

Psoriasis and Comorbidities

Epidemiological studies

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Papers

This thesis is based on research carried out during my time as a PhD student at the Department of Cardiology and the Department of Dermato-Allergology, Herlev and Gentofte Hospital, affiliated with the Graduate School of Health and Medical Sciences (Graduate programme in Immunology and Infectious Diseases), at the University of Copenhagen. The following scientific papers form the backbone of this PhD thesis. In the text, the papers are referred to by their roman numerals.

Paper I

Egeberg A, Khalid U, Gislason GH, Mallbris L, Skov L, Hansen PR. The impact of depression on the risk of myocardial infarction, stroke, and cardiovascular death in patients with psoriasis: a Danish nationwide study. *Acta Derm Venereol.* 2015 Aug 17. [Epub ahead of print]

Paper II

Egeberg A, Khalid U, Gislason GH, Mallbris L, Skov L, Hansen PR. Association of psoriatic disease and uveitis: a Danish nationwide cohort study. *JAMA Dermatol.* 2015 Nov 1;151(11):1200-5.

Paper III

Egeberg A, Mallbris L, Gislason GH, Skov L, Hansen PR. Risk of multiple sclerosis in patients with psoriasis: a Danish nationwide cohort study. *J Invest Dermatol.* 2015 Sep 9. [Epub ahead of print].

1. Introduction

Psoriasis is a chronic systemic inflammatory disease with a prevalence of 2-3% in Europeans, and up to 8% in certain Nordic countries.¹ Plaque psoriasis (psoriasis vulgaris) is the most common form of psoriasis accounting for 90% of all cases, and approximately 70-80% of all patients are considered to have mild psoriasis that can be managed with topical treatment alone.^{2,3}

The disease is characterized by either localized or widespread thick raised silvery-white scaling plaques, and common extracutaneous manifestations include nail psoriasis and psoriatic arthritis.⁴ In recent years however, compelling evidence have shown that patients with psoriasis, in particular in the moderate-to-severe form, have increased risk of a range of other comorbidities including CVD, and of CV mortality.⁵⁻⁸ Hypertension, dyslipidaemia, and diabetes mellitus (DM) frequently occur in patients with psoriasis, and there is a high prevalence of obesity, smoking, and alcohol consumption among these patients.⁹⁻¹⁰ Also, patients with psoriasis have significantly increased risk of depression, and the presence of psoriasis is strongly associated with decreased quality of life.¹¹⁻¹²

The inflammatory response in psoriasis is promoted by T helper (Th)1 and Th17 cells, and pro-inflammatory mediators such as interleukin (IL)-6, IL-12, IL-17, IL-22, IL-23, and tumour necrosis factor- α (TNF) play a crucial role in the pathogenesis of psoriasis.¹³ Interestingly, research in neuroinflammation associated with diseases of the CNS has in recent years increasingly also focused on the role of the aforementioned cytokines, particularly IL-17 and TNF.¹⁴⁻¹⁵ Indeed, psoriasis and depression share striking similarities in their inflammatory pathways.¹⁶ For example, IL-6, IL-12, and TNF all have been found in increased circulating levels in patients with depression, and depression is also suspected to be an independent risk factor for the development of psoriasis.¹⁷⁻¹⁹ In addition, although it is not observed as commonly as, e.g. nail psoriasis, uveitis has been reported to occur in patients with psoriasis, and in particular in patients with psoriatic arthritis.²⁰ As the fifth leading cause of vision loss in Europe, uveitis is responsible for between 5% and 20% of all cases of blindness.²¹ While human leukocyte antigen (HLA)-B27 has been linked to psoriatic arthritis and uveitis, research also suggests that Th1 and Th17 cells are involved in the pathogenesis of uveitis, and there is an overlap between the inflammatory pathways in psoriasis and uveitis.¹³⁻²⁰⁻²¹ Along this line, studies have shown CNS infiltration of Th17 cells with production of IL-17 in patients with multiple sclerosis (MS), as well as the occurrence of psoriasis following onset of MS, although paradoxical immune activation and MS exacerbation following treatment with anti-TNF agents in patients with MS have been reported.²²⁻²⁴ Notwithstanding, certain systemic anti-inflammatory therapies including anti-TNF agents and fumarates used in psoriasis have shown some promise for the treatment of depression, uveitis, and MS, respectively, suggesting that these conditions may be more closely linked than previously believed.²⁵⁻²⁸

Since psoriasis is a common and easily identifiable disease, an improved understanding of potential comorbid conditions and associated risk factors can have significant clinical implications in terms of increased early detection and treatment of these conditions in patients with psoriasis.

2. Objectives

With the underlying hypothesis that pathophysiological links exist between psoriasis, and CNS diseases, the present thesis had the following objectives:

Paper I

To examine the impact of incident depression on the risk of MI, stroke, and CV death in patients with psoriasis.

Paper II

To examine the potential bidirectional relationship between psoriasis and uveitis.

Paper III

To examine the risk of new-onset multiple sclerosis in patients with psoriasis.

3. Materials and methods

Data sources

The nationwide administrative and healthcare registries in Denmark form the basis of this thesis. All citizens have free, equal and universal healthcare access in Denmark, and at birth or immigration all Danish citizens receive a 10-digit permanent and unique personal identification number, which enables individual-level linkage of data between registries in Denmark.²⁹ The Civil Registration System records information such as date of birth, gender, and vital status, and the Danish Fertility of Women and Couples Dataset contains a parent-child link with information (such as the personal identification number of the mother and father, and adoption status, respectively) on live and stillbirths in Denmark since 1942.^{29,30} Information on tax-reported household income is registered by Statistics Denmark.³¹ Since 1978, all hospital admissions and diagnoses are recorded in the Danish National Patient Register. The register used the International Classification of Diseases, Eight Revision (ICD-8) codes until 1994, and Tenth Revision (ICD-10) codes hereafter (for administrative reasons ICD-9 was never used in Denmark).³¹ Surgical and hospital treatment procedures (including hospital-based pharmacological treatment) are coded as *Sundhedsvæsenets Klassifikationssystem* (SKS, the Health Service Classification System) codes.³² In the Danish National Patient Register, the SKS procedure codes marked with the symbol “[\$]” are used for reimbursement of expenses. This is the case for hospital-based treatment with biological therapy, which is thus only reimbursed if the treatment is accurately recorded. Most prescription-based medication in Denmark is partially reimbursed by the Danish health care system, and the Danish Registry of Medicinal Products Statistics records detailed and accurate information (e.g. date of dispensing, formulation, and quantity) on all prescription medications dispensed from Danish pharmacies according to the international Anatomical Therapeutic Chemical (ATC) classification since 1994.³³ All deaths and causes of deaths (including primary, contributory, and underlying causes) are registered in the National Causes of Death Registry using ICD codes.³⁴

4. Data security, study approvals and ethics

Data from the Danish registers are encrypted and rendered anonymous when used for research purposes, and data were accessed and analysed through secure servers located at the Office for National Statistics (Statistics Denmark). Approval for the studies of the present thesis was obtained from the Danish Data Protection Agency (ref. 2007-58-0015, int. ref. GEH-2014-018, I-Suite 02736), and approval from an ethics committee is not required for register studies in Denmark.

5. Study population

The population and design varied according to the specific research questions that were addressed in the individual substudies of the current thesis. In the following section, the populations and designs for Papers I-III are outlined.

6. Identification and severity classification of patients with psoriasis

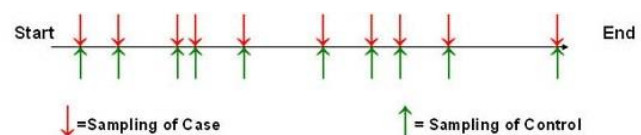
Patients with psoriasis were identified when they claimed their second pharmacy-dispensed prescription of topical vitamin D derivatives with or without glucocorticoids (ATC Code D05AX), which is the favoured first-line treatment for psoriasis in Denmark, or by their first in- or outpatient consultation for psoriasis or psoriatic arthritis (ICD-8 codes 696.09-10, 696.19 and ICD-10 codes L40, M070-M073), respectively. Previous Danish epidemiological studies from our group have identified patients with mild psoriasis by this method, and classified patients with severe psoriasis by their third in- or outpatient hospital diagnosis of psoriasis or psoriatic arthritis.³⁵ However, healthcare consumption alone as a measure of psoriasis severity can potentially lead to misclassification, and patients seen exclusively in private dermatology clinics would thereby be classified with mild psoriasis regardless of their actual psoriasis severity. To overcome this issue, we used a psoriasis severity classification similar to that used by Gelfand et al.⁶ Accordingly, patients were classified with mild disease from onset of psoriasis and until if and when they fulfilled the criteria for severe disease. Severe psoriasis was defined as receiving systemic antipsoriatic treatment consistent with severe disease, i.e. treatment with biological drugs (ATC codes L04AB01, L04AB02, L04AB04, L04AC05, L04AA21, and SKS codes BOHJ18A1-BOHJ18A3, BOHJ18B3), cyclosporine (ATC code L04AD01 and SKS code BOHJ20), psoralens (ATC code D05BA and SKS code BNGA1), retinoids (ATC code D05BB and SKS code BQHB30), or methotrexate (ATC code L03BA01 and L04AX03, and SKS code BWHA115), respectively. To ensure accuracy of this method for identification and severity classification of patients with psoriasis, we validated this algorithm against data in the nationwide DERMBIO registry of patients with psoriasis treated with biological agents (Paper III).

7. Cohorts

Paper I

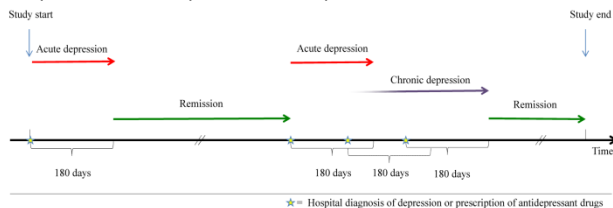
As study cases, the investigations comprised all Danish citizens with psoriasis and incident depression between 1 January 1997 and 31 December 2011. Each case was matched on age, sex, and calendar time with up to 4 controls (that is, patients with psoriasis without depression), and we controlled for variations in severity of psoriasis by adjustment for use of systemic antipsoriatic treatment. The study comprised 6,244 patients with psoriasis and incident depression as cases, and 23,162 matched controls, respectively. This design had the advantage that it allowed for direct comparison of psoriasis patients with and without depression, and matching on calendar time ensured similar between-group follow-up time.

Figure 1 Example of study sampling in Paper I.



Depression activity was modelled as a time-dependent variable, and divided into acute depression, chronic depression, and remission from depression (hereafter denoted as “remission”). We defined acute depression as the first 180 days from the hospitalization for depression and/or initiation of antidepressant therapy. Episodes of chronic depression were defined as those which succeeded acute episodes if additional hospitalizations or antidepressant prescriptions had taken place within the 180 days from an episode of acute depression. Patients were considered in remission 180 days after last hospitalization or prescription of antidepressants, and remission ended at the time of reinitiating of antidepressant therapy or hospitalization for depression.

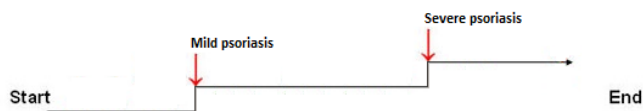
Figure 2 Example of modelling of depression activity in a psoriasis patient with depression in Paper I.



Papers II-III

In these studies we used the entire Danish population aged ≥ 18 years, and each individual was included on 1 January 1997, or on the subsequent day they turned 18 years of age. We excluded patients with a history of the exposure (psoriasis, and, in Paper II, also uveitis) or the investigated outcome disease prior to study inclusion, and thus patients were considered “healthy” at study start. Patients therefore contributed with risk time in the reference population until the onset of mild psoriasis, and in the mild psoriasis group until the onset of severe psoriasis, if appropriate.

Figure 3 Example of risk time allocation and modelling of psoriasis severity in Papers II-III.



The advantage of such a design was that it allowed for large-scale analyses and provided the total number of events representative of all adult citizens of Denmark.

In Papers II and III, the cohorts comprised the entire Danish population aged ≥ 18 years from 1 January 1997. In all three papers, subjects were followed until the occurrence of an endpoint, migration, death from any cause, or 31 December 2011, whichever came first. Individuals described as having “incomplete migration information” entailed those citizens who had emigrated, and returned to Denmark prior to study start. Since medical conditions diagnosed while living abroad would not have been captured in the Danish registries, these patients were excluded from the analyses. Specifically, in Paper II, where we investigated bidirectional risk-time estimates, these individuals were censored at study start, and in Paper I and III they were excluded.

8. Covariates

Based on prescription claims, baseline pharmacological therapy was described up to 6 months prior to study start. Comorbidity was described up to five years before study start based solely on ICD codes, except for diabetes and hypertension. Diabetes was

defined as either a hospital diagnosis of diabetes (ICD-8 code 250, and ICD-10 codes E10–E14), or by use of glucose-lowering agents (ATC code A10). Hypertension was defined by a hospital diagnosis of hypertension (ICD-8 codes 400-404, and ICD-10 codes I10-I15), or if the patient received treatment with at least two of the following classes of antihypertensive drugs within a 90 day period: α -adrenergic blockers, non-loop diuretics, vasodilators, β -blockers, calcium channel blockers, and renin-angiotensin system inhibitors. This method was previously validated with a positive predictive value of 80% and a specificity of 95%.³⁶ Based on data from Statistics Denmark, we calculated an age-standardized index of socioeconomic status between 0 and 4 based on the average gross annual income during a 5-year period before study inclusion. In Paper III we identified patients with a history of smoking, by diagnoses of smoking, tobacco use, chronic obstructive pulmonary disease (COPD), and lung cancer, as well as pharmacological treatment and therapeutic interventions for smoking cessation (Paper III, e-supplement). A recent survey by the Danish Health and Medicines Authority of 5,020 randomly selected Danish citizens reported that 80% of smokers had tried smoking cessation at least once.³⁷

9. Outcomes

We assessed the following endpoints in Papers I-III:

Paper I

MI (ICD-10 codes I21-I22), ischemic stroke (ICD-10 codes I63-I64), CV death (ICD-10 codes I00–I99), respectively, and a secondary composite endpoint of MI, stroke, and cardiovascular death.

Paper II

Uveitis (ICD-10 code H20), mild psoriasis (≥ 2 prescriptions of topical vitamin D derivatives [ATC code D05AX] or ≥ 1 ICD-10 code L40, *without* systemic antipsoriatic treatment), severe psoriasis psoriasis (≥ 2 prescriptions of topical vitamin D derivatives [ATC code D05AX] or ≥ 1 ICD-10 code L40, *with* systemic antipsoriatic treatment), psoriatic arthritis (ICD-10 codes M070-M073), and a secondary endpoint of psoriatic spondylitis (ICD-10 codes M072).

Paper III

MS (ICD-10 code G35).

The diagnoses of MI, stroke, CV death, and MS have previously been validated in the Danish National Patient Register with very high accuracy.³⁸⁻⁴⁰

10. Statistical analyses

Baseline characteristics were presented as frequencies with percentages for categorical variables and means with standard deviations for continuous variables. We presented incidence rates for the reference and psoriasis groups as appropriate. In Papers II-III, outcomes before an index date in the psoriasis groups were allocated to the reference group in order to obtain a more accurate exposure time allocation, and patients contributed risk time in the mild psoriasis group until they fulfilled the criteria for severe psoriasis, if appropriate. However, it should be noted that the time of onset of psoriasis was only an approximation, as patients may not seek medical attention early in the course of psoriasis, especially in mild cases. We fitted Poisson regression models and calculated incidence rate ratios (IRRs) in crude, age- and sex-adjusted, and multivariable analyses (henceforth denoted “fully adjusted analyses”), and results were reported with 95% confidence

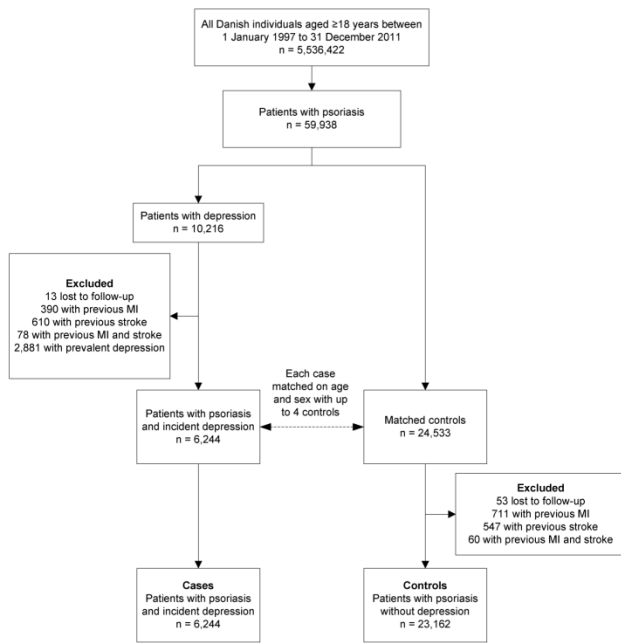
intervals (CIs) in all three papers. In Paper I, matching was performed based on age, sex, and calendar time, whereby cases and control subjects could be compared in terms of covariates while ensuring similar follow-up time between the two groups.

11. Results

Below are provided brief summaries of the 3 papers which form the basis of this thesis. Further details are apparent in the full papers enclosed in the Appendix section.

12. Paper I: The impact of depression on the risk of myocardial infarction, stroke, and cardiovascular death in patients with psoriasis: a Danish nationwide study

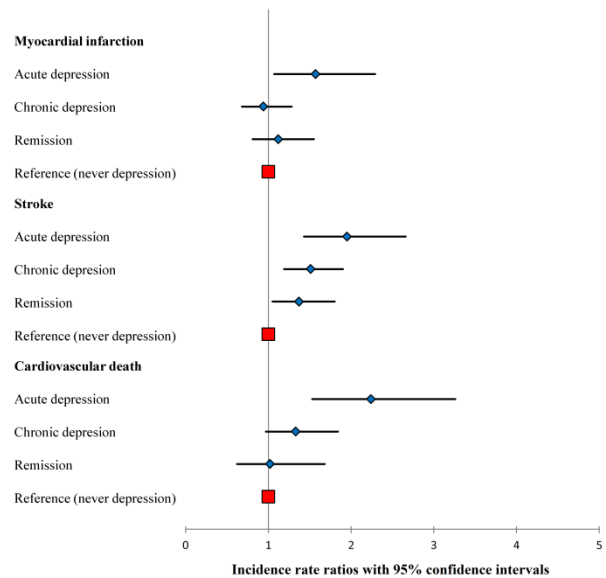
Figure 4 Study flow chart in Paper I.



Between 1 January 1997 and 31 December 2011 we identified 6,244 patients with psoriasis and incident depression, i.e. new-onset depression after the patient was categorized with psoriasis (Figure 4). Each patient was matched on age, sex, and calendar time with up to four controls (that is, patients with psoriasis without depression). Patients with psoriasis and depression experienced 129, 188, and 314 MIs, strokes, and CV deaths, respectively, compared with 387, 472, and 659, respectively, in the control population. The number of events stratified by depression activity are described in Paper I. Adjustments were made for age, sex, socio-economic status, comorbidity, medication, and severity of psoriasis. As shown in Figure 5, during acute depression, case subjects had a significantly increased risk of MI (IRR 1.57, 95% CI 1.07-2.29), stroke (IRR 1.95, 95% CI 1.43-2.66), and CV death (IRR 2.24, 95% CI 1.53-3.26), respectively. During chronic depression the risk of stroke was also significantly increased (IRR 1.51, 95% CI 1.19-1.90), and the risk estimate of CV death was borderline significant (IRR 1.33, 95% CI 0.97-1.84, $p=0.080$), while the risk of MI was similar to the control population (IRR 0.94, 95% CI 0.68-1.28, $p=0.679$). During remission from depression, there were no significant differences in the risk of MI and CV death; however the risk of stroke remained increased (IRR 1.37, 95% CI 1.05-1.80). Similar results were observed with altered criteria for the duration of acute and chronic depression.

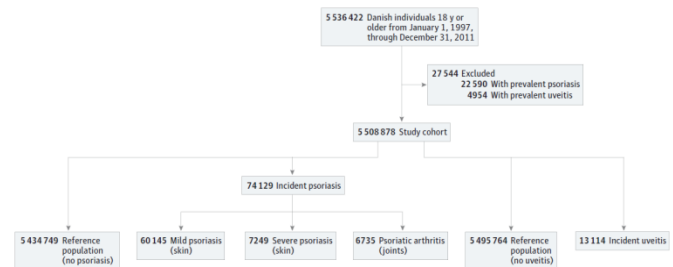
In conclusion, this nationwide study demonstrated a significant negative impact of depression, and especially acute depression, on the CV risk in patients with psoriasis.

Figure 5 Risk of MI, stroke and CV death in patients in Paper I.



13. Paper II: Relationship between psoriatic disease and uveitis: a Danish nationwide cohort study

Figure 6 Study flow chart in Paper II.



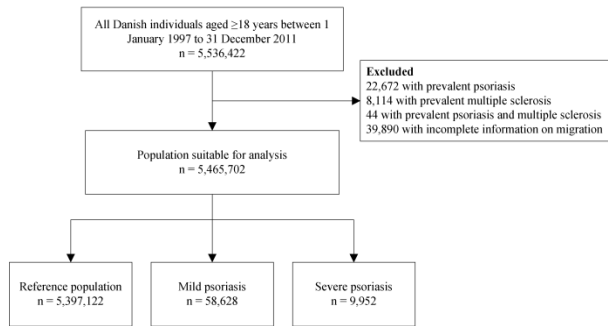
During the 15 year period from 1997-2011 we identified 74,129 and 13,114 cases of incident psoriasis and uveitis, respectively (Figure 6). The Danish population ≥ 18 years of age without these conditions served as the reference population in separate analyses which were performed to estimate the risk of new-onset uveitis in patients with mild psoriasis, severe psoriasis, and psoriatic arthritis, respectively, and vice versa. There were 13,000, 86, 12, and 16 incident cases of uveitis in the reference population, mild psoriasis, severe psoriasis, and psoriatic arthritis, respectively, corresponding to incidence rates (95% CI) per 10,000 person-years of 2.02 (1.99-2.06), 2.88 (2.33-3.56), 4.23 (2.40-7.45), and 5.49 (3.36-8.96), respectively. After adjustment for potential confounding factors (including age, sex, socio-economic status, inflammatory bowel disease [IBD], herpes zoster, and sarcoidosis) the IRRs (95% CI) of uveitis were 1.38 (1.11-1.70), 1.40 (0.70-2.81, $p=0.338$), and 2.50 (1.53-4.08), in mild psoriasis, severe psoriasis, and psoriatic arthritis, respectively. Conversely, there were 60,030, 7,229, and 6,730 cases of mild psoriasis, severe psoriasis, and psoriatic arthritis in the reference population versus 115, 20,

32 cases, respectively, in the uveitis population. The corresponding incidence rates were 9.37 (9.30-9.45), 1.12 (1.10-1.15), and 1.04 (1.01-1.06), respectively, in the reference population, and 15.51 (12.92-18.62), 2.66 (1.72-4.13), and 4.25 (3.00-6.01) in patients with uveitis. The fully adjusted IRRs of mild psoriasis, severe psoriasis, and psoriatic arthritis were 1.59 (1.32-1.91), 2.17 (1.40-3.38), and 3.77 (2.66-5.34), respectively.

In conclusion, the risk of uveitis was significantly increased in patients with mild psoriasis, and psoriatic arthritis, and the risk of mild psoriasis, severe psoriasis, and psoriatic arthritis, respectively, was increased in patients with uveitis.

14. Paper III: Risk of multiple sclerosis in patients with psoriasis: a Danish nationwide cohort study

Figure 7 Study flow chart in Paper III.



During a maximum of 15 years of follow-up, there were a total of 9,713 cases of new-onset MS in our cohort, which comprised 58,628 and 9,952 cases of mild and severe psoriasis, respectively, and 5,397,122 individuals without psoriasis, serving as controls (Figure 7). Covariates included age, sex, socio-economic status, smoking, IBD, treatment with statins, therapy with ultraviolet (UV) light, treatment with TNF inhibitors, and type 1 DM. The incidence rates (95% CI) per 10,000 person-years of MS were 1.78 (1.74-1.82), 3.22 (2.57-4.04), and 4.55 (2.52-8.22) in the reference population, mild psoriasis, and severe psoriasis, respectively. In fully adjusted analyses, the IRRs (95% CI) of MS were 1.84 (1.46-2.30) and 2.61 (1.44-4.74) in mild and severe psoriasis, respectively. The risk was significantly different ($p < 0.001$) between mild and severe psoriasis, and similar results were observed in sub-analyses with adjustment for family history of MS.

In conclusion, we observed a psoriasis-severity dependent increased risk of new-onset MS, independent of measured confounders.

15. Study psoriasis diagnosis and severity definition: Validation study

In brief, Danish patients with moderate-to-severe psoriasis treated with biologic drugs in private clinics claim their prescriptions from pharmacies, and patients treated at hospital departments receive the drug directly from the hospital. Therefore, biologic therapies for patients treated in private clinics are recorded as ATC codes in the Danish Registry of Medicinal Products Statistics, and biologic therapies for patients treated at hospital departments are recorded as SKS codes in the Danish National Patient Register. To examine the accuracy of the psoriasis diagnosis used in the current work, and the recording of biologic therapy in these

two registries, we performed a validation study with the DERM-BIO registry as the gold standard. Since 2007, the DERM-BIO registry covers all patients with moderate-to-severe psoriasis treated with biologic drugs in Denmark in hospital dermatology departments, and in private dermatology clinics, respectively. The National Patient Register and the Registry of Medicinal Products Statistics together captured treatment with biologic therapy (ustekinumab, adalimumab, etanercept, and infliximab) in 97% of all patients recorded in DERM-BIO. When we included off-label treatment and clinical trials with non-approved agents, the sensitivity was 96%. Our definition of psoriasis captured 98% of individuals in DERM-BIO, as did our classification of severe psoriasis.

16. Methodological considerations

Statistical methods

Since our cohorts had a vast number of observations, varied in follow-up time, and included time-varying covariates, we used Poisson regression which, as compared with Cox regression, is more efficient (albeit that these methods generally produce very similar results). We created 1-year time bands during the study period, and age was updated for each time band. We tested model assumptions and found them to be valid unless specified in the respective papers, and covariate interactions were tested, and stratified analyses were presented in cases where significant interactions were present. We categorized continuous variables into quartiles, thereby demonstrating linearity since they did not improve the model fit.

Potential bias and confounding

The nationwide Danish registries lack information on certain potential confounding risk factors, especially with regards to CVD (Paper I). Information on risk factors such as obesity, blood pressure, lipid levels, physical activity, alcohol consumption, and smoking, were unavailable, albeit that we attempted to adjust for the majority of these, e.g. by use of an index for socioeconomic status (which to some extent captures many of the aforementioned confounders) and surrogates such as statin therapy as a proxy for hyperlipidaemia, and COPD as proxy for smoking (Paper I). For Paper III, we developed an algorithm for identification of individuals with a history of smoking (Paper III, e-supplement). To account for differences in covariates that may change over the 15 years of study follow-up, we continually updated this information during follow-up. However, while this allowed for time-varying analyses, it is possible that certain covariates, such as hypertension, may have been mediators of the true exposure-associated risk, whereby continuous update of covariates could result in over-adjustment of our models.⁴¹

Misclassification, detection bias, and immortal time bias

In Paper I, duration of episodes of acute and chronic depression was based on ICD codes and pharmacological treatment with antidepressants. While the Danish Registry of Medicinal Products Statistics holds information on certain treatment-related variables such as drug pack size and quantity, we did not have information on why the prescribing physician had initiated therapy with antidepressants. It is therefore plausible that some misclassification may have occurred, as patients may have received antidepressant therapy for other conditions, e.g. anxiety disorders.

Although the diagnosis of uveitis to our knowledge is not validated in the Danish registries, any bias caused by misclassification in this regards would likely bias the results towards the null, since

we performed analyses where uveitis served as the exposure variable. Thus, it is conceivable that the true relationship between uveitis and psoriasis is even stronger than what was observed in Paper II. We cannot refute that increased medical scrutiny in patients with psoriasis may have led to increased detection (detection bias) of the outcome of interest. However, the observed psoriasis-severity dependent increased risk (“dose-response relationship”) in Papers II-III supports the observed relationships. Moreover, since relatively little attention previously has been given to the occurrence of MS and uveitis in patients with psoriasis, we do not suspect that detection bias posed a major problem in our studies, and the risk of MS remained increased in a range of sensitivity analyses. Furthermore, the “hard” endpoints used in Paper I (MI, stroke, and CV death) are not likely to be significantly affected by detection bias.

Immortal time bias arises when an exposure group is conditioned on events occurring in the future, and will lead to bias which favours the exposed group.⁴² For example in Paper I, if the index date of cases (i.e. patients with psoriasis and incident depression) had been at the onset of psoriasis, such patients would have been “immortal” from onset of psoriasis and until the depression criteria was fulfilled. To address this issue, we performed a matched case-control study, where the index date of cases was the first occurrence of depression in patients with psoriasis. In Papers II-III we used the second dispensed prescription of topical vitamin D derivatives as the index date of psoriasis, to avoid immortal time bias, which would have occurred if we had set the index date at the first of the two claimed prescriptions.

Protopathic bias and confounding by indication

Protopathic bias can occur when the exposure drug is inadvertently prescribed for an early manifestation of the outcome disease, before this has been properly diagnosed. In our studies, topical vitamin D derivatives and hospital consultations were used to identify patients with psoriasis, and severe psoriasis was defined as subsequent treatment with systemic anti-psoriatic therapy such as methotrexate or biological agents. Although some forms of systemic anti-psoriatic therapy have shown efficacious in uveitis (e.g. certain TNF inhibitors), initiation of such treatment would arguably take place in a hospital setting after failure of conventional first-line treatments, whereby it is unlikely that patients would not already have received a proper diagnosis by a trained ophthalmologist. Importantly, the increased risk of the various outcomes observed in cases of mild psoriasis cannot be sufficiently explained by protopathic bias, since topical Vitamin D therapy is not used for treatment of CVD, uveitis, or MS, respectively. Confounding by indication is one of the most important limitations of observational studies, and occurs when prognostic factors influence the course of therapy. The increased focus on effects of systemic inflammation, and in particular on the CV comorbidities in patients with psoriasis, may potentially lead to a more intense treatment of risk factors for such conditions in these patients. However, in Papers I-III we adjusted for a wide range of established risk factors for the respective outcomes, and result generally remained consistent after such adjustments were made.

17. Discussion

The results described in this thesis add to the growing sum of evidence which suggest that psoriasis has far-reaching systemic implications. Importantly, we provide nationwide data which suggest that the association between psoriasis and CVD is even more

complex than previously believed, and that psoriasis is an independent risk factor for selected diseases of the CNS. Indeed, the main findings were that depression in patients with psoriasis was associated with significantly increased risk of CVD, that there was a bidirectional relationship between psoriasis and uveitis, and that psoriasis conferred an independent risk of MS, respectively. As Papers I-III provide novel data on previously unexplored disease associations in patients with psoriasis, we believe that this thesis adds considerably to the current literature on psoriasis as a systemic disease.

Inflammation and genetics

Psoriasis is one of the most common immune-mediated diseases, and although substantial advances have been made, several areas in the understanding of the pathogenesis of psoriasis remain unresolved.³ For instance, it is puzzling that more severe psoriatic arthritis often occurs in patients with lesser degrees of skin involvement.⁴³ However, it is well-established that psoriasis is the result of a complex interplay between genetics, environmental triggers, and the immune system.⁴⁴ Although many genes are involved, psoriasis is strongly associated with the major histocompatibility complex human leukocyte antigen (HLA), class I, Cw6, and approximately 60% of patients with psoriasis display HLA-Cw0602 which has been identified as the major risk gene on psoriasis susceptibility locus 1, and shown to increase the risk of psoriasis up to 20-fold.⁴⁵⁻⁴⁷ Moreover, the presence of HLA-Cw0602 is an established predictor for an early onset and a more severe course of psoriasis.^{47 48} On the other hand, genome-wide association studies have also linked psoriasis to, for example, the IL-23 pathway.⁴⁴ While Th1 cells were previously believed to be the major drivers of the inflammatory response in psoriasis, the discovery of IL-17-producing cells, e.g. Th17 cells, have deepened the immunological understanding of psoriasis.^{13 44 49} In psoriasis, the immune dysregulation results in chronic inflammation mediated by cytokines (including IL-17, IL-23, and TNF), immune cells and keratinocytes.⁵⁰ Cytokines and other mediators produced in the skin (or other organs) can be released into the systemic circulation, and thus may contribute to the increased risk of CVD and other inflammatory diseases.

Cardiovascular disease

Data from large cohorts have shown increased CV risk factors, e.g. smoking, obesity, DM, hypertension, and hyperlipidaemia, and CVD, e.g. MI, stroke, and CV death, respectively, in patients with psoriasis and the increased risk of CVD was found to be independent of the adverse CV risk profile in these patients.^{5-8 35} In contrast, after adjustment for known CV risk factors a minority of studies have failed to reproduce the apparent increased risk of CVD in patients with psoriasis.⁵¹⁻⁵⁴ Interestingly, atherosclerosis is a dynamic process which is prompted by immune activation and migration of macrophages and leukocytes into the arterial walls.⁵⁵ Indeed, inflammation is associated with endothelial cell activation, leukocyte migration, smooth muscle cell proliferation, leading to endothelial dysfunction, atherogenesis, and, ultimately, atherosclerotic disease.^{55 56} In support of the link between psoriasis and CVD, preliminary studies have shown increased vascular inflammation in patients with psoriasis by use of [18F]-fluorodeoxyglucose-positron emission tomography/computed tomography, and treatment with TNF inhibitors and methotrexate may reduce CV risk in patients with moderate-to-severe plaque psoriasis.^{57 58}

Depression

We found a significant association between depression, especially during its acute stages, and risk of MI, stroke, and CV death in patients with psoriasis (Paper I). While the vast impact of psoriasis on quality of life has been proposed to be a mechanism for development of depression, increased inflammatory cytokine production may be a contributory factor.^{17 59} Interestingly, in our study the risk of stroke remained increased during chronic depression and remission from depression, respectively, and it is tempting to speculate that a more prolonged state of cerebrovascular inflammation in patients with psoriasis and depression may explain this observation. However, a very recent small study of patients with moderate-to-severe psoriasis examined by [¹¹C]-(R)-PK11195 positron emission tomography did not find significant neuroinflammatory differences between cases and controls.⁶⁰ Yet, patients suffering from affective disorders were excluded from this study, and while other studies have found increased plasma levels of certain cytokines in patients with depression, these were reduced to normal during remission from depression.⁶⁰⁻⁶² Along this line, patients with psoriasis have shown significant reduction of depressive symptoms following anti-TNF or anti-IL12/23 treatment.^{26 63}

In addition to these considerations, the observed association between the different stages of depression (acute, chronic, and remission, respectively) and risk of CVD observed in Paper I may also be explained, in part, by other unmeasured factors such as increased smoking, physical inactivity, noncompliance with pharmacotherapy, and unhealthy diet, respectively, during acute and chronic stages of depression.⁶⁴

Uveitis

Uveitis comprises an extensive range of ocular conditions, and while a strong link exists between uveitis and HLA-B27, the immunopathogenesis also includes disease activity-correlated increases of IL-17 levels in the aqueous humor of patients with uveitis compared with healthy controls.^{65 66} Uveitis has previously been associated with several autoimmune diseases, e.g. IBD and spondyloarthropathies including psoriatic arthritis, however, little attention has been given to the relationship between uveitis and psoriasis without joint symptoms.^{66 67} Although the co-occurrence of psoriasis and uveitis in our study (Paper II) was rare, we observed a significant association between uveitis and risk of new-onset psoriasis and psoriatic arthritis, as well as an increased risk of uveitis in patients with psoriasis and psoriatic arthritis. While the risk of uveitis in our study was increased in patients with mild psoriasis, this was not the case for patients with severe psoriasis. It is likely that this latter result was simply a result of insufficient study power owing to few events in this cohort, or it may be that uveitis occurred prior to the diagnosis of severe psoriasis, whereby these events would have been ascribed to the mild psoriasis, or reference population, as appropriate. Notwithstanding this limitation, our results suggest that even patients with mild skin psoriasis, without manifest joint symptoms, have an increased risk of uveitis and the reciprocal association may clearly also be of clinical importance.

Multiple sclerosis

MS is a chronic CNS disease associated with significant disability, and although it is primarily considered to be a progressive neurodegenerative condition, recent findings suggests that MS is driven by a peripheral immune response targeting the CNS during the early stages of the disease.^{68 69} In fact, several of the very same

cytokines involved in the initiation and maintenance of the inflammatory response in psoriasis, e.g. TNF and IL-17, are found in increased levels in MS plaques.^{70 71} Also, shared genetic links between psoriasis and MS, such as polymorphisms of the IL-23R gene have been described, and anti-IL-17 agents are currently being investigated in clinical trials for MS as well as psoriasis.⁷²⁻⁷⁵ However, previous studies and case reports have described onset of MS, and paradoxical immune activation and MS exacerbation in patients with MS following treatment with anti-TNF agents, and thus current Danish guidelines on the treatment of psoriasis do not recommend use of TNF inhibitors in patients with a personal or family history of MS.^{23 76} Published data on the relationship between psoriasis and MS are scarce but case reports have described onset of psoriasis following treatment of MS symptoms, e.g. with β -interferon.^{77 78} We are the first, to our knowledge, to systematically investigate the risk of new-onset MS in patients with psoriasis, and we demonstrated a psoriasis-severity dependent increased risk of MS, which remained even after adjustment for potential confounding factors including smoking, UV phototherapy, use of TNF inhibitors, and family history of MS (Paper III). These results suggest that a clinical focus on MS symptoms in patients with psoriasis is warranted.

18. Study strengths and weaknesses

The present thesis was strengthened by the high accuracy of the Danish nationwide registries, as well as the statistical adjustments made in the studies for presence of a range of comorbidities and use of pharmacotherapy for which data were continuously updated during follow-up. Taken together with the length and accuracy of follow-up, the use of information on household income, and the large number of individuals, respectively, this adds credibility to our findings. As with all observational studies, we cannot establish causality between exposure and outcome, although when assessed according to the Bradford Hill criteria, causation in our studies is not unlikely.⁷⁹ These criteria include strong, consistent, and specific associations, temporal relationship, dose-response relationship, biological plausibility, experimental evidence, and argument by analogy (in complex relationships), respectively. While the observed results in our studies would appear to fulfil the abovementioned criteria, we lacked information on potentially important confounding factors, especially those relevant for CV risk assessment in Paper I. Information such as blood pressure, lipid levels, physical activity levels, cigarette and alcohol intake, and body-mass index, respectively, was not available, albeit that we attempted to adjust for these using surrogates as appropriate. Nevertheless, we cannot refute the fact that some bias may have occurred. Furthermore, although the diagnoses of MI, stroke, CV death, and MS have been validated in the Danish registries, we are not aware of the validity of the uveitis diagnosis in the Danish National Patient Register.

19. Novelty of the results

Few countries have the possibility to conduct nationwide studies with available information to the same level as is possible in Denmark. We presented epidemiological evidence to suggest that depression may significantly modify the risk of CVD in patients with psoriasis and that psoriasis is an independent risk factor for uveitis and MS. Our findings highlight the importance of a holistic approach in the assessment and treatment of patients with psoriasis, especially since certain treatment interventions may positively affect multiple conditions simultaneously, while other therapies can have detrimental effects in some patients. Moreover we have added to mounting evidence which suggest that psoriasis should

probably be viewed as an umbrella term for several diverse phenotypes, of which the skin is a readily available marker of disease activity.

20. Conclusion

The results of present thesis suggest that diseases of the CNS are closely linked with psoriasis. The results presented in Papers I-III, i.e. that depression is associated with a negative impact on the risk of CVD in patients with psoriasis, and that the presence of uveitis and MS appears to be independently associated with the presence and severity of psoriasis highlight the need for individualised treatment of patients with psoriasis based not only on the symptoms of the skin and joints.

21. Clinical implications and future research

We found an association between depression and CVD in patients with psoriasis, as well as a bidirectional relationship between psoriasis and uveitis, and a significantly increased risk of MS in patients with mild and severe psoriasis, respectively. The negative impact of depression on the risk of CVD in patients with psoriasis again exemplifies the devastating health effects of depression and call for more studies of the interface between the two diseases. Fortunately, the absolute numbers of patients with psoriasis who developed uveitis and MS, respectively, in our nationwide studies were low. However, uveitis and MS are serious medical conditions where increased awareness by dermatologists and other health-care professionals may lead to increased early detection and intervention, which potentially could result in milder disease courses for the patients. Indeed, several studies have revealed significant benefit of early intervention in patients with MS, and the same relationship may be true for psoriasis as well.⁸⁰⁻⁸³ While additional studies are warranted to assess the reproducibility of our findings in populations with different patient characteristics, and with adjustment for confounders for which data were unavailable in the Danish registries, future randomised studies of effects of established and novel therapeutic targets aimed at the immunological pathways of psoriasis and its comorbidities may provide valuable information, e.g. on whether a more aggressive treatment of psoriasis and depression can reduce the risk of uveitis, MS, and CVD, respectively, and whether early systemic treatment of uveitis may reduce the risk of psoriasis.

ABSTRACT

Psoriasis is a prevalent chronic inflammatory disease whose exact etiology is not fully understood, but both genetic and environmental factors have been implicated in the onset and progression of the disease. At the skin level, psoriasis is characterized by localized or widespread thick raised silvery-white scaling and pruritic plaques and studies have shown that psoriasis negatively affects patients' quality of life, and depression occurs more often in patients with psoriasis. However, data have shown that psoriasis is a systemic disease which affects the joints, vasculature, and other tissues as well. Indeed, approximately one-third of patients with psoriasis develop psoriatic arthritis, and patients with severe psoriasis have a shortened life expectancy. Although our knowledge of the pathogenesis of psoriasis has advanced significantly in the past decade, as have the pharmacological treatment options which are now available, several important knowledge gaps remain.

Many of the proinflammatory mediators involved in psoriasis have also been implicated in some central nervous system (CNS)

diseases. However, studies on associations between psoriasis and CNS diseases are scarce. Based on nationwide registry data from the entire Danish population, the present thesis examined the associations between psoriasis and certain CNS diseases. The specific objectives of this work were to investigate the independent impact of depression on the risk of cardiovascular disease (CVD) in patients with psoriasis, the relationship between psoriasis and uveitis, and the risk of incident multiple sclerosis (MS) following the onset of psoriasis, respectively.

The main results were a significantly increased risk of myocardial infarction (MI), stroke, and CV death in patients with psoriasis during stages of acute depression. Moreover, we found a bidirectional relationship between psoriasis and uveitis, where the occurrence of either disease significantly increased the risk of the other. Perhaps most notably, however, was that we found a psoriasis-severity dependent increased risk of MS.

In conclusion, psoriasis was significantly associated with certain CNS diseases, and the risk of CVD was strongly associated with acute depression in these patients. These novel findings suggest an important link between psoriasis and CNS diseases, and highlight the necessity for a holistic approach to the diagnosis and treatment of patients with psoriasis.

22. References

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