# Prevalence of Metabolic Syndrome in Patients with Psoriasis: A Population-Based Study in the United Kingdom

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Increasing epidemiological evidence suggests independent associations between psoriasis and cardiovascular and metabolic disease. Our objective was to test the hypothesis that directly assessed psoriasis severity relates to the prevalence of metabolic syndrome and its components. A population-based, cross-sectional study was undertaken using computerized medical records from the Health Improvement Network Study population including individuals in the age group of 45–65 years with psoriasis and practice-matched controls. The diagnosis and extent of psoriasis were determined using provider-based questionnaires. Metabolic syndrome was defined using the National Cholesterol Education Program Adult Treatment Panel III criteria. A total of 44,715 individuals were included: 4,065 with psoriasis and 40,650 controls. In all, 2,044 participants had mild psoriasis ($\leqslant$2% body surface area (BSA)), 1,377 had moderate psoriasis (3–10% BSA), and 475 had severe psoriasis (>10% BSA). Psoriasis was associated with metabolic syndrome, adjusted odds ratio (adj. OR 1.41, 95% confidence interval (CI) 1.31–1.51), varying in a "dose–response" manner, from mild (adj. OR 1.22, 95% CI 1.11–1.35) to severe psoriasis (adj. OR 1.98, 95% CI 1.62–2.43). Psoriasis is associated with metabolic syndrome and the association increases with increasing disease severity. Furthermore, associations with obesity, hypertriglyceridemia, and hyperglycemia increase with increasing disease severity independently of other metabolic syndrome components. These findings suggest that screening for metabolic disease should be considered for psoriasis, especially when it is severe.

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## INTRODUCTION

The metabolic syndrome is a clustering of cardiovascular risk factors, specifically obesity, hypertension, dyslipidemia, and insulin resistance (Eckel *et al.*, 2005), which has been associated with an increased risk of cardiovascular disease (CVD) beyond traditional risk factors (Mente *et al.*, 2010). The prevalence of metabolic syndrome is increasing in the United States (US; Ford *et al.*, 2002) and partly in Europe, paralleling the rising prevalence of obesity worldwide (Mokdad *et al.*, 2003; Mente *et al.*, 2010). Systemic inflammation is associated with metabolic syndrome, with T helper type 1 proinflammatory cytokines such as tumor necrosis factor-α and nonspecific measures of inflammation such as C-reactive protein levels being elevated in patients with the syndrome compared with those without (Lakka *et al.*, 2002). However, there is a limited understanding of the relationship between chronic inflammatory diseases and the prevalence of metabolic syndrome.

Psoriasis is the most common T helper type 1 inflammatory disease, affecting more than 125 million people worldwide (National Psoriasis Foundation). The severity of psoriasis in the general population is variable, with most patients having mild disease (Kurd and Gelfand, 2009), defined as involving $\leqslant$2% of the body surface area (BSA). Epidemiological evidence suggests that psoriasis is associated with an increased frequency of cardiovascular risk factors and adverse cardiovascular outcomes, including myocardial infarction (Gelfand *et al.*, 2006), stroke (Gelfand *et al.*, 2009), and cardiovascular death (Mehta *et al.*, 2010a). Psoriasis, especially if severe, may be a risk factor for atherosclerotic CVD, beyond traditional risk factors (Gelfand *et al.*, 2006, 2009; Mehta *et al.*, 2010a). Moreover, patients with

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*Abbreviations: AIS, Additional Information Services; ATP, Adult Treatment Panel; BMI, body mass index; BSA, body surface area; CI, confidence interval; CVD, cardiovascular disease; GP, general practitioner; NCEP, National Cholesterol Education Program; OR, odds ratio; THIN, The Health Improvement Network*

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severe psoriasis die at an age approximately 5 years younger than patients without psoriasis, with CVD being the most common cause of the excess mortality in these patients (Abuabara *et al.*, 2010). Mechanistic studies of the metabolic syndrome (Shah *et al.*, 2009) and insulin resistance (Mehta *et al.*, 2010b) suggest that chronic T helper type 1 inflammation that characterizes psoriasis, metabolic syndrome, diabetes, and CVD may partly explain the association between these phenotypically distinct diseases.

A number of small, epidemiological studies have reported associations between psoriasis and the metabolic syndrome (Azfar and Gelfand, 2008; Gisondi and Girolomoni, 2009; Al-Mutairi *et al.*, 2010; Mebazaa *et al.*, 2011); however, population-based data in which the severity of psoriasis is objectively determined and individual components of the metabolic syndrome are directly measured are lacking (Augustin *et al.*, 2010). Therefore, our objective was to examine whether there is an association between psoriasis and the metabolic syndrome in a broadly representative population of patients. We also investigate whether the degree of association varies with the extent of skin involvement with psoriasis.

## RESULTS

Table 1 describes the demographics of the study population. At the end of the survey collection period, 4,634 of 4,900 provider-based surveys were completed, giving a response rate of 95%. Our cohort included 4,065 people with confirmed psoriasis and 40,650 matched controls. The mean age of psoriasis patients was 1.2 years higher than that of controls ($P<0.001$), and 51% of psoriasis patients were male compared with 48% of controls ($P<0.001$). A total of 2,044 (53%) participants had mild psoriasis (⩽2% BSA), 1,377 (35%) had moderate psoriasis (3–10% BSA), and 475 (12%) had severe psoriasis (>10% BSA). Information on body mass index (BMI), blood pressure, high-density lipoprotein, glucose, and triglyceride levels was available for 41,249 (92%), 44,019 (98%), 25,234 (56%), 28,743 (64%), and 25,067 (56%) of the patients, respectively (Table 2a). These measurements were available in similar numbers of patients with and without psoriasis.

Metabolic syndrome was identified in 34% of participants with psoriasis compared with 26% of controls (odds ratio (OR) 1.50, 95% confidence interval (CI) 1.40–1.61). This association persisted after adjusting for age, gender, and follow-up (adjusted (adj.) OR 1.41, 95% CI 1.31–1.51). Adjusting for smoking and social class did not change the study findings, and these were not retained in the final model. Psoriasis severity affected the degree of association, with the metabolic syndrome seen in 32% of the patients with mild disease (adj. OR 1.22, 95% CI 1.11–1.35), 36% with moderate disease (adj. OR 1.56, 95% CI 1.38–1.76), and 40% with severe psoriasis (adj. OR 1.98, 95% CI 1.62–2.43). Modest but statistically significant interactions were detected between psoriasis and age, and between psoriasis and sex, whereby the OR of metabolic syndrome and psoriasis was slightly higher in the younger age groups and in women (data not shown).

**Table 1. Demographic details of the cohort**

| Characteristic | No psoriasis, *n* (%) | Psoriasis, *n* (%) |
|---|---|---|
| Overall | 40,650 (90.9) | 4,065 (9.1) |
| *By psoriasis extent* | | |
| ⩽2% | N/A | 2,044 (52.5) |
| 3–10% | N/A | 1,377 (35.3) |
| >10% | N/A | 475 (12.2) |
| *Gender* | | |
| Men | 19,304 (47.5) | 2,081 (51.2) |
| Women | 21,346 (52.5) | 1,984 (48.8) |
| *Age group (years)* | | |
| <50 | 13,348 (32.8) | 1,082 (26.6) |
| 50–54 | 10,040 (24.7) | 1,000 (24.6) |
| 55–59 | 9,271 (22.8) | 945 (23.3) |
| >60 | 7,991 (19.7) | 1,038 (25.5) |
| | **Median (interquartile range) of maximum individual measurements** | |
| Body mass index ($kg\,m^{-2}$) | 27.1 (23.7–31.2) | 28.4 (24.9–32.9) |
| Systolic blood pressure (mm Hg) | 144 (130–162) | 149 (135–168) |
| Diastolic blood pressure (mm Hg) | 90 (80–100) | 90 (82–100) |
| Triglyceride level (mmol/l) | 1.7 (1.1–2.5) | 1.9 (1.2–2.8) |
| Cholesterol level (mmol/l) | 5.8 (5.1–6.7) | 6.0 (5.2–6.8) |
| High-density lipoprotein (mmol/l) | 1.5 (1.2–1.8) | 1.4 (1.2–1.7) |
| Low-density lipoprotein (mmol/l) | 3.6 (2.9–4.3) | 3.7 (3.0–4.3) |
| Glucose ($mmol\,l^{-1}$) | 5.4 (4.9–6.4) | 5.6 (4.9–6.6) |
| C reactive protein ($mg\,l^{-1}$) | 5 (3–10) | 7 (4–13) |
| Metabolic syndrome, *n* (%) | 10,515 (25.9) | 1,389 (34.2) |

On studying the components of the metabolic syndrome, the following factors were found to be more common in psoriasis patients than in controls: obesity in 38% vs. 31% (OR 1.38, 95% CI 1.29–1.48), raised triglyceride levels in 36% vs. 28% (OR 1.49, 95% CI 1.39–1.60), diagnosed hypertension in 31% vs. 28% (OR 1.20, 95% CI 1.11–12.9), and raised glucose levels in 22% vs. 16% (OR 1.44, 95% CI 1.33–1.56; Table 2a).

On studying the fully adjusted model to understand which components of the metabolic syndrome were associated with psoriasis after adjusting for other elements of the metabolic syndrome and age, gender, and duration of follow-up, the strongest association of a component of the metabolic syndrome and psoriasis was found with obesity (adj. OR 1.25, 95% CI 1.16–1.34). The association with

## Table 2a. Factors associated with the metabolic syndrome

| Factors associated with metabolic syndrome | No psoriasis, *n* (%) | Psoriasis, *n* (%) | OR (95% CI) |
|---|---|---|---|
| Body mass index $<25\,kg\,m^{-2}$ [1] | 10,744 (28.7) | 827 (21.9) | 1.0 |
| Body mass index 25–$<30\,kg\,m^{-2}$ [1] | 14,143 (37.7) | 1,401 (37.1) | 1.30 (1.19–1.42) |
| Body mass index 30–$<35\,kg\,m^{-2}$ [1] | 7,678 (20.5) | 887 (23.5) | 1.52 (1.37–1.68) |
| Body mass index $>35\,kg\,m^{-2}$ [1] | 4,907 (13.1) | 662 (17.5) | 1.78 (1.59–1.98) |
| Triglyceride levels $\geqslant 1.7\,mmol\,l^{-1}$ [2] | 11,181 (27.5) | 1,453 (35.7) | 1.49 (1.39–1.60) |
| Low HDL ($<1.04\,mmol\,l^{-1}$ (men) and $<1.29\,mmol\,l^{-1}$ (women))[3] | 8,180 (20.1) | 1,007 (24.7) | 1.32 (1.22–1.43) |
| Raised BP (systolic $\geqslant 130$ mm Hg or diastolic $\geqslant 85$ mm Hg)[4] | 24,187 (59.5) | 3,571 (87.9) | 1.36 (1.24–1.50) |
| Hypertension diagnosis | 11,204 (27.6) | 1,265 (31.1) | 1.20 (1.11–12.9) |
| Type 2 diabetes mellitus | 3,445 (8.5) | 454 (11.2) | 1.36 (1.23–1.51) |
| High-glucose measurement ($>6.1\,mmol\,l^{-1}$)[5] | 6,644 (16.3) | 884 (21.8) | 1.44 (1.33–1.56) |

Abbreviations: BP, blood pressure; CI, confidence interval; HDL, high-density lipoprotein; OR, odds ratio.
[1]BMI measured in 41,249: 3,777 (93%) with psoriasis, 37,472 (92%) controls.
[2]Triglycerides measured in 25,067: 2,545 (63%) with psoriasis, 22,522 (55%) controls.
[3]HDL measured in 25,234: 2,538 (62%) with psoriasis, 22,696 (56%) controls.
[4]BP measured in 44,019: 4,023 (99%) with psoriasis, 39,996 (98%) controls.
[5]Glucose measured in 28,743: 2,599 (64%) with psoriasis, 26,144 (64%) controls.

## Table 2b. Factors including psoriasis extent associated with the metabolic syndrome

| Factors associated with the metabolic syndrome | No psoriasis (*n*, %) | Mild psoriasis (*n*, %), OR (95% CI) | Moderate psoriasis (*n*, %), OR (95% CI) | Severe psoriasis (*n*, %), OR (95% CI) |
|---|---|---|---|---|
| Body mass index $<25\,kg\,m^{-2}$ [1] | 10,744 (28.7) | 472 (24.7), 1.0 | 247 (19.4), 1.0 | 72 (16.6), 1.0 |
| Body mass index 25–$<30\,kg\,m^{-2}$ [1] | 14,143 (37.7) | 715 (35.0), 1.15 (1.02–1.30) | 483 (35.1), 1.49 (1.27–1.74) | 140 (32.2), 1.48 (1.11–1.96) |
| Body mass index 30–$<35\,kg\,m^{-2}$ [1] | 7,678 (20.5) | 415 (21.7), 1.23 (1.07–1.41) | 316 (24.8), 1.79 (1.51–2.12) | 126 (29.0), 2.45(1.83–3.28) |
| Body mass index $>35\,kg\,m^{-2}$ [1] | 4,907 (13.1) | 310 (16.2), 1.44 (1.24–1.67) | 228 (17.9), 2.02 (1.68–2.43) | 97 (22.3), 2.94 (2.17–4.01) |
| Triglycerides $\geqslant 1.7\,mmol\,l^{-1}$ [2] | 11,181 (27.5) | 686 (33.6), 1.33 (1.21–1.46) | 511 (37.1), 1.56 (1.39–1.74) | 202 (42.5), 1.95 (1.62–2.34) |
| Low HDL ($<1.04\,mmol\,l^{-1}$ (men) and $<1.29\,mmol\,l^{-1}$ (women))[3] | 8,180 (20.1) | 480 (23.5), 1.22 (1.10–1.35) | 348 (25.3), 1.34 (1.19–1.52) | 139 (29.3), 1.64 (1.35–2.00) |
| Raised BP (Systolic $\geqslant 130$ mm Hg or diastolic $\geqslant 85$ mm Hg)[4] | 24,187 (59.5) | 1,306 (63.9), 1.20 (1.10–1.32) | 907 (65.9), 1.31 (1.17–1.47) | 329 (69.3), 1.53 (1.26–1.87) |
| Hypertension diagnosis | 11,204 (27.6) | 627 (30.7), 1.16 (1.06–1.28) | 433 (31.5), 1.21 (1.07–1.35) | 151 (31.8), 1.21 (0.98–1.49) |
| Type 2 diabetes mellitus | 3,445 (8.5) | 220 (10.8), 1.28 (1.11–1.48) | 150 (10.9), 1.30 (1.10–1.56) | 58 (12.2), 1.50 (1.14–1.98) |
| High-glucose measurement ($>6.1\,mmol\,l\,mm\,Hg$)[5] | 6,644 (16.3) | 429 (21.0), 1.36 (1.22–1.52) | 291 (21.1), 1.37 (1.20–1.57) | 129 (27.2), 1.91 (1.56–2.34) |

Abbreviations: BP, blood pressure; CI, confidence interval; HDL, high-density lipoprotein; OR, odds ratio.
[1]BMI measured in 41,249: 3,777 (93%) with psoriasis, 37,472 (92%) controls.
[2]Triglycerides measured in 25,067: 2,545 (63%) with psoriasis, 22,522 (55%) controls.
[3]HDL measured in 25,234: 2,538 (62%) with psoriasis, 22,696 (56%) controls.
[4]BP measured in 44,019: 4,023 (99%) with psoriasis, 39,996 (98%) controls.
[5]Glucose measured in 28,743: 2,599 (64%) with psoriasis, 26,144 (64%) controls.

obesity demonstrated a dose–response relationship, with a 14% increase in obesity in those with mild psoriasis (adj. OR 1.14, 95% CI 1.03–1.27), 34% increase in obesity in those with moderate psoriasis (adj. OR 1.34, 95% CI 1.18–1.53), and a 66% increased odds of being obese in those with severe psoriasis (adj. OR 1.66, 95% CI 1.33–2.07; Tables 2b and 3). Hypertriglyceridemia and hyperglycemia showed similar dose–response relationships with severity of psoriasis. There was a 20% increased odds of having raised triglyceride levels in individuals with psoriasis overall, independent of obesity (adj. OR 1.20, 95% CI 1.10–1.31). This association also demonstrated an increased odds of having raised triglyceride levels, from 10% in those with mild psoriasis (adj. OR 1.10, 95% CI 0.98–1.25) to 46% in those with severe psoriasis (adj. OR 1.46, 95% CI 1.13–1.88). Raised glucose level was also associated with psoriasis independent of

**Table 3. Association between psoriasis severity and components of the metabolic syndrome independent of other components**

| Psoriasis extent | High blood pressure, OR (95% CI) | Raised triglyceride levels, OR (95% CI) | Low HDL, OR (95% CI) | Hyperglycemia, OR (95% CI) | Obesity (BMI $>30\,kg\,m^{-2}$), OR (95% CI) |
|---|---|---|---|---|---|
| No psoriasis, *n*=40,650 | 1.0 | 1.0 | 1.0 | 1.0 | 1.0 |
| Psoriasis overall, *n*=4,065 | 1.07 (0.96–1.19) | 1.20 (1.10–1.31) | 0.98 (0.89–1.08) | 1.16 (1.06–1.27) | 1.25 (1.16–1.34) |
| *By extent* | | | | | |
| Mild psoriasis (⩽2%), *n*=2,044 | 1.03 (0.89–1.20) | 1.10 (0.98–1.25) | 0.99 (0.87–1.13) | 1.11 (0.97–1.26) | 1.14 (1.03–1.27) |
| Moderate psoriasis (3–10%), *n*=1,377 | 1.02 (0.85–1.24) | 1.31 (1.13–1.51) | 0.94 (0.80–1.11) | 1.16 (0.99–1.35) | 1.34 (1.18–1.53) |
| Severe psoriasis (>10%), *n*=475 | 1.32 (0.91–1.92) | 1.46 (1.13–1.88) | 1.05 (0.80–1.39) | 1.31 (1.00–1.71) | 1.66 (1.33–2.07) |

Abbreviations: BMI, body mass index; CI, confidence interval; HDL, high-density lipoprotein; OR, odds ratio.

obesity, with a 16% increased odds of raised glucose overall (adj. OR 1.16, 95% CI 1.06–1.27), with the association being strongest in the group with the most severe disease (Table 3).

Sensitivity analysis using the revised Adult Treatment Panel (ATP) III, International Diabetes Federation criteria or by limiting lab values to the first or most recent observation, and excluding individuals on psoriasis treatments that are known to have an impact on components of the metabolic syndrome, e.g., ciclosporin or acitretin, did not significantly change the study conclusions (data not shown).

## DISCUSSION

Psoriasis is associated with the metabolic syndrome in a ''dose–response''manner, with a 22% increase in the odds of developing the metabolic syndrome in those with mild psoriasis, 56% increase in those with moderate disease, and a 98% increase in those with severe psoriasis. In a fully adjusted model looking at associations between factors comprising the metabolic syndrome and psoriasis after adjusting for other components, independent associations were seen between psoriasis and obesity (25% increased odds), raised triglyceride levels (20% increased odds), and raised serum glucose levels (16% increased odds in a ''dose–response'' manner from mild to severe psoriasis).

The strengths of this investigation are that it is a large population-based study with a population broadly representative of the UK population in the age group of 45–65 years, which minimizes selection bias and increases the external validity (i.e., generalizability) of the findings. The ''dose–response'' association detected provides compelling evidence for an association between psoriasis and the metabolic syndrome. Study findings were based on laboratory values and objectively measured disease extent, which allowed observation of findings that are to our knowledge previously unreported. Observational study designs are associated with a number of limitations. These include the cross-sectional nature of this study, which does not allow us to determine which developed first— psoriasis or the metabolic syndrome. Second, we cannot be certain that psoriasis caused the metabolic syndrome; factors including diet, physical inactivity, alcohol, or genetic predisposition, which have not been evaluated in this study, may be functioning as confounding or effect-modifying factors in this relationship (Davidovici *et al.*, 2010), leading to the possibility of residual confounding. In terms of information bias, two aspects of this study make this an unlikely explanation for the findings: (1) laboratory and clinical values were recorded at similar rates in psoriasis patients and controls as part of routine medical care by general practitioners (GPs) unaware of the hypothesis under study; (2) the persistence of the study findings in the sensitivity analysis restricted to the first laboratory or clinical value per person. Disease severity was determined by asking the GPs to rate the extent of skin involvement with psoriasis into simple discrete categories.

Although previous studies have suggested that UK GPs are reasonably accurate in terms of diagnosing psoriasis (Basarab *et al.*, 1996), direct data on the accuracy of GP assessment of the extent of skin involvement with psoriasis are not, to our knowledge, available. We have previously demonstrated the ''construct validity'' of this approach in that patients rated by GPs as having higher BSA categories are more likely to require frequent visits for psoriasis and require systemic therapy specific for psoriasis or phototherapy (Seminara *et al.*, 2011). Moreover, we used the same categories used in the epidemiological studies conducted by NHANES and NPF in which patients are asked to rate their degree of skin involvement with psoriasis, suggesting that this approach is acceptable (i.e., ''face'' validity; Dommasch *et al.*, 2010; Krueger *et al.*, 2001; Seminara *et al.*, 2011). Moreover, these data represent ''real-world'' data, where the extent of psoriasis has been assessed by hundreds of GPs around the UK and resulted in discrimination of the prevalence of metabolic disorders based on these clinical assessments, demonstrating the usefulness of this approach. Nevertheless, our findings are subject to a form of error (i.e., misclassification of the extent of skin involvement) that would be expected to be non-differential and thus bias toward the null. GPs were asked to assess the BSA of involvement that the patient typically demonstrates; this measure may not be stable over time, although a previous large cohort study demonstrated

that despite various therapeutic interventions the severity of psoriasis for individuals did not generally change over time (Nijsten *et al.*, 2007).

This study significantly advances the existing literature on psoriasis and the metabolic syndrome, as this is the first population-based study to use objective measures of psoriasis severity, direct measurement of the components of metabolic syndrome, and standard criteria for diagnosis of metabolic syndrome. Of special interest is the clear ''dose–response'' relationship between psoriasis severity and the metabolic syndrome. No previous study has, to our knowledge, shown a directional increase in the association with raised triglyceride levels and increasing psoriasis severity independent of the effects of obesity. The consistency with other study findings (Gisondi and Girolomoni, 2009; Al-Mutairi *et al.*, 2010; Augustin *et al.*, 2010; Love *et al.*, 2011; Mebazaa *et al.*, 2011), presence of a ''dose–response'' relationship, strong associations, and biological plausibility support some causality, but further mechanistic and longitudinal studies are required (Rothman and Greenland, 2005).

A possible biological mechanism that may account for this association is that the proinflammatory state associated with psoriasis functions as a central driving force for development of the metabolic syndrome. In psoriasis patients, Th1 inflammatory cytokines, e.g., tumor necrosis factor-α, IL-1, and IL-6, are increased in skin and blood (Azfar and Gelfand, 2008). These inflammatory mediators may have a range of effects on insulin signaling, lipid metabolism, and adipogenesis. In addition, inflammation-induced insulin resistance may lead to the development of a systemic insulin-resistant state (Mehta *et al.*, 2010b). Further mechanistic studies will be needed to test this hypothesis.

Study findings demonstrate a strong association between psoriasis and the metabolic syndrome, with increasing psoriasis severity being associated with increasing odds of metabolic syndrome. Increased odds of raised triglyceride levels and serum glucose were seen in individuals with psoriasis independent of the effects of obesity. The results of this study firmly establish that the metabolic syndrome is an important comorbidity with psoriasis, and that vigilance and enhanced screening may be important in psoriasis patients, particularly those with severe disease. Examining the components of metabolic syndrome associated with psoriasis, weight reduction is clearly a key step to prevent CVD; however, our findings also show the importance of screening for the other components of metabolic syndrome, particularly hypertriglyceridemia and raised glucose levels, as these tests are more likely to be abnormal in patients with psoriasis independent of traditional risk factors (such as obesity). Small increases in the individual components of metabolic syndrome have led to an 8% absolute increase in the prevalence of metabolic syndrome overall and a 14% increase in those with severe psoriasis. Further prospective studies are required to determine the directionality of the association between psoriasis and metabolic syndrome and to study other unexplored confounders, including diet, physical activity, alcohol, and genetic factors, which may be important residual confounders in this relationship.

## MATERIALS AND METHODS

### Study design

We conducted a cross-sectional study using The Health Improvement Network (THIN).

### Study population

THIN is a computerized longitudinal general-practice database with demographic data similar to the general United Kingdom (UK) population. THIN has anonymized medical record data on 3.4 million ''active'' patients followed up for a cumulative 50 million person years, and is broadly representative of the UK population. The THIN database contains demographic details, diagnoses, laboratory results, and prescriptions recorded by GPs, the gatekeepers for medical care in the UK. The version of THIN we used contained data from 413 general practices that use the ''In Practice Vision'' software. A number of studies have confirmed that THIN data are highly accurate, thus making it ideal for use in epidemiological research (Lewis *et al.*, 2007; Seminara *et al.*, 2011). The cohort was identified from individuals in the age group of 45–64 years with at least one psoriasis Read code (using a previously validated coding algorithm (Seminara *et al.*, 2011)) in the 2 years before the survey. Patients were required to be registered with a general practice contributing actively to Additional Information Services (AIS). AIS practices have an agreement to respond to questionnaires; 55% ($n=228$) of THIN practices were AIS active at the time of sampling. A total of 4,900 eligible patients with psoriasis diagnostic codes were randomly sampled, and questionnaires were sent to their GPs through AIS to verify the presence of psoriasis and the extent of disease. Up to 10 controls in the age group of 45–64 years were randomly matched to each psoriasis patient based on practice; similar to cases, controls needed to be alive and actively registered with at least one GP visit within 2 years at the time of sampling.

### Outcomes

Patients were defined as having psoriasis if their diagnosis was confirmed by a questionnaire completed by their GP. The questionnaire also determined the severity of psoriasis, namely mild psoriasis (<2% BSA), moderate psoriasis (3–10% BSA), and severe psoriasis (>10% BSA). This approach has been previously well accepted (Feldman, 2004). Cardiovascular risk factors, specifically BMI calculated using standard formulation (overweight was defined as BMI $\geqslant 25\,kg\,m^{-2}$ and $<30\,kg\,m^{-2}$, obese was defined as $\geqslant 30\,kg/m^2$), hypertension, hyperlipidemia, smoking, and diabetes mellitus, were identified by the presence of diagnostic Read codes and additional recording and laboratory values in the Additional Health Details portion of the database.

Subjects were defined as having metabolic syndrome using the National Cholesterol Education Program (NCEP) ATP III diagnostic criteria (Expert Panel on Detection, 2001). Using NCEP criteria, a person with metabolic syndrome fulfills three or more of the following criteria: central obesity (determined by a BMI $\geqslant 30\,kg\,m^{-2}$ in THIN), hypertriglyceridemia $\geqslant 1.7\,mmol\,l^{-1}$, low high-density lipoprotein cholesterol (in men $<1.03\,mmol\,l^{-1}$ and in women $<1.29\,mmol\,l^{-1}$), high blood pressure ($\geqslant 130/85\,mm\,Hg$) and high fasting glucose level ($\geqslant 6.1\,mmol\,l^{-1}$). Time-varying variables were dealt with by selecting the maximum laboratory value or clinical measurement and using the most recent value for BMI. Conditions

were measured from the patients' start date (defined as the latest of the Vision software or computerization in the practice and registration dates of the patient), whereas the end of the study was defined as the earliest date of transfer out, death, or end of the study period in February 2009.

### Study size

We calculated that a sample size of 4,900 would yield 4,190 patients, which would be sufficient to detect increased relative risks of 1.14 for a BMI of $\geqslant 25\,kg\,m^{-2}$, 1.37 for hypertension, 1.71 for hyperlipidemia, and 2.0 for diabetes mellitus, with 80% power, respectively, assuming a two-sided test and a significance level of 0.05, and we were satisfied that such differences would be clinically meaningful.

### Statistical methods

ORs and 95% CIs for the association between psoriasis overall and by psoriasis extent were calculated using conditional logistic regression. Multiplicative interaction terms were fitted to assess the effect modification by age and sex. Adjusted ORs were determined by adjusting for confounders including age, sex, and duration of follow-up time in THIN. Other possible confounders that were explored included smoking and social class, which were measured using Townsend scores (Phillimore *et al.*, 1994). Further analyses were undertaken of the association between psoriasis and disease extent and the components of the metabolic syndrome to ensure that the findings were not explained by individual components such as obesity. Sensitivity analyses were undertaken using the revised NCEP ATP III definition (glucose cut point $>5.6\,mmol\,l^{-1}$) and the International Diabetes Federation definitions of metabolic syndrome (Zimmet *et al.*, 2005). Sensitivity analyses were also carried out using only the first and most recent laboratory value for each individual and in patients who did not receive psoriasis treatments that may affect blood pressure and lipid levels (i.e., ciclosporin or acitretin). All analyses were carried out in Stata SE10 (Stata Corporation, College Station, TX).

### Ethics

This study was approved by the University of Pennsylvania institutional review board and the Cambridgeshire Research Ethics Committee, and was funded by the National Heart Lung and Blood Institute of the NIH.

### Role of the funding source

The sponsors had no role in the conduct or interpretation of the study. The corresponding and senior author had full access to all data in the study and had final responsibility for the decision to submit for publication.

## CONFLICT OF INTEREST

JMG has received grants from Amgen, Pfizer, Novartis, and Abbott, and is a consultant for Amgen, Celgene, Pfizer, Novartis, and Centocor; DJM is on separate data safety monitoring boards for Abbott and Astellas, which might have an interest in the submitted work in the previous 3 years; the remaining authors state no conflict of interest.

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### Author contributions

JMG, DJM, NMS, ABT, and SEK were involved in the conception of the research question, planning of the study, and application for funding. DBS extracted the data from the THIN database and assisted with data management and guidance on the use of THIN. Further data management was carried out by SML and NMS. SML, NMS, ABT, and JMG were involved in analysis of the data. SML and JMG drafted the manuscript, which was reviewed by all authors. SML is the guarantor. All authors had full access to all of the data (including statistical reports and tables) in the study and can take responsibility for the integrity of the data and the accuracy of the data analysis.

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