Population-based Studies on the Natural History of Psoriasis – and their Role in the Drug Development Process and in Clinical Practice

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Dekan

Science truly does „progress“ in the sense of
gaining, albeit in a fitful and meandering way
through time, more useful knowledge that,
without mincing words, must record an
improving understanding of an objective
external world

(*Stephen Jay Gould, Science 2000, Vol. 287, pp. 253-261)*

Das Gras wächst nicht schneller,
wenn man daran zieht

(aus Ostafrika)

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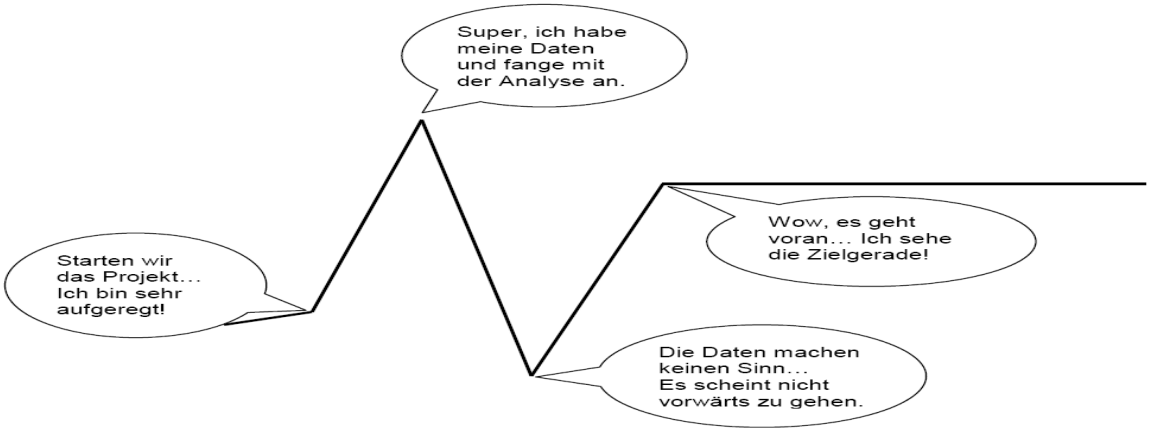

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SUMMARY

Pharmacoepidemiology has been defined as the study of the uses and the effects of drugs in large numbers of people and is important for the surveillance of drugs after marketing. With the recent movement from a reactive to a rather proactive pharmacovigilance, (pharmaco)epidemiological research plays an increasing role in basically all stages of the drug development process. Data on the disease planned to be treated with a new drug have to be gained which can be useful e.g. for the risk-benefit analysis of that compound (e.g. for the comparison of rates of adverse events in the treated population with the disease with rates of such events in the untreated population with the disease). Additionally, good knowledge of diseases is valuable for daily clinical practice. Hence, apart from the classical drug safety studies, pharmacoepidemiology groups conduct more and more disease epidemiology or drug utilisation studies in order to learn more about the natural history of diseases. The aim of this thesis was to increase the knowledge of psoriasis by providing new information and complementing existing data. Psoriasis is a chronic inflammatory skin disease which is common in certain parts of the world. The gain of new insights into the pathogenesis of this disease has prompted the recent development of new therapeutic drugs, primarily biologicals, and vice versa.

The studies of this thesis were conducted with data from the General Practice Research Database, which contains longitudinal primary care clinical records from several million patients representative of the United Kingdom population. The general practitioners have been trained to record information on patient demographics and characteristics, lifestyle factors, symptoms, medical diagnoses, referrals to hospitals or specialists, and therapies in a standard and anonymous way. Several hundred studies have been conducted using this extensively validated database.

In the first three case-control studies, the influence of beta-blockers and other antihypertensives (Study 3.1), of lithium and antipsychotics (Study 3.2), and of thiazolidinediones and other antidiabetics (Study 3.3) on the risk of developing psoriasis were investigated. The study population consisted of 36,702 patients with a first-time psoriasis diagnosis between 1994 and 2005 and the same number of patients without psoriasis, matched on age, sex, index date, general practitioner, and history in the database. Exposure to the drug classes was evaluated taking duration and timing of use and potential confounding into account. In contrast to the notion in the literature (including standard dermatology textbooks), which was mainly based on

data from case reports and case series, use of beta-blockers and other antihypertensives did not materially alter the risk of incident psoriasis. On the contrary, the second study confirmed the suggestion that long-term exposure to lithium can induce psoriasis. Furthermore, for atypical antipsychotics, primarily olanzapine, a statistically significantly decreased psoriasis risk was found for current exposure of longer duration. This observation needs further confirmation. Small clinical trials had shown potential clinical benefits of thiazolidinediones on psoriasis symptoms. Study 3.3 additionally suggested that longer-term exposure to thiazolidinediones reduces the risk of developing psoriasis. The risk also tended to be decreased after use of metformin, however, this needs further investigation.

Studies 3.4 to 3.6 were cohort studies with a nested case-control analysis in which the study population defined for Studies 3.1 to 3.3 (= cohort population) was followed for identification of incident diabetes mellitus (Study 3.4), myocardial infarction (MI) or stroke / transient ischaemic attack (TIA) (Study 3.5), and cancer (Study 3.6) in patients with or without psoriasis. Incidence rates (IRs) and unadjusted incidence rate ratios (IRRs) were calculated. In the nested case-control analysis, patients with the outcome of interest were matched on age, sex, and index date to four control patients from the cohort population, and the psoriasis history stratified by duration and severity (using treatment as proxy) was compared by calculating adjusted odds ratios (ORs). The overall diabetes IR in psoriatic patients was about 35% higher than in psoriasis-free patients. Psoriasis patients with intensive systemic treatment for their skin disease and a disease history of longer duration showed an about 2.5 times increased risk of diabetes compared to psoriasis-free patients. For MI and stroke / TIA the overall risk was not increased, but further analyses showed increased risks in subpopulations (e.g. severe psoriasis patients or patients <60 years of age [for MI]). The risk of lymphohaematopoietic or certain types of solid cancers was statistically significantly increased in patients with psoriasis, for solid cancers primarily in patients with a longer-term disease history.

These large population-based studies further analysed existing hypotheses and raised new ones. The results may be valuable for healthcare professionals in their daily clinical practice and for pharmaceutical companies in the risk-benefit analysis of their drugs. Additionally, the example of the association between use of beta-blockers and psoriasis showed that there should be no place for dogmas in medicine and that conclusions can be challenged.

ZUSAMMENFASSUNG

Die Pharmakoepidemiologie studiert die Anwendung und Effekte von Medikamenten in grossen Patientenpopulationen und ist wichtig für die Arzneimittelüberwachung. Da diese vermehrt proaktiv (nicht nur reaktiv) handelt, spielt die (pharmako)epidemiologische Forschung eine immer bedeutendere Rolle in der Entwicklung eines Medikamentes. Die Verfügbarkeit von Daten über die zu behandelnde Krankheit ist z.B. wichtig für die Nutzen-Risikoanalyse eines neuen Medikaments (z.B. Vergleich von Nebenwirkungsraten in der behandelten Bevölkerung mit der Erkrankung mit Raten solcher Ereignisse in der unbehandelten Bevölkerung mit der Erkrankung). Ausserdem ist ein breites Wissen über Erkrankungen von Bedeutung für den klinischen Alltag. Pharmakoepidemiologische Gruppen führen deshalb neben klassischen Sicherheitsstudien zu Medikamenten auch Studien zur Epidemiologie von Krankheiten und Medikamentengebrauch durch. Das Ziel dieser Arbeit war es, das Wissen über Psoriasis durch neue Informationen und Ergänzung vorhandener Daten zu vergrössern. Psoriasis ist eine chronische inflammatorische Hauterkrankung, die in gewissen Teilen der Welt häufig vorkommt. Neue Erkenntnisse über den Pathomechanismus haben in letzter Zeit zur Markteinführung neuer Medikamente geführt (v.a. Biologika) und umgekehrt.

Die Daten für die Studien dieser Arbeit stammten von der *General Practice Research Database*, einer Datenbank, die Hausarztdaten von mehreren Millionen Patienten in England enthält und repräsentativ für die Bevölkerung ist. Die Hausärzte wurden ausgebildet, Daten zu Demographie, Lebensstil, Diagnosen, Überweisungen und Therapien der Patienten anonymisiert und standardisiert zu erfassen. Mehrere hundert Studien wurden auf dieser validierten Datenbank bereits durchgeführt.

In den Fall-Kontrollstudien 3.1-3.3 wurde der Einfluss von Betablockern und anderen Antihypertensiva (Studie 3.1), von Lithium und Antipsychotika (Studie 3.2) und von Glitazonen und anderen Antidiabetika (Studie 3.3) auf das Risiko, Psoriasis zu entwickeln, untersucht. Die Studienpopulation bestand aus 36'702 Patienten mit einer Erstdiagnose von Psoriasis zwischen 1994 und 2005 und 36'702 Kontrollpatienten, die auf Alter, Geschlecht, Indexdatum, Hausarzt und Jahre auf der Datenbank gematcht waren. Die Medikamentenexposition wurde, stratifiziert nach Dauer und Zeitpunkt der Einnahme und adjustiert auf potentielle Störfaktoren, untersucht. Im Gegensatz zu gängigen Angaben in der Literatur (inkl. Standardliteratur der Dermatologie), welche v.a. auf Daten von Fallberichten und -

serien beruhen, beeinflussten Betablocker und Antihypertensiva das Psoriasisrisiko nicht. Die zweite Studie hingegen bestätigte die Annahme, dass langzeitige Einnahme von Lithium Psoriasis induzieren kann. Ausserdem konnte für eine Langzeiteinnahme von atypischen Antipsychotika, v.a. Olanzapin, ein statistisch signifikanter protektiver Effekt gezeigt werden. Diese Beobachtung muss weiter bestätigt werden. Kleine klinische Studien hatten für Glitazone einen potentiellen Nutzen auf Psoriasissymptome gezeigt. Die Resultate der Studie 3.3 zeigten zusätzlich einen statistisch signifikanten protektiven Effekt unter Langzeiteinnahme von Glitazonen auf das Risiko, Psoriasis zu entwickeln. Auch für Metformin konnte eine solche Tendenz gezeigt werden, doch muss dies weiter untersucht werden.

Die Studien 3.4 bis 3.6 waren Kohortenstudien mit integrierten Fall-Kontroll Analysen, in welchen die Studienpopulation (= Kohorte), welche für die Studien 3.1-3.3 definiert worden war, beobachtet wurde, um Erstdiagnosen von Diabetes (Studie 3.4), Myokardinfarkt (MI) oder Schlaganfall / transitorische ischämische Attacke (TIA) (Studie 3.5) und Krebs (Studie 3.6) in Patienten mit und ohne Psoriasis zu identifizieren. Inzidenzraten (IR) und Verhältnisse von IR (IRR) wurden berechnet. In der Fall-Kontrollstudie wurden diejenigen Patienten, die die Krankheit entwickelten, mit jeweils vier Kontrollpatienten aus der Kohorte, gematcht auf Alter, Geschlecht und Indexdatum, in Bezug auf Psoriasisanamnese stratifiziert nach Dauer und Schweregrad (Therapie als Proxy) verglichen und die Resultate als adjustierte Odds Ratios dargestellt. Die IR von Diabetes war in Psoriasispatienten ca. 35% höher als in Kontrollpatienten. Psoriasispatienten, die unter eher intensiver oraler Therapie für ihre Hauterkrankung standen und länger an Psoriasis litten, hatten ein ca. 2.5-fach erhöhtes Diabetesrisiko. Das Risiko, einen MI oder Schlaganfall / TIA zu erleiden, war in Psoriasispatienten generell nicht grösser als in der Kontrollpopulation, gewisse Subgruppen zeigten jedoch ein erhöhtes Risiko (z.B. schwere Psoriatiker und Patienten <60 Jahre alt [für MI]). Das Risiko, an lymphohämatopoietischen oder gewissen soliden Krebsarten zu erkranken, war statistisch signifkant höher in Psoriatikern, für solide Krebsarten v.a. in Patienten mit längerer Psoriasisanamnese.

Diese grossen populationsbezogenen Studien untersuchten existierende Hypothesen und warfen neue auf. Die Resultate können hilfreich sein für die tägliche Arbeit von Personen im Gesundheitswesen und für die pharmazeutische Industrie. Ausserdem zeigte das Beispiel der Assoziation zwischen dem Gebrauch von Betablockern und Psoriasis, dass bestehendes Wissen hinterfragt werden sollte.

ABBREVIATIONS

ACE	angiotensin-converting enzyme
ADME	Absorption, Distribution, Metabolism, Excretion
AT II	angiotensin II
BCDSP	Boston Collaborative Drug Surveillance Program
BMI	body mass index
CCB	calcium channel blocker
CI	confidence interval
COPD	chronic obstructive pulmonary disease
CRP	C-reactive protein
CTCL	cutaneous T cell lymphoma
DMARD	disease-modifying antirheumatic drug
DSRU	Drug Safety Research Unit
EBM	Evidence-based Medicine
EMEA	European Medicines Agency
EU	European Union
FDA	Food and Drug Administration
GP	general practitioner
GPRD	General Practice Research Database
HIV	human immunodeficiency virus
HLA	human leukocyte antigen
HMO	health maintenance organisation
ICH	International Conference on Harmonisation
IL	interleukin
IND	Investigational New Drug
IFN	interferon
IR	incidence rate
IRR	incidence rate ratio
ISAC	Independent Scientific Advisory Committee
MHC	Major Histocompatibility Complex
MHRA	Medicines Healthcare Products Regulatory Agency
MI	myocardial infarction
NCE	new chemical entity
NSAID	nonsteroidal anti-inflammatory drug

OR	odds ratio
OXMIS	Oxford Medical Information System
PPAR	peroxisome proliferator-activated system
PPI	proton pump inhibitor
PUVA	psoralen and ultraviolet A
py	person-years
QoL	quality of life
RMP	risk management plan
RR	relative risk
SSRI	serotonin re-uptake inhibitor
TGF	transforming growth factor
TIA	transient ischaemic attack
TNF	tumour necrosis factor
Th	T helper cell
UK	United Kingdom
US	United States
UV	ultraviolet
VAMP	Value Added Medical Products
WHO	World Health Organisation

Chapter 1

INTRODUCTION

1 INTRODUCTION

1.1 GENERAL ASPECTS OF PHARMACOEPIDEMIOLOGY

1.1.1 Pharmacoepidemiology yesterday and today

Pharmacoepidemiology - the word is composed of *pharmaco* and *epidemiology* - bridges between clinical pharmacology and epidemiology.[1] It is defined as the study of the uses and the effects (beneficial and adverse) of drugs in large numbers of people[1, 2] and uses methods from epidemiology which investigates the distribution of disease and health in human populations.[2] The discipline has mainly evolved because drugs can also cause harm to the population. According to a prospective observational study in England, 6.5% of all hospital admissions were due to adverse drug reactions, with a fatality rate of 0.15%.[3]

Pharmacoepidemiology can support regulatory bodies in their task to protect public health by providing safe and efficacious drugs of high quality.[1] However, the development and marketing of drugs were not regulated strictly from the beginning. Disasters such as the death of 100 people from renal failure due to the elixir sulfanilimide dissolved in diethylene glycol (1937), the development of aplastic anaemia following exposure to chloramphenicol (early 1950s), and mainly the 'thalidomide disaster' with a high increase in the number of babies born with phocomelia after maternal use of thalidomide during pregnancy (1961)[1] increased awareness and finally resulted in today's strict regulations with three phases of clinical testing before marketing of a drug and surveillance of the drug after marketing (figure 1.1.1). The beginning of pharmacoepidemiology dates back to the mid-1960s when in the United States (US) the Boston Collaborative Drug Surveillance Program (BCDSP) and the Johns Hopkins Hospital monitored drug use in the hospital and conducted cohort studies to identify risks.[1, 4] Postmarketing observational studies as well as the collection of spontaneous reports on adverse drug reactions or events in the international database of the World Health Organisation (WHO) Collaborative Centre for International Drug Monitoring, located in Uppsala, Sweden[1, 2] became increasingly important, mainly because adverse events which occur seldom or after long-term drug exposure can hardly be detected in Phase I-III clinical trials and because drugs may be used in different patient populations or other indications (off label use) after market launch.[1, 2, 5] According to the *rule of three* the number of

subjects needed to detect an adverse event of a certain frequency is three times that of the estimated frequency, i.e. if an adverse event occurs with an estimated frequency of 1 / 5000, about 15,000 users would need to be observed to detect the event with a 95% likelihood.[1, 2]

While the focus of pharmacoepidemiology may have been on the postmarketing phase in the past, the field is gaining more and more importance in the premarketing period (figure 1.1.1).[1]

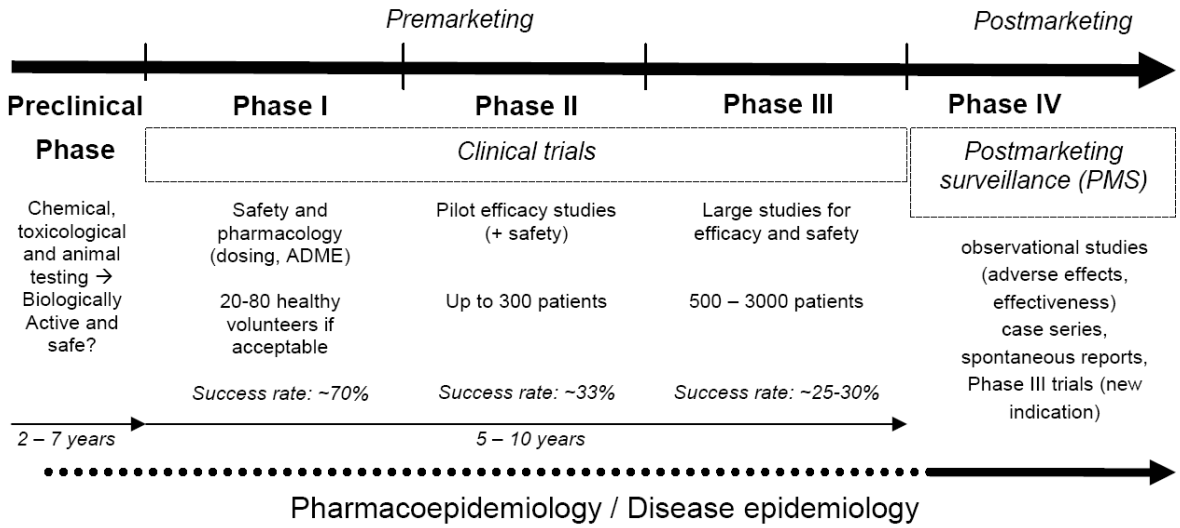

Figure 1.1.1 Different phases of the drug development process and pharmacoepidemiology[2, 6]

Population-based studies on the natural history of the disease to be treated by a potential new agent (new chemical entity [NCE] in preclinical phase or investigational new drug [IND] in phases I-III) in development can provide valuable information on the burden and the severity of that disease and the characteristics of the patients (e.g. drug use, comorbidities) and give input for the choice of the indication, the development process (e.g. planning of interaction studies based on patients' drug use), the market strategy, and also the viability of an entire project. Additionally, during phases II, III, and early IV, serious adverse events infrequently observed during clinical trials with the IND or early in the postmarketing period can be quantified in a population not exposed to the IND to decide if the observed events are in the expected range for the population expected to use the drug (= background incidence rates). If so, then development programs can be saved, otherwise, appropriate actions may be put in place more rapidly.[1, 6] Such information as well as frequency and characteristics data of the disease to be treated with an IND are – according to the International Conference on Harmonisation (ICH) guideline E2E -

requested in the safety specification upon submission of a drug license application to the authorities.[7] Another example where pharmacoepidemiology could have a supportive role is in the accelerated approval process of the Food and Drug Administration (FDA), the corresponding process of the European Medicines Agency (EMEA), the conditional marketing authorisation, or in a similar process of the Swissmedic in Switzerland, 'das beschleunigte Zulassungsverfahren'. Under these processes, drugs for serious, debilitating, or life-threatening diseases, emergency situations, or for rare diseases (orphan drugs) can receive marketing authorisation before the usually required data have been collected or with clinical trials using surrogate rather than clinical endpoints.[6, 8-10]

Data gained from above-mentioned epidemiological studies, which are often initiated by the pharmaceutical industry or regulatory bodies, are of importance for healthcare professionals in their daily practice. The more is known about a disease or a drug, the better patients can be treated.

Hence, over the past decades and in a changing regulatory environment, pharmacoepidemiology has evolved from the study of adverse reactions of marketed drugs to a scientific discipline involved in basically all stages of the development process of a drug[1] and provides important data on the epidemiology of diseases.

1.1.2 Pharmacoepidemiology and risk management

While the safety surveillance of drugs has been rather reactive in the past, a proactive pharmacovigilance is required today, and risk management is getting more and more important. Risk management in general is the identification and implementation of strategies to reduce risk to individuals and populations.[6] The EMEA 'guideline on risk management systems for medicinal products for human use' defines such a system as *a set of pharmacovigilance activities and interventions designed to identify, characterise, prevent, or minimise risks relating to medicinal products, including the assessment of the effectiveness of those interventions.* The aim of the system is that the benefits of a drug outweigh its risks.[11] It is the art and science of getting the right drug to the right patient at the right time.[6] According to the EMEA guideline,[11] a risk management plan (RMP) encompasses a *Part I* with a safety specification and a pharmacovigilance plan (according to the ICH E2E guideline) and a *Part II* with an evaluation of the need for risk minimisation activities and a risk minimisation plan if needed. A RMP may have to be submitted at any time

of a product's life-cycle. Pharmacoepidemiological expertise is needed for the compilation, implementation, and execution of such a plan (table 1.1.1).

Table 1.1.1 Risk management plan (according to EMEA guideline[11])

P A R T I		**P A R T II**
Safety specification	**Pharmacovigilance (PV) Plan**	**Risk minimisation plan**
- identified risks - potential risks - missing information - populations potentially at risk - safety questions **Tools:** Apart from nonclinical / clinical data, information from disease epidemiology studies or classical pharmaco-epidemiological studies could be helpful	- Routine PV (collecting of adverse event reports) - Active surveillance **Tools:** sentinel sites, intensive monitoring schemes, prescription event monitoring, registries, cross-sectional / cohort / case-control studies, clinical trials, disease epidemiology studies, drug utilisation studies	Actions taken depending on nature and / or seriousness of risk (if not adequately addressed by PV Plan) **Tools:** provision of information, educational material, legal status of a medicine, control at pharmacy level, control of prescription size or validity, informed consent, restricted access programs, patient registries (e.g. pregnancy)

Risk management is a complex field which has to constantly examine and balance the risks and benefits of a drug, taking into consideration data from the drug development process and - after the drug has reached the market - from the postmarketing surveillance. Hence, risk management deals on the one hand with *efficacy* data gained from randomised controlled clinical trials according to a strict protocol which show if an intervention *can* accomplish a particular outcome under ideal circumstances and on the other hand with (cost-)*effectiveness* data from mostly observational studies which provide information if an intervention *does* accomplish a particular outcome in the real world (figure 1.1.2).[2]

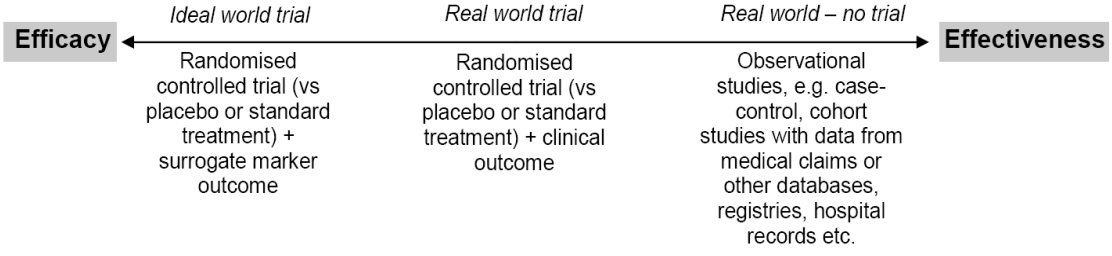

Figure 1.1.2 Efficacy versus effectiveness data *(adapted from a presentation by Richard Bergström at the European Centre for Pharmaceutical Medicine (ECPM) course in 2007)*

As the recent example of natalizumab (Tysabri®) - an α_4-integrin-inhibitor for the treatment of multiple sclerosis - has shown, a risk minimisation plan can help to re-introduce a drug on the market after withdrawal due to a serious adverse reaction. Natalizumab was taken from the market in 2005 only three months after market authorisation in the US due to suspected association with progressive multifocal leukoencephalopathy. With the help of the Prescribing Program TOUCH™, the drug is now available on the market again. Prescribers and infusion / distribution centers of the drug have to be registered with and patients receiving the drug have to be enrolled into the program, and safety surveillance is being conducted.[12]

1.1.3 Study designs in pharmacoepidemiology

Epidemiological or clinical research uses a number of different study designs which can be separated into descriptive observational and analytical studies (figure 1.1.3).[2] According to the Oxford Centre for Evidence-based Medicine (EBM),[13] results from randomised controlled trials provide the highest level of evidence for the evaluation of an intervention and case reports the lowest (apart from expert opinions). In EBM, clinical decisions are based on a process of systematically finding, appraising, and using contemporary research findings.[14] The above-mentioned hierarchy of strengths of research designs has been defined long ago and is well known. In his article on observational research and randomised trials, JP Vandenbroucke[15] proposed apart from the established hierarchy for the ① *evaluation of interventions* the opposite direction of the hierarchy for ② *discoveries and explanations of causes of diseases* (e.g. due to adverse effects of drugs) (figure 1.1.3). For ① *evaluation of interventions*, or in other words to study intended effects of a treatment, randomisation is necessary due to the risk of 'confounding by indication', meaning the worse the prognosis, the more (efficacious) therapy would be given. For ② *discoveries and explanations of causes of disease*s or to study unintended, unplanned, or adverse effects of an intervention, randomisation is often not necessary because 'confounding by indication' is seldom an issue due to the unexpectedness and unpredictability of the effect.[15] Furthermore, randomised controlled trials are rarely used in this approach because randomisation is most of the time not possible, e.g. due to ethical reasons.[1, 16] Both approaches (① and ②) are necessary because without ② discoveries leading to potentially better diagnosis, prevention, or therapy there would be nothing to ①

evaluate or to do randomised controlled trials on and without ① evaluation we would not know if a ② discovery was useful.[15]

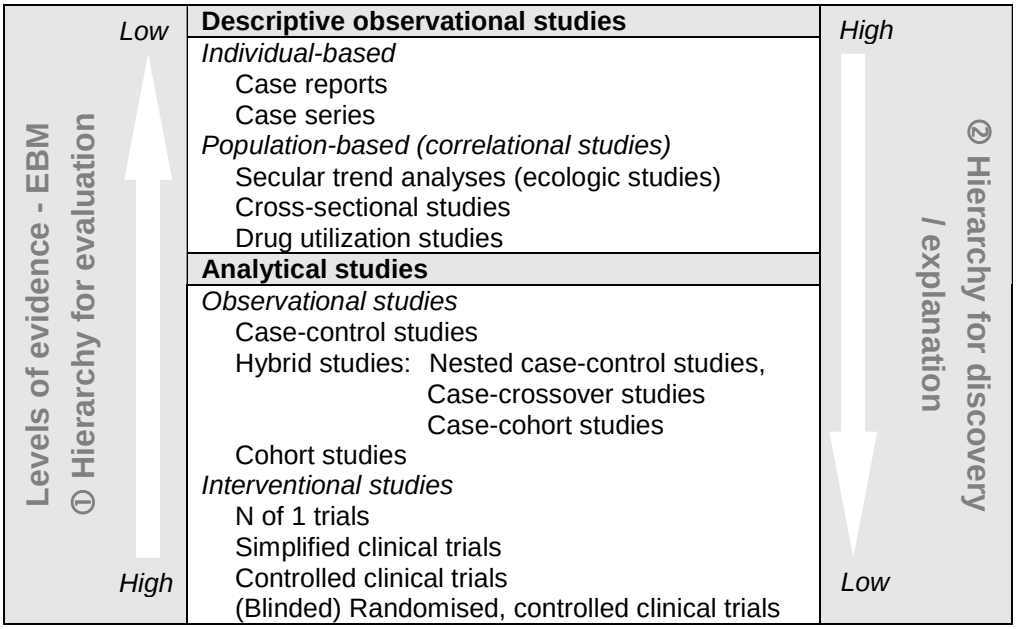

Figure 1.1.3. Design strategies in epidemiology or clinical research and two ways of classifying level of evidence depending on research area (① evaluation or ② discovery / explanation) [2, 15, 16]

A frequently criticised point in observational research is the execution of multiple and subgroup analyses.[15-17] However, these are necessary to make discoveries. Hence, the replication of findings with several studies of different designs, with different methods of data collection, and with different analyses as well as the assessment of the advantages and disadvantages of the individual studies is an important cornerstone of observational research.[15] For a thorough evaluation of the available studies, a correct and complete reporting of observational studies is a requirement. Thus, an international group of epidemiologists, methodologists, statisticians, and editors have composed and recently published the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) statement, which comprises guidelines for the reporting of observational studies,[18] similar to the CONSORT (Consolidated Standards of Reporting Trials) statement for randomised clinical trials.[19]

The study designs listed in figure 1.1.3 have been described in various textbooks on (pharmaco)epidemiology.[1, 2, 16] In this context, only a brief summary on case-control and cohort studies with a nested case-control analysis will be given because these designs were used for the studies conducted within the framework of this thesis. The

three designs are also illustrated in appendix 5.1. In theory, a hypothesis can be tested with both designs,[16] but in practice there are unique advantages and disadvantages of cohort and of case-control studies (e.g. in terms of cost, time, efficiency, frequency or type of outcome / risk factor). However, they will not be discussed in this context as a lot of them do not apply for the kind of retrospective database research conducted in this thesis. Interested readers are referred to (pharmaco)epidemiological textbooks.[1, 2, 16] Only one major difference between case-control and cohort studies is emphasised at this point because it influenced the choice of study designs for this thesis: in case-control studies, multiple exposures / risk factors for a disease / an event can be studied, and cohort studies allow the investigation of multiple outcomes of interest after an exposure or an event / disease.

1.1.3.1 Case-control studies[1, 2, 16]

In a case-control design, the study population comprises cases who have an outcome (e.g. a disease) of interest and controls who do not. Controls need to represent the population who would have been cases had they also developed the disease. If matching is used as a technique to control for confounding factors, one or more controls who are equal with respect to the matching criteria (e.g. age, sex, timing etc.) will be searched for each case. The statistical power of the study increases with the number of controls matched to each case. The proportions of exposure history to risk factors (e.g. drugs) will then be compared between cases and controls, and the risk of developing an outcome in relation to the risk factor will be quantified by providing odds ratios (ORs). A relative risk (RR) (defined as the ratio of the incidence rate (IR) of the outcome in the exposed group to the rate in the unexposed group) cannot be calculated because case-control studies do not provide information on the IR of the disease in exposed and unexposed individuals. Hence, the risks are expressed as ORs (ratio of the odds of the outcome in the exposed group compared to the odds in the unexposed group, whereby the odds of an outcome is defined as the probability that the outcome does happen divided by the probability that it does not[20]).

1.1.3.2 Cohort studies[1, 2, 16]

A cohort refers to a group of people who have something in common at a defined point in time, i.e. in cohort studies, a group of people is studied who have not (yet) experienced the outcome of interest.[2] In *controlled* cohort studies,[2] subjects

(matched on potential confounders or not) are selected depending on the presence ('cases') or absence ('controls') of exposure to a particular factor. They form the cohort population, and this should be an inception cohort, which means that the 'cases' are observed from the *first* exposure to that particular factor.[2] The cohort is then followed until the subjects develop an outcome of interest, until they die, or follow-up / the study ends. With this design, IRs of one or several outcomes in patients with or without a certain exposure can be obtained, and by comparing these rates, incidence rate ratios (IRR) or RR can be calculated. Cohort studies are retrospective or prospective depending on if the outcome of interest has occurred at the time the investigator initiates the study.

1.1.3.3 Nested case-control studies[1, 2, 16]

For this design, a cohort population is followed for a period of time until a number of incident outcomes (diseases or adverse drug events) are identified. These cases and a sample of noncases (controls; matched or not) from the cohort are then compared with regard to prior exposure to a risk factor. The design is particularly interesting when the hypothesis to be tested is generated after the prospective cohort study has been initiated and upon availability of stored biologic specimens in order not to analyse the specimens of the whole cohort population. Furthermore, the design is efficient in terms of time (effort of data collection) and cost.[1, 2, 16, 21] In retrospective database research, this design is also commonly applied with the advantage that adjustment for confounders which change over time is better than in cohort designs. The time of the diagnosis of the outcome is known, and it is the same for controls when matched on time.[22]

1.1.4 Causality assessment in routine pharmacovigilance and epidemiology

The WHO defined pharmacovigilance as *the science and activities relating to the detection, assessment, understanding, and prevention of adverse effects or any other possible drug-related problems*.[23] Reports on suspected adverse events to a drug are collected in the international WHO database (chapter 1.1.1). They have to be accompanied by a causality assessment. For this purpose, a number of scores had been developed, such as the one by Naranjo et al.[24] However, as they were too complex for routine clinical practice, the WHO provided its own score[25] as summarised below:

Association	Conditions
Certain	- Plausible temporal relationship between drug exposure and event - Plausible response to withdrawal (dechallenge) - Recurrence of the event after rechallenge or other evidence - No alternative explanation for the event
Probable	- Plausible temporal relationship between drug exposure and event - Plausible response to withdrawal (dechallenge) - Alternative explanation for event unlikely
Possible	- Plausible temporal relationship between drug exposure and event - Other explanation for event possible
Unlikely	- None of the above-mentioned conditions

Each report on an adverse drug event contributes to the generation of a possible signal which has to be assessed in greater detail (Examples of published case reports by *Brauchli YB et al*.[26] in the appendix 5.2 or the publication list). For this task, pharmacoepidemiological studies are very useful. The evidence of such a study (or studies) to support a causal relationship between a drug exposure and an outcome has to be evaluated as well. AB Hill[27] suggested a first model on the interpretation of an epidemiological study in the 1960s which was enhanced by Hennekens et al.[16] two decades later:

1. Valid statistical association (Study design)? Or due to
    a. Chance? *(an unsystematic, or random, variation; quantified by statistics)*[1]
    b. Bias? *(a systematic variation, a consistent manner in which two groups are evaluated / treated differentially; e.g. selection bias, information bias (such as recall, interviewer bias))*[1]
    c. Confounding? *(an association is created or masked by a third variable which is independently related to the risk factor and the outcome)*[1]
2. If valid, can the association be judged as cause and effect? Points to consider
    a. Strong association?
    b. Biological credibility to the hypothesis?
    c. Consistency with other studies?
    d. Time sequence compatible?
    e. Evidence of a dose-response relationship?

Replication of results with different methods or in different populations is important in pharmacoepidemiological research: In epidemiology, a relative risk of less than 2 is usually considered to indicate a weak association,[1] but for adverse reactions of marketed drugs often only low risks can be detected; drugs with a high incidence of serious adverse reactions would have been too toxic to be marketed. The consistency of results from different studies is important for the evaluation of causality in such situations.[28]

For a detailed explanation of bias and confounding, the reader is referred to a textbook on (pharmaco)epidemiology.[1, 2, 16]

1.1.5 Database research

In phase III clinical trials, between 500 and 3,000 patients are exposed to a drug in development. Considering the *'rule of three'*, drug effects which occur with an incidence lower than 1 per 1,000 can hardly be detected during the drug development process. Hence, after marketing, monitoring of the safety of a drug has to continue, and large study populations are necessary to evaluate rare adverse events. However, such studies are expensive, take long, and are often difficult to perform. For these reasons, there has been an increasing use of computerised or automated databases with medical care data for conducting pharmacoepidemiological studies.[1] Databases can be classified into claims databases created primarily for administrative purposes to get reimbursement for clinical services and therapies (e.g. databases of health maintenance organisations (HMO); Medicaid databases from Medicare, a health insurance program funded by the US government; or the Health Services Databases in Saskatchewan, Canada) and into medical record databases in which medical records of patients are captured electronically (e.g. the General Practice Research Database (GPRD)[29] in the United Kingdom (UK)). There are also combinations of the two, e.g. the PHARMO system in the Netherlands[30] which links data from general practitioner (GP) registries with pharmacy and hospital data. Usually, the validity of the diagnoses is better in medical records as compared with claims databases while the recording of drug exposure is of similar completeness.[1] When working with a database, it is important to know it very well, e.g. the structure, the way data are collected, the advantages, and the disadvantages.[31] Below are listed some of the strengths and weaknesses of database research in general.[1]

Strengths	Weaknesses
- Provision of large sample size - Relatively inexpensive use - Cost of data collection can be saved - Can be population-based - No recall or interviewer bias - Not influenced by study question	- Uncertain validity of diagnosis data - Possible lack of information on potential confounding variables (e.g. smoking, alcohol, body mass index (BMI), lifestyle factors etc.) - Continuous enrolment / disenrolment of members in claims databases - Usually only recording of diagnoses severe enough to come to medical attention - Generalisability may be an issue - Usually no data on compliance; data on over the counter drugs questionable

1.1.6 Short history about the GPRD

The studies of this thesis were conducted with data from the UK-based GPRD which encompasses about 5% of the UK population.[1] In the UK, information on all relevant medical care of each patient congregates with the GP with whom the patient is registered. Hence, in the mid 1980s Value Added Medical Products (VAMP) Health, a commercial company, designed a system which allowed recording of this information on office computers. The company acquired GPs to participate in the recording of patient data and providing them anonymised as to patient identification. In return, they received compensation. VAMP entered into an agreement with the BCDSP who had experience with computerised data and evaluated the use of the GPRD for drug safety studies.[4] In the meantime, the database has been validated extensively[32-34] and is managed today by the UK Medicines and Healthcare products Regulatory Agency (MHRA).[1] Up to September 2008, more than 630 epidemiological studies using this database have been published.[35] Further information about the database is provided in the methods sections of the studies of this thesis, and interested readers are referred to review articles, which describe the database (including its history) in detail,[31, 36-39] or to the website (www.gprd.com).

1.1.7 Prescription-event monitoring and registries[1, 2]

Prescription-event monitoring is another approach to drug surveillance in the postmarketing setting. The technique was introduced 1981 in the UK at the Drug Safety Research Unit (DSRU) and focuses on newly-marketed drugs. In the UK, practically all patients are registered with a National Health Service GP who

prescribes drugs which the patient collects at a pharmacy. After dispensing the drug, the pharmacy sends the prescription for reimbursement to a central prescription pricing authority which provides the DSRU with an electronic copy of the prescription. This process lasts until data of a cohort of about 20'000 to 30'000 patients have been gained. After 3-12 (usually 6) months of the first prescription for each patient, the DSRU sends the prescriber a questionnaire asking for any adverse events in connection with the drug. Information gained with this system is very useful for hypothesis generation, but less for hypothesis confirmation, mainly because an appropriate control group is lacking, and the physicians' response rate may be low.

In *registries*, defined events (e.g. medicine-induced cardiac arrhythmias) or product exposures are collected in a patient population defined by a particular disease, condition, or exposure. It is an organised system which uses observational study methods to collect uniform data. Patients are observed when they present for care.[40] Registries are mainly used for information gathering and hypothesis generation, but can also serve as risk minimisation tools (see RMP chapter 1.1.2). As an example, the clozapine registries were created to minimise the risk of agranulocytosis following exposure to the drug. Patients were registered, and blood tests had to be linked to the dispensing of clozapine. The agranulocytosis rates were 1% to 2% before the registry was set up in the US and 0.38% after the implementation.[41] Another well-known example is the thalidomide registry to prevent foetal exposures to the drug.[42]

1.2 PSORIASIS – SHORT OVERVIEW

1.2.1 Introduction

What did or do celebrities such as Winston Churchill (politician), Jossif Wissarionowitsch Stalin (politician), Romy Schneider (actress), Karin Holstein (German model), John Updike (writer), or Art Garfunkel (singer and actor) have in common? They all seem to (have) suffer(ed) from psoriasis.[43]

Psoriasis had been described already before Christ and was later considered as a form of leprosy. Only in the 19th century, the disease was distinguished from leprosy by Ferdinand von Hebra and Robert Willan, although the latter still named certain occurrences of psoriasis *Lepra Graecorum* and *Psora leprosa*. The word psoriasis derives from the Greek *psora* (= to itch).[43, 44]

Psoriasis is a chronic immune-mediated erythematous-squamous skin disorder. When applying the definition of autoimmune disease provided by Davidson A et al. 'a clinical syndrome caused by the activation of T cells or B cells, or both, in the absence of an ongoing infection or other discernible cause',[45] psoriasis qualifies as an autoimmune disorder because it is characterised by T cell-mediated hyperproliferation of keratinocytes and inflammatory processes based on a complex genetic background and without an obvious cause.[46] However, a definite (auto-) antigen has not been identified yet,[47] and autoimmunity in the case of psoriasis is still being discussed.[44]

1.2.2 Pathophysiology

Until the late 1970s, the primary cause for the initiation of epidermal hyperproliferation in psoriasis was supposed to be an aberrant keratinocyte metabolism. A number of observations in the following two decades (such as therapeutic success with ciclosporin, which diminishes T cell proliferation and cytokine production, or healing of psoriatic lesions after haematopoietic stem cell transplantation) provided evidence for a primary role of the immune system, mainly the T cells, in the activation and maintenance of the disease.[48] Research over the past years shed more and more light on the pathogenesis of the skin disorder which Sabat et al.[48] summarised in a comprehensive review article. According to his theory, the onset of psoriasis is similar to an immune reaction with a sensitisation, a silent,

and an effector phase. In the sensitisation phase, naïve T cells are activated by antigen-presenting cells, the dendritic cells, which present (exogenous) antigen to the T cells in secondary lymphatic organs. T cells mainly of the T helper cell (Th)1 and Th17 lineage are generated which produce specific cytokines. After a silent phase, T cells and various other immune cells infiltrate the skin and activate each other as well as keratinocytes via mediators (e.g. interferon (IFN)-γ, interleukin (IL)-23, IL-6, IL-22, IL-17, IL-20, tumour necrosis factor (TNF)-α, or transforming growth factor (TGF)-α) which seem to play a central role in the pathogenesis of psoriasis (effector phase). This process leads to an increased proliferation of keratinocytes and inflammation.

1.2.3 Clinical picture

Psoriasis presents with different types of manifestation (table 1.2.1, including characteristics), with psoriasis vulgaris being the most common one (90%).[44] This form usually presents with well-delineated erythematous-squamous plaques covered by silvery-white scales and of different thickness and dissemination[44, 49, 50] and is usually easy to diagnose.[50] Histopathologically, Munro's microabscesses (neutrophil granulocytes in the subcorneal layer), spongiform pustules of Kogoj (neutrophils in the spinous layer), and dilatation of papillary dermal capillaries with thinning of the suprapapillary epidermis are quite characteristic features.[50]

Table 1.2.1 Clinical variants of psoriasis[44, 49, 51-53]

Psoriasis vulgaris (PV) or **plaque psoriasis** *Chronic fixed type*	Persistent erythematous-squamous plaques at defined locations (figure 1.2.1)
Psoriasis guttata *Acute exanthematous type*	Raindrop-like erythematous papules over trunk and extremities (mainly type I psoriasis and triggered by pharyngeal streptococcal infection)
Psoriasis inversa / intertriginosa	Other localisation than PV (figure 1.2.1); rare
Psoriasis pustulosa (PP) *Several clinical variants*	Rare; Clinically distinct from PV; mainly sterile subcorneal pustules; generalised form can be life-threatening (von Zumbusch psoriasis)
Psoriatic erythroderma	Primary or resulting from PV or PP; generalised, erythematous, and scaly integument; severe form, can be life-threatening
Psoriatic nail changes	In combination with other forms or isolated
Psoriatic arthritis (5-42% of psoriasis patients)	Mainly distal joints of toes or fingers and sacroiliacal joints, often enthesitis; mainly rheumatic factor negative

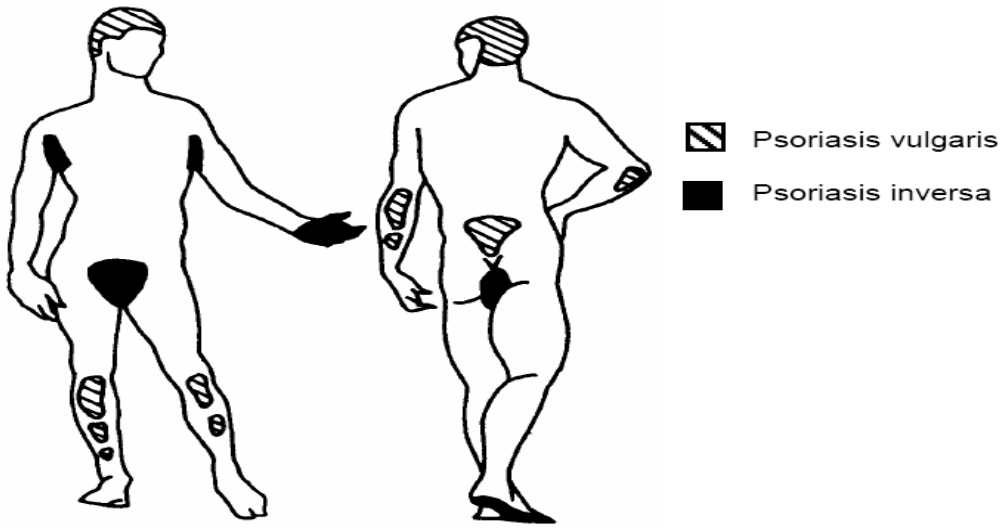

Figure 1.2.1 Common locations of psoriasis

Depending on the extent of body surface involvement of less than 5%, 5-10%, or more than 10%, severity of psoriasis is defined as mild, moderate, or severe, respectively.[54] Of all patients, about 75% suffer from mild to moderate disease.[55] A variety of outcome measures have been developed and used to evaluate the severity of psoriasis as well as the efficacy of treatments in clinical trials. While the strength of the *body surface area* (BSA) is its ease of use, the *psoriasis area and severity index* (PASI) considers besides the skin area involvement also the degree of erythema, desquamation, and induration of the psoriatic plaque. Currently, this score is most commonly used in clinical trials for the evaluation of new therapeutic agents. However, psychosocial disability as an additional influencing factor on disease severity is gaining more and more importance, and a tool combining both, physical symptoms and quality of life (QoL) measurements,[56] is needed.

1.2.4 Treatment

The diversity of psoriasis asks for an individualised treatment plan adapted to the nature / phenotype, extent, and localisation of the disease, the patient's QoL and lifestyle, age, sex, comorbidities / triggering factors, compliance, and previous treatment. Furthermore, education of patients plays an important role.[54, 57, 58] There are different treatment options which are adopted (as monotherapy or in combination) depending on disease severity (figure 1.2.2), however, they are not curative. Moderate to severe disease is usually treated with systemic therapy,

ultraviolet (UV), or psoralen and UVA (PUVA) with or without topical agents, whereas topical treatment is adequate for mild disease. Basic therapeutic agents are used in and between all acute stages across all severity grades.[54] There are several good review articles on the treatment of psoriasis (e.g. by Menter A, et al.[54], Shear NH[59], Ashcroft DM, et al.[57]), and the treatment guidelines by the German Dermatology Society[60] and the British Association of Dermatologists[61] provide a very comprehensive overview.

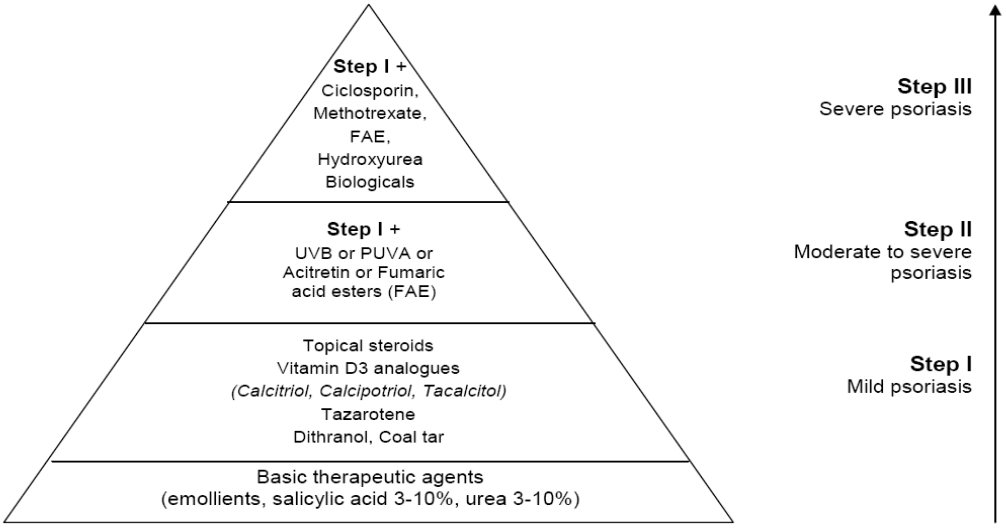

Figure 1.2.2 Treatment options depending on psoriasis severity *(adapted from Ashcroft DM et al.[57])*

1.2.5 Epidemiology

1.2.5.1 Prevalence and incidence rates

In most studies, the prevalence *(proportion of individuals in a population who have the disease at a specific point in time[16])* of psoriasis lied somewhere between 0.6% and 4.8%,[62] but the designs of the studies sometimes differed considerably. Higher and lower rates were also reported for certain regions:[63] The rate is dependent on ethnicity (Caucasians are more affected than other races, and the disease does not exist in aboriginal Australians and Indians from South America [64]) and geographical region (more common in colder northern climates than in tropical regions).[63] The only two published population-based studies on IRs *(number of new events or cases of disease that develop in a population of individuals at risk during a specified time interval[16])* of psoriasis provided overall annual IRs of 6 per 10,000 persons-years

(py)[65] and 14 per 10,000 py,[66] respectively. The rates peaked before the age of 40 years and again at or after 50 years and were lowest in old patients (≥80 years). The annual IR was slightly higher in male than female patients, except for patients between 0-29 and 50-59 years of age. The female IRs peaked in the age groups 20-29 years and 50-59 years.[66] Between 1994 and 2005 the IRs were stable (figure 1.2.3; Brauchli YB 2008. Unpublished data gained from the GPRD).

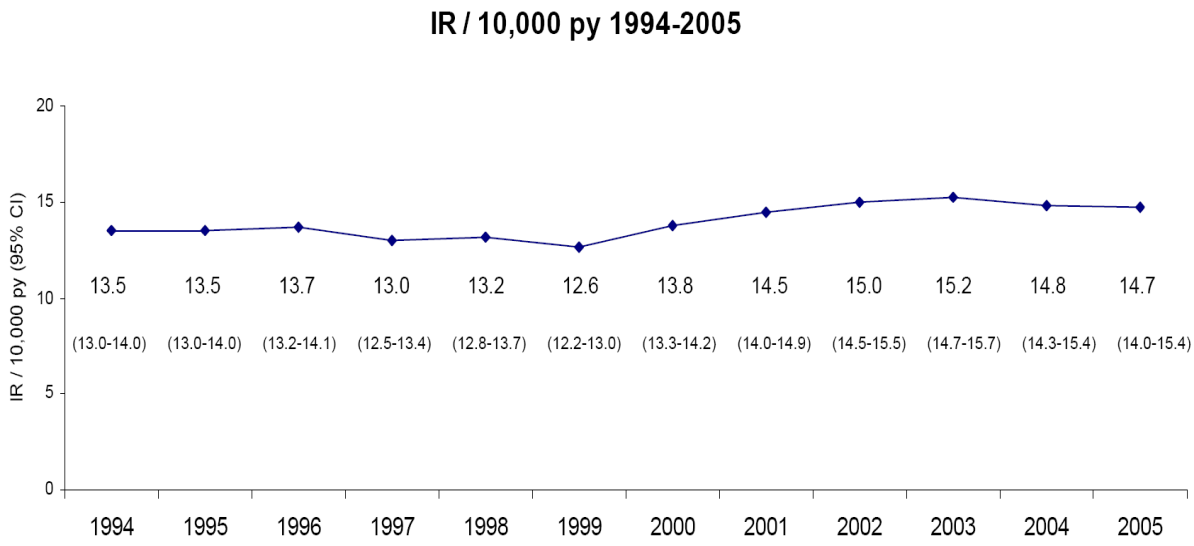

Figure 1.2.3 Stable psoriasis incidence rates between 1994 and 2005

1.2.5.2 Aetiology of psoriasis

The aetiology of psoriasis is complex, probably resulting from an interaction between environmental factors and genetics. The incidence of the skin disorder is greater in first and second degree relatives of patients than in the general population, and the risk of psoriasis in monozygotic twins is two to three times higher than in dizygotic twins. The chromosomal locus termed psoriasis susceptibility 1 or PSORS1 (Major Histocompatibility Complex [MHC] region on chromosome 6) is the major genetic determinant, mainly the gene variant or allele Human Leucocyte Antigen (HLA) Cw6. Further eight linkage loci to psoriasis (PSORS1-5 and PSORS7-10) have been accepted by the Human Genome Nomenclature Committee, and additional ones have been reported. Phenotypic variants of psoriasis have shown to be genetically heterogeneous.[44, 67]

Epidemiologically, Henseler et al. differentiated two types of psoriasis depending on age of first onset.[68] Type I psoriasis is characterised by age of onset before 40 years, by an increased risk of heritability, by a strong association with HLA, e.g. HLA Cw6, and by severe disease which is difficult to treat. About 75% of the patients have this type of psoriasis.[55] Patients with type II psoriasis develop the disease after the age of 40 years, the association with familiar genetics and HLA is smaller, and the disease is generally less severe.[51, 68]

1.2.5.3 Psychosocial and economic burden

Although psoriasis is seldom life-threatening (estimated 0.64 deaths per 100,000 psoriasis patients annually in the US)[69], the psychosocial burden for patients is often considerable, and, despite the distinction of psoriasis from leprosy in the 19th century, stigmatisation is still an issue. Impairment of QoL may be significant (similar or worse than for patients with other chronic diseases such as ischaemic heart disease, diabetes, or cancer)[64, 70, 71] and may not always be proportional to skin involvement.[72, 73] Hence, QoL should be considered in the definition of psoriasis severity[44, 56, 64, 73] and should influence treatment decisions.[54] Two psoriasis-specific QoL measures have been described, the *Psoriasis Disability Index (PDI)* and the *Psoriasis Life Stress Inventory*.[51, 73]

Apart from the psychosocial aspect, psoriasis also carries a substantial economic burden, be it direct costs including expensive treatment, treatment failures, treatment of comorbidities or adverse events to psoriasis treatment, or hospitalisations, indirect costs including e.g. time not at work, or intangible costs including e.g. loss of QoL.[74-77]

1.2.5.4 Risk factors and comorbidities

A number of risk or triggering factors and comorbidities have been reported for psoriasis (table 1.2.2), however, data were mainly derived from case reports and case series (especially in the case of drugs reported as risk factors[78-80]) or from epidemiological studies which were cross-sectional or nonpopulation-based (but e.g. hospital-based). Hence, there are conflicting results in the literature (e.g. the association between psoriasis and cancer[81, 82]), and the temporal sequence of the association between psoriasis and the comorbidities or risk factors is often inconclusive.[70] Neimann et al. provided a comprehensive review article on the risk factors and diseases associated with psoriasis.[80]

Table 1.2.2 Risk factors and comorbidities associated with psoriasis

Risk- / Triggering factors	Comorbidities
▪ Family history and genetics[44, 83, 84] ▪ Bacterial and viral infections, mainly streptococcal pharyngitis[62, 85-87] ▪ Smoking, alcohol consumption, and diet / high BMI[62, 66, 84, 85, 88-94] ▪ Drugs (mainly beta-blockers, lithium, antimalarials)[62, 79, 85, 87, 95-98] ▪ Stress[62, 85, 88]	▪ Diabetes and metabolic syndrome[86, 99-106] ▪ Cardiovascular diseases (incl. hypertension and hyperlipidaemia)[102, 103, 105, 107-112] ▪ Cancer[86, 113-121] ▪ Immune-mediated inflammatory diseases (Crohn's disease,[122-126] multiple sclerosis,[127-129] coeliac disease[130, 131]) ▪ Psychiatric disorders (e.g. anxiety, depression)[132, 133] ▪ Comorbidities due to treatment: nephrotoxicity, hepatotoxicity, non-melanoma skin cancer[59, 134-136]

1.2.6 Psoriasis and research

Over the past years, research on psoriasis has been intensive, and knowledge has progressed considerably. In a recent commentary, MP Schön used the appropriate title 'Psoriasis in the limelight: the remarkable career of an old skin disease'.[137] Psoriasis has become a model disorder for chronic inflammatory diseases[137] despite the lack of a complete animal model.[138] New insights into the pathogenesis of the disease allowed the identification of the mode of action of some established antipsoriatic therapies and the development of novel therapies (mainly biologicals), which in return helped in elucidating further the pathomechanism of psoriasis.[137] Driven - amongst others - by the recent development of a proactive pharmacovigilance in the regulatory environment (chapter 1.1.1 and 1.1.2) and the market launch of a number of biologicals, interest in gaining or supplementing information on the epidemiology of psoriasis has risen amongst healthcare providers and the pharmaceutical industry.

Chapter 2

AIMS OF THE THESIS

2 AIMS OF THE THESIS

The major aim of this thesis was to contribute to the understanding of the natural history of psoriasis by providing new information on or complementing existing knowledge of risk or protecting factors for as well as comorbidities of psoriasis using data from the GPRD. Additionally, the study designs used (see introduction 1.1.3 and appendix 5.1) should allow a statement about the temporal sequence of the association between psoriasis and the factors investigated.

Drugs are not well defined risk factors for the development of psoriasis due to knowledge being mainly based on case reports or case series. Some of the reports on a possible association could also have been chance findings because psoriasis is a common disease. Already in the 1980s, a group of researchers indicated this issue in the case of beta-blockers,[95] but the association between this class of drugs as well as lithium and the induction of psoriasis has in the meantime been recorded in several standard dermatology textbooks (e.g. Fitzpatrick's Dermatology in General Medicine, sixth edition 2003; Dermatology, Jean L Bolognia et al., 2003; Dermatologie und Venerologie, Braun-Falco et al., 5. Auflage, 2005). The objective was to study these reported associations in two large population-based case-control studies. Study 3.1 should investigate the association between exposure to beta-blockers or other antihypertensives and psoriasis and Study 3.2 the association between exposure to lithium or antipsychotics and psoriasis. Scientifically sound knowledge of risk factors for a disease is important for healthcare professionals to make the right decisions in clinical practice and can be helpful in the evaluation of the pathomechanism of a disease.

Small clinical trials suggested thiazolidinediones as possible treatment options for patients with psoriasis. However, the results were somewhat inconclusive, and data on the potential of the drug class to prevent the *induction* of the skin disorder were not available. Thus, the objective of Study 3.3 – also a case-control study – was to investigate the association between use of thiazolidinediones or other antidiabetic drugs and the induction of psoriasis.

Several studies on the association between psoriasis and comorbidities such as cardiovascular diseases, diabetes or metabolic syndrome, or cancer have been reported in the literature. However, these studies were often cross-sectional, nonpopulation-based, included prevalent rather than incident outcomes, or provided conflicting results (mainly for cancer). True incidence rates of the above-mentioned comorbidities in patients with psoriasis were lacking, and the temporal relationship between the comorbidities and psoriasis was often unclear. The objectives of Studies 3.4 – 3.6 were to provide IRs of diabetes (Study 3.4), myocardial infarction (MI) and stroke / transient ischaemic attack (TIA) (Study 3.5), and cancer overall and stratified by type (Study 3.6) for patients with psoriasis, to compare them with a population without psoriasis, and to investigate the influence of psoriasis severity or duration on these outcomes.

Chapter 3

PSORIASIS PROJECT

3 PSORIASIS PROJECT

3.1 ASSOCIATION BETWEEN BETA-BLOCKERS, OTHER ANTIHYPERTENSIVE DRUGS AND PSORIASIS: POPULATION-BASED CASE-CONTROL STUDY

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Br J Dermatol 2008;158:1299-307

3.1.1 Abstract

Background: Several case reports have associated use of beta-blockers with an increased risk of psoriasis or psoriasiform drug eruptions.

Objective: To study the association between use of beta-blockers and other antihypertensive drugs and the risk of developing a first-time diagnosis of psoriasis.

Methods: We conducted a case-control analysis on the UK-based GPRD. We identified cases with an incident psoriasis diagnosis between 1994 and 2005 and matched them to one control patient on age, sex, general practice, calendar time (same index date), and years of history in the database. Conditional logistic regression was used to estimate adjusted ORs with 95% confidence intervals (CIs) of developing a first-time psoriasis diagnosis in relation to previous exposure to antihypertensive drugs, stratified by exposure timing (current versus past use) and exposure duration based on the number of prescriptions.

Results: The study encompassed 36,702 cases with a first-time psoriasis diagnosis and the same number of matched controls. Adjusted ORs for current use of 1-4, 5-19, or ≥20 prescriptions for beta-blockers, as compared with nonuse, were 0.93 (95% CI 0.76-1.13), 1.10 (95% CI 0.97-1.24), and 1.10 (95% CI 1.01-1.20), respectively. The risk estimates for current use of other antihypertensives at any exposure duration were all close to 1.0.

Conclusions: This large population-based case-control analysis does not support the current proposition that beta-blocker use is associated with an increased risk of psoriasis, nor did we find evidence for a substantially altered psoriasis risk for other antihypertensive drugs.

3.1.2 Background

Psoriasis is a common autoimmune inflammatory skin disease with an estimated prevalence between 0.6% and 4.8% and even higher rates for some regions.[62, 63] In a recent study using the UK-based GPRD, Gelfand et al. reported a prevalence rate of 1.5% in the UK.[139] The disease is characterised by T cell-mediated hyperproliferation of keratinocytes and inflammatory processes based on a strong and complex genetic background.[46] Various potential risk or triggering factors have been described such as smoking, alcohol consumption, increased BMI, trauma, infections, endocrine factors, stressful life events as well as exposure to drugs such as beta-blockers, angiotensin-converting enzyme inhibitors (ACE-inhibitors), antimalarials, nonsteroidal anti-inflammatory drugs (NSAIDs), lithium, interferons as well as the acute withdrawal of systemic or potent topical corticosteroids.[62, 85, 88, 91, 95, 96]

Beta-blockers and ACE-inhibitors are widely used drugs for the treatment of hypertension, a disease which has been associated with psoriasis.[86, 102, 103] Numerous case series have reported a possible association between use of beta-blockers and the induction or exacerbation of psoriasis, including case reports on timolol-containing eye drops. In many of these reports, the reaction was described as psoriasiform drug eruption rather than psoriasis, and histological testing was either not done or did not support a diagnosis of psoriasis.[95, 96, 140-142] Due to disparate histological presentations, it has recently been suggested that the pathophysiology of drug-induced psoriasis may differ from that of idiopathic psoriasis.[143] Although it was proposed in the 1980s that further studies were needed to explore whether use of beta-blockers alters the risk of psoriasis,[95] such a possible association has - to our knowledge - not been studied in more detail.

Even though cutaneous adverse effects of ACE-inhibitors are common (8.3% - 58.3%),[96] a possible link to psoriasis has been reported only rarely, particularly for captopril.[96] Psoriasis and psoriasiform eruptions have also been associated with use of other antihypertensives such as angiotensin II (AT II) antagonists,[144] calcium channel blockers (CCB),[145] or clonidine.[146] A recently published hospital-based case-control (110 patients, 515 controls) and case-crossover study (98 patients) reported a possible association between use of ACE-inhibitors and an increased relative psoriasis risk in the case-control analysis. A suggestion of an increased risk associated with use of ACE-inhibitors as well as with use of beta-blockers was also reported in the case-crossover study.[78]

The currently available evidence on a possible association between use of antihypertensive drugs and psoriasis is based mainly on case reports and case series, and there is no consensus on the mechanism by which beta-blockers might induce such a reaction.[143] We conducted a large population-based case-control study to further explore the association between use of beta-blockers or other antihypertensive drugs and the risk of developing a first-time diagnosis of psoriasis.

3.1.3 Methods

We conducted a matched case-control analysis within the GPRD on the risk of having a first-time psoriasis diagnosis in relation to previous use of beta-blockers, ACE-inhibitors, AT II antagonists, CCBs, diuretics, and clonidine.

Data Source

The GPRD is a large UK-based database established around 1987 which encompasses some five million patients who are actively enrolled with selected GPs. The GPs have agreed to provide data for research purposes to the GPRD. GPs have been trained to record medical information in a standard manner and to supply it anonymously. The patients enrolled in the GPRD are representative of the UK with regard to age, sex, geographical distribution, and annual turnover rate. The information recorded includes patient demographics and characteristics (e.g. age, sex, height, weight, smoking status), symptoms, medical diagnoses, referrals to consultants, hospitalisations, and all drug prescriptions, as the doctors generate prescriptions directly with the computer using a coded drug dictionary. Prescriptions contain the name of the preparation (active compound), the route of administration, the dose of a single unit, the number of units prescribed, and, in most instances, the intake regimen prescribed by the GP. Hospital discharge and referral letters are available for review to validate the diagnoses recorded in the computer record.[31, 36] This database, which has been described in detail[31, 36] and validated extensively,[34] has been the source for numerous published epidemiological studies. Several studies on psoriasis using GPRD data have been published.[103, 108, 115, 116, 139, 147]

The study protocol was approved by ISAC, the Independent Scientific Advisory Committee for MHRA database research.

Case definition and ascertainment

We identified patients with a first-time diagnosis of psoriasis between 1 January 1994 and 31 December 2005 via OXMIS (Oxford Medical Information System) and Read codes. We did not include patients with less than three years of active history in the database prior to the first-time diagnosis of psoriasis, and patients with a code for 'history of psoriasis' at the index date were also not eligible.

The validity of psoriasis diagnoses in the GPRD has been examined by Gelfand et al. who have published several GPRD-based studies on psoriasis.[103, 108, 115, 116, 139, 147] They showed that the epidemiology of psoriasis in the GPRD is similar to data from other population-based studies in the UK and that 92% of patients with a psoriasis code receive psoriasis therapies.[115, 139] In addition, among a random sample of 100 GPs who recorded a psoriasis code, approximately 90% confirmed the diagnosis after four years of follow-up.[147]

Controls

From the base population we identified at random one control subject per psoriasis case, matched on calendar time (same index date), age (same year of birth), sex, general practice, and years of history in the GPRD. Thus, controls were also required to have at least three years of active history in the GPRD.

Exposure to antihypertensives

For each case and control we assessed from the computer record the exposure history for beta-blockers, ACE-inhibitors, AT II antagonists, or combinations thereof, CCBs, diuretics, and clonidine prior to the index date. Patients were classified as 'current users' if the last prescription was recorded <90 days, or as 'past users' if it was recorded ≥90 days prior to the index date. We also classified users by duration of use prior to the index date, using the number of prescriptions as proxy (1-4, 5-19, or ≥20 prescriptions for beta-blockers, ACE-inhibitors, CCBs, and diuretics and 1-9 or ≥10 for AT II antagonists and clonidine due to lower exposure prevalence), and we also evaluated duration by timing of use.

For the main analysis we created two models: first, subsequent or concurrent use of various antihypertensive drugs prior to the index date was possible, and we adjusted for such overlapping use in the multivariate model. In the second model, subjects were categorised into mutually exclusive groups of users of one antihypertensive

drug class, while combined use of antihypertensives ('switchers' or combined therapies) formed a separate group.

Statistical analysis

We conducted conditional logistic regression analyses using the SAS statistical software (version 9.1; SAS Institute Inc, Cary, NC, U.S.A.). We displayed relative risk estimates as ORs with 95% CIs. We adjusted ORs for the potential confounders age, sex, general practice, calendar time, and years of recorded history in the database by matching, and for smoking status (non, current, ex, or unknown) and BMI (<18.5, 18.5-24.9, 25.0-29.9, ≥30 kg/m^2, or unknown) in the multivariate model. The risk estimates were further adjusted for a history of cardiac arrhythmia, congestive heart failure, ischaemic heart disease, stroke/TIA, hypertension, diabetes, hyperlipidaemia, chronic obstructive pulmonary disease (COPD), asthma, and alcoholism, as well as for use of coronary vasodilatators (1-9 or ≥10 prescriptions). Potential confounding was further tested for a number of other covariates which were not included in the final model because they were not materially associated with the exposure or with the outcome, such as allergic skin disease, allergic rhinoconjunctivitis, atopic dermatitis, contact dermatitis, tonsillectomy, candidiasis/aspergillosis, cellulitis, viral infections, respiratory infections, hyper-/hypothyroidism, affective disorders, gout, epilepsy, neurosis, inflammatory bowel disease, rheumatoid arthritis, migraine, tremor, and use of antihistamines, benzodiazepines, beta-agonists, cardiac glycosides, NSAIDs, paracetamol, cyclooxygenase-2 inhibitors, lipid-lowering agents, selective serotonin re-uptake inhibitors (SSRI), terbinafine, levothyroxine, carbimazole, and antidiabetic agents.

3.1.4 Results

We identified 36,702 cases with a first-time diagnosis of psoriasis between 1 January 1994 and 31 December 2005 and the same number of matched controls. Table 3.1.1 displays age and sex distribution of cases and controls as well as the distribution of smoking status, BMI, a number of cardiovascular risk factors, and other diseases.

Table 3.1.1 Characteristics of case patients with psoriasis and matched controls

Variable	Cases No (%) (n = 36,702)		Controls No (%) (n = 36,702)		Adjusted OR* (95% CI)	
Sex**						
Men	16,969	(46.2)	16,969	(46.2)	-	-
Women	19,733	(53.8)	19,733	(53.8)	-	-
Agegroup (years)**						
<20	5801	(15.8)	5801	(15.8)	-	-
20-29	4336	(11.8)	4339	(11.8)	-	-
30-39	5187	(14.1)	5187	(14.1)	-	-
40-49	5173	(14.1)	5171	(14.1)	-	-
50-59	5989	(16.3)	5997	(16.3)	-	-
60-69	5109	(13.9)	5102	(13.9)	-	-
≥70	5107	(13.9)	5105	(13.9)	-	-
Smoking status						
Non smoker	13,390	(36.5)	15,594	(42.5)	1.00	(reference)
Current smoker	8787	(23.9)	6913	(18.8)	1.52	(1.46 - 1.58)
Ex smoker	4690	(12.8)	3763	(10.3)	1.46	(1.38 - 1.53)
Unknown	9835	(26.8)	10,432	(28.4)	1.08	(1.02 - 1.14)
BMI (kg/m^2)						
12-18.4	523	(1.4)	574	(1.6)	0.92	(0.81 - 1.04)
18.5-24.9	10,244	(27.9)	10,887	(29.7)	1.00	(reference)
25-29.9	8330	(22.7)	7934	(21.6)	1.14	(1.09 - 1.19)
30-60	4881	(13.3)	3882	(10.6)	1.38	(1.31 - 1.45)
Unknown	12,724	(34.7)	13,425	(36.6)	0.99	(0.94 - 1.04)
Comorbidities						
Arrhythmias	1098	(3.0)	1133	(3.1)	0.94	(0.86 - 1.03)
CHF	713	(1.9)	673	(1.8)	0.97	(0.86 - 1.09)
IHD	2587	(7.1)	2232	(6.1)	1.01	(0.92 - 1.10)
Stroke/TIA	996	(2.7)	923	(2.5)	1.04	(0.94 - 1.15)
Hypertension	5295	(14.4)	5140	(14.0)	0.98	(0.94 - 1.03)
Diabetes	1355	(3.7)	1294	(3.5)	0.95	(0.87 - 1.03)
Hyperlipidaemia	2169	(5.9)	1950	(5.3)	1.06	(0.99 - 1.14)
Alcoholism	1031	(2.8)	725	(2.0)	1.34	(1.22 - 1.49)

* Adjusted for all covariates listed in the table plus asthma, chronic obstructive pulmonary disease, and use of coronary vasodilatators; ** Matching variables

Percentages may not sum to 100% due to rounding

BMI = body mass index; CHF = congestive heart failure; IHD = ischaemic heart disease; TIA = transient ischaemic attack; OR = odds ratio; CI = confidence interval

The study population encompassed 53.8% female patients, and 41.7% were below the age of 40 years. Current smoking (OR 1.52, 95% CI 1.46-1.58) and obesity (BMI ≥30 kg/m^2) (OR 1.38, 95% CI 1.31-1.45) were associated with a small increased psoriasis risk. None of the cardiovascular diseases we tested in the analysis was associated with a materially altered psoriasis risk (table 3.1.1).

Compared with the reference group of nonuse, the adjusted ORs for current use of the antihypertensive drug groups of interest were all close to one.

The results of the analyses in which we evaluated duration and timing of use are displayed in table 3.1.2 for the first adjusted model and in table 3.1.3 for the mutually exclusive drug use model. In both models, most ORs were close to one. The adjusted ORs for current use of ≥20 beta-blocker prescriptions were 1.10 (95% CI 1.01-1.20) in the first model and 1.13 (95% CI 0.98-1.30) in the mutually exclusive model.

Table 3.1.2 Risk of first-time psoriasis diagnosis associated with the use of antihypertensive drugs

Exposure (No of Rx)	Cases No (%) (n = 36,702)	Controls No (%) (n = 36,702)	Unadjusted OR (95% CI)	Adjusted OR* (95% CI)
ACE inhibitors				
nonuse	34,117 (93.0)	34,212 (93.2)	1.00 (reference)	1.00 (reference)
current				
1-4	158 (0.43)	142 (0.39)	1.12 (0.89 - 1.41)	1.04 (0.82 - 1.31)
5-19	494 (1.35)	473 (1.29)	1.05 (0.92 - 1.19)	0.95 (0.83 - 1.08)
≥20	1015 (2.77)	1045 (2.85)	0.98 (0.89 - 1.07)	0.90 (0.81 - 0.99)
past				
1-4	418 (1.14)	359 (0.98)	1.17 (1.02 - 1.35)	1.04 (0.89 - 1.22)
5-19	321 (0.87)	282 (0.77)	1.15 (0.97 - 1.35)	1.01 (0.84 - 1.20)
≥20	179 (0.49)	189 (0.51)	0.96 (0.78 - 1.18)	0.86 (0.69 - 1.07)
Beta-blockers				
nonuse	30,907 (84.2)	31,241 (85.1)	1.00 (reference)	1.00 (reference)
current				
1-4	212 (0.58)	224 (0.61)	0.97 (0.80 - 1.17)	0.93 (0.76 - 1.13)
5-19	608 (1.66)	527 (1.44)	1.18 (1.05 - 1.33)	1.10 (0.97 - 1.24)
≥20	1686 (4.59)	1501 (4.09)	1.16 (1.07 - 1.25)	1.10 (1.01 - 1.20)
past				
1-4	2009 (5.47)	1982 (5.40)	1.03 (0.97 - 1.10)	0.99 (0.92 - 1.06)
5-19	753 (2.05)	731 (1.99)	1.05 (0.95 - 1.17)	0.99 (0.89 - 1.10)
≥20	527 (1.44)	496 (1.35)	1.10 (0.97 - 1.24)	1.03 (0.90 - 1.18)

Table 3.1.2 (cont.)

Exposure (No of Rx)	Cases No (%) (n = 36,702)	Controls No (%) (n = 36,702)	Unadjusted OR (95% CI)	Adjusted OR* (95% CI)
AT II antagonists				
nonuse	36,225 (98.7)	36,277 (98.8)	1.00 (reference)	1.00 (reference)
current				
1-9	119 (0.32)	111 (0.30)	1.08 (0.83 - 1.40)	1.01 (0.77 - 1.32)
≥10	250 (0.68)	221 (0.60)	1.14 (0.95 - 1.37)	1.05 (0.86 - 1.28)
past				
1-9	81 (0.22)	72 (0.20)	1.13 (0.82 - 1.56)	1.09 (0.78 - 1.52)
≥10	27 (0.07)	21 (0.06)	1.30 (0.73 - 2.34)	1.26 (0.69 - 2.28)
CCBs				
nonuse	33,500 (91.3)	33,755 (92.0)	1.00 (reference)	1.00 (reference)
current				
1-4	135 (0.37)	143 (0.39)	0.96 (0.76 - 1.22)	0.89 (0.70 - 1.13)
5-19	494 (1.35)	444 (1.21)	1.14 (1.00 - 1.30)	1.02 (0.89 - 1.17)
≥20	1216 (3.31)	1146 (3.12)	1.09 (1.00 - 1.18)	0.97 (0.88 - 1.07)
past				
1-4	683 (1.86)	598 (1.63)	1.16 (1.04 - 1.30)	1.06 (0.94 - 1.19)
5-19	370 (1.01)	328 (0.89)	1.16 (0.99 - 1.34)	1.04 (0.88 - 1.21)
≥20	304 (0.83)	288 (0.78)	1.08 (0.92 - 1.28)	0.97 (0.81 - 1.16)
Clonidine				
nonuse	36,228 (98.7)	36,236 (98.7)	1.00 (reference)	1.00 (reference)
current				
1-9	23 (0.06)	25 (0.07)	0.93 (0.53 - 1.63)	0.82 (0.46 - 1.45)
≥10	22 (0.06)	27 (0.07)	0.81 (0.46 - 1.44)	0.81 (0.45 - 1.45)
past				
1-9	389 (1.06)	368 (1.00)	1.06 (0.91 - 1.23)	1.01 (0.87 - 1.18)
≥10	40 (0.11)	46 (0.13)	0.88 (0.57 - 1.34)	0.85 (0.55 - 1.31)
Diuretics				
nonuse	30,949 (84.3)	31,488 (85.8)	1.00 (reference)	1.00 (reference)
current				
1-4	291 (0.79)	267 (0.73)	1.14 (0.97 - 1.35)	1.11 (0.93 - 1.32)
5-19	828 (2.26)	759 (2.07)	1.15 (1.03 - 1.27)	1.09 (0.98 - 1.22)
≥20	1981 (5.40)	1941 (5.29)	1.08 (1.01 - 1.16)	1.05 (0.96 - 1.14)
past				
1-4	1608 (4.38)	1366 (3.72)	1.23 (1.14 - 1.33)	1.17 (1.08 - 1.27)
5-19	624 (1.70)	544 (1.48)	1.20 (1.07 - 1.35)	1.16 (1.03 - 1.32)
≥20	421 (1.15)	337 (0.92)	1.32 (1.14 - 1.53)	1.27 (1.09 - 1.48)

* Adjusted for arrhythmias, congestive heart failure, chronic obstructive pulmonary disease, ischaemic heart disease, stroke/transient ischaemic attack, hypertension, asthma, diabetes, hyperlipidaemia, alcoholism, use of coronary vasodilatators, body mass index, smoking, and antihypertensives not under investigation

Rx = prescriptions; ACE = angiotensin converting enzyme; AT = angiotensin; CCB = calcium channel blocker; OR = odds ratio; CI = confidence interval

Table 3.1.3 Risk of first-time psoriasis diagnosis associated with the use of antihypertensive drugs in mutually exclusive groups

Exposure (No of Rx)	Cases No (%) (n = 36,702)	Controls No (%) (n = 36,702)	Unadjusted OR (95% CI)	Adjusted OR* (95% CI)
Nonuse	26,544 (72.3)	27,153 (74.0)	1.00 (reference)	1.00 (reference)
ACE inhibitors				
current				
1-4	23 (0.06)	17 (0.05)	1.40 (0.75 - 2.63)	1.39 (0.73 - 2.65)
5-19	65 (0.18)	70 (0.19)	0.96 (0.68 - 1.35)	0.92 (0.65 - 1.32)
≥20	111 (0.30)	120 (0.33)	0.99 (0.76 - 1.28)	0.96 (0.74 - 1.26)
past				
1-4	23 (0.06)	28 (0.08)	0.88 (0.51 - 1.53)	0.84 (0.48 - 1.47)
5-19	15 (0.04)	12 (0.03)	1.29 (0.60 - 2.75)	1.29 (0.60 - 2.78)
≥20	8 (0.02)	9 (0.02)	0.91 (0.35 - 2.37)	0.90 (0.34 - 2.38)
Beta-blockers				
current				
1-4	106 (0.29)	123 (0.34)	0.89 (0.69 - 1.16)	0.86 (0.66 - 1.12)
5-19	203 (0.55)	188 (0.51)	1.13 (0.92 - 1.38)	1.05 (0.86 - 1.29)
≥20	504 (1.37)	458 (1.25)	1.17 (1.03 - 1.33)	1.13 (0.98 - 1.30)
past				
1-4	1248 (3.40)	1259 (3.43)	1.02 (0.94 - 1.11)	0.99 (0.91 - 1.08)
5-19	241 (0.66)	261 (0.71)	0.96 (0.81 - 1.15)	0.93 (0.77 - 1.11)
≥20	99 (0.27)	80 (0.22)	1.32 (0.98 - 1.78)	1.28 (0.95 - 1.74)
AT II antagonists				
current				
1-9	0 (0.00)	7 (0.02)	0.00 (NA)	0.00 (NA)
≥10	6 (0.02)	6 (0.02)	1.06 (0.34 - 3.29)	1.10 (0.35 - 3.44)
past				
1-9	2 (0.01)	3 (0.01)	0.70 (0.12 - 4.24)	0.81 (0.13 - 4.93)
≥10	0 (0.00)	0 (0.00)	NA (NA)	NA (NA)
CCBs				
current				
1-4	19 (0.05)	32 (0.09)	0.61 (0.35 - 1.09)	0.57 (0.32 - 1.01)
5-19	68 (0.19)	58 (0.16)	1.25 (0.88 - 1.78)	1.15 (0.80 - 1.64)
≥20	174 (0.47)	168 (0.46)	1.10 (0.89 - 1.36)	1.03 (0.83 - 1.29)
past				
1-4	137 (0.37)	135 (0.37)	1.05 (0.83 - 1.34)	0.98 (0.76 - 1.24)
5-19	33 (0.09)	26 (0.07)	1.32 (0.79 - 2.21)	1.19 (0.71 - 2.01)
≥20	24 (0.07)	28 (0.08)	0.92 (0.53 - 1.61)	0.90 (0.51 - 1.58)

Table 3.1.3 (cont.)

Exposure (No of Rx)	Cases No (%) (n = 36,702)	Controls No (%) (n = 36,702)	Unadjusted OR (95% CI)	Adjusted OR* (95% CI)
Clonidine				
current				
1-9	15 (0.04)	14 (0.04)	1.13 (0.54 - 2.35)	1.00 (0.48 - 2.10)
≥10	8 (0.02)	12 (0.03)	0.74 (0.30 - 1.83)	0.78 (0.31 - 1.94)
past				
1-9	150 (0.41)	167 (0.46)	0.94 (0.75 - 1.17)	0.93 (0.74 - 1.17)
≥10	7 (0.02)	16 (0.04)	0.45 (0.18 - 1.09)	0.43 (0.17 - 1.07)
Diuretics				
current				
1-4	114 (0.31)	114 (0.31)	1.08 (0.83 - 1.40)	1.09 (0.83 - 1.42)
5-19	244 (0.66)	219 (0.60)	1.20 (0.99 - 1.44)	1.17 (0.96 - 1.41)
≥20	481 (1.31)	481 (1.31)	1.09 (0.95 - 1.24)	1.04 (0.91 - 1.19)
past				
1-4	876 (2.39)	713 (1.94)	1.30 (1.17 - 1.44)	1.21 (1.09 - 1.34)
5-19	203 (0.55)	168 (0.46)	1.29 (1.05 - 1.58)	1.24 (1.01 - 1.53)
≥20	100 (0.27)	66 (0.18)	1.63 (1.19 - 2.23)	1.65 (1.20 - 2.27)
Mixed use	4851 (13.22)	4491 (12.24)	1.16 (1.10 - 1.22)	1.09 (1.02 - 1.17)

* Adjusted for arrhythmias, congestive heart failure, chronic obstructive pulmonary disease, ischaemic heart disease, stroke/transient ischaemic attack, hypertension, asthma, diabetes, hyperlipidaemia, alcoholism, use of coronary vasodilatators, body mass index, smoking

Rx = prescriptions; ACE = angiotensin converting enzyme; AT = angiotensin; CCB = calcium channel blocker; OR = odds ratio; CI = confidence interval

Neither stratification by sex nor by age (<40 vs. ≥40 years) provided evidence for effect modification, although exposure prevalence was low in patients below the age of 40 years for most antihypertensives (data not shown).

The results of the analyses of beta-blockers stratified by physicochemical properties or pharmacological mechanism of action, based on the adjusted model with overlapping use, are displayed in table 3.1.4. Most ORs were around one. While other beta-blockers were not associated with an increased psoriasis risk, the adjusted OR for ≥20 timolol prescriptions was 2.44 (95% CI 1.16-5.14), based on 25 exposed cases and 10 exposed controls, and 1.18 (95% CI 1.01-1.37) for users of 5-19 atenolol prescriptions, based on 425 cases and 344 controls.

We also stratified current users of CCBs, AT II antagonists, or ACE-inhibitors by physicochemical properties or pharmacological mechanism of action and by individual agents. We found a statistically significantly reduced psoriasis risk for use of ≥20 verapamil prescriptions (OR 0.33, 95% CI 0.16-0.71) and for 1-4 diltiazem

prescriptions (OR 0.25, 95% CI 0.07-0.93) in the mutually exlusive model and an adjusted OR of 1.60 (95% CI 1.02-2.51) for use of ≥10 prescriptions for the AT-II-antagonist candesartan, while the risk estimates for individal ACE-inhibitors were close to one.

Table 3.1.4 Risk of first-time psoriasis diagnosis associated with current beta-blocker use

Exposure (No of Rx)	Cases No (%) (n = 36,702)	Controls No (%) (n = 36,702)	Adjusted OR** (95% CI)
Cardioselective*			
1-4	142 (0.39)	137 (0.37)	1.01 (0.79 - 1.29)
5-19	491 (1.34)	422 (1.15)	1.10 (0.96 - 1.27)
≥20	1351 (3.68)	1218 (3.32)	1.08 (0.99 - 1.19)
Noncardioselective*			
1-4	70 (0.19)	87 (0.24)	0.80 (0.58 - 1.10)
5-19	117 (0.32)	105 (0.29)	1.08 (0.83 - 1.42)
≥20	335 (0.91)	283 (0.77)	1.18 (1.00 - 1.40)
Hydrophilic*			
1-4	144 (0.39)	138 (0.38)	1.03 (0.81 - 1.31)
5-19	485 (1.32)	415 (1.13)	1.11 (0.96 - 1.27)
≥20	1350 (3.68)	1209 (3.29)	1.10 (1.00 - 1.20)
Lipophilic*			
1-4	62 (0.17)	79 (0.22)	0.78 (0.56 - 1.10)
5-19	97 (0.26)	82 (0.22)	1.15 (0.85 - 1.55)
≥20	242 (0.66)	216 (0.59)	1.11 (0.92 - 1.34)
Mixed*			
1-4	6 (0.02)	7 (0.02)	0.69 (0.22 - 2.12)
5-19	26 (0.07)	30 (0.08)	0.82 (0.48 - 1.41)
≥20	94 (0.26)	76 (0.21)	1.21 (0.88 - 1.65)

* cardioselective (acebutolol, atenolol, betaxolol, bisoprolol, celiprolol, esmolol, metoprolol, nebivolol), noncardioselective (carteolol, carvedilol, labetalol, nadolol, oxprenolol, penbutolol, pindolol, propranolol, sotalol, timolol); lipophilic (nebivolol, oxprenolol, penbutolol, propranolol), hydrophilic (acebutolol, atenolol, bisoprolol, carteolol, celiprolol, esmolol, labetalol, nadolol, pindolol, sotalol), or mixed (betaxolol, carvedilol, metoprolol, timolol) beta-blockers.

** Adjusted for arrhythmias, congestive heart failure, chronic obstructive pulmonary disease, ischaemic heart disease, stroke/transient ischaemic attack, hypertension, asthma, diabetes, hyperlipidaemia, alcoholism, use of coronary vasodilatators, body mass index, smoking, antihypertensives not under investigation

Reference: nonuse of beta-blockers

Rx = prescriptions; OR = odds ratio; CI = confidence interval

We further conducted various sensitivity analyses. First, we ran the two final models (adjusted and mutually exclusive antihypertensive drug use) in a subgroup of case patients (n = 20,726) and their controls who received calcipotriol, coal tar, dithranol, tazarotene, or acitretin in the first year after the psoriasis diagnosis. Second, we restricted an analysis to psoriasis cases (n = 29,170) and their controls who did not have any prescription recorded for any of the five drugs mentioned above at any time prior to the first-time psoriasis diagnosis. Third, we ran a final model with 15,336 cases who received drug treatment in the first year after their psoriasis diagnosis and who did not have any of these medications at any time prior to the first-time psoriasis diagnosis. Fourth, we conducted analyses restricted to psoriasis cases (n = 32,304) without any evidence of previous or concomitant allergic skin diseases, contact dermatitis, or atopic dermatitis as well as restricted to psoriasis cases (n = 35,092) without diagnosed skin infections prior to the index date. We ran these analyses as patients with other skin diseases may be more likely to be misdiagnosed with psoriasis. In all these subgroups, the findings related to use of antihypertensives remained virtually unchanged (data not shown). Fifth, guttate psoriasis is believed to be triggered mainly by drugs, and we therefore ran the first adjusted model in the subgroup of cases with a diagnosis of guttate psoriasis (n = 2866). In this analysis, past use of ≥20 beta-blocker prescriptions yielded an OR of 2.17 (95% CI 0.90-5.24), and past use of 1-4 ACE-inhibitor prescriptions yielded an OR of 3.70 (95% CI 1.20-11.35).

3.1.5 Discussion

The findings of this large population-based case-control analysis do not support the current notion that use of any antihypertensives is associated with a materially altered risk of developing a first-time psoriasis diagnosis. We cannot make a statement about the association between use of these drugs and the risk of an exacerbation of existing psoriasis as this would require a different approach.

Current long-term use of ≥20 beta-blocker prescriptions was associated with a relative risk estimate of 1.10 (95% CI 1.01-1.20). We also created more exposure duration categories for users of beta-blockers, but there was no evidence for an increasing psoriasis risk with increasing duration of use of up to ≥70 prescriptions (data not shown). Thus, these findings provide evidence that cumulative exposure

duration to beta-blockers is not a substantial risk factor for psoriasis. However, we cannot exclude the possibility that certain beta-blockers may be able to trigger psoriasiform eruptions in individual patients with a high individual susceptibility based on a particular genetic or metabolic predisposition.

We did not find differences for cardioselective (β_1 receptor antagonists) vs. non-selective beta-blockers (β_1 and β_2 receptor antagonists), nor for hydrophilic vs. lipophilic agents. However, when we analysed individual beta-blockers, we found a substantially increased OR of 2.44 (95% CI 1.16-5.14) for current users of ≥20 timolol prescriptions. This finding, based on 25 exposed cases and 10 exposed controls, may be real, but it may also be a chance finding despite statistical significance.

Previous reports in the literature on a possible association between beta-blockers and psoriasis were based mainly on case reports and case series[78, 79] or on animal models.[96] Despite several reports on psoriasiform eruptions and psoriasis following treatment with beta-blockers, biopsy was performed in only a few cases (propranolol, practolol), and when done it rarely confirmed psoriasis.[95, 140, 142] In a recent review[143] it was postulated that the origin and treatment of drug-induced psoriasis was different from true psoriasis based on a study by Heng and Heng[148] who demonstrated histopathological and immunohistochemical differences between true psoriasis and beta-blocker-induced psoriasis as well as between drug-induced and drug-aggravated psoriasis, the latter being more similar to true psoriasis. Another group examined 21 patients with drug-induced rashes from practolol (14 with a psoriasiform eruption) and made a similar observation.[141] In the 1970s it was proposed that practolol-induced skin lesions could be distinguished from psoriasis with careful clinical examination.[149] The mechanism by which beta-blockers might induce or exacerbate psoriasis is largely unknown, even though a blockade of beta-adrenergic receptors resulting in a decrease of cyclic adenosine monophosphate (cAMP) and calcium, followed by stimulation of epidermal growth, has been proposed as a leading hypothesis.[143] However, it is an open question why noncardioselective as well as cardioselective beta-blockers have both been associated with psoriasis in previous reports even though the predominant adrenergic receptor in epidermal keratinocytes is the β_2-subtype. In addition, the wide latency ranges which were reported between the start of use of a beta-blocker therapy and the onset of a psoriatic skin eruption (several days up to 26 months in patients without a history of psoriasis) do not necessarily support a causal relation.[95, 96]

For ACE inhibitors and AT II antagonists there are only few case reports in the literature on a possible induction of psoriasis with a typical psoriasiform histology and with cessation of symptoms after discontinuation of the therapy.[96, 144] A recent study suggested that patients with an ACE gene genotype of low ACE-activity, which seems often to occur in patients with familial psoriasis, were more susceptible to the onset of psoriasis.[150] The results of our study do not support the notion of a substantially altered psoriasis risk for users of ACE-inhibitors or AT II antagonists, but again we cannot exclude the possibility that individual patients with a particular susceptibility may develop such reactions while taking an ACE-inhibitor.

A small hospital-based case-control study of 150 patients hospitalised for psoriasis or psoriasiform eruptions and 150 controls was done to investigate a possible association between CCB use and psoriasis. A significantly increased OR was observed for CCB use, with a median latency between initiation of therapy and onset of the disease of 28 months (range 4-143 months).[145] In our study we did not find an increased risk, but a slightly reduced risk for short-term use of diltiazem and long-term use of verapamil. This observation may be a chance finding, or it may reflect a pharmacological effect by some CCBs on psoriasis, e.g. via an anti-inflammatory effect which has been described in several articles.[151, 152]

Previous literature suggests an increased prevalence of cardiovascular risk factors (such as diabetes, hypertension, and hyperlipidaemia) as well as other cardiovascular diseases in patients with psoriasis.[86, 102, 103, 108, 112] In our study we did not find an increased prevalence of such diseases in patients with psoriasis prior to the first psoriasis diagnosis, but patients with psoriasis may develop such diseases after the onset of psoriasis. Neimann et al. reported a higher prevalence of diabetes, hypertension, hyperlipidaemia, smoking, and obesity in patients with psoriasis, with a higher prevalence of these diseases with increasing psoriasis severity.[103] In addition, Gelfand et al. documented an increased risk of MI in patients with psoriasis, particularly in younger patients with severe psoriasis.[108] It is conceivable that lifestyle, antipsoriatic medication (e.g. potent corticosteroids) as well as the inflammatory process of the disease itself may increase the risk of cardiovascular diseases in patients with psoriasis. We found a significantly higher prevalence of smokers and obese subjects among patients with psoriasis at the time of the first diagnosis, as previously described in the literature.[88]

We explored the association between use of antihypertensive drugs and the risk of developing a first-time diagnosis of psoriasis. Thus, we cannot exclude the possibility that some of these agents may cause a worsening or exacerbation of pre-existing psoriasis. It was postulated that any drug that can cause skin eruptions can also exacerbate psoriasis as a result of a Koebner reaction.[85]

A limitation of our study is the fact that we cannot exclude the possibility of a certain degree of diagnosis misclassification, leading to the inclusion of psoriasis cases who in fact did not have a first-time diagnosis of psoriasis because other previous skin eruptions may have been misdiagnosed. Gelfand et al. studied psoriasis in previous GPRD-based studies, and their validation procedures documented that the psoriasis diagnoses are generally of high validity in the GPRD.[115, 139, 147] In addition, we conducted various sensitivity analyses to improve the validity of our study, which left the findings virtually unchanged. Another limitation is the fact that the exposure prevalence of antihypertensives among patients below the age of 40 years is low, and that our conclusions are therefore mainly based on patients above the age of 40 years. Thus, we cannot exclude the possibility that antihypertensives may have a different effect on younger age groups with type I psoriasis.

Although we tested a large number of potential confounding factors and included the most relevant ones in our model, we cannot exclude the possibility that other unknown confounders or biases may have affected our results to some degree.

In summary, the present population-based case-control study is, to our knowledge, the largest study so far to explore a possible association between use of beta-blockers or other antihypertensives and the risk of developing psoriasis. The findings provide evidence that use of beta-blockers or other antihypertensives does not substantially alter the risk of developing a first-time psoriasis diagnosis.

3.2 LITHIUM, ANTIPSYCHOTICS, AND RISK OF PSORIASIS

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3.2.1 Abstract

Background: Observations in controlled trials and case reports have linked lithium exposure to induction or exacerbation of psoriasis. A causal relationship between lithium exposure and incident psoriasis has been questioned, and observational studies are lacking.

Methods: We conducted a case-control analysis using the UK-based GPRD to study the association between use of lithium or antipsychotics and the risk of developing an incident psoriasis diagnosis. We identified cases with an incident psoriasis diagnosis between 1994 and 2005, and controls were matched to cases on age, sex, general practice, calendar time, and years of history in the database. We used conditional logistic regression to estimate the risk of developing a first-time psoriasis diagnosis in relation to previous exposure to lithium and antipsychotic drugs, stratified by exposure timing and duration. We calculated ORs with 95% CI adjusted for smoking, BMI, and additional potential confounders.

Results: We identified 36,702 incident psoriasis cases and the same number of matched controls. Compared with nonuse, current use of ≥5 prescriptions for lithium or atypical antipsychotics yielded adjusted ORs of 1.68 (95% CI 1.18-2.39, p <0.01) and 0.76 (95% CI 0.55-1.06, p = 0.11), respectively. The OR for olanzapine was 0.50 (95% CI 0.28-0.89, p = 0.02).

Conclusions: Long-term use of lithium was associated with a small increase in risk of incident psoriasis. There was a suggestion of a possible reduced psoriasis risk associated with the use of atypical antipsychotics, mainly olanzapine, a finding which needs further evaluation.

3.2.2 Background

Psoriasis is a chronic inflammatory skin disease with an estimated prevalence ranging between 0.6% and 4.8%[62] depending on region or ethnicity.[63] Psoriasis has a considerable impact on a patient's QoL.[44, 62] The disease is characterised by T cell-mediated hyperproliferation of keratinocytes and inflammatory processes. Naïve T cells are converted to T cells of the Th1 and Th17 lineage in secondary lymphatic organs which produce cytokines such as IL-22, IFN-γ, TNF-β and IL-6, IL-17, IL-22, respectively. These and other immune cells infiltrate the skin and activate each other and the keratinocytes via the previously mentioned cytokines and additional ones (such as TNF-α, IL-20, IL-23, TGF-α), which sustains an inflammatory process.[48] A variety of potential risk or triggering factors have been described such as smoking, alcohol consumption, BMI, trauma, infections, stressful life events, endocrine factors, diet, or exposure to drugs. Among the drugs, beta-blockers, lithium, and antimalarial drugs have been associated with psoriasis, but there have also been reports for NSAIDs, ACE-inhibitors, interferons, SSRIs, benzodiazepines, and the acute withdrawal of systemic or potent topical corticosteroids.[62, 85, 87, 88, 91, 95, 96]

Lithium was introduced in the 1960s for the treatment of bipolar disorders. In the 1970s the first case reports on exacerbation or induction of psoriasis emerged, although the latter seems to be less common.[87, 95] In controlled trials, 3.4% to 45% of lithium-exposed patients developed cutaneous reactions, mainly acne and psoriasis.[153] The latency period has been reported to be relatively long, on average 20 weeks for exacerbation and 48 weeks for induction of psoriasis. However, the hypothesis that lithium increases the risk of developing psoriasis has not been fully accepted.[87, 154] Some reports have described patients with psoriasisform dermatitis rather than true psoriasis, and the mechanism of lithium action on psoriasis is still under discussion.[87, 97] We therefore decided to study the association between lithium exposure and new-onset psoriasis in a large population-based case-control analysis, similar to a recent analysis on the use of beta-blockers and psoriasis.[155]

With the exception of three reports on induction or exacerbation of psoriasis after exposure to olanzapine,[156, 157] we could not find any published reports of a potential association between other antipsychotics and psoriasis. Stressful life events have been reported to trigger psoriasis,[88] and the prevalence of psychiatric diseases, mainly depression and anxiety, is high in psoriatic patients.[132]

As, to our knowledge, no large population-based study has been published investigating the association between antipsychotic exposure and the risk of developing an incident psoriasis diagnosis, we investigated the role of antipsychotics and lithium exposure in a case-control analysis.

3.2.3 Methods

We conducted a matched case-control analysis within the UK-based GPRD to investigate the risk of developing a first-time psoriasis diagnosis in relation to previous use of lithium, phenothiazines, butyrophenones, atypical antipsychotics, or other antipsychotic drugs.

Data Source

The GPRD is a large UK-based database established around 1987 which encompasses some five million patients who are actively enrolled with selected GPs. The GPs have agreed to provide data for research purposes to the GPRD. GPs have been trained to record medical information in a standard manner and to supply it anonymously. The patients enrolled in the GPRD are representative of the UK in age, sex, geographic distribution, and annual turnover rate. The information recorded includes patient demographics and characteristics (e.g. age, sex, height, weight, and smoking status), symptoms, medical diagnoses, referrals to consultants, and hospitalisations. Because the physicians generate drug prescriptions directly with the computer using a coded drug dictionary, all prescriptions including the name of the preparation (active compound), the route of administration, the dose of a single unit, the number of units prescribed and, in most instances, the intake regimen are recorded. The database has been described in detail elsewhere[36, 38] and validated extensively.[34] It has been the source for numerous published epidemiological studies including several studies on psoriasis.

The study protocol was approved by ISAC for MHRA database research.

Case definition and ascertainment

We identified patients with a first-time diagnosis of psoriasis between 1 January 1994 and 31 December 2005 via OXMIS and Read codes. Patients with less than three years of active history in the database prior to the first-time diagnosis of

psoriasis and those with a code for 'history of psoriasis' at the index date were excluded.

The validity of psoriasis diagnoses in the GPRD is high, [115, 139, 147] and we thus included all patients with a recorded psoriasis diagnosis in the main analysis. In addition, we conducted a number of sensitivity analyses in patients with definitive and incident psoriasis who fulfilled stringent treatment requirements as was done in previous GPRD-based studies on psoriasis.[155, 158]

Controls

From the base population we randomly identified one control subject per psoriasis case, matched on calendar time (same index date), age (same year of birth), sex, general practice, and years of history in the GPRD. Thus, the controls were also required to have at least three years of active history in the GPRD.

Exposure to lithium and antipsychotics

From the computer record, we assessed exposure to lithium, phenothiazines, butyrophenones, atypical antipsychotics, and other antipsychotics prior to the index date for cases and controls. Patients were classified as 'current users' if the last prescription was recorded <90 days, or as 'past users' if it was recorded ≥90 days prior to the index date. We also classified users by duration of use prior to the index date, based on the number of prescriptions (1-2, 3-14, or ≥15 prescriptions for phenothiazines or 1-4 or ≥5 for the other drug classes). Finally, we combined duration and timing of use into one exposure variable.

We conducted two main analyses: in the first model, patients could have been exposed to lithium or various antipsychotics subsequently or concurrently prior to the index date, and we adjusted for such overlapping use in the multivariate model. In the second model, subjects were categorised into mutually exclusive groups of users of lithium or one antipsychotic drug class, whereas combined use of lithium or antipsychotics ("switchers" or concurrent therapies) formed a separate group.

Statistical analysis

We conducted conditional logistic regression analyses using the SAS statistical software (version 9.1; SAS Institute Inc, Cary, NC, U.S.A.) to calculate relative risk estimates as ORs with 95% CI. We controlled for the potential confounders age, sex,

general practice, calendar time, and years of recorded history in the database by matching, and we further adjusted the ORs for smoking status (non, current, ex, or unknown) and BMI (<18.5, 18.5-24.9, 25.0-29.9, ≥30 kg/m^2, or unknown) in the multivariate model. The risk estimates were additionally adjusted for a history of atopic and contact dermatitides, hypothyroidism, and neurotic or affective disorders and for use of NSAIDs, SSRIs, and benzodiazepines. A variety of other covariates were tested for potential confounding but were not included in the final model because they were not materially associated with the exposure or with the outcome, such as allergic skin disease, ischaemic heart disease, urticaria / angio-oedema, hypertension / hypotension, hyperlipidaemia, hyperthyroidism, skin infections, alcoholism, diabetes, epilepsia, rheumatoid arthritis, cancer, intestinal anti-inflammatory agents, use of mono-amine re-uptake inhibitors, mono-amine oxidase inhibitors, or other antidepressives.

3.2.4 Results

We identified 36,702 cases with a first-time psoriasis diagnosis between 1994 and 2005 and the same number of matched controls. Table 3.2.1 displays the age and sex distribution of cases and controls and the distribution of smoking status, BMI, and additional parameters.

Of the newly diagnosed psoriasis patients, 53.8% were women and 46.2% men, and 41.8% were younger than 40 years. Current smoking (OR 1.51, 95% CI 1.45-1.57, p <0.0001), obesity (BMI ≥30 kg/m^2; OR 1.33, 95% CI 1.26-1.40, p <0.0001), and current exposure to ≥5 prescriptions of NSAIDs (OR 1.36. 95% CI 1.26-1.46, p <0.0001) were associated with an increased relative psoriasis risk. Furthermore, cases had a higher prevalence of first-time diagnoses of affective or neurotic disorders around the index date (table 3.2.1).

Table 3.2.1: Characteristics of case patients with psoriasis and matched controls

Variable	Cases No (%) (n = 36,702)		Controls No (%) (n = 36,702)		Adjusted OR* (95% CI)	
Sex**						
Men	16,969	(46.2)	16,969	(46.2)	-	-
Women	19,733	(53.8)	19,733	(53.8)	-	-
Agegroup (years)**						
<40	15,324	(41.8)	15,327	(41.8)	-	-
40-59	11,162	(30.4)	11,168	(30.4)	-	-
≥60	10,216	(27.8)	10,207	(27.8)	-	-
Smoking status						
Non smoker	13,390	(36.5)	15,594	(42.5)	1.00	(reference)
Current smoker	8787	(23.9)	6913	(18.8)	1.51	(1.45 - 1.57)
Ex smoker	4690	(12.8)	3763	(10.3)	1.46	(1.39 - 1.54)
Unknown	9835	(26.8)	10,432	(28.4)	1.09	(1.03 - 1.16)
BMI (kg/m^2)						
12-18.4	523	(1.4)	574	(1.6)	0.92	(0.81 - 1.04)
18.5-24.9	10,244	(27.9)	10,887	(29.6)	1.00	(reference)
25-29.9	8330	(22.7)	7934	(21.6)	1.12	(1.07 - 1.17)
30-60	4881	(13.3)	3882	(10.6)	1.33	(1.26 - 1.40)
Unknown	12,724	(34.7)	13,425	(36.6)	0.99	(0.94 - 1.04)
Comorbidities						
Atopic dermatitis	2092	(5.7)	1042	(2.8)	2.10	(1.94 - 2.28)
Contact dermatitis	1439	(3.9)	903	(2.5)	1.52	(1.39 - 1.65)
Hypothyroidism	1130	(3.1)	908	(2.5)	1.21	(1.11 - 1.33)
Neurotic disorder	5463	(14.9)	4851	(13.2)	1.07	(1.02 - 1.13)
recent Dx	129	(0.4)	59	(0.2)	2.20	(1.60 - 3.03)
past Dx	5334	(14.5)	4792	(13.1)	1.06	(1.01 - 1.11)
Affective disorder	5887	(16.0)	5116	(13.9)	1.11	(1.05 - 1.17)
recent Dx	147	(0.4)	72	(0.2)	1.94	(1.45 - 2.61)
past Dx	5740	(15.6)	5044	(13.7)	1.09	(1.03 - 1.15)
Drug exposure (current long-term use)						
NSAID	2290	(6.2)	1768	(4.8)	1.36	(1.26 - 1.46)
SSRI	413	(1.1)	361	(1.0)	0.93	(0.80 - 1.09)
Benzodiazepines	947	(2.6)	773	(2.1)	1.14	(1.03 - 1.27)

* Adjusted for all covariates listed in the table plus drug exposure categories not listed in the table; ** Matching variables

BMI = body mass index; NSAID = nonsteroidal anti-inflammatory drug; SSRI = selective serotonin re-uptake inhibitor; Dx = Diagnosis; Recent = 0-60 days before index date; Past = >60 days; OR = odds ratio; CI = confidence interval

Compared with the reference group of nonuse, the adjusted OR for any use of lithium (not stratified by duration or timing) was 1.59 (95% CI 1.00-2.51, p = 0.048) in the mutually exclusive model and 1.27 (95% CI 0.97-1.65, p = 0.08) in the model adjusted for concurrent or subsequent use of antipsychotic study drugs. We then assessed the risk estimates of developing psoriasis associated with lithium and other study drugs stratified by duration and timing, again in two separate models. As compared with nonuse of lithium, the ORs for current use of ≥5 lithium prescriptions were 1.68 (95% CI 1.18-2.39, p <0.01) in the model adjusted for use of antipsychotic study drugs and 2.19 (95% CI 1.15-4.18, p = 0.02) in the mutually exclusive drug use model. The results from these two models are displayed in detail in tables 3.2.2 and 3.2.3 and the ORs stratified by age and sex in table 3.2.4.

For current users of ≥5 prescriptions for atypical antipsychotics, the psoriasis risk tended to be decreased, mainly in male and younger patients; olanzapine mainly accounted for this relative risk reduction (tables 3.2.2 – 3.2.4). For butyrophenones (94% haloperidol use), there was a suggestion of a decreased psoriasis risk for past users but not for current users (tables 3.2.2 / 3.2.3). For phenothiazines and other antipsychotics, most ORs were around one.

Table 3.2.2 Risk of first-time psoriasis diagnosis associated with the use of antipsychotic drugs

Exposure (No of Rx)	Cases No (%) (n = 36,702)	Controls No (%) (n = 36,702)	Unadjusted OR (95% CI)	Adjusted OR* (95% CI)
Lithium				
nonuse	36,561 (99.6)	36,594 (99.7)	1.00 (reference)	1.00 (reference)
current				
1-4	3 (0.01)	3 (0.01)	1.00 (0.20 - 4.96)	1.09 (0.21 - 5.59)
≥5	92 (0.25)	53 (0.14)	1.73 (1.24 - 2.43)	1.68 (1.18 - 2.39)
past				
1-4	21 (0.06)	22 (0.06)	0.97 (0.53 - 1.76)	0.93 (0.50 - 1.74)
≥5	25 (0.07)	30 (0.08)	0.84 (0.50 - 1.43)	0.78 (0.45 - 1.36)
Atypical anti-psychotics				
nonuse	36,547 (99.6)	36,519 (99,5)	1.00 (reference)	1.00 (reference)
current				
1-4	15 (0.04)	17 (0.05)	0.88 (0.44 - 1.77)	0.98 (0.48 - 2.02)
≥5	73 (0.20)	89 (0.24)	0.82 (0.60 - 1.12)	0.76 (0.55 - 1.06)
past				
1-4	38 (0.10)	37 (0.10)	1.03 (0.65 - 1.62)	0.91 (0.57 - 1.46)
≥5	29 (0.08)	40 (0.11)	0.73 (0.45 - 1.17)	0.71 (0.43 - 1.16)

Table 3.2.2 (cont.)

Exposure (No of Rx)	Cases No (%) (n = 36,702)	Controls No (%) (n = 36,702)	Unadjusted OR (95% CI)	Adjusted OR* (95% CI)
Butyro-phenones				
nonuse	36,584 (99.7)	36,550 (99.6)	1.00 (reference)	1.00 (reference)
current				
1-4	9 (0.02)	11 (0.03)	0.82 (0.34 - 1.97)	0.72 (0.29 - 1.81)
≥5	25 (0.07)	23 (0.06)	1.09 (0.62 - 1.92)	0.98 (0.54 - 1.75)
past				
1-4	56 (0.15)	86 (0.23)	0.65 (0.47 - 1.91)	0.59 (0.42 - 0.84)
≥5	28 (0.08)	32 (0.09)	0.88 (0.53 - 1.45)	0.78 (0.45 - 1.35)
Phenothia-zines				
nonuse	31,935 (87.0)	32,330 (88.1)	1.00 (reference)	1.00 (reference)
current				
1-2	148 (0.40)	149 (0.41)	1.01 (0.81 - 1.27)	0.90 (0.71 - 1.14)
3-14	133 (0.36)	110 (0.30)	1.24 (0.96 - 1.60)	1.14 (0.88 - 1.48)
≥15	231 (0.63)	204 (0.56)	1.16 (0.96 - 1.41)	1.05 (0.86 - 1.28)
past				
1-2	3276 (8.93)	3027 (8.25)	1.11 (1.05 - 1.17)	1.05 (1.00 - 1.11)
3-14	829 (2.26)	750 (2.04)	1.14 (1.03 - 1.26)	1.04 (0.94 - 1.16)
≥15	150 (0.41)	132 (0.36)	1.17 (0.92 - 1.49)	1.02 (0.80 - 1.31)
Other typical antipsychotic				
nonuse	36,299 (98.9)	36,322 (98.7)	1.00 (reference)	1.00 (reference)
current				
1-4	11 (0.03)	10 (0.03)	1.10 (0.47 - 2.59)	1.04 (0.44 - 2.48)
≥5	43 (0.12)	35 (0.10)	1.23 (0.79 - 1.92)	1.20 (0.76 - 1.91)
past				
1-4	270 (0.74)	251 (0.68)	1.08 (0.91 - 1.29)	0.94 (0.78 - 1.13)
≥5	79 (0.22)	84 (0.23)	0.94 (0.69 - 1.28)	0.89 (0.65 - 1.23)

* Adjusted for atopic dermatitis, contact dermatitis, hypothyroidism, neurotic and affective disorders, use of nonsteroidal anti-inflammatory drugs, selective serotonin re-uptake inhibitors, benzodiazepines, body mass index, smoking, and antipsychotics not under investigation; Rx = prescriptions; OR = odds ratio; CI = confidence interval

Table 3.2.3: Risk of first-time psoriasis diagnosis associated with the use of antipsychotic drugs in mutually exclusive groups

Exposure (No of Rx)	Cases No (%) (n = 36,702)	Controls No (%) (n = 36,702)	Unadjusted OR (95% CI)	Adjusted OR* (95% CI)
Nonuse	31,430 (85.6)	31,802 (86.7)	1.00 (reference)	1.00 (reference)
Lithium				
current				
1-4	2 (0.01)	0 (0.00)	NA NA	NA NA
≥5	31 (0.08)	14 (0.04)	2.25 (1.20 - 4.23)	2.19 (1.15 - 4.18)
past				
1-4	7 (0.02)	6 (0.02)	1.21 (0.40 - 3.59)	0.97 (0.31 - 3.03)
≥5	10 (0.03)	11 (0.03)	0.93 (0.39 - 2.18)	0.95 (0.40 - 2.27)
Atypical anti-psychotics				
current				
1-4	10 (0.03)	9 (0.02)	1.14 (0.46 - 2.82)	1.13 (0.45 - 2.86)
≥5	41 (0.11)	60 (0.16)	0.69 (0.46 - 1.03)	0.65 (0.43 - 0.98)
past				
1-4	17 (0.05)	20 (0.05)	0.86 (0.45 - 1.64)	0.74 (0.38 - 1.43)
≥5	15 (0.04)	22 (0.06)	0.69 (0.36 - 1.34)	0.66 (0.34 - 1.29)
Butyro-phenones				
current				
1-4	6 (0.02)	10 (0.03)	0.61 (0.22 - 1.68)	0.52 (0.18 - 1.48)
≥5	12 (0.03)	11 (0.03)	1.12 (0.49 - 2.53)	1.02 (0.45 - 2.35)
past				
1-4	18 (0.05)	37 (0.10)	0.49 (0.28 - 0.87)	0.44 (0.25 - 0.80)
≥5	6 (0.02)	8 (0.02)	0.77 (0.27 - 2.21)	0.78 (0.26 - 2.30)
Phenothiaz.				
current				
1-2	148 (0.40)	148 (0.40)	1.02 (0.81 - 1.29)	0.91 (0.72 - 1.15)
3-14	126 (0.34)	95 (0.26)	1.36 (1.04 - 1.78)	1.25 (0.95 - 1.64)
≥15	178 (0.48)	163 (0.44)	1.12 (0.91 - 1.39)	1.01 (0.81 - 1.26)
past				
1-2	3249 (8.85)	2996 (8.16)	1.11 (1.05 - 1.17)	1.06 (1.00 - 1.12)
3-14	752 (2.05)	695 (1.89)	1.11 (1.00 - 1.23)	1.01 (0.91 - 1.13)
≥15	118 (0.32)	101 (0.28)	1.21 (0.92 - 1.58)	1.04 (0.79 - 1.37)
Other typical antipsychotic				
current				
1-4	7 (0.02)	8 (0.02)	0.90 (0.33 - 2.48)	0.82 (0.29 - 2.27)
≥5	31 (0.08)	26 (0.07)	1.23 (0.73 - 2.07)	1.07 (0.63 - 1.83)
past				
1-4	178 (0.48)	171 (0.47)	1.07 (0.86 - 1.32)	0.88 (0.71 - 1.10)
≥5	38 (0.10)	39 (0.11)	0.99 (0.63 - 1.55)	0.88 (0.56 - 1.40)

Table 3.2.3 (cont.)

Exposure (No of Rx)	Cases No (%) (n = 36,702)	Controls No (%) (n = 36,702)	Unadjusted OR (95% CI)	Adjusted OR* (95% CI)
Mixed use	272 (0.74)	250 (0.68)	1.12 (0.94 - 1.33)	0.95 (0.79 - 1.14)

* Adjusted for atopic dermatitis, contact dermatitis, hypothyroidism, neurotic and affective disorders, use of nonsteroidal anti-inflammatory drugs, selective serotonin re-uptake inhibitors, benzodiazepines, body mass index, and smoking

Rx = prescriptions; OR = odds ratio; CI = confidence interval

Table 3.2.4 Odds ratios for current use of ≥5 prescriptions for lithium or atypical antipsychotics compared with nonuse, stratified by age and sex (exposure not in mutually exclusive groups)

	Cases No (%)	Controls No (%)	Adjusted OR* (95% CI)	p-value effect modification
Lithium				
Age (years)				
<40	9 (0.06)	12 (0.08)	0.71 (0.27 - 1.84)	<0.005
≥40	83 (0.39)	41 (0.19)	1.97 (1.33 - 2.91)	
<60	49 (0.19)	30 (0.11)	1.53 (0.94 - 2.47)	ns
≥60	43 (0.42)	23 (0.23)	1.83 (1.08 - 3.12)	
Sex				
Men	31 (0.18)	24 (0.14)	1.37 (0.78 - 2.40)	ns
Women	61 (0.31)	29 (0.15)	1.92 (1.21 - 3.06)	
Atypical antipsychotics				
Age (years)				
<40	18 (0.12)	36 (0.23)	0.45 (0.24 - 0.82)	<0.01
≥40	55 (0.26)	53 (0.25)	1.02 (0.68 - 1.53)	
<60	42 (0.16)	70 (0.26)	0.54 (0.36 - 0.81)	<0.05
≥60	31 (0.30)	19 (0.19)	1.63 (0.89 - 2.99)	
Sex				
Men	34 (0.20)	54 (0.32)	0.62 (0.39 - 0.98)	ns
Women	39 (0.20)	35 (0.18)	1.01 (0.62 - 1.65)	
Active substance				
Olanzapine	20 (0.05)	35 (0.10)	0.50 (0.28 - 0.89)	

* Adjusted for atopic dermatitis, contact dermatitis, hypothyroidism, neurotic and affective disorders, use of nonsteroidal anti-inflammatory drugs, selective serotonin re-uptake inhibitors, benzodiazepines, body mass index, smoking, and antipsychotics not under investigation

OR = odds ratio; CI = confidence interval; ns = not significant

Number of patients (for calculation of proportions): cases / controls

Age <40: 15,324 / 15,327; **≥40**: 21,378 / 21,375; **Age <60**: 26,486 / 26,495; **≥60**: 10,216 / 10,207; **men**: 16,969 / 16,969; **women:** 19,733 / 19,733; **total:** 36,702 / 36,702

We conducted various sensitivity analyses. First, we ran the two final models (adjusted and mutually exclusive use of lithium or antipsychotics) in a subgroup of case patients with high validity of the psoriasis diagnosis (n = 20,726) defined as those who received calcipotriol, coal tar, dithranol, tazarotene, or acitretin in the first year after the psoriasis diagnosis. Second, to increase the likelihood of detecting incident psoriasis, we restricted an analysis to psoriasis cases (n = 29,170) who did not have any prescriptions recorded for any of the five drugs mentioned previously (calcipotriol, coal tar, dithranol, tazarotene, or acitretin) at any time prior to the first-time psoriasis diagnosis. Third, we combined these two requirements and ran an analysis which encompassed 15,336 case patients. Fourth, we conducted a number of analyses restricted to patients who did not have certain skin diseases ([1] without allergic skin disease or contact or atopic dermatitis, [2] without skin infections, and [3] without any of the diagnoses mentioned previously) before their psoriasis diagnosis because their conditions may have been more likely to have been misdiagnosed as psoriasis. In all these subgroups, the findings related to use of lithium or antipsychotics remained virtually unchanged (data not shown).

3.2.5 Discussion

The findings of this large population-based case-control analysis support the hypothesis that long-term use of lithium increases the risk of developing a first-time psoriasis diagnosis.

Psoriasis has been associated with substantial psychiatric comorbidity such as stress,[88] anxiety, or depression, but the temporal association between these disorders is inconclusive.[132] We found an increased psoriasis risk for patients with a first psychiatric diagnosis within 60 days prior to the psoriasis diagnosis date. The use of SSRIs[87, 159, 160] and benzodiazepines[78, 87] has been associated with psoriasis in case reports or one small observational study or both; we did not find a suggestion of an increased psoriasis risk for current long-term use of SSRIs or benzodiazepines.

Aside from beta-blockers, lithium is one of the drugs most commonly associated with triggering or inducing psoriasis. However, both for beta-blockers and lithium, observations are mainly based on case reports and case series, and the causal association between drug use and development of the disease has been questioned.[87] In a recent case-control analysis using data from the same database, we found no evidence for a substantially altered psoriasis risk for users of beta-

blockers.[155] The current study, however, provides evidence that long-term (≥5 prescriptions) therapy with lithium increases the risk of developing psoriasis.

Although the two most commonly reported skin reactions possibly related to the use of lithium were acne and psoriasis in case reports and controlled trials, there have been few studies exploring the histology of such skin reactions.[87, 95, 96] Furthermore, the reaction has not always been dose-related,[87] and it has been suspected that some of the reports were psoriasiform drug eruptions rather than true psoriasis.[87, 95-97] However, elevated lithium plasma concentrations have been reported for psoriasis patients without any treatment history with this compound, originating possibly from the lithosphere or mineral water springs, and the clinical picture of lithium-associated psoriasis is very similar to idiopathic psoriasis without different histological findings.[95, 97] Although various possible mechanisms have been described to explain how lithium may induce or exacerbate psoriasis, the exact mechanism is not known, and it has even been suggested that the mechanisms for regular and lithium-induced psoriasis may not be the same.[143, 161]

In a small interview-based study, the authors found a higher incidence of cutaneous reactions (only two cases with psoriasis) after exposure to lithium, but only in female patients. Furthermore, the only two patients in this study who developed psoriasis after exposure to lithium were older than 50 years.[154] These observations are supported by our data which suggest an increased risk mainly in female patients older than 40 years (where a test for interaction by sex did not reach statistical significance). As the lithium mechanism on psoriasis is largely unknown, it is difficult to interpret these observations. Increased skin consciousness of women and patients ≥40 years of age may be a possible explanation. The age effect could also be explained by the reported heterogeneity of psoriasis, that is, psoriasis type I with early onset (<40 years of age) and type II with late onset (≥40 years of age).[68]

We also observed a reduced relative risk of developing a first-time psoriasis diagnosis for current users of ≥5 prescriptions of atypical antipsychotics, whereby olanzapine primarily accounted for the reduced psoriasis risk observed for atypical antipsychotics. This may be explained by an effect of antipsychotics on cytokines,[162] which play a major role in the pathomechanism of psoriasis.

Sex differences in pharmacokinetic properties and adverse effect profiles have been described for atypical antipsychotics.[163] Although the test for interaction by sex did not reach statistical significance in our study, there was evidence for a possibly

reduced psoriasis risk for men using atypical antipsychotics, a finding which may deserve attention in future studies.

We cannot exclude the possibility of some misclassification of outcome, that is, some people classified as cases may not have psoriasis. Gelfand et al. reported a high validity of psoriasis diagnoses in the GPRD.[115, 139, 147] In our study, we conducted various sensitivity analyses which left the findings virtually unchanged suggesting that misclassification does not account for our findings.

Although we tested a large number of potential confounding factors and included the most relevant ones in our model, we cannot exclude the possibility that other unknown confounders or biases may have affected our results to some degree. As stress has been reported to be a risk factor for psoriasis, it is possible that a stressful psychiatric crisis may be responsible for the induction of psoriasis rather than the treatment with lithium. However, this does not seem to be likely because we would then expect to see an increased psoriasis risk also for short-term lithium users, which was not the case, and we may also expect an increased risk for other classes of antipsychotics, which we did not see. Furthermore, our analysis was adjusted for diagnosed affective and neurotic disorders.

As we explored the association between use of lithium and antipsychotic drugs and the risk of developing a first-time diagnosis of psoriasis, we cannot make a statement about the effect of lithium exposure on the risk of exacerbation of pre-existing psoriasis.

In summary, we explored the association between the use of lithium or antipsychotics and the risk of new-onset psoriasis in this, to the best of our knowledge, first large population-based case-control analysis. The findings provide further evidence that the use of lithium may increase the risk of developing a first-time psoriasis diagnosis, particularly with long-term exposure. Furthermore, the suggested protective effect of long-term olanzapine use on psoriasis risk has not been reported so far and merits further investigation.

3.3 ASSOCIATION BETWEEN USE OF THIAZOLIDINEDIONES OR OTHER ORAL ANTIDIABETICS AND PSORIASIS: A POPULATION-BASED CASE-CONTROL STUDY

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3.3.1 Abstract

Background: Small clinical trials suggest that thiazolidinediones may exert a beneficial effect on skin lesions of patients with psoriasis. Little is known about other classes of antidiabetic drugs and the psoriasis risk.

Objective: We sought to study the association between use of thiazolidinediones, sulfonylureas, biguanides, or acarbose and the risk of developing a first-time diagnosis of psoriasis.

*Methods***:** We conducted a case-control analysis on the UK-based GPRD. We identified patients with an incident psoriasis diagnosis from 1994 to 2005 and matched one control subject to each patient on age, sex, general practice, calendar time, and years of history in the database. Conditional logistic regression was used to estimate the ORs with 95% CIs of developing a first-time psoriasis diagnosis in relation to previous exposure to antidiabetic drugs, stratified by exposure timing and duration of use and adjusted for a variety of potential confounders.

*Results***:** We identified 36,702 patients with a first-time psoriasis diagnosis and the same number of matched control subjects. As compared with no use, the adjusted ORs for current use of 1 to 4 prescriptions or ≥5 prescriptions for thiazolidinediones were 1.01 (95% CI 0.34-3.01) and 0.33 (95% CI 0.16-0.66), respectively. Current use of ≥15 prescriptions for metformin or sulfonylureas yielded adjusted ORs of 0.77 (95% CI 0.62-0.96) and 1.07 (95% CI 0.88-1.31), respectively.

*Limitations***:** The findings are based on a small number of patients exposed to thiazolidinediones (100 in total, 48 current users of ≥5 prescriptions).

*Conclusions***:** The findings of this large observational study provide further evidence for a potentially beneficial effect of thiazolidinediones on psoriasis. While current long-term use of metformin was also associated with a suggestion of a reduced psoriasis risk, no such effect was seen for use of other oral antidiabetics.

3.3.2 Background

Psoriasis is a common autoimmune skin disease with an estimated prevalence between 0.6% and 4.8% or even higher for certain regions.[62, 63] In a recent study on the GPRD, Gelfand et al.[139] reported a prevalence rate of 1.5% in the UK. The disease is characterised by T cell-mediated hyperproliferation of keratinocytes and inflammatory processes based on a complex genetic background.[46] Thiazolidinediones, also called peroxisome proliferator-activated receptor (PPAR)-γ agonists because of their action at the nuclear hormone receptor PPAR-γ, are relatively new drugs for the treatment of type 2 diabetes mellitus. The thiazolidinediones pioglitazone, rosiglitazone, and troglitazone have anti-inflammatory and antiproliferative effects in malignant and nonmalignant human cells including keratinocytes.[164] Human keratinocytes express messenger RNA and protein for the nuclear hormone receptor PPAR-γ. Furthermore, PPAR-γ messenger RNA expression was found in human peripheral blood T lymphocytes, and it could be shown that PPAR-γ ligands inhibited IL-2 production in a dose-dependent manner.[165, 166] IL-2 plays an essential role in controlling T cell proliferation, an early step in the pathogenesis of psoriasis.[167] An important role of PPAR-γ in immunoregulation was proposed, even though some of the anti-inflammatory effects of thiazolidinediones may be independent from PPAR-γ.[168, 169]

Potential clinical benefits of thiazolidinediones were documented in small open-label studies on up to 10 patients with psoriasis[164, 165, 170] and in a prospective, randomised, double-blind study involving 45 patients exposed to pioglitazone and 25 patients exposed to placebo, in which a dose-dependent beneficial effect of pioglitazone on psoriasis symptoms was observed.[171] In addition, rosiglitazone at 2, 4, or 8 mg/d showed some improvement of psoriasis symptoms in individual patients, even though the overall effects did not differ significantly from placebo in two larger double-blind placebo-controlled studies conducted by the manufacturer.[172] The authors of a recent review article emphasised that neither the potential clinical effectiveness of this drug class in psoriasis, nor a possible mechanism of action are fully understood yet.[173]

Little information is available on the association between other classes of oral antidiabetic drugs and psoriasis. Psoriasiform drug eruptions have been reported in two cases, one related to the biguanide metformin and one to the sulfonylurea

glibenclamide.[174, 175] On the other hand, two patients were described in the 1970s whose psoriasis improved while being treated with the biguanide phenformin.[176]
To our knowledge no studies have been published exploring the association between use of thiazolidinediones and risk of developing an incident psoriasis diagnosis. We, therefore, conducted a large population-based case-control study to evaluate the association between use of thiazolidinediones or other oral antidiabetics and the risk of developing a first-time psoriasis diagnosis.

3.3.3 Methods

We conducted a matched case-control analysis to explore the risk of developing a first-time psoriasis diagnosis in relation to a prevalent diabetes diagnosis and to previous use of thiazolidinediones, the biguanide derivative metformin, sulfonylureas, or acarbose within the GPRD.

Data Source: GPRD

The GPRD is a large UK-based database established around 1987 that encompasses some five million patients who are enrolled with selected GPs. The GPs have agreed to provide data for research purposes to the GPRD and receive a small fee for their service. GPs have been trained to record medical information in a standard manner and to supply it anonymously. Data are collected on a daily basis, independent of any potential study question. Practice-based measures are applied to derive the practice up-to-standard. The patients enrolled in the GPRD are representative for the UK with regard to age, sex, geographic distribution, and annual turnover rate. The information recorded includes patient demographics and characteristics (e.g. age, sex, height, weight, smoking status), symptoms, medical diagnoses, referrals to consultants, hospitalisations, and all drug prescriptions because the doctors generate prescriptions directly with the computer using a coded drug dictionary. Prescriptions contain the name of the preparation (active compound), the route of administration, the dose of a single unit, the number of units prescribed, and, in most instances, the intake regimen prescribed by the GPs. Hospital discharge and referral letters are available for review to validate the diagnoses recorded in the computer record.[31, 36, 37, 177] This database, which has been described in detail elsewhere[31, 37] and validated extensively,[32-34] has been the source for numerous published epidemiological studies. Studies on psoriasis using GPRD data have been

published recently.[103, 108, 115, 116, 139, 147] For the current study, we selected all patients from active general practices that were up-to-standard in the study period.
The study protocol was approved by ISAC for MHRA database research.

Case definition and ascertainment

We identified patients with a first-time diagnosis of psoriasis between 1 January 1994 and 31 December 2005 via OXMIS or Read codes. Patients with less than three years of active history in the database before the first-time diagnosis of psoriasis and patients with a code for history of psoriasis were not included.
The validity of psoriasis diagnoses in the GPRD has been examined by Gelfand et al.[108, 115, 116, 139, 147] and Neimann et al.[103] who have recently published several GPRD-based studies on psoriasis. They have shown that the epidemiology of psoriasis in the GPRD is similar to data from other population-based studies in the UK and that 92% of patients with a psoriasis code receive psoriasis therapies.[115, 139] In addition, among a random sample of 100 GPs who recorded a diagnostic code for psoriasis, approximately 90% confirmed the diagnosis after four years of follow-up.[147]

Control subjects

We identified at random one control subject per patient with psoriasis, matched on calendar time (same index date), age (same year of birth), sex, general practice, and years of history in the GPRD. Thus, control subjects were also required to have at least three years of active history in the GPRD.

Exposure to oral antidiabetics

For each patient and control subject we assessed from the computer record the exposure to thiazolidinediones, metformin, sulfonylureas, and acarbose before the index date. Patients were classified as current users of a study drug if the last prescription was recorded within 89 days prior to the index date or as past users if the last prescription was recorded ≥90 days before the index date. We also assessed the duration of use before the index date, using the number of prescriptions as proxy (1-4, 5-14, or ≥15 prescriptions for sulfonylureas and metformin and 1-4 or ≥5 prescriptions for thiazolidinediones and acarbose; we used two categories only for the latter two because of a smaller number of users). In addition, we also classified

participants according to a combination of number of prescriptions and timing of the last prescription.

For the main analysis we created a model in which we compared use of oral antidiabetic drugs with nonusers, whereby use of more than one oral antidiabetic drug before the index date was possible. We adjusted for such sequential or concurrent use of various antidiabetics in the multivariate model. In addition, we also ran a model in which participants were categorised into mutually exclusive groups of users of thiazolidinediones only, sulfonylureas only, metformin only, acarbose only, or any combination of these antidiabetics (switchers or combined use) and compared them with nonusers of any antidiabetic drugs. However, as the number of exposed patients with thiazolidinediones or acarbose was small, this model was only used as sensitivity analysis to confirm findings of the main analysis.

Statistical analysis

We conducted conditional logistic regression analyses using statistical software (SAS, version 9.1, SAS Institute Inc, Cary, NC, U.S.A.). We displayed relative risk estimates as OR with 95% CI. We adjusted ORs for the potential confounders age, sex, practice, calendar time, and years of recorded history in the database by matching, and for smoking status (non, current, ex, or unknown) and BMI (<18.5, 18.5-24.9, 25.0-29.9, ≥30 kg/m^2, or unknown) in the multivariate model. Additional potential confounders were tested in univariate analyses; if they were statistically significantly associated with psoriasis they were entered in the final model in which we explored the association between antidiabetic drug use and psoriasis. If they changed the relative risk estimate of interest by 10% or more, they were part of the final model. Thus, the risk estimates were further adjusted for a history of diagnosed atopic dermatitis, skin infections, other infections such as candidiasis, aspergillosis, cellulitis, abscess, lymphadenitis, or empyema, affective disorders, ischaemic heart disease, hyperlipidaemia, use of terbinafine (1-4 or ≥5 prescriptions), use of antimycotics (1 or ≥2 prescriptions), use of coronary vasodilators (1-9 or ≥10 prescriptions), use of prandial glucose regulators (glinides, 1-4 or ≥5 prescriptions), and use of insulin (current 1-9 or ≥10 prescriptions, past 1-9 or ≥10 prescriptions). Potential confounding was also tested for a number of other covariates that were not included in the final model because they were not materially associated with the exposure or the outcome, such as allergic skin disease, allergic rhinoconjunctivitis,

asthma, congestive heart failure, contact dermatitis, urticaria and/or angio-oedema, hypertension, stroke/TIA, tonsillectomy, respiratory infections, viral infections, hyper- or hypothyroidism, alcoholism, gout, epilepsy, neurosis, inflammatory bowel disease, rheumatoid arthritis, COPD, use of various antidepressants, antihistamines, benzodiazepines, beta-agonists, cardiac glycosides, NSAIDs, paracetamol, cyclooxygenase-2-inhibitors, lipid-lowering agents, levothyroxine, carbimazole, antihypertensive agents, antibiotics, or antivirals.

3.3.4 Results

We identified 36,702 patients with a first-time diagnosis of psoriasis between 1 January 1994 and 31 December 2005 and the exact same number of matched control subjects. Table 3.3.1 displays the age and sex distribution and the distribution of smoking status, BMI, and various comorbidities of patients and control subjects. The study population encompassed 53.8% women, and 41.7% of patients were younger than 40 years at the time of the diagnosis. Current smoking was associated with a statistically significantly increased psoriasis risk (OR 1.52, 95% CI 1.46-1.58), as was a BMI ≥30 kg/m^2 (OR 1.34, 95% CI 1.27-1.41), as compared with the reference group of non smokers and patients of normal weight, respectively.

Table 3.3.1 Characteristics of case patients with psoriasis and matched controls

Variable	Cases No (%) (n = 36,702)		Controls No (%) (n = 36,702)		Adjusted OR* (95% CI)	
Sex**						
Men	16,969	(46.2)	16,969	(46.2)	-	-
Women	19,733	(53.8)	19,733	(53.8)	-	-
Agegroup (years)**						
<20	5801	(15.8)	5801	(15.8)	-	-
20-29	4336	(11.8)	4339	(11.8)	-	-
30-39	5187	(14.1)	5187	(14.1)	-	-
40-49	5173	(14.1)	5171	(14.1)	-	-
50-59	5989	(16.3)	5997	(16.3)	-	-
60-69	5109	(13.9)	5102	(13.9)	-	-
≥70	5107	(13.9)	5105	(13.9)	-	-

Table 3.3.1 (cont.)

Variable	Cases No (%) (n = 36,702)	Controls No (%) (n = 36,702)	OR adjusted* (95% CI)
Smoking status			
Non smoker	13,390 (36.5)	15,594 (42.5)	1.00 (reference)
Current smoker	8787 (23.9)	6913 (18.8)	1.52 (1.46 - 1.58)
Ex smoker	4690 (12.8)	3763 (10.3)	1.44 (1.36 - 1.52)
Unknown	9835 (26.8)	10,432 (28.4)	1.11 (1.04 - 1.17)
BMI (kg/m^2)			
12-18.4	523 (1.4)	574 (1.6)	0.94 (0.83 - 1.06)
18.5-24.9	10,244 (27.9)	10,887 (29.7)	1.00 (reference)
25-29.9	8330 (22.7)	7934 (21.6)	1.13 (1.08 - 1.18)
30-60	4881 (13.3)	3882 (10.6)	1.34 (1.27 - 1.41)
Unknown	12,724 (34.7)	13,425 (36.6)	1.00 (0.95 - 1.05)
Comorbidities			
IHD	2587 (7.1)	2232 (6.1)	1.00 (0.91 - 1.09)
Hyperlipidaemia	2169 (5.9)	1950 (5.3)	1.05 (0.98 - 1.13)
Atopic dermatitis	2092 (5.7)	1042 (2.8)	2.06 (1.90 - 2.23)
Infections	11,068 (30.2)	9153 (24.9)	1.21 (1.17 - 1.25)
Skin infections	10,450 (28.5)	7388 (20.1)	1.46 (1.41 - 1.52)
Affective disorder	5931 (16.2)	5158 (14.1)	1.10 (1.05 - 1.15)

* Adjusted for all covariates listed in the table plus use of coronary vasodilatators, terbinafine, antimycotics, prandial glucose regulators, and insulin; ** Matching variables

Percentages may not sum to 100% due of rounding

BMI = body mass index; IHD = ischaemic heart disease; OR = odds ratio; CI = confidence interval

Table 3.3.2 displays the prevalence of treated and untreated diabetes in patients with psoriasis and control subjects. The relative risk estimates of developing psoriasis among users of sulfonylureas or acarbose were close to one (data not shown). On the other hand, we found adjusted ORs of 0.44 (95% CI 0.25-0.78) and 1.00 (95% CI 0.49-2.05) for current and past thiazolidinedione use, respectively, as compared with nonuse. The ORs for current and past biguanide use were 0.82 (95% CI 0.69-0.97) and 0.70 (95% CI 0.52-0.94), respectively.

Table 3.3.2 Prevalence of treated or untreated diabetes before the index date

	Cases No (%) (n = 36,702)	Controls No (%) (n = 36,702)	Unadjusted OR (95% CI)	Adjusted OR* (95% CI)
No diabetes	35,347 (96.3)	35,408 (96.5)	1.00 (reference)	1.00 (reference)
Diabetes	1355 (3.69)	1294 (3.53)	1.05 (0.97 - 1.14)	0.89 (0.81 - 0.96)
No treatment	368 (1.00)	313 (0.85)	1.18 (1.01 - 1.37)	1.01 (0.86 - 1.18)
Treatment	987 (2.69)	981 (2.67)	1.01 (0.92 - 1.11)	0.85 (0.77 - 0.93)
oral only	640 (1.74)	648 (1.77)	0.99 (0.89 - 1.11)	0.83 (0.74 - 0.93)
insulin only	171 (0.47)	188 (0.51)	0.91 (0.74 - 1.12)	0.83 (0.67 - 1.02)
combination	176 (0.48)	145 (0.40)	1.22 (0.98 - 1.53)	0.95 (0.75 - 1.20)

* Adjusted for atopic dermatitis, skin infections, infections such as candidiasis, aspergillosis, cellulitis, abscess, lymphadenitis, and empyema, use of terbinafine and antimycotics, affective disorders, ischaemic heart disease, hyperlipidaemia, use of coronary vasodilatators, body mass index, and smoking; OR = odds ratio; CI = confidence interval

Table 3.3.3 displays the results for duration combined with timing of use. The adjusted OR for current use of ≥5 thiazolidinedione prescriptions compared with no use was 0.33 (95% CI 0.16-0.66), and for current use of ≥15 metformin prescriptions compared with no use the OR was 0.77 (95% CI 0.62-0.96). Further stratification of current thiazolidinedione users of ≥5 prescriptions by individual drug yielded adjusted ORs of 0.29 (95% CI 0.13-0.66; based on 8 exposed patients and 29 control subjects) for rosiglitazone and of 0.45 (95% CI 0.13-1.60; based on 4 exposed patients and 7 control subjects) for pioglitazone.

Table 3.3.3 Risk of first-time psoriasis diagnosis associated with use of antidiabetics

Exposure (No of Rx)	Cases No (%) (n = 36,702)	Controls No (%) (n = 36,702)	Unadjusted OR (95% CI)	Adjusted OR* (95% CI)
Thiazoli-dinediones				
nonuse	36,662 (99.9)	36,642 (99.8)	1.00 (reference)	1.00 (reference)
current				
1-4	8 (0.02)	7 (0.02)	1.14 (0.41 - 3.15)	1.01 (0.34 - 3.01)
≥5	12 (0.03)	36 (0.10)	0.33 (0.17 - 0.64)	0.33 (0.16 - 0.66)
past				
1-4	9 (0.02)	6 (0.02)	1.50 (0.53 - 4.23)	1.21 (0.41 - 3.60)
≥5	11 (0.03)	11 (0.03)	1.02 (0.44 - 2.35)	0.93 (0.38 - 2.31)

Table 3.3.3 (cont.)

Exposure (No of Rx)	Cases No (%) (n = 36,702)	Controls No (%) (n = 36,702)	Unadjusted OR (95% CI)	Adjusted OR* (95% CI)
Biguanides				
nonuse	36,127 (98.4)	36,115 (98.4)	1.00 (reference)	1.00 (reference)
current				
1-4	54 (0.15)	51 (0.14)	1.05 (0.72 - 1.54)	0.87 (0.58 - 1.31)
5-14	107 (0.29)	101 (0.28)	1.06 (0.81 - 1.39)	0.86 (0.64 - 1.15)
≥15	280 (0.76)	283 (0.77)	0.99 (0.84 - 1.17)	0.77 (0.62 - 0.96)
past				
1-4	53 (0.14)	50 (0.14)	1.06 (0.72 - 1.56)	0.88 (0.57 - 1.36)
5-14	29 (0.08)	40 (0.11)	0.73 (0.45 - 1.17)	0.66 (0.39 - 1.11)
≥15	52 (0.14)	62 (0.17)	0.84 (0.58 - 1.21)	0.58 (0.37 - 0.91)
Sulfonyl-ureas				
nonuse	36,064 (98.3)	36,090 (98.3)	1.00 (reference)	1.00 (reference)
current				
1-4	41 (0.11)	35 (0.10)	1.17 (0.74 - 1.83)	1.13 (0.71 - 1.82)
5-14	74 (0.20)	79 (0.22)	0.94 (0.68 - 1.29)	0.92 (0.66 - 1.29)
≥15	311 (0.85)	296 (0.81)	1.05 (0.90 - 1.24)	1.07 (0.88 - 1.31)
past				
1-4	61 (0.17)	41 (0.11)	1.49 (1.00 - 2.21)	1.50 (0.98 - 2.30)
5-14	37 (0.10)	52 (0.14)	0.71 (0.47 - 1.09)	0.72 (0.45 - 1.15)
≥15	114 (0.31)	109 (0.30)	1.05 (0.81 - 1.36)	1.24 (0.87 - 1.76)
Acarbose				
nonuse	36,654 (99.9)	36,645 (99.8)	1.00 (reference)	1.00 (reference)
current				
1-4	4 (0.01)	6 (0.02)	0.67 (0.19 - 2.36)	0.59 (0.15 - 2.22)
≥5	14 (0.04)	10 (0.03)	1.38 (0.61 - 3.10)	1.33 (0.56 - 3.16)
past				
1-4	16 (0.04)	25 (0.07)	0.65 (0.34 - 1.21)	0.58 (0.29 - 1.14)
≥5	14 (0.04)	16 (0.04)	0.88 (0.43 - 1.79)	0.86 (0.40 - 1.87)

* Adjusted for atopic dermatitis, skin infections, infections such as candidiasis, aspergillosis, cellulitis, abscess, lymphadenitis, and empyema, use of terbinafine and antimycotics, affective disorders, ischaemic heart disease, hyperlipidaemia, use of coronary vasodilatators, use of insulin and prandial glucose regulators, body mass index, smoking, and antidiabetics not under investigation

Rx = prescriptions; OR = odds ratio; CI = confidence interval

Stratification of the final model by age (<40 vs. ≥40 years) did not suggest effect modification, whereby the number of exposed subjects in the younger age group was rather low. Stratification by sex yielded an OR of 0.20 (95% CI 0.07-0.59) for female and of 0.49 (95% CI 0.19-1.25) for male current users of ≥5 thiazolidinedione prescriptions (P >.1). Current metformin exposure of ≥15 prescriptions yielded an

adjusted OR of 0.56 (95% CI, 0.41-0.76) for male and of 1.10 (95% CI 0.80-1.51) for female participants (P <.05).

We further conducted various sensitivity analyses. First, we ran the final model in a subgroup of 20,726 patients (and their control subjects) who were treated with calcipotriol, coal tar, dithranol, tazarotene, or acitretin in the first year after their psoriasis diagnosis, a pharmacologically treated subgroup of psoriasis patients who were likely to have a confirmed psoriasis diagnosis. The adjusted ORs for current users of ≥5 thiazolidinedione or ≥15 metformin prescriptions were 0.28 (95% CI 0.11-0.73; based on 6 exposed patients and 22 control subjects) and 0.71 (95% CI 0.54-0.95; based on 159 exposed patients and 168 control subjects), respectively. Second, we restricted an analysis to 29,170 patients with psoriasis (and their control subjects) who did not have any prescriptions recorded for any of the five medications mentioned above at any time before the first-time psoriasis diagnosis. The date of the first-time recording of a disease such as psoriasis in a large primary care database is unlikely to be the exact date of the first disease manifestation; the onset of the disease and, therefore, the correct index date occurred in reality some time before. Thus, to reduce the risk of including patients with a long-term psoriasis history, only patients without evidence of previous treatment were eligible for this analysis. The adjusted ORs for current use of ≥5 prescriptions for thiazolidinediones or ≥15 prescriptions for metformin were 0.42 (95% CI 0.19-0.92; based on 10 exposed patients and 25 control subjects) and OR 0.78 (95% CI 0.61-1.01; based on 192 exposed patients and 208 control subjects), respectively. Third, we ran the final model in 15,336 patients with psoriasis (and their control subjects) who had both received treatment with calcipotriol, coal tar, dithranol, tazarotene, or acitretin in the first year after their psoriasis diagnosis and did not have any of these drugs at any time before the index date. In this subgroup, current use of ≥5 thiazolidinedione prescriptions or ≥15 metformin prescriptions yielded adjusted ORs of 0.50 (95% CI 0.17-1.53; based on 5 exposed patients and 12 control subjects) and 0.68 (95% CI 0.48-0.97; based on 96 exposed patients and 113 control subjects), respectively. Fourth, we ran the final model in 18,798 patients with psoriasis (and their control subjects) whose index date was in the year 2000 or thereafter, i.e., when all antidiabetics of interest were on the market. Current use of ≥5 thiazolidinedione prescriptions or ≥15 metformin prescriptions yielded adjusted ORs of 0.30 (95% CI 0.15-0.60; based on 12 exposed patients and 36 control subjects) and 0.84 (95% CI

0.64-1.10; based on 206 exposed patients and 188 control subjects), respectively. Finally, we conducted another model in patients with diabetes only whose index date was in the year 2000 or later, which yielded closely similar results (adjusted OR for current use of ≥5 thiazolidinedione prescriptions 0.45, 95% CI 0.25 – 0.81).

3.3.5 Discussion

The findings of this large population-based case-control analysis support the hypothesis of a possible beneficial effect of thiazolidinediones in psoriasis in patients with an existing diabetes diagnosis, as previously observed in small clinical trials.

We found a statistically significantly decreased risk of developing a first-time psoriasis diagnosis in current users of ≥5 thiazolidinedione prescriptions (reflecting a treatment duration of approximately one year), suggesting a possible effect of this drug class on the risk of developing psoriasis. While previous studies investigated a possible effect of thiazolidinediones as therapeutic agents for patients with manifest psoriasis, we conducted the (to our knowledge) first published retrospective case-control study on the association between use of these drugs and the risk of developing a first-time psoriasis diagnosis.

There are few and inconclusive data on a possible association between use of metformin and psoriasis in the literature because potentially beneficial and negative drug effects have been described.[174, 176] We found a suggestion of a reduced risk for current metformin use of ≥15 prescriptions of 0.77 (95% CI 0.62-0.96), whereas the OR for past use of ≥15 prescriptions was even lower (0.58, 95% CI 0.37-0.91). While the crude ORs of both current and past longer-term use of metformin were around one, the risk estimates decreased below one after adjusting for BMI, use of other oral antidiabetics, and smoking. Metformin is often used in overweight diabetics and often in combination with other antidiabetics such as thiazolidinediones. The OR for current use of ≥15 prescriptions for metformin users only in the model in which we used mutually exclusive exposure groups was also 0.73 (95% CI 0.52-1.04), based on 69 exposed patients and 71 control subjects. However, the low OR of past use of ≥15 prescriptions for metformin is not easy to explain. Possible explanations are a chance finding or a causal association with a metformin effect lasting beyond the actual exposure. As opposed to the similar thiazolidinedione findings in both men and women, we found different relative risks for male or female metformin users, with an

OR below one only for male users. To our knowledge there are no studies published in the literature on the mechanism by which biguanides might affect psoriasis. However, thiazolidinediones and biguanides share a common effect on the adenosine 5'-monophosphate-activated protein kinase that was hypothesised to be dysregulated in patients with the metabolic syndrome (insulin resistance, obesity, and a predisposition to hypertension, dyslipidaemia, pancreatic β-cell dysfunction, type 2 diabetes mellitus, and premature atherosclerosis).[178] Findings of a possible anti-inflammatory effect seem to be inconclusive.[179]

Diabetes has been associated with psoriasis in several hospital- and population-based studies[86, 102-106] with a higher diabetes prevalence in patients with severe psoriasis[103] possibly as a result of therapy with corticosteroids[105] or chronic inflammation and the production of pro-inflammatory cytokines.[106] In the current study population, the diabetes prevalence was not higher in patients with psoriasis at the time of the first psoriasis diagnosis as compared with control subjects without psoriasis. On the contrary, diabetes treated with certain oral antidiabetics was associated with a lower psoriasis risk.

Our study population included patients and control subjects between 1994 and 2005, thus also a time period in which thiazolidinediones, in contrast to sulfonlyureas, metformin, and other oral antidiabetics, were not yet available on the market. In addition, we did not restrict our study to diabetics only. We, therefore, ran a sensitivity analysis in which we restricted the study to patients and control subjects with diabetes and to those with index date in the year 2000 or thereafter. The association between use of thiazolidinediones or other oral antidiabetics and the risk of developing psoriasis remained virtually unchanged.

A limitation of our study is that there were only 48 patients who were current users of thiazolidinediones with 5 or more prescriptions recorded (0.065% of the study population) and only 63 current users in total. This led to analyses with limited power, particularly after stratification into subgroups. Future studies in the GPRD and in other databases will have more power because use of thiazolidinediones is increasing. Nevertheless, the observed reduced psoriasis risk associated with current use of thiazolidinediones is an intriguing finding that reached statistical significance despite the rather low exposure prevalence.

Another limitation is the fact that there may be some misclassification of diagnosis, leading to the inclusion of patients who did not have psoriasis. In addition, the index

date for chronic diseases without acute onset is often not precisely recorded in large databases, leading to a certain degree of exposure misclassification. However, Gelfand et al.[115, 139, 147] used the GPRD to study patients with psoriasis in previous studies, and their validation procedure documented that psoriasis diagnoses in the GPRD are in general of high validity. We conducted various sensitivity analyses to improve the validity of our findings; the risk estimates in these analyses were closely similar to the ones seen in the entire case-control set. In addition, our analyses are based on GP-recorded prescriptions, but not on the patients' actual drug intake, which is of course not known.

We further tested a large number of potential confounders and included the most relevant ones in our model, but, as in all observational studies, we cannot exclude the possibility that unidentified confounders or biases may have distorted the results to some degree. We did not have information on smoking status and BMI for approximately a third of all patients and control subjects. Including a category of missing values in an analysis can introduce distortion if this parameter is indeed a confounder of the main exposure – outcome association. In this case, however, neither smoking nor BMI confounded the association between use of thiazolidinediones and the risk of developing psoriasis, as we explored in several sensitivity analyses, and so the issue of some missing smoking and BMI values is not relevant. We further ran a model restricted to those patients and controls subjects with known values only, which left the result unchanged.

Furthermore, we were not in a position to explore the risk of antidiabetic drug use on psoriasis in patients without diabetes because the antidiabetic drugs are currently used only in patients with diabetes.

In summary, this population-based case-control study provides evidence that use of thiazolidinediones may reduce the risk of developing a psoriasis diagnosis. These findings are consistent with previous observations from small randomised studies in which patients with psoriasis benefited from therapy with thiazolidinediones. These findings and the somehow inconclusive findings for metformin need to be confirmed by further studies to learn more about the effect of oral antidiabetics on psoriasis and to further elucidate the possible mechanism of antidiabetic drugs on psoriasis.

3.4 PSORIASIS AND THE RISK OF INCIDENT DIABETES MELLITUS: A POPULATION-BASED STUDY

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3.4.1 Abstract

Background: Cross-sectional studies, mostly in hospitalised patients, reported a possible positive association between psoriasis and diabetes mellitus. However, information on the temporal relation is scarce, and incidence rates of new-onset diabetes mellitus in patients with psoriasis are lacking.

Objective: To assess and compare incidence rates of new-onset diabetes mellitus between patients with psoriasis and a comparison group without psoriasis and to explore the role of psoriasis severity and BMI.

Methods: We conducted a follow-up study with a nested case-control analysis within the UK-based GPRD. The study population consisted of patients with a first-time diagnosis of psoriasis between 1994 and 2005 and a matched group of psoriasis-free patients. We used psoriasis duration and treatment as proxy for disease severity, and we applied conditional logistic regression to obtain ORs with 95% CIs.

Results: Within the study population of 65,449 patients we identified 1061 incident cases of diabetes mellitus. Of these, 59% had a history of psoriasis, yielding a crude IRR of 1.36 (95% CI 1.20-1.53). The adjusted OR for patients with ≥2 years disease duration and >2 prescriptions per year for oral psoriasis treatment was 2.56 (95% CI 1.11-5.92). In an analysis restricted to patients with normal BMI, the adjusted OR was 2.02 (95% CI 1.31-3.10).

Conclusions: In this large observational study the risk of incident diabetes mellitus was increased for patients with psoriasis as compared with a psoriasis-free comparison group. The risk increased with psoriasis duration and severity and was not driven by high BMI alone.

3.4.2 Background

Psoriasis is an immune-mediated inflammatory skin disease with an estimated prevalence of 1.5% in the UK.[139] The prevalence varies across geographical regions of the world.[63] The disease is characterised by T cell-mediated hyperproliferation of keratinocytes and inflammatory processes based on a complex genetic background. After activation of naïve T cells by antigen-presenting cells, effector/memory T cells mainly of the Th1 and Th17 lineage are generated which produce cytokines such as IL-22, INF-γ, and TNF-β and IL-6, IL-17, and IL-22, respectively. These cytokines, which seem to play a central role in the pathogenesis of psoriasis, can activate keratinocytes directly or via macrophages/dendritic cells leading to increased proliferation of keratinocytes as well as production of other cytokines (e.g. TNF-α) and growth factors which sustain the inflammatory processes.[48] This inflammation is thought to be a reason for an increased cardiovascular risk in patients with psoriasis as is thought to be the case for other diseases with systemic inflammation such as rheumatoid arthritis or lupus erythematosus.[180] Other possible reasons for an altered cardiovascular risk associated with psoriasis are an increased prevalence of smoking and high BMI.[88] Previous studies on comorbidities of psoriasis reported an increased prevalence of diabetes mellitus among patients with psoriasis[86, 102] including one study in which the effect was restricted to women.[86] TNF-α is involved in the pathogenesis of psoriasis and has been shown to induce insulin resistance, and inflammatory processes have also been hypothesised to play a role in the pathogenesis of diabetes mellitus.[181-183] One cross-sectional study in patients with a BMI <30 kg/m^2 did not provide evidence for a material difference in insulin secretion or sensitivity between patients with psoriasis and healthy controls, but a subanalysis related psoriasis duration with decreased insulin sensitivity, and the authors of another study described the metabolic state in patients with psoriasis to be shifted towards insulin resistance.[184, 185] In addition, several epidemiological studies[86, 99, 101-106] reported an increased prevalence of diabetes mellitus or metabolic syndrome (including central obesity, atherogenic dyslipidaemia, hypertension, and glucose intolerance) in patients with psoriasis. However, all of the studies were cross-sectional, and most of them involved hospitalised patients. Furthermore, diabetes mellitus was the primary outcome of interest in only one of these studies.[105]

It was the aim of the present study to elucidate further the association between psoriasis and the risk of developing new-onset diabetes mellitus in a large population-based observational study.

3.4.3 Methods

We conducted a matched follow-up study and a nested case-control analysis to quantify the risk of new-onset diabetes mellitus in patients with psoriasis and to compare it with that in a matched population without psoriasis.

Data source

We used the GPRD, a large UK-based database established around 1987 which encompasses some five million patients who are actively enrolled with selected GPs. The GPs have agreed to provide data for research purposes to the GPRD. GPs have been trained to record medical information in a standard manner and to supply it anonymously. The patients enrolled in the GPRD are representative of the UK with regard to age, sex, geographical distribution, and annual turnover rate. The information recorded includes patient demographics and characteristics (e.g. age, sex, height, weight, smoking status), symptoms, medical diagnoses, referrals to consultants, hospitalisations, and all drug prescriptions, as the doctors generate prescriptions directly with the computer using a coded drug dictionary. Prescriptions contain the name of the preparation (active compound), the route of administration, the dose of a single unit, the number of units prescribed, and, in most instances, the intake regimen prescribed by the GP. This database, which has been described in detail elsewhere[31, 37] and validated extensively,[32-34] has been the source for numerous epidemiological studies published in peer-reviewed journals.

The study protocol was approved by ISAC for the UK MHRA database research.

Study population

The study population consisted of all patients with a first-time diagnosis of psoriasis between 1 January 1994 and 31 December 2005 and of a comparison group of the exact same number of patients free of psoriasis, matched on calendar time (date of the psoriasis diagnosis), age (same year of birth), sex, general practice, and years of history in the GPRD. We excluded patients with less than three years of history in the database prior to the first-time diagnosis of psoriasis (or the corresponding date in

the comparison group). In previous GPRD-based studies on psoriasis, Gelfand et al. documented a high validity of psoriasis diagnoses in the GPRD,[115, 139, 147] and we therefore included all patients with a recorded psoriasis diagnosis in the analyses.

Follow-up and identification of incident diabetes cases

From the study population we excluded all patients with a prevalent diagnosis of diabetes mellitus as well as of cancer or human immunodeficiency virus (HIV) prior to the psoriasis diagnosis (or the corresponding date in the comparison group). We then followed all patients until they developed a first-time diagnosis of diabetes mellitus, died, or follow-up in the medical record ended, whichever came first. The date of the diagnosis of diabetes mellitus will subsequently be referred to as 'index date'. Cases with diabetes mellitus were included in the analyses if they had a first-time diabetes mellitus code recorded plus at least one prescription for an antidiabetic drug such as insulin, sulfonylureas, biguanides, thiazolidinediones, acarbose, glinides, or guar gum within 30 days prior to or at any time after the first-time diagnosis of diabetes mellitus. In addition, patients with a recorded diagnosis of diabetes mellitus who did not receive any drug treatment but who were started on a diet were included. We excluded potential cases who did not fulfil these criteria as well as those who received antidiabetic drugs more than 30 days prior to the first recorded diagnosis of diabetes mellitus, as they were considered to be prevalent rather than incident. We applied these criteria for inclusion or exclusion of potential cases of diabetes mellitus after having manually reviewed a random sample of computer profiles of potential cases of diabetes mellitus.

Nested case-control analysis

To each case patient with an incident diagnosis of diabetes mellitus we matched at random up to four control patients from the study population on age (same year of birth), sex, and calendar time (same index date, i.e. the date when the case developed diabetes mellitus). We applied the same exclusion criteria to controls as we did to cases.

We compared the prevalence of diagnosed psoriasis prior to the index date between cases of diabetes mellitus and controls and stratified patients with psoriasis by severity of disease, thereby taking into account 1) duration of psoriasis (<2 versus ≥2 years), 2) psoriasis treatment (no treatment, topical treatment only [emollients,

salicylic acid, calcipotriol, coal tar, dithranol or tazarotene preparations, or corticosteroids] and/or UV/oral treatment [azathioprine, ciclosporin, methotrexate, acitretin, hydroxyurea, mycophenolate mofetil, or UV/PUVA therapy]) and (3) intensity of psoriasis treatment (no treatment, ≤4 versus >4 prescriptions per year for topical treatment, ≤2 versus >2 prescriptions per year for oral treatment).

Statistical analysis

In the follow-up analysis we assessed person-time for all patients in the study population from the date of first psoriasis diagnosis (or the corresponding date in the comparison group) until a patient developed diabetes mellitus, died, or follow-up in the medical record ended. We assessed the crude IR of a first-time diagnosis of diabetes mellitus among patients with or without psoriasis, stratified by age and sex as well as a crude IRR with 95% CI.

In the nested case-control analysis we conducted conditional logistic regression analyses using the SAS statistical software (version 9.1; SAS Institute Inc, Cary, NC, U.S.A.). We displayed relative risk estimates as OR with 95% CI. The analyses were controlled for the potential confounders age, sex, and calendar time by matching. We further adjusted the ORs for smoking status (non, current, ex, unknown) and BMI (<18.5, 18.5-24.9, 25.0-29.9, ≥30 kg/m^2, unknown) in the multivariate model, as well as for hyperlipidaemia (diagnosis or antihyperlipidaemic treatment recorded), hypertension, use of oral steroids (1-4 or ≥5 prescriptions), and previous infections (candidiasis/aspergillosis, cellulitis). We also tested potential confounding for a number of other covariates which were not included in the final model because they were not materially associated with the exposure or the outcome, such as ischaemic heart disease, congestive heart failure, arrhythmias, cerebrovascular diseases, arterial thrombosis, venous thrombosis, renal failure, schizophrenia, affective disorders, skin infections, respiratory/chest infections, viral infections, and use of aspirin, NSAIDs, antipsychotics, SSRIs, oral contraceptives, and oestrogens.

3.4.4 Results

The initial study population consisted of 73,404 patients, 36,702 with psoriasis and 36,702 psoriasis-free patients in the matched comparison group (16,969 [46.2%] men and 19,733 [53.8%] women). Patients with psoriasis were more likely to be

current (23.9% vs. 18.8%) or ex smokers (12.8% vs. 10.3%), and they tended to have a higher BMI (22.7% vs. 21.6% with BMI 25-29.9 kg/m^2 and 13.3% vs. 10.6% with BMI ≥30 kg/m^2) prior to the first-time psoriasis diagnosis than patients in the comparison group without psoriasis.

Incidence rates of diabetes in the person-time analysis

After the exclusion of patients with prevalent diabetes mellitus, cancer, or HIV, the remaining study population consisted of 65,449 patients (32,593 cases and 32,856 controls). Within this population we identified 1061 cases with an incident diagnosis of diabetes mellitus of whom 626 (59%) had a history of psoriasis and 435 (41%) did not. The IR for diabetes mellitus was 4.06 (95% CI 3.75-4.39) per 1000 py in patients with psoriasis and 2.98 (95% CI 2.72-3.28) per 1000 py in the comparison group without psoriasis, yielding a crude IRR of 1.36 (95% CI 1.20-1.53) for patients with psoriasis compared with the comparison group. The crude IRs and IRRs, stratified by age and sex, are displayed in table 3.4.1.

Table 3.4.1 Incidence rates and incidence rate ratios of diabetes mellitus stratified by age and sex

	Person-years	Cases	IR / 1000 py (95% CI)	IRR (95% CI)
Psoriasis (P)	154,316.1	626	4.06 (3.75 - 4.39)	1.36 (1.20 - 1.53)
No psoriasis (NP)	145,783.8	435	2.98 (2.72 - 3.28)	
Sex				
Men P	71,084.7	332	4.67 (4.20 - 5.20)	1.23 (1.04 - 1.44)
NP	66,270.5	252	3.80 (3.36 - 4.30)	
Women P	83,231.3	294	3.53 (3.15 - 3.96)	1.53 (1.28 - 1.83)
NP	79,513.4	183	2.30 (1.99 - 2.66)	
Age (years)				
0-29 P	40,246.0	18	0.45 (0.28 - 0.71)	2.75 (1.24 - 6.13)
NP	36,928.7	6	0.16 (0.07 - 0.35)	
30-59 P	70,072.0	237	3.38 (2.98 - 3.84)	1.33 (1.09 - 1.61)
NP	65,861.4	168	2.55 (2.19 - 2.97)	
60-79 P	37,008.4	330	8.92 (8.01 - 9.93)	1.43 (1.21 - 1.69)
NP	36,312.4	226	6.22 (5.47 - 7.09)	
80+ P	6989.7	41	5.87 (4.33 - 7.95)	1.12 (0.71 - 1.75)
NP	6681.5	35	5.24 (3.77 - 7.28)	

P = psoriasis; NP = no psoriasis; IR = incidence rate; py = person-years; CI = confidence interval; IRR = incidence rate ratio

Nested case-control analysis

The nested case-control analysis encompassed 1061 incident cases of diabetes mellitus and 4244 matched control patients. The background characteristics of cases and controls are displayed in table 3.4.2.

Table 3.4.2 Background characteristics of diabetes cases and controls in the nested case-control analysis

Variable	Cases No (%) (n = 1061)	Controls No (%) (n = 4244)	Adjusted OR* (95% CI)
Smoking status			
Non smoker	479 (45.2)	1937 (45.6)	1.00 (reference)
Current smoker	197 (18.6)	948 (22.3)	0.97 (0.79 - 1.20)
Ex smoker	271 (25.5)	826 (19.5)	1.10 (0.90 - 1.34)
Unknown	114 (10.7)	533 (12.6)	1.11 (0.82 - 1.51)
BMI (kg/m^2)			
12-18.4	2 (0.2)	49 (1.2)	0.47 (0.11 - 1.99)
18.5-24.9	97 (9.1)	1304 (30.7)	1.00 (reference)
25-29.9	320 (30.2)	1398 (32.9)	3.10 (2.41 - 3.99)
30-60	476 (44.9)	619 (14.6)	9.95 (7.68 - 12.89)
Unknown	166 (15.6)	874 (20.6)	2.53 (1.87 - 3.43)
Comorbidities			
Hypertension	494 (46.6)	1151 (27.1)	1.93 (1.64 - 2.28)
Hyperlipidaemia without treatment	59 (5.6)	206 (4.9)	1.05 (0.75 - 1.47)
Hyperlipidaemia with treatment	230 (21.7)	477 (11.2)	2.13 (1.72 - 2.64)
Infections	419 (39.5)	1331 (31.4)	1.25 (1.06 - 1.47)

*Adjusted for all covariates listed in the table plus use of systemic corticosteroids

BMI = body mass index; OR = odds ratio; CI = confidence interval

Infections include: cellulitis, candidiasis, and aspergillosis

As compared with patients without psoriasis, the relative risk estimate (OR) of developing diabetes mellitus associated with psoriasis was 1.31 (95% CI 1.13-1.51), adjusted for smoking status, BMI, hypertension, hyperlipidaemia, infections, and use of systemic steroids. We found increasing ORs with increasing psoriasis severity, based on assessments of treatment type and duration (<2 vs. ≥2 years) prior to the index date. An additional stratification of the duration of psoriasis prior to the index date into categories of <2, 2 to <4, or ≥4 years yielded increasing adjusted ORs with increasing psoriasis duration of 1.24 (95% CI 1.03-1.51), 1.26 (95% CI 1.01-1.59),

and 1.43 (95% CI 1.16-1.76), respectively. The OR for patients with a history of psoriasis of ≥2 years who received >2 prescriptions per year for oral psoriasis treatment was 2.56 (95% CI 1.11-5.92), as compared with those without psoriasis (table 3.4.3).

Table 3.4.3 Diabetes risk and psoriasis stratified by severity, nested case-control analysis

	Cases No (%) (n = 1061)		Controls No (%) (n = 4244)		Adjusted OR* (95% CI)	
No Psoriasis	435	(41.0)	2154	(50.8)	1.00	(reference)
Psoriasis	626	(59.0)	2090	(49.2)	1.31	(1.13 - 1.51)
Short-term disease (<2 years)	238	(22.4)	866	(20.4)	1.24	(1.03 - 1.51)
Long-term disease (≥2 years)	388	(36.6)	1224	(28.8)	1.35	(1.14 - 1.60)
Untreated psoriasis	32	(3.0)	132	(3.1)	1.20	(0.77 - 1.87)
Short-term	20	(1.9)	83	(2.0)	1.10	(0.64 - 1.90)
Long-term	12	(1.1)	49	(1.2)	1.41	(0.69 - 2.86)
Topical treatment	572	(53.9)	1909	(45.0)	1.30	(1.12 - 1.51)
Short-term	216	(20.4)	773	(18.2)	1.27	(1.04 - 1.55)
Long-term	356	(33.5)	1136	(26.8)	1.33	(1.11 - 1.58)
Low intensity	333	(31.4)	1212	(28.6)	1.20	(1.01 - 1.43)
High intensity	239	(22.5)	697	(16.4)	1.47	(1.21 - 1.80)
Long-term/high intensity	90	(8.5)	202	(4.8)	1.71	(1.27 - 2.32)
Oral treatment (+/- topical)	22	(2.1)	49	(1.1)	1.61	(0.90 - 2.88)
Short-term	2	(0.2)	10	(0.2)	0.55	(0.11 - 2.76)
Long-term	20	(1.9)	39	(0.9)	1.98	(1.06 - 3.70)
Low intensity	7	(0.7)	22	(0.5)	1.40	(0.55 - 3.60)
High intensity	15	(1.4)	27	(0.6)	1.77	(0.86 - 3.66)
Long-term/high intensity	13	(1.2)	18	(0.4)	2.56	(1.11 - 5.92)

*Adjusted for body mass index, smoking, hypertension, hyperlipidaemia, infections, and use of oral corticosteroids

OR = odds ratio; CI = confidence interval

We further analysed the role of BMI and hyperlipidaemia in the association of psoriasis and diabetes mellitus risk. As compared with patients without psoriasis and with normal BMI, the risk of developing diabetes mellitus was substantially elevated for overweight (BMI ≥25 kg/m^2) patients without psoriasis (adjusted OR 7.04, 95% CI 4.86-10.19), and the point estimate was even slightly higher for overweight patients with psoriasis (OR 8.27, 95% CI 5.75-11.90). In order to distinguish between the role of BMI and the role of psoriasis on the risk of developing diabetes mellitus, we restricted an analysis to patients with normal BMI. Among them, the diabetes mellitus

risk was increased twofold for patients with psoriasis (OR 2.02, 95% CI 1.31-3.10) as compared with patients without psoriasis. As compared with patients without psoriasis and without hyperlipidaemia, the adjusted relative risk estimate of developing diabetes mellitus for patients with both psoriasis and hyperlipidaemia was 2.23 (95% CI 1.74-2.85) (table 3.4.4).

Table 3.4.4 Diabetes risk and psoriasis, role of body mass index and hyperlipidaemia

		Cases No (%) (n = 1061)		Controls No (%) (n = 4244)		Adjusted OR* (95% CI)	
Psoriasis and BMI (kg/m^2)							
BMI <25	NP	35	(3.3)	732	(17.3)	1.00	(reference)
	P	64	(6.03)	621	(14.6)	2.02	(1.31 - 3.10)
BMI ≥25	NP	327	(30.8)	949	(22.4)	7.04	(4.86 - 10.19)
	P	469	(44.2)	1068	(25.2)	8.27	(5.75 - 11.90)
Psoriasis and Hyperlipidaemia							
No hyperlipidaemia	NP	328	(30.9)	1841	(43.4)	1.00	(reference)
No hyperlipidaemia	P	444	(41.9)	1720	(40.5)	1.33	(1.12 - 1.57)
Hyperlipidaemia	NP	107	(10.1)	313	(7.4)	1.80	(1.35 - 2.39)
Hyperlipidaemia	P	182	(17.2)	370	(8.7)	2.23	(1.74 - 2.85)

* Adjusted for body mass index (BMI) or hyperlipidaemia, smoking, hypertension, infections, and use of oral corticosteroids
Number of cases / controls in the model with BMI do not sum up to the total number of cases / controls as patients with unknown BMI are not in analysis.; NP = no psoriasis; P = psoriasis; OR = odds ratio; CI = confidence interval

Stratification by age <60 and ≥60 years yielded similar risk estimates of developing diabetes mellitus (OR 1.31, 95% CI 1.03-1.68 and OR 1.26, 95% CI 1.05-1.52, respectively), and the ORs after stratification by sex were 1.17 (95% CI 0.96-1.41) for male and 1.54 (95% CI 1.23-1.94) for female patients with psoriasis, as compared with those without psoriasis.

In an additional analysis, we stratified cases of diabetes mellitus into type I and type II diabetes mellitus (type I diabetes mellitus was defined either by a diagnostic code for type I and/or by treatment with insulin only). We found a higher prevalence of type I diabetes mellitus in younger patients with psoriasis and a higher prevalence of type II diabetes mellitus in older patients. About two-thirds of the patients with type I diabetes mellitus had a history of psoriasis (table 3.4.5). Only two of the patients with type I diabetes mellitus had oral psoriasis treatment (data not shown).

Table 3.4.5 Prevalence of psoriasis in patients with type I or type II diabetes mellitus stratified by age

	Type I diabetes mellitus (n = 32)		**Type II diabetes mellitus (n = 1029)**	
	Psoriasis (n / %)	*No Psoriasis (n / %)*	*Psoriasis (n / %)*	*No Psoriasis (n / %)*
Age (years)				
0-29	11 (34.4)	4 (12.5)	7 (0.7)	2 (0.2)
30-39	3 (9.4)	3 (9.4)	17 (1.7)	14 (1.4)
40-49	1 (3.1)	0 (0.0)	72 (7.0)	50 (4.9)
50-59	0 (0.0)	0 (0.0)	144 (14.0)	101 (9.8)
60-69	5 (15.6)	1 (3.1)	197 (19.1)	128 (12.4)
70-79	1 (3.1)	1 (3.1)	127 (12.3)	96 (9.3)
≥80	0 (0.0)	2 (6.3)	41 (4.0)	33 (3.2)
Total	*21 (65.6)*	*11 (34.4)*	*605 (58.8)*	*424 (41.2)*

3.4.5 Discussion

The findings of this large population-based study suggest that the risk of developing diabetes mellitus is slightly increased in patients with psoriasis as compared with patients without psoriasis. The risk estimates were highest for patients with psoriasis with a longer psoriasis history who regularly received systemic treatment, possibly reflecting greater disease severity.

Unlike in previous cross-sectional studies, we were in a position to distinguish between prevalent diabetes mellitus and new-onset diabetes mellitus after the first psoriasis diagnosis. The overall diabetes mellitus incidence rate in the psoriasis-free comparison group (3 per 1000 py) is similar to the findings of another GPRD-based study reporting an IR of 3.3 / 1000 py[186] and slightly higher than the IR of 2.2 / 1000 py in a study from the Netherlands.[187] As previously reported,[187] we also observed an age-dependent increase in the diabetes mellitus incidence rate which again decreased in the highest age groups. In our study population the diabetes mellitus IR overall was higher than in the psoriasis-free comparison group, reaching a peak (8.92 per 1000 py) in patients aged 60 to 79 years. The rates were slightly higher among men than women, which is also consistent with previous literature.[186] When we compared the diabetes mellitus IR between patients with or without psoriasis, the IRR was highest for patients <30 years of age, most likely driven by cases with type I diabetes mellitus which tends to be increased in young patients with psoriasis. In a subgroup analysis encompassing 32 patients with type I diabetes mellitus, 11

(34.4%) had psoriasis and were <30 years of age, as compared with four (12.5%) without psoriasis below 30 years of age. Like psoriasis, type I diabetes mellitus is considered to be an autoimmune disease mediated by Th1 helper T cells, and the two diseases may share mechanistic characteristics.[188]

In the nested case-control analysis, the prevalence of psoriasis was slightly higher among cases of diabetes mellitus than among controls (adjusted OR 1.31, 95% CI 1.13-1.51), and a BMI above 25 kg/m^2 as well as comorbidities related to the metabolic syndrome were also more common in cases with diabetes mellitus than in controls. The slightly increased relative diabetes mellitus risk associated with psoriasis was similar to findings from previous studies in nonhospitalised patients and from cross-sectional designs.[103, 105] Another cross-sectional study in hospitalised patients found an OR of 2.48 (95% CI 1.70-3.61), however, the result was not adjusted for BMI.[106] We compared the diabetes prevalence prior to the first-time psoriasis diagnosis in a previous analysis and did not find a substantial difference between patients with psoriasis and the comparison group without psoriasis.[158]

After stratification by psoriasis duration and type of treatment we found higher ORs for patients with a longer history of psoriasis and / or oral treatment, both markers of disease severity. The authors of another cross-sectional analysis on the GPRD who also used pharmacological treatment as a marker for disease severity reported an OR for diabetes mellitus of 1.62 (95% CI 1.30-2.01)[103] for patients with psoriasis using oral treatment, a similar finding to our OR of 1.61 (95% CI 0.90-2.88), and another study also reported increasing diabetes mellitus ORs with increasing psoriasis severity (defined by type of treatment).[105] In our study population, the diabetes mellitus risk for patients with psoriasis who received intensive topical treatment and had a longer disease duration was 1.71 (95% CI 1.27-2.32), and it was 2.56 (95% CI 1.11-5.92) for patients with intensive oral treatment and longer disease duration.

As methotrexate has been shown to increase progression of diabetes mellitus in a randomised trial[189] and as ciclosporin has been associated with hyperglycaemia and acitretin with alterations in glucose tolerance,[190] we conducted several sensitivity analyses to explore the role of pharmacological treatment on the risk of developing diabetes mellitus. In a model restricted to patients with psoriasis without recorded use of oral treatment, the relative risk of developing diabetes mellitus remained

higher for psoriasis patients (adjusted OR 1.31, 95% CI 1.11-1.57) with a longer-term psoriasis history.

The herein reported association between the chronic inflammatory skin disease psoriasis and diabetes mellitus may support the notion that insulin resistance, diabetes mellitus, and the metabolic syndrome are triggered by chronic inflammation, i.e. that they are associated with a cytokine-mediated activation of innate immunity.[191] C-reactive protein (CRP), a sensitive marker of inflammation, as well as other inflammatory mediators have been related to insulin sensitivity as well as to BMI.[192, 193] Cytokines (e.g. IL-1, IL-6, and TNF-α) stimulate hepatic production of acute-phase proteins, such as CRP,[191, 192] which is also supposed to be increased in mild and severe psoriasis.[194] The beneficial effect of thiazolidinediones in both diabetes mellitus and psoriasis[158] additionally supports the link via inflammation between the two diseases, as these substances are supposed to have anti-inflammatory properties. [195]

Our study has several limitations. In large observational studies one can never rule out a certain degree of misclassification which may have led to the inclusion of cases of psoriasis or of cases of diabetes mellitus who in fact did not have such a diagnosis. However, in previous GPRD-based studies on psoriasis, Gelfand et al.[115, 139, 147] documented a high validity of this diagnosis. In order to reduce the likelihood of including cases of diabetes mellitus who did not have an incident diagnosis of diabetes mellitus, we applied a stringent previously defined algorithm and reviewed a large sample of case profiles so that we were confident that misclassification was not a major issue in this study. Nevertheless, it is possible that high blood glucose was detected by chance or due to increased medical attention in some cases, and that in some instances the index date may not have been accurate, or the person may not have had diabetes mellitus. The number of patients with psoriasis who were exposed to oral treatment is rather low in our study population. As this subgroup reflects patients with the highest disease severity, we do not have much information on this subgroup; most patients with psoriasis in our study population had mild to moderate psoriasis. In addition, it is possible that our classification of disease severity which was based on drug treatment is not always accurate, as patients may have received some treatment on an irregular basis by the dermatologist, and this may not have been recorded for all patients by the GP.

Although we tested for a large number of potential confounding factors and included the most relevant ones in our model, we cannot exclude the possibility that unknown confounders or biases may have affected our results to some degree.

Particularly BMI is a strong risk factor for type II diabetes mellitus, and patients with psoriasis have been shown to have higher BMI. Thus, BMI is likely to confound the association between psoriasis and the risk of diabetes mellitus. We therefore adjusted the various models for BMI and ran sensitivity analyses to distinguish further between the role of BMI and of psoriasis as risk factors for new-onset diabetes mellitus. Nevertheless, we cannot rule out the possibility that a certain proportion of misclassified or missing BMI values may have led to some residual confounding. There was, however, substantial evidence from these various analyses that the association between psoriasis and an increased diabetes mellitus risk remained independent of BMI.

In conclusion, this is, to the best of our knowledge, the first study which explored the association between incident psoriasis and the risk of developing an incident diagnosis of diabetes mellitus. In our study population patients with psoriasis were at an increased risk of developing new-onset diabetes mellitus, and there was a suggestion that the risk increased with psoriasis severity and duration. Finally, the risk of developing a diagnosis of diabetes mellitus did not seem to be explained by high BMI alone.

3.5 PSORIASIS AND RISK OF INCIDENT MYOCARDIAL INFARCTION, STROKE, OR TRANSIENT ISCHAEMIC ATTACK: AN INCEPTION COHORT STUDY WITH A NESTED CASE-CONTROL ANALYSIS

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3.5.1 Abstract

Background: Systemic inflammation may increase the risk for cardiovascular diseases in psoriasis patients, but data on this risk in patients with early psoriasis are scarce.

Objective: To assess and compare the risk of developing incident MI, stroke, or TIA between an inception cohort of psoriasis patients and a psoriasis-free population.

Methods: We conducted an inception cohort study with a nested case-control analysis within the UK-based GPRD. The study population encompassed 36,702 patients with a first-time recorded diagnosis of psoriasis between 1994 and 2005, matched 1:1 to psoriasis-free patients. We assessed crude IRs and applied conditional logistic regression to obtain ORs with 95% CIs.

Results: Overall, the IRs of MI (n = 449), stroke (n = 535), and TIA (n = 402) were similar among patients with or without psoriasis. However, the adjusted OR of developing MI for psoriasis patients aged <60 years was 1.66 (95% CI 1.03-2.66) compared with patients without psoriasis, while the OR for patients aged ≥60 years was 0.99 (95% CI 0.77-1.26). The adjusted ORs of developing MI for patients of all ages with ≤2 or >2 prescriptions/year for oral psoriasis treatment were 2.48 (95% CI 0.69-8.91) and 1.39 (95% CI 0.43-4.53), respectively, with a similar finding for stroke and TIA.

Conclusions: The risk of developing a cardiovascular outcome was not materially elevated for patients with early psoriasis overall. In subanalyses, however, there was a suggestion of an increased (but low absolute) MI risk for psoriasis patients aged <60 years, mainly for those with severe disease.

3.5.2 Background

Psoriasis, a disease with an estimated prevalence of 1.5% in the UK,[139] is characterised by T cell-mediated hyperproliferation of keratinocytes on a complex genetic background. Pro-inflammatory Th1 and Th17 cytokines such as IL-22, IFN-γ, TNF-β, IL-6, and IL-17 play a central role in the pathogenesis together with other cytokines (e.g. TNF-α, IL-20, IL-23, and TGF-α).[48] Increased levels of the acute-phase CRP were reported in mild and severe psoriasis.[194] Atherosclerosis, a main risk factor for MI, ischaemic stroke, and TIA, is also an inflammatory process driven by Th1 cells with a predominance of pro-inflammatory cytokines.[196] Atherosclerosis has been associated with psoriasis in recent observational studies,[105, 197, 198] and chronic systemic inflammatory processes are thought to be a possible reason for the increased cardiovascular risk seen in patients with other systemic inflammatory diseases such as rheumatoid arthritis or lupus erythematosus.[180, 199] In addition, smoking, metabolic syndrome, high BMI, alcohol consumption,[88, 101, 200] and a pro-atherogenic lipoprotein profile[112, 201, 202] may also increase the risk for cardiovascular diseases in psoriatic patients. Hospital-based studies reported a higher prevalence of cardiovascular diseases in psoriatic patients, particularly in those with severe disease activity at young age.[102, 111, 203] Whereas population-based outpatient studies from the 1980s did not or only partially support these findings,[86, 120] recent observational studies provided evidence for an increased prevalence of diabetes, hypertension, hyperlipidaemia, obesity, and smoking[103, 110] as well as of MI[108, 110] in psoriatic patients, mainly with severe disease. In one of the studies,[108] a cohort study on the GPRD conducted by Gelfand et al., the increased MI risk was independent from other cardiovascular risk factors. However, a history of MI prior to start of observation could not have been determined completely in that study because patients who already had a diagnosis of psoriasis at registration in the GPRD were included in the study cohort.[108]

One study showed an increased mortality from cerebrovascular diseases for patients hospitalised for psoriasis, a finding which was not accompanied by an increased mortality from cardiovascular events (MI, stroke, and pulmonary embolism) in outpatients.[111] Recently, two groups reported a slightly increased risk of stroke in outpatient psoriatic patients.[107, 109, 110]

It was the aim of the present study to investigate the reported association between psoriasis and MI, stroke, or TIA using primary care data from the UK and applying a slightly different study design from that used in the earlier reports.

3.5.3 Methods

We conducted a matched follow-up study with a nested case-control analysis to quantify the risk of an incident MI, stroke, or TIA diagnosis in patients after a first-time recorded psoriasis diagnosis and to compare it with a matched population without psoriasis.

Data source

We used the GPRD, a large UK-based database established around 1987 which encompasses some five million patients who are actively enrolled with selected GPs. The GPs have agreed to provide data for research purposes to the GPRD. GPs have been trained to record medical information in a standard manner and to supply it anonymously. The patients enrolled in the GPRD are representative of the UK with regard to age, sex, geographic distribution, and annual turnover rate. The information recorded includes patient demographics and characteristics (e.g. age, sex, height, weight, smoking status), symptoms, medical diagnoses, referrals to consultants, hospitalisations, and all drug prescriptions, as the doctors generate prescriptions directly with the computer using a coded drug dictionary. This database, which has been described in detail elsewhere[31, 37] and validated extensively,[32-34] has been the source for numerous epidemiological studies published in peer-reviewed journals.
The study protocol was approved by ISAC for MHRA database research.

Study population

The study population consisted of all patients with a first-time recorded diagnosis of psoriasis between 1 January 1994 and 31 December 2005 and of a comparison group of the same number of psoriasis-free patients, matched to psoriasis patients on calendar time (date of the psoriasis diagnosis), age (same year of birth), sex, general practice, and years of history in the GPRD. We excluded patients with <3 years of history in the database prior to the first-time psoriasis diagnosis (or the corresponding date in the comparison group). We included all patients with a recorded psoriasis diagnosis in the analyses, as we did in previous GPRD-based

studies on psoriasis.[155, 158]

Follow-up and identification of MI, stroke, and TIA

From the study population we excluded all patients with a history of ischaemic heart disease or cerebrovascular diseases, cancer, or HIV prior to the psoriasis diagnosis (or the corresponding date in the comparison group). We then followed all patients until they developed a first-time diagnosis of MI, stroke, or TIA, they died, or follow-up in the medical record ended. The date of the MI, stroke, or TIA diagnosis will be subsequently referred to as the 'index date'. We validated all potential cases with a recorded code for incident MI, stroke, or TIA using a computer-based algorithm and manual computer profile review, thereby focusing on newly started pharmacological therapies after the cardiovascular diagnosis, on hospitalisations, and on referrals to identify eligible first-time cases of interest and to classify stroke cases into haemorrhagic, thrombotic, or unspecified stroke, or into cases with TIA. This validation process was done blinded as to whether the cases had psoriasis or not.

Nested case-control analysis

To each case patient with an MI, stroke, or TIA diagnosis identified in the follow-up part we matched at random up to four control patients from the study population on age (same year of birth), sex, and calendar time (same index date, i.e. the date when the case developed MI or stroke/TIA). We applied the same exclusion criteria to controls as we did to cases.

We compared the prevalence of diagnosed psoriasis prior to the index date between cases with a cardiovascular outcome and their matched controls, and we stratified psoriasis patients by duration of psoriasis (<2 vs. ≥2 years) and treatment (no treatment, topical treatment only [emollients, salicylic acid, calcipotriol, coal tar, dithranol or tazarotene preparations, or corticosteroids] and/or UV/oral treatment [azathioprine, ciclosporin, methotrexate, acitretin, hydroxyurea, mycophenolate mofetil, or UV/PUVA therapy]). Treatment was used as a proxy for severity of psoriasis whereby prescription of at least one oral preparation or UV therapy classified for severe disease. We further stratified patients by treatment intensity (no treatment, ≤4 vs. >4 prescriptions/year for topical treatment, ≤2 vs. >2 prescriptions/year for oral treatment).

Statistical analysis

In the follow-up part we assessed person-time for all patients in the study population from the date of first psoriasis diagnosis (or the corresponding date in the comparison group) until a patient developed an outcome of interest, died, or follow-up in the medical record ended. We assessed crude IRs of a first-time MI, stroke, or TIA diagnosis among patients with or without psoriasis, stratified by age and sex, and we calculated a crude IRR with 95% CI.

In the nested case-control analysis we conducted conditional logistic regression analyses using the SAS statistical software (version 9.1; SAS Institute Inc, Cary, NC, U.S.A.), displaying relative risk estimates as ORs with 95% CIs. The analyses controlled for the potential confounders age, sex, and calendar time by matching. We further adjusted the ORs for smoking status (non, current, past, unknown) and BMI (<18.5, 18.5-24.9, 25.0-29.9, ≥30 kg/m^2, unknown) in the multivariate model as well as for hyperlipidaemia, diabetes, hypertension, other cardiac diseases (congestive heart failure, arrhythmia), and affective disorders. Depression has been reported to increase the risk of coronary heart disease[204] and stroke,[205] and psychiatric disorders, including depression, seem to be fairly common in patients with psoriasis.[132] In addition, we adjusted the analyses of MI for acute chest infections (<30 days before index date) as well as for use of oral steroids (last prescription <90 or ≥90 days before index date) because acute respiratory tract infections[206] and use of oral corticosteroids[207] have been associated with MI and infections (primarily streptococcal throat infections) with psoriasis.[87] Additionally, patients with psoriasis may be less likely to receive oral corticosteroids due to fear of potential corticosteroid dependence and exacerbation of psoriasis upon withdrawal.[95] The analyses of stroke and TIA were further adjusted for a history of ischaemic heart disease, use of acetylsalicylic acid and nonsteroidal anti-inflammatory drugs (last prescription <90 or ≥90 days before index date), alcoholism, and epilepsy. The latter three factors have been reported to alter the risk of stroke.[208-210] We also evaluated the effects of other covariates for potential confounding, which were not included in the final model because they were not materially associated with either the exposure or the outcome.

3.5.4 Results

The initial study population encompassed 73,404 patients, 36,702 with psoriasis and 36,702 matched psoriasis-free patients (16,969 [46.2%] men and 19,733 [53.8%] women). Psoriasis patients were more likely to be current smokers (23.9% vs. 18.8%) and overweight (22.7% vs. 21.6% with BMI 25-29.9 kg/m^2 and 13.3% vs. 10.6% with BMI ≥30 kg/m^2) than patients in the comparison group. The mean time of follow-up was 4.6 years.

Incidence rates of myocardial infarction in the person-time analysis

After excluding patients with a history of ischaemic heart disease, cancer, or HIV, the remaining study population consisted of 63,639 patients (31,568 cases and 32,071 controls). Within this population we identified 449 cases with an incident MI diagnosis, of whom 238 (53%) had a history of psoriasis. The overall IR for MI was 1.58 (95% CI 1.39 – 1.79) / 1000 py in patients with psoriasis, and the crude IRR was 1.07 (95% CI 0.89 – 1.29) (table 3.5.1).

Table 3.5.1 Incidence rates and incidence rate ratios of myocardial infarction

Outcome	Group	Events	Person-years	IR/1000 py (95% CI)		IRR (95% CI)	
MI							
Psoriasis	All	238	150,972.2	1.58	(1.39 - 1.79)	1.07	(0.89 - 1.29)
	Men	151	68,503.1	2.20	(1.88 - 2.58)	1.06	(0.84 - 1.33)
	Women	87	82,469.0	1.05	(0.86 - 1.30)	1.09	(0.80 - 1.48)
	Age 0-29	0	40,383.7	NA	NA	NA	NA
	Age 30-59	76	70,212.8	1.08	(0.86 - 1.35)	1.99	(1.37 - 2.88)
	Age 60-80+	162	40,375.7	4.01	(3.44 - 4.68)	0.92	(0.75 - 1.14)
No Psoriasis	All	211	143,231.5	1.47	(1.29 - 1.69)	1.0	
	Men	135	64,707.2	2.09	(1.76 - 2.47)	1.0	
	Women	76	78,524.3	0.97	(0.77 - 1.21)	1.0	
	Age 0-29	1	37,068.7	0.03	(0.00 - 0.15)	1.0	
	Age 30-59	36	66,180.7	0.54	(0.39 - 0.75)	1.0	
	Age 60-80+	174	39,982.1	4.35	(3.75 - 5.05)	1.0	

MI = myocardial infarction; IR = incidence rate; IRR = incidence rate ratio; CI = confidence interval; py = person-year; age in years; Reference group: patients in the same age and / or sex group without psoriasis

Incidence rates of stroke and TIA in the person-time analysis

After excluding patients with a history of cerebrovascular diseases, cancer, or HIV, the remaining study population consisted of 66,139 patients (32,930 cases and 33,209 controls). Within this population we identified 535 cases with an incident stroke diagnosis (327 thrombotic, 69 haemorrhagic, 139 unspecified), of whom 264 (49%) had psoriasis, and 402 cases with an incident TIA diagnosis, of whom 205 (51%) had psoriasis. The crude IRs and IRRs are displayed in table 3.5.2.

Table 3.5.2 Incidence rates and incidence rate ratios of stroke and transient ischaemic attack

Outcome	Group	Events	Person-years	IR/1000 py (95% CI)		IRR (95% CI)	
Stroke							
Psoriasis	All	264	156,492.8	1.69	(1.50 - 1.90)	0.92	(0.77 - 1.09)
	Men	135	72,208.3	1.87	(1.58 - 2.21)	1.02	(0.80 - 1.31)
	Women	129	84,284.5	1.53	(1.29 - 1.82)	0.83	(0.65 - 1.05)
	Age 0-29	1	40,392.1	0.02	(0.00 - 0.14)	NA	NA
	Age 30-59	37	71,800.5	0.52	(0.37 - 0.71)	0.75	(0.49 - 1.16)
	Age 60-80+	226	44,300.3	5.10	(4.48 - 5.81)	0.98	(0.81 - 1.18)
No Psoriasis	All	271	147,287.7	1.84	(1.63 - 2.07)	1.0	
	Men	123	67,279.2	1.83	(1.53 - 2.18)	1.0	
	Women	148	80,008.5	1.85	(1.58 - 2.17)	1.0	
	Age 0-29	0	37,076.6	NA	NA	NA	NA
	Age 30-59	46	67,094.7	0.69	(0.51 - 0.91)	1.0	
	Age 60-80+	225	43,116.3	5.22	(4.58 - 5.94)	1.0	
TIA							
Psoriasis	All	205	156,492.8	1.31	(1.14 - 1.50)	0.98	(0.81 - 1.19)
	Men	92	72,208.3	1.27	(1.04 - 1.56)	0.88	(0.66 - 1.18)
	Women	113	84,284.5	1.34	(1.12 - 1.61)	1.07	(0.82 - 1.40)
	Age 0-29	0	40,392.1	NA	NA	NA	NA
	Age 30-59	28	71,800.5	0.39	(0.27 - 0.56)	1.14	(0.66 - 1.97)
	Age 60-80+	177	44,300.3	4.00	(3.45 - 4.63)	0.99	(0.80 - 1.22)
No Psoriasis	All	197	147,287.7	1.34	(1.16 - 1.54)	1.0	
	Men	97	67,279.2	1.44	(1.18 - 1.76)	1.0	
	Women	100	80,008.5	1.25	(1.03 - 1.52)	1.0	
	Age 0-29	0	37,076.6	NA	NA	NA	NA
	Age 30-59	23	67,094.7	0.34	(0.23 - 0.51)	1.0	
	Age 60-80+	174	43,116.3	4.04	(3.48 - 4.68)	1.0	

TIA = transient ischaemic attack; IR = incidence rate; IRR = incidence rate ratio; CI = confidence interval; py = person-year; age in years; Reference group: patients in the same age and / or sex group without psoriasis

Nested case-control analysis – MI

The nested case-control analysis encompassed the 449 incident MI cases and 1796 matched controls (table 3.5.3).

Table 3.5.3 Characteristics of myocardial infarction cases and controls in the nested case-control analysis

Variable	Cases No (%) (n = 449)		Controls No (%) (n = 1796)		Adjusted OR* (95% CI)	
Smoking status						
Non smoker	154	(34.3)	822	(45.8)	1.00	(reference)
Current smoker	142	(31.6)	363	(20.2)	2.21	(1.68 - 2.90)
Ex smoker	97	(21.6)	378	(21.0)	1.30	(0.96 - 1.76)
Unknown	56	(12.5)	233	(13.0)	1.50	(0.97 - 1.76)
BMI (kg/m^2)						
12-18.4	9	(2.0)	19	(1.1)	1.93	(0.82 - 4.54)
18.5-24.9	113	(25.2)	500	(27.8)	1.00	(reference)
25-29.9	157	(35.0)	620	(34.5)	1.11	(0.84 - 1.47)
30-60	77	(17.1)	258	(14.4)	1.20	(0.84 - 1.72)
Unknown	93	(20.7)	399	(22.2)	1.07	(0.74 - 1.53)
Comorbidities						
Hyperlipidaemia without treatment	24	(5.4)	76	(4.2)	1.35	(0.82 - 2.22)
Hyperlipidaemia with treatment	64	(14.3)	174	(9.7)	1.41	(0.99 - 2.02)
Hypertension	177	(39.4)	555	(30.9)	1.41	(1.11 - 1.78)
Diabetes without treatment	10	(2.2)	30	(1.7)	1.30	(0.61 - 2.76)
Diabetes with treatment	49	(10.9)	108	(6.0)	1.75	(1.18 - 2.59)
CHF, arrhythmia	64	(14.3)	172	(9.6)	1.52	(1.08 - 2.12)
Acute infection	17	(3.8)	33	(1.8)	1.82	(0.97 - 3.42)
Affective disorder	109	(24.3)	322	(17.9)	1.31	(1.01 - 1.71)

*Adjusted for all covariates listed in the table and use of oral corticosteroids

BMI = body mass index; OR = odds ratio; CI = confidence interval; CHF = congestive heart failure

Compared with patients without psoriasis, the adjusted OR of developing MI for patients with psoriasis was 1.14 (95% CI 0.93-1.41). Compared with patients without psoriasis, the OR for patients with psoriasis who received ≤2 prescriptions/year for oral psoriasis treatment tended to be higher (OR 2.48, 95% CI 0.69-8.91) than for those who received >2 prescriptions/year (OR 1.39, 95% CI 0.43-4.53) (table 3.5.4),

although these estimates are relatively imprecise as shown by the rather wide 95% CIs.

The risk estimates of developing MI associated with psoriasis were similar between men (OR 1.10, 95% CI 0.85-1.43) and women (OR 1.19, 95% CI 0.82-1.71). Stratification by age yielded higher ORs for patients aged <60 years (OR 1.66, 95% CI 1.03-2.66) than for those ≥60 years of age (OR 0.99, 95% CI 0.77-1.26) (table 3.5.4). When we further stratified patients <60 years of age by psoriasis treatment, the adjusted ORs were 2.64 (95% CI 0.85-8.20) for those without treatment, 1.48 (95% CI 0.91-2.41) for those with topical, and 11.3 (95% CI 1.54-82.8) for those with oral treatment. This latter risk estimate was based on only 4 cases and 3 controls.

Table 3.5.4 Psoriasis and myocardial infarction risk stratified by age, sex, duration, and severity, in the nested case-control analysis

	Cases No (%) (n = 449)		Controls No (%) (n = 1796)		Adjusted OR* (95% CI)	
No Psoriasis	211	(47.0)	912	(50.8)	1.00	(reference)
Psoriasis	238	(53.0)	884	(49.2)	1.14	(0.93 - 1.41)
<60 years	76	(16.9)	227	(12.6)	1.66	(1.03 - 2.66)
≥60 years	162	(36.1)	657	(36.6)	0.99	(0.77 - 1.26)
Short-term disease (<2 years)	98	(21.8)	367	(20.4)	1.15	(0.87 - 1.51)
Women	37	(8.2)	108	(6.0)	1.43	(0.88 - 2.33)
Men	61	(13.6)	259	(14.4)	0.97	(0.69 - 1.38)
Long-term disease (≥2 years)	140	(31.2)	517	(28.8)	1.14	(0.89 - 1.47)
Women	50	(11.2)	208	(11.6)	1.04	(0.67 - 1.61)
Men	90	(20.0)	309	(17.2)	1.21	(0.89 - 1.65)
Untreated psoriasis	11	(2.4)	53	(2.9)	0.98	(0.49 - 1.96)
<60 years	6	(1.3)	17	(0.9)	2.64	(0.85 - 8.20)
≥60 years	5	(1.1)	36	(2.0)	0.55	(0.21 - 1.46)
Topical treatment	219	(48.8)	811	(45.2)	1.14	(0.92 - 1.41)
<60 years	66	(14.7)	207	(11.5)	1.48	(0.91 - 2.41)
≥60 years	153	(34.1)	604	(33.7)	1.02	(0.80 - 1.30)
Low intensity	135	(30.1)	490	(27.3)	1.17	(0.91 - 1.50)
High intensity	84	(18.7)	321	(17.9)	1.09	(0.82 - 1.46)
Oral treatment (+/- topical)	8	(1.8)	20	(1.1)	1.78	(0.74 - 4.28)
<60 years	4	(0.9)	3	(0.2)	11.27	(1.54 - 82.77)
≥60 years	4	(0.9)	17	(0.9)	0.86	(0.24 - 3.08)
Low intensity	4	(0.9)	7	(0.4)	2.48	(0.69 - 8.91)
High intensity	4	(0.9)	13	(0.7)	1.39	(0.43 - 4.53)

* Adjusted for body mass index, smoking, hyperlipidaemia, hypertension, diabetes, other cardiac diseases, affective disorders, acute infections, and use of oral corticosteroids

OR = odds ratio; CI = confidence interval

Nested case-control analysis – stroke and TIA

This analysis encompassed 535 incident stroke cases (61% thrombotic, 13% haemorrhagic, 26% unspecified) and 2137 matched controls, and 402 incident TIA cases and 1604 matched controls, respectively (tables 3.5.5 and 3.5.6).

Table 3.5.5 Characteristics of stroke cases and controls in the nested case-control analysis

Variable	Cases No (%) (n = 535)		Controls No (%) (n = 2137)		Adjusted OR* (95% CI)	
Smoking status						
Non smoker	223	(41.7)	1050	(49.1)	1.00	(reference)
Current smoker	135	(25.2)	364	(17.0)	1.84	(1.41 - 2.40)
Ex smoker	112	(20.9)	484	(22.7)	1.02	(0.78 - 1.35)
Unknown	65	(12.2)	239	(11.2)	1.48	(1.01 - 2.18)
BMI (kg/m^2)						
12-18.4	13	(2.4)	34	(1.6)	1.28	(0.63 - 2.59)
18.5-24.9	170	(31.8)	623	(29.2)	1.00	(reference)
25-29.9	141	(26.4)	701	(32.8)	0.69	(0.53 - 0.89)
30-60	100	(18.7)	353	(16.5)	0.85	(0.62 - 1.16)
Unknown	111	(20.7)	426	(19.9)	1.00	(0.73 - 1.38)
Comorbidities						
Hyperlipidaemia without treatment	24	(4.5)	87	(4.1)	0.99	(0.61 - 1.62)
Hyperlipidaemia with treatment	92	(17.2)	300	(14.0)	0.87	(0.63 - 1.20)
Hypertension	248	(46.4)	731	(34.2)	1.60	(1.29 - 1.98)
Diabetes without treatment	18	(3.4)	44	(2.1)	1.67	(0.93 - 3.02)
Diabetes with treatment	61	(11.4)	168	(7.9)	1.31	(0.93 - 1.84)
CHF, arrhythmia	121	(22.6)	317	(14.8)	1.60	(1.23 - 2.09)
Affective disorder	117	(21.9)	430	(20.1)	1.00	(0.78 - 1.29)
IHD	134	(25.1)	419	(19.6)	0.96	(0.72 - 1.28)
Epilepsy	16	(3.0)	20	(0.94)	3.83	(1.82 - 8.02)
Alcoholism	25	(4.7)	55	(2.6)	1.57	(0.92 - 2.70)

*Adjusted for all covariates listed in the table and use of oral nonsteroidal anti-inflammatory drugs or acetylsalicylic acid

BMI = body mass index; CHF = congestive heart failure; IHD = ischaemic heart disease; OR = odds ratio, CI = confidence interval

Table 3.5.6 Characteristics of transient ischaemic attack cases and controls in the nested case-control analysis

Variable	Cases No (%) (n = 402)		Controls No (%) (n = 1604)		Adjusted OR* (95% CI)	
Smoking status						
Non smoker	202	(50.2)	792	(49.4)	1.00	(reference)
Current smoker	71	(17.7)	289	(18.0)	1.08	(0.78 - 1.49)
Ex smoker	92	(22.9)	340	(21.2)	0.99	(0.73 - 1.34)
Unknown	37	(9.2)	183	(11.4)	0.85	(0.52 - 1.37)
BMI (kg/m^2)						
12-18.4	9	(2.2)	29	(1.8)	1.64	(0.73 - 3.71)
18.5-24.9	117	(29.1)	485	(30.2)	1.00	(reference)
25-29.9	114	(28.4)	518	(32.3)	0.78	(0.58 - 1.05)
30-60	83	(20.6)	239	(14.9)	1.09	(0.77 - 1.54)
Unknown	79	(19.7)	333	(20.8)	1.12	(0.76 - 1.64)
Comorbidities						
Hyperlipidaemia without treatment	21	(5.2)	83	(5.2)	1.04	(0.62 - 1.75)
Hyperlipidaemia with treatment	83	(20.7)	201	(12.5)	1.29	(0.90 - 1.85)
Hypertension	194	(48.3)	557	(34.7)	1.59	(1.25 - 2.03)
Diabetes without treatment	12	(3.0)	36	(2.2)	1.03	(0.52 - 2.05)
Diabetes with treatment	44	(11.0)	98	(6.1)	1.34	(0.89 - 2.02)
CHF, arrhythmia	81	(20.2)	226	(14.1)	1.28	(0.94 - 1.75)
Affective disorder	102	(25.4)	280	(17.5)	1.52	(1.15 - 2.02)
IHD	116	(28.9)	310	(19.3)	1.08	(0.79 - 1.47)
Epilepsy	10	(2.5)	17	(1.1)	2.38	(1.04 - 5.44)
Alcoholism	14	(3.5)	43	(2.7)	1.03	(0.53 - 1.99)

*Adjusted for all covariates listed in the table and use of oral nonsteroidal anti-inflammatory drugs or acetylsalicylic acid

BMI = body mass index; CHF = congestive heart failure; IHD = ischaemic heart disease; OR = odds ratio; CI = confidence interval

The overall ORs of developing stroke or TIA associated with psoriasis were around one. Stratification of stroke cases into thrombotic or haemorrhagic stroke yielded overall adjusted ORs of 0.87 (95% CI 0.68-1.12) and 0.54 (95% CI 0.29-1.02), respectively. Patients with more intense oral psoriasis treatment (>2 prescriptions/year) seemed to have lower risk estimates than those with less intense oral treatment, a similar observation as for MI (tables 3.5.7 and 3.5.8).

Stratification by age and psoriasis treatment yielded a higher risk of stroke and TIA for psoriasis patients receiving oral treatment who were ≥60 years of age (tables 3.5.7 and 3.5.8).

Table 3.5.7 Psoriasis and stroke risk stratified by age, duration, and severity, in the nested case-control analysis

	Cases No (%) (n = 535)		Controls No (%) (n = 2137)		Adjusted OR* (95% CI)	
No Psoriasis	271	(50.6)	1054	(49.3)	1.00	(reference)
Psoriasis	264	(49.4)	1083	(50.7)	0.93	(0.77 - 1.13)
<60 years	38	(7.1)	179	(8.4)	0.52	(0.29 - 0.93)
≥60 years	226	(42.2)	904	(42.3)	0.99	(0.80 - 1.22)
Short-term disease (<2 years)	87	(16.3)	479	(22.4)	0.69	(0.52 - 0.91)
Women	47	(8.8)	238	(11.1)	0.77	(0.53 - 1.13)
Men	40	(7.5)	241	(11.3)	0.65	(0.43 - 0.97)
Long-term disease (≥2 years)	177	(33.1)	604	(28.3)	1.14	(0.91 - 1.42)
Women	82	(15.3)	325	(15.2)	0.94	(0.69 - 1.30)
Men	95	(17.8)	279	(13.1)	1.54	(1.10 - 2.15)
Untreated psoriasis	15	(2.8)	58	(2.7)	1.02	(0.56 - 1.86)
<60 years	2	(0.4)	13	(0.6)	0.37	(0.06 - 2.35)
≥60 years	13	(2.4)	45	(2.1)	1.18	(0.61 - 2.27)
Topical treatment	240	(44.9)	997	(46.7)	0.91	(0.75 - 1.11)
<60 years	35	(6.6)	155	(7.3)	0.56	(0.31 - 1.02)
≥60 years	205	(38.3)	842	(39.4)	0.95	(0.76 - 1.18)
Low intensity	127	(23.8)	541	(25.3)	0.87	(0.68 - 1.11)
High intensity	113	(21.1)	456	(21.4)	0.96	(0.74 - 1.23)
Oral treatment (+/- topical)	9	(1.7)	28	(1.3)	1.40	(0.64 - 3.08)
<60 years	1	(0.2)	11	(0.5)	0.23	(0.02 - 2.23)
≥60 years	8	(1.5)	17	(0.8)	2.24	(0.93 - 5.36)
Low intensity	4	(0.8)	10	(0.5)	1.98	(0.58 - 6.72)
High intensity	5	(0.9)	18	(0.8)	1.13	(0.41 - 3.16)

* Adjusted for body mass index, smoking, hyperlipidaemia, hypertension, diabetes, other cardiac diseases, affective disorders, epilepsy, ischaemic heart disease, alcoholism, use of nonsteroidal anti-inflammatory drugs or acetylsalicylic acid

OR = odds ratio; CI = confidence interval

Table 3.5.8 Psoriasis and transient ischaemic attack risk stratified by age, duration, and severity, in the nested case-control analysis

	Cases No (%) (n = 402)		Controls No (%) (n = 1604)		Adjusted OR* (95% CI)	
No Psoriasis	197	(49.0)	806	(50.3)	1.00	(reference)
Psoriasis	205	(51.0)	798	(49.7)	1.00	(0.81 - 1.25)
<60 years	28	(7.0)	116	(7.2)	1.28	(0.61 - 2.68)
≥60 years	177	(44.0)	682	(42.5)	1.02	(0.80 - 1.29)
Short-term disease (<2 years)	67	(16.7)	331	(20.6)	0.81	(0.59 - 1.10)
Women	38	(9.5)	163	(10.2)	0.98	(0.63 - 1.52)
Men	29	(7.2)	168	(10.5)	0.62	(0.38 - 1.00)
Long-term disease (≥2 years)	138	(34.3)	467	(29.1)	1.15	(0.89 - 1.48)
Women	75	(18.7)	263	(16.4)	1.16	(0.81 - 1.65)
Men	63	(15.7)	204	(12.7)	1.14	(0.78 - 1.67)
Untreated psoriasis	11	(2.7)	48	(3.0)	0.93	(0.46 - 1.87)
<60 years	2	(0.5)	9	(0.6)	0.59	(0.07 - 5.09)
≥60 years	9	(2.2)	39	(2.4)	0.97	(0.45 - 2.06)
Topical treatment	186	(46.3)	735	(45.8)	0.99	(0.79 - 1.24)
<60 years	25	(6.2)	106	(6.6)	1.29	(0.60 - 2.82)
≥60 years	161	(40.1)	629	(39.2)	0.99	(0.78 - 1.26)
Low intensity	112	(27.9)	405	(25.3)	1.12	(0.86 - 1.46)
High intensity	74	(18.4)	330	(20.6)	0.83	(0.61 - 1.12)
Oral treatment (+/- topical)	8	(2.0)	15	(0.9)	2.16	(0.87 - 5.35)
<60 years	1	(0.3)	1	(0.1)	NA	NA
≥60 years	7	(1.7)	14	(0.8)	2.56	(0.96 - 6.86)
Low intensity	4	(1.0)	7	(0.4)	2.90	(0.81 - 10.43)
High intensity	4	(1.0)	8	(0.5)	1.64	(0.47 - 5.78)

* Adjusted for body mass index, smoking, hyperlipidaemia, hypertension, diabetes, other cardiac diseases, affective disorders, epilepsy, ischaemic heart disease, alcoholism, use of nonsteroidal anti-inflammatory drugs or acetylsalicylic acid

OR = odds ratio; CI = confidence interval;

3.5.5 Discussion

In our population-based study we quantified the risk of developing an incident diagnosis of MI, stroke, or TIA in association with psoriasis. In contrast to the study by Gelfand et al.,[108] the follow-up period in our cohort study started at the first-time recording of a psoriasis diagnosis. While in our study there was no evidence for an overall increased risk of MI, stroke, or TIA associated with psoriasis, there was a suggestion of a slightly elevated risk associated with severe psoriasis. For MI, this effect was particularly elevated in younger patients. However, the absolute risk was low with 0.51 / 1000 py (patients 0-60 years of age).

The MI incidence rate in our psoriasis-free comparison group (OR 1.47, 95% CI 1.29-1.69) was similar to the MI incidence rates reported in a population-based study in the UK,[211] while Gelfand et al.[108] reported an MI rate in their psoriasis-free comparison group (OR 3.58, 95% CI 3.52-3.65) which was comparable with the (nonincident) MI rates reported in the above-mentioned study.[211]

Several methodological differences can explain the different rates: Gelfand et al.[108] included all patients with a psoriasis diagnosis (prevalent or incident) between 1987 and 2002, who contributed at least one day of observation time to the study, not excluding patients with a previous history of MI. In contrast, we only included patients with a documented first-time psoriasis diagnosis between 1994 and 2005 after having been in the database for at least 3 years, and we only included incident MI cases thereafter; thus, we excluded potential cases who had diagnosed ischaemic heart disease prior to the first psoriasis diagnosis. Due to these differences, our study only encompassed some 30% of patients included by Gelfand et al.[108] As we only included patients with a first-time psoriasis diagnosis in or after 1994, the proportion of patients with early psoriasis was likely to be higher in our study population. Of our initial psoriasis cohort 2.3% received oral treatment as compared with 2.9% in the study by Gelfand et al.[108] We assessed an IR for MI among patients with severe psoriasis only (defined as having had ≥1 prescription for an oral psoriasis treatment at some point in time; n = 946), and we found an overall crude IR of MI of 5.24 (95% CI 3.23-8.49) / 1000 py (data not shown).

In contrast to the study by Gelfand et al.[108] and another recently published study using the GPRD,[110] we did not find an overall increased risk of MI in all psoriatic patients. This discrepancy may be explained by the different study designs. Consistent with the study by Gelfand et al.,[108] we found the highest IRR of MI for

psoriasis patients compared with their comparison group in the age group 30-39 years with an IRR of 5.48 (95% CI 1.24-24.2) (data not shown in table 3.5.1). In the nested case-control analysis restricted to patients below the age of 60 years, we also found a more than 60% increased MI risk for psoriasis patients compared with psoriasis-free patients and a relative risk estimate which was even higher for patients who additionally received oral treatment. Considering psoriasis patients across all age groups, the risk tended to be highest in patients who received UV/oral treatment (of whom 75% received methotrexate, 14% azathioprine, 11% UV/PUVA therapy, and none acitretin or ciclosporin). However, the risk was not related to the duration of psoriasis, a finding which has also been observed in a previous, although much smaller study.[212] Interestingly, the OR tended to be higher for patients with less intense oral treatment (≤2 prescriptions/year) than for those with >2 prescriptions/year. This may be a chance finding due to the wide CIs and the not statistically significant results, or it supports the current notion that disease-modifying antirheumatic drugs (DMARDs), mainly methotrexate, may reduce not only the disease activity in the skin (or in joints in rheumatoid arthritis), but also the risk of cardiovascular morbidity and mortality due to their systemic anti-inflammatory activity.[213-215]

The overall stroke and TIA incidence rates found in our study population were similar to background rates from other UK-based analyses.[211, 216] They did not materially differ between psoriasis patients and the psoriasis-free comparison group which is in contrast to other reports on the association between stroke and psoriasis using the same database.[107, 109, 110] However, in two of these,[107, 109] the same approach was applied as for MI discussed before, and the third one[110] was a crude analysis without validation of stroke cases or adjustment for risk factors. As for MI, we found a tendency among severe psoriasis patients towards higher ORs in patients with less intense oral treatment.

Our study has several limitations. In large observational studies one can never rule out a certain degree of misclassification which may have led to the inclusion of psoriasis or of MI, stroke, or TIA cases who in fact did not have such a diagnosis. However, in previous GPRD-based studies psoriasis had a high validity.[115, 139, 147] Additionally, we applied a stringent predefined algorithm and reviewed a large sample of case profiles so that we were confident that misclassification of MI, stroke, or TIA patients was not a major issue in this study. The first-time recording of a

psoriasis diagnosis by the GP may not be the onset of the disease but rather the first time the disease was brought to medical attention (due to some clinical manifestation). By starting follow-up at that point in time for all patients, we intended to increase the likelihood of beginning follow-up for all patients at a similar stage of the disease. Due to this study design, the number of psoriasis patients exposed to oral treatment was low in our study population, and thus we did not have much information on this subgroup which is thought to have the highest disease severity. It is further possible that some patients may have received some oral or injectable treatment from a specialist which was not recorded by the GP. Such misclassification may have diluted any possible risk differences caused by disease severity to some degree, if indeed any were present. Although we tested for a large number of potential confounding factors, we cannot exclude the possibility that unknown confounders or biases may have affected our results to some degree. The relatively short follow-up time (4.6 years) is also a limitation of the study, as chronic systemic inflammation may take longer to cause adverse cardiovascular outcomes.

In summary, we conclude that by using a different study design than Gelfand et al.[108] we did not find an overall increased risk of MI, stroke, or TIA in all psoriatic patients. However, the MI risk was elevated in psoriatic patients under 60 years of age (mainly with severe psoriasis) independent of other cardiovascular risk factors. The observed trend for a risk reduction with longer-term systemic treatment may be the result of systemic anti-inflammatory effects of methotrexate and other DMARDs, but this observation needs further confirmation due to the limited information in this study.

3.6 PSORIASIS AND RISK OF INCIDENT CANCER: AN INCEPTION COHORT STUDY WITH A NESTED CASE-CONTROL ANALYSIS

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3.6.1 Abstract

Psoriasis has been associated with lymphohaematopoietic and solid cancers; however, reports have been inconsistent.

Cancer incidence was compared between psoriasis and psoriasis-free patients and the roles of psoriasis duration and treatment explored in this observational study using the UK GPRD.

Among 67,761 patients, 1703 patients had incident cancer; 54% had a history of psoriasis (IRR 1.13, 95% CI 1.02-1.24). IRRs for lymphohaematopoietic and pancreatic cancers were 1.81 (95% CI 1.35-2.42) and 2.20 (95% CI 1.18-4.09). In a nested case-control analysis, adjusted ORs for cancer overall were 1.50 (95% CI 1.30-1.74) for psoriasis ≥4 years duration and 1.53 (95% CI 0.97-2.43) for patients receiving systemic treatment (marker of disease severity). Lymphohaematopoietic malignancy risk was highest in patients with systemic treatment (OR 10.17, 95% CI 3.24-31.94). The OR for patients without systemic treatment was 1.59 (95% CI 1.01-2.50) for psoriasis of <2 years and 2.12 (95% CI 1.45-3.10) for ≥2 years duration. Risks of bladder/kidney and colorectal cancers were increased with longer-duration psoriasis.

Psoriasis patients may have an increased overall risk of incident cancer (mainly lymphohaematopoietic and pancreatic). Longer-term psoriasis and more severe disease may increase the risk of some cancers.

3.6.2 Background

Psoriasis is a chronic inflammatory disease with an estimated prevalence in the general population of between 1% and 3%;[139, 217] its impact on QoL is considerable.[64] The disease is characterised by T cell-mediated hyperproliferation of keratinocytes and inflammatory processes based on a complex genetic background. T cells and various other immune cells infiltrate the skin and activate each other and keratinocytes via cytokines, which appear to play a central role in the pathogenesis of psoriasis. This process leads to an increased proliferation of keratinocytes, as well as to the production of other cytokines and growth factors, thereby sustaining the inflammatory process.[48]

A derailed immune response is believed to be involved in the pathogenesis of psoriasis-associated comorbidities. Psoriasis has classically been associated with high physical and psychological morbidity. Better understanding of the underlying immunopathogenesis and intensified epidemiological research suggest that psoriasis is linked to additional comorbid conditions, such as psoriatic arthritis, Crohn's disease, atherosclerosis, myocardial infarction, and metabolic syndrome.[82] The incidence of some cancers, in particular lymphoma, has been reported to be increased in patients with psoriasis. This is due, in part, to the use of immune-suppressive and potentially carcinogenic treatments, such as ciclosporin, methotrexate, and psoralen and ultraviolet A (PUVA) therapy.[81]

Many published studies on the prevalence of cancer in patients with psoriasis have been hospital-based or conducted in patients with PUVA treatment, and results have been inconsistent or difficult to interpret.[113, 114, 117, 119-121, 218-220] Among the population-based studies reported to date, two studies conducted using the GPRD focused on the risk of lymphoma[115, 116] and one using an American claims records database[118] evaluated the risk of all cancers combined, but did not stratify the results by type of cancer.

The aim of the present population-based, observational study was to further elucidate the association between psoriasis and the risk of developing cancer and to provide baseline IRs of different types of cancer in patients followed for a maximum of 11 years after the diagnosis of psoriasis. The effect of disease duration and treatment received was also evaluated.

3.6.3 Methods

This observational study with a nested case-control analysis was conducted to quantify the risk of various cancer types in patients with early psoriasis and to compare results with a matched population without psoriasis.

Data source

We used data from the GPRD, a large UK-based database established in 1987 that includes approximately five million patients who are actively enrolled with selected GPs. These GPs provide data for research purposes; they have been trained to record medical information in a standard manner and to supply it anonymously. Patients enrolled in the GPRD are representative of the UK population with regard to age, sex, geographical distribution, and annual turnover rate. The information recorded includes patient demographics and characteristics (e.g. age, sex, height, weight, and smoking status), symptoms, medical diagnoses, referrals to consultants, hospitalisations, and all drug prescriptions, as the doctors generate prescriptions directly with the computer using a coded drug dictionary. This database has been the source for numerous epidemiological studies (including those of psoriasis) published in peer-reviewed journals and has been described in detail[36, 38] and validated extensively.[34]

The study protocol was approved by ISAC for MHRA database research.

Study population

We included all patients with a first-time diagnosis of psoriasis between 1 January 1994 and 31 December 2005, along with a comparison group of the same number of patients without psoriasis. Patients in the control group were matched to the psoriasis patients on calendar time (follow-up for the matched patient started at the same date as for the psoriasis patient, i.e. at the date of the psoriasis diagnosis), age (same year of birth), sex, general practice, and years of history in the GPRD. Patients with <3 years of history in the database prior to the first-time psoriasis diagnosis (or the corresponding date in the comparison group) were excluded. The validity of psoriasis diagnoses in the GPRD has been documented to be high,[115, 139, 147] and as a result, all patients with a recorded psoriasis diagnosis were included in the analyses, as in previous GPRD-based studies on psoriasis.[155, 158, 221]

Follow-up and identification of incident cancer cases

We excluded patients if they had a history of cancer (malignant or *in situ*; except nonmelanoma skin cancer) or HIV prior to the psoriasis diagnosis or the corresponding date in the comparison group and followed all patients until one of the following events: a first-time diagnosis of cancer (malignant or *in situ*, other than nonmelanoma skin cancer); death; end of follow-up in the medical record; or end of the follow-up period. The date of the cancer diagnosis will be referred to as the index date hereafter. We validated all potential patients with a recorded code for incident cancer using both a computer-based algorithm and manual computer profile review. We included patients if they received cancer treatment (chemotherapy, endocrine therapy, or radiotherapy), were referred to a specialist, were hospitalised, underwent surgery, and/or died within 180 days after the diagnosis. We excluded patients if they did not fulfil these criteria or if there was evidence that the cancer may have been pre-existing rather than newly diagnosed.

Nested case-control analysis

Each patient with cancer was matched with four control patients chosen at random from the study population based on age (same year of birth), sex, and calendar time (same index date, i.e. the date when the patient was first diagnosed with cancer).

We compared the prevalence of diagnosed psoriasis prior to the index date in patients with cancer (overall and stratified by type) and matched controls. Psoriasis patients were classified by duration of disease (<2, ≥2 years or <2 years, 2 to <4 years, or ≥4 years) and treatment (no treatment, topical treatment alone [emollients, salicylic acid, calcipotriol, coal tar, dithranol or tazarotene preparations, or corticosteroids], and/or UV/oral treatment [azathioprine, ciclosporin, methotrexate, acitretin, hydroxyurea, mycophenolate mofetil, or UV/PUVA therapy]). Patients who received treatment were further classified by treatment intensity, defined as ≤4 or >4 prescriptions per year for topical treatment and ≤2 versus >2 prescriptions per year for oral treatment.

Statistical analysis

In the follow-up analysis, we assessed person-years for all patients in the study population from the date of first psoriasis diagnosis (or the corresponding date in the comparison group) until a patient developed an outcome of interest or died, or

follow-up in the medical record ended. We assessed crude IRs of a first-time cancer diagnosis (overall and stratified by cancer type) in patients with or without psoriasis, stratified by age and sex; crude IRRs were calculated with the 95% CI.

In the nested case-control analysis, we performed conditional logistic regression analyses using SAS (version 9.1, SAS Institute Inc, Cary, NC, U.S.A.) to calculate relative risk estimates as ORs with 95% CI. These analyses were controlled for the potential confounders age, sex, and calendar time by matching and were further adjusted for smoking status (none, current, past, or unknown) and BMI (<18.5, 18.5–24.9, 25.0–29.9, ≥30 kg/m^2, or unknown) in the multivariate model, as well as for the presence of benign cancer diagnoses before the index date. In addition, the analysis of digestive organ cancers was adjusted for gastro-oesophageal reflux disease and use of proton pump inhibitors (none, 1–9, or ≥10 prescriptions), the analysis of lung cancer was adjusted for COPD, and the analysis of breast cancer was adjusted for use of oestrogens, progestagens, or oral contraceptives (none, 1–9, or ≥10 prescriptions). The presence of other potential confounding covariates (including alcoholism) not included in the final model because they were not materially associated with the exposure or the outcome was also investigated. A test for trend was performed in the conditional regression analysis to investigate the influence of psoriasis duration on the risk of the different types of cancer. We did not perform any sample size calculation because our main focus was on a high quality analysis by e.g. excluding psoriasis patients with less than three years of active history before the psoriasis diagnosis date, by excluding patients with a history of cancer before the psoriasis diagnosis, and by calculating cancer incidence rates only in patients with a first-time psoriasis diagnosis. Hence, we took all the information we could get within this large database.

3.6.4 Results

The study population consisted of 73,404 patients, including 36,702 with psoriasis (16,969 [46.2%] men and 19,733 [53.8%] women) and 36,702 matched psoriasis-free patients. Compared with those in the comparison group, psoriasis patients were more likely to be current smokers (23.9% vs. 18.8% for psoriasis and non psoriasis patients, respectively) and overweight (BMI 25–29.9 kg/m^2 in 22.7% vs. 21.6% and BMI ≥30 kg/m^2 in 13.3% vs. 10.6%, respectively). The average follow-up time was 4.6 years.

Incidence rates of cancer in the person-time analysis

After excluding patients with a history of cancer or HIV, the remaining study population consisted of 67,761 patients, including 33,760 with psoriasis (46.9% men and 53.1% women) and 34,001 psoriasis-free patients (46.8% men and 53.2% women). Within this population, we identified 1703 patients with an incident cancer diagnosis. The IR was 5.83 (95% CI 5.47-6.22) per 1000 py in patients with psoriasis and 5.18 (95% CI 4.83-5.55) per 1000 py in patients without psoriasis. Among the 1703 cancer cases, 927 (54%) had a history of psoriasis and 776 (46%) did not, resulting in a crude IRR of 1.13 (95% CI 1.02-1.24) for all cancers combined. IRs and IRRs for the different cancers are shown in table 3.6.1 and table 3.6.2, respectively. Overall, the risk of developing lymphohaematopoietic malignancies and cancers of the digestive tract (in particular pancreatic cancer) was statistically significantly increased for patients with psoriasis, although this was not the case for other types of cancer (table 3.6.2). Lymphohaematopoietic malignancies included leukaemia (including other myeloproliferative disorders) and lymphoma. All eight patients with cutaneous T cell lymphoma (CTCL) had psoriasis, therefore the IRR for lymphomas excluding CTCL was also calculated.

Table 3.6.1 Cancer incidence rates stratified by cancer type in patients with or without psoriasis

	Non Psoriasis			Psoriasis		
	Cases	**IR / 1000 py (95% CI)**		**Cases**	**IR / 1000 py (95% CI)**	
All cancer	776	5.18	(4.83 - 5.55)	927	5.83	(5.47 - 6.22)
Lymphohaematopoietic malignancies	62	0.41	(0.32 - 0.53)	119	0.75	(0.63 - 0.90)
CTCL	0	NA	NA	8	0.05	(0.03 - 0.10)
Lymphoma (ex. CTCL)	36	0.24	(0.17 - 0.33)	59	0.37	(0.29 - 0.48)
Leukaemia / MD	26	0.17	(0.12 - 0.25)	52	0.33	(0.25 - 0.43)
Lung	101	0.67	(0.55 - 0.82)	85	0.53	(0.43 - 0.66)
Melanoma	33	0.22	(0.16 - 0.31)	29	0.18	(0.13 - 0.26)
Breast	139	1.71	(1.45 - 2.02)	153	1.79	(1.53 - 2.10)
Prostate	95	1.38	(1.13 - 1.69)	85	1.16	(0.93 - 1.43)
Digestive organs	107	0.71	(0.59 - 0.86)	159	1.00	(0.86 - 1.17)
Pancreas	12	0.08	(0.05 - 0.14)	28	0.18	(0.12 - 0.25)
Oesophagus	16	0.11	(0.07 - 0.17)	23	0.14	(0.10 - 0.22)
Colorectal	55	0.37	(0.28 - 0.48)	79	0.50	(0.40 - 0.62)
Other digestive	24	0.16	(0.11 - 0.24)	29	0.18	(0.13 - 0.26)
Female genital organs	35	0.43	(0.31 - 0.60)	51	0.60	(0.45 - 0.79)
Bladder/kidney	43	0.29	(0.21 - 0.39)	57	0.36	(0.28 - 0.46)
Brain	16	0.11	(0.07 - 0.17)	22	0.14	(0.09 - 0.21)
Other cancers	97	0.65	(0.53 - 0.79)	126	0.79	(0.67 - 0.94)
Metastasis	48	0.32	(0.24 - 0.42)	41	0.26	(0.19 - 0.35)

CTCL = cutaneous T cell lymphoma ; ex. = excluding; MD = other myeloproliferative disorders; IR = incidence rate; py = person-years; CI = confidence Interval; Other cancers: oral cavity, bone, male genital organs, parathyroid carcinoma, thymoma, and unspecified; Person times in non psoriasis patients: overall 149,900.2 py, men 68,843.7 py, women 81,056.6 py, <60 years 104,108.4 py, ≥60 years 45,791.9 py; in psoriasis patients: overall 158,906.0 py, men 73,553.5 py, women 85,352.5 py, <60 years 111,945.2 py, ≥60 years 46,960.8 py

Table 3.6.2 Incidence rate ratios of cancer, stratified by type, sex, and age (reference group: patients without psoriasis)

Type	overall		men		women		<60 years		≥60 years	
	IRR	(95% CI)	IRR	(95% CI)	IRR	(95% CI)	IRR	(95% CI)	IRR	(95% CI)
All cancer	1.13	(1.02 - 1.24)	1.11	(0.97 - 1.28)	1.14	(1.00 - 1.30)	1.19	(0.99 - 1.43)	1.13	(1.02 - 1.27)
Lymphohaematopoietic malignancies	1.81	(1.35 - 2.42)	2.45	(1.67 - 3.59)	1.24	(0.79 - 1.94)	2.17	(1.25 - 3.78)	1.74	(1.24 - 2.45)
Lymphoma overall	1.76	(1.19 - 2.58)	2.15	(1.27 - 3.63)	1.40	(0.79 - 2.48)	2.38	(1.19 - 4.75)	1.59	(1.00 - 2.53)
Lymphoma (ex. CTCL)	1.55	(1.03 - 2.31)	1.76	(1.01 - 3.08)	1.35	(0.76 - 2.41)	2.07	(1.00 - 4.28)	1.41	(0.87 - 2.28)
Leukaemia + MD	1.89	(1.21 - 2.94)	2.88	(1.65 - 5.05)	1.02	(0.49 - 2.11)	1.86	(0.74 - 4.69)	1.95	(1.18 - 3.23)
Lung	0.79	(0.60 - 1.06)	0.80	(0.56 - 1.13)	0.78	(0.48 - 1.29)	0.74	(0.35 - 1.58)	0.83	(0.61 - 1.13)
Melanoma	0.83	(0.50 - 1.36)	0.73	(0.36 - 1.46)	0.95	(0.46 - 1.94)	0.83	(0.43 - 1.60)	0.84	(0.39 - 1.80)
Breast	1.04	(0.83 - 1.31)	NA	NA	1.04	(0.83 - 1.31)	0.98	(0.68 - 1.40)	1.11	(0.82 - 1.49)
Prostate	0.84	(0.63 - 1.12)	0.84	(0.63 - 1.12)	NA	NA	0.76	(0.32 - 1.83)	0.88	(0.65 - 1.20)
Digestive organs	1.40	(1.10 - 1.78)	1.25	(0.91 - 1.71)	1.64	(1.14 - 2.38)	1.80	(1.00 - 3.25)	1.38	(1.06 - 1.79)
Pancreas	2.20	(1.18 - 4.09)	2.43	(0.97 - 6.13)	2.03	(0.88 - 4.69)	NA	NA	2.11	(1.12 - 3.99)
Oesophagus	1.36	(0.72 - 2.54)	1.40	(0.64 - 3.08)	1.27	(0.44 - 3.61)	2.48	(0.76 - 8.09)	1.13	(0.54 - 2.36)
Colorectal	1.35	(0.97 - 1.90)	1.30	(0.82 - 2.05)	1.42	(0.86 - 2.36)	1.21	(0.53 - 2.74)	1.43	(0.99 - 2.07)
Other digestive	1.14	(0.67 - 1.95)	0.80	(0.42 - 1.52)	2.85	(1.07 - 7.59)	2.79	(0.70 - 11.17)	1.02	(0.57 - 1.83)
Female genital organs	1.38	(0.91 - 2.11)	NA	NA	1.38	(0.91 - 2.11)	1.93	(1.04 - 3.59)	1.06	(0.60 - 1.90)
Bladder/kidney	1.25	(0.84 - 1.85)	1.11	(0.70 - 1.76)	1.71	(0.81 - 3.59)	0.78	(0.24 - 2.53)	1.37	(0.90 - 2.08)
Brain	1.30	(0.69 - 2.45)	1.74	(0.72 - 4.18)	0.95	(0.38 - 2.39)	1.70	(0.66 - 4.41)	1.07	(0.46 - 2.52)
Other cancers	1.23	(0.94 - 1.59)	1.14	(0.77 - 1.67)	1.31	(0.91 - 1.88)	1.06	(0.68 - 1.67)	1.35	(0.98 - 1.87)
Metastasis	0.81	(0.53 - 1.22)	1.25	(0.64 - 2.42)	0.60	(0.35 - 1.03)	1.49	(0.50 - 4.42)	0.75	(0.48 - 1.17)

ex. = excluding; CTCL = cutaneous T cell lymphoma; MD = other myeloproliferative disorders; IRR = incidence rate ratio; CI = confidence interval

Other cancers: includes oral cavity, bone, male genital organs, parathyroid carcinoma, thymoma, and unspecified

Nested case-control analysis – overall cancer risk

We included all 1703 incident cancer cases and 6812 matched controls without cancer in the nested case-control analysis; patient characteristics are summarised in table 3.6.3.

Table 3.6.3 Characteristics of cancer cases and controls in the nested case-control analysis

Variable	Cases No (%) (n = 1703)		Controls No (%) (n = 6812)		Adjusted OR* (95% CI)	
Sex**						
Men	828	(48.6)	3312	(48.6)	-	-
Women	875	(51.4)	3500	(51.4)	-	-
Agegroup (years)**						
<30	34	(2.0)	137	(2.0)	-	-
30-59	418	(24.5)	1687	(24.8)	-	-
≥60	1251	(73.5)	4988	(73.2)	-	-
Smoking status						
Non smoker	726	(42.6)	3232	(47.4)	1.00	(reference)
Current smoker	396	(23.3)	1361	(20.0)	1.31	(1.14 - 1.51)
Ex smoker	418	(24.5)	1498	(22.0)	1.26	(1.10 - 1.45)
Unknown	163	(9.6)	721	(10.6)	1.07	(0.85 - 1.35)
BMI (kg/m^2)						
12-18.4	46	(2.7)	95	(1.4)	1.71	(1.18 - 2.48)
18.5-24.9	548	(32.2)	2092	(30.7)	1.00	(reference)
25-29.9	496	(29.1)	2173	(31.9)	0.87	(0.76 - 1.00)
30-60	313	(18.4)	1149	(16.9)	1.05	(0.89 - 1.23)
Unknown	300	(17.6)	1303	(19.1)	0.89	(0.75 - 1.07)
Benign cancer	372	(21.8)	1072	(15.7)	1.53	(1.34 - 1.76)

* Adjusted for all covariates listed in the table; ** matching variable; BMI = body mass index; OR = Odds ratio; CI = confidence interval

The adjusted OR of developing cancer for patients with psoriasis was slightly over one relative to patients without psoriasis; this increased with duration of psoriasis (OR of 1.50, 95% CI 1.30-1.74 in patients with ≥4 years psoriasis duration), mainly among patients ≥60 years of age (table 3.6.4 and figure 3.6.1). A possible link with severity of psoriasis using treatment as a proxy was observed: the OR was 1.53 (95% CI 0.97-2.43) for all patients receiving oral treatment and 2.48 (95% CI 1.08-5.72) for male patients receiving high-intensity oral treatment (table 3.6.4). In total, 96

patients received oral psoriasis treatment, 72% of whom received methotrexate. In patients who did not receive oral treatment, the adjusted OR was 1.31 (95% CI 1.16-1.48) for psoriasis patients with ≥2 years disease duration. The cancer risk also remained increased for patients with longer-term psoriasis duration in sensitivity analyses [1] excluding all patients with a prescription for biologicals, ciclosporin, or methotrexate at any time and irrespective of indication and [2] adjusting the main models for any use of ciclosporin, methotrexate, and biologicals.

Table 3.6.4 Relative cancer risk stratified by age, sex, duration, and severity of psoriasis in the nested case-control analysis

	Cases No (%) (n = 1703)		Controls No (%) (n = 6812)		Adjusted OR* (95% CI)	
No Psoriasis	776	(45.6)	3394	(49.8)	1.00	(reference)
Psoriasis	927	(54.4)	3418	(50.2)	1.13	(1.02 - 1.26)
Short-term disease (<2 years)	334	(19.6)	1517	(22.3)	0.91	(0.79 - 1.05)
Women	168	(9.9)	802	(11.8)	0.84	(0.69 - 1.03)
Men	166	(9.7)	715	(10.5)	0.98	(0.80 - 1.20)
<60 years	112	(6.6)	387	(5.7)	1.29	(0.99 - 1.68)
≥60 years	222	(13.0)	1130	(16.6)	0.79	(0.66 - 0.93)
Long-term disease (≥2 years)	593	(34.8)	1901	(27.9)	1.31	(1.17 - 1.48)
Women	309	(18.1)	991	(14.5)	1.29	(1.09 - 1.53)
Men	284	(16.7)	910	(13.4)	1.33	(1.13 - 1.58)
<60 years	142	(8.3)	533	(7.8)	1.14	(0.90 - 1.45)
≥60 years	451	(26.5)	1368	(20.1)	1.37	(1.19 - 1.57)
Untreated psoriasis	48	(2.8)	245	(3.6)	0.81	(0.59 - 1.12)
Women	24	(1.4)	139	(2.0)	0.70	(0.45 - 1.09)
Men	24	(1.4)	106	(1.6)	0.95	(0.60 - 1.51)
Topical treatment	853	(50.1)	3103	(45.6)	1.15	(1.03 - 1.28)
Women	440	(25.8)	1613	(23.7)	1.12	(0.97 - 1.30)
Men	413	(24.3)	1490	(21.9)	1.18	(1.02 - 1.38)
Oral treatment (+/- topical)	26	(1.5)	70	(1.0)	1.53	(0.97 - 2.43)
High intensity	16	(0.9)	43	(0.6)	1.56	(0.87 - 2.80)
Women	13	(0.8)	41	(0.6)	1.25	(0.66 - 2.36)
High intensity	7	(0.4)	26	(0.4)	1.06	(0.45 - 2.46)
Men	13	(0.8)	29	(0.4)	1.99	(1.02 - 3.91)
High intensity	9	(0.5)	17	(0.2)	2.48	(1.08 - 5.72)
<60 years	7	(0.4)	21	(0.3)	1.56	(0.64 - 3.82)
≥60 years	19	(1.1)	49	(0.7)	1.47	(0.85 - 2.54)

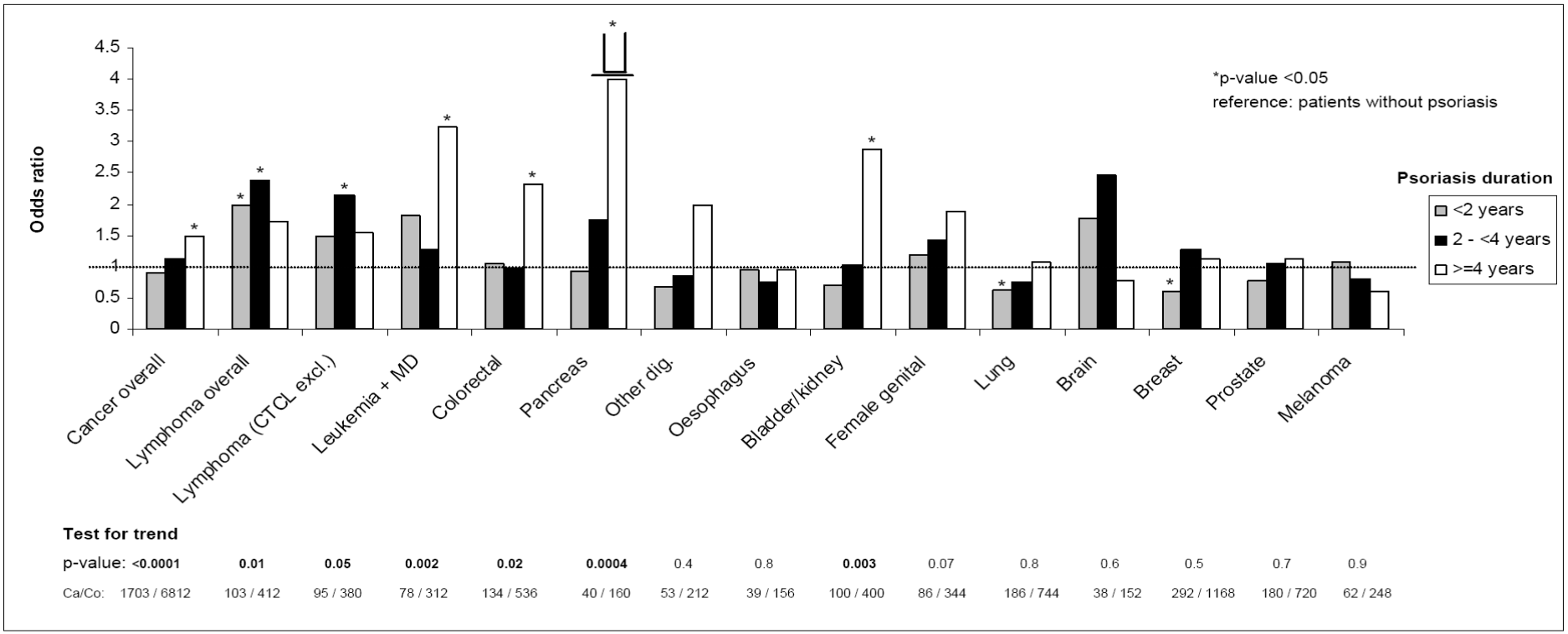
* Adjusted for body mass index, smoking, benign cancers; OR = odds ratio; CI = confidence interval

In a further analysis including only case patients who developed cancer ≥6 months after the start of follow-up (n = 1539), an OR of 1.44 (95% CI 1.28-1.63) was observed for patients with psoriasis of ≥2 years duration compared with the psoriasis-free comparison group. Among those who had no benign neoplasms before the index date (372 cases and 1072 controls), the OR was 1.30 (95% CI 1.13-1.49) for patients with psoriasis of ≥2 years duration compared with the psoriasis-free reference group.

Nested case-control analysis – stratified by type of cancer

Figure 3.6.1 shows the risks of different cancer types in patients with psoriasis in relation to duration of psoriasis and compared with psoriasis-free patients. The overall relative risk of developing a lymphohaematopoietic malignancy was increased by about two-fold for patients with psoriasis compared with the psoriasis-free control group. The risk was highest in patients who received oral treatment, resulting in an OR of 10.17 (95% CI 3.24-31.94) for any treatment and 16.79 (95% CI 3.23-87.22) for those with >2 prescriptions. An analysis restricted to patients without oral treatment yielded adjusted ORs of 1.59 (95% CI 1.01-2.50) for patients with psoriasis of <2 years duration and 2.12 (95% CI 1.45-3.10) for those with psoriasis of ≥2 years duration. Stratification by age yielded increased overall risks for both age groups (OR 2.77, 95% CI 1.39-5.52 for patients aged <60 years and OR 1.84, 95% CI 1.24–2.73 for those aged ≥60 years). When the risks of developing lymphoma or leukaemia were explored separately, the highest OR was 3.22 (95% CI 1.64-6.35) for leukaemia in patients with psoriasis of ≥4 years duration. The relative risk was increased for lymphoma already in patients with early psoriasis (figure 3.6.1), particularly among patients <60 years of age (data not shown). All eight patients with CTCL had a history of psoriasis, compared with only 34% of the 32 controls.

For cancers of the colon/rectum, pancreas, and bladder/kidney, the risk increased with duration of psoriasis (see test for trend in figure 3.6.1). Furthermore, an analysis restricted to patients with a normal BMI yielded an OR of 6.10 (95% CI 1.27-29.32) for pancreatic cancer in psoriasis patients compared with psoriasis-free patients. The relative risk of melanoma tended to decrease in patients with psoriasis of longer duration (figure 3.6.1). A tendency towards an increased risk of brain cancer was observed in male patients with psoriasis duration ≥2 years (OR 3.38, 95% CI 0.92–12.45), although the number of cases of brain cancer was low overall (data not shown).



Ca/Co = number of cases and controls on which the results are based; CTCL = cutaneous T cell lymphoma; dig = digestive organs; excl. = excluded; MD = other myeloproliferative disorders.

Odds ratios are adjusted for age, sex, and calendar time by matching, and for smoking, body mass index, presence of benign cancer (all cancers), presence of gastro-oesophageal reflux disease (digestive organ cancers), use of proton pump inhibitors (digestive organ cancers), presence of chronic obstructive pulmonary disease (lung cancer) and use of oestrogens, progestagens, or oral contraceptives (breast cancer).

Figure 3.6.1.Psoriasis duration and risk of cancer by specific cancer type

3.6.5 Discussion

The findings of this large population-based study suggest that patients with psoriasis appear to be at an increased risk of developing certain cancers, especially patients with long psoriasis duration and possibly severe disease. Findings to date have been inconsistent, however, and, with the exception of evidence that is strongly suggestive of an increased incidence of lymphoma in this population,[115, 116] no clear links between specific cancers and psoriasis have been identified. Some studies in which the overall cancer risk was not stratified by duration or severity of psoriasis reported an increased risk,[113, 114, 117, 119] but not all.[115, 218, 220] The findings of the present population-based study, based on a follow-up of a large group of patients, provide evidence of an association between psoriasis and specific cancers that increases with disease duration.

There is a suggestion, in the present data, that the overall risk of developing cancer (excluding nonmelanoma skin cancers) is slightly increased in patients with psoriasis compared with psoriasis-free patients. Furthermore, patients with long-duration psoriasis appeared to be at increased risk for colorectal, bladder, and kidney cancers, as well as pancreatic and lymphohaematopoietic cancers. Patients receiving oral treatment, which can be considered a proxy for disease severity, were also at increased risk of developing cancer, with the greatest effect observed in men receiving high-intensity treatment.

Other studies have reported that patients with psoriasis are at an increased risk of developing leukaemia[86, 222, 223] and other myeloproliferative disorders, in particular lymphoma.[115-118, 219, 224-226] In the present study, the increased risk was most prominent in male patients (as observed by Margolis et al.[118]) and, in the case of lymphoma, in patients with psoriasis of shorter duration. Similar results were seen when all lymphomas and lymphoma excluding CTCL were considered, allowing for the possibility of misclassification of psoriasis and CTCL. One explanation for the increase in these cancers may be the antigen-driven proliferation of lymphocytes in chronic inflammation caused by psoriasis (antigenic stimulation hypothesis).[223]

Previous studies have identified associations between psoriasis and a range of cancers, including those of the lung,[86, 113, 114, 117, 119] liver,[113] oropharynx,[113, 114, 117, 119] colon,[114, 119, 120] kidney,[113, 119, 219, 220] breast,[113, 120, 121, 220] central nervous system,[120, 121] pancreas,[113] genital organs,[113] and thyroid.[121] The results of the various studies were conflicting, possibly due to differences in study designs. With the exception of

pancreatic and lymphohaematopoietic cancers, we did not find an increased risk for these cancers in the overall psoriasis population. In the case of smoking-related cancers, this may be due, at least in part, to the fact that we adjusted for smoking, whereas similar adjustment was not undertaken in earlier studies. The risk of cancers of the colon/rectum, pancreas, bladder, and kidney significantly increased in patients with psoriasis of long duration. As chronic inflammation influences initiation and progression of neoplastic growth,[227] it is conceivable that the chronic inflammation sustained with psoriasis of longer duration may play a role in the development of cancer in patients with severe psoriasis. Like psoriasis, lupus erythematodes and rheumatoid arthritis are also chronic inflammatory diseases, and they have also been associated with certain types of cancer.[228, 229]

In this study, there was a tendency of an increase in the risk of cancer with increasing disease severity. Other studies have also shown an association between the severity of psoriasis and increased cancer. In a study performed using the Medicaid databases,[118] patients with severe psoriasis had an increased cancer risk of 78% compared with the reference group of hypertensive patients. As patients with severe psoriasis may receive drugs, such as methotrexate, ciclosporin, or PUVA therapy, all of which have been associated with lymphoproliferative disorders[230-233] and malignancies (particularly nonmelanoma skin cancers),[59, 234-236] we conducted a number of sensitivity analyses in which patients with these treatments were excluded. A longer-term history of psoriasis (≥2 years) remained associated with an increased relative cancer risk in this subset of patients, indicating that this effect was independent of treatment received.

Our study has several limitations. First, in large observational studies, a certain degree of diagnosis misclassification cannot be ruled out. However, in previous GPRD-based studies on psoriasis or cancer, the validity of these diagnoses has been high.[115, 139, 147, 237] The epidemiology of psoriasis in the GPRD is similar to other population-based studies in the UK, 92% of patients with a psoriasis code received psoriasis treatment, and, of a random sample of GPs, about 90% confirmed the psoriasis diagnosis after four years of follow-up. Furthermore, the incidence rate of psoriasis in our study population (not shown) is closely similar to the rate of another study on the GPRD with validated psoriasis patients.[66] In contrast to the USA, most psoriasis patients in the UK are diagnosed and managed in primary care and are not referred to a specialist.[54, 66] Second, the initial recording of a psoriasis diagnosis by

the GP is not the date of onset of the disease but rather the point in time when the disease was brought to medical attention for the first time. Follow-up was started at the first recorded psoriasis diagnosis to increase the likelihood of beginning follow-up for all patients at a similar stage of the disease. Third, the number of psoriasis patients exposed to oral therapies was low in our study population, and therefore information on this subgroup, which may have the greatest disease severity, is limited. It is possible that some patients may have received oral or injectable treatment from a specialist that was not recorded by the GP; such misclassification, if indeed present, may have diluted differences in risk caused by disease severity. Fourth, although we tested for a large number of potential confounding factors, we cannot exclude the possibility that unknown confounders or biases may have affected our results.

On the other hand, this study has an important strength: it reports the findings of a follow-up of a large population of people with psoriasis whose medical information was recorded prior to the cancer diagnosis, thereby eliminating concerns about biased reporting of date of psoriasis diagnosis, treatments, and other potential confounders.

In conclusion, this observational study conducted on a large population-based data resource explored the association between early psoriasis and the risk of incident cancers. Patients with psoriasis had an increased risk of developing lymphohaematopoietic or certain types of solid cancers. The risk for solid cancers was increased primarily in psoriasis patients with a longer-term disease history. Further investigation into common mechanisms underlying psoriasis and the cancers identified in this study is warranted.

Chapter 4

DISCUSSIONS, CONCLUSIONS, OUTLOOK

4 DISCUSSION, CONCLUSIONS, AND OUTLOOK

4.1 DISCUSSION

In past years, an increasing number of epidemiological research on psoriasis has been published, in parallel with the investigation of new drugs for the treatment of this skin disorder and their introduction on the market (primarily biologicals). The aim of this work was to contribute to the current knowledge of the natural history of psoriasis by addressing uncertain issues due to conflicting results in the literature or due to weak or lack of data.

Detailed evaluations of the results of Studies 3.1 – 3.6 are presented in the discussion sections of the respective studies. In appendix 5.3 the aims and the main results of the six studies are briefly summarised. In the following, some general aspects which these studies may have raised will be discussed.

Use of beta-blockers or lithium and the risk of psoriasis (Study 3.1 / 3.2)

The fact that Study 3.1 did not suggest a materially altered risk of a first-time psoriasis diagnosis after exposure to beta-blockers, emphasises the importance of not taking an observation for granted, but to re-evaluate a hypothesis upon availability of new data. Beta-blockers are, along with lithium and antimalarials, the drugs which have been most commonly related to the induction or exacerbation of psoriasis. They are mentioned in most standard dermatology textbooks as risk factors for the skin disease. However, evidence of a potential association was primarily based on case reports and case series, which have a low level of evidence according to the Oxford Centre for EBM.[13] Although case reports are important to indicate early a rare adverse event to a drug or to raise hypotheses, it is difficult to rule out that an observed event did not happen by chance, especially if the latency period was long, if the event happens quite frequently independent of drug exposure (e.g. psoriasis with a prevalence between 2% - 3% in northern Europe[87]), if the event was not pharmacologically predictable (type B reactions; in contrast to type A reactions which are pharmacologically predictable), or if the reaction was not confirmed by dechallenge and rechallenge. Furthermore, the chance that an event is reported in relation to exposure to a certain drug increases once such an association has become public. Several articles have warned against publication bias and

overinterpretation of case reports in the literature.[2] A review published 1982 in the British Medical Journal[238] elucidated this problem. The author showed that of 47 anecdotal reports published in four highly ranked journals of internal medicine, causality was doubtless or reasonable for 28 (60%), while the 19 (40%) remaining required verification which was done for 7 (15%). In total, 12 (25%) had not been verified within approximately 20 years. While 8 reported *rare* clinical syndromes with no further published associations with the suspected drugs, the other 4 reactions were relatively *common* clinical syndromes. Although there had been further reports for two of them, this was not enough for verification; this is an epidemiological problem[238] and would require investigation with sound epidemiological methods. The purpose of Study 3.1 was to investigate the reported (in case reports and case series) association between beta-blockers and *induction* of psoriasis, and it could not be confirmed. Apart from this observation, the alternating theory on the pathogenesis of psoriasis as described in the introduction (chapter 1.2.2) is another example in the research history of psoriasis which should have taught researchers not to establish dogmas and to be open to new hypotheses.[239]

One could argue that the results of Study 3.1 were distorted because for some patients in the study the psoriasis diagnosis may not have been incident, or it may have been misclassified first as another skin disorder. Due to the notion of a possible association between beta-blockers and psoriasis (and other skin reactions), these patients may have received another drug instead of a beta-blocker to treat the underlying disease (= protopathic bias, a type of selection bias[1]). However, three points contradict this argument: First, sensitivity analyses only including subgroups of patients with a high probability of incident psoriasis or without any skin reactions before the first recording of psoriasis left the results virtually unchanged. Second, past exposure to beta-blockers did not show an increased risk of psoriasis either. Third, Study 3.2 could show an increased risk of psoriasis after mainly long-term exposure to lithium, and this drug had also been associated with psoriasis (and other skin reactions) in several case reports.

The association between antimalarial drugs and psoriasis was not studied because recording of the exposure to this drug class may be incomplete in the GPRD, and this could lead to biased results.

Use of thiazolidinediones, other antidiabetics, and psoriasis (Study 3.3)

Study 3.3 shows that observational epidemiological studies can also have a place in identifying or confirming potential new indications of a drug or of drug classes. An early example was a study conducted by the BCDSP in 1974[240] with the finding of a protective effect of acetylsalicylic acid on the development of acute MI. By studying the potential mechanism of action of such a drug in relation to the disease, it may be possible to learn more about the pathomechanism and the risk factors of this disease or to get ideas for predictive tests.[241] However, one can measure such a protective effect of a drug on an outcome that can be expected only as long as this effect is not known yet because afterwards, future case patients may receive the drug in an attempt to prevent the disease or to treat first signs of the disease not (yet) confirmed (= protopathic bias[1]). A protective effect can then not be measured anymore.

While randomised controlled trials deliver primarily results of efficacy, observational studies provide effectiveness data. In combination they can improve the understanding of the outcomes associated with certain therapies. An example of such a 'synergism' was the understanding of the value of cholesterol control in the prevention and treatment of coronary heart disease.[2] However, observational effectiveness studies may be prone to *confounding by indication* if they focus on *expected* drug effects. Confounding by indication refers to 'an extraneous determinant of the outcome parameter that is present if a perceived high risk or poor prognosis is an indication for intervention',[242] i.e. the drug of interest is prescribed selectively depending on the severity or prognosis of the underlying disease to be treated, and this influences the outcome of interest. The use of propensity scores is a relatively new statistical approach for a better control of such selective prescribing in observational research. The probability or propensity of receiving a treatment depending on an individual's covariates or risk factors is determined for each individual, and this score can be considered in the analysis (by matching, adjusting, or stratification).[1] In Study 3.3, confounding by indication was not an issue because effectiveness of thiazolidinediones was investigated *before* the patients developed psoriasis, i.e. it was tested if the drugs could prevent the disease, and a protective effect could not be anticipated by the GPs. The effectiveness data of Study 3.3 together with the partly favourable results of thiazolidinediones in the treatment of psoriasis may strengthen the hypothesis that this drug class influences the pathophysiology of psoriasis in a positive way.

Psoriasis and diabetes (Study 3.4)

Several published studies reported an increased prevalence of diabetes in patients with psoriasis. However, most of them were cross-sectional.[243] A major disadvantage of this design is that exposure and outcome data are collected at the same time. Hence, the temporal relation between the two measures (in this case psoriasis and diabetes) cannot be determined, i.e. it is hardly possible to tell which came first. Cross-sectional studies belong to the *descriptive* observational studies (see figure 1.1.3 in the introduction section) and are primarily useful for the generation of hypotheses, not for testing them.[2, 16] With Study 3.4, a cohort study with a nested case-control analysis, incidence rates of diabetes in patients with or without psoriasis could be determined and psoriasis, particularly severe psoriasis of longer-term duration, be identified as a risk factor for diabetes. Additionally, the results of Study 3.3 suggested that patients with psoriasis did not have an increased prevalence of diabetes *before* the first-time recorded diagnosis of their skin disorder. This observation was confirmed by another case-control study investigating the medical history of patients with psoriasis.[244]

Psoriasis and cardiovascular diseases (Study 3.5)

There has been much discussion about the association between psoriasis and cardiovascular diseases recently, mainly also after Gelfand et al.[108] had published a population-based cohort study using GPRD data in the Journal of the American Medical Association concluding that psoriasis patients, primarily those of young age and with severe disease, had an increased risk to develop MI. In the past, there had been conflicting results about this association in the literature. Study 3.5 was designed to investigate this association by using a different approach than the one by Gelfand et al.[108] (The differences between the two approaches are pointed out in the discussion section of Study 3.5.) In Study 3.5, the incidence rates of MI in patients with psoriasis and the control group were lower than in the approach by Gelfand et al.[108] Furthermore, there was no overall increased risk of MI in patients with psoriasis, but only in subgroups, mainly of young patients and patients with severe disease, as reported by Gelfand et al.[108] In his article on interventional and observational studies JP Vandenbroucke[15] emphasised the importance of replicating findings from observational studies with different methods and of discussing the differences due to the potential of bias, confounding, or multiple analyses in

observational research. This was done in this case: While both studies showed an increased risk of MI in subgroups of patients with psoriasis, Study 3.5 slightly attenuated the association in that sense that patients with mild psoriasis may be less worried (if at all) to develop an MI.

The different incidence rates of MI found with the two different study designs, may point to an emerging caveat in the reporting of observational studies in the future: While the rates provided by Gelfand et al.[108] may not be incidence rates in the stricter sense due to inclusion of patients with a potential history of an MI in the study, they are useful for the comparison of rates of spontaneous MI reports in relation with a drug because the 'real life situation' is reflected; spontaneous reports are generated irrespective of a patient's MI anamnesis. The rates in Study 3.5 are first-ever (incident) rates of MI in patients with psoriasis and may be rather valuable for an analytical (or causal) evaluation of the association between psoriasis and MI.

The different findings of two nested case-control studies on the association between PPIs and fracture risk may reflect a similar situation. While the first study,[245] in which all potential confounders of the association were adjusted for in the analyses, yielded an increased fracture risk after long-term exposure to PPIs, the second one,[246] which excluded all patients with potential confounders in their characteristics, could not confirm this association. The latter study may have been more an analytical approach to study a potential relation between exposure and outcome by trying to exclude as many potential confounders as possible (comparable to the strict in- and exclusion criteria of interventional trials), while the first study may rather reflect the 'real life situation'.

In future, it may be important to report more accurately the exact purpose of the study, i.e. rather reflection of the 'real life situation' or a more analytical investigation to learn more about a potential causal association between exposure and outcome (bearing always in mind that causality cannot be proven with observational research alone).

Psoriasis and cancer (Study 3.6)

The medical literature encompasses several studies on the association between psoriasis and cancer, often with conflicting results (appendix 5.4). Looking at these studies in detail, one realises that different study designs were applied or different study populations investigated. This underpins the statement by JP Vandenbroucke[15]

that systematic reviews of observational studies may be difficult, and that the advantages and disadvantages of the different studies should be discussed. The aim of Study 3.6 was to analyse a potential association between psoriasis and cancer by including only patients with a first-time recording of a psoriasis diagnosis and following them for a potential incident cancer diagnosis. The findings suggest duration of psoriasis as a risk factor for the development of solid cancers. This may explain some of the conflicting results of this association in the literature because in most previous studies follow up of patients with psoriasis began at different stages of the skin disease.

Incident psoriasis, validation of diagnoses, and severity of psoriasis

The study population of the three case-control and the three cohort studies consisted of patients with a first-time diagnosis of psoriasis. To increase the likelihood of only including patients with a first-time diagnosis, patients had to have at least three years of active history in the database. One could argue that for psoriasis, being a chronic and not an acute disorder, the disease may have begun already before the first-time recording in the medical records. In a *cohort study*, however, the study population should by definition be followed from the beginning of the exposure[2] (here 'psoriasis'). The start of follow-up at the first recording of a psoriasis diagnosis was probably a good solution to consider this requirement in database research; follow-up started for all patients when the disease was first brought to medical attention which increased the likelihood that patients were in a similar stage of the disease. In the *case-control studies*, sensitivity analyses including only patients who did not have quite specific treatment for psoriasis or who did not have skin disorders before the first recording of psoriasis were conducted to confirm the results.

An advantage of selecting patients with a first-time recording of psoriasis and looking back in time with a case-control design and forward in time with a cohort design was the possibility to learn more about the temporal sequence of the association between psoriasis and other diseases or risk factors.

In general, research in pharmacoepidemiology seems to move more and more from infectious diseases or acute events to chronic diseases. Defining the beginning of such a chronic state may always be a challenge, also due to genetic predisposition, and one should accept that the optimal solution can only be approached at the moment.

Misclassification of diseases can be an issue in observational database research. For psoriasis however, Gelfand et al.[115, 139, 147] could show a high validity of the diagnosis in the GPRD. Furthermore, the incidence rates of psoriasis in our study population (chapter 1.2.5.1, figure 1.2.3) were similar to the rates of another study conducted with data from the GPRD.[66] The authors of that study only included validated patients and conducted sensitivity analyses to confirm the results in patients with a high likelihood of having an incident psoriasis diagnosis. In the *case-control studies* of this thesis, sensitivity analyses in a subgroup of patients with quite specific treatment for psoriasis after the diagnosis were done in addition to the sensitivity analyses in patients with highly probable incident psoriasis diagnoses. In the *cohort studies,* the patients for the outcomes studied (i.e. diabetes, MI, stroke, TIA, and cancer) were selected with a stringent predefined algorithm based on precedent profile review and blinded with regard to the exposure status.

For the studies of this thesis, severity of psoriasis was primarily defined by treatment of the disease. This approach was chosen in previous studies by other groups as well, but is only an approximation to the optimum. Even in clinical practice the definition of severity of psoriasis has proven to be difficult (chapter 1.2.3). The number of patients classifying for having severe psoriasis in the studies of this thesis was low, probably due to selection of only patients with a first-ever recording of psoriasis in the database.

Major advantages and disadvantages of database research

Database research permits the generation and analysis of hypotheses within a usually large study population, and - depending on how long the database has been in place - effects with long latency periods can be studied. Studies can be conducted at a relatively low cost and often within a short time because data are already available (although not always in the format required). Timing may be an important aspect in the evaluation of an adverse drug reaction. Furthermore, certain databases, such as the GPRD, are representative of the population and hence, allow the execution of population-based studies.

Bias is inherent in observational study designs and can influence the validity of these studies. *Information / observation bias* results from systematic differences in the way data on exposure or outcome are obtained from the various study groups, e.g.

differences in patients' recall on exposure (= recall bias) or differences in collecting or recording of information from the patients (= interviewer bias).[16] As data from the GPRD result from medical records, they are collected independent of any research question, and thus the likelihood of such a bias in Studies 3.1 – 3.6 is small. Other biases[1, 2] such as *selection bias*, which results from different criteria applied to enrol cases and controls in a study, *misclassification bias*, which results from error in classifying study participants with regard to their exposure or disease status, or *confounding* (in particular *residual confounding*) may be of concern also in database research. For Studies 3.1 – 3.6 these types of biases are discussed in the respective manuscript or in the discussion sections above. Finally, in database research, information on drug use is usually based on prescription data. Hence, it is not sure if and when the patient took the drug.

In summary, when doing this type of research, it is important to understand the database used in great detail to be able to decide what is feasible and what is not and to critically discuss the findings.

4.2 CONCLUSIONS

Pharmacoepidemiology plays an increasing role in the development process of drugs and is an important tool for the constant risk-benefit analysis and the risk management of drugs. Apart from the traditional studies on adverse or beneficial drug reactions, studies on disease epidemiology to gain (more) information on the burden of a disease (incidence, prevalence data), on risk factors and comorbidities, or on drug utilisation are more and more conducted because such information helps in the risk-benefit analysis of a drug developed or marketed for that particular disease. Furthermore, increased knowledge of diseases helps healthcare professionals to make decisions in their daily clinical practice.

Psoriasis exemplifies this trend. It is a common chronic disorder, and a couple of innovative drugs (mainly biologicals) have emerged on the market recently or are in the development stage. Hence, much research is currently being conducted in this area, and, as mentioned above, epidemiological data play an important role. One focus of this thesis was on two areas of the natural history of psoriasis which may have been neglected so far: (1) Drugs as potential risk or protective factors to develop psoriasis and (2) the temporal sequence of the association between psoriasis and other diseases or risk factors. In the following, the main findings of the six studies are briefly summarised.

- In contrast to the current proposition in the literature, use of beta-blockers as well as of other antihypertensive drugs was not associated with a materially altered psoriasis risk. The data, however, do not allow inferences on the relation between these drug classes and the exacerbation of pre-existing psoriasis.
- Consistent with the literature (case reports and case series), exposure to lithium, mainly long-term, increased the risk of developing psoriasis by 70 – 100%. This seemed to be the case mainly in older and female patients.
- Long-term use of atypical antipsychotics, primarily olanzapine, may have a protective effect on the development of psoriasis, primarily in young and male patients. The effect of atypical antipsychotics on cytokines could explain this observation and merits further investigation.
- The risk of diabetic patients with long-term exposure to thiazolidinediones to develop psoriasis was decreased yielding an OR of 0.33 (95% CI 0.16-0.66). This finding was intriguing despite the low number of patients exposed. The

observation of a reduced psoriasis risk after long-term exposure to metformin needs further investigation.

- Several factors may lead to a small increased psoriasis risk, such as smoking, high BMI, alcoholism, skin infections, or a psychiatric diagnosis in close proximity to the psoriasis diagnosis date.
- A precedent diagnosis of diabetes did not seem to alter the psoriasis risk, but patients with psoriasis had an overall increased diabetes risk of about 30% which increased to about 150% for patients with long-term psoriasis receiving oral treatment. This risk seemed independent from high BMI alone.
- The overall risk of MI, stroke, and TIA was not elevated in patients with early psoriasis. In subgroups of patients <60 years of age and with severe psoriasis, however, the MI risk was increased. Cardiovascular diseases did not seem to alter the risk of a first psoriasis diagnosis.
- The proposition that longer-term treatment of psoriasis with methotrexate or other DMARDs may decrease a potential cardiovascular risk in patients with psoriasis needs further investigation.
- Duration of psoriasis seemed to increase the risk of developing certain solid cancers in patients with psoriasis. While psoriasis patients had an overall increased risk of lymphohaematopoietic and pancreatic cancers, the risks of bladder/kidney and colorectal cancers were only increased in patients with longer-term psoriasis duration. Severity of psoriasis was also suggested to alter the risk of developing cancer, mainly lymphohaematopoietic cancers.
- The proposed dependency of the risk of certain solid cancers from duration of psoriasis may partially explain the conflicting results in the literature due to different study designs and start of follow-up at different stages of the psoriasis disease.
- Severity of psoriasis seemed to increase the risk of diabetes, cardiovascular diseases, and cancer while duration of psoriasis only appeared to alter the risk of diabetes and cancer, but not of cardiovascular diseases. A hypothesis might be that cardiovascular diseases develop only under severe inflammatory processes, diabetes and cancer also under less severe processes if they are enduring. This suggestion would need further investigation.

4.3 OUTLOOK

4.3.1 Psoriasis project

In this thesis, the influence of beta-blocker and lithium use on the risk of *induction* of psoriasis was studied in a large number of patients. In a further step, it would be interesting to investigate if these drugs can *exacerbate* pre-existing psoriasis. This was also already postulated based on weak data. However, it is difficult to study this aspect on the GPRD because of the uncertainty of correct recordings of exacerbations of a disease. Additionally, the current notion that beta-blockers or lithium exacerbate psoriasis may lead to confounding, meaning that severity of psoriasis, patient attitude, or location / phenotype of psoriasis may lead to selected prescribing of these drugs to the patients; patients with more severe or more unstable psoriasis may be less likely to receive such a drug. The best way would be to conduct a randomised clinical trial, but, as this may ethically not be possible, one could consider a prospective cohort study with careful control for confounding, e.g. by using propensity scores.

The findings of Study 3.3 have shown that potential protective effects of drugs on psoriasis can be shown with GPRD data. There are indications[247-249] in the literature that statins may improve psoriasis. Hence, in a further study it would be interesting to investigate the association between this drug class and induction of psoriasis.

Protective effects on the induction of psoriasis have been suggested for atypical antipsychotics (mainly olanzapine) and metformin. In a next step, it would be interesting to study if these drugs may be useful treatment options for psoriasis. One could conduct randomised controlled trials or prospective observational cohort studies (with careful control for confounding) in patients with psoriasis and psychiatric disorders or diabetes who need antipsychotics or oral antidiabetics.

There are now quite a lot of consistent data showing an increased risk of diabetes in patients with psoriasis, and the association may be causal. Common inflammatory mechanisms have been suggested in the pathomechanism of both diseases. It would now be interesting to study the mechanism in greater detail in laboratory research. Genetics should also be further investigated; like diabetes type I, psoriasis is a complex HLA-associated disease,[250] but there are also data which suggest a genetic overlap with type II diabetes.[251] Furthermore, (bio)markers should be searched for which identify the psoriasis patients most at risk to develop diabetes.

The observed effect of methotrexate to decrease the cardiovascular morbidity in patients with rheumatoid arthritis[213-215] should also be studied in patients with severe psoriasis, but with a larger number of patients than in Study 3.5. One could conduct a retro- or prospective cohort study with a nested case-control analysis comparing severe psoriasis patients who receive methotrexate with severe psoriasis patients who do not receive this drug.

The observed dependency of the risk of certain types of cancer from psoriasis duration should be confirmed in a study with longer-term follow-up.

4.3.2 In general

Safety surveillance of drugs has shifted from a rather passive to an active approach. Additionally, regulatory actions such as the accelerated approval process in the US and the conditional marketing authorisation in the European Union (EU) make high demands on the monitoring of such drugs. Hence, it is important that new methods are being developed which allow the surveillance of *newly* marketed drugs and a fast recognition of a safety issue. Two methods were described in the introduction section (chapter 1.1.7), namely the use of registries, which, e.g. in the case of natalizumab, allowed the drug to be re-introduced onto the market despite safety issues (chapter 1.1.2), and prescription-event monitoring. Another interesting approach[252] was presented at the *24th annual international conference on pharmacoepidemiology and therapeutic risk management (2008)*. Patients who filled their first prescription for a recently marketed drug in a pharmacy in the Netherlands were asked to participate in a program and received a questionnaire via e-mail four times during six months, in which they were asked regarding any adverse events. The three approaches can only generate hypotheses because a control group is usually lacking. However, data from such programs could for example be compared to data from studies on the natural history of the disease to be treated with the drug under surveillance, and relative risks could be approximated. A prerequisite would be a high participation in the programs and a high response rate to the questionnaires.

Programs as described above may be part of a risk management program for a drug. Risk management is a growing field, and pharmacoepidemiology can make valuable contribution (as shown in the introduction section). New methods have to be developed for this field, and the benefit of entire risk management programs may have to be evaluated in future.

Since 2007, pharmaceutical companies in the EU have to submit a paediatric investigation plan for a drug in development and, if feasible, studies have to be conducted to show the efficacious and safe use of these drugs in this patient population. However, data on the use of older drugs in children are often missing, and over half of the pharmacological interventions in hospitalised children are off-label or unlicensed drugs.[253] Although awareness has increased and clinical trials involving paediatric patients will be conducted, it may take time until useful data are available. Furthermore, even if trials will be conducted in the paediatric population, these may be underpowered to detect safety signals (especially in the case of uncommon adverse events) due to a smaller target population.[254] UK clinical databases, in particular also the GPRD, are suitable to conduct studies in the paediatric population,[255] and one should benefit more from this potential in the future.

In the following, three areas will be briefly mentioned where pharmacoepidemiology could contribute if availability of the necessary data was guaranteed.
1) In clinical practice, it is rather common to use drugs off label (e.g. in dermatology). If this usage was recorded in databases as off label, the extent to which a certain drug is used off label could be quantified. Based on such data, pharmaceutical companies could then decide on label extensions of their products. 2) The population's interest in herbal and other alternative medications (e.g. chinese medicine) has been increasing in recent years.[1] However, several examples have shown that the use of such products is not unproblematic (e.g. drug drug interaction between Hypericum perforatum and ciclosporin[256] or potential bleeding due to ginkgo biloba[257]). If exposure to such products was recorded in large databases in a standardised manner and almost completely, the safety of such medicines could be better evaluated. 3) With the development of new, noninvasive methods to collect DNA (e.g. with buccal swabs),[1] interest has grown to link databases with genetic information of patients (also in the GPRD). If such information as well as complete laboratory parameters and environmental factors were recorded in databases or clinical notes, pharmacoepidemiology may contribute to the concept of personalised medicine (defined as 'a form of medicine that uses information about a person's genes, proteins, and environment to prevent, diagnose, and treat disease'[258]) by e.g. defining patients most at risk to develop adverse events to drugs.

There are many efforts in resource poor settings to increase the access to effective drugs. However, less than 27% of lower middle and low income countries have national pharmacovigilance systems registered with the WHO programme, which is mainly due to lack of resources, infrastructure, and expertise.[259] Pharmacoepidemiologists and experts in pharmacovigilance and public health should draw attention to the issue that the availability of drugs in these countries should be linked to an – at least minimal – risk-benefit plan. Healthcare professionals in these regions should be educated on drug surveillance, and national solutions should be elaborated on with the government. Data from the high income countries are often of limited value due to other environmental and genetic influences. The only contribution may be the conduct of studies in immigrants from such low or middle income countries which might at least indicate if there are genetic influences on the safety of a drug.

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Chapter 5

APPENDIX

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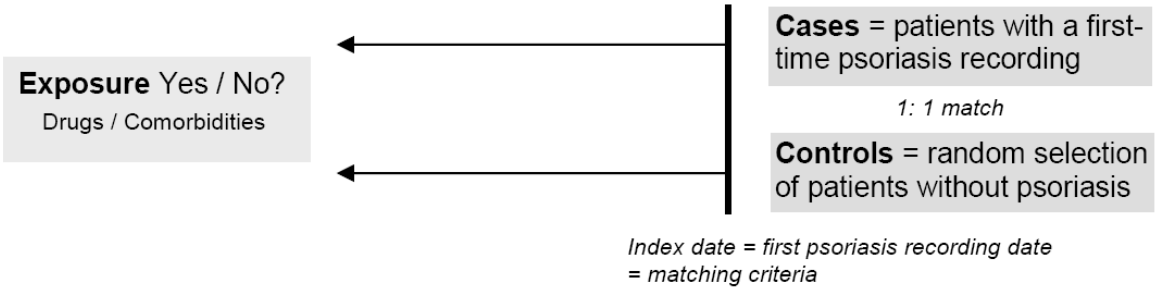
5 APPENDIX

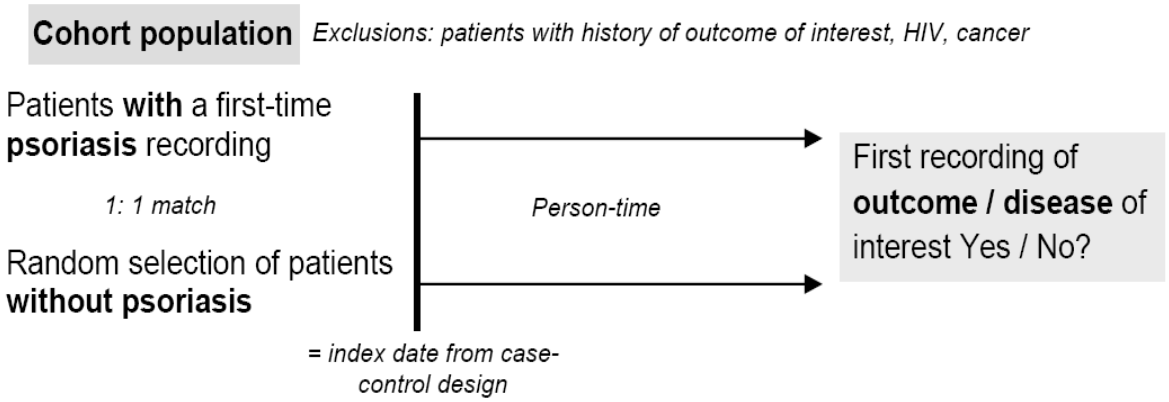
5.1 STUDY DESIGNS OF THE THESIS

Case-control design

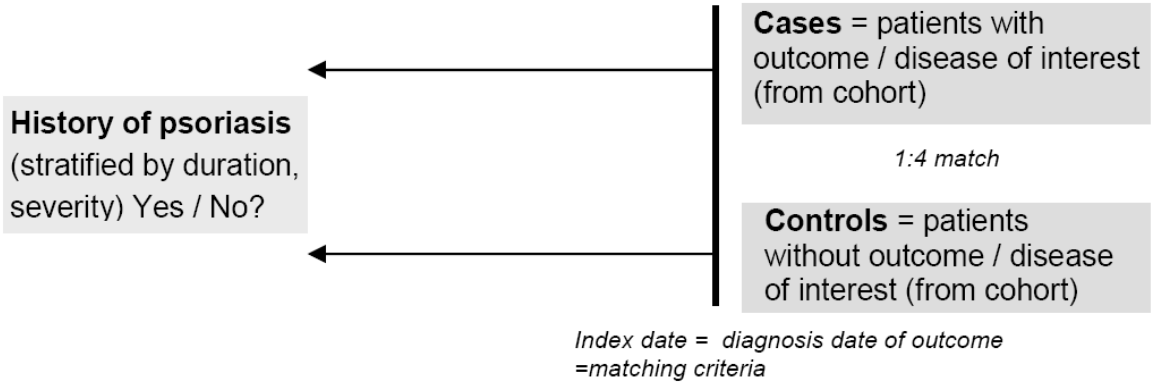


Follow-up design with nested case-control analysis

Cohort study



Nested case-control study



5.2 EXAMPLE OF A CASE REPORT

A fatal tick bite occurring during the course of tick-borne encephalitis vaccination

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ABSTRACT

In Western Europe tick-borne encephalitis virus infections with fatal outcome are rare, especially in children. We report the case of an adolescent who died of meningoencephalitis after a tick bite that occurred between the first two tick-borne encephalitis vaccinations. The case demonstrates the difficulty of differentiating possible adverse events associated with the immunization from symptoms of simultaneous infection with tick-borne encephalitis virus.

INTRODUCTION

In Europe, tick-borne encephalitis (TBE) is the commonest viral infection of the central nervous system (CNS) transmitted by ticks. Vaccines on the basis of an inactivated virus are available from two manufacturers and both products have been shown to be effective and safe.[1] The seroconversion rates are ≥97% 21-35 days after the second vaccination and ≥99% 21-28 days after the third.[2] Data from a surveillance system in Austria, where the majority of the population has been vaccinated, indicate that the protection rate after two and three doses of the vaccine is between 96% and 100%.[1] The manufacturers suggest to start with the first two vaccinations of the three-step vaccination schedule (0 months, 1-3 months, (5) 9-12 months) in the winter months to provide protection in the peak season for ticks (spring and summer). To avoid difficulties in differentiating possible adverse events following immunization from symptoms of a simultaneous infection with tick-borne encephalitis virus (TBEV) the preferential vaccination during the cold months may offer an additional benefit. This case report demonstrates the above-mentioned difficulties and, in addition, discusses a possible role of an antibody-dependent enhancement of infection (ADEI).

CASE REPORT

A 15-year-old girl from an endemic area for TBEV was admitted to our hospital with a presumptive diagnosis of meningitis. She had suffered from fever and headache for one day. Two weeks before, she had had a tick bite (without informing her general practitioner) and four days before hospitalization she had received the second vaccination against TBEV (first dose had been administered one month earlier). The patient had no relevant medical history. On admission, her body temperature was 38.8℃, she was well oriented but somnolent (Glasgow Coma Score, 14-15) and suffered from neck stiffness and photophobia. The cerebrospinal fluid (CSF) revealed pleocytosis (189 polynuclear cells/mm^3, 26 mononuclear cells/mm^3), normal glucose, and slightly elevated protein and lactate. Serum C-reactive protein and blood leukocyte count were normal. Cultures for bacteria remained negative in CSF, and acute infections with *Borrelia burgdorferi*, herpes simplex virus, enteroviruses, Epstein Barr Virus, measles, and mumps virus were ruled out. Enzyme-linked immunosorbent assay (ELISA) IgG and IgM antibodies against TBEV were positive in the serum but negative in the CSF. The patient became increasingly somnolent (Glasgow Coma Score, 13-14). The following day a cranial computed tomography (CT) demonstrated signs of brain edema, and the patient was transferred to the intensive care unit. During the night from day 4 to 5 of hospitalization she complained of drowsiness and experienced seizures. A second and third CT confirmed increasing cerebral edema. Decompression was not possible, and the patient died on day 5.

The brain autopsy revealed cerebral edema with herniation, and histology showed the picture of severe lymphocytic meningoencephalitis. Further investigations revealed high titers of TBEV-neutralizing antibodies, which had increased from 1:20 on day 1 to 1:320 on day 5, and TBEV ELISA IgG and IgM antibodies, which had risen from 2,660 Vienna units (VIEU) to 220,000 VIEU and from borderline to >1000 VIEU, respectively. RNA-polymerase chain reaction (PCR) for TBEV was negative in CSF, but positive in the brain stem, cortex, and cerebellum. Immunohistochemically, visualization of TBE viral antigen was successful in the dentate nucleus (Fig.1), while tests for herpes simplex virus (HSV), varicella zoster virus (VZV), cytomegalovirus (CMV), measles, and toxoplasmosis were negative. These findings demonstrated the presence of a multifocal encephalitis compatible with TBE. Culture of the virus was unsuccessful, but sequencing of a PCR fragment from the conserved region NS5 revealed differences at several locations when compared with the virus used for the vaccine applied in this patient. These results confirm an infection with a wild-type TBEV, transmitted most probably by the tick bite between the first and the second vaccination.

DISCUSSION

Symptom onset occurred two-to-three days after the second TBE vaccination and about two weeks after the patient experienced a tick bite in an area endemic for TBEV and *B.burgdorferi.* Possible causes for the symptoms were: an adverse reaction to the vaccine; tick-borne infection of the central nervous system (CNS), and other acute CNS infections or diseases. Infection with TBEV is mainly diagnosed by clinical and laboratory findings. During the viremic phase, which usually begins a few days to two weeks after the tick bite, the virus can be isolated from the blood, or it can be detected by reverse-transcriptase-polymerase chain reaction (RT-PCR). During this period patients may be asymptomatic or present non-specific symptoms.[3] Our patient was hospitalized with neurologic symptoms, and the viremic phase had probably already passed. In such cases the diagnosis of TBE relies mainly on the identification of specific serum antibodies. At the onset of disease, specific antibodies in CSF are only detectable in about 50% of patients, they can, however, be identified in almost all patients within 10 days of disease progression.[3] The presence and rapid increase of serum IgM and IgG antibodies against TBEV are considered to be indicative of an infection with TBEV. In our case, however, vaccination could also have been responsible for the presence of serum TBEV antibodies. Post mortem brain biopsies allowed the identification of viral RNA in several parts of the brain by RT-PCR. Using sequencing techniques the virus could be differentiated from the virus used in the vaccine, confirming an infection with a wild-type virus.

Permanent morbidity and case fatality rates after infection with the Western European TBEV subtype are low, especially in children.[4] One fatal case has been reported: an 11-year-old boy who was operated on for a suspected appendicitis.[5] Postexposure prophylaxis with hyperimmunoglobulin has been associated with an unfavorable course in a few pediatric patients.[4, 6] A possible ADEI, which is supposed to be responsible for a serious course of Dengue fever after reinfection with another serotype,[7] was put forward by the authors.[6] This phenomenon was demonstrated in vitro for TBEV in mouse macrophages exposed to mouse monoclonal antibodies against TBEV and polyclonal antisera against six other flaviviruses.[8] Subneutralizing concentrations of neutralizing antibodies were proposed to play a potentiating role in viral infection, either by virus-antibody complex binding via the Fc portion to cells bearing Fc- type

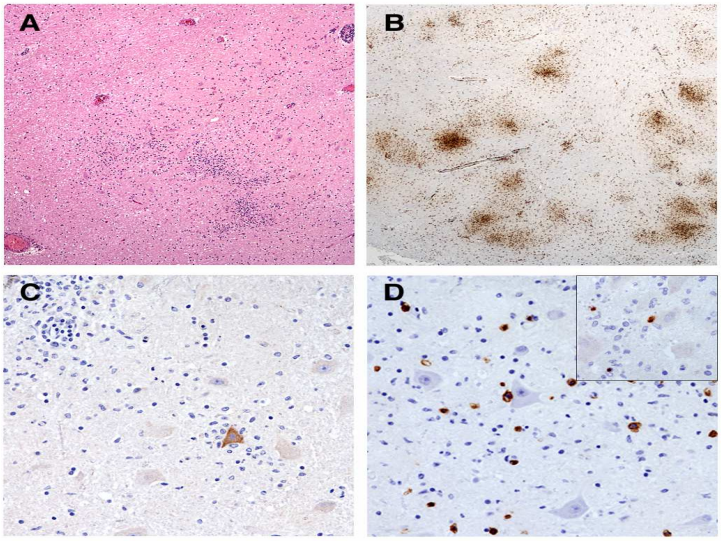

FIGURE 1. A: Haematoxylin and eosin stain showing patchy mononuclear inflammatory infiltrates in dentate nucleus (H&E x40). B: Multinodular aggregates of macrophages/ microglia in inferior olives of medulla oblongata (anti-CD68 x20). C: Anti-TBEV immunostaining reveals diffuse cytoplasmic labeling of single neurons in dentate nucleus (anti-TBEV x200). D: Abundant CD8-positive T-lymphocytes, some of them in direct contact with morphologically intact neurons in dentate nucleus (anti-CD8 x200). Inset, granzyme-B-releasing cytotoxic T cells in close contact with neurons (antigranzyme-B x600).

receptors (macrophages, monocytes, B-cells, neutrophils and granulocytes) or by binding to complement receptor type 3 (CR3).[7]

In vivo, however, ADEI could not be demonstrated in a mouse infection model, although the same antibodies enhanced the infection of macrophages.[9] Epidemiologically, the large number of fully or only partially vaccinated children and adults in Austria, together with the nonexistence of severe or lethal TBE cases after active immunization, contradicts a possible ADEI. [1, 10] However, ADEI cannot be excluded completely in our patient due to the possibility of a low concentration of neutralizing antibodies in the time period between the tick bite and shortly after the second vaccination.

During the course of active immunization against TBEV vaccine should be withheld for up to four weeks after a known tick bite, as the incubation period for TBE lasts up to 30 days. To be well protected a vaccine series with at least two doses should be completed before the spring season.

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5.3 BRIEF SUMMARY OF ALL STUDIES OF THIS THESIS

	Study	*Aim*	*Main results*
Case – control studies	3.1	To explore further the association between use beta-blockers and other antihypertensives and the risk of a first-time psoriasis diagnosis because the current knowledge is based on weak data (as for lithium)	- Adjusted OR for current use of ≥20 prescriptions for beta-blockers 1.10 (95% CI 1.01-1.20); no increasing risk with duration of use. - Risk estimates for the other antihypertensives also close to one - No increased psoriasis risk due to cardiovascular diseases/risk factors
	3.2	To explore further the association between use of lithium and antipsychotics and the risk of a first-time psoriasis diagnosis	- Adjusted OR for current use of ≥5 prescriptions for lithium 1.68 (95% CI 1.18-2.39) and for olanzapine 0.50 (95% CI 0.28-0.89)
	3.3	To evaluate the association between use of thiazolidinediones and other oral antidiabetics and the risk of a first-time psoriasis diagnosis	- Adjusted OR for current use of ≥5 prescriptions for thiazolidinediones and ≥15 prescriptions for metformin 0.33 (95% CI 0.16-0.66) and 0.77 (95% CI 0.62-0.96), respectively - Prevalence of diabetes not increased in patients before the first-time psoriasis diagnosis
Cohort studies with nested case-control analysis	3.4	To elucidate further the association between psoriasis and the risk of new-onset diabetes mellitus	- Incidence rate of diabetes in patients with psoriasis 4.06 (95% CI 3.75-4.39); about 35% higher than in patients without psoriasis - Diabetes risk highest in patients receiving oral treatment and with a long-term psoriasis history; independent of BMI
	3.5	To investigate the reported association between psoriasis and myocardial infarction (MI), stroke, or transient ischaemic attack (TIA) using primary care data from the UK and applying a slightly different study design than the earlier reports	- Overall IRs of MI, stroke, and TIA similar among patients with and without psoriasis - Increased risks in younger psoriasis patients (MI OR <60 years of age: 1.66, 96% CI 1.03-2.66) and with severe disease
	3.6	To further elucidate the association between psoriasis and the risk of developing cancer, and to provide baseline incidence rates (IR) of different types of cancer in psoriatic patients	- Overall risk of incident cancer may be increased in patients with psoriasis (mainly lymphohaematopoietic (LC) and pancreatic cancers) - Overall cancer risk increased with duration of psoriasis (OR for ≥4 years duration 1.50, 95% CI 1.30-1.74) and severity (OR for patients with systemic treatment 1.53, 95% CI 0.97-2.43; mostly for LC)

5.4 SUMMARY OF STUDIES ON THE ASSOCIATION PSORIASIS AND CANCER

Study	*Design*	*Data from*	*Follow up from*	*Increased cancer risk of:*
Lindegard B.[86] 1986	Cross-sectional; diagnoses at hospital discharge	Population register Sweden	NA	Lung, Haematological
Stern RS et al.[120] 1988	Cohort study: psoriasis patients with PUVA treatment; Comparison with expected rate from SEER* program	Photochemotherapy follow up study	Entry into cohort	All noncutaneous, gastro-intestinal tract, breast, central nervous system
Lindelof B et al.[220] 1990	Cross-sectional; Comparison with expected cancer rate in Sweden	Linkage: Swedish Psoriasis Association membership registry / Swedish Cancer registry	NA	Male breast, female kidney
Olsen JH et al.[119] 1992	Follow up after hospital discharge; Comparison with expected rate in Denmark	Linkage: National Hospital Discharge Register Denmark / Danish Cancer Registry	From hospital discharge	Nonmelanoma skin cancer, lung, larynx / pharynx, colon, kidney
Bhate SM et al.[218] 1993	Cross-sectional case-control analysis	General practitioner notes	NA	Skin cancer
Stern RS et al.[121] 1997	See Stern RS et al. 1988	See Stern RS et al. 1988	See Stern RS et al. 1988	Thyroid, breast, central nervous system
Frentz G et al.[114] 1999	See Olsen JH et al. 1992	See Olsen JH et al. 1992	See Olsen JH et al. 1992	All sites, nonmelanoma skin cancer, oral cavity, larynx / pharynx, colon, lung, connective tissue, mycosis fungoides
Hannuksela-Svahn A et al.[117] 2000	Follow up after hospital discharge; Comparison with expected rate in Finland	Linkage: Finnish Hospital Discharge Register / Finnish Cancer Registry	From hospital discharge	All sites, nonmelanoma skin cancer, Hodgkin und non-Hodgkin lymphoma, larynx, pancreas, lung, bronchus

Study	*Design*	*Data from*	*Follow up from*	*Increase cancer risk of:*
Bofetta P et al.[113] 2001	Follow up after hospital discharge; Comparison with expected rate in Sweden	Linkage: In-patient Register Sweden / Swedish Cancer Registry	From hospital discharge	All sites, oral cavity, oesophagus, liver, pancreas, lung, squamous cell carcinoma, breast, male genitals, bladder, kidney / pelvis, mycosis fungoides
Margolis D et al.[118] 2001	Population-based controlled cohort study; psoriasis patients classified into mild or severe psoriasis according to treatment	Medicaid database	From point of time when patients classified for study group (e.g. severe psoriasis)	All sites, lymphoproliferative cancers, nonmelanoma skin cancer, other cancers (in severe psoriasis patients)
Gelfand JM et al.[115] 2003	Population-based controlled cohort study (patients age ≥65 years)	General Practice Research Database	Maximum of patient registration, practice up-to-standard, or psoriasis diagnosis date	Lymphoma
Gelfand JM et al.[116] 2006	Population-based controlled cohort study; psoriasis patients classified into mild or severe according to treatment	General Practice Research Database	Maximum of patient registration, practice up-to-standard, or psoriasis diagnosis date	Lymphoma (mainly Hodgkin lymphoma and cutaneous T cell lymphoma)

* SEER = Surveillance Epidemiology and End Results (US National Cancer Institute)

Chapter 6

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Chapter 7

CURRICULUM VITAE

7 CURRICULUM VITAE

Personal Data	
Name	Yolanda Bettina Brauchli
Date of birth	October 01, 1976
Hometown	Binningen / BL, Andelfingen / ZH
Marital status	unmarried
Address	Güterstrasse 126, CH-4053 Basel
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Education	
2006 - 2008	**PhD thesis** at the Division of Clinical Pharmacology & Toxicology, Pharmacoepidemiology Unit, University Hospital Basel, Switzerland Title: '*Population-based studies on the natural history of psoriasis – and their role in the drug development process and in clinical practice'* Supervised by Prof. Dr. Christoph Meier
2005 - 2007	**ECPM course with diploma in Pharmaceutical Medicine** at the European Centre for Pharmaceutical Medicine (ECPM), University of Basel, Switzerland
1997 - 2002	**Study of Pharmacy with Swiss Federal Diploma in Pharmacy** at the University of Basel, Switzerland February to July 2002 public health diploma thesis at the Swiss Tropical Institute Basel, Switzerland, on the evaluation of a diabetes project in Dar es Salaam, Tanzania, including a one-month stay in the country
1996 - 1997	**Diploma as manager's assistant**, with specialisation in marketing, at the Neue Sprach-und Handelsschule (NSH) Basel, Switzerland
1995	**Matura typus B** (latin), Gymnasium Oberwil, Switzerland

Professional Experience	
2006 - 2008	Assistance in **Regional Pharmacovigilance Center** **Clinical Pharmacological Service (KLIPS)** including regular oral presentations at the KLIPS seminar **Therapeutic Drug Monitoring Service** at the Division of Clinical Pharmacology & Toxicology, University Hospital Basel, Switzerland **Author for i.m@il Offizin** (since 2007), Pharmaceutical Care Research Unit, University Basel, Switzerland

12/2005 - 12/2006	**Pharmacist** at the Notfall-Apotheke, Basel For two nights per month and additional days/nights if required
01/2005 - 09/2005	**Hospital pharmacist** at the Kantonsspital Baden, Switzerland
05/2003 - 12/2004	**Management and International Medical Associate Trainee** at F. Hoffmann-La Roche, Basel, Switzerland Supervision of access programs in Africa including involvement in the organisation of an HIV training program for physicians in Africa Phase IV clinical trials in the HIV area
12/2002 - 04/2003	**Pharmacist** at the Pharmacie du Golf, Crans-sur-Sierre, Switzerland Support of the team during the winter season
2000 - 2002	**Assistant pharmacist** at the Bahnhof Apotheke, Zurich, Switzerland and the Goldene Apotheke, Basel, Switzerland
2001	**EPSA delegate for ASEP** EPSA (European Pharmaceutical Students Association), ASEP (Association Suisse des Étudiants Pharmaciens)
2001-2002	**Member of the organisation committee of the seminar for pharmacy students 2002**
1998	**Traineeship** of 7 weeks at Roche Pharma Schweiz, Consumer Health section.
1997	**Traineeship** of 3 months at Roche Pharma Schweiz, Consumer Health section
1996	**Hostess** at the Mustermesse in Basel

Major Lectures and Symposia	
2006 - 2008	▪ University of Basel, Switzerland: Public Health/Epidemiology, Molecular Mechanisms of Toxicology, Drug Discovery and Development, Biostatistics I, Scientific Writing, KLIPS ▪ ‘Pharmathemen’ organised by the Division of Clinical Pharmacology & Toxicology, University Hospital Basel, Switzerland
2005	▪ Various courses for hospital pharmacists ▪ Schnittstellen erfolgreich verknüpfen/Zusammenarbeit zwischen Abteilungen und Unternehmensbereichen: ETH Zürich ▪ Public Health für OffizinapothekerInnen; Swiss Tropical Institute
2003 - 2004	▪ Introduction to the EU Clinical Trial Directive; Roche internal ▪ Introduction to Good Clinical Practice; Vienna School of Clinical Research

Attendance and Presentations at Congresses	
2008	▪ 24th International Conference on Pharmacoepidemiology and Therapeutic Risk Management in Copenhagen, Denmark *Poster 1*: Psoriasis – independent risk factor for diabetes? *Poster 2*: Lithium increased risk of incident psoriasis ▪ 24th Boston Collaborative Drug Surveillance Program (BCDSP) Symposium on Drug Safety and Pharmacoepidemiology in Nice, France; *Presentation:* The natural history of patients with psoriasis: two exemplary studies
2007	▪ 23rd International Conference on Pharmacoepidemiology and Therapeutic Risk Management in Quebec, Canada *Presentation 1*: Association between use of thiazolidinediones, other oral antidiabetics and psoriasis *Presentation 2:* Beta-blockers, other antihypertensives and psoriasis ▪ 23rd BCDSP Symposium on Drug Safety and Pharmacoepidemiology in Nice, France
2006	▪ 22nd BCDSP Symposium on Drug Safety and Pharmacoepidemiology in Nice, France
2003	▪ International Aids Society (IAS) Conference on HIV Pathogenesis and Treatment in Paris, France

Language skills	
	German, mother tongue **English**, advanced proficiency in speaking, writing, and comprehension Diploma: First Certificate and certificate from the British Swiss Chamber of Commerce **French**, advanced proficiency in speaking, writing, and comprehension Diploma: Chambre de Commerce et d'Industrie de Paris **Spanish**, Advanced proficiency in speaking, writing, comprehension Diploma from the Escuela Internacional Sampere/Spain – 3 months stay in Salamanca/Spain

Computer skills	
	Microsoft office: Word, Excel, Powerpoint, Outlook **SAS** statistical program: basic knowledge **Pharmacy** programs: Golden Gate; ProPharma **Internet**: experienced on the use of

Hobbies	
	Sports (biking, snowboarding, surfing, jogging, climbing, swimming, diving), **Travelling, Reading, Music**

Publications

1. Brauchli YB, Jick SS, Miret M, Meier CR. Psoriasis and risk of incident cancer: an inception cohort study with a nested case-control analysis. Under review with the Journal of Investigative Dermatology November 2008.
2. Brauchli YB, Jick SS, Curtin F, Meier CR. Lithium, antipsychotics, and risk of psoriasis. J Clin Psychopharmacol 2009 (in press).
3. Brauchli YB, Jick SS, Miret M, Meier CR. Psoriasis and the risk of incident myocardial infarction, stroke, or transient ischaemic attack: an inception cohort study with a nested case-control analysis. Br J Dermatol 2009 (Epub ahead of print).
4. Brauchli YB, Jick SS, Meier CR. Psoriasis and the risk of incident diabetes mellitus: a population-based study. Br J Dermatol 2008;159:1331-7.
5. Brauchli YB, Jick SS, Curtin F, Meier CR. Association between beta-blockers, other antihypertensive drugs and psoriasis: population-based case-control study. Br J Dermatol. 2008;158:1299-307.
6. Brauchli YB, Gittermann M, Michot M, Krähenbühl S, Gnehm HE. A fatal tick bite occurring during the course of tick-borne encephalitis vaccination. Pediatr Infect Dis J. 2008;27:363-5.
7. Brauchli YB, Jick SS, Curtin F, Meier CR. Association between use of thiazolidinediones or other oral antidiabetics and psoriasis: A population based case-control study. J Am Acad Dermatol. 2008;58:421-9.
8. Brauchli YB, Scholer A, Schwietert M, Krähenbühl S. Undetectable phenytoin serum levels by an automated particle-enhanced turbidimetric inhibition immunoassay in a patient with monoclonal IgMλ. Clin Chim Acta. 2008;389:174-6.
9. Krähenbühl S, Brauchli Y, Kummer O, et al. Acute liver failure in two patients with regular alcohol consumption ingesting paracetamol at therapeutic dosage. Digestion 2007;75:232-7.

i.m@il Offizin Articles:

1. Psoriasis, Nr. 10, Mai 2008
2. Pharmakovigilanz, Nr. 2, Januar 2008
3. Fibromyalgie, Nr. 18, September 2007

Victory lies in tenacious efforts

(Daisaku Ikeda)