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

Sinéad M. Langan1,2, Nicole M. Seminara2, Daniel B. Shin2, Andrea B. Troxel3,4, Stephen E. Kimmel5, Nehal N. Mehta3,5, David J. Margolis2,3 and Joel M. Gelfand2,3,4

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 (≤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.

Journal of Investigative Dermatology (2012) 132, 556-562; doi:10.1038/jid.2011.365; published online 24 November 2011

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 ≤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
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-Mutaair 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).

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 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)    |

| Mediterranean | Median (interquartile range) of maximum individual measurements |
|--------------|---------------------------------------------------------------|
| Body mass index (kg m\(^{-2}\)) | 27.1 (23.7–31.2) |
| Systolic blood pressure (mm Hg) | 144 (130–162) |
| Diastolic blood pressure (mm Hg) | 90 (80–100) |
| Triglyceride level (mmol/l) | 1.7 (1.1–2.5) |
| Cholesterol level (mmol/l) | 5.8 (5.1–6.7) |
| High-density lipoprotein (mmol/l) | 1.5 (1.2–1.8) |
| Low-density lipoprotein (mmol/l) | 3.6 (2.9–4.3) |
| Glucose (mmol l\(^{-1}\)) | 5.4 (4.9–6.4) |
| C reactive protein (mg l\(^{-1}\)) | 5 (3–10) |
| Metabolic syndrome, n (%) | 10,515 (25.9) | 1,389 (34.2) |
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 2a. Factors associated with the metabolic syndrome

| Factors associated with the 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 ²               | 14,143 (37.7)       | 1,401 (37.1)    | 1.30 (1.19–1.42) |
| Body mass index 30–35 kg m⁻² ³               | 7,678 (20.5)        | 887 (23.5)      | 1.52 (1.37–1.68) |
| Body mass index >35 kg m⁻² ⁴               | 4,907 (13.1)        | 662 (17.5)      | 1.78 (1.59–1.98) |
| Triglyceride levels >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 >130 mm Hg or diastolic >85 mm Hg)⁴ | 24,187 (59.5) | 3,571 (87.9) | 1.36 (1.24–1.50) |
| Hypertension diagnosis                     | 11,204 (27.6)       | 2,665 (68.1)    | 1.20 (1.11–1.29) |
| 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.

1BMI measured in 41,249: 3,777 (93%) with psoriasis, 37,472 (92%) controls.
2Triglycerides measured in 25,067: 2,545 (63%) with psoriasis, 22,522 (55%) controls.
3HDL measured in 25,234: 2,538 (62%) with psoriasis, 22,696 (56%) controls.
4BP measured in 44,019: 4,023 (99%) with psoriasis, 39,996 (98%) controls.
5Glucose 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 ²               | 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 ³               | 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 ⁴               | 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 >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 >130 mm Hg or diastolic >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⁻¹)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.

1BMI measured in 41,249: 3,777 (93%) with psoriasis, 37,472 (92%) controls.
2Triglycerides measured in 25,067: 2,545 (63%) with psoriasis, 22,522 (55%) controls.
3HDL measured in 25,234: 2,538 (62%) with psoriasis, 22,696 (56%) controls.
4BP measured in 44,019: 4,023 (99%) with psoriasis, 39,996 (98%) controls.
5Glucose measured in 28,743: 2,599 (64%) with psoriasis, 26,144 (64%) controls.
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- \( \alpha \), 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 \( \geq 25 \) \( \text{kg/m}^2 \) and \( <30 \) \( \text{kg/m}^2 \), obese was defined as \( \geq 30 \) \( \text{kg/m}^2 \)), 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 \( \geq 30 \) \( \text{kg/m}^2 \) in THIN), hypertriglyceridemia \( \geq 1.7 \) \( \text{mmol/l} \), low high-density lipoprotein cholesterol (in men \( <1.03 \) \( \text{mmol/l} \) and in women \( <1.29 \) \( \text{mmol/l} \)), high blood pressure (\( \geq 130/85 \) mm Hg) and high fasting glucose level (\( \geq 6.1 \) \( \text{mmol/l} \)). 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 \( \geq 25 \text{ kg m}^{-2} \), 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 \( > 5.6 \text{ mmol l}^{-1} \)) 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.

ACKNOWLEDGMENTS
This study was supported by an R01 grant and a Graduate Research Supplement (NMS) grant from the National Heart, Lung, and Blood Institute of the NIH RO1HL089744 (JMG). The funders had no role in the design, analysis, or interpretation of this research. Dr Langan is funded by fellowships from the British Association of Dermatologists and the National Psoriasis Foundation. Ms Seminara is funded by a Graduate Research Supplement grant from the National Heart, Lung, and Blood Institute of the NIH RO1HL089744. Dr Mehta is funded by a grant from the National Psoriasis Foundation and from the National Heart, Lung, and Blood Institute of the NIH K23 HL097151.

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.

REFERENCES
Abuabara K, Azfar RS, Shin DB et al. (2010) Cause-specific mortality in patients with severe psoriasis: a population-based cohort study in the U.K. Br J Dermatol 163:586-92
Al-Mutairi N, Al-Farag S, Al-Mutairi A et al. (2010) Comorbidities associated with psoriasis: an experience from the Middle East. J Dermatol 37:146-55
Augustin M, Reich K, Glaeske G et al. (2010) Co-morbidity and age-related prevalence of psoriasis: analysis of health insurance data in Germany. Acta Dermatol Venereol 90:147-51
Azfar R, Gelfand J (2008) Psoriasis and metabolic disease: epidemiology and pathophysiology. Curr Opin Rheumatol 20:416-22
Basarab T, Munn SE, Jones RR (1996) Diagnostic accuracy and appropriate-ness of general practitioner referals to a dermatology out-patient clinic. Br J Dermatol 135:70-3
Davidovici BB, Sattar N, Prinz JC et al. (2010) Psoriasis and systemic inflammatory diseases: potential mechanistic links between skin disease and co-morbid conditions. J Invest Dermatol 130: 1785-96
Dommasch E, Shin D, Troxel A et al. (2010) Reliability, validity and responsiveness to change of the Patient Report of Extent of Psoriasis Involvement (PREPI) for measuring body surface area affected by psoriasis. Br J Dermatol 162:835-42
Eckel RH, Grundy SM, Zimmet PZ (2005) The metabolic syndrome. Lancet 365:1415-28
Expert Panel on Detection Ea, and Treatment of High Blood Cholesterol in Adults (2001) Executive summary of the third report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, And Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III). JAMA 285:2486-97
Feldman SR (2004) A quantitative definition of severe psoriasis for use in clinical trials. J Dermatol Treat 15:25-27
Ford ES, Giles WH, Dietz WH (2002) Prevalence of the metabolic syndrome among US adults: findings from the third National Health and Nutrition Examination Survey. JAMA 287:356-9
Gelfand J, Dommasch E, Shin D et al. (2009) The risk of stroke in patients with psoriasis. J Invest Dermatol 129:2411-8
Gelfand J, Neumann A, Shin D et al. (2006) Risk of myocardial infarction in patients with psoriasis. JAMA 296:1735-41
Gisondi P, Girolomoni G (2009) Psoriasis and atherothrombotic diseases: disease-specific and non-disease-specific risk factors. Semin Thromb Hemost 35:313-24
Krueger G, Koo J, Lebwohl M et al. (2001) The impact of psoriasis on quality of life: results of a 1998 National Psoriasis Foundation patient-membership survey. Arch Dermatol 137:280-4
Kurd SK, Gelfand JM (2009) The prevalence of previously diagnosed and undiagnosed psoriasis in US adults: results from NHANES 2003–2004. J Am Acad Dermatol 60:218–24
Lakka HM, Laaksonen DE, Lakka TA et al. (2002) The metabolic syndrome and total and cardiovascular disease mortality in middle-aged men. JAMA 288:2709–16
Lewis J, Schinnar R, Bilker W et al. (2007) Validation studies of The Health Improvement Network (THIN) database for pharmacoepidemiology research. Pharmacoepidemiol Drug Saf 16:393–401
Love TJ, Qureshi AA, Karlson EW et al. (2011) Prevalence of the metabolic syndrome in psoriasis: results from the national health and nutrition examination survey, 2003–2006. Arch Dermatol 147:419–24
Mebazaa A, El Asmi M, Zidi W et al. (2011) Metabolic syndrome in Tunisian psoriatic patients: prevalence and determinants. J Eur Acad Dermatol Venereol 25:705–9
Mehta N, Azfar R, Shin D et al. (2010a) Patients with severe psoriasis are at increased risk of cardiovascular mortality: cohort study using the General Practice Research Database. Eur Heart J 31:1000–6
Mehta NN, McGillicuddy FC, Anderson PD et al. (2010b) Experimental endotoxemia induces adipose inflammation and insulin resistance in humans. Diabetes 59:172–81
Mente A, Yusuf S, Islam S et al. (2010) Metabolic syndrome and risk of acute myocardial infarction: a case-control study of 26,903 subjects from 52 countries. J Am Coll Cardiol 55:2390–8
Mokdad AH, Ford ES, Bowman BA et al. (2003) Prevalence of obesity, diabetes, and obesity-related health risk factors, 2001. JAMA 289:76–9
National Psoriasis Foundation. <http://www.psoriasis.org/netcommunity/learn_statistics> Accessed 22 November 2010
Nijsten T, Looman CW, Stern RS (2007) Clinical severity of psoriasis in last 20 years of PUVA study. Arch Dermatol 143:1113–21
Phillimore P, Beattie A, Townsend P (1994) Widening inequality of health in northern England, 1981–91. BMJ 308:1125–8
Rothman K, Greenland S (2005) Causation and causal inference in epidemiology. Am J Public Health 95(Suppl 1):S144–50
Seminara NM, Abuabara K, Shin DB et al. (2011) Validity of The Health Improvement Network (THIN) for the study of psoriasis. Br J Dermatol 164:602–9
Shah R, Lu Y, Hinkle CC et al. (2009) Gene profiling of human adipose tissue during evoked inflammation in vivo. Diabetes 58:2211–9
Zimmet P, Magliano D, Matsuzawa Y et al. (2005) The metabolic syndrome: a global public health problem and a new definition. J Atheroscler Thromb 12:295–300