Psoriasis, cardiovascular risk factors and metabolic disorders: sex-specific findings of a population-based study

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Abstract

Background Scientific evidence suggests an association between psoriasis and cardiovascular and metabolic diseases. However, there are hardly any sex-specific results from population-based studies reporting the prevalence of cardiovascular risk factors in patients with psoriasis and point estimates of the association between psoriasis and cardiovascular and metabolic disorders.

Objective Aims are to evaluate the sex-specific prevalence of psoriasis and cardiovascular risk factors, and to estimate sex-specific associations between psoriasis and diabetes type 2 (DM) and metabolic syndrome (MetS).

Methods We used data of 3723 participants (45–75 years, 54.1% women) without coronary heart disease and missing data (psoriasis, DM, MetS) from the Heinz Nixdorf Recall study. Standardized information on health outcomes and risk factors was assessed. We performed descriptive statistics and multiple regression analyses to calculate prevalence rate ratios (PR) and 95% confidence intervals (95% CI).

Results The prevalence of psoriasis was 3.8% (n = 143), with no differences between sex. We observed more often metabolic and cardiovascular risk factors in women with psoriasis compared to women without psoriasis. Interestingly, in men, this pattern was partly reversed. Multiple regression analyses revealed distinctly elevated PRs for DM for both women and men with psoriasis (fully adjusted PR: 2.43; 95% CI: 1.17–5.07, resp. 1.16–3.76). Regarding the MetS, the results were inconsistent, showing a positive association between psoriasis and MetS in women (1.84; 1.14–2.98), but a negative association in men, even though with a wide 95% CI (0.69; 0.42–1.12).

Conclusion The results of our cross-sectional, population-based analysis show a distinct association between psoriasis and DM, whereas for the MetS the results contrasted between men and women, translating in women with MetS showing a higher and in men a lower chance to be psoriatic. Our results emphasize the urgent need for sex-specific research, studying the effects of psoriasis on metabolic disorders as well as effective sex tailored prevention measures.

Conflict of interests

WS received travel expenses for attending meetings and/or (speaker) honoraria from Abbvie, Almirall, Bristol-Myers Squibb, Celgene, Janssen, LEO Pharma, Lilly, MSD, Novartis, Pfizer, Roche, Sanofi Genzyme and UCB.
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Introduction

Psoriasis is a chronic inflammatory cutaneous disease with a prevalence of 2–4% in industrialized countries.1–3 It is a prototypical T-helper (Th) 1 and Th17 inflammatory disease that is classified as an immune-mediated inflammatory disease (IMID) of the skin.4 A substantial body of evidence suggests that patients with IMIDs are at a higher risk of developing systemic comorbidities, e.g. cardiovascular disease (CVD), metabolic syndrome (MetS) and diabetes mellitus (DM) since they harbour shared genetic risks and similar inflammatory pathways.4,5

In psoriasis, Th 1- and Th 17-inflammatory cytokines, such as Interleukin (IL)-17, IL-23 and tumour necrosis factor-α, are increased in the skin and in the blood. These proinflammatory mediators have multiple effects on different processes such as immune cell trafficking, angiogenesis, insulin signalling, adipogenesis and lipid metabolism. Thus, the metabolic aspects of chronic Th1- and Th17-inflammation in psoriasis have the potential to influence other conditions such as atherosclerosis, obesity and diabetes. Reciprocally, proinflammatory cytokines and hormones produced in conditions like obesity, atherosclerosis and diabetes may impact the pathogenesis of psoriasis by promoting a proinflammatory state that elevates the susceptibility to the development or worsening of existing psoriasis.4

A large number of epidemiological studies not only have shown an increased prevalence of cardiovascular risk factors, hypertension6–11 and CVD,12–15 like myocardial infarction and cerebrovascular disease6,14,16–20 in psoriasis, but also have identified psoriasis as an independent risk factor for developing CVD.12,21

Furthermore, a large body of evidence revealed that psoriasis is related to obesity7,22–25 and especially central obesity.26,27 Accordingly, psoriasis patients are more likely to suffer from insulin resistance compared to normal controls28 and various studies have found that the prevalence rate (PR) of DM is higher in patients with psoriasis.6,7,11,29,30 Metabolic syndrome is a highly prevalent, multifaced condition characterized by a constellation of abnormalities that include abdominal obesity, hypertension, dyslipidemia and elevated blood glucose.31 Various studies could show that psoriasis is associated with an increased prevalence of MetS7,22,32–34 and that the association increases with disease severity.35–37

It is well known that cardiovascular risk factors and metabolic disorders are unequally distributed between men and women. In general, CVD risk is lower in women than in men.29 Women, especially younger women, have better cardiovascular risk profile compared with same-aged men including a lower prevalence of dysglycemia, dyslipidemia and hypertension.39–42 However, sex-specific results from population-based studies reporting (i) the prevalence of cardiovascular risk factors in patients with psoriasis; and (ii) point estimates of the association between psoriasis and metabolic disorders are extremely scarce and indicate the presence of sex variations in the risk of MetS among individuals with psoriasis with female psoriatics harbouring a higher risk.32

Thus, aims are (i) to evaluate in a population-based cohort without prevalent CVD the sex-specific prevalence of psoriasis and cardiovascular risk factors; and (ii) to estimate sex-specific associations between psoriasis and diabetes disorders, here diabetes type 2 (DM) and MetS.

Patient and methods

Study design and population

We used baseline data from the Heinz Nixdorf Recall (Risk factors, Evaluation of Coronary Calcium and Lifestyle) study, a population-based, ongoing cohort study in the highly urbanized Ruhr Area in Western Germany. Rationale and design of the study have been described in detail.43 Briefly, 3723 men (45.9%) and women (54.1%) aged 45–75 years, randomly selected from mandatory lists of residents of Essen, Bochum and Mülheim, were recruited between 2000 and 2003. The baseline response was 56%.44 The study has been approved by the institutional local ethics committees and comprises extended quality management procedures, including a certification according to DIN ISO 9001:2000/2008. Informed consent has been obtained from all participants.

Data assessment

Standardised computer assisted face-to-face interviews (CAPI) were performed at the study centre located in Essen by trained and certified study personnel. Interviewed data included information for medical history, family history of coronary heart disease, smoking and socio-economic status. Ascertainment of current use of medication was performed by the brown bag method by asking participants to bring along all medication taken in the last 7 days. Current medications were coded according to the Anatomical Therapeutic Chemical (ATC) Classification Index. Participants were classified as having psoriasis if they reported in CAPI to ever have received a physician diagnosis of psoriasis or reported the intake of any medications listed in Table 1.

Diabetes mellitus was defined by self-reported, physician-diagnosed diabetes or intake of glucose-lowering drugs or in case of (i) a fasting glucose of ≥7.0 mmol/L or a random blood glucose ≥11.1 mmol/L measured on the survey day.45 A total of 79% of the study participants were in a fasting state >8 h. MetS was defined according to the most widely used definition for the diagnosis of MetS from the AHA/NHLBI.46

Blood pressure was measured using an automated oscillometric blood pressure device (Omron, Omron Healthcare, Inc., Bannockburn, IL, USA, HEM-705CP-E) with participants in sitting position, using the mean of the second and third value of three measurements.44,47,48 According to the definition of the European Society of Hypertension and the European Society of Cardiology 2013 and in accordance with the Seventh Joint National
Committee for Prevention Detection and Treatment of High Blood Pressure (JNC 7) guidelines, blood pressure levels above 140/90 mmHg were defined as hypertension. Additionally, the verified intake of antihypertensive medication lead to categorization of these participants as having hypertension.49,50

Standardized measures of body weight to the nearest 0.1 kg and height to the nearest 0.5 cm with participants in light underwear without shoes were used for calculating the body mass index [BMI (kg/m²)]. Waist circumference was measured according to standard operation procedures.

The smoking variables included indicator variables for current regular smoker and former smoker (cessation of smoking more than 1 year ago). Socio-economic status was assessed through educational attainment using total years of formal education, classified into ≤10 and >10 years of education.

Venous blood samples were obtained from participants while they were sitting. Enzymatic methods were used to determine total cholesterol (T-C), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C) and triglycerides (TG). High sensitive C-reactive protein (hs-CRP) and glyced haemoglobin (HbA1c) were measured by immunonephelometry (Dade Behring, Germany). All analyses have been done within 12 h at one central laboratory (University Hospital of Essen, Germany).

Descriptive statistics were done according to standard methods. Additionally, we stratified all data to sex. To estimate PR ratios, sex-specific log-binomial regression analysis (PROC GENMOD) were performed with psoriasis as outcome and diabetes, respective MetS as exposure variable. In all regression analyses, three models were fitted: for diabetes a crude model, an age-adjusted model; and a model additionally adjusted for smoking, blood pressure, BMI, physical activity, socio-economic status, triglycerides and intake of lipid-lowering drugs. For Mets a crude model, an age-adjusted model; and a model additionally adjusted for smoking, socio-economic status and physical activity was fitted.

All statistical analyses were performed using SAS version 9.4. We calculated and reported 95% confidence intervals (CI) to assess the precision of our estimates because our goal was estimation and not significance testing.51,52 We wish to avoid publication bias by preferential reporting of significant results.

**Results**

A diagnosis of psoriasis (n = 130) and/or intake of psoriasis relevant medication (n = 13) was reported by 3.8% (n = 143) of the study participants, differing not between men (3.9%) and women (3.8%). Characteristics of the entire study population and results stratified by diagnosis of psoriasis and sex are presented in Fig. 1. Mean age of the whole cohort was 59 years (±8 years). In women, the prevalence of psoriasis decreased with increasing age, whereas in men we observed a roughly U-shaped pattern (45–54 years: 34%; 55–64: 27%; 65–75: 39%).

Overall, the prevalence of hypertension was 35.3%. Hypertension in men with psoriasis was more prevalent compared to men without psoriasis (49.3% vs 43.1%), whereas in women no differences could be observed (29% vs 28.3%). Interestingly, intake of antihypertensive medication was similar between men with psoriasis (31.8%) and without psoriasis (30%), whereas intake of antihypertensives was more often reported by females with psoriasis (36.2%) compared to females without psoriasis (31.7%).

Looking at smoking, we found less female non-smokers and more female ex-smokers in the psoriasis group compared to women without psoriasis (44.7% vs 55.8%, resp. 34.2% vs 22.3%). On the other hand, we could not observe any differences in men in regard to actual and former smoking behaviour between the psoriasis and the non-psoriasis group (31.3% vs 30.8%).

A waist circumference above the upper limit according to the 2004 MetS-definition (men: ≥102 cm, women: ≥88 cm) was distinctly more often observed in women with psoriasis than in women without psoriasis (61.8% vs 42.6%). Surprisingly, in men this pattern was rather the other way around: men without psoriasis more often had an elevated waist circumference than men with psoriasis (35.8% vs 31.3%). Accordingly, we found similar results in regard to obesity (BMI > 30) with strikingly

**Table 1** List of pharmacological/therapeutic subgroups (5th level) to identify participants with psoriasis

| Chemical substance        | ATC code      |
|---------------------------|---------------|
| Fumaric acid              | D05AX01       |
| Fumaric acid, combinations| D05BX51       |
| Acitretin                 | D05BB02       |
| Methotrexate              | L01BA01, L04AX03 |
| Methoxsalen               | D05BA02, D05AD02 |
| Ciclosporin               | L04AD01       |
| Adalimumab                | L04AB04       |
| Etanercept                | L04AB01       |
| Infliximab                | L04AB02       |
| Efalizumab                | L04AA21       |
| Dithranol                 | D05AC01       |
| Dithranol, combinations   | D05AC51       |
| Tars                      | D05AA         |
| Calcipotriol              | D05AX02       |
| Calcipotriol, combinations| D05AX52       |
| Tacalcitol                | D05AX04       |
| Calcitriol                | D05AX03       |

ATC code, Anatomical Therapeutic Chemical (ATC) Classification System.
more obese women with psoriasis (39.5%) than without (25.4%), and no difference in men (23.9% vs 23.6%).

Corresponding to the sex-specific pattern of the prevalence of obesity, we found a higher share of women with psoriasis with increased triglycerides compared to women without psoriasis (26.5% vs 17.8%), whereas in men this pattern was again rather the other way around (24.2% vs. 30.3%). However, distinctly less women with psoriasis reported intake of lipid-lowering drugs.

![Figure 1](image-url)  
**Figure 1** Study population characteristics. (a) Study population characteristics of the entire cohort. (b) Study population characteristics of men with and without psoriasis. (c) Study population characteristics of women with and without psoriasis. BMI, body mass index; HDL, high-density lipoprotein; mmHg, millimetres/mercury; mmol/L, millimoles per litre.
drugs (2.9%) compared to women without psoriasis (9.5%), whereas in men this difference could not be observed (11.1% vs 8.7%).

Same results can be reported with respect to increased blood glucose levels (fasting glucose > 5.5 mmol/L), with a higher share of women with psoriasis than without psoriasis performing increased blood glucose levels (54.1% vs 47.4%). In contrast, men with psoriasis were less likely to have increased blood glucose levels compared to men without psoriasis (60.3% vs 66.9%).

In respect to MetS, the sex-specific pattern described above is particularly clear, which means we measured MetS strikingly more often in women than without psoriasis (36.8% vs 25.4%) and the other way around strikingly less often in men with than without psoriasis (26.9% vs 38.3%).

Surprisingly to these results, we observed no sex differences in regard to diabetes and psoriasis, with remarkably higher prevalences of diabetes in both men and women with psoriasis (women: 11.8% vs 5.3%; men 11.9% vs 8%). Correspondingly, intake of antidiabetics was reported more often by women and men with psoriasis (5.8% and 9.5%) compared to women and men without psoriasis (3.7% and 6%). An overview of the main sex-specific results according to the prevalence of psoriasis is summarized in Table 2.

### Results of the regression analyses

Table 3a depicts the PR of the regression analyses for the exposure diabetes. All models revealed substantially increased PR for diabetes in women and men with psoriasis (age-adjusted PR women: 2.32, 95% CI: 1.25–4.31; men: 1.69, 95% CI: 1.00–2.85; fully adjusted PR women: 2.43, 95% CI: 1.17–5.07; men: 2.09, 95% CI: 1.16–3.76). Further adjustments for smoking, blood pressure, BMI, physical activity, triglycerides and intake of lipid-lowering drugs. Adjustment sets (b): Model 1: crude, Model 2: age, Model 3: Model 2 + smoking, blood pressure, body mass index, physical activity, socio-economic status, triglycerides and intake of lipid-lowering drugs. Adjustment sets (b): Model 1: crude, Model 2: age, Model 3: Model 2 + smoking, socio-economic status and physical activity. CI, confidence interval; PR, prevalence rate ratio.

| Model | PR | 95% CI | PR | 95% CI |
|-------|----|--------|----|--------|
| Model 1 | 0.69 | 0.43–1.09 | 1.65 | 1.06–2.56 |
| Model 2 | 0.67 | 0.42–1.06 | 1.82 | 1.16–2.86 |
| Model 3 | 0.69 | 0.42–1.12 | 1.84 | 1.14–2.98 |

59% CI: 1.16–2.86; fully adjusted PR: 1.84, 95% CI: 1.14–2.98. According to the descriptive results, the PRs in men showed an inverse association with distinct decreased PRs psoriasis in men with MetS. However, with less confidence than the results in women (age-adjusted PR men: 0.67, 95% CI: 0.42–1.06; fully adjusted PR men: 0.69, 95% CI: 0.42–1.12). Similar to the regression analyses of diabetes further adjustments for smoking, socio-economic status and physical activity did not change the outcomes substantially (data not shown).

### Discussion

There is solid epidemiological evidence linking psoriasis to cardiovascular risk factors and an increased risk of developing cardiovascular and metabolic diseases.53–55 The results of our study show the presence of considerable sex differences in cardiometabolic risk factors among individuals with psoriasis. In the female group, nearly all cardiometabolic risk factors were more prevalent in women suffering from psoriasis. Unexpectedly, in men, this pattern was the other way around.

It is well known that cardiovascular risk factors and metabolic disorders are unequally distributed between men and women.56,57 The underlying mechanisms explaining sex-specific differences are not fully understood up to now, but are currently being researched intensively.58 So far, differences are mainly explained by biological conditions between women and men, which are foremost due to differences in gene expression from the sex chromosomes and subsequent differences in sexual hormones leading to differences in gene expression and function in the cardiovascular system.59

However, it is not yet clear to what extent sex may alter the association between psoriasis and cardiometabolic disorders. Sex-specific results from population-based studies with focus on

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**Table 2** Summary of sex-specific results

| Higher prevalence with psoriasis than without psoriasis | Women | Men |
|-------------------------------------------------------|-------|-----|
| Waist circumference | Hypertension |  | |
| Obesity | DM |  | |
| Elevated triglycerides | Intake of antidiabetics and lipid-lowering drugs |  | |
| Elevated blood glucose |  | DM | |
| MetS |  | Intake of antihypertensives and antidiabetics | |

BMI, body mass index; DM, diabetes mellitus; MetS, metabolic syndrome.
the prevalence of cardiovascular risk factors in patients with psoriasis as well as sex-specific associations between psoriasis and metabolic disorders are rare. To the best of our knowledge, there is only one paper reporting comprehensive sex- and age-specific results in a population-based study. The Tromsø study by Danielsen and co-workers is a Norwegian cross-sectional study performed between 2007 and 2008 including 10 521 participants aged 30–79 years. In this study, the prevalence of MetS and its components by psoriasis status was reported by age-stratified analyses (30–44, 45–59 and 60–79 years). In the Tromsø study, 10% of the participants reported ever experiencing psoriasis with a mainly mild course. It is well known that the Scandinavian region has one of the highest psoriasis prevalences in the world. In the following, our results will primarily be discussed in comparison with the results of Danielsen et al.

In our study, overall 25.8% of the women had MetS, which comes close to reported prevalences of MetS in women of other German studies (18–23%). The prevalence of MetS was more prevalent in women with psoriasis than without (36.8% resp. 25.4%), which was also observed in the Tromsø study. Similar to MetS, we observed more women with psoriasis having diabetes (12%) than those without psoriasis (5%). Similar results were reported by Cohen et al. performing a cross-sectional study by using a large medical data set of the Clalit Health Services in Israel. The data set includes 16 851 patients with psoriasis and 74 987 subjects without psoriasis. As in our study, women with psoriasis more often had diabetes than women without psoriasis (12% resp. 9%). The higher prevalence of diabetes in the female control group might be due to the special health service data.

In Germany, the reported prevalence of MetS in men ranges between 24% and 32%, which is slightly lower, than the observed prevalence of 37.9% in our study. Contrary to women, men with psoriasis less often had MetS than men without psoriasis (27% vs. 38%). In the Tromsø study, men with psoriasis had an approximately 35% increased risk of MetS regardless of age (OR 1.35, 95% CI 1.1–1.6), which is in contrast to our data, as our results suggest a negative association between MetS and psoriasis in men (fully adjusted PR: 0.69, 95% CI: 0.42–1.12).

In men with psoriasis, the prevalence of DM was slightly higher compared to men without psoriasis (12% vs 8%). Similar results are reported in the study by Cohen et al., with a diabetes prevalence of 12% in men with psoriasis and 9% without psoriasis.

Strengths and limitations

Strengths of our study are the population-based approach, the comprehensive data assessment, including computer-based personal interviews as well as standardized medical examinations including a high data quality. Our study is not without limitations. Diagnosis of psoriasis was only based on self-report which is not without concern. However, self-report of data is a widely used method in epidemiological studies of skin diseases and it is well known that the addition of ‘to ever have received a medical diagnosis of psoriasis’ considerably increases the validity of the self-reports. Further, the reported intake of antipsoriatic medication may be prone to error, since some antipsoriatic substances (e.g. methotrexate) are also used for treatment of other indications like rheumatic diseases, e.g. rheumatoid arthritis. However, in our study, only 13 participants were identified via current use of certain medication and in only five cases patients reported to take substances which are not exclusively used for treatment of psoriasis. There are two limitations regarding the cohort of the psoriasis patients. Firstly, the absolute number of 143 participants suffering from psoriasis is rather small. However, all participants ran through a face-to-face evaluation ensuring a high data quality and, apart from the Tromsø study, there are hardly any other comparable sex-specific results available up to now. Secondly, participants included in this study were 45 years of age or older so that the age range of younger patients suffering from psoriasis is not reflected in this population. In the Tromsø study, men with psoriasis had an increased risk of MetS regardless of age. However, younger male psoriasis patients were shown to have a higher risk for cardiovascular disorders like myocardial infarction. Thus, gathering of sex-specific population-based data also on younger psoriasis patients would be interesting maybe in a next step.

Another limitation of our study is that the Psoriasis Area and Severity Index (PASI) was not investigated so that we cannot make a statement on disease severity in our cohort.

Conclusion

The results of our cross-sectional analysis showed a distinct association between psoriasis and metabolic and cardiovascular disorders in men and women. The comparison of both sexes is essential for the identification of protective or maladaptive mechanisms. A knowledge of such mechanisms in gene transcription, intracellular signalling, organelle function and interorgan crosstalk could reveal new targets that may be used for the activation or inhibition of specific aspects of the cardiovascular system that are linked to sex hormones or other differences between men and women. The reasons behind the unexpected comparably low cardiometabolic risk in males with psoriasis compared to males without psoriasis in our cohort urgently need to be examined in further studies.

In sum, our results emphasize the crucial need for sex-specific analyses, when further studying the effects of psoriasis on metabolic and cardiovascular disorders. As a near-term consequence, there may be a benefit from targeted screening of metabolic and cardiovascular disorders among individuals with psoriasis with a special focus on women.
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