. The mean age of those who did not respond to the psoriasis question was even slightly younger compared with responders. Potential recall bias may be caused by retrospective enquiry of the main outcome. However, the healthcare-related professional background of our participants was reassuring and psoriasis self-reports have reached a confirmation rate of 92%[12]. Case ascertainment of clinician-diagnosed PsA by PASE questionnaire among self-reported psoriatics could be another major concern which may lead to misclassification bias. However, PASE was testified to be a valid and reliable screening tool for PsA, particularly active PsA among psoriasis cases in previous pilot studies[13, 14]. The prevalence of PsA among confirmed psoriatics from 1991 is 21.2%, falling within the range of previous reports[1]. There may be concerns about possible misclassification with other musculoskeletal diseases. Previous studies reported an adverse effect of obesity on osteoarthritis and fibromyalgia [4, 5, 32]. However, PASE can distinguish the symptoms of PsA from osteoarthritis, albeit less of a concern in a younger cohort. Fibromyalgia seldom occurs in psoriatics. It would be worth noting that central obesity was only asked once during the follow-up while we had the opportunity to update BMI and weight change over time. However, a previous study has indicated validity of the measurements [11]. PsA cases without concomitant psoriasis were excluded in our analysis. The effect of obesity on these cases, known as sero-negative inflammatory arthritis or spondyloarthritis, needs to be clarified further. The participants were primarily younger and middle-aged female Caucasians. Although the biological effects of adiposity should be similar and homogeneity of study participants led to less confounding by socioeconomic status, the generalizability to other populations, particularly men, and other racial/ethnic minorities, may be made cautiously.

In conclusion, our large well-characterized cohort study provides evidence of a dose-dependent relationship between overall obesity, central adiposity and increased risk of PsA in women. The effect of obesity on PsA goes beyond that on psoriasis skin phenotypes alone. In this issue, another paper on the similar topic by Love TJ et al was also published which followed-up a cohort of psoriasis patients by general practitioners in northern UK, providing further testifying evidence to our study. The implication of the observations may be substantial as obesity is a modifiable factor which is becoming increasingly prevalent. Further studies are warranted to elucidate the underlying mechanisms and clarify the causative association.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Characteristics of study participants by body mass index in 1991, NHS II *

	Body mass index			
	<25.0	25.0–29.9	30.0–34.9	≥35.0
n	**58,947**	**18,225**	**7,144**	**4,733**
Age †, mean (SD), years	35.9 (4.6)	36.6 (4.7)	37.0 (4.6)	37.3 (4.4)
Current smokers (yes, %)	11.3	12.1	11.4	10.9
Alcohol intake, g/d, mean (SD)	3.5 (6.3)	2.8 (6.0)	2.0 (5.0)	1.6 (4.7)
Vigorous physical activity, metabolic equivalent hours/wk, mean (SD)	15.3 (24.3)	11.6 (19.2)	9.4 (16.1)	7.5 (14.2)
Height, inches, mean (SD)	64.9 (2.5)	64.8 (2.7)	64.7 (2.7)	64.7 (3.0)
Weight at Age 18, lb, mean (SD)	120.7 (15.4)	133.0 (20.5)	143.8 (25.3)	161.8 (33.3)
Weight change from age 18, lb, mean (SD)	9.3 (13.4)	28.8 (18.4)	47.9 (23.1)	75.9 (33.9)
Waist circumference, inches, mean (SD)	28.8 (3.1)	33.5 (3.9)	37.9 (4.5)	42.8 (5.7)
Hip circumference, inches, mean (SD)	37.5 (2.6)	41.7 (3.3)	45.6 (3.9)	51.0 (5.4)
Waist-hip ratio, mean (SD)	0.77 (0.07)	0.81 (0.08)	0.83 (0.08)	0.84 (0.09)
Mental Health Index ≤ 52 (yes, %) #	12.2	14.1	15.9	17.4
Antidepressants use (yes, %) #	9.6	11.5	13.5	17.1
Post Menopausal (yes, %)	3.1	3.5	4.1	5.6
Personal history of chronic diseases (yes, %)				
Diabetes	0.3	0.5	1.4	2.6
Cancer	1.5	1.2	1.1	0.9
Cardiovascular disease	0.4	0.4	0.7	0.9
Hypertension	1.6	4.0	8.0	14.7
Hypercholesterolemia	7.3	11.7	16.3	16.9

* Characteristics of participants at the beginning of follow-up (return date of the 1991 questionnaire). Values are means (SD) or percentages and are standardized to the age distribution of the study population.

† Values are not age-adjusted.

Mental Health Index and antidepressants use in 1993.

Table 2

Age- and multivariate-adjusted RRs for the association of adiposity measurements with risk of psoriatic arthritis among all participants *

	Cases	Person-years	Age-adjusted RR (95% CI)	Multivariate- adjusted RR † (95% CI)
Updated BMI (kg/m^2)	146	1,231,693		
<25.0	40	703,190	1.00	1.00
25.0–29.9	35	297,149	1.88 (1.19–2.96)	1.83 (1.15–2.89)
30.0–34.9	28	133,146	3.22 (1.98–5.26)	3.12 (1.90–5.11)
≥35.0	43	98,208	6.60 (4.26–10.23)	6.46 (4.11–10.16)
P for trend			<0.0001	<0.0001
BMI at age 18 (kg/m^2)	145	1,222,076		
<21.0	67	701,559	1.00 (0.64–1.58)	1.04 (0.66–1.64)
21.0–22.9	26	272,700	1.00	1.00
23.0–24.9	24	125,453	2.01 (1.15–3.50)	1.93 (1.11–3.37)
25.0–29.9	17	93,857	1.88 (1.02–3.46)	1.74 (0.94–3.21)
≥30.0	11	28,508	4.07 (2.01–8.24)	3.55 (1.75–7.23)
P for trend			<0.0001	<0.0001
Weight change from age 18 (lb)	145	1,222,076		
Loss or increase of < 20.0	32	563,364	1.00	1.00
Increase of 20.0–49.9	45	435,087	1.68 (1.06–2.65)	1.72 (1.09–2.72)
Increase of 50.0–99.9	50	191,981	3.88 (2.46–6.13)	3.67 (2.31–5.84)
Increase of ≥100.0	18	31,645	8.09 (4.48–14.64)	7.00 (3.78–12.96)
P for trend			<0.0001	<0.0001
Waist circumference (inch)	72	599,200		
Tertile 1, <28.0	7	168,183	1.00	1.00
Tertile 2, 28.0–31.9	17	227,235	1.72 (0.71–4.16)	1.65 (0.68–4.00)
Tertile 3, ≥32.0	48	203,782	5.05 (2.28–11.20)	4.82 (2.15–10.83)
P for trend			<0.0001	<0.0001
Hip circumference (inch)	70	597,544		
Tertile 1, <38.0	13	233,613	1.00	1.00
Tertile 2, 38.0–40.9	13	187,362	1.18 (0.55–2.56)	1.25 (0.58–2.72)
Tertile 3, ≥41.0	44	176,569	4.02 (2.16–7.51)	4.32 (2.27–8.24)
P for trend			<0.0001	<0.0001
Waist-Hip Ratio	70	596,835		
Tertile 1, <0.744	12	199,028	1.00	1.00
Tertile 2, 0.744–0.800	20	207,096	1.58 (0.77–3.23)	1.49 (0.73–3.06)
Tertile 3, >0.800	38	190,712	3.12 (1.63–5.98)	2.84 (1.48–5.48)
P for trend			0.0002	0.0006

Abbreviations: BMI, body mass index; CI, confidence interval; RR, relative risk.

* Psoriasis cases with only skin phenotypes were excluded during the follow-up.

† Adjusted for age (continuous variable), smoking (never, past, current with 1–14, 15–24, or ≥25 cigs/day), alcohol drinking (no, <4.9, 5.0–9.9, 10–14.9, 15–29.9 or ≥30.0 g/d), vigorous physical activity (metabolic equivalent hours/wk, in quintile), and height (inches, for the analysis of waist circumference, hip circumference, and waist-hip ratio), and weight at 18 years (for the analysis of weight change from 18 y).

Table 3

Age- and multivariate-adjusted RRs for the association of adiposity measurements with risk of psoriatic arthritis among participants with confirmed psoriasis

	Cases	Person- years	Age-adjusted RR (95% CI)	Multivariate- adjusted RR * (95% CI)
Updated BMI (kg/m^2)	146	6,838		
<25.0	40	3,245	1.00	1.00
25.0–29.9	35	1,533	1.80 (1.12–2.88)	1.81 (1.12–2.93)
30.0–34.9	28	1,051	1.98 (1.19–3.28)	1.90 (1.13–3.18)
≥35.0	43	1,009	2.97 (1.88–4.69)	2.98 (1.86–4.78)
P for trend			<0.0001	<0.0001
BMI at age 18 (kg/m^2)	145	6,791		
<21.0	67	3,265	1.23 (0.77–1.96)	1.28 (0.79–2.06)
21.0–22.9	26	1,668	1.00	1.00
23.0–24.9	24	858	1.74 (0.98–3.09)	1.73 (0.96–3.13)
25.0–29.9	17	610	1.69 (0.89–3.20)	1.69 (0.88–3.26)
≥30.0	11	390	1.61 (0.76–3.42)	1.53 (0.71–3.29)
P for trend			0.10	0.20
Weight change from age 18 (lb)	145	6,791		
Loss or increase of < 20.0	32	2,669	1.00	1.00
Increase of 20.0–49.9	45	2,285	1.36 (0.84–2.18)	1.34 (0.82–2.17)
Increase of 50.0–99.9	50	1,513	2.31 (1.46–3.68)	2.42 (1.49–3.91)
Increase of ≥100.0	18	324	3.28 (1.76–6.11)	3.84 (1.93–7.63)
P for trend			<0.0001	<0.0001
Waist circumference (inch)	72	3,272		
Tertile 1, <28.0	7	746	1.00	1.00
Tertile 2, 28.0–31.9	17	1,045	1.67 (0.63–4.38)	1.46 (0.54–3.99)
Tertile 3, ≥32.0	48	1,481	3.23 (1.36–7.69)	3.02 (1.21–7.56)
P for trend			0.002	0.004
Hip circumference (inch)	70	3,245		
Tertile 1, <38.0	13	931	1.00	1.00
Tertile 2, 38.0–40.9	13	917	1.31 (0.56–3.05)	1.24 (0.51–3.00)
Tertile 3, ≥41.0	44	1,397	2.35 (1.15–4.79)	2.59 (1.18–5.69)
P for trend			0.009	0.006
Waist-Hip Ratio	70	3,245		
Tertile 1, <0.744	12	1,008	1.00	1.00
Tertile 2, 0.744–0.800	20	996	1.43 (0.67–3.06)	1.41 (0.63–3.15)
Tertile 3, >0.800	38	1,241	2.36 (1.18–4.74)	2.48 (1.20–5.15)
P for trend			0.009	0.008

Abbreviations: BMI, body mass index; CI, confidence interval; RR, relative risk.

* Adjusted for age (continuous variable), smoking (never, past, current with 1–14, 15–24, or ≥25 cigs/day), alcohol drinking (no, <4.9, 5.0–9.9, 10–14.9, 15–29.9 or ≥30.0 g/d), vigorous physical activity (metabolic equivalent hours/wk, in quintile), and height (inches, for the analysis of waist circumference, hip circumference, and waist-hip ratio), and weight at 18 years (for the analysis of weight change from 18 y).