

# Epidemiology, Comorbidity and Risk Factors for Psoriatic Arthritis: A Health Insurance Claims Database Analysis

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**Psoriatic arthritis is a frequent manifestation of psoriasis, and has a high level of impact on physical functioning, work ability and quality of life. However, there have been few studies of the epidemiology, development of and risk factors for concomitant psoriatic arthritis in patients with psoriasis. This study analysed data from a German public health insurance database of >2 million individuals. Factors influencing the development of psoriatic arthritis were determined by descriptively analysing comorbidities and Cox regression modelling. The prevalences of psoriasis and psoriatic arthritis were 2.63% and 0.29% in adults (18+ years) and, respectively, 0.30% and 0.01% in children (0–17 years). The proportion of adult patients with incident psoriasis who developed concomitant psoriatic arthritis within five years after diagnosis of psoriasis (mean 2.3 years) was 2.6%. Cardiovascular diseases are the most frequent comorbidity in patients with psoriasis with or without concomitant psoriatic arthritis. Depression and neurosis/stress disorder were identified as indicators for the development of psoriatic arthritis.**

**Key words:** psoriasis; psoriatic arthritis; epidemiology; risk factors; health services research.

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Psoriasis (PsO) is a common chronic inflammatory skin disease with a prevalence of 2–3% in industrialised countries (1, 2). Psoriatic skin lesions are often itchy, painful and socially stigmatising. Although PsO is mainly associated with its characteristic skin lesions, it is increasingly understood as a multisystem disorder associated with numerous comorbidities, including diabetes, cardiovascular disease and autoimmune diseases (3, 4). PsO comorbidity can start in childhood, and remains a risk factor throughout life (5). Psoriatic arthritis (PsA) is a very common rheumatic manifestation of PsO. PsA constitutes a significant additional burden for patients, heavily affecting musculoskeletal functionality, work ability and quality of life (3, 6–9). The rate

## SIGNIFICANCE

Psoriatic arthritis is an inflammatory joint disease that often occurs in connection with psoriasis and impairs physical functioning, work ability and quality of life. This study evaluated the occurrence and possible risk factors for psoriatic arthritis using data from a German health insurance company from 2010 to 2015. The results show that concomitant psoriatic arthritis can appear even after a short time in patients with psoriasis, and that depression and stress increase the probability of developing psoriatic arthritis. These data emphasise that the early detection of psoriatic arthritis must continue to be a priority goal, in order to avoid non-reversible damage to the joints; hence cross-disciplinary collaborations should be strengthened.

of PsA in patients diagnosed with PsO is estimated to range from 7% to 27% (10). In Germany, independent studies indicate a prevalence of PsA of approximately 20% in patients attending dermatologists (3, 11). PsA is often diagnosed with a latency period of 8–15 years (12, 13). A considerable number of patients with PsA remain undiagnosed (3, 9). Diagnosis of PsA can be complex due to its varying clinical presentation and the need for referral to a rheumatologist (14). Subclinical inflammatory joint lesions were detected in almost half of patients in a cohort of patients with cutaneous PsO by magnetic resonance imaging (MRI) (15). Untreated PsA may lead to permanent joint destruction and deformation; hence early and subsequent screening of all patients with PsO from the time of initial diagnosis is crucial (16–18). The reported epidemiological numbers for development of PsA in patients with PsO shows significant variability. Reasons may include geographical variations and differing methodology of published studies. Specifically, indicators for the development of PsA and the temporal occurrence of onset of PsA after the diagnosis of PsO are still poorly understood. The aim of this study was to obtain valid data on demographics and clinical characteristics, including comorbidity profiles, of adults with prevalent and incident PsO case in Germany. Of particular interest was the latency period from diagnosis of PsO to diagnosis of PsA. Moreover, the study aimed to identify risk factors for the development of PsA in patients with PsO.

## MATERIALS AND METHODS

### Study design and data source

For this retrospective, epidemiological and healthcare research study, pseudonymised data from a German health insurance database (DAK-Gesundheit) were evaluated. The routine data cover a random 40% sample of all individuals insured by DAK-Gesundheit on 31 December 2010 (approximately 2.3 million insureds). Sociodemographic data, such as age, sex and federal state, as well as outpatient and inpatient care data, were analysed and presented as aggregated data (19).

### Prevalence

A prevalent case was defined as an insured with a reliable outpatient or main and/or secondary inpatient diagnosis of PsO or PsA in 2010. The diagnoses of PsO and PsA were defined in accordance with the International Classification of Diseases, 10<sup>th</sup> Revision, German Modification (ICD-10-GM) codes: psoriasis vulgaris (L40.0), generalized pustular psoriasis (L40.1), acrodermatitis continua suppurativa (L40.2), pustulosis palmaris et plantaris (L40.3), guttate psoriasis (L40.4), other psoriasis (L40.8), psoriasis, unspecified (L40.9), arthropathic psoriasis (L40.5), distal interphalangeal psoriatic arthropathy (M07.0), arthritis mutilans (M07.1), psoriatic spondylitis (M07.2), juvenile arthritis in psoriasis (M09.0), and other psoriatic arthropathies (M07.3).

### Incidence

For the calculation of incidence, the same selection criteria for PsO and PsA diagnoses were used as for prevalence. Diagnosis-free intervals were set to minimise overestimation of incidence. This ensures that the PsO and PsA diagnoses were initial events and not pre-existing diseases. A sensitivity analysis, comparing diagnosis-free intervals of 4 and 8 consecutive quarter years, yielded a false positive rate of 10% for both time periods. In order to maximise the available observation period, we opted for evaluation of diagnosis-free intervals of 4 quarters for both PsO and PsA. The incident PsO cohort thus comprised insureds with PsO in 2011 who are insured until 2015, excluding patients with PsO in 2010. For development of PsA after diagnosis of PsO, the consecutive observation period in the current analysis was limited to a window of 5 years. In order to minimise overestimation of PsA development after diagnosis of PsO, incident PsA succeeding PsO diagnosis was determined by excluding patients who had a PsA diagnosis 4 quarters before diagnosis of PsO, within the same quarter of diagnosis of PsO or one quarter after their first diagnosis of PsO in order to focus on subsequent development of PsA after the onset of PsO.

Sex, age (at the year of PsO diagnosis) and comorbidities of incident patients were analysed as potential risk factors. For comorbidities to be included in the analysis, they had to be diagnosed in the same quarter as the diagnosis of PsO, and they had to be coded together with at least one diagnosis confirmed during outpatient care or at least one hospital-made primary discharge or secondary diagnosis according to ICD-10-GM.

### Statistical analyses

In order to ensure that the results were representative for the general German population, the epidemiological indicators age and sex were analysed and the rates were standardised by these indicators according to the distribution within the general German and German federal states population in 2012 (20). Based on the guidelines for “Good Epidemiological Practice” and “Good Practice in Secondary Data Analysis”, ethics committee approval was not required (21, 22). The analyses were performed according to current methodological standards and followed already published previous work (21–23).

The duration of an incident PsA diagnosis was given in quarters because, for historical reasons, the outpatient care system is based on a quarterly administrative period (24). Differences in the occurrence of risk factors between patients with incident PsO who did or did not develop PsA between 2011 and 2015 were tested for significance using Wilcoxon or  $\chi^2$  tests.

The influence of potential risk factors on the development of PsA was assessed using a multivariable Cox regression analysis. Hazard ratios (HRs) and 95% confidence intervals (95% CIs) were calculated. All included variables were tested graphically (survival curves) and statistically (Kolmogorov’s supremum test) for proportionality. Data were right censored if the event did not occur until the end of the observation period (31 December 2015) or until the end of the insurance period due to death or due to an insureds’ switch to a different health insurance. In the Cox regression model, adjustments were made for the included variables (backward selection). The individual influences of the covariates age (continuous), sex (male vs female) and comorbidities (yes vs no) were tested before incorporating into the regression model. The variable was included in the adjusted Cox model with a *p*-value up to 0.99. The significance level of the Cox regression was 5%. Therefore, covariates with a *p* > 0.05 were excluded from the model.

As statistical measures, HRs with the respective 95% CI, *p*-values (two-sided tests) and C-statistics were given.

The analyses were performed using SAS 9.4 (SAS Institute, Cary, NC, USA).

## RESULTS

### Population

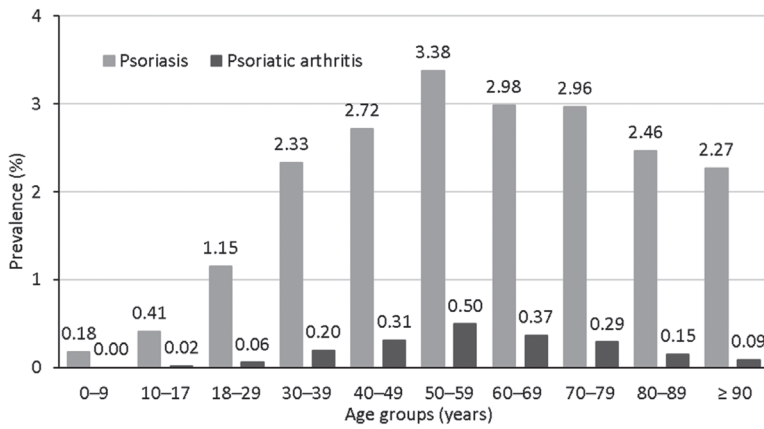
In 2010, 2,319,584 people were insured throughout the DAK-Gesundheit sample (Table SI<sup>1</sup>). In this sample, two-thirds (62%) of insured subjects were female. The age group 18–29 years was the most frequently represented among males, at over 16%; for females, the 50–59 years age group was also the most frequently represented, with over 16% of the total female population.

### Prevalence analysis

In 2010, 55,734 (2.78%) of 2,006,003 insured adults and 1,003 (0.32%) of 313,581 insured children were diagnosed with PsO. The age- and sex-adjusted rates were 2.63% for adults and 0.30% for children (Fig. 1). The adjusted prevalence of PsO increased with age, peaking in the age group 50–59 years (3.38%). The prevalence of PsA in adults was 0.31% (*n* = 6,127) and 0.01% in children (*n* = 37). The adjusted rates were 0.29% in adults and 0.01% in children, and peaked in the age group 50–59 years (0.50%).

Regional differences in the prevalence of PsO (range 2.22% (Saarland) to 3.48% (Saxony-Anhalt)) and PsA (range 0.18% (Saarland) to 0.39% (Thuringia)) were observed in adults between the German federal states (Bundesländer; Table SII<sup>1</sup>). The prevalence of PsO in children also differed between the federal states and ranged between 0.25% (Thuringia) and 0.51% (Saxony-Anhalt).

<sup>1</sup><https://medicaljournalssweden.se/actadv/article/view/323>



**Fig. 1. Prevalence of psoriasis and psoriatic arthritis of statutory health insurance (SHI) insured individuals by age group.** Patient population: statutory health insurance, SHI; SHI insured population at 31 December 2010,  $n=2,319,584$ . Age- and sex-adjusted prevalence rates.

### Incidence analysis

In 2011, there were 1,717,352 people who were continuously insured until the end of 2015. Of this cohort, 44,422 patients were already diagnosed with PsO in 2010 and, thus, excluded from the incidence analysis (Fig. S1<sup>1</sup>). The proportion of insureds without a prior diagnosis of PsO who developed PsO in 2011 was 0.75% (12,579 of 1,672,930 individuals). The incidence rate

for adults was 0.83% (12,251 of 1,481,808) and for children 0.17% (328 of 191,122). After adjusting for age and sex, the incidence rates were 0.78% for adults and 0.17% for children. The age group 50–59 years showed the highest adjusted incidence rate (0.93%) (Fig. 2a). Of 12,251 incident and adult PsO patients, 315 (2.6%) developed PsA during the consecutive observation period (2011 to 2015). The highest incidences for concomitant PsA were observed for patients aged 30–59 years (Fig. 2b).

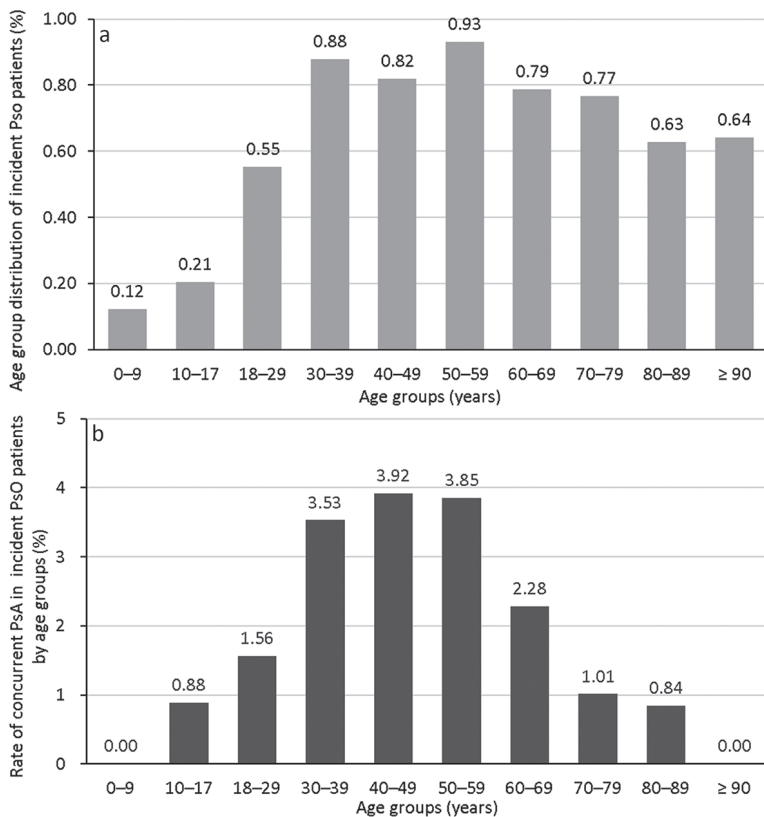
Two (0.61%) of 328 children with an incident PsO diagnosis developed PsA until 2015.

In adults, the mean  $\pm$  standard deviation (SD) time from PsO to PsA diagnosis was  $2.3 \pm 1.26$  years. PsA was diagnosed at the earliest 6 months after the diagnosis of PsO.

The mean time until diagnosis of PsA was comparable regarding age and sex (men  $2.38 \pm 1.32$  years, minimum 0.5 years, maximum 4.75 years; women  $2.45 \pm 1.23$  years, minimum 0.5 years, maximum 4.75 years) (Fig. S2<sup>1</sup>).

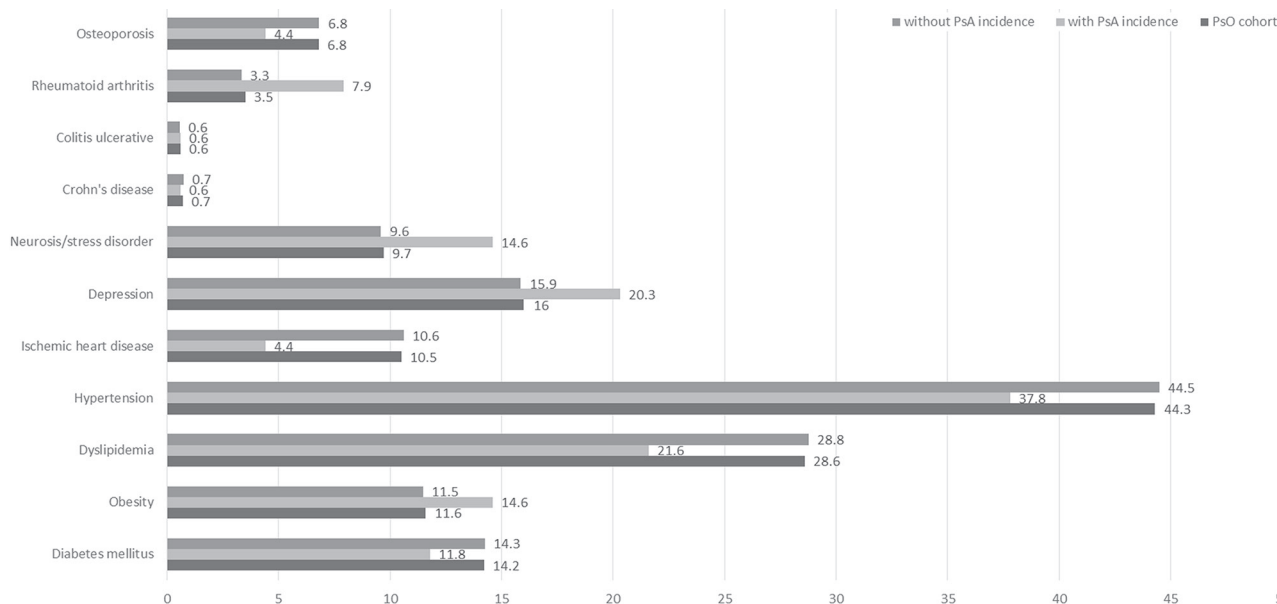
### Comparison of comorbidity profiles and risk factor analysis for development of psoriatic arthritis

In order to compare the frequencies of the most clinically relevant comorbidities (25) between PsO patients who developed subsequent PsA (PsA incidence) and those who did not (no PsA incidence), comorbid diseases, which were diagnosed within the same quarter of the PsO diagnosis, were collected. The relative risk (RR) was calculated to compare the occurrence of comorbidities in both the PsA cohort and the no PsA cohort. The overall comorbidity frequencies were similar between both cohorts (Fig. 3). The most frequent comorbidity was hypertension (no PsA incidence 44.49%; PsA incidence 37.78%), followed by dyslipidaemia (no PsA incidence 28.77%; PsA incidence 21.59%) and depression (no PsA incidence 15.86%; PsA incidence 20.32%). Patients with PsO who developed concomitant PsA were more affected by rheumatoid arthritis (no PsA incidence 3.34%; PsA incidence 7.90%, RR 2.37), neurosis/stress disorder (no PsA incidence 9.59%; PsA incidence 14.60%, RR 1.52) and depression (no PsA incidence 15.86%; PsA incidence 20.32%, RR 1.28) than patients with no PsA. The PsA cohort was less affected than the no PsA cohort by ischaemic heart diseases (no PsA incidence 10.61%; PsA incidence 4.40%, RR 0.41), followed by osteoporosis (no PsA incidence



**Fig. 2. (a) Age group distribution of patients with incident psoriasis and (b) rate of concurrent diagnosis of psoriatic arthritis in patients with incident psoriasis by age group.** Patient population: statutory health insurance (SHI); SHI-insured population with diagnosis of psoriasis in 2011.





**Fig. 3. Prevalence of comorbidities in psoriasis (PsO) cohort with and without concurrent psoriatic arthritis (PsA) diagnosis.** Patient population: statutory health insurance (SHI); SHI-insured population with diagnosis of PsO in 2011.

6.82%; PsA incidence 4.40%, RR 0.65) and dyslipidaemia (no PsA incidence 28.77%; PsA incidence 21.59%, RR 0.75). In children with PsO, the most frequent comorbidity was obesity (4.27%), followed by psychiatric comorbidities (depression 2.44%; and neurosis/stress disorder 2.44%).

Cox regression modelling for risk factors of concomitant PsA incidence was calculated. The baseline characteristics include age, sex, comorbidities and the duration time for concomitant PsA (Table SIII<sup>1</sup>). No variables violated the proportional hazards assumption, and all variables could be taken into account for Cox regression. The adjusted Cox model included the variables with a significant effect on developing PsA. These variables were: age, depression, ischaemic heart disease and neurosis/stress disorder (Table I). Depression (HR 1.38 [95% CI 1.92, 1.87],  $p=0.0351$ ) and neurosis/stress disorder (HR 1.46 [95% CI 1.03, 2.05],  $p=0.0322$ ) were positively (and significantly) associated with concomitant PsA. Ischaemic heart disease was significant negatively associated with concomitant PsA (HR 0.49 [95% CI 0.27, 0.98],  $p=0.0164$ ). This suggests that ischaemic heart disease has a protective effect against developing concomitant PsA. Older age at onset of PsO was also associated with a significantly lower risk of developing PsA during the consecutive 5-year observation period (HR 0.98 [0.98, 0.99],  $p=0.0001$ ).

**Table I. Cox model for psoriatic arthritis incidence**

Characteristics	Hazard ratio	95% CI	<i>p</i> -value
Age	0.98	0.977–0.990	<0.0001
Depression	1.38	1.023–1.870	0.0351
Ischaemic heart disease	0.49	0.270–0.976	0.0164
Neurosis/stress disorder	1.46	1.032–2.052	0.0322

95% CI: 95% confidence interval; C-statistic: 0.62.

## DISCUSSION

The objective of the current study was to determine the prevalence of PsO and PsA in Germany based on a large cohort of insured people. This is of high scientific and clinical importance, as PsA is one of the most frequent and important comorbidities of PsO (3, 11). Early diagnosis and treatment of PsA are included in the National Health Care Goals in Psoriasis 2015 to 2020 in Germany (26).

A similar dataset based on health insurance data has been used in previous studies (1, 2, 23). When health insurance data are used, however, inadequate disease detection may be included in the epidemiological results. This is also to be assumed here, as German primary data from various nationwide samples have shown a higher prevalence of PsO-associated arthritis (approximately 20%) when examining all patients having dermatological treatment (3, 11). The difference between the prevalences in the present study compared with primary studies might be due to insufficient concomitant diagnosis, but also due to the concentration of more severely affected patients among dermatologists. Importantly, there is no data on the frequency of PsA in patients with PsO under general medical care in Germany to date.

The observed prevalences of PsO in adults (2.63%) and children (0.30%) in Germany are in line with the corresponding global numbers (adults 0.5–11.4%, children 0.0–1.3%) and previous studies from Germany (2.1–2.5%) (2, 26, 27). In this study, the prevalence of PsA (0.29%) was relatively low compared with other studies (0.3–1.0%) (28). A lower prevalence of development of PsA in patients with incident PsO can occur in health insurance claims studies, because specific International Statistical Classification of Diseases and Related Health Problems (ICD) coding requires a definite diagnosis,

which may underestimate the true number of cases encompassing unrecognised, and therefore uncoded, milder forms of PsA. In addition, routine data lack the clinical parameters that would be required to apply more complex selection algorithms. Reaching an established diagnosis of PsA is complicated by the fact that early-stage joint lesions often remain subclinical, and early musculoskeletal symptoms, such as enthesitis, are rather unspecific. Furthermore, access to rheumatologists can be limited or delayed (15, 29).

Notably, the prevalence of PsA is highest in middle age. This has also been observed in the large German primary data studies in line with age distribution (7, 30).

The highest incidence of PsA in patients with PsO was observed in middle-aged patients (30–59 years). Although the effect size is relatively small, older age at onset of PsO was significantly associated with a lower risk of developing PsA later on (age: HR 0.98 [95% CI 0.98, 0.99],  $p=0.0001$ ). In turn, this means that patients diagnosed with PsO at a younger age are at higher risk of developing PsA within the first 5 years after a diagnosis of PsO. This phenomenon is not only likely to be an exercise-triggered effect, but probably also a higher inflammatory activity induced by occupational activities and/or younger biological age. The duration of the observation period was identical across patients' age, i.e., the effect is not caused by a shorter observation period in patients with higher age.

The mean latency between diagnosis of PsO and concomitant PsA was 2.3 years (minimum 6 months) with no substantial differences between age groups and sex. Latency was only slightly shorter in younger patients. In the youngest adult population (18–29 years), however, latency was second highest (2.50 years), with only the age group of 80–89 years having an even higher latency of 3.08 years. Unspecific musculoskeletal symptoms, such as enthesitis and joint pain in young, otherwise healthy, patients might be even less likely to be attributed to PsA, and thus not comprehensively examined for their psoriatic origin (15, 29).

The observed incidence rate of PsA in patients with PsO in this German cohort is at the lower end compared with cohorts from other countries, such as the USA and Sweden (31). Notably, the prevalence of PsA in patients with PsO has been reported to be markedly higher in the US population compared with the German population (31). This considerable difference in the selected cohorts is likely to result in the differences in the incidence rates of PsA. In a Swedish study using registry data, the estimated incidence rate of PsA in adult patients with PsO was 1.53 per 100 patient-years, which is more than twice the rate reported in the current study. The likelihood of early diagnosis of PsA in this population was, however, higher, since the study used registry data of patients who were under specialist care. Health insurance claims data, on the other hand, contain information about patients

who might not see a rheumatologist or dermatologist frequently, potentially delaying diagnosis, and resulting in lower incidence rates. In addition to marked differences in cohort selection and methodological approaches, such as diagnosis-free intervals, between the 3 studies, the varying ethnic diversity of the populations of the USA and Germany might cause the observed discrepancies in incidence rates (31). Moreover, differences in healthcare systems and their respective reimbursement models were observed to influence the encoding of diagnosis (31–33).

Comorbidity frequencies of patients with PsO were consistent with known epidemiological data (31). Importantly, hypertension (no PsA incidence 44.49%; PsA incidence 37.78%) and dyslipidaemia (no PsA incidence 28.77%; PsA incidence 21.59%) being major cardiovascular risk factors, occur very frequently in patients with PsO, both those who develop concurrent PsA and those who do not. This underlines the need for effective cardiovascular risk factor control in this population (27). The increased risk of comorbidities has been attributed not only to a higher prevalence of traditional risk factors, such as hypertension, obesity, diabetes and hyperlipidaemia, but also to chronic systemic inflammation (34–36).

In patients with PsO with incident PsA, depression and neurosis/stress disorder were more common than in patients without incident PsA (no PsA incidence: depression 15.86%, neurosis/stress disorder 9.59%; PsA incidence: 20.32%, 14.60%, respectively). Cox regression modelling confirmed a significant association. This suggests that these psychiatric comorbid diseases might be indicators of PsA development in patients with PsO. Paying attention to these potential psychiatric comorbidities in routine clinical care could therefore be helpful to identify patients at higher risk of development of concomitant PsA (37). The increased occurrence of these psychiatric disorders with the onset of PsA could stem from subclinical PsA lesions already existing in patients with PsO and potentially affecting their psychological well-being by causing pain and limiting the function of the affected joints (16). Proinflammatory cytokines, such as interleukin (IL)-1 and IL-6, are elevated in both, psoriasis and depression (37). This endorses another interesting hypothesis, that chronic inflammation is a shared pathomechanistic pathway of PsO/PsA and depression, and that systemic inflammatory processes may be involved in the progression of both diseases (37). Ischaemic heart disease is a risk factor for PsO or PsA (5, 25, 31). However, the direction of the association is surprising (HR 0.49 [95% CI 0.27, 0.98],  $p=0.0164$ ). The results indicate that insured patients with ischaemic heart disease have a lower risk of developing concomitant PsA than those without. This cannot be clinically proven and can only be explained by methodological limitations of the accounting data. Studies suggest that undercoding, overcoding or miscoding may occur in the coding of heart diseases, thus distorting the results (38, 39). In order

to obtain a more precise coding of heart diagnoses in future studies, additional criteria have to be used, e.g., continuity of outpatient medical care (diagnosis in more than 25%) or drug treatments (39).

In summary, it can be assumed that a relevant proportion of patients with PsO and joint complaints were still not detected, based on the PsO-PsA rate described in the literature (11). This is of great preventive importance in view of the risk of progression of arthritis leading to non-reversible damage.

These data highlight that early detection of PsA must continue to be a priority goal, as set out in the German National Health Care Goals in Psoriasis 2015 to 2020 (40). It can be seen from the primary data analyses that dermatologists' focus on, and competence regarding, the early diagnosis and treatment of PsA has increased significantly in recent years (41). This also has to be implemented in the wider range of care. A bottleneck in these programmes is the comparatively small number of rheumatologists, even in Germany. For this reason, cross-disciplinary collaborations should be strengthened and, if necessary, include further disciplines, such as orthopaedics or radiology. The competence for early detection, through cooperation of dermatologists and general practitioners, should also be enhanced.

#### *Strengths and limitations*

This analysis of a large patient cohort, comprising all available data from one of the leading statutory health insurances in Germany, provides a comprehensive data analysis without considerable selection bias.

Data regarding health insurance claim analyses may underestimate the reality of care, as services can be invoiced only when insured people use the health system. Due to regular treatment of chronic diseases, such as PsO, we can assume that we have not missed any insured persons who have the disease but do not have doctor contact in the observation period (42). Milder or unclear presentations of PsA requiring thorough rheumatological examination in order to reach a definite diagnosis might not be included in this analysis in many cases. In addition, ICD codes do not include information regarding disease severity of PsO, which may influence the development of several disease manifestations, such as PsA. Diagnosis of PsA is complex and may produce false-positives if no comprehensive clinical work-up is performed. Nevertheless, with the help of validity criteria, such as confirmed outpatient diagnoses, the health insurance data provide an important source for epidemiological and health services research (43).

The overall observation time was limited to 6 years due to data protection laws. The time to monitor for PsA development after diagnosis of PsO was therefore limited to 5 years. In a previous study with long-term observation data, the median latency between the diagnosis of PsO and PsA was 7–8 years, which is markedly longer than in

the current study (13). A longer observation period would have enabled an extended analysis of the rates and latency periods for concomitant PsA in patients with PsO. However, the shorter observation period in the current study highlights the finding that concomitant PsA can occur within a short latency period soon after diagnosis of PsO.

#### *Conclusion*

This study indicates that PsA can develop shortly after PsO diagnosis, especially in younger adult patients. The overall comorbidity profiles of patients with PsO with or without concomitant PsA are comparable, with cardiovascular diseases being highly prevalent in both populations. Interestingly, depression and neurosis/stress disorder can be indicators of the development of concomitant PsA in patients with PsO. Due to the high disease burden and socioeconomic impact caused by significant disease symptoms, and the increased frequency of cardiovascular and psychiatric comorbidities, early diagnosis and comprehensive treatment is critical for adequate patient care. This analysis provides important data for epidemiological research, especially for the European population.

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