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Cardiovascular comorbidity and cardiovascular risk factors in patients with chronic inflammatory skin diseases: A case-control study utilising a population-based administrative database

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Abstract

Background: : Psoriasis (PSO) and atopic eczema (AE) are chronic inflammatory disorders that primarily affect the skin. Data on cardiovascular comorbidity in PSO is scarce, and studies on the association of cardiovascular disease/cardiovascular risk factors and AE are missing.
Methods: We performed two separate case-control studies for PSO and AE utilising an administrative health care database including approximately 250,000 individuals from Germany. Cases with AE (n=6,296) and cases with PSO (n=3,156) were individually-matched (1:1) to controls with the same age and sex. Odds ratios (OR) and 95% confidence intervals (95%CI) were calculated based on the observed prevalences of cardiovascular morbidity among cases and controls.
Results: Patients with AE had a higher risk of obesity (OR,95%CI 1.24, 1.07-1.44). None of the other cardiovascular risk factors or diseases studied was associated with AE. PSO was significantly associated with hypertension (OR,95%CI 1.45, 1.27-1.66), diabetes mellitus type-2 (OR,95%CI 1.35, 1.13-1.61), obesity (OR,95%CI 1.58, 1.34-1.85), dyslipidemia (OR,95%CI 1.42, 1.14-1.77), and atherosclerosis (OR,95%CI 1.81, 1.37-2.41). Despite their unfavorable cardiovascular risk factor profile, patients with PSO were not at increased risk of adverse cardiovascular events (myocardial infarction OR,95%CI 1.14, 0.74-1.77; cerebral apoplexy OR,95%CI 0.94, 0.57-1.55).
Conclusions: Chronic inflammation due to AE does not appear to cause adverse cardiovascular comorbidities. In contrast, PSO is associated with an adverse cardiovascular risk factor profile, but this does not necessarily appear to translate into a higher risk for cardiovascular events. This study does not rule out that specific treatments for AE or PSO modify the risk of cardiovascular disease.

Key words: atopic dermatitis, cardiovascular diseases, case-control study, hypertension, obesity, psoriasis

Background

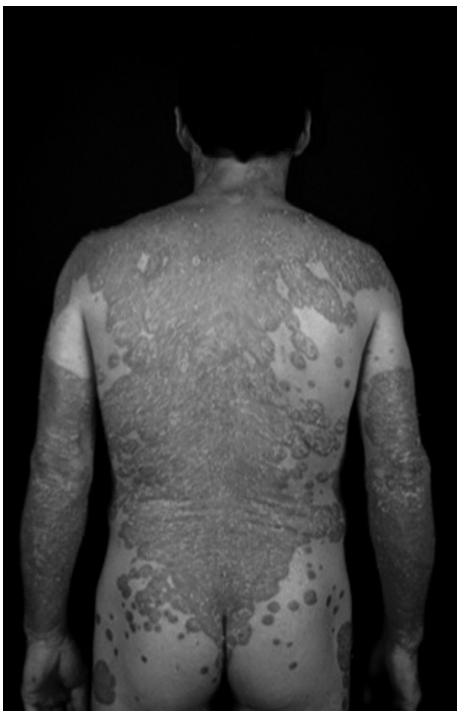
Psoriasis (PSO) and atopic eczema (AE, synonym: atopic dermatitis) are highly prevalent chronic inflammatory diseases with significant relevance not only for dermatology, but also for general medicine and public health.[1, 2]

PSO has a prevalence of about 3%, can occur at any age and is equally distributed between men and women.[3, 4] The typical thickened, red, scaly plaques are often disfiguring and may cause substantial problems in everyday life (figure 1).[5]

AE affects up to 20% of children, and 3-6% of adults.[6-8] It is characterised by erythema, edema, vesicules, and weeping in the acute stage, and skin thickening and scaling in the chronic stage with a predilection for the skin flexures (figure 2).[2]

The course of AE and PSO may be chronic relapsing or persistent.[1, 2] PSO and AE both are currently incurable, but several topical and systemic remedies exist for symptomatic treatment.[9-11] Even patients with clinically mild AE or PSO frequently report substantial problems in everyday life.[12, 13] From the societal perspective, severe AE and PSO both are considered as severe as alcohol dependence,

Figure 1. Psoriasis: thickened, red, scaly plaques.

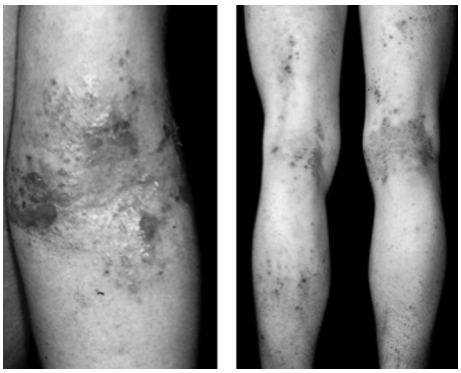


chronic back pain, or severe ophthalmologic conditions.[14] AE and PSO both impose a high economic burden with total cost and out-of-pocket expenses similar to those of asthma.[15-17]

Recent advances in the immunopathogenesis and genetics of PSO and AE have shown that – although these conditions primarily affect the skin – both AE and PSO have to be considered systemic inflammatory diseases.[1, 18] The role of chronic inflammation causing metabolic and vascular disorders is increasingly recognised. Patients with other immune disorders, such as rheumatoid arthritis or systemic lupus erythematosus, are known to be at increased risk of cardiovascular disease. Proinflammatory cytokines contribute to atherogenesis, peripheral insulin resistance, and the development of hypertension and type II diabetes.[19-21] Cardiovascular diseases are the major cause of morbidity and mortality and are therefore critically relevant for public health research and practice.[22, 23]

It has recently been reported that patients with severe PSO are at increased risk of heart disease and have an unfavourable profile of cardiovascular risk factors.[19, 24-27] It has also been suggested that myocardial infarction rates are significantly increased in young patients with severe PSO who received systemic anti-inflammatory treatment.[28] However, most studies are limited to hospitalised patients with severe PSO, whereas

Figure 2. Atopic eczema. Left side: acute stage; right side: chronic stage



data that can be considered as generalizable to the general population is scarce.[24, 27]

Although the vascular system, including endothelial cells and smooth muscle cells, is ultimately involved in clinical symptoms of AE, the association of AE and cardiovascular disease has not been investigated yet.[29] A Japanese investigation found a low point prevalence of hypertension in adults with AE, but controlled studies are missing.[30] The comorbidity of AE with other cardiovascular risk factors like obesity, dyslipidemia, atherosclerosis, and type-2 diabetes mellitus is also unknown.

We performed a large population-based case-control study to investigate cardiovascular comorbidity in patients with AE and in patients with PSO.We hypothesized that patients with PSO are at increased risk, i.e. have higher prevalences of cardiovascular disease and more unfavourable cardiovascular risk profiles. The analysis of the association between AE and cardiovascular disease was exploratory.

Methods

Two different case-control studies were designed to evaluate cardiovascular comorbidity in patients with PSO and cardiovascular comorbidity in patients with AE.The study utilised a population-based, interdisciplinary, administrative health care database that covers complete information on outpatient health care, diagnoses (ICD-10) and prescription data (ATC-Code) of more than 250,000 individuals from Germany in 2003 and 2004. The study was approved by the local institutional review board. Informed consent was not required because all personal identifiers had been removed from the database prior to its use for research.

Description of the research database utilized

The GKV-database Saxony was initiated in 2006.

It is one of the first databases in Germany that offers complete information on diagnoses (ICD-10 codes) and prescriptions (ATC codes) from all medical disciplines for a large sample (257,347 persons with statutory health care coverage).The database is representative for 90 to 95% of the German general population. Prescription data and diagnoses came from 2 different sources, i.e. statutory health insurance and Regional Association of Statutory Health Insurance Physicians, and were joined and pseudonymized by the Institute of Clinical Pharmacology, Technical University Dresden, Germany.

Methodological advantages of the secondary database utilised include high degree of generalizability, completeness (i.e. absence of non-response bias), and absence of recall bias due to prospective input of diagnoses and prescription data independent from hypotheses and research questions. The main drawback is that additional data not included in the secondary database, but potentially relevant for our research questions (e.g. family history of chronic inflammatory disorders and cardiovascular diseases, quality of life, physical activity, smoking) could not be collected due to patients' privacy protection issues.[31, 32]

Because diagnostic codes documented in outpatient care do not always accurately indicate the presence or absence of medical conditions, internal validation methods were defined a priori aiming to avoid misclassification bias.[33]

Patients were defined as having PSO, if the diagnosis of psoriasis (ICD-10 L40) was documented at least twice and if topical anti-psoriatic treatment (emollients, topical corticosteroids, antipsoriatics for topical use (ACT-Codes: D02A, D07, D05A)) was prescribed at least once within the 2-year study period.

Case definition for AE included documentation of the diagnosis AE (ICD-10 L20) at least twice and prescription of any topical anti-eczematous treatment (emollients, topical corticosteroids, tars, topical calcineurin inhibitors (ACT-Codes: D02A, D07, D05AA, D11AX)).

Patients having both AE and PSO were excluded from the study. Patients who were diagnosed as having AE or PSO, but who were not prescribed any typical treatment for the condition of interest were excluded from the analysis, because their disease status was considered as unclear.

Definitions applied for cardiovascular risk factors and cardiovascular diseases are summarised in table 1.

For each case patient with AE and for each case patient with PSO a single individually-matched control with the same age and sex, but without AE and without PSO was randomly selected.

We compared the prevalences of cardiovascular risk factors (obesity, hypertension, dyslipidemia, atherosclerosis, diabetes mellitus type-2) and cardiovascular diseases (angina pectoris, myocardial infarction, cerebral apoplexy) among cases with PSO and their age- and sex-matched controls and among cases with AE and their age- and sex-matched controls. To avoid misclassification we only considered patients as having the comorbidity if a typical treatment was prescribed by the diagnosing physician (table 1). Patients who were diagnosed a comorbidity of interest, but who were not prescribed any typical treatment for this condition, were excluded from the analysis.

The severity of AE and PSO was evaluated by using the total number of physician visits due to the case defining condition within the study period as a surrogate marker (2-5 physician visits within 2-year study period: mild disease; ≥ 6 visits: moderate-to-severe disease). We did not use the prescription of any specific medications as a measurement for disease severity to avoid confounding due to a possible association of cardiovascular diseases and systemic antiinflammatory treatment.[34] Validated markers for disease severity such as the Psoriasis area severity index (PASI) or the Scoring atopic dermatitis (SCORAD) index could not be applied as this information could not be derived from the available data.[35, 36]

Our hypothesis was that AE and PSO are not in general associated with an unfavourable cardiovascular risk profile, but that patients with severe AE and PSO are at increased risk of cardiovascular diseases.

Odds ratios (OR) and corresponding 95% confidence intervals (95%CI) were calculated using McNemar's test for matched pairs.[37] Statistical analysis was performed using STATA version 8 (STATA Corp, College Station, Tex).[38]

Results

The study population for the case-control study on cardiovascular comorbidity of AE consisted of 12.592 individuals (6.296 cases and 6.296 age- and sex-matched controls). Mean age was 29 years (standard deviation (SD) 26 years). 51% of study subjects age 18 or older, 25% were 48 years or older, 10% were 71 years or older, and 63% were female. 3,873 cases (61.5%) were classified as having mild AE, 2,423 cases (38.5%) were classified as having moderate-to-severe AE.

For PSO, the study population consisted of

3,156 cases and 3,156 controls with a mean (SD) age of 56 (19) years (97% age 18 or older, 25% age 72 or older, 10% age 80 or older, 55% female). 1,446 (44.5%) and 1,801 (55.5%) of all cases with PSO were classified as having mild and moderate-to-severe PSO, respectively.

Cases with AE and PSO and their controls were well balanced in terms of insurance status (surrogate for socioeconomic position[39]).

Table 2 summarises the results on cardiovascular comorbidity in patients with AE. Patients with AE had a higher risk of obesity (OR, 95%CI 1.24, 1.07-1.44), but the association was stronger in patients with mild AE than in the subgroup of patients with moderate-to-severe AE (table 2). Patients with AE tended to have a lower risk of diabetes mellitus type-2 (OR, 95%CI 0.83, 0.66-1.04). The odds for concurrent diabetes decreased with the severity of AE (table 2). Patients with moderate-to-severe AE had an increased risk of atherosclerosis (OR, 95%CI 2.00; 1.09-3.82). None of the other cardiovascular risk factors or cardiovascular diseases studied was significantly associated with AE (table 2).

As summarised in Table 3, patients with PSO were at significantly increased risk of all cardiovascular risk factors studied. The risk of hypertension and angina pectoris increased with the severity of PSO, whereas the risk of dyslipidemia was equally high in patients with mild PSO and in patients with moderate-to-severe PSO, and the risk of diabetes was highest in patients with mild PSO (Table 3).

Despite their increased risk of cardiovascular risk factors, patients with PSO (both in general and also within the subgroup of patients with moderate-to-severe disease) were not at increased risk of adverse cardiovascular events (myocardial infarction OR, 95%CI 1.14, 0.74-1.77; cerebral apoplexy OR, 95%CI 0.94, 0.57-1.55) (Table 3).

Table 2. Cardiovascular comorbidity in patients with atopic eczema.

Condition	n‡	Prevalence (%) (cases; controls)	Odds ratio (95%CI)	95%CI
Diabetes mellitus type 2				
Total study population	5859	3,16; 3,67	0.83 (0.66-1.04)	0.094
Cases with mild disease	3599	3,53; 3,83	0.90 (0.68-1.19)	0.449
Cases with moderate-to-severe disease	2260	2,57; 3,41	0.71 (0.47-1.05)	0.071
Obesity				
Total study population	5899	7,80; 6,42	1.24 (1.07-1.44)	0.003
Cases with mild disease	3627	8,13; 6,51	1.28 (1.07-1.54)	0.007
Cases with moderate-to-severe disease	2272	7,26; 6,29	1.17 (0.92-1.50)	0.185
Dyslipidemia				
Total study population	5549	2,52; 2,20	1.18 (0.90-1.57)	0.219
Cases with mild disease	3419	2,63; 2,34	1.16 (0.81-1.67)	0.348
Cases with moderate-to-severe disease	2130	2,35; 1,97	1.21 (0.77-1.93)	0.377
Atherosclerosis				
Total study population	6183	1,37; 1,28	1.08 (0.78-1.50)	0.628
Cases with mild disease	3800	1,29; 1,58	0.81 (0.54-1.21)	0.278
Cases with moderate-to-severe disease	2380	1,51; 0,80	2.00 (1.09-3.82)	0.017
Hypertension				
Total study population	5602	14,28; 14,07	1.03 (0.90-1.20)	0.652
Cases with mild disease	3460	14,74; 14,28	1.07 (0.89-1.30)	0.447
Cases with moderate-to-severe disease	2142	13,54; 13,73	0.97 (0.76-1.24)	0.855
Angina pectoris				
Total study population	6005	1,02; 1,08	0.93 (0.63-1.37)	0.706
Cases with mild disease	3692	1,11; 1,12	0.94 (0.58-1.54)	0.816
Cases with moderate-to-severe disease	2313	0,86; 0,95	0.90 (0.45-1.79)	0.746
Myocardial infarction				
Total study population	6235	0,32; 0,34	0.95 (0.49-1.85)	0.876
Cases with mild disease	3837	0,39; 0,44	0.88 (0.41-1.88)	0.724
Cases with moderate-to-severe disease	2398	0,21; 0,17	1.25 (0.27-6.30)	0.739
Cerebral apoplexy				
Total study population	6275	0,43; 0,59	0.73 (0.43-1.23)	0.211
Cases with mild disease	3858	0,47; 0,60	0.78 (0.40-1.52)	0.435
Cases with moderate-to-severe disease	2417	0,37; 0,58	0.64 (0.25-1.59)	0.297

‡ matched pairs with same age and sex

Table 3. Cardiovascular comorbidity in patients with psoriasis.

Condition	n‡	Prevalence (%) (cases; controls)	Odds ratio (95%CI)	p-value
Diabetes mellitus type 2				
Total study population	2521	14,88; 11,78	1.35 (1.13-1.61)	< 0.001
Cases with mild disease	1102	13,52; 9,53	1.57 (1.17-2.12)	0.002
Cases with moderate-to-severe disease	1419	15,93; 13,53	1.23 (0.99-1.54)	0.061
Obesity				
Total study population	2916	16,02; 10,97	1.58 (1.34-1.85)	< 0.001
Cases with mild disease	1249	14,25; 10,81	1.41 (1.09-1.83)	0.007
Cases with moderate-to-severe disease	1667	17,34; 11,10	1.69 (1.38-2.09)	<0.001
Dyslipidemia				
Total study population	2161	11,10; 8,33	1.42 (1.14-1.77)	< 0.001
Cases with mild disease	975	9,43; 7,18	1.40 (0.98-2.01)	0.056
Cases with moderate-to-severe disease	1186	12,48; 9,27	1.43 (1.08-1.89)	0.010
Atherosclerosis				
Total study population	3004	4,89; 2,76	1.81 (1.37-2.41)	< 0,001
Cases with mild disease	1294	3,71; 2,24	1.68 (1.03-2.78)	0.028
Cases with moderate-to-severe disease	1710	5,79; 3,16	1.88 (1.33-2.70)	< 0.001
Hypertension				
Total study population	2468	47,93; 41,05	1.45 (1.27-1.66)	< 0.001
Cases with mild disease	1055	41,42; 37,63	1.26 (1.02-1.57)	0.031
Cases with moderate-to-severe disease	1413	52,78; 43,60	1.59 (1.34-1.89)	0.001
Angina pectoris				
Total study population	2915	4,25; 2,78	1.57 (1.17-2.13)	0,002
Cases with mild disease	1269	3,70; 3,15	1.18 (0.75-1.87)	0.442
Cases with moderate-to-severe disease	1646	4,68; 2,49	1.97 (1.31-3.01)	< 0.001
Myocardial infarction				
Total study population	3094	1,55; 1,36	1.14 (0.74-1.77)	0.527
Cases with mild disease	1332	1,50; 1,27	1.17 (0.58-2.39)	0.622
Cases with moderate-to-severe disease	1762	1,59; 1,42	1.12 (0.63-2.00)	0.680
Cerebral apoplexy				
Total study population	3130	1,15; 1,21	0.94 (0.57-1.55)	0.811
Cases with mild disease	1343	1,27; 0,97	1.33 (0.59-3.09)	0.450
Cases with moderate-to-severe disease	1787	1,06; 1,40	0.75 (0.38-1.44)	0.345

‡ matched pairs with same age and sex

Discussion

This investigation included two separate case-control studies on cardiovascular comorbidity of 6.296 cases with AE and of 3,873 cases with PSO, and the same numbers of age- and sex-matched controls.

AE is a highly prevalent chronic inflammatory condition that does not only affect the skin, but also the vascular system, including endothelial cells and smooth muscle cells.[29] Although cardiovascular diseases are the major cause of morbidity and mortality in Europe and in the US, we did not identify any published evidence on the association between AE and cardiovascular disease.[22, 23, 40, 41] Our study suggests that patients with AE might be at increased risk for obesity and at decreased risk of diabetes mellitus type 2. However, the latter association was not statistically significant (OR, 95%CI 0.83, 0.66-1.04) so that future research is needed to confirm this association. Dyslipidemia and hypertension were not associated with AE (Table 2). Our study therefore does not confirm a Japanese investigation which suggested a decreased risk of hypertension in patients with AE.[30] Our study further suggests that moderate-to-severe AE is a risk factor for atherosclerosis (OR, 95%CI 2.00, 1.09-3.82). However, despite this risk factor patients with moderate-to-severe AE were not at increased risk of myocardial infarction (OR, 95%CI 1.25, 0.27-6.30) and cerebral apoplexy (OR, 95%CI 0.64, 0.25-1.59).

In accordance with previous studies [19, 24-27] patients with PSO, were at significantly increased risk of several cardiovascular risk factors including diabetes mellitus type-2, obesity, hypertension, dyslipidemia, and atherosclerosis (Table 3). The increased prevalence of cardiovascular risk factors has to be considered in the routine management of patients with PSO.

In contrast to other studies, however, patients with PSO in general and also the subgroup of patients with moderate-to-severe PSO were not at increased risk of the adverse cardiovascular outcomes myocardial infarction and cerebral apoplexy (Table 3).[28] The discrepancy of our results and previous studies might be explained by the different definition of disease severity. Others who investigated the association of myocardial infarction and PSO defined severe PSO

by means of systemic anti-inflammatory treatment, whereas we defined disease severity by means of the frequency of physician contacts.[28] Based on previous studies it has been suggested that patients with moderate-to-severe PSO should be treated systemically in order to avoid adverse cardiovascular outcomes.[21] It has been reported that methotrexate reduces the incidence of cardiovascular diseases in patients with psoriasis.[34] Our study highlights that further (ideally prospective) data is needed regarding the association of different systemic anti-inflammatory treatment modalities approved for moderate-to-severe PSO and cardiovascular diseases, before adopting the mentioned recommendations to clinical practice.[21]

Strengths and limitations of the study

This study utilised a large existing interdisciplinary database with complete observations of patients from the general population. Compared to conventional epidemiologic studies, major strengths of the use of such an administrative database include the avoidance of non-response bias, the large sample size, the high degree of external validity, and the high efficiency in terms of both monetary and human resources by using existing data.[31, 32, 42]

Recall bias, which is considered the major threat to internal validity in most epidemiologic case-control studies, is not present in our analysis, as all information used was collected prospectively and without reference to the study hypotheses.[42]

Non-differential misclassification bias due to inaccurate reporting of diagnostic codes in clinical practice was avoided by establishing specific criteria for the definition of case status and the presence / absence of cardiovascular comorbidities (table 1). Our approach is in accordance with existing guidelines for the use of administrative databases for scientific purposes.[33, 43] The drawback of this approach, however, is that cases with very mild AE or PSO might have been excluded from our analysis. Another limitation of this study is the failure to adjust for family history of cardiovascular risk factors and outcomes, all of which have a strong genetic background. Socioeconomic position is one of the most important confounders in comorbidity studies. In our study cases with AE and PSO and their controls were well balanced in terms of insurance status, which is a good surrogate parameter for socioeconomic position.[39] Information on other possible confounding factors (e.g. smoking) was not available for this analysis.[44]

Other possible limitations include the possibility of selection bias that may occur as individuals who are seeking medical care are more likely to report AE and associated illnesses. A third limitation regards the causal effect between occurrence of cardiovascular risk factors and chronic inflammatory skin diseases: As we analysed prevalent conditions only associations, but no causal relationships can be established by our study.. Naldi et al. recently reported that patients with incident PSO are not at increased risk of hypertension, diabetes mellitus, and dyslipidemia, suggesting a causal effect.[45]

Another possible methodological limitation concerns the definition of disease severity of PSO and AE. Unfortunately, validated outcome measures such as the Psoriasis Area and Severity Index (PASI) [35] or the Scoring Atopic Dermatitis index (SCORAD) [36] are not recorded in the secondary dataset utilized for this study. In accordance with similar investigations on other chronic conditions such as asthma we used healthcare utilization attributable to the condition of interest to grade disease severity.[46] When interpreting our results it has to be considered, however, that a higher number of physician visits does not necessarily imply more severe disease.

Unanswered questions and future research

Future research is necessary to explore whether patients with AE who are treated with systemic anti-inflammatory drugs (e.g. glucocorticosteroids) are still at increased risk of cardiovascular diseases. Additionally, it needs to be explored why patients with moderate-to-severe PSO (defined as patients with frequent contacts with their physician) are not at increased risk of adverse cardiovascular outcomes (i.e. myocardial infarction and cerebral apoplexy) despite their adverse cardiovascular risk factor profile.

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