

Psoriasis and Cardiometabolic Traits: Modest Association but Distinct Genetic Architectures

Manja Koch¹, Hansjörg Baurecht², Janina S. Ried³, Elke Rodriguez², Sabrina Schlesinger¹, Natalie Volks², Christian Gieger^{4,5}, Ina-Maria Rückert⁴, Luise Heinrich⁶, Christina Willenborg⁷, Catherine Smith⁸, Annette Peters⁴, Barbara Thorand⁴, Wolfgang Koenig⁹, Claudia Lamina¹⁰, Henning Jansen¹¹, Florian Kronenberg¹⁰, Jochen Seissler¹², Joachim Thiery¹³, Wolfgang Rathmann¹⁴, Heribert Schunkert¹¹, Jeanette Erdmann⁷, Jonathan Barker⁸, Rajan P. Nair¹⁵, Lam C. Tsoi¹⁶, James T. Elder^{15,17}, Ulrich Mrowietz², Michael Weichenthal², Sören Mucha¹⁸, Stefan Schreiber^{18,19}, Andre Franke¹⁸, Jochen Schmitt^{6,20}, Wolfgang Lieb^{1,20} and Stephan Weidinger^{2,20}

Psoriasis has been linked to cardiometabolic diseases, but epidemiological findings are inconsistent. We investigated the association between psoriasis and cardiometabolic outcomes in a German cross-sectional study ($n = 4,185$) and a prospective cohort of German Health Insurance beneficiaries ($n = 1,811,098$). A potential genetic overlap was explored using genome-wide data from $>22,000$ coronary artery disease and $>4,000$ psoriasis cases, and with a dense genotyping study of cardiometabolic risk loci on 927 psoriasis cases and 3,717 controls. After controlling for major confounders, in the cross-sectional analysis psoriasis was significantly associated with type 2 diabetes (T2D, adjusted odds ratio (OR) = 2.36; 95% confidence interval CI = 1.26–4.41) and myocardial infarction (MI, OR = 2.26; 95% CI = 1.03–4.96). In the longitudinal study, psoriasis slightly increased the risk for incident T2D (adjusted relative risk (RR) = 1.11; 95% CI = 1.08–1.14) and MI (RR = 1.14; 95% CI = 1.06–1.22), with highest risk increments in systemically treated psoriasis, which accounted for 11 and 17 excess cases of T2D and MI per 10,000 person-years. Except for weak signals from within the major histocompatibility complex, there was no evidence of genetic risk loci shared between psoriasis and cardiometabolic traits. Our findings suggest that psoriasis, in particular severe psoriasis, increases the risk for T2D and MI, and that the genetic architecture of psoriasis and cardiometabolic traits is largely distinct.

Journal of Investigative Dermatology advance online publication, 19 February 2015; doi:10.1038/jid.2015.8

¹Institute of Epidemiology, Christian-Albrechts University Kiel, Kiel, Germany; ²Department of Dermatology, Allergy, and Venerology, University Hospital Schleswig-Holstein, Campus Kiel, Kiel, Germany; ³Institute of Genetic Epidemiology, Helmholtz Zentrum München—German Research Center for Environmental Health, Neuherberg, Germany; ⁴Institute of Epidemiology II, Helmholtz Zentrum München—German Research Center for Environmental Health, Neuherberg, Germany; ⁵Research Unit of Molecular Epidemiology, Helmholtz Zentrum München—German Research Center for Environmental Health, Neuherberg, Germany; ⁶Center for Evidence-Based Healthcare, University Hospital Carl Gustav Carus, Technical University Dresden, Dresden, Germany; ⁷Institute for Integrative and Experimental Genomics and DZHK (German Research Centre for Cardiovascular Research), partner site Hamburg/Lübeck/Kiel, University Hospital Schleswig-Holstein, Campus Lübeck, Lübeck, Germany; ⁸St John's Institute of Dermatology, Division of Genetics and Molecular Medicine, Kings College London, London, UK; ⁹Department of Internal Medicine II-Cardiology, University of Ulm Medical Center, Ulm, Germany; ¹⁰Division of Genetic Epidemiology, Department of Medical Genetics, Molecular and Clinical Pharmacology, Innsbruck Medical University, Innsbruck, Austria; ¹¹Deutsches Herzzentrum Munich, Technische Universität München, Munich, Germany; ¹²Medizinische Klinik und Poliklinik IV, Diabetes Zentrum, Klinikum der Ludwig-Maximilians-Universität, Munich, Germany; ¹³Institute of Laboratory Medicine, Clinical Chemistry and Molecular Diagnostics, University Hospital Leipzig, Leipzig, Germany; ¹⁴German Diabetes Center, Leibniz Institute at Heinrich Heine University Düsseldorf, Institute of Biometrics and Epidemiology, Düsseldorf, Germany; ¹⁵Department of Dermatology, University of Michigan Medical School, Ann Arbor, Michigan, USA; ¹⁶Department of Biostatistics, Center for Statistical Genetics, University of Michigan, Ann Arbor, Michigan, USA; ¹⁷Ann-Arbor Veteran Affairs Hospital, Ann Arbor, Michigan, USA; ¹⁸Institute of Clinical Molecular Biology, Christian-Albrechts-University of Kiel, Kiel, Germany and ¹⁹Department of Internal Medicine I, University Medical Center Schleswig-Holstein, Kiel, Germany

²⁰These authors contributed equally to this work.

Correspondence: Stephan Weidinger, Department of Dermatology, Allergy, and Venerology, University Hospital Schleswig-Holstein, Schittenhelmstraße 7, Kiel 24105, Germany. E-mail: sweidinger@dermatology.uni-kiel.de

Abbreviations: AP, angina pectoris; CI, confidence interval; CAD, coronary artery disease; CARDIoGRAM, coronary artery disease genome-wide replication and meta-analysis; GWAS, genome-wide association study; ICD, International Statistical Classification of Diseases; KORA, Cooperative Health Research in the Region of Augsburg; MHC, major histocompatibility complex; MI, myocardial infarction; OR, odds ratio; RR, relative risk; SNP, single nucleotide polymorphism; T2D, type 2 diabetes

Received 10 September 2014; revised 19 December 2014; accepted 24 December 2014; accepted article preview online 19 January 2015

INTRODUCTION

Psoriasis is one of the most common chronic inflammatory skin diseases and affects 2–4% of the general population with, however, variations between and within countries (Parisi *et al.*, 2013), and causes a significant social and pharmacoeconomic burden (Suarez-Farinas *et al.*, 2012). Experimental data indicate that chronic skin inflammation has a systemic component, affects different metabolic pathways, and drives inflammation in other tissues (Wang *et al.*, 2012). In line with this concept, epidemiological studies reported an elevated risk for inflammatory comorbidities such as cardiovascular disease (CVD) and metabolic diseases, in particular in younger individuals with severe psoriasis—that is, those with a higher genetic component (Gelfand *et al.*, 2006; Lu *et al.*, 2013; Miller *et al.*, 2013; Shaharyar *et al.*, 2014). However, most published studies were carried out in selected populations and suffer from methodological limitations such as insufficient phenotyping and incomplete adjustment for potential confounders. Further, results on cardiometabolic risk factors associated with psoriasis are inconsistent (Armstrong *et al.*, 2013; Miller *et al.*, 2013; Samarasekera *et al.*, 2013). Results from disease-by-disease gene mapping indicate a considerable overlap in the genetic basis of different immune-mediated diseases (Zhernakova *et al.*, 2013), and data from candidate gene studies suggest that some genetic variants associated with the risk of inflammatory diseases, e.g. rheumatoid arthritis, also predispose to cardiovascular and metabolic diseases (Krawczak *et al.*, 2006; Ellinghaus *et al.*, 2012; Lieb and Vasan, 2013). However, comprehensive analyses on the potential overlap in the genetic architectures of psoriasis and cardiometabolic traits are lacking. In the current study, we aimed to analyze the association between psoriasis and cardiometabolic risk factors and clinical disease outcomes using two different epidemiological data sets: the population-based Cooperative Health Research in the Region of Augsburg (KORA) study ($n=4,185$) and data from German Health insurance beneficiaries ($n=1,811,098$). Furthermore, we performed comprehensive genetic analyses in order to assess whether and to which degree the genetic architectures of psoriasis and CVD overlap. To this end, we carried out *in silico* analyses of genetic coronary artery disease (CAD) and psoriasis risk variants identified through genome-wide association studies (GWAS) in $>22,000$ CVD cases, $>4,000$ psoriasis cases, and $>60,000$ controls. In addition, we used the Metabochip custom array to densely genotype and analyze established cardiometabolic risk loci in a set of 927 psoriasis cases and 3,717 controls.

RESULTS

Cross-sectional association of psoriasis with cardiometabolic traits in KORA

The prevalence of psoriasis in the KORA study sample including German adults ($n=4,185$; mean age 56 years, 48.5% men) was 4.8%, which is slightly above the prevalence reported from German secondary health care data on adults of the same age range (4%) (Schafer *et al.*, 2011). This might in part be attributable to mild cases that may not seek medical attention (Table 1). In terms of the cardiovascular risk factor

profile, individuals with psoriasis were less likely to be never smokers (36.7 vs. 45.4%), had a higher educational attainment (education ≥ 11 years; 29.2 vs. 22.7%), had higher waist circumference (98 vs. 93 cm), and had higher levels of C-reactive protein (6.3 vs. 5.9 ng l^{-1}) and leukocyte count (1.7 vs. 1.2 mg l^{-1}) as compared with individuals without psoriasis. No statistically significant differences in body mass index, blood pressure, total cholesterol-to-high-density lipoprotein cholesterol ratio, or carotid intima-media thickness were observed between individuals with and those without psoriasis. In multivariable linear regression analysis psoriasis was statistically significantly associated with waist circumference ($\beta=1.70$; 95% confidence interval (CI)=0.14–3.26), type 2 diabetes (T2D) (OR=2.36; 95% CI=1.26–4.41), and myocardial infarction (MI) (OR=2.26; 95% CI=1.03–4.96), but not with hypertension, metabolic syndrome, angina pectoris (AP), or peripheral arterial disease (Table 2, Supplementary Table S1 online). No evidence for effect modification by age was observed (all P for interaction >0.05).

Longitudinal association of psoriasis with incident cardiometabolic events in German Health Insurance beneficiaries

A total of 44,623 patients with prevalent psoriasis in 2005/2006 and 1,766,475 individuals without psoriasis were followed up for incident cardiometabolic end points from 2007 to 2012 with a median follow-up time of 6 years. Participant characteristics are provided in Table 3. In the fully adjusted model, patients with psoriasis had a significantly increased relative risk (RR) for T2D (RR=1.11; 95% CI: 1.08–1.14), AP (RR= 1.27; 95% CI=1.20–1.34), and MI (RR=1.14; 95% CI=1.06–1.22) compared with patients without psoriasis (Table 4, Supplementary Table S2 online). After adjusting for age, sex, cardiovascular risk factors, and comorbidities, psoriasis accounted for an excess risk of 17.89 incident cases of T2D, 10.43 incident cases of AP, and 3.25 incident MIs per 10,000 person-years. The association of psoriasis with MI was not modified by age (P for interaction >0.05). However, we observed effect modification by age for T2D (P for interaction $=4.2 \times 10^{-36}$), AP (P for interaction $=0.026$), and stroke (P for interaction $=3.2 \times 10^{-4}$). Specifically, we observed evidence for a decreasing strength of association between psoriasis and incident diabetes (multivariable adjusted RRs (95% CI) for age ≤ 40 years: 1.27 (1.06, 1.52); for age 41–60 years: 1.10 (1.04, 1.16); and for age >60 years: 1.04 (1.00, 1.07)). For stroke, stratified analyses do not suggest a qualitative or quantitative linear association (for age ≤ 60 years: 1.03 (0.89, 1.19); for age 61–70 years: 1.20 (1.07, 1.34); and for age >70 years: 1.07 (1.00, 1.13)). The association between AP and psoriasis increased with increasing age categories (for age ≤ 60 years: 1.16 (1.04, 1.29); for age 61–70 years: 1.21 (1.08, 1.35); and for age >70 years: 1.25 (1.16, 1.35)).

In sensitivity analyses the risk increments were markedly higher in psoriasis patients receiving systemic treatment, which is often used as a proxy for severe psoriasis (Gelfand *et al.*, 2006) (Table 4). Systemically treated psoriasis (see Supplementary Table S3 online in the Supplementary

Table 1. Characteristics¹ of the analytical study population of KORA survey participants (n = 4,185)

	No psoriasis (n = 3986)	Psoriasis (n = 199)	P-value ²
Age, years	56 (45, 67)	56 (46, 65)	0.971
Male, n (%)	1918 (48.1)	110 (55.3)	0.049
Smoking status, n (%)			
Never	1808 (45.4)	73 (36.7)	0.016
Former	1466 (36.8)	87 (43.7)	0.048
Current	712 (17.9)	39 (19.6)	0.534
Education, n (%) ³			
≤ 9 years	2075 (52.1)	100 (50.3)	0.619
10 years	1001 (25.1)	41 (20.6)	0.151
≥ 11 years	905 (22.7)	58 (29.2)	0.035
Alcohol intake, g per day	5.7 (0.0, 20.9)	5.7 (0.0, 28.6)	0.299
Physical activity, n (%) ⁴			
No activity	933 (23.4)	49 (24.6)	0.623
Low activity	523 (13.1)	32 (16.1)	0.230
Moderate activity	1557 (39.1)	75 (37.7)	0.698
High activity	973 (24.4)	43 (21.6)	0.368
BMI, kg m ^{-2.5}	26.9 (24.2, 30.1)	27.6 (24.5, 30.4)	0.117
Waist circumference, cm ⁶	93 (84, 103)	98 (87, 105)	0.003
Systolic blood pressure, mm Hg	123 (111, 136)	123 (111, 136)	0.727
Diastolic blood pressure, mm Hg	76 (70, 84)	77 (71, 84)	0.423
Hypertension, n (%)	1704 (42.8)	91 (45.7)	0.407
Hypertension treatment, n (%)	1188 (29.8)	60 (30.2)	0.917
Total cholesterol-to-HDL cholesterol ratio	3.9 (3.1, 4.7)	3.9 (3.3, 5.1)	0.080
Lipid-lowering treatment, n (%)	463 (11.6)	29 (14.6)	0.206
Type 2 diabetes, n (%)	207 (5.2)	21 (10.6)	0.001
Type 2 diabetes treatment, n (%)	169 (4.2)	17 (8.5)	0.004
Metabolic syndrome, n (%) ⁷	993 (35.2)	51 (40.2)	0.253
Myocardial infarction, n (%)	101 (2.5)	11 (5.5)	0.011
Peripheral arterial disease, n (%) ⁸	196 (6.9)	14 (9.0)	0.315
Angina pectoris, n (%) ⁹	194 (4.9)	12 (6.1)	0.450
Carotid intima-media thickness ¹⁰	0.8 (0.7, 0.9)	0.8 (0.7, 0.9)	0.684
CRP, mg l ^{-1.11}	1.2 (0.6, 2.6)	1.7 (0.8, 3.5)	0.001
Leukocytes, n nl ⁻¹⁹	5.9 (5.0, 7.1)	6.3 (5.1, 7.4)	0.024

Abbreviations: BMI, body mass index; CRP, C-reactive protein; HDL, high-density lipoprotein; KORA, Cooperative Health Research in the Region of Augsburg.

¹Values are median (25th and 75th percentile) or n (percent).

²Based on Wilcoxon–Mann–Whitney test for continuous variables and χ^2 -test for categorical variables.

³n = 4180.

⁴Defined as: no activity (no sports in summer or winter season), low activity (engaging in sports < 1 h per week in summer or winter season), moderate activity (engaging in sports 1–2 h per week regularly in summer or winter season), high activity (engaging in sports > 2 h per week in summer and winter season).

⁵n = 4167.

⁶n = 4173.

⁷n = 2948.

⁸n = 2990.

⁹n = 4182.

¹⁰Average of right and left common carotid artery; n = 2646.

¹¹n = 3024.

Table 2. Multivariable-adjusted beta coefficient or odds ratio (OR; 95% confidence interval in parentheses)¹ for cardiometabolic outcomes by psoriasis status (n = 4,185)

	Psoriasis, beta coefficient or OR (95% CI)	
	Model 1	Model 2
<i>Continuous outcomes</i>		
BMI, kg m ⁻²	0.51 (−0.14, 1.16) ²	0.44 (−0.17, 1.05) ³
Waist circumference, cm	2.03 (0.36, 3.70) ⁴	1.70 (0.14, 3.26) ⁵
Systolic blood pressure, mm Hg	−0.09 (−2.56, 2.38)	−0.04 (−2.49, 2.40) ⁶
Diastolic blood pressure, mm Hg	0.48 (−0.98, 1.95)	0.67 (−0.78, 2.13) ⁶
Total cholesterol-to-HDL cholesterol ratio	0.15 (−0.01, 0.31)	0.16 (<0.01, 0.32) ⁶
Carotid intima-media thickness	−0.01 (−0.03, 0.01) ⁷	−0.01 (−0.03, 0.01) ⁸
CRP, mg l ⁻¹	0.46 (−0.46, 1.37) ⁹	0.29 (−0.62, 1.20) ¹⁰
Leukocytes, n nl ⁻¹	0.20 (−0.06, 0.46) ¹¹	0.16 (−0.09, 0.41) ¹²
<i>Dichotomous outcomes</i>		
Hypertension	1.15 (0.83, 1.59)	1.08 (0.77, 1.50) ⁶
Type 2 diabetes	2.31 (1.41, 3.80)	2.37 (1.40, 4.02) ⁶
Metabolic syndrome	1.25 (0.85, 1.85) ¹³	1.25 (0.85, 1.86) ¹⁴
Myocardial infarction	2.29 (1.17, 4.46)	2.26 (1.03, 4.96) ⁶
Peripheral arterial disease	1.46 (0.82, 2.60) ¹⁵	1.19 (0.64, 2.22) ¹⁶
Angina pectoris	1.33 (0.72, 2.44) ¹⁷	1.22 (0.65, 2.27) ¹²

Abbreviations: BMI, body mass index; CRP, C-reactive protein; HDL, high-density lipoprotein.

¹Beta coefficient for continuous outcomes or OR for binary outcomes. Model 1 was adjusted for sex and age (continuous). Model 2 was adjusted for sex, age (continuous), smoking status (never, former, current), years of education (≤9 years, 10 years, or ≥11 years), alcohol intake (continuous), physical activity (no activity, low activity, moderate activity, high activity), systolic blood pressure (continuous; except systolic, diastolic blood pressure, hypertension and metabolic syndrome), hypertension treatment (no, yes; except hypertension and metabolic syndrome), type 2 diabetes (no, yes; except type 2 diabetes and metabolic syndrome), type 2 diabetes treatment (no, yes; except type 2 diabetes and metabolic syndrome), lipid-lowering treatment (no, yes; except metabolic syndrome).

²n = 4167.

³n = 4162.

⁴n = 4173.

⁵n = 4168.

⁶n = 4180.

⁷n = 2646.

⁸n = 2642.

⁹n = 3024.

¹⁰n = 3019.

¹¹n = 4182.

¹²n = 4177.

¹³n = 2948.

¹⁴n = 2943.

¹⁵n = 2990.

¹⁶n = 2987.

¹⁷n = 4182.

Data online) accounted for ~41, 17, and 11 excess cases of AP, MI, and T2D, respectively, per 10,000 person-years (Table 4).

Association analysis of established CAD risk SNPs with psoriasis

Except for two polymorphisms that map to HLA-C/HCG27 (rs2894181) and C6orf10/BTNL2 (rs6932542), none of the established CAD-single nucleotide polymorphisms (SNPs) was significantly associated with psoriasis after conservative

Bonferroni correction for multiple testing (see Supplementary Table S4 online in the Supplementary Data online). Both major histocompatibility complex (MHC) polymorphisms represented signals independent from the major psoriasis HLA-C*0602 risk allele, an observation reported before (Feng *et al.*, 2009; Davies *et al.*, 2012). Effects on CAD and psoriasis risk were in the same direction, but the reported effect sizes on CAD were modest (OR<1.2) (Lu *et al.*, 2012).

Table 3. Characteristics¹ of the allgemeine Ortskrankenkasse Saxony database by psoriasis status (*n* = 1,811,098)

	Psoriasis				Total (<i>n</i> = 44,623)	P-value ² Psoriasis versus no Psoriasis
	No Psoriasis (<i>n</i> = 1,766,475)	No medication (<i>n</i> = 9,213)	Exclusively topical medication (<i>n</i> = 31,139)	Systemic medication (<i>n</i> = 4,271)		
Age (years) in 2005	49 (30, 68)	57 (43, 70)	61 (45, 72)	54 (42, 66)	59 (44, 71)	<1E–300
Male, <i>n</i> (%)	811,180 (45.9)	4,384 (47.6)	14,343 (46.1)	2,020 (47.3)	20,747 (46.5)	0.016
Hypertension, <i>n</i> (%) ^{3,4}	205,831 (19.5)	1,063 (26.3)	3,682 (28.9)	580 (29.7)	5,325 (28.4)	1.3E–204
Type 2 diabetes, <i>n</i> (%) ^{3,5}	120,507 (8.1)	787 (11.3)	2,860 (12.6)	394 (12.0)	4,041 (12.3)	2.1E–162
Myocardial infarction, <i>n</i> (%) ^{3,6}	20,103 (1.2)	143 (1.6)	574 (1.9)	80 (1.9)	797 (1.9)	3.2E–39
Peripheral arterial disease, <i>n</i> (%) ^{3,7}	31,138 (1.8)	234 (2.7)	918 (3.1)	103 (2.5)	1,255 (3.0)	1.8E–68
Angina pectoris, <i>n</i> (%) ^{3,8}	32,350 (1.9)	251 (3.0)	959 (3.4)	125 (3.2)	1,335 (3.3)	2.4E–82
Stroke, <i>n</i> (%) ^{3,9}	41,778 (2.5)	289 (3.3)	1,134 (3.9)	113 (2.7)	1,536 (3.6)	3.8E–54
Obesity, <i>n</i> (%) ^{3,10}	102,601 (6.7)	578 (7.8)	2,172 (8.8)	362 (10.8)	3,112 (8.8)	3.0E–53
Disorders of lipoprotein metabolism and other lipidemias, <i>n</i> (%) ^{3,11}	165,526 (11.8)	1,045 (16.7)	3,584 (16.8)	517 (17.1)	5,146 (16.8)	4.3E–158
Mortality, <i>n</i> (%) ³	174,642 (9.9)	1,076 (11.7)	4,272 (13.7)	371 (8.7)	5,719 (12.8)	1.3E–92

¹Values are given as median (25th and 75th percentile) or *n* (percentage).

²Based on the Wilcoxon–Mann–Whitney test for age and the χ^2 -test for categorical variables.

³Incidence in 2007–2012.

⁴*n* = 1,075,121.

⁵*n* = 1,514,541.

⁶*n* = 1,773,833.

⁷*n* = 1,751,381.

⁸*n* = 1,715,269.

⁹*n* = 1,746,355.

¹⁰*n* = 1,567,015.

¹¹*n* = 1,436,629.

Association analysis of established psoriasis risk SNPs with CAD

None of the established psoriasis risk SNPs was significantly associated with CAD after conservative Bonferroni correction for multiple testing (see Supplementary Table S5 online and Supplementary Figure S1 online in the Supplementary Data online). Suggestive evidence for association ($P < 0.05$) was observed for three SNPs (rs1265181, rs12191877, rs10484554) at the major psoriasis locus PSORS-1 in the MHC. These three polymorphisms are in moderate to strong linkage disequilibrium with the psoriasis HLA-C*0602 risk allele ($r^2 \geq 0.6$) and show weak opposing effects on CAD risk. Further suggestive evidence for association with CAD was observed for a variant near the interleukin enhancer-binding factor 3 (*ILF3*) and coactivator-associated arginine methyltransferase 1 (*CARM1*) genes ($P = 1.74 \times 10^{-3}$).

Proportion of CAD SNPs associated with psoriasis and vice versa

In 61.7% of the investigated psoriasis SNPs the same risk alleles showed a positive association ($OR > 1$) with CAD, which is in the range of expectation by chance ($P = 0.1439$). In the reverse comparison, in 65.5% of the CAD SNPs the same risk allele showed a positive association with psoriasis, which is slightly more than the expected 50% by chance ($P = 0.030$). However, none of these SNPs showed nominal significance ($P < 0.05$).

Metabochip analysis in the psoriasis case-control study

Multiple SNPs from within the MHC locus displayed a strong association with psoriasis. The top SNP was rs10484554 (see Supplementary Table S6 online in the Supplementary Data online), which tags the HLA-C*0602 risk allele ($P = 5.84 \times 10^{-16}$, $OR = 2.03$, 95% $CI = 1.86–2.20$) (Figure 1). Conditioning upon rs10484554, the P -values for all other SNPs at the MHC locus were substantially mitigated, which, however, could be due to a lack of power given that robust evidence for several independent signals from within the MHC has been provided in previous studies (Knight *et al.*, 2012). No non-MHC SNP exceeded the conservative array-wide significance level ($P = 5.03 \times 10^{-7}$). Suggestive evidence for association ($P < 5 \times 10^{-6}$) was observed for five loci comprising the genes *TMEM2*, *ZMIZ1*, *ARHGAP42*, and two intergenic regions (see Supplementary Table S7 online in the Supplementary Data online). Of the 43 previously reported psoriasis susceptibility loci (Hindorff *et al.*), 32 reached nominal significance ($P < 0.05$) in the Metabochip analysis. No association was seen for the loci *IL28RA*, *LCE3D*, *B3GNT2*, *ZDHHC23*, *TNFAIP3*, *TAGAP*, *ELMO1*, *ZC3H12C*, *SDC4*, and *UBE2I3*, which, however, are sparsely covered by the Metabochip (see Supplementary Table S8 online in the Supplementary Data online).

Table 4. Multivariable-adjusted relative risk (RR; 95% confidence interval in parentheses) and excess risk per 10,000 person-years¹ for cardiometabolic diseases by psoriasis status (*n* = 1,811,098)

	RR (95% CI)		Excess risk per 10,000 person-years ²	
	Model 1	Model 2	Model 1	Model 2
<i>Type 2 diabetes 2007–2012³</i>				
Psoriasis (present vs. absent)	1.21 (1.18, 1.25)	1.11 (1.08, 1.14)	34.16	17.89
Psoriasis, no medication	1.16 (1.08, 1.23)	1.06 (0.99, 1.13)	26.03	9.76
Psoriasis, exclusively topical medication	1.21 (1.17, 1.25)	1.10 (1.07, 1.14)	34.16	16.27
Psoriasis, systemic medication	1.38 (1.26, 1.51)	1.25 (1.14, 1.37)	61.81	40.67
<i>Myocardial infarction 2007–2012⁴</i>				
Psoriasis (present vs. absent)	1.24 (1.15, 1.33)	1.14 (1.06, 1.22)	5.58	3.25
Psoriasis, no medication	1.10 (0.94, 1.30)	1.01 (0.86, 1.19)	2.32	0.23
Psoriasis, exclusively topical medication	1.23 (1.14, 1.34)	1.13 (1.05, 1.23)	5.34	3.02
Psoriasis, systemic medication	1.62 (1.30, 2.01)	1.48 (1.19, 1.84)	14.40	11.15
<i>Angina pectoris 2007–2012⁵</i>				
Psoriasis (present vs. absent)	1.38 (1.30, 1.45)	1.27 (1.20, 1.34)	14.68	10.43
Psoriasis, no medication	1.29 (1.14, 1.46)	1.17 (1.04, 1.33)	11.21	6.57
Psoriasis, exclusively topical medication	1.38 (1.29, 1.47)	1.28 (1.20, 1.36)	14.68	10.82
Psoriasis, systemic medication	1.57 (1.32, 1.86)	1.43 (1.21, 1.70)	22.03	16.62
<i>Stroke 2007–2012⁶</i>				
Psoriasis (present vs. absent)	1.17 (1.11, 1.23)	1.11 (1.06, 1.17)	8.34	5.39
Psoriasis, no medication	1.10 (0.99, 1.24)	1.05 (0.94, 1.18)	4.90	2.45
Psoriasis, exclusively topical medication	1.19 (1.12, 1.26)	1.13 (1.07, 1.20)	9.32	6.37
Psoriasis, systemic medication	1.14 (0.95, 1.36)	1.08 (0.90, 1.29)	6.86	3.92

¹Model 1 was adjusted for sex and age (continuous). Model 2 was adjusted for sex, age (continuous), hypertonia (no, yes), type 2 diabetes (no, yes; except type 2 diabetes), obesity and disorders of lipoprotein metabolism and other lipidemias (no, yes).

²Excess risks calculated on the basis of adjusted risk ratios.

³*n* = 1,514,541.

⁴*n* = 1,773,833.

⁵*n* = 1,715,269.

⁶*n* = 1,746,355.

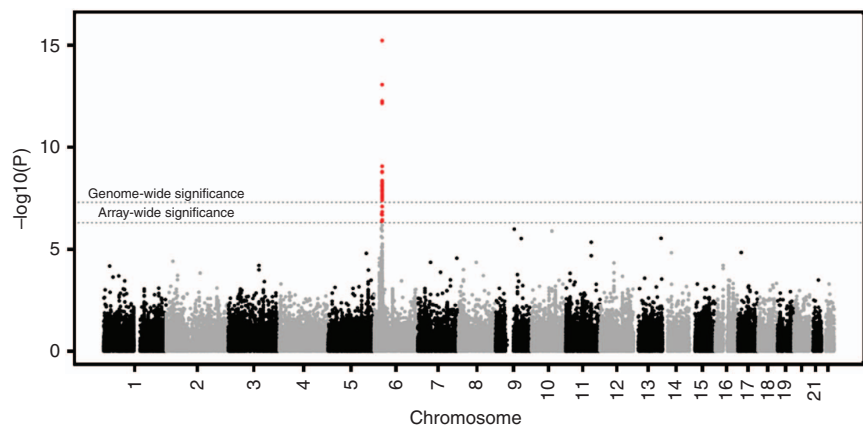


Figure 1. Manhattan plot of MetaboChip results on psoriasis.

DISCUSSION

Main findings

Using different large-scale epidemiological and genetic data sets, we assessed the interrelation of psoriasis and cardiometabolic outcomes as well as a potential common genetic underpinning of these traits. In both our cross-sectional and cohort study, psoriasis was an independent yet modest risk factor for T2D and MI. Sensitivity analyses in the cohort study provided evidence for a “dose–response” association as severe psoriasis was associated with higher risks for T2D, AP, and MI relative to mild psoriasis. Except for two psoriasis risk loci from within the MHC with small effects ($OR < 1.2$) on CAD risk, none of the established psoriasis risk polymorphisms showed a robust association with CAD, and no gene variant previously associated with CAD was robustly associated with psoriasis. Likewise, while confirming the vast majority of known psoriasis risk loci, our dense genotyping study did not indicate that validated loci for cardiometabolic traits have a notable effect on psoriasis risk, although we cannot rule out the probability that we may have missed rare variants or variants with minor effects.

In the context of the published literature

The first study that claimed an increased cardiovascular risk in patients with psoriasis stems from a large prospective, population-based cohort study using UK electronic medical record data (Gelfand *et al.*, 2006). Subsequently, a series of multiple studies reported a higher risk for various cardiometabolic traits (including hypertension, T2D, hyperlipidemia, hypercholesterolemia, and obesity) in patients with psoriasis, in particular in those with severe and widespread forms (Kimball and Wu, 2009; Langan *et al.*, 2012; Yeung *et al.*, 2013). However, most of these studies were hospital-based and investigated selected patient groups, and multiple biases including publication bias must be considered when interpreting them (Nijsten and Wakke, 2009; Stern and Nijsten, 2012). Further, the results in the published literature are not unambiguous. For example, in the population-based Rotterdam Study and in the National Health and Nutrition Examination Survey, psoriasis was not associated with the risk for coronary heart disease, stroke, or heart failure (Dowlathshahi *et al.*, 2013a), nor with fasting glucose (Love *et al.*, 2011), and in the Nurses' Health Study the association of psoriasis with T2D was very modest and only among younger patients (Li *et al.*, 2012). Finally, in line with our results, meta-analyses indicated that the association of psoriasis with cardiometabolic diseases is rather modest and driven by severe cases (Armstrong *et al.*, 2013; Ma *et al.*, 2013; Miller *et al.*, 2013; Samarasekera *et al.*, 2013). The degree to which the association is directly attributable to psoriasis remains controversial.

Although providing sufficient sample sizes and statistical power, routine data from health insurance databases commonly suffer from incomplete information on important confounders and potential detection, diagnostic, and observation bias (Swart *et al.*, 2014). In turn, population-based cross-sectional studies capture many outcomes and risk factors but are often underpowered to analyze diseases with a low

prevalence and do not allow to make causal inference, nor to establish the time sequence of events. In this paper, we have used both approaches in a complementary manner, and have analyzed primary cross-sectional data from the well-characterized KORA survey as well as secondary prospective data from the allgemeine Ortskrankenkasse Saxony administrative health care database. In the cross-sectional analysis, psoriasis was significantly associated with T2D and MI, and no substantial attenuation upon adjustment for multiple possible confounders was observed.

In line with the results from the cross-sectional analysis, after adjusting for major known risk factors in the prospective cohort study for psoriasis at large after a median follow-up time of 6 years, we observed a moderately increased RR for incident T2D and MI, as well as an increased risk for AP, which translates into estimated excess risks of 18, 11, and 3 cases of T2D, AP, and MI, respectively, per 10,000 person-years.

A recent *in silico* analysis on 363 SNPs in 4,482 psoriasis cases and 7,463 controls reported statistically significant associations of psoriasis with seven SNPs primarily implicated in dyslipidemia, hypertension, and CAD (Lu *et al.*, 2013). In our more comprehensive genetic approach including both large-scale GWAS data for psoriasis and CAD as well as high-density genotyping data for roughly 100,000 cardiometabolic candidate loci, we did not observe robust associations of psoriasis with genetic risk markers primarily associated with cardiometabolic risk factors and related end points, including CAD and T2D. On a similar note, genetic psoriasis loci displayed no evidence for association with CAD in the coronary artery disease genome-wide replication and meta-analysis (CARDIoGRAM) data set with $> 20,000$ CAD cases and $\sim 60,000$ controls, except for very modest effects of markers tagging the HLA-Cw6 allele. It has to be kept in mind, though, that we focused on relatively common genetic variation. Growing evidence indicates that inflammation participates centrally in all stages of CAD and that thus variations in MHC genes, which regulate inflammation and T-cell responses, might have effects across inflammatory traits. In particular, *BTNL2*, which has been linked with various immune-related diseases (Clancy *et al.*, 2010; Jin *et al.*, 2011; Valentonyte *et al.*, 2005), probably functions as a T-cell costimulatory molecule. Furthermore, T-cell activation regulated by costimulatory molecules has been implicated in both psoriasis and CAD (Lahoute *et al.*, 2011). Of note, we focused on common variants, and additional studies are warranted to assess the significance of rare genetic variants.

Given the lack of evidence for a joint genetic basis of psoriasis and cardiometabolic traits and the consistently observed “dose–response” relationship, we speculate that shared non-genetic risk factors not captured in our analysis and/or an increased inflammatory status of (severe) psoriatics might contribute to the slightly increased risk for comorbidities—e.g. inflammatory cytokines such as interleukins and tumor necrosis factor- α , which increase oxidative stress and drive insulin resistance (Dowlathshahi *et al.*, 2013b). The latter hypothesis would also be supported if early and efficient psoriasis treatment lowered risk for comorbidities in a prospective setting. Some support for this hypothesis is

provided by a recent large retrospective analysis demonstrating a reduced risk for T2D in patients with RA or psoriasis who had received a TNF inhibitor (Solomon *et al.*, 2011), compared with patients on other disease-modifying antirheumatic drugs. However, it has to be considered that even for severe psoriasis the excess risks for cardiometabolic diseases reported and observed here are very modest in absolute terms, and that, so far, the potential impact of early intervention with antipsoriatic agents has not been sufficiently investigated.

Strengths and limitations

The major strengths of our epidemiological analysis are the use of both a cross-sectional and a prospective population-based approach. In the cross-sectional analysis, psoriasis assessment and cardiometabolic risk profiling were stringent, known potential confounders were taken into account, and both soft and hard end points were analyzed. However, the number of patients with psoriasis and cardiovascular events was modest, and no stratification by psoriasis disease severity was possible. The prospective cohort was sufficiently powered to track and compare incident disease events in health care beneficiaries with and without psoriasis, but the observation period was relatively short. As no direct information on disease severity was available, systemic therapy was used as a surrogate marker. Further, although health administrative data appear to be rather reliable for MI and T2D (Muggah *et al.*, 2013), and we used stringent outcome definitions, the remaining limitations of disease ascertainment accuracy and surveillance bias must be taken into account. One related limitation is that exact time-to-event data could not be inferred from the database utilized. We therefore assumed that every participant adds 6 years of person-time when estimating excess risks, which may be an overestimation and may thus lead to a conservative estimate of the true excess risk.

Conclusions

Psoriasis at large appears to be an independent yet modest risk factor for T2D and MI. For the subgroup of patients with severe psoriasis, however, risk increments are considerably higher. Thus, although on a population level the association between severe psoriasis and CVD is rather modest and the increase in absolute disease risk is minor, this risk might be clinically relevant in individual patients. The excess comorbidity cannot fully be attributed to major known environmental/lifestyle determinants of MI and T2D risk and appears not to be due to shared genetic risk factors. Prospective and sufficiently large cohort studies are needed to further clarify the relationship between psoriasis and cardiometabolic traits, and randomized controlled trials should test whether and which psoriasis treatment has beneficial effects regarding comorbidity risk.

METHODS

Study samples

KORA sample. Within the Monitoring of Trends and Determinants in Cardiovascular Disease/KORA, southern Germany)

framework, different population-based surveys were performed. The present analysis included KORA-C, which is a subset of the KORA S3 as well as the KORA F4 survey conducted in 1994/95 and 1999/2001, respectively. The design and selection criteria for these surveys have been described previously (Holle *et al.*, 2005). Participants received a standardized interview and a self-administered questionnaire to gather information on medical history, and a physical and dermatological (F4) examination was performed and blood was drawn. Additional information on data ascertainment strategy of the KORA F3 and F4 study is provided (see Methods section in this article's Supplementary Data online). A total of 4,185 individuals with full phenotypic information were used for the present cross-sectional analysis.

German Health insurance beneficiaries. For the prospective cohort analyses relating psoriasis to incident T2D and MI, we utilized the allgemeine Ortskrankenkasse Saxony database, an anonymized population-based administrative health care database, which holds complete information on outpatient health care (diagnoses according to the International Statistical Classification of Diseases (ICD-10), treatment procedures according to Anatomical Therapeutic Chemical Classification-Code) and demographic characteristics (age and sex) of 2.4 million individuals from the state of Saxony, Germany, from 2005 to 2012. All individuals continuously insured until 2012 or until death were included in the present analysis ($n = 1,811,098$).

CARDIoGRAM study. The CARDIoGRAM consortium combines 14 GWAS for CAD with >22,000 CAD patients and >60,000 individuals free of CAD, as previously described in detail elsewhere (Schunkert *et al.*, 2011).

Psoriasis genetic case-control study. To investigate the association of known CAD SNPs and psoriasis, GWAS data from 4,489 psoriasis cases and 8,240 control subjects of European Caucasian descent recruited from Germany, UK, and the US were included (Nair *et al.*, 2009; Ellinghaus *et al.*, 2010; Strange *et al.*, 2010).

All participating studies were approved by relevant institutional review boards, and all participants provided written or oral consent for genetic research using protocols approved by the relevant institutional body.

Epidemiological analyses

Descriptive characteristics. The Kolmogorov-Smirnov test was used to assess the normality of continuous variables. Non-normally distributed continuous variables are presented as median (25th and 75th percentile), and categorical variables are presented as proportions stratified by psoriasis status. Differences by psoriasis status were assessed using the Wilcoxon-Mann-Whitney test for continuous variables and the χ^2 -test for categorical variables.

Cross-sectional analysis. The association of psoriasis status with continuous (body mass index, waist circumference, systolic blood pressure, diastolic blood pressure, total cholesterol-to-high-density lipoprotein cholesterol ratio, carotid intima-media thickness, C-reactive protein, or leukocytes) and dichotomous (hypertension, T2D, metabolic syndrome, MI, peripheral arterial disease, or AP) cardiometabolic characteristics in the KORA study was analyzed using multivariable adjusted linear and logistic

regression models, respectively. All models were adjusted for sex and age. Model 2 ("fully adjusted model") additionally adjusted for smoking status (never, former, current), years of education (≤ 9 years, 10 years, ≥ 11 years), alcohol intake (g per day), physical activity (no activity, low activity, moderate activity, high activity), systolic blood pressure, hypertension treatment (no, yes), T2D (no, yes), T2D treatment (no, yes), and lipid-lowering treatment (no, yes). In the sensitivity analysis, effect modification by age was investigated by inclusion of interaction terms of age and psoriasis status. All *P*-values were two-sided, and *P*-values < 0.05 were considered statistically significant. Statistical analyses were performed with SAS statistical analysis software (version 9.3).

Longitudinal analysis. For analyzing the association of psoriasis with incident cardiometabolic events in German Health Insurance beneficiaries, prevalent psoriasis in 2005 and 2006 was defined as the primary exposure variable. To minimize misclassification, we defined *a priori* that the ICD-10 code for psoriasis (L40) had to be documented at least twice in 2005 and 2006 or once in 2005 and 2006 and at least once in 2007 until 2012. If the last documented psoriasis diagnosis was a rule-out diagnosis, patients were considered nonexposed. For cardiovascular risk factors and other potentially confounding comorbidities, analogous internal validation methods were applied. Incident cardiometabolic events were identified through health insurance records. Health Insurance beneficiaries entered the study in 2005–2006 and were followed up from 2007 (start of person time) until the end of the follow-up period in 2012 (end of person time). Outcomes of interest were incident MI (ICD-10 code I21–I23), incident AP (ICD: I20), incident stroke (ICD: I63 and I64), and incident T2D (ICD: E11) in 2007 through 2012. Incident cases were defined as patients having no respective diagnosis documented in 2005 and 2006, and documentation of the respective ICD-10 code at least twice in 2007 until 2012. Patients with prevalent MI or T2D in 2005/2006 were excluded. The association between prevalent psoriasis (present in 2005/2006) and new-onset cardiometabolic diseases after 2006 (until 2012) was analyzed with generalized linear models using Poisson regression with robust error variances. All models were adjusted for sex and age. A second model was additionally adjusted for prevalent hypertension (ICD: I10; no, yes), T2D (no, yes), obesity (ICD: E66; no, yes), and for disorders of lipoprotein metabolism and other lipidemias (ICD: E78; no, yes). We attempted to deal with unmeasured disease severity by stratification by psoriasis-specific medication; that is, data on systemic therapy (including ultraviolet therapy, adalimumab, etanercept, infliximab, acitretin, cyclosporine, fumaric acid, methotrexate, methotrexate, azathioprine, cyclosporine, and hydroxyurea) were used to further differentiate psoriasis participants into those with "mild" and those with "severe" psoriasis as reported previously (Gelfand *et al.*, 2006). In sensitivity analysis, effect modification by age was investigated by inclusion of interaction terms of age and psoriasis status. The statistical analyses were performed with STATA data analysis and statistical software (version 12.1).

Genetic analyses

In silico analysis. A composite list of variants reported to be associated with psoriasis with genome-wide significance

($P < 5 \times 10^{-8}$) was compiled using the Catalogue of Published GWAS (Hindorff *et al.*) and associated reference lists (Tsoi *et al.*, 2012). A total of 57 SNPs were then evaluated for association with CAD in the CARDIoGRAM data set (Preuss *et al.*, 2010). In analogy, a total of 73 SNPs associated with CAD with genome-wide significance (Hindorff *et al.*; Lieb and Vasan, 2013) were tested for association with psoriasis in a meta-analysis of German, UK, and US case-control GWAS data sets with a total of 4489 psoriasis cases and 8240 controls. Details of the meta-analysis have been previously reported (Nair *et al.*, 2009; Ellinghaus *et al.*, 2010). SNPTEST was used to associate the imputed dosage for each SNP with psoriasis status separately in each study sample with adjustment for the first three principal components from a multidimensional scaling analysis of population stratification. The association test results of those SNPs with relatively high confidence (PROPER_Info > 0.4) were then meta-analyzed with METAL using the inverse-variance method based on a fixed-effect model. We had at least 96% power to detect an OR ≥ 1.2 for an SNP with $\geq 10\%$ allele frequency, applying a lenient significance threshold of $P < 0.01$ as proposed by Ellinghaus *et al.* (2012).

Proportion of psoriasis risk SNPs with a positive association with CAD and vice versa. We assessed the proportion of psoriasis risk-increasing alleles with a positive association with CAD (OR > 1) and vice versa. We tested whether this proportion differed from 0.5 (proportion of SNPs with an OR > 1 for CAD by chance) using an exact binomial test as proposed elsewhere (Lieb *et al.*, 2013).

Metachip study. A total of 927 German psoriasis patients and 3,713 controls were genotyped using the Metachip, a custom Illumina iSelect genotyping array of nearly 200,000 SNP markers, which was designed to analyze and fine-map association signals identified through GWAS meta-analyses of cardiometabolic traits and to fine-map established loci (Voight *et al.*, 2012). The patients were recruited from tertiary dermatology clinics based at the Technische Universität Munich and the University of Kiel (Ellinghaus *et al.*, 2012); controls were derived from the population-based KORA and POPGEN studies (Holle *et al.*, 2005; Krawczak *et al.*, 2006). The genotyping and calling of the Metachip were performed using Illumina GenomeStudio software. Genotype data of all subsamples underwent the same basic quality control as detailed in the online supplement. After a quality control procedure, 99,362 SNPs were analyzed. Within the cleaned Metachip data set, we performed two sets of analyses: First, we related all 99,362 SNPs to psoriasis using a logistic regression model, adjusting for sex and the first eight principal components from the multidimensional scaling of population stratification. Second, we looked in detail at regions that have been previously reported to be associated with psoriasis. From these regions, only four lead SNPs were directly genotyped on the Metachip. For the remaining previously reported psoriasis regions, we investigated the surrounding regions (± 500 kb) of each previously reported psoriasis lead SNP and reported the SNP with the lowest *P*-value. All association analyses were performed in PLINK (Purcell *et al.*, 2007). We applied a suggestive and array-wide significance level of $P = 5 \times 10^{-6}$ and $P = 5.03 \times 10^{-7}$, respectively. We had $> 79\%$ power to detect an OR ≥ 1.25 for an SNP, assuming the allele frequency is $\geq 10\%$ at the 5×10^{-6} significance level.

CONFLICT OF INTEREST

JTE reports receiving grants from National Institutes of Health during the conduct of the study. JSch reports grants from MSD, grants from Wyeth, grants from Novartis, and personal fees from Genentech, outside the submitted work. SW reports grants from the German Federal Ministry of Education and Research during the conduct of the study, grants from Pfizer, grants and personal fees from Biogen, grants and personal fees from Novartis, and personal fees from Roche-Posay, outside the submitted work. HS reports grants from e:AtherosSysMed, grants from DZHK/MHA, grants from CVgenes@target, personal fees from AstraZeneca Germany, personal fees from AstraZeneca India, personal fees from SERVIER GmbH Germany, personal fees from Boehringer-Ingelheim Germany, personal fees from MSD Sharp & Dohme GmbH Germany, personal fees from AMGEN GmbH Germany, and personal fees from BERLIN-CHEMIE AG Germany, outside the submitted work.

ACKNOWLEDGMENTS

We thank all individuals with psoriasis and CAD, their families, control individuals, and clinicians for their participation. The KORA study was initiated and financed by the Helmholtz Zentrum München—German Research Center for Environmental Health, which is funded by the German Federal Ministry of Education and Research and by the State of Bavaria. The project received infrastructure support through the DFG Clusters of Excellence “Inflammation at Interfaces” (grants EXC306 and EXC306/2), and was supported by the German Federal Ministry of Education and Research (BMBF) within the framework of the e:Med research and funding concept (e:AtherosSysMed and sysINFLAME, grant 01ZX1306A) and the PopGen 2.0 network (01EY1103). Support for the case-control psoriasis sample used for this study was provided by the National Institutes of Health (R01AR042742, R01AR050511, R01AR054966, R01AR062382, and R01AR065183 to JTE). JTE is supported by the Ann Arbor Veterans Affairs Hospital. This study makes use of data generated by the CARDIoGRAM Consortium and the Wellcome Trust Case-Control Consortium. Members of the consortia are listed in the Data Supplement. A full list of the Wellcome Trust Case-Control Consortium investigators who contributed to the generation of the data is available from www.wtccc.org.uk. Funding for the project was provided by the Wellcome Trust under award 076113 and 085475. We also acknowledge support from the Department of Health via the NIHR BioResource Clinical Research Facility and comprehensive Biomedical Research Centre award to Guy's and St Thomas' NHS Foundation Trust in partnership with King's College London and King's College Hospital NHS Foundation Trust. The funders had no role in the study design, in the collection, analysis, and interpretation of data, in the writing of the manuscript, and in the decision to submit the article for publication.

SUPPLEMENTARY MATERIAL

Supplementary material is linked to the online version of the paper at <http://www.nature.com/jid>

REFERENCES

- Armstrong AW, Harskamp CT, Armstrong EJ (2013) Psoriasis and metabolic syndrome: a systematic review and meta-analysis of observational studies. *J Am Acad Dermatol* 68:654–62
- Clancy RM, Marion MC, Kaufman KM *et al.* (2010) Identification of candidate loci at 6p21 and 21q22 in a genome-wide association study of cardiac manifestations of neonatal lupus. *Arthritis Rheum* 62:3415–24
- Davies RW, Wells GA, Stewart AF *et al.* (2012) A genome-wide association study for coronary artery disease identifies a novel susceptibility locus in the major histocompatibility complex. *Circ Cardiovasc Genet* 5:217–25
- Dowlathshahi EA, Kavousi M, Nijsten T *et al.* (2013a) Psoriasis is not associated with atherosclerosis and incident cardiovascular events: the Rotterdam Study. *J Invest Dermatol* 133:2347–54
- Dowlathshahi EA, van der Voort EA, Arends LR *et al.* (2013b) Markers of systemic inflammation in psoriasis: a systematic review and meta-analysis. *Br J Dermatol* 169:266–82
- Ellinghaus D, Ellinghaus E, Nair RP *et al.* (2012) Combined analysis of genome-wide association studies for Crohn disease and psoriasis identifies seven shared susceptibility loci. *Am J Hum Genet* 90:636–47
- Ellinghaus E, Ellinghaus D, Stuart PE *et al.* (2010) Genome-wide association study identifies a psoriasis susceptibility locus at TRAF3IP2. *Nat Genet* 42:991–5
- Feng BJ, Sun LD, Soltani-Arabshahi R *et al.* (2009) Multiple Loci within the major histocompatibility complex confer risk of psoriasis. *PLoS Genet* 5:e1000606
- Gelfand JM, Neimann AL, Shin DB *et al.* (2006) Risk of myocardial infarction in patients with psoriasis. *JAMA* 296:1735–41
- Hindorf L, MacArthur J, Morales J *et al.* A Catalog of Published Genome-Wide Association Studies <www.genome.gov/gwastudies>, Accessed December 2013
- Holle R, Happich M, Lowel H *et al.* (2005) KORA—a research platform for population based health research. *Gesundheitswesen* 67(Suppl 1): S19–25
- Jin Y, Birlea SA, Fain PR *et al.* (2011) Genome-wide analysis identifies a quantitative trait locus in the MHC class II region associated with generalized vitiligo age of onset. *J Invest Dermatol* 131:1308–12
- Kimball AB, Wu Y (2009) Cardiovascular disease and classic cardiovascular risk factors in patients with psoriasis. *Int J Dermatol* 48:1147–56
- Knight J, Spain SL, Capon F *et al.* (2012) Conditional analysis identifies three novel major histocompatibility complex loci associated with psoriasis. *Hum Mol Genet* 21:5185–92
- Krawczak M, Nikolaus S, von Eberstein H *et al.* (2006) PopGen: population-based recruitment of patients and controls for the analysis of complex genotype-phenotype relationships. *Community Genet* 9:55–61
- Lahoute C, Herbin O, Mallat Z *et al.* (2011) Adaptive immunity in atherosclerosis: mechanisms and future therapeutic targets. *Nat Rev Cardiol* 8:348–58
- Langan SM, Seminara NM, Shin DB *et al.* (2012) Prevalence of metabolic syndrome in patients with psoriasis: a population-based study in the United Kingdom. *J Invest Dermatol* 132:556–62
- Li W, Han J, Hu FB *et al.* (2012) Psoriasis and risk of type 2 diabetes among women and men in the United States: a population-based cohort study. *J Invest Dermatol* 132:291–8
- Lieb W, Jansen H, Loley C *et al.* (2013) Genetic predisposition to higher blood pressure increases coronary artery disease risk. *Hypertension* 61:995–1001
- Lieb W, Vasan RS (2013) Genetics of coronary artery disease. *Circulation* 128:1131–8
- 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
- Lu X, Wang L, Chen S *et al.* (2012) Genome-wide association study in Han Chinese identifies four new susceptibility loci for coronary artery disease. *Nat Genet* 44:890–4
- Lu Y, Chen H, Nikamo P *et al.* (2013) Association of cardiovascular and metabolic disease genes with psoriasis. *J Invest Dermatol* 133:836–9
- Ma C, Harskamp CT, Armstrong EJ *et al.* (2013) The association between psoriasis and dyslipidaemia: a systematic review. *Br J Dermatol* 168:486–95
- Miller IM, Ellervik C, Yazdanyar S *et al.* (2013) Meta-analysis of psoriasis, cardiovascular disease, and associated risk factors. *J Am Acad Dermatol* 69:1014–24
- Muggah E, Graves E, Bennett C *et al.* (2013) Ascertainment of chronic diseases using population health data: a comparison of health administrative data and patient self-report. *BMC Public Health* 13:16
- Nair RP, Duffin KC, Helms C *et al.* (2009) Genome-wide scan reveals association of psoriasis with IL-23 and NF-kappaB pathways. *Nat Genet* 41:199–204
- Nijsten T, Wakkee M (2009) Complexity of the association between psoriasis and comorbidities. *J Invest Dermatol* 129:1601–3
- Parisi R, Symmons DP, Griffiths CE *et al.* (2013) Global epidemiology of psoriasis: a systematic review of incidence and prevalence. *J Invest Dermatol* 133:377–85
- Preuss M, König IR, Thompson JR *et al.* (2010) Design of the Coronary ARtery Disease Genome-Wide Replication And Meta-Analysis (CARDIoGRAM) Study: a genome-wide association meta-analysis involving more than 22 000 cases and 60 000 controls. *Circ Cardiovasc Genet* 3:475–83

- Purcell S, Neale B, Todd-Brown K *et al.* (2007) PLINK: a tool set for whole-genome association and population-based linkage analyses. *Am J Hum Genet* 81:559–75
- Samarasekera EJ, Neilson JM, Warren RB *et al.* (2013) Incidence of cardiovascular disease in individuals with psoriasis: a systematic review and meta-analysis. *J Invest Dermatol* 133:2340–6
- Schafer I, Rustenbach SJ, Radtke M *et al.* (2011) [Epidemiology of psoriasis in Germany—analysis of secondary health insurance data]. *Gesundheitswesen* 73:308–13
- Schunkert H, König IR, Kathiresan S *et al.* (2011) Large-scale association analysis identifies 13 new susceptibility loci for coronary artery disease. *Nat Genet* 43:333–8
- Shaharyar S, Warraich H, McEvoy JW *et al.* (2014) Subclinical cardiovascular disease in plaque psoriasis: association or causal link? *Atherosclerosis* 232:72–8
- Solomon DH, Massarotti E, Garg R *et al.* (2011) Association between disease-modifying antirheumatic drugs and diabetes risk in patients with rheumatoid arthritis and psoriasis. *JAMA* 305:2525–31
- Stern RS, Nijsten T (2012) Going beyond associative studies of psoriasis and cardiovascular disease. *J Invest Dermatol* 132:499–501
- Strange A, Capon F, Spencer CC *et al.* (2010) A genome-wide association study identifies new psoriasis susceptibility loci and an interaction between HLA-C and ERAP1. *Nat Genet* 42:985–90
- Suarez-Farinas M, Li K, Fuentes-Duculan J *et al.* (2012) Expanding the psoriasis disease profile: interrogation of the skin and serum of patients with moderate-to-severe psoriasis. *J Invest Dermatol* 132:2552–64
- Swart E, Stallmann C, Powietzka J *et al.* (2014) [Data linkage of primary and secondary data: a gain for small-area health-care analysis?]. *Bundesgesundheitsblatt Gesundheitsforschung Gesundheitsschutz* 57:180–7
- Tsoi LC, Spain SL, Knight J *et al.* (2012) Identification of 15 new psoriasis susceptibility loci highlights the role of innate immunity. *Nat Genet* 44:1341–8
- Valentonyte R, Hampe J, Huse K *et al.* (2005) Sarcoidosis is associated with a truncating splice site mutation in BTNL2. *Nat Genet* 37:357–64
- Voight BF, Kang HM, Ding J *et al.* (2012) The metabochip, a custom genotyping array for genetic studies of metabolic, cardiovascular, and anthropometric traits. *PLoS Genet* 8:e1002793
- Wang Y, Gao H, Loyd CM *et al.* (2012) Chronic skin-specific inflammation promotes vascular inflammation and thrombosis. *J Invest Dermatol* 132:2067–75
- Yeung H, Takeshita J, Mehta NN *et al.* (2013) Psoriasis severity and the prevalence of major medical comorbidity: a population-based study. *JAMA Dermatol* 149:1173–9
- Zhernakova A, Withoff S, Wijmenga C (2013) Clinical implications of shared genetics and pathogenesis in autoimmune diseases. *Nat Rev Endocrinol* 9:646–59