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Psoriasis and cardiometabolic traits: modest association but distinct genetic architectures

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Conflict of Interest

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Abstract

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 (CAD) and >4.000 psoriasis cases, and with a dense genotyping study of cardiometabolic risk loci on 927 psoriasis cases and 3.717 controls. Controlling for major confounders, in the cross-sectional analysis psoriasis was significantly associated with type 2 diabetes (T2D, adjusted odd's 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 MHC, there was no evidence for genetic risk loci shared between psoriasis and cardiometabolic traits. Our findings suggest that psoriasis, in particular severe psoriasis, increases risk for T2D and MI, and that the genetic architecture of psoriasis and cardiometabolic traits is largely distinct.

Introduction

Psoriasis is one of the most common chronic inflammatory skin diseases that 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; i.e. 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 (Ellinghaus *et al*., 2012; Krawczak *et al*., 2006; 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 2 different epidemiological datasets: the population-based 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 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 analyse 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 healthcare 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 I). In terms of the cardiovascular risk factor profile, individuals with psoriasis were less likely to be never smoker (36.7% vs. 45.4%), had a higher educational attainment (education ≥11y; 29.2% vs. 22.7%), higher waist circumference (98 vs. 93 cm) and higher levels of CRP (6.3 n/nL vs. 5.9 n/nL) and leukocyte count (1.7 vs. 1.2 mg/L) as compared to individuals without psoriasis. No statistically significant differences in BMI, blood pressure,

total cholesterol-to-HDL cholesterol ratio or carotid intima-media thickness were observed between individuals with vs. without psoriasis. In multivariable linear regression analysis psoriasis was statistically significantly associated with waist circumference (β=1.70; 95% CI=0.14–3.26), T2D (OR=2.36; 95%CI=1.26–4.41) and MI (OR=2.26, 95%CI=1.03–4.96), but not with hypertension, metabolic syndrome, AP, nor peripheral arterial disease (PAD) (Table II, Table S1). 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 endpoints from 2007 to 2012 with a median follow-up time of 6 years. Participant characteristics are provided in Table III. In the fully adjusted model, patients with psoriasis had a significantly increased relative risk 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 IV, Table S2). 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 with 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 type 2 diabetes (p for interaction = $4.2x10^{-36}$), angina pectoris (p for interaction = 0.026), and stroke (p for interaction= $3.2x10^{-4}$). Specifically, we observed evidence for a decreasing strength of association between psoriasis and incident diabetes (multivariable adjusted RRs (95%CI) age ≤ 40 years 1.27 (1.06, 1.52); age 41–60 years 1.10 (1.04, 1.16); age > 60 years 1.04 (1.00, 1.07)). For stroke, stratified analyses do not suggest a qualitative or quantitative linear association (age ≤ 60 years 1.03 (0.89, 1.19); age 61–70 years 1.20 (1.07, 1.34); age > 70 years 1.07 (1.00, 1.13). The association between angina pectoris and psoriasis increased with increasing age categories (age ≤ 60 years 1.16 (1.04, 1.29); age 61–70 years 1.21 (1.08, 1.35); 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 IV). Systemically treated psoriasis (see Table S3 in the Supplemental Data) accounted for approximately 41, 17 and 11 excess cases of AP, MI and T2D, respectively, per 10,000 person-years (Table IV).

Association analysis of established CAD risk SNPs with psoriasis

Except for two polymorphisms which map to HLA-C/HCG27 (rs2894181) and C6orf10/BTNL2 (rs6932542) none of the established CAD-SNPs was significantly associated with psoriasis after conservative Bonferroni correction for multiple testing (see Table S4 in the Supplemental Data). Both MHC polymorphisms represent signals independent from the major psoriasis HLA-C*0602 risk allele, an observation reported before (Davies *et al*., 2012; Feng *et al*., 2009). Effects on CAD and psoriasis risk were into the same direction, but the reported effect sizes on CAD are modest (OR<1.2) (Lu *et al*., 2012).

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 Table S5 and Figure S1 in the Supplemental Data). 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 LD with the psoriasis HLA-C*0602 risk allele ($r2\geq0.6$) 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 ($P = 1.74x10^{-3}$).

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 nominally 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 Table S6 in the Supplemental Data), which tags the HLA-C*0602 risk allele ($P = 5.84x10^{-16}$, 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 ($P = 5.03x10^{-7}$). Suggestive evidence for association ($P<5x10^{-6}$) was observed for 5 loci comprising the genes *TMEM2*, *ZMIZ1*, *ARHGAP42* and two intergenic regions (see Table S7 in the Supplemental Data). 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 *UBE2l3*, which, however, are sparsely covered by the Metabochip (see Table S8 in the Supplemental Data).

Discussion

Main findings

Using different large-scale epidemiological and genetic datasets, 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 since 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 that we 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 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 Wakkee, 2009; Stern and Nijsten, 2012). Further, the results in the published literature are not unambiguous. E.g., in the population-based Rotterdam Study and in the National Health and Nutrition Examination Survey, psoriasis was not associated with the risk of coronary heart disease, stroke or heart failure (Dowlatshahi *et al*., 2013a), neither 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.

While 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 analyse diseases with a low prevalence, and do not allow to make causal inference nor to establish the time sequence of events. In the present manuscript, we used both approaches in a complementary fashion, and analyzed primary cross-sectional data from the well characterized KORA survey as well as secondary prospective data from the AOK Saxony administrative healthcare 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, 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 relative risk for incident T2D and MI, as well as an increased risk for AP, which translates in 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 endpoints, including CAD and T2D. On a similar note, genetic psoriasis loci displayed no evidence for association with CAD in the CARDIoGRAM data set with more than 20,000 CAD cases and approximately 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 tumour necrosis factor-alpha which increase oxidative stress and drive insulin resistance (Dowlatshahi *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 to 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 anti-psoriatic agents has not been sufficiently investigated.

Strengths and limitations

Major strengths of our epidemiological analysis are the use of both a cross-sectional and prospective population-based approach. In the cross-sectional analysis, psoriasis assessment and cardiometabolic risk profiling was 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. Since no direct information on disease severity was available, systemic therapy was used as surrogate marker. Further,

although health administrative data appears to be rather reliable for MI and T2D (Muggah *et al*., 2013), and we used stringent outcome definitions, 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 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, while 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 to be not 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 MONICA/KORA (Monitoring of Trends and Determinants in Cardiovascular Disease/Cooperative Health Research in the Region of Augsburg, 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 were 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 Supplemental Data). 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 type 2 diabetes and myocardial infarction, we utilized the AOK Saxony database, an anonymized population-based administrative healthcare database, which holds the 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 (ATC–Code)) and demographic characteristics (age, sex) of 2.4 million individuals from the state of Saxony, Germany from 2005 until 2012. All individuals continuously insured until 2012 or until death were included into the present analysis (n=1.811.098).

CARDIoGRAM study—The coronary artery disease genome-wide replication and meta-analysis (CARDIoGRAM) consortium combines 14 genome-wide association studies (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 single nucleotide polymorphisms (SNPs) and psoriasis, GWAS data from 4.489 psoriasis cases and 8.240 control subjects of European Caucasian descent recruited in Germany, UK and US were included (Ellinghaus *et al*., 2010; Nair *et al*., 2009; 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, 75th percentile) and categorical variables are presented as proportions stratified by psoriasis status. Differences by psoriasis status were assessed using a Wilcoxon-Mann-Whitney test for continuous variables and a Chi-square test for categorical variables.

Cross-sectional analysis—The association of psoriasis status with continuous (BMI, waist circumference, systolic blood pressure, diastolic blood pressure, total cholesterol-to-HDL cholesterol ratio, carotid intima-media thickness, CRP, or leukocytes respectively) and dichotomous (hypertension, type 2 diabetes, metabolic syndrome, myocardial infarction, peripheral arterial disease, or angina pectoris respectively) 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 y, 10 y, ≥ 11 y), alcohol intake (g/d), physical activity (no activity, low activity, moderate activity, high activity), systolic blood pressure, hypertension treatment (no, yes), type 2 diabetes (no, yes), type 2 diabetes treatment (no, yes), and lipid-lowering treatment (no, yes). In sensitivity analysis, effect modification by age was investigated by inclusion of interaction terms of age and psoriasis status. All p-values were 2-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 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 as non-exposed. 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* myocardial infarction (MI) (ICD-10-code I21-I23), incident angina pectoris (ICD: I20), incident stroke (ICD: I63, I64) and incident type 2 diabetes (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 type 2 diabetes 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 using 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), type 2 diabetes (no, yes), obesity (ICD: E66; no, yes) and for disorders of lipoprotein metabolism and other lipidaemias (ICD: E78; no, yes). We attempted to deal with unmeasured disease severity by stratification by psoriasis-specific medication, i.e. data on systemic therapy (including UV therapy, adalimumab, etanercept, infliximab, acitretin, cyclosporine, fumaric acid, methotrexate methotrexate, azathioprine, cyclosporine, hydroxyurea) were used to further differentiate psoriasis participants into those with ‘mild’ or ‘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 ($P<5x10^{-8}$) was compiled using the Catalogue of Published GWAS (Hindorff *et al*.) and associated reference lists (Tsoi *et al*., 2012). A total of 57 SNPs was then evaluated for association with CAD in the CARDIoGRAM dataset (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 datasets with a total of 4489 psoriasis cases and 8240 controls. Details of the meta-analysis have been previously reported (Ellinghaus *et al*., 2010; Nair *et al*., 2009). 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 (MDS) 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 a SNP with ≥10% allele frequency applying a lenient significance threshold of P<0.01 as proposed by Ellinghaus et al. (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 proportions 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).

Metabochip study—927 German psoriasis patients and 3.713 controls were genotyped using the Metabochip®, a custom Illumina iSelect genotyping array of nearly 200,000 SNP markers, which was designed to analyze and finemap 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 Metabochip were performed using the Illumina GenomeStudio software. Genotype data of all subsamples underwent the same basic quality control as detailed in the online supplement. After quality control procedure, 99,362 SNPs were analyzed. Within the cleaned Metabochip dataset, we performed 2 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 MDS of population stratification. Second, we looked in detail at regions that have been previously reported to be associated with Psoriasis. From these regions, only 4 lead SNPs were directly genotyped on the Metabochip. For the remaining previously reported psoriasis regions, we investigated the surrounding regions (+/−500kb) of each previously reported psoriasis lead SNP and report 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 $P = 5x10^{-6}$ and $P = 5.03x10^{-7}$, respectively. We had >79% power to detect an OR≥1.25 for a SNP assuming the allele frequency is ≥10% at the $5x10^{-6}$ significance level.

Online Repository

methods

KORA sample—In the MONICA/KORA surveys, data on sex, age, smoking habit, educational attainment, alcohol intake, physical activity, medical history and medication use was assessed during a standardized face-to-face computer assisted personal interview by trained study personnel.

Participants were asked to report the amount of beer, wine, and spirits consumed on the previous workday and previous weekend. The alcohol intake (in g/day) was obtained from this information as previously published (Wellmann *et al*., 2004). Participants were asked to provide the time per week spent engaging in sports in summer and winter seasons using the four response options ‘none’, ‘<1 h/week’, ‘1-2 h/week’, ‘>2 h/week’ (Ziegler *et al*., 2008). All participants underwent a medical examination by trained medical staff, which comprised anthropometrical, and blood pressure measurements according to standardized protocols previously published (Rathmann *et al*., 2003). BMI (in kg/m^2) was calculated as weight divided by height squared. The diagnosis of psoriasis was based on a reported physician’s diagnosis ever (KORA C), and a dermatological skin examination at the time of follow-up

(KORA F4). Venous blood samples were drawn from all subjects. Plasma CRP concentrations were measured using a high-sensitive immuneradiometric assay (range, 0.05–10 mg/l). White blood cell count was determined from fresh samples (Coulter counter STKS). Total cholesterol was determined by cholesterol esterase method (CHOL Flex, Dade-Behring, CHOD-PAP method), HDL-cholesterol was measured using the AHDL Flex (Dade-Behring, CHOD-PAP method after selective release of HDL) and triglycerides were measured using a TGL Flex (Dade Behring, enzymatic colorimetric test, GPO-PAP method). HsCRP was measured by particle enhanced immunonephelometry using a BN II (Fa. Siemens Healthcare Diagnostics Products, Marburg, Germany; level of detection 0.16 mg/L). Blood glucose was analysed using a hexokinase method (Gluco-quant;Roche Diagnostics, Mannheim, Germany). In participants of the F4 study, lipids were measured using the Dimension RxL (Dade Behring) (van Vliet-Ostaptchouk *et al*, 2014). In participants of the F4 study, the thickness of the carotid intima-media and ankle-brachial index were assessed according to methods previously published (Kowall *et al*., 2012; Stöckl *et al*., 2013). Measurements of the right and left common carotid artery thickness were averaged to obtain the overall common carotid artery thickness. Peripheral arterial disease was defined by an ankle-brachial index <0.9 and/or the self-reported presence of claudication, assessed by the Edinburgh questionnaire (Stöckl *et al*, 2013).

Variable categorization—The years of education were categorized as follows: ≤9 y (secondary general school-leaving certificate), 10 y (intermediate school-leaving certificate), or ≥ 11 y (university of applied sciences or university entrance qualification). Physical activity was categorized as follows: no activity (no sports in summer or winter season), low activity (engaging in sports <1 h/week in summer or winter season), moderate activity (engaging in sports 1 – 2 h/week regularly in summer or winter season), high activity (engaging in sports >2 h/week in summer and winter season). Hypertension was defined as systolic blood pressure ≥ 140 mm Hg or diastolic blood pressure as ≥90 mmHg or antihypertensive treatment. In participants of the F4 study, which provided fasting blood samples, the metabolic syndrome was defined as published by Alberti *et al*. (Alberti *et al*, 2009).

Test of association of variants in cardiometabolic candidate genes with psoriasis (Metabochip analysis)—The test of association of variants in cardiometabolic candidate genes with psoriasis was executed with PLINK (Purcell *et al*, 2007) and R . Monomorphous SNPs, SNPs with a callrate<0.98, a minor allele frequency<5% and p-value of deviation from Hardy Weinberg Equilibrium $<10^{-6}$ were removed. Furthermore, individuals with very low call rate (<50%), duplicates, close relatedness (below 2^{nd} to 3^{rd} degree) as well as population outliers (n=6) from the MDS analysis were excluded: Finally, a total of 936 psoriasis cases (56.6% female, mean age 50.0 years, mean BMI 27.57 kg/m^2) and 3713 controls (50.2% female, mean age 55.7 years, mean BMI 27.20 kg/m^2) and 99.362 SNPs were analyzed.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

AP	angina pectoris
CAD	coronary artery disease
CARDIoGRAM	coronary artery disease genome-wide replication and meta-analysis
CVD	cardiovascular diseases
GWAS	genome-wide association study
ICD	International Statistical Classification of Diseases
MI	myocardial infarction
MDS	multidimensional scaling
PAD	peripheral arterial disease
SNPs	single nucleotide polymorphisms
T2D	type 2 diabetes

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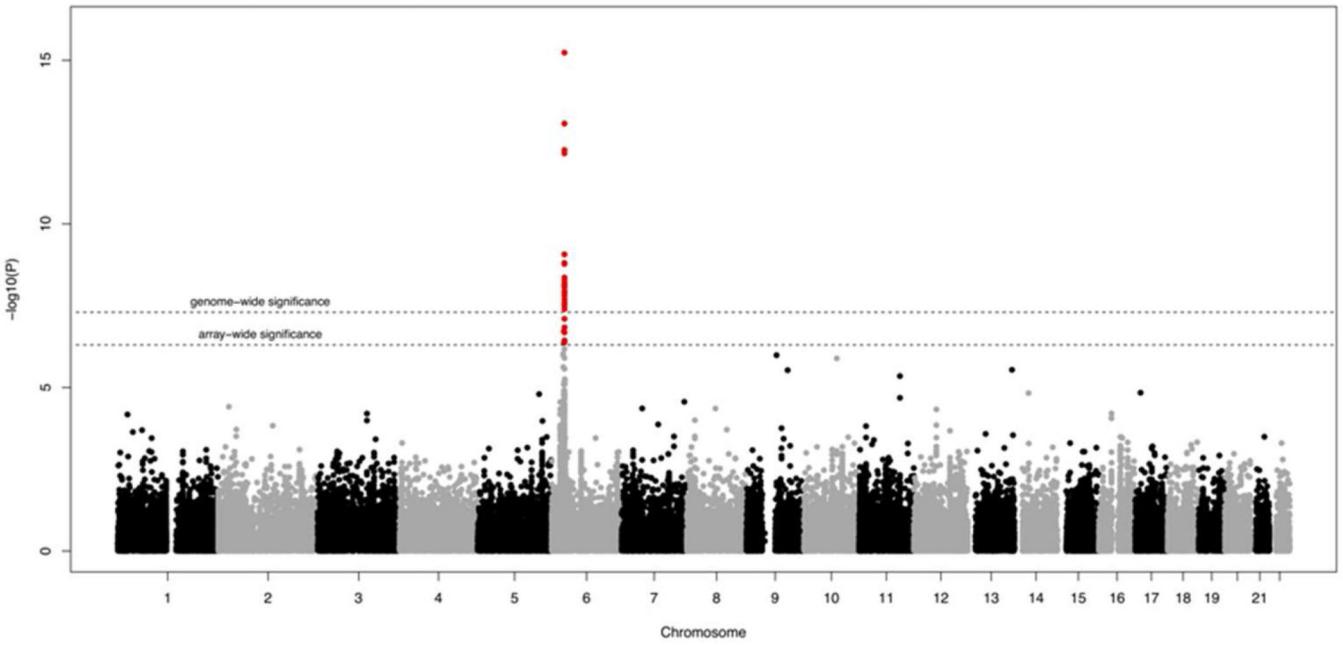

Figure 1.
Manhattan plot of Metabochip results on psoriasis.

Table 1

Characteristics[1] of the analytical study population of KORA survey participants (n=4,185).

	No Psoriasis (n=3986)	Psoriasis (n=199)	P value[2]
Age, y	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 y	2075 (52.1)	100 (50.3)	0.619
10 y	1001 (25.1)	41 (20.6)	0.151
≥ 11 y	905 (22.7)	58 (29.2)	0.035
Alcohol intake, g/d	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[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[11]	1.2 (0.6, 2.6)	1.7 (0.8, 3.5)	0.001
Leukocytes, n/nL[9]	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.

[1] Values are median (25th, 75th percentile) or n (percent).

[2] Based on Wilcoxon-Mann-Whitney test for continuous variables and Chi-square test for categorical variables.

[3] n = 4180.

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

[5] n = 4167.

[6] n = 4173.

[7] n=2948.

[8] n = 2990.

[9] n = 4182.

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

[11] n = 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**
Continuous outcomes		
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	0.46 (−0.46, 1.37)[9]	0.29 (−0.62, 1.20)[10]
Leukocytes, n/nL	0.20 (−0.06, 0.46)[11]	0.16 (−0.09, 0.41)[12]
Dichotomous outcomes		
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)1[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.

[1] Beta 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 y, 10 y, or ≥11 y), 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).

[2] n=4167.

[3] n=4162.

[4] n=4173.

[5] n=4168.

[6] n=4180.

[7] n=2646.

[8] n=2642.

[9] n=3024.

[10] n=3019.

[11] n=4182.

[12] n=4177.

[13] n=2948.

[14] n=2943.

[15] n=2990.

[16] n=2987.

[17] n=4182.

Table 3

Characteristics[1] of the AOK Saxony database by psoriasis status (n=1,811,098).

	No Psoriasis (n= 1,766,475)	Psoriasis				P value[2]
		No medication (n= 9,213)	Exclusively topical medication (n= 31,139)	Systemic medication (n= 4,271)	Total (n= 44,623)	Psoriasis vs no Psoriasis
Age (years) in 2005	49 (30, 68)	57 (43, 70)	61 (45, 72)	54 (42, 66)	59 (44, 71)	<1E-300
Male, n(%)	811,180 (45.9)	4,384 (47.6)	14,343 (46.1)	2,020 (47.3)	20,747 (46.5)	0.016
Hypertension, n(%)[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, n(%)[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, n(%)[3,6]	20,103 (1.2)	143 (1.6)	574 (1.9)	80 (1.9)	797 (1.9)	3.2E-39
Peripheral arterial disease, n(%)[3,7]	31,138 (1.8)	234 (2.7)	918 (3.1)	103 (2.5)	1,255 (3.0)	1.8E-68
Angina pectoris, n(%)[3,8]	32,350 (1.9)	251 (3.0)	959 (3.4)	125 (3.2)	1,335 (3.3)	2.4E-82
Stroke, n(%)[3,9]	41,778 (2.5)	289 (3.3)	1,134 (3.9)	113 (2.7)	1,536 (3.6)	3.8E-54
Obesity, n(%)[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 lipidaemias, n(%)[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, n(%)[3]	174,642 (9.9)	1,076 (11.7)	4,272 (13.7)	371 (8.7)	5,719 (12.8)	1.3E-92

[1] Values are median (25^{th}, 75^{th} percentile) or n (percent).

[2] Based on Wilcoxon-Mann-Whitney test for age and Chi-square test for categorical variables.

[3] Incidence 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.

Table 4

Multivariable-adjusted Risk Ratios (RR; 95% confidence interval in parentheses) and excess risk per 10,000 person years[1] for cardiometabolic diseases by psoriasis status (n= 1,811,098).

	RR (95%CI)		Excess risk per 10,000 person-years[6]	
	Model 1	**Model 2**	**Model 1**	**Model 2**
Type 2 diabetes 2007–2012[2]				
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
Myocardial infarction 2007–2012[3]				
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
Angina pectoris 2007–2012[4]				
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
Stroke 2007–2012[5]				
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

[1] Model 1 was adjusted for sex, 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 lipidaemias (no, yes).

[2] n=1,514,541.

[3] n=1,773,833.

[4] n=1,715,269.

[5] n=1,746,355.

[6] Excess risks calculated based on adjusted risk ratios.