Psoriasis and the metabolic syndrome - a population-based study of age and gender differences

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What is known about this topic?

- Evidence suggests an association between psoriasis and the metabolic syndrome; however population-based studies including age and gender variation and information on confounding factors are scarce.

What does this study add?

- This study from a large general population sample discloses large age and gender variations in risk of metabolic syndrome among individuals with psoriasis after adjustment for lifestyle confounders.
- Young women with psoriasis had up to fourfold increased risk of metabolic syndrome.
- The results support a probable benefit from targeted screening for metabolic risk factors in psoriasis patients.

Abstract

Background

Evidence suggests an association between psoriasis and the metabolic syndrome; important questions remain, however, concerning the extent to which age and gender influence the risk of metabolic syndrome in psoriasis.

Objectives

To investigate the association between psoriasis and the metabolic syndrome within an ongoing population-based cohort by age and gender.

Methods

A cross-sectional study including 10,521 participants age 30-79 years from the population-based Tromsø Study was performed; 1,137 participants reported lifetime psoriasis of mainly mild character. The new harmonized definition of the metabolic syndrome was used in the multivariable logistic regression analysis.

Results

In women, psoriasis was associated with a 3.8 times higher odds of metabolic syndrome at age 30 (95% confidence interval, CI 1.5-9.7). While the odds decreased with age, the difference in prevalence of metabolic syndrome between women with and without psoriasis remained quite stable (e.g. 30-44 years, 21%/11%; 60-79 years, 37%/30%). In men, psoriasis was associated with a 1.35 times higher odds of metabolic syndrome (95% CI 1.1-1.6) in all ages. Abdominal obesity was the most frequent metabolic syndrome component in women in this study, and there was indication of a dose-response relationship between psoriasis severity, indicated through treatment, and having a high waistline in women.

Conclusions

This study discloses age and gender variations in risk of metabolic syndrome among individuals with psoriasis. Given the high prevalence of psoriasis and the significant increase of metabolic syndrome among individuals even with mild disease, this supports a probable benefit in screening this patient group for metabolic risk factors from a relatively early age.

Introduction

There is growing evidence of an association between the chronic relapsing inflammatory skin disease psoriasis, and the obesity-related systemic inflammatory and prothrombotic condition metabolic syndrome (MetS).[1-3] Important questions remain, however, concerning the link between psoriasis and MetS in the general unselected population and the extent to which gender and age influence the risk of MetS in psoriasis.[1] The MetS is a cluster of risk factors associated with a doubling of cardiovascular disease risk and a five times greater risk for developing type II diabetes.[4] Obesity and MetS have reached epidemic proportions worldwide during the last decades.[5-7] Meanwhile, studies suggest a parallel increase in the prevalence and incidence of psoriasis in some populations,[8-12] with the highest prevalence's being reported from general health surveys among adults in Scandinavia.[10,13,14]

A recent meta-analysis including 12 heterogeneous observational studies reported a pooled odds ratio (OR) for MetS of 2.26 among subjects with psoriasis compared to their reference groups.[3] A limitation of this analysis was the scarcity of studies with data gathered outside of clinical settings or patient databases, as well as being performed with uniform screening procedures for psoriasis, MetS and confounding lifestyle factors.[15-18] There was also indication of publication bias.[3] Two population-based health surveys have provided conflicting results. The North-American National Health and Nutrition Examination Survey (NHANES) 2003-2006 reported a 2-fold increase in the risk of MetS among persons with psoriasis, and suggested that the association may be restricted to women.[1] In contrast, a cross-sectional health study in Denmark (2006-2008) reported no association between self-reported psoriasis and MetS.[14] Interestingly, age and gender modification of a "dose-response" association between severity of psoriasis and odds of MetS was observed in a large study from a UK general practice database, with the highest effect estimates in middle-age subjects and women.[2]

The first-ever public health agenda for psoriasis recently released by the United States Centers for Disease Control and Prevention points to needs for more population-based cohort studies to analyze age and gender disparities of relationships to obesity and cardiovascular disease,[19] and underlines that there is not a sufficient evidence base in order to recommend establishing targeted preventive measures for psoriasis patients as suggested by several expert groups.[20,21]

The purpose of this study was to describe the association between psoriasis and the MetS according to age and gender in a general adult population including the largest age-range to date using uniform screening procedures and clinical measurements within the well-established Tromsø Study cohort.

Material & Methods

Study population and design

The Tromsø Study is a single centre multipurpose population-based study with repeated high quality health surveys of inhabitants in the subarctic municipality of Tromsø, Norway, population approximately 65,000 (2007).[22] The design and cohort profile have been described in detail.[10,23] In total 9,625 men and 10,137 women aged 30-87 years were invited to the sixth Tromsø Study in 2007-2008, and 12,984 participants attended (66%).[24] Two participants have since withdrawn their consent.

Trained health professionals at the screening centre conducted clinical examinations (height, weight, hip and waist circumference, blood pressure) and collected blood samples according to standardized procedures. Details concerning the measurements, biological specimens and analytical methods are published elsewhere.[24] Two questionnaires were used to collect data on general health, education, disease, medication use and lifestyle (Supporting information).[22,24]

All subjects over the age of 79 (n=531), pregnant women (n=28), as well as participants with missing data on self-reported psoriasis (n=1,176) or measured MetS components (n=726), were excluded; giving a total of 10,521 individuals, 5,499 women and 5,022 men, for the present analysis.

Ethics

Each participant gave written informed consent prior to the examinations. The study was approved by the Norwegian Data Protection Authority and the Regional Committee for Medical and Health Research Ethics, North Norway.

Psoriasis diagnosis and severity

Psoriasis was assessed by self-report of lifetime psoriasis using the following questions: "Do you have or have you ever had psoriasis?" and/or "Have you ever been diagnosed with psoriasis by a physician?" Answers to both questions were coded as yes or no. A total of 1,137 participants reported lifetime psoriasis (Supporting information).

Information on medication from the Norwegian Prescription Database (NorPD) was used as a proxy for disease severity (Supporting information). Due to a restricted set of variables in the NorPD-file, the relationship between psoriasis severity and the MetS could not be evaluated. A total of 584 individuals (49%) received a registered prescription indicative of psoriasis during the time period 2006-2009; systemic drugs were prescribed to 66 patients in total (6%). This implies that at least 5% of the sampled population had active psoriasis around the time of survey.

Metabolic syndrome (MetS)

The MetS was assessed using the unified definition of the International Diabetes Federation (IDF) as well as the National Heart, Lung and Blood Institute, and others.[4] In order to be defined as having the MetS participants were required to have minimum three of the five criteria related to MetS; central obesity defined by waist circumference (WC), raised triglyceride, reduced HDL-C, raised blood pressure, and/or raised fasting plasma glucose (Supporting information).

Statistical analysis

Due to apparent gender differences in the data, most analyses were stratified by gender. Descriptive characteristics were reported with means (standard deviation, SD) for continuous variables and proportions for binary variables. Age-adjusted differences in means or proportions between individuals with and without psoriasis were assessed using linear or logistic regression models. Comparisons of the prevalence of MetS and its components by psoriasis status were done in age-stratified analysis; i.e. 30-44, 45-59, and 60-79 years,

according to approximate cut-off for premenopause in women (<45 years) and premature cardiovascular disease (<60 years). The odds ratio (OR) for MetS according to the presence of psoriasis, was assessed in an age-adjusted logistic regression model (n=10,521/n=9,662), and in a multivariable model adjusted for age, gender, smoking, educational level and recreational physical activity (n=9,662; observations with missing covariates excluded) (Supporting information). Alcohol and statin use did not affect the analysis and were not included in the final model. In order to account for age as a possible effect modifier, age was also modelled using second-degree fractional polynomial terms. The main effect of age terms and two-way interactions with psoriasis were included in the models. All *P* values were two-sided using a 5% significance level. The analyses were performed with SAS 9.2 (SAS Institute, Inc., Cary, NC) and SPSS 20 (SPSS Inc., Chicago, IL).

Results

Among the 5,499 women, with mean age 55.9 years, mean body mass index (BMI) was 26.5 kg/m^2, and mean WC was 90.6 cm. The 5,022 men had a mean age of 56.5 years, mean BMI of 27.3 kg/m^2, and mean WC of 99.3 cm. The overall prevalence of self-reported lifetime psoriasis was 10.8 %; 10.1% in women and 11.6% in men (*P*=0.019). Psoriasis was associated with older age, lower education level, and current smoking (Table 1). Among women, psoriasis was also associated with low leisure-time physical activity.

Psoriasis was positively associated with markers of adiposity and high-sensitivity CRP (hs-CRP) in age-adjusted analysis (Table 2). In women, psoriasis was also associated with more unfavorable serum lipid and glucose profiles, as well as higher diastolic blood pressure.

The MetS, explored using the two established WC criteria [WC_{higher} / WC_{lower} [4]], was more frequent in men, 28%/37%, than in women, 23%/27%; *P* for difference between genders was <0.001 using both WC cut-offs. Psoriasis was associated with a higher prevalence of the MetS in women of all age groups; however statistical significance was not reached in middle-aged women using WC_{higher} (Figure 1). The difference in prevalence was largest in women age 30-44 and thereafter slightly decreased and remained stable. In men, the difference in prevalence

of the MetS was almost uniform across all age groups and reached statistical significance from middle age depending on the waist criteria.

In the total population, 32% of individuals with psoriasis, versus 24% of the reference population had MetS defined using WC_{higher}. In the corresponding age-adjusted logistic regression analysis, the odds of MetS was 43% higher among individuals with psoriasis (n=10,521: OR 1.43, 95% confidence interval, 95% CI 1.25-1.63; n=9,662, individuals with complete data on covariates: OR 1.41, 95% CI 1.22-1.62). This association persisted when the model was further adjusted for gender, smoking, physical activity and educational level (n=9,662: OR 1.35, 95% CI 1.17-1.56).

Due to the apparent interaction with age and gender we used fractional polynomial models to further explore the association between psoriasis and the MetS using WC_{higher} (Figure 2; test for interaction between gender and psoriasis, *P*=0.06). We observed a U-shaped pattern among women, with significantly increased odds in younger and non-significantly increased odds in older women (multivariable model, tests for interaction: psoriasis-age in women, *P*=0.10; psoriasis-gender below age 40, *P*=0.056). In men, the multivariable adjusted OR for MetS in men with vs. without psoriasis did not vary by age (test for interaction, psoriasis-age, *P*=0.67). Thus, men with psoriasis had an approximately 35% increased risk of MetS (OR 1.35, 95% CI 1.11-1.64). In women, the strongest association was observed at age 30; where psoriasis was associated with a 3.8-fold increased odds of MetS defined by WC_{higher} (Figure 1 and Table 3). Overall, the same patterns were found using both waist criteria; lower ORs were evident in women using WC_{lower}, while estimates in men were almost unchanged (Table 3).

A sensitivity analysis with a redefined definition of the exposure variable was made; only participants reporting a doctor's diagnosis were considered to have psoriasis (n=886), and participants with only self-report of diagnosis were excluded. The psoriasis−MetS association remained almost unchanged in multivariable analyses (WC_{higher}; n=9,566: OR 1.33, 95% CI 1.14-1.55). The same patterns were observed in both genders (e.g. WC_{higher}; women age 30: OR 3.13, 95% CI 1.14-8.57), except for men age 70 (WC_{higher}; OR 1.39, 95% CI 1.03-1.88).

To assess present medication use as a proxy for severity of psoriasis, we used data from the Norwegian Prescription Database; we observed a dose-response relation between psoriasis

treatment in women with psoriasis; 1=no prescription, 2=prescription without systemic medication, 3=prescription with systemic medication, and odds of high WC in age-adjusted analysis (WC_{higher}, OR 1.33, 95% CI 1.001-1.77). There was no such association in men.

Discussion

In this population-based study, including mostly mild psoriasis cases, the association between psoriasis and risk of the MetS was modified by gender and age. Young women with psoriasis had an almost four-fold increased odds of MetS compared to women without a history of psoriasis. While, the odds decreased with age, the absolute difference in prevalence of the MetS between women with and without psoriasis remained quite stable. Across all ages, men with psoriasis had a 35% increase in the odds of MetS compared to men without psoriasis. These associations were independent of potentially confounding lifestyle factors.

The mechanisms contributing to the U-shaped pattern by age in the psoriasis-associated odds of MetS in women are not clearly understood (Figure 2). Abdominal obesity, which was the most frequent MetS-component in women in this study, is also a key initiator of insulin resistance,[25] and for a given level of WC women exhibit more adverse metabolic disturbances than men.[26] In women 30-44 years, approximately 75% of those with psoriasis and 45% of those without psoriasis had WC ≥ 88 cm. There have been large secular changes in lifestyle in the Tromsø Study population, and younger female birth cohorts have increasingly higher BMI and waistlines compared to prior generations.[10,22,27] This may explain some of the U-shaped association of psoriasis with MetS. Among the elderly the prevalence of the MetS and hypertension in particular is high; in this age group about 80% have hypertension independent of their psoriasis status. This age-related increase in metabolic components is primarily driven by other factors than psoriasis, possibly attenuating the OR estimates. Furthermore, the suggested higher cardiovascular mortality among individuals with psoriasis,[28-30] could produce lower effect estimates in the older age groups, due to a healthy survivor bias.

To our knowledge, no prior study has evaluated the risk of MetS in psoriasis by age and gender using non-linear risk models which generally give better fit to data than traditional linear models.[31] The MetS was assessed using the new harmonized criteria including two cut-

offs for measured WC. Further strengths include the largest sample from a general population survey; including a wide age-range, high attendance, comprehensive assessment of lifestyle factors and clinical examinations using standardized and validated methods by trained health professionals, performed within a short time frame.[24]

To our knowledge, all but two studies[1,14] estimating the psoriasis−MetS association have been conducted in clinical settings or within samples from insurance or health care databases[2,3,32-36], which potentially introduces a range of biases and limits generalizability.[14-18] In this study from a general health survey with no publicity to recruit individuals with psoriasis, we may assume that selection bias in terms of psoriasis diagnosis was minimal.[37] However, there were relatively few persons invited and even fewer attending in the youngest age groups with attendance of 44% in men and 58% in women below age 45. This gives greater uncertainty to the validity of the estimates from these age groups, mainly in men. When excluding individuals with incomplete information on covariates, there were no evident changes in the age-adjusted odds ratios (Table 3), indicating limited bias due to missing data. Longitudinal studies have demonstrated a tendency to recruitment of healthier individuals.[23,24] Thus, overweight participants may be underrepresented in health surveys,[38] which may lead to attenuation of the effect estimates.

Psoriasis has a major impact on a person's quality of life.[39-41] This may lead to unhealthy lifestyle choices, which in turn, increases the risk of several diseases including the MetS. This study evolves present knowledge of the psoriasis−MetS relationship, by its thorough adjustment of important lifestyle confounders, something which has been missing in most studies investigating this association.[15,19] However, factors which have not been evaluated in this study, including genetic predisposition, mental health and diet, may lead to residual confounding of the association. All blood samples were taken non-fasting, which could lead to non-differential misclassification of serum lipid levels and bias the psoriasis−MetS association towards the null value. Several drugs given for psoriasis are known to induce weight-gain or affect the blood-lipid profile. Due to the low number of persons on systemic drugs in this study this was not further investigated.

Self-report of data is a widely used method in epidemiological studies of skin disease;[42-45] however, there are concerns about the accuracy of psoriasis diagnosis with this approach

(Supplementary information).[10] Approximately 90% of cases are classical plaque phenotypes,[46] which are adequately diagnosed by trained general practitioners,[16,47,48] who care for the majority of patients with psoriasis in Norway. Several studies have pointed out that up to 50% of mild psoriasis cases may go undiagnosed by a doctor,[42,49,50] something which could potentially attenuate the effect estimates. It is unlikely that a misclassification of the diagnosis explains the higher odds of MetS among persons with psoriasis in this cohort. One could expect an even stronger association with a more specific definition of psoriasis.[1,51] However, limiting the analysis to include only participants reporting a physician's diagnosis led to a slight reduction in the effect estimates. This may reflect a detection bias in physician's diagnosis where persons with a less favorable metabolic profile consult their physician less frequently. Due to the small number of psoriasis cases without confirmed diagnosis, this could not be further evaluated.

The results of this study confirm findings from the smaller NHANES[1] as well as the large-scale UK general practice database;[2] these studies also suggested that the association between psoriasis and the MetS may be strongest among women. Despite having a database design, an age range from 45 to 65 years, different assessment criteria for MetS and incomplete information on potential confounders, the UK study reported almost identical overall odds as in this study, adjusted OR 1.41, 95% CI 1.31–1.51, and the MetS was found in 34% of individuals with psoriasis versus 26% of controls.[2] Comparably, in our population; 33-39% of participants with psoriasis versus 25-31% of controls were affected depending on the used waist circumference criteria, supporting the external validity of the findings. In the NHANES study, with subjects aged 20-59 years, 40% of psoriatics versus 23% of controls fulfilled the definition of the MetS; while in the Tromsø cohort the doubled prevalence of MetS among individuals with psoriasis was present in young women only. However, the US study population had an increased waistline compared to the Tromsø population,[1] while the Danish study, which found no difference in distribution of the MetS in persons with and without psoriasis, had a lower mean WC.[14]

Interestingly, there was indication of a dose-response relationship between psoriasis severity, indicated through treatment, and an increased waistline in women; in line with findings of a dose-dependent increase in risk of MetS by disease severity from the UK general practice database.[2] A longitudinal study suggested that obesity-related chronic inflammation may

increase the risk of developing psoriasis in women.[52] Evidence, also indicates that weight loss and reduction in waist circumference may improve psoriasis disease severity.[53] Insulin-resistance has been seen to block keratinocyte differentiation, and may contribute in the pathogenesis of both psoriasis as well as metabolic and cardiovascular disease.[54-56] Presently, it is not established if psoriasis is a driving factor behind the MetS or if the MetS leads to a debut and/or worsening of psoriasis.[57] The cross-sectional design of this study limits the possibility of drawing conclusions in terms of causality. However, it seems unlikely that the substantially elevated prevalence of MetS in the cohort should be due to the inflammatory load from the skin disease alone.[58] Although women with psoriasis displayed a particularly unfavorable metabolic profile; both genders had substantially elevated hs-CRP indicating low-grade systemic inflammation. It is plausible that psoriasis serves as a marker of a common genetic susceptibility bridging the association between psoriasis and systemic manifestations such as the MetS and cardiovascular disease given the right environmental conditions.[59-62]

The increased burden of the MetS among individuals with psoriasis in this cohort is grounds for concern from a public health perspective; while the total prevalence of psoriasis is highest in Scandinavia,[10,13,14] doubled figures are also reported in the US and Asia, suggesting a global trend.[8,9,11] In this cohort the odds of having the MetS are substantially increased, especially among young women with psoriasis, also after adjusting for relevant confounding factors. These findings support that there may be a benefit from targeted screening for the MetS among individuals with psoriasis from a relatively early age, in order to reduce the risk of diabetes and cardiovascular outcomes in this patient group.

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Table 1. Characteristics of the Study Population: Women and men with and without psoriasis (N = 10,521*). Values are age-adjusted means (standard deviation, SD) and proportions. The sixth Tromsø Study.

	Psoriasis	**No Psoriasis**	*P*-value**
Women			
N*	557	4942	
Age, years	57.3 (11.0)	55.7 (11.9)	0.003
Live with spouse	70.5	72.0	0.45
College/University education	31.9	39.0	0.002
Low income	23.4	21.1	0.22
Present use of statins	11.2	11.2	0.99
Present smoker	31.0	20.1	<0.001
Alcohol higher,	19.9	21.2	0.48
Low leisure activity	22.0	18.0	0.03
Men			
N*	580	4442	
Age, years	57.6 (11.5)	56.3 (11.2)	0.01
Live with spouse	84.1	82.8	0.44
College/University education	37.1	42.1	0.03
Low income	13.8	12.9	0.49
Present use of statins	18.1	15.6	0.10
Present smoker	22.8	18.6	0.02
Alcohol higher	23.7	25.5	0.33
Low leisure activity	21.8	20.4	0.44

*Numbers may vary due to missing information.

**Test: Means assessed by Generalized linear model, binary logistics for dichotomous variables or scale response for linear, adjusted for age. P-values generated through Wald statistics.

Low income: Proportion with approximately lowest income quartile.

Low leisure activity: Proportion reporting mostly sedentary leisure time activity.

Alcohol higher: Proportion with alcohol intake 2-3 times a week or more.

Table 2. Means (standard deviation, SD) of metabolic risk factors in women and men with and without psoriasis (n = 10,521*). The sixth Tromsø study.

	Psoriasis		No Psoriasis		
	Mean	(SD)	Mean	(SD)	*P*-value**
Women					
Weight, kg	72.4	(13.1)	70.9	(13.1)	0.01
Body mass index, kg/m^2	27.1	(4.6)	26.4	(4.6)	0.002
Waist circumference, cm	92.3	(12.2)	90.4	(12.1)	0.001
Waist-hip-ratio	0.88	(0.07)	0.87	(0.07)	<0.001
Systolic blood pressure, mmHg	133.1	(24.7)	132.0	(23.8)	0.22
Diastolic blood pressure, mmHg	75.8	(10.3)	74.7	(10.1)	0.01
Triglycerides, mmol/l	1.54	(0.9)	1.35	(0.7)	<0.001
Total cholesterol, mmol/l	5.79	(1.1)	5.66	(1.1)	0.006
LDL-cholesterol, mmol/l	3.64	(1.0)	3.52	(1.0)	0.003
HDL-cholesterol, mmol/l	1.59	(0.4)	1.66	(0.4)	0.001
Nonfasting glucose, mmol/l	5.16	(1.2)	5.08	(1.0)	0.06
HbA1c, %	5.62	(0.6)	5.56	(0.6)	0.006
hs-CRP, mg/L	3.07	(6.2)	2.32	(4.3)	<0.001
Men					
Weight, kg	86.5	(13.8)	85.6	(13.0)	0.11
Body mass index, kg/m^2	27.6	(3.9)	27.2	(3.7)	0.03
Waist circumference, cm	100.3	(11.0)	99.2	(10.4)	0.01
Waist-hip-ratio	0.96	(0.06)	0.95	(0.07)	0.003
Systolic blood pressure, mmHg	137.5	(19.6)	137.4	(20.2)	0.95
Diastolic blood pressure, mmHg	80.8	(10.4)	81.3	(10.2)	0.24
Triglycerides, mmol/l	1.75	(1.0)	1.67	(1.0)	0.06
Total cholesterol, mmol/l	5.55	(1.1)	5.52	(1.1)	0.53
LDL-cholesterol, mmol/l	3.59	(0.9)	3.57	(0.9)	0.50
HDL-cholesterol, mmol/l	1.34	(0.4)	1.36	(0.4)	0.15
Nonfasting glucose, mmol/l	5.40	(1.3)	5.38	(1.4)	0.73
HbA1c, %	5.70	(0.7)	5.68	(0.7)	0.56
hs-CRP, mg/L	2.99	(4.9)	2.37	(4.5)	0.002

*Number may vary due to missing information.

**Test: Means assessed by Generalized linear model, scale response for continuous variables, adjusted for age. P-values generated through Wald statistics.

LDL: Low density Lipoprotein Cholesterol

HDL: High density Lipoprotein Cholesterol

HbA1c: Glycated Hemoglobin

hs-CRP: serum High sensitive C-reactive protein

Table 3. Odds ratio (OR) and 95% Confidence Interval (95% CI) for metabolic syndrome in persons with psoriasis compared to persons without psoriasis estimated from logistic regression analysis with age modelled using second-degree fractional polynomial terms. The sixth Tromsø Study.

	Total n	**30 years** OR (95% CI)	**40 years** OR (95% CI)	**50 years** OR (95% CI)	**60 years** OR (95% CI)	**70 years** OR (95% CI)	**79 years** OR (95% CI)
Women							
MetS, WC_{higher}							
Unadjusted	5,499	3.86 (1.59, 9.38)	2.27 (1.43, 3.61)	1.50 (1.16, 1.95)	1.23 (0.95, 1.60)	1.39 (1.04, 1.86)	2.23 (1.03, 4.81)
Unadjusted*	4,971	4.21 (1.68, 10.54)	2.38 (1.48, 3.83)	1.51 (1.15, 1.97)	1.18 (0.89, 1.56)	1.27 (0.92, 1.74)	1.92 (0.83, 4.42)
Adjusted**	4,971	3.82 (1.51, 9.66)	2.18 (1.35, 3.53)	1.40 (1.07, 1.84)	1.13 (0.85, 1.50)	1.27 (0.92, 1.75)	2.03 (0.87, 4.75)
MetS, WC_{lower}							
Unadjusted	5,499	2.98 (1.25, 7.10)	1.99 (1.27, 3.12)	1.45 (1.12, 1.86)	1.24 (0.96, 1.60)	1.35 (1.02, 1.80)	1.92 (0.90, 4.10)
Unadjusted*	4,971	3.21 (1.31, 7.88)	2.07 (1.30, 3.29)	1.45 (1.12, 1.89)	1.21 (0.92, 1.58)	1.28 (0.93, 1.74)	1.76 (0.78, 4.01)
Adjusted**	4,971	2.89 (1.16, 7.16)	1.89 (1.18, 3.02)	1.35 (1.04, 1.77)	1.15 (0.88, 1.52)	1.27 (0.92, 1.74)	1.84 (0.80, 4.22)
Men							
MetS, WC_{higher}							
Unadjusted	5,022	1.50 (0.92, 2.47)	1.45 (1.03, 2.05)	1.40 (1.12, 1.75)	1.35 (1.12, 1.63)	1.30 (0.99, 1.71)	1.26 (0.85, 1.87)
Unadjusted*	4,691	1.38 (0.83, 2.31)	1.38 (0.96, 1.97)	1.37 (1.09, 1.73)	1.37 (1.12, 1.66)	1.36 (1.02, 1.81)	1.36 (0.89, 2.05)
Adjusted**	4,691	1.32 (0.78, 2.21)	1.33 (0.92, 1.91)	1.34 (1.06, 1.69)	1.35 (1.10, 1.65)	1.36 (1.01, 1.82)	1.37 (0.90, 2.08)
MetS, WC_{lower}							
Unadjusted	5,022	1.36 (0.85, 2.17)	1.36 (0.98, 1.89)	1.37 (1.10, 1.69)	1.37 (1.14, 1.64)	1.37 (1.04, 1.78)	1.38 (0.94, 2.01)
Unadjusted*	4,691	1.35 (0.84, 2.19)	1.35 (0.96, 1.89)	1.34 (1.08, 1.67)	1.34 (1.11, 1.61)	1.33 (1.01, 1.76)	1.33 (0.89, 1.98)
Adjusted**	4,691	1.30 (0.80, 2.12)	1.31 (0.93, 1.84)	1.31 (1.05, 1.64)	1.32 (1.09, 1.59)	1.32 (1.00, 1.75)	1.33 (0.89, 1.99)

*Unadjusted analysis including individuals with complete information on covariates used in the adjusted analysis. **Adjusted model includes: smoking, physical activity in leisure time, educational level.

MetS, WC_{higher}: Harmonized definition of the Metabolic syndrome using the higher Waist circumference criteria (Women ≥ 88 cm; Men≥ 102 cm).

MetS, WC_{lower}: Harmonized definition of the Metabolic syndrome using the lower Waist circumference criteria (Women ≥ 80 cm; Men ≥ 94 cm)

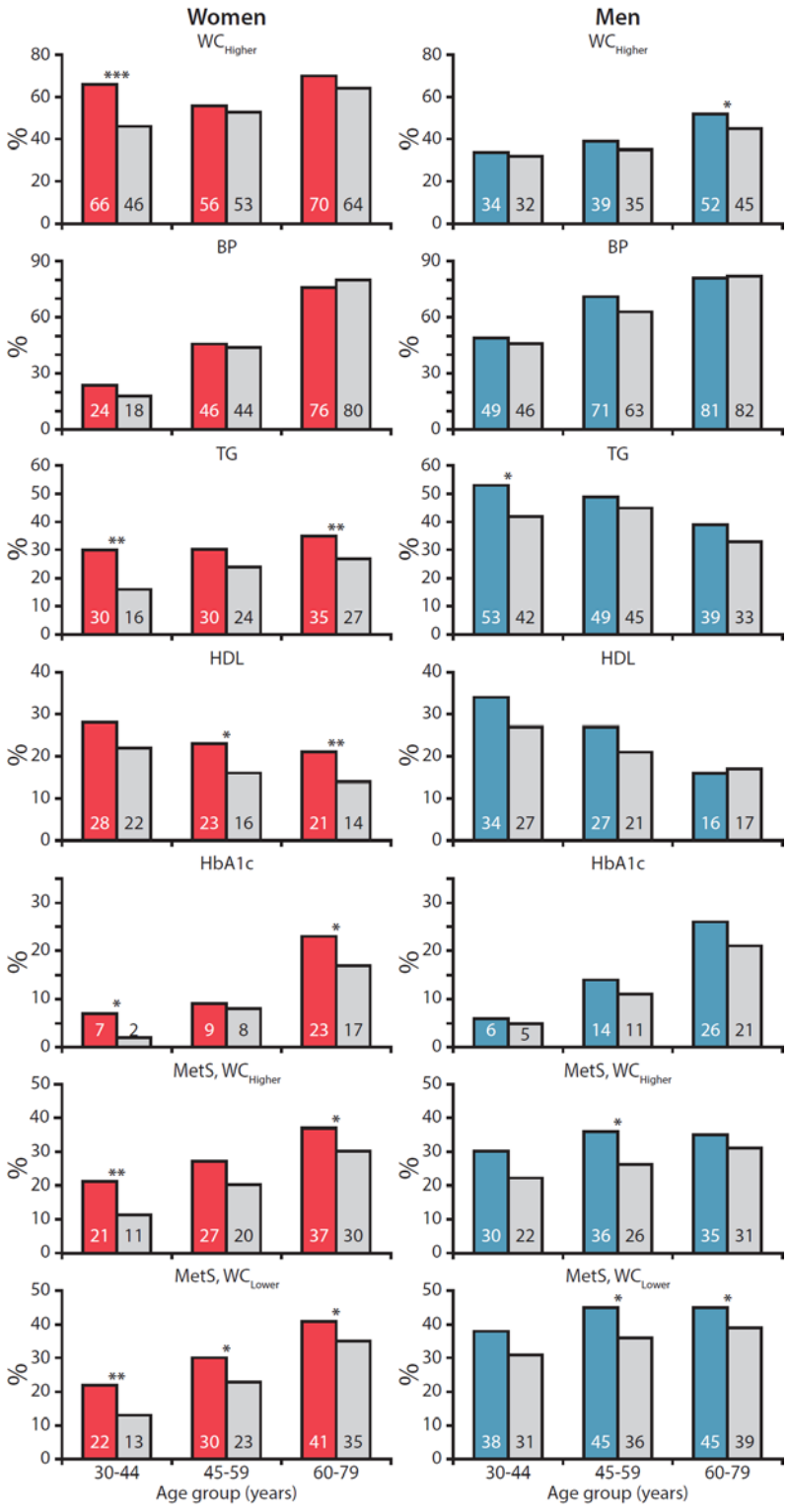

Figure 1: Prevalence of metabolic syndrome (MetS) components and the full syndrome by gender and age, the sixth Tromsø Study. Women, n=5,499: Red bars: psoriasis; Grey bars: no psoriasis. Men, n=5,022: Blue bars: psoriasis; Grey bars: no psoriasis. WC_{higher}: waist circumference women ≥ 88 cm and men ≥ 102 cm. WC_{lower}: waist circumference women ≥ 80 cm and men ≥ 94 cm. TG: triglyceride level ≥ 1.7 mmol/l. HDL: HDL-C < 1.03 mmol/l in males and < 1.29 mmol/l in females. BP: systolic blood pressure ≥ 130 mmHg or diastolic blood pressure ≥ 85 mmHg, or treatment for hypertension. HbA1c: HbA1c ≥ 6.1% or treatment for diabetes. MetS, WC_{higher}: MetS using WC_{higher}. MetS, WC_{lower}: MetS using WC_{lower}. *P < 0.05; **P < 0.01; ***P < 0.001.

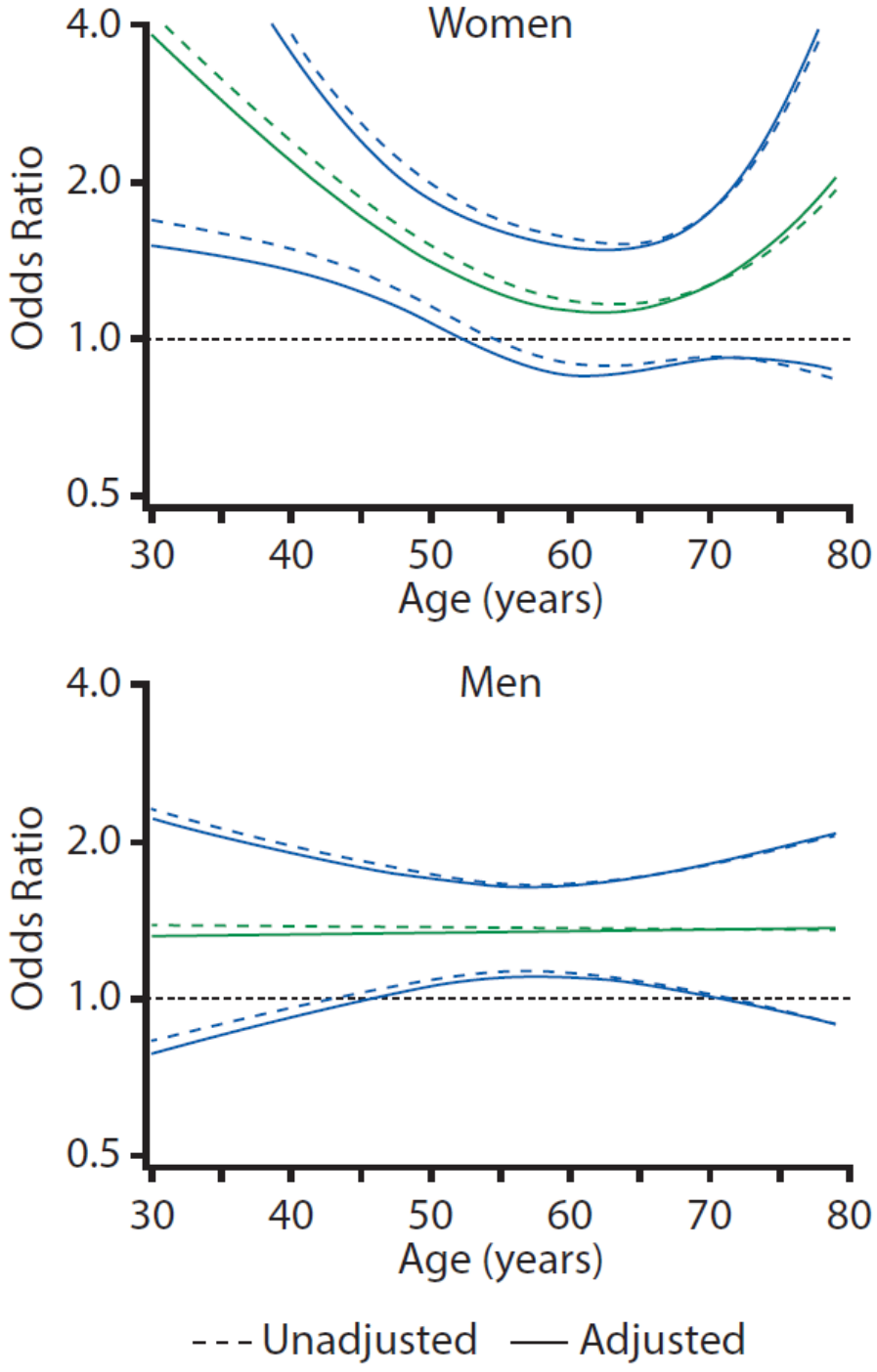

Figure 2: Odds ratio for metabolic syndrome (green line) with 95% confidence interval (blue lines) among women and men with psoriasis compared to the reference population, the sixth Tromsø Study. Metabolic syndrome defined using the higher waist circumference criteria (Women ≥ 88 cm; Men ≥ 102 cm). Fractional polynomial model: unadjusted (dotted lines; Women, n=5,499; Men, n=5,022) and adjusted for smoking, educational level and physical activity in leisure time (solid lines; Women, n=4,971; Men, n=4,691).

Supplementary Information

Material and Methods

Study population and design

In the sixth Tromsø study (Tromsø 6), the invited population was comprised of all persons age 40-42 and 60-87 (n=12,578), a 10% random sample of persons age 30-39 (n=1,056), and a 40% random sample of persons age 43-59 (n=5,787), as well as all participants from the second visit of the fourth survey, if not already included in the three groups above (n=341).[1] Due to possible recall bias or healthy survivor bias among the elderly, all subjects over the age of 79 (n=531) were excluded from the present analysis. Furthermore, pregnant women (n=28), as well as participants with missing data on self-reported psoriasis (n=1,176) or measured MetS components (n=726), were excluded.

In the study sample (n=10,521), the number of individuals with/without psoriasis within strata of women was: 30-44 years 99/1,249, 45-59 years 176/1,461, and 60-79 years 282/2,232; and men: 30-44 years 105/996, 45-59 years 173/1,342, and 60-79 years 302/2,104.

In terms of ethnicity, 93% of the study population described themselves as ethnic Norwegian (Europid), while the rest were indigenous Sami, Kven/Finnish or from other nationalities.

Assessment of psoriasis

Altogether 99% of individuals with psoriasis answered the question regarding doctor's diagnosis of psoriasis; 84% of men and 91% of women confirmed having received a doctor's diagnosis (p=<0.001). Reproducibility of self-report of psoriasis among repeated attendees in the Tromsø study has been reported to be between 84-91%.[2]

The self-reported present severity of psoriasis was assessed through rating current symptoms using a scale from 0-10 in the questionnaire. A total of 828 participants provided data. Among these 16% stated no symptoms, 56% mild (1-4), 23% moderate (5-7), and 5% severe symptoms (8-10). The level of self-assessed present disease severity was slightly lower than the objective measurements found in the studies based on health databases, as could be expected,[3-5] and in line with the validated psoriasis data from the Rotterdam cohort study (Tromsø/ Rotterdam: Mild= 72/76%, Moderate to Severe= 28/24%).[6]

Information on medication from the Norwegian Prescription Database (NorPD) was used as a proxy for disease severity. Information on all registered prescriptions relevant for treatment of psoriasis from 1 October 2006 to 1 June 2009 was linked with data on a selected set of variables from Tromsø 6. This analysis included all individuals age 30-79 with self-reported psoriasis and measured WC, n=1,192. Due to the restricted set of variables, the application of the full metabolic syndrome based exclusion criteria could not be evaluated within this data set. A total of 584 individuals (49%) received one or more registered prescription(s) during the time period 2006-09: 39% received moderate/strong topical steroids; 14% mild topical steroids; 13% vitamin D analogs and other topical psoriasis drugs. Systemic drugs were prescribed to 66 patients in total (6%), including Methotrexate (n=48), TNF-alpha inhibitors (n=14), Acitretin (n=9), and Ciclosporin (n=1). Disregarding missing entries and misclassification, the data indicate that half of the psoriatic population was in remission, did not seek medical treatment, or received UV-treatment or other hospital based treatment in the time period (not registered in NorPD).

The fact that half of the population was not receiving treatment at the time of survey is in line with other studies which have validated self-report of psoriasis diagnosis and found a point prevalence of approximately 25-70%.[4,7-10] Several studies have pointed out that up to 50% of mild psoriasis cases may be undiagnosed.[7-9] Prior studies have also found that persons with skin disease tend to not seek medical attention,[4,5,8,11] and that there may be a gender difference in the degree that they seek medical consultation,[5] as also seen in our data. Due to the fluctuating course of psoriasis the validation of lifetime psoriasis through point prevalent examination or relying on medical record from a short time frame may lead to an underestimation of the lifetime prevalence of the disease.[12,13] An American validation study of an electronic medical records database supports that the relapsing and remitting course of psoriasis challenges the identification of prevalent cases in database studies.[13]

Clinical measurements and laboratory tests

All measurements were performed by trained health personnel at the screening centre. Hip and waist circumference were measured without outerwear by using a measuring tape. Hip circumference was measured around the widest part of the thigh while WC was measured at the umbilical line to the nearest centimetre. Height (cm) and weight (kg) were measured to the nearest 0.1 unit with participants wearing light clothes and no shoes. BMI was computed as weight divided by height squared (kg/m^2). Blood pressure was recorded three times in a

sitting position after 2 minutes rest, by the use of an automatic blood pressure measurement device, and the mean of the two last readings was generated. Non-fasting blood samples were collected from an antecubital vein and analyzed at the Department of Laboratory Medicine, University Hospital of North Norway, Tromsø.[1]

Assessment of the metabolic syndrome (MetS)

In order to be defined as having the MetS participants were required to have minimum three of the following five criteria: 1) Central obesity with WC ≥ 102 cm in men and ≥ 88 cm in women (WC_{higher}). Analysis using the newly presented lower cut-off values: WC ≥ 94 cm and ≥ 80 cm in Europid men and women respectively, were also performed (WC_{lower}).[14] 2) Raised triglyceride level ≥ 1.7 mmol/l. 3) Reduced HDL-C < 1.03 mmol/l in males and < 1.29 mmol/l in females. There were no persons taking the specific medications for isolated high triglycerides or low HDL-C stated in the definition of the MetS.[15] 4) Raised blood pressure; systolic ≥ 130 mmHg or diastolic ≥ 85 mmHg, or treatment for hypertension. 5) Raised fasting plasma glucose > 5.5 mmol/l, or treatment for diabetes.[15] In the present analysis, raised fasting glucose was replaced with HbA1c ≥ 6.1% according to cut-off value for pre-diabetes 6.1–6.4%.[16]

In a sensitivity analysis using HbA1c ≥ 6.0% as cut-off point for pre-diabetes, which was the best cut-off for impaired glucose tolerance among 3,476 participants undergoing an oral glucose tolerance test in T6,[17] there was little or no change in the association of psoriasis with risk of MetS (results not shown).

Covariates

Information on potential lifestyle confounders and socioeconomic status was collected by questionnaires.[1,18] Education level was dichotomized as College/University versus all lower levels of education combined. Total household income was dichotomized at the level of approximately the lowest quartile of household income. Alcohol intake was assessed using number of alcohol units per week as well as a binary variable where intake above 2-3 times per week was defined as higher consumption. Smoking status was reported with three categories; current daily smoking, former daily smoking and never smoking. Usual level of leisure activity in the past year (4 categories) was dichotomized into low physical activity (i.e. reading, watching television) and others, due to sedentary lifestyle being the most stable measure of physical activity level throughout life.[19]

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