A study on the epidemiology of rosacea

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Dekan

(An old man and his grandson, by Domenico Ghirlandaio [1449-1494], Louvre, Paris. Early evidence of rhinophyma)

"Data! Data! Data!" he cried impatiently. "I can't make bricks without clay."

Sherlock Holmes, The Adventure of the Copper Beeches

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“I know there's a proverb that says 'To err is human,' but a human error is nothing to what a computer can do if it tries.”

Agatha Christie, Hallowe'en Party

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Table of Contents

Summary ..... **i**
Abbreviations ..... **iii**
1 Introduction **3**
1.1 Pharmacoepidemiology 3
1.1.1 Development of a young science 3
1.1.2 Observational research and particularities of pharmacoepidemiology 4
1.1.3 Causality 7
1.1.4 Study designs, bias, and confounding 8
1.1.5 Data sources 14
1.2 Rosacea 17
1.2.1 History of rosacea 17
1.2.2 Epidemiology 18
1.2.3 Clinical manifestation, classification, and diagnosis 18
1.2.4 Triggers and risk factors of rosacea 20
1.2.5 Pathomechanism 21
1.2.6 Treatment 22
2 Aims of the thesis **27**
3 Rosacea project **31**
3.1 A study on the epidemiology of rosacea in the UK (Study 3.1) 31
3.1.1 Abstract 32
3.1.2 Introduction 33
3.1.3 Materials and Methods 34
3.1.4 Results 36
3.1.5 Discussion 42
3.2 Migraine, triptans, and the risk of developing rosacea (Study 3.2) 47
3.2.1 Abstract 48
3.2.2 Introduction 49
3.2.3 Materials and Methods 49
3.2.4 Results 52
3.2.5 Discussion 57
3.3 Spironolactone may reduce the risk of incident rosacea (Study 3.3) 61
3.3.1 Abridged report 62
3.4 Risk of rosacea in patients with diabetes using insulin or oral antidiabetic drugs (Study 3.4) 67
3.4.1 Abridged report 68
3.5 The association between psychiatric diseases, psychotropic drugs and the risk of incident rosacea (Study 3.5) 75
3.5.1 Abstract 76
3.5.2 Introduction 77

3.5.3 Materials and Methods 77
3.5.4 Results 80
3.5.5 Discussion 85
3.6 Antihypertensive drugs and the risk of incident rosacea (Study 3.6) 89
3.6.1 Abstract 90
3.6.2 Introduction 91
3.6.3 Materials and Methods 91
3.6.4 Results 94
3.6.5 Discussion 99
4 Discussion and outlook 105
4.1 Discussion 105
4.1.1 Study 3.1 107
4.1.2 Study 3.2 108
4.1.3 Study 3.3 109
4.1.4 Study 3.4 110
4.1.5 Study 3.5 111
4.1.6 Study 3.6 113
4.2 Limitations of the rosacea project 115
4.2.1 Incident rosacea and validation of the diagnosis 115
4.2.2 Rosacea sub-type and disease severity 116
4.3 Strengths and limitations of database research 118
4.4 Outlook 120
5 References 125
6 Index of Tables 141

Summary

Pharmacoepidemiology is the science of the use and the effects of drugs in large human populations. Although its original role was confined to post-marketing surveillance of rare or long-latency adverse drug events, the science is gaining increasing importance across different stages of drug development, where it has been applied to assess drug utilization patterns and cost-effectiveness, to characterize target populations of drugs in development, to evaluate undiscovered beneficial or detrimental drug effects, or to provide evidence of effectiveness when randomized controlled trials face ethical or practical barriers.

Rosacea is a common but under-investigated inflammatory skin disease, characterized by relapses and remissions. The exact pathomechanism of the skin disease remains to be elucidated, but recent findings indicate a key etiologic role of the innate immune system. Evidence-based treatment options for the skin disease are sparse and greatly needed.

The aim of the comprehensive rosacea project presented within this thesis was to contribute to the general understanding of the skin disease, thereby focusing on the impact of different drugs and diseases on incident rosacea. The project comprises six individual studies, set up in a case-control study design, using data from the General Practice Research Database (GPRD). This United Kingdom (UK)-based database contains longitudinal primary-care records of millions of patients, representative of the UK population. Information is recorded by general practitioners including demographics, lifestyle factors, medical diagnoses, referrals to secondary care, laboratory and diagnostic results, and a complete history of drug prescriptions.

The study population consisted of 53,927 patients with an incident rosacea diagnosis between 1995 and 2009 and the same number of rosacea-free controls, matched on age, sex, index date, general practice, and history in the database. Study 3.1 builds the basis of the project, and describes the study population in terms of demographics, lifestyle characteristics, and ocular symptoms. An overall incidence rate of diagnosed rosacea in the UK of 1.65 / 1,000 person-years was calculated, and stratified by age, gender, calendar time, and geographic region. While cigarette smoking seemed to prevent patients from developing rosacea, alcohol consumption yielded a marginal risk increase.

Studies 3.2 and Study 3.5 fathom the insufficiently supported notion regarding the association of rosacea with migraine (Study 3.2) and with psychiatric diseases (Study 3.5). Drug effects of triptans (Study 3.2) and of psychotropic drugs (Study 3.5) on incident rosacea were also studied. In contrast to previous findings, pre-existing migraine was not generally associated with incident rosacea, but post-menopausal women with severe migraine may be at a slightly increased risk of rosacea. Although mechanistically conceivable, triptans did not alter the risk of developing rosacea. Neither depression nor other affective disorders affected the relative risk of rosacea, but patients with diagnosed schizophrenia were diagnosed with rosacea less frequently. Although the latter finding is intriguing, it requires further investigation, as diagnostic bias cannot be ruled out. Of all psychotropic drugs, current lithium exposure may protect patients from developing the skin disease. Topical lithium has been proven to be effective in seborrheic dermatitis, and might be an interesting approach for rosacea therapy.

Two further studies evaluate the effect of diuretics (focus spironolactone, Study 3.3) and of other antihypertensive drugs (including β-blockers and calcium channel blockers, Study 3.6) on incident rosacea. In line with one previous study, spironolactone yielded a significantly decreased rosacea risk, whereas no other diuretic drug class showed an effect. Despite a generally assumed detrimental effect of calcium channel blockers on rosacea, Study 3.6 did not reveal an increased risk of rosacea for users of this drug class. β-blockers, which have been suggested as an off-label treatment for erythematotelangiectatic rosacea, revealed a small risk decrease, which is probably larger in erythematotelangiectatic rosacea patients alone. Especially with abundantly used therapeutics, such as antihypertensive drugs, sound evidence is required in order for healthcare professionals to make the right decisions in clinical practice.

Finally, Study 3.4 reports a previously uninvestigated decreased rosacea risk for patients with diabetes at an advanced disease stage, potentially due to impaired vasodilation. It remains to be clarified whether insulin enhances this effect.

In summary, these large population-based studies contribute to the understanding of rosacea yielding important evidence and raising new hypotheses. While some results may directly support clinicians in their daily decisions on rosacea treatment, yet others might spark follow-up projects on potential new treatment approaches for rosacea as well as on pathomechanistic aspects of the skin disease.

Abbreviations

ACEI	Angiotensin converting enzyme inhibitor
ADE	Adverse drug event
AIDS	Acquired immune deficiency syndrome
ARB	Angiotensin receptor blocker
BB	β-blockers
BMI	Body mass index
BCDSP	Boston Collaborative Drug Surveillance Program
CCB	Calcium channel blocker
CPRD	Clinical Practice Research Datalink
DM	Diabetes mellitus
EBM	Evidence based medicine
ETR	Erythematotelangiectatic rosacea
GP	General practitioner
GPRD	General Practice Research Database
$HbA1_c$	Hemoglobin $A1_c$
HES	Hospital episode statistics
HIV	Human immunodeficiency virus
HRT	Hormone replacement therapy
ID	Index date
IMS	Intercontinental Marketing Services
IR	Incidence rate
ISAC	Independent Scientific Advisory Committee
MHRA	Medicines and Healthcare Products Regulatory Agency
NHS	National Health Service

NIHR	National Institute for Health Research
NRSEC	National Rosacea Society Expert Committee
OAD	Oral antidiabetic drug
OTC	Over-the-counter
PPR	Papulopustular rosacea
py	person-years
RCT	Randomized controlled trial
ROSIE	ROSacea Independent Expert
SAS	Statistical analysis software
THIN	The Health Improvement Network
UK	United Kingdom
US	United States
UV	Ultra violet
VAMP	Value Added Medical Products

Chapter 1

Introduction

1 Introduction

1.1 Pharmacoepidemiology

1.1.1 Development of a young science

Pharmacoepidemiology is a relatively young science that applies epidemiologic methods to study adverse drug events (ADEs), drug use patterns, and drug effectiveness in large human populations. This discipline mainly evolved in answer to the need to monitor drugs with regard to rare or long-latency side effects beyond their market introduction. This demand for post-marketing drug surveillance mainly roots in the 1950's, when the 'thalidomide disaster' caused several thousand children to be born with phocomelia (a congenital limb deformation), due to in-utero exposure to the hypnotic thalidomide. In consequence, spontaneous reporting systems were implemented in the United States (US) and Europe, in which health care professionals could report suspected ADEs to local authorities. Although spontaneous reports of ADEs have led to market withdrawal of several drugs (e.g. practolol due to oculomucocutaneous symptoms) their efficacy is severely compromised by underreporting and insurmountable bias. Whereas long-latency drug reactions (e.g. carcinogenicity) are rarely reported, media attention can stimulate over-reporting of others. Furthermore, reporting rates generally decline over time upon marketing of a drug, and reporting levels correlate with the likeliness of diagnostic suspicion; diagnoses, such as agranulocytosis, which are pharmacologically induced in 60-70% of cases, are reported much more frequently than acute myocardial infarction for instance. These limitations, combined with the limited capability of spontaneous reporting systems to quantitatively assess observed effects, prompted the demand for more efficient methods allowing also the quantitative assessment of drug hazards in post-marketing drug surveillance.

Pharmacoepidemiology originated in the mid 1960's in the United States (US), when the Boston Collaborative Drug Surveillance Program (BCDSP) and the Johns Hopkins Hospital started monitoring in-hospital drug use and related risks in cohort studies.[3] The original focus of pharmacoepidemiology lay on the assessment of drug effects that are insufficiently captured in pre-marketing randomized controlled trials (RCT), due to their limited size, their relatively short duration, as well as their strictly selected volunteering study population. Such drug effects mainly comprise rare

and/or long-latency ADEs, or drug hazards in untested patient groups, such as children, pregnant or lactating women, or elderly patients. However, due to ever-increasing regulatory requirements, pharmacoepidemiology has developed into a discipline involved across the entire process of drug development (Figure 1.1-1). Today's risk management in drug safety requires a continuous risk-benefit evaluation across the entire life cycle of a drug. Pharmacoepidemiologic studies have been used, for instance, to evaluate background incidence rates (IRs) of serious ADEs in the non-exposed general population to appraise serious ADEs encountered during clinical trials, or to identify risk factors for specific observed ADEs in retrospective analyses of clinical trial data. Furthermore, epidemiologic studies on the natural history of a certain disease to be treated by a new drug performed early in the drug development process can provide a characterization of the target population (e.g. drug use and comorbidities).[3-7]

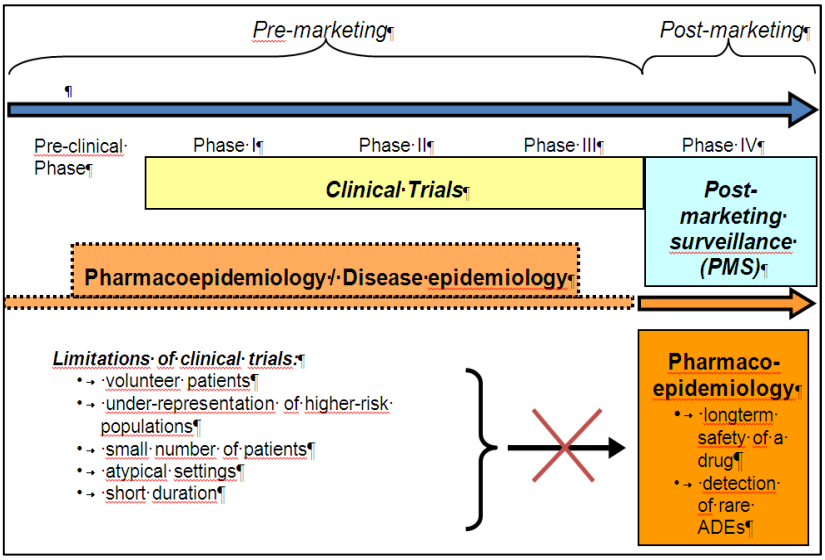

Figure 1.1-1: Pre- and post-marketing phases of drug development and the role of pharmacoepidemiology.

1.1.2 Observational research and particularities of pharmacoepidemiology

Clinical research is categorized into experimental and observational research. Experimental research includes randomized and non-randomized clinical trials, in which a patient's exposure status is actively assigned. Observational research observes usual clinical practice and falls into two general categories; analytical and descriptive research. While descriptive studies (i.e. case series and case reports) describe clinical observations, analytical observational studies (i.e. case-control

studies, cohort studies, and cross-sectional studies) feature a control group allowing the quantification of associations. Such analytical observational study designs are the basis for pharmacoepidemiologic research.

In terms of evidence based medicine (EBM), studies on the evaluation of intended therapy effects are classified according to grades of evidence on the basis of their research design, using internal validity as the criterion for hierarchical ranking. The quality of individual studies may sometimes be rated within each grade. According to this hierarchy, RCTs are evidence of the highest grade, and as the only study design allow causal inference due to minimized selection bias and confounding, whereas observational studies fall into an intermediate level of evidence (Table 1.1-1).[7-11]

Table 1.1-1: Hierarchy of clinical evidence according to the US Preventive Services Task Force (USPSTF). Table adapted from[9]

Quality of evidence according to the US preventive services task force[9]	
I	Evidence from one or more properly randomized controlled trials
II-1	Evidence from well-designed non-randomized controlled trials
II-2	Evidence from methodologically sound cohort or case-control studies, if possible from several independent research centers
II-3	Evidence from multiple time series (with or without interventions), or of important / dramatic results in uncontrolled experiments
III	Expert opinions based on clinical experience, descriptive studies, and expert committee reports

Significance of observational research in medicine

The lack of randomization makes observational studies prone to bias and confounding, since prognoses naturally differ between the exposed and the unexposed group. However, the corollary that causal inference cannot be drawn from observational studies has often been based on results from poorly designed example studies, while recent evidence shows that results between RCTs and observational studies do not need to show substantial differences.[12, 13] Hernan et al.[14] and Danaei et al.[15, 16] demonstrated that previously disputed discrepant findings between observational studies and RCTs were attributable to differences in the study question; after the observational study designs were changed so they would emulate the RCT of interest in design and analysis (only difference was adjustment for

baseline non-time-varying confounders) results of the cohort studies and the RCTs were congruent.

Furthermore, although RCTs are the gold standard to demonstrate drug efficacy, in practice they face different practical and ethical barriers, which is when epidemiologic studies are the method of choice to tackle a research question. 1) First, deliberately exposing patients to potentially harmful drugs is unethical. Putatively harmful effects can thus never be tested in an RCT. It was pharmacoepidemiologic research that led to the withdrawal of appetite suppressant drugs due to cardiac-valve regurgitation, or that uncovered the association between prescription drug use and the risk of motor vehicle accidents. 2) Second, due to less restrictive eligibility criteria, external validity / generalizability is increased in observational studies when compared to RCTs (selected volunteers). Thus, results of observational studies more accurately represent the heterogeneous target population of a certain drug, often including children and elderly poly-morbid people. 3) Third, RCTs do not accurately capture rare and long-latency ADEs. The fact that rare ADEs are not foreseen by the GP minimizes confounding by indication, which makes observational studies especially suitable for evaluating such effects. 4) Fourth, when it comes to ranking study types that give the best chance of discovery, the hierarchical order of study designs in medical research needs to be inversed either way.[17] It is the natural path in research that descriptive studies (e.g. case reports) or results from basic science spark analytical observational studies which may be followed-up by RCTs. Several important hypotheses such as the association between aspirin and myocardial infarction were raised by means of observational research, based on basic scientific considerations and clinical observations. 5) Finally, the greater timeliness and lower costs make observational research designs a desirable tool to achieve quick and affordable answers to urgent study questions. Thus, it is the interplay between different types of research for different types of questions that advances modern medicine. [4, 5, 7, 18-21]

Particularities of drugs as an exposure variable

Analytical epidemiology is the science that is concerned with uncovering associations between exposures and outcomes using specifically developed methods. The particular nature of the assessed exposure variable in pharmacoepidemiology (i.e. drug exposure) introduces some additional unique methodologic needs to the

science of pharmacoepidemiology. First, drug exposure is a time-varying factor, demanding for an exact exposure definition in terms of timing and duration of drug use. Second, ADEs are often rare disorders with a complex association to the causing agent, with different mechanisms behind most disorders. This requires a deeper understanding of the relation between the outcome and exposure, as well as accurate and complete information on drug exposure and covariates to adequately address potential confounding and biases.[4, 19] Finally, all drugs are prescribed for a medical reason, which raises complexion to another level as a putative causal drug effect needs to be distinguished from a disease effect. Thus, meticulous attention has to be paid to methodologic aspects, such as changes in prescription habits over time, potential confounding by indication, prevailing contraindications for the drug in the study population, disease severity, the natural course of the disease, the changing risk of an adverse drug reaction across treatment period, or simply compliance of people, some of which are discussed in detail below (section 1.1.4).[4] However, despite a sound methodology, observational studies are always subject to a certain degree of residual confounding and chance, which has to be considered for all results and causal inference should be drawn considerately.[3, 5, 19]

1.1.3 Causality

'Who knows, asked Robert Browning, but the world may end tonight? True, but on available evidence most of us make ready to commute on the 8.30 next day.' [22]

Pharmacoepidemiology, like clinical epidemiology, is an empirical science mainly aimed at uncovering relationships between exposures and outcomes. However, determining whether a given relation is causal may be complex, since empirical sciences involve naturalistic observations that are inherently fallible and incomplete. In 1965, Sir Austin Bradford Hill published a checklist of 9 criteria, known as the 'Hill criteria', as a means to support inference upon causality in medical research.[22] However, as helpful and desirable as such checklists may be, they will always fail to deliver a clear verdict of causation (Table 1.1-2). The same is true for complex statistical / methodologic approaches that may be used to address causality questions; a statistical test may give us a measure for the role of chance within our findings as well as an idea about the size of the effect. This can guide causal

inference, but even the most elaborate tool will never 'prove' or 'dismiss' a hypothesis. It is and always will be the way that such tools are applied in combination with scientists' critical scrutiny of a hypothesis by conjecture and refutation that will evaluate causality over time.[10, 11, 13, 22] In essence, decisions are made on the best evidence available applying critical thinking combined with a profound understanding of the matter under question on behalf of the decision maker. And nobody has expressed this more accurately than Sir Austin Bradford Hill himself:

'*All scientific work is incomplete – whether it be observational or experimental. All scientific work is liable to be upset or modified by advancing knowledge. That does not confer upon us a freedom to ignore the knowledge we already have, or to postpone the action that it appears to demand at a given time*.'[22]

Table 1.1-2: ‚Hill criteria' on causality in medical research with their inherent problems. Table adapted from [10]

Criterion	Problems
1. Strength	Other causes that might confound the association. ADEs rarely reveal high risk estimates.
2. Consistency / Repeatability	Exceptions might only be understood with hindsight / errors may be carried over across experiments.
3. Specificity	One cause can have several effects.
4. Temporality	Not always easy to establish.
5. Biologic gradient / dose-response curve	Could be confounded / threshold phenomena do not show progressive relation.
6. Plausibility	Subjective – might be understood with hindsight.
7. Coherence	Same as consistency or plausibility?
8. Experimental evidence	Not always available.
9. Analogy	Analogies are abundant and may guide or mislead.

1.1.4 Study designs, bias, and confounding

The special nature of drug exposure and the continuous advancements in methodology, statistical methods, data availability, and computer software have introduced new challenges as well as preferred solutions to estimate risk and benefit in pharmacoepidemiology. Some of the most important study designs and methodologic aspects are discussed below. [3, 5, 19]

Case-control studies

A case-control study design captures patients (cases) with a certain outcome of interest (e.g. a certain disease) and then looks backwards in time for an exposure of interest. Along with the cases, a group of control patients is defined without the specific outcome. The proportion of individuals exposed to this specific exposure variable in both the cases and the controls then allows the calculation of a measure of association, defined as the odds ratio (OR). Although case-control studies do not yield relative risks, an OR is a good approximation of the true relative risk, especially when the IR of the outcome of interest is low (<5%) in the general population. While an OR greater than 1 indicates a potentially increased risk for the outcome in exposed patients, an OR below 1 suggests a protective effect. An equal distribution of the exposure variable between cases and controls yields an OR of 1. Case control studies are increasingly popular, as they are relatively cheap and allow a fast and efficient approach to a study question. The study design is especially useful for rare outcomes (e.g. autism), and for outcomes with a long latency (e.g. cancer). However, a meticulously sound methodology is required to ensure valid results, as case-control studies are more vulnerable to bias and confounding. The selection of an appropriate control group is crucial; controls should be free of the outcome of interest, but otherwise represent the population at risk of becoming cases as closely as possible. Furthermore, sufficient exposure information is essential to account for bias and confounding during the study design stage or with analytical techniques.[4, 18, 23]

Cohort studies

Cohort studies trace people forward in time from exposure to outcome. Two groups are identified at the beginning of a cohort study: one group exposed to some factor of interest (e.g. use of antihypertensives) and a control group without the respective exposure. Both groups are then followed forward in time to assess for the outcome of interest (e.g. myocardial infarction). While a higher incidence of the outcome within the exposed group than in the unexposed group indicates an increased risk for the outcome in exposed patients, the exposure has protective properties otherwise. Risk estimates used in cohort studies are IRs, relative risks, survival curves and hazard ratios.[18, 24] Cohort studies can be performed prospectively, by moving forward in time from the present, but they may as well be conducted retrospectively, thereby comprising the cohort in the past and following them up into the present. Thus, while

in either case the study moves in the same direction, data collection may already be completed by the time of patient selection in the case of a retrospective study. Cohort studies are especially useful to study rare exposures, and allow investigation of multiple outcomes after a single exposure (e.g. cigarette smoking and the development of stroke, emphysema, oral cancer, and heart disease). Cohort studies do however also have important limitations. Firstly, the choice of an accurate control group is important because selection bias (discussed below) often imposes a major challenge, and secondly, especially in cohort studies that continue for decades, differential losses of follow-up between exposed and unexposed individuals or a time-varying factors such as change in exposure status may cause bias in the results.[4, 20, 24, 25]

Nested case-control studies

The nested case-control study depicts a case-control study embedded within a cohort study, and is especially important in epidemiologic research on drug effects. Analogously to a cohort study, a cohort of individuals is assembled and followed forward in time to assess the occurrence of an outcome of interest. But instead of analyzing data for everyone in the cohort, the analysis is conducted as a case-control study in individuals who developed the outcome of interest (cases) only, to each of which a defined number of controls (i.e. individuals who did not develop the outcome of interest) is selected from the initial cohort. The number of selected controls per case usually ranges between 4 and 10, depending on the statistical power of the study. Nested case-control studies combine strengths of cohort studies and of case-control studies. Their main advantage is a better control for potential bias such as age, calendar time, or disease duration through matching, thereby avoiding complex statistical techniques such as propensity scores. This matching of cases and controls on time (i.e. on the date of outcome diagnosis) also minimizes bias which can be introduced by time-dependent variables such as drug exposure, allowing a relatively straight-forward time-stratified analysis of drug exposure by duration of use. Such time varying factors would have to be addressed by elaborate time-dependent Cox proportional hazard models (an advanced version of the traditional time-independent Cox model) in a regular cohort study. Additionally, data collection and analysis is less expensive and less time-consuming, especially compared to large cohorts that are followed over a long period of time. [4, 24, 26, 27]

Particular pharmacoepidemiologic study designs

Study designs such as the case-crossover and the case-time-control design are more recent refinements of the original case-control and cohort study designs, aiming to overcome specific confounding, inherent to pharmacoepidemiologic research. The case-crossover study design allows the study of the association of acute transient effects (e.g. myocardial infarction) with intermittent drug exposure (e.g. short acting nifedipine), using the exposure history of each case as his, or her, own control. This mitigates between-person time-invariant confounding (e.g. by chronic co-morbidities). Several further methods have been suggested to overcome suspected time trend bias (e.g. healthy-user / sick-stopper or protopathic bias), which are introduced by changes in prescribing patterns or disease severity within patients over time. Such methods include the case-time-control design, in which results of a case-crossover study are adjusted by means of the exposure history of a conventional control group, or the case-case time control design, where use of concomitantly used non-causal but prognosis-related drugs within patients, or pre-event time of future cases is used to adjust results of the drug of interest. However, inconsiderate use of such methods can also introduce additional bias by over-adjustment due to selection bias, or it may unnecessarily reduce statistical power due to reduction of eligible cases. Thus application of such methods has to be considered carefully. [4, 28-30]

Bias

Bias is the lack of internal validity, i.e. if a systematic error causes the statistic estimate of a certain association not to represent the true value. Roughly three broad categories of bias can be distinguished. Namely, selection bias, information bias, and confounding.[31]

Selection bias

Selection bias occurs when the study population does not accurately represent the target population, and can be introduced at several stages of research conduction; poorly defined eligibility criteria, inaccurate sampling frame, and uneven diagnostic procedures in the target population. Various selection biases have been defined in the literature, such as the ‘healthcare access bias’, the ‘Neyman bias / selective survival bias’, the ‘healthy patient bias’, ‘detection bias’, or bias introduced by the ‘healthy worker effect’ that may occur in occupational studies. As the association

between exposure and outcome among those who are not included in the study is usually unknown, the presence of selection bias must usually be inferred rather than observed.[32] Thus, bias should be addressed at the stage of study design by matching of the study population. However, matching itself may introduce bias by overmatching, when matching is performed on non-confounding variables that might produce an underestimation of an association. [31, 33]

Information bias

Information bias usually arises during data collection. The three main types of information bias are misclassification bias, ecological fallacy, and regression to the mean. Misclassification bias is highly relevant in database research and originates if a patient is placed in the wrong category due to a lack of sensitivity and / or specificity of the procedure in detecting exposure. Misclassification of study subjects is either differential or non-differential. Differential misclassification bias is present when misclassification differs in the groups being compared, whereas non-differential misclassification bias is present when the misclassification is the same across the groups being compared. Misclassification can be introduced by several biases, including detection bias, recall bias, or reporting bias. Ecological fallacy occurs when results achieved at group level are inadequately used to make inferences at the individual level. Another type of information bias that is relevant to pharmacoepidemiology is ‘protopathic bias’, which is often mistaken as confounding by indication, whereby a drug is inadvertently prescribed for an early manifestation of a disease that has not yet been diagnosed. When the disease is later discovered, a causal association between the drug and the disease may be incorrectly inferred.[31-35]

Further biases in pharmacoepidemiology

One bias particular to the epidemiologic study of drug effects is the immortal time bias in cohort studies, which arises from an improper exposure definition ascribing a survival advantage to exposed patients as compared to unexposed patients; e.g. if a study aims to analyze overall mortality, thereby defining exposure as being prescribed a certain drug within a certain time period upon cohort entry. Exposed patients are then per definition ‘immortal’ during this time lag whereas unexposed patients could die any time after cohort entry. Such imbalances may cause an underestimation of the outcome rate among exposed patients. To avoid such bias in

the analysis of complex time-varying drug exposure data, the application of time-dependent Cox proportional hazard analyses or nested case-control designs are indicated.[4] Furthermore, publication bias plays a greater role in observational research as compared to RCTs, as results showing an effect tend to be published more often than null-results.[36]

Confounding

Confounding occurs when a variable is a risk factor for an effect among non-exposed persons and is at the same time associated with the exposure of interest in the population from which the effect derives, without being an intermediate step in the causal pathway. Confounding can substantially distort the risk estimate, and is a central issue in analytical observational research. [32, 33] Confounding can be neutralized at the design stage of a study by matching or restriction of the study population (i.e. in observational studies) or randomization (i.e. in RCTs), and/or at the analysis-level by stratifying results at the level of the potential confounder or by performing multivariate analysis, given that sufficient and accurate information on potential confounders is available.[31, 32] A particular type of confounding frequently encountered in pharmacoepidemiology is 'confounding by indication'. This type of confounding bias is present if the indication for the prescription of a drug of interest is related to the outcome of interest. For example, confounding by indication could be present in a study of the association of L-tryptophan with myalgia syndrome, because L-tryptophan is indicated to treat insomnia and depression, both of which are commonly associated with myalgia. Confounding by indication may also be present as 'confounding by disease severity – channeling bias'. In case of confounding by indication, results may simulate a lack of effectiveness of the drug under study, as exposed patients reveal higher IRs of the outcome when compared to unexposed patients. Confounding by indication is often difficult to control, especially in large database studies, as the precise drug indication is rarely explicitly labeled. Thus, control of confounding by indication has to be implemented as far as possible by eligibility restrictions at the design level of a study, and needs to be discussed critically when discussing results.[4, 33, 35, 37]

Propensity scores in pharmacoepidemiology

The lack of randomization in observational research introduces systematic differences between patients in terms of measured and unmeasured confounders. Propensity scores are a relatively new method in mitigating such confounding (mainly addressing confounding by indication). The propensity score represents the probability of a patient receiving a certain drug with a defined set of covariates. It depicts a single summary variable, made up of several variables that are associated with treatment allocation, and may also represent a proxy for variables that were not captured in the data. Study subjects may be matched or stratified on their propensity scores, or scores can be integrated into the multivariate regression analysis. Although propensity scores are increasingly popular, incomplete data / incomplete variable inclusion into the score may distort findings just as much. Propensity scores are mainly useful in the case of a limited study size that does not allow matching or adjusting for all individual factors, whereby sufficient information on relevant covariates needs be available. Since our study encompassed some 50'000 cases and 50'000 controls, the application of such scores was not indicated. After all, missing data on residual confounders such as nutrition, ethnicity, sun light exposure, and other life-style factors could not have been augmented by the use of propensity scores. [4, 38]

1.1.5 Data sources

Before the mid-1980's, most data for pharmacoepidemiologic studies were hospital-based, and information was specifically retrieved to answer the study question via patient interviews. However, over the last two decades, utilization of existing data sources, such as multipurpose cohorts or large health databases have become increasingly popular, as this allows approaching a research question with more efficiency.[4, 19]

Multipurpose cohorts

Multipurpose cohorts are study cohorts that consist of a defined population which is followed over time and which is not assembled by a specific exposure. Such cohorts allow studying a variety of research hypotheses. Exposure variability is usually sufficient to allow the evaluation of the association between specific drug exposures

and a disease, as long as the outcome, as well as sufficient information on potential confounders, has been captured. One of the most frequently used multipurpose cohorts for pharmacoepidemiologic research is the US Nurses' Health Study, in which female nurses within the US were followed prospectively from 1976 by biannually mailed follow-up questionnaires inquiring about different exposures (particularly hormone use), lifestyle factors (e.g. smoking status, exercise habits), and the development of chronic conditions (e.g. cancer, cardiovascular diseases). Later, questions about dietary habits and issues related to quality of life were added. Although the study was initially designed to investigate the association between oral contraceptive use and the risk of breast cancer, it has also been extensively used to study other pharmacoepidemiologic research questions.[4]

Health Databases

Over the last decades, large computerized health databases have become an increasingly important source for pharmacoepidemiologic research, as they offer an efficient approach in assessing the hundreds of marketed drugs. Currently, there are two main types of such databases; i.e. administrative databases and physician-based databases. Administrative claims databases have mainly emerged in the US and Canada with the main purpose of health care reimbursement administration. These databases usually contain patient-level data from several files (population registry, pharmacy dispensation file, hospitalization file, ambulatory physician visits file), linked via a unique anonymized identification number (usually the social security number). Longitudinal patient files can be tailored to the research question by linking several files of interest. Some databases additionally allow linkage to registries, such as cancer registries or birth malformation registries. Other examples of administrative databases include the US Group Health Cooperative databases, the Kaiser Permanente databases, or the Medicaid databases, with the main differences between them arising from the health care system in the respective country.

The United Kingdom (UK), Scotland and some other countries built up large primary care based databases, where enrolled general practitioners (GPs) electronically enter patient data. Of these, the General Practice Research Database (GPRD) is probably the best-known example, which is also the database used for the rosacea project presented in this thesis. Because the UK offers a unique medical environment with the GP operating as the gatekeeper and as the central health care provider, the

GPRD was initiated in 1987 in the UK under the name Value Added Medical Products (VAMP) research databank. VAMP provided GPs with practice computers and the corresponding software and in turn GPs agreed to undertake data quality training and to provide anonymized data to the centralized database. After several organizational and managerial changes, the database was donated to the UK Department of Health and at the same time VAMP was renamed as GPRD.

In April 2012 the GPRD was transferred into the Clinical Practice Research Datalink (CPRD), the new English National Health Service (NHS) observational data and interventional research service, jointly funded by the NHS National Institute for Health Research (NIHR) and the Medicines and Healthcare products Regulatory Agency (MHRA). Since data collection of the studies presented within this thesis has been conducted before the GPRD was transferred into the CPRD, the database will be referred to as the GPRD throughout this thesis. A more detailed description of the characteristics of the GPRD is found in the methods section of the studies in this thesis. Other examples of physician-based databases include The Health Improvement Network (THIN) database, which also uses medical records from UK patients, or the Intercontinental Marketing Services (IMS) disease analyzer (previously known as MediPlus) databases, which contains patient records from the UK, Germany, and France.[3, 4, 7]

1.2 Rosacea

1.2.1 History of rosacea

Some of the first evidence of a general perception of rosacea in the society dates back to the late 14th century, when Geoffrey Chaucer, a preeminent English poet, drew a vivid picture of the skin condition within his *Canterbury Pilgrims*, suggesting its etiology in a sanguine constitution and alcoholic habits. Shakespeare also described men with red faces and enlarged noses in his *Henry V.*

A somnour was ther with us in that place,
That hadde a fyr-reed chrubbines face,
For sawcefleem[a] he was, with eyen narwe.
As hoot he was and lecherous as a sparwe,
With scalled browes blake and piled berd;
Of his visage children were afred.
Ther nas quik-silver, litharge ne brimstoon,
Boras, ceruce, ne oille of tarter noon,
Ne oynement that wolde clense and byte,
That him highte helpen of his whelks whyte,
Nor of the knobbes sittinge on his chekes.
Wel loved he garllk, oynons and eek lekes,
And for to drinken strong wyn red as blood.
Canterbury pilgrims, Prologue, 623-635.[39]

Further artistic tribute to rosacea can be found throughout the centuries, such as in the painting in the Louvre *"The Old Man and His Grandson"* by the Italian painter Domenico Ghirlandaio from around the year 1480 (see title page). The first medical description of rosacea appeared in the 14th century, when Dr. Guy de Chauliac, a French surgeon, described "red lesions in the face, particularly on the nose and cheeks," and named the condition ‘goutterose’ (French for ‘pink droplet’) or ‘couperose’. Dr. Thomas Bateman introduced the term ‘acne rosacea’ in 1812, when he wrote: "The perfect cure of acne rosacea is, in fact, never accomplished." While many 19th century references listed rosacea as a sub-type of acne, in 1891, Dr. Henri G. Piffard, a professor of dermatology in New York, called for distinctions among different forms of acne.[39, 40]

[a] *afflicted with pimples, supposed to be caused by too much salt phlegm.*

1.2.2 Epidemiology

Although rosacea appears to be rather common, it remains sparsely investigated. Previously reported prevalence rates span over a wide range. A Swedish observational study from 1989 screened 809 office employees and reported a rosacea prevalence of 10%,[41] whereas a German study (48,665 employees) and an Estonian study reported prevalences of 2.2% and 22%, respectively.[42, 43] Differences might be attributable to a lacking official disease definition, to potential misclassification of actinic damage, but also to varying disease susceptibility across geographic regions. Since fair-skinned people of Celtic origin seem to be at a greater rosacea risk than people with darker skin, demographic data of rosacea cannot invariably be extrapolated onto other ethnic groups.[44]Rosacea is more frequent in women and is usually diagnosed after the age of 30 years.[45] A more detailed background on the epidemiology of facial and ocular rosacea is given in Study 3.1.[46]

1.2.3 Clinical manifestation, classification, and diagnosis

Rosacea is a chronic skin disease of the facial convexities (chin, cheeks, nose, forehead), characterized by remissions and relapses.[47] It can manifest with a broad diversity of clinical features such as prolonged flushing (especially at early disease stages), burning, stinging, erythema, papules, pustules, edema, telangiectasia, ocular leasions, or phymatous changes,[48] whereby specific symptoms usually appear in defined clusters in any given patients. In 2002, an expert committee assembled by the National Rosacea Society (NRSEC) introduced a provisinoal classification system that categorized rosacea into 4 clinical sub-types and one variant form (granulomatous rosacea), differentiated by the appearance of certain conglomerates of symptoms.[48] Symptoms of different sub-types often overlap, but usually manifestation of one sub-type dominates the clinical picture.[45, 47] In 2004 the NRSEC further released a standard grading system for assessing the relative severity of the disease.[48, 49] Both tools are aimed to homogenize disease classification in clinical practice and in the communication of research findings on rosacea.[49] The following four rosacea sub-types were introduced, defined by the minimum of symptoms sufficient for diagnosis.

Erythematotelangiectatic rosacea (ETR) is probably the most frequent rosacea sub-type and is characterized by prolonged flushing with persistent central facial erythema, often accompanied by telangienctasia. Edema, stinging burning, rougness or scaling of the skin may coexist.[47, 48] This rosacea sub-type may be difficult to distinguish from chronic actinic damage.[47] Although flushing is a central main feature of rosacea, flushing symptoms alone do not qualify for a rosacea diagnosis, as many patients with flushing symptoms never develop the skin disease.[45, 47]

Papulopustular rosacea (PPR) presents with persistent central facial erythema with transient papules and/or pustules. Plaques can form from inflammatory lesions in severe forms of the disease, and burning and stinging sensations may be reported. This sub-type resembles acne vulgaris, does not prevent with comedones. Additionally, patients with acne are usually younger and have less erythema but oilier skin. However, acne vulgaris and rosacea may also coexist. Papulopustular rosacea often overlaps with an erythematotelangiectatic manifestation of rosacea presenting with telangiectasia.[47, 48]

Phymatous rosacea includes thickening of the sebaceous glands and the connective tissue, resulting in nodular changes and enlargement of the skin surface, most frequently presenting as rhinophyma (phymatous thickening of the nose). Phymatous changes may also occur on the chin, forehead, cheeks and ears. Other subtypes often, but not always, coexist (PPR > ETR).[47, 48] The rhinophyma can be socially stigmatizing since it is arbitrarily referred to as a ‘whiskey nose’ or a ‘rum blossom’.[47] While other rosacea sub-types show a strong female preponderance, the rhinophyma appears about 20 times more often in men than in women.[45, 47]

Ocular rosacea is defined by the presence of one of the following symptoms; watery or bloodshot eyes, foreign body sensation, burning or stinging, dryness, itching, light sensitivity, blurred vision, telangiectases of the conjunctiva or the lid-margin, or lid-edema. Blepharitis, conjunctivitis, irregularities of the lid-margins, and hordeola and chalazia also occur. Ocular rosacea most often, but not always, coexists with cutaneous rosacea.[2, 48] Symptoms are usually mild to moderate and nonspecific, but severe cases of keratitis, which can even lead to visual loss, have been reported.[45, 47]

Diagnosis

In the absence of confirmatory histologic or serologic markers, rosacea is diagnosed based on the clinical picture and the exclusion of differential diagnoses, such as acne vulgaris, perioral dermatitis, seborrheic dermatitis, or lupus erythematosus, which may differ between rosacea sub-types. Biopsies may be warranted at most to rule out alternative diagnoses.[2, 47]

1.2.4 Triggers and risk factors of rosacea

The predominant presumption that rosacea, and especially rhinophyma, originates in alcoholic indulgence is drawn through the early medical literature and even led to an early reference to the disease as 'pustule de vin' ('French for 'pimples of wine').[39, 40] Although this belief has never been proven, it is still widespread in present general thinking, making rosacea a socially stigmatizing disease.[47] Among experts, however, it is now accepted that alcohol may aggravate the condition, but that the symptoms are just as frequently observed in teetotalers.

> *‚Sauf, dass dir die Nase glüht, rot wie ein Karfunkel, damit du eine Leuchte hast, in des Daseins Dunkel.'*
>
> *Philosophie einer Eckkneipe, Author and Date unknown*

Over the last decades, an abundance of further pathomechanistic hypotheses of environmental and genetic origins have been raised, albeit mostly with inconclusive findings. The incomplete understanding of the pathology of the skin disease also caused the distinction between suggested etiologic and aggravating / triggering factors to often remain unclear.

Rosacea flare-ups seem to be triggered by environmental or lifestyle factors, mostly related to flushing. Among the most commonly referred to rosacea triggers are sun exposure, emotional stress, temperature extremes, wind, exercise, alcohol consumption, spicy foods, humidity, certain skin care products / cosmetics, and hot beverages.[50, 51] Factors that have been discussed in the etiology of the skin disease are abundant and frequently based on inconclusive results, such as gastrointestinal disorders (mainly Helicobacter Pylori), psychogenic factors such as traumatic events or stress, skin mite infestation (Demodex folliculorum, Bacillus oleronius), UV radiation, menopause, reactive oxygen species, certain proteases and other

neuropeptides, epidermal barrier defects, small blood vessel abnormalities, and childhood styes.[47, 48, 52-55]

1.2.5 Pathomechanism

Although the exact pathomechanism of rosacea remains to be elucidated, recent evidence points toward a key role of the innate immune system in the skin disease causing neurovascular dysregulation and neurogenic inflammation.[1] This hypothesis is especially interesting, as it links most of the previously postulated etiologic and / or triggering factors (Section 1.2.4) in a plausible model (Figure 1.2-1). According to this hypothesis, a genetically predisposed hypersensitive skin activates the innate immune system upon contact with certain trigger factors (e.g. UV radiation, skin mites, emotional stress, temperature extremes etc.) via a mechanism that is not yet completely understood. This leads to hyper-stimulation of cutaneous sensory neurons and to a consequent release of vasoactive and inflammatory neuropeptides, resulting in vasodilation (flushing, telangiectasia, edema and burning-stinging sensation), and chronic neurogenic inflammation. Chronic neurogenic stimulation may further lead to persistent erythema and ultimately to a rearrangement of the extracellular matrix, resulting in fibrosis (i.e. rhinophyma). The exact link between the neuronal and the innate immune component remains to be clarified. Various inflammatory mediators, such as cytokines, antimicrobial peptides, or radical oxygen species, seem to additionally aggravate the inflammatory response. For instance, an abundance of aberrantly processed cathelicidines (LL37, vasoactive and inflammatory antimicrobial peptide) was observed in rosacea-affected skin, which induced rosacea like pathologic changes in mice when injected under the skin. However, a systematic profiling and the exact role of such compounds is not yet available.[1, 55-57]

In summary, rosacea seems to be an inflammatory skin disease characterized by neuroimmune dysfunction and neurovascular dysregulation. Meanwhile, an abundance of open questions remain to be answered; Can this neuroinfalmmatory / neurovascular hypothesis be proven over the years? What are the exact mechanisms and their interaction among each other? What is their relevance in the entire complex process? And may these mechanisms have potential as drug targets for rosacea treatment?

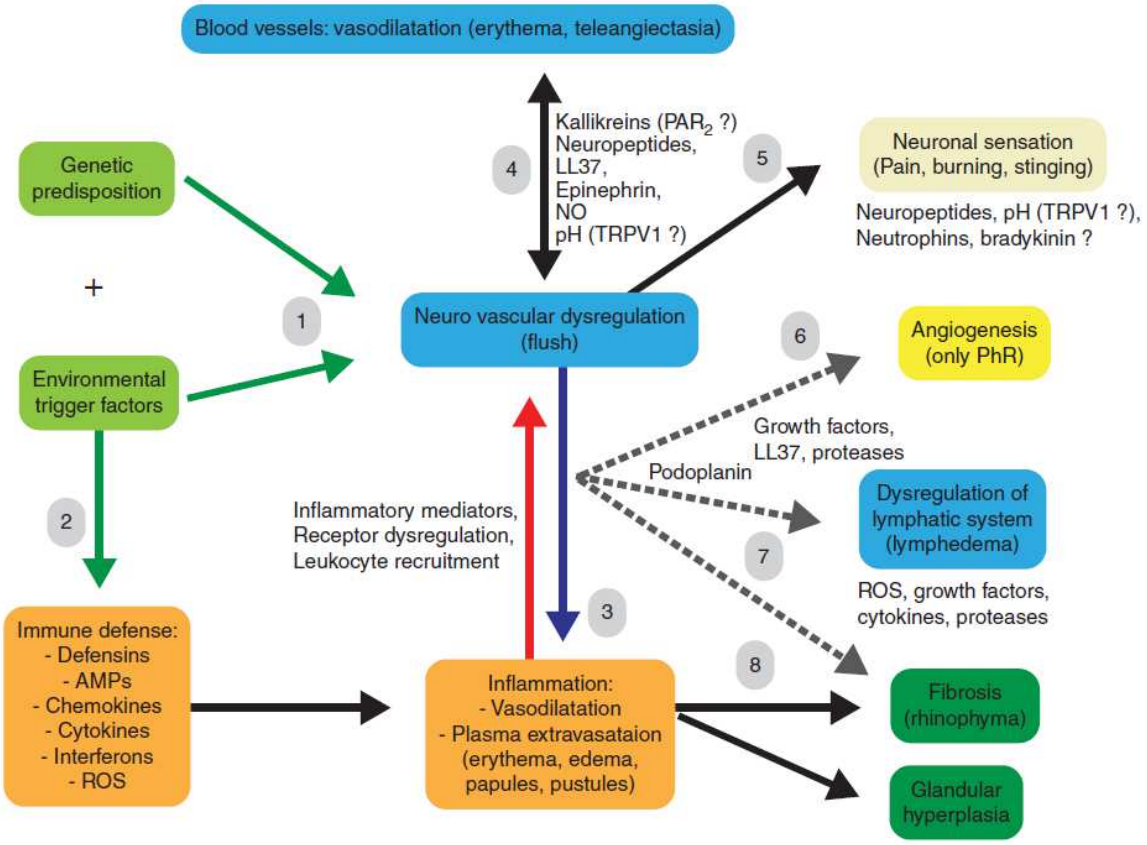

Figure 1.2-1: Suggested pathomechanism of rosacea. Reprinted by permission from Macmillan Publishers Ltd: [Journal of Investigative Dermatology. Symposium proceedings][1] copyright (2011)

1.2.6 Treatment

Historically, rosacea was treated by means of bloodlettings and application of leeches on rosacea-affected skin.[40] Although rosacea therapy has advanced since this time, a curative treatment approach has not yet been developed, and the main substances used in rosacea treatment are relatively old. Because official treatment guidelines are yet lacking, treatment methods have to be applied more or less in a trial and error strategy. The main focus of rosacea therapy is on patients' quality of life, aiming to alleviate the prevailing symptoms, to improve appearance, as well as to prevent progression or sustain remission. An abundance of drug therapies and physical treatments (e.g. surgical or laser procedures) have been suggested, but only few are backed up by clinical evidence. [2, 47, 51]

Topical treatments are the mainstay in the therapy of mild to moderate rosacea. The three primary drugs that are approved and supported by efficacy data are azelaic acid, metronidazole, and sodium sulfacetamide-sulphur. Metronidazole was first used, based on the belief in a microbial origin of the skin disease, but it is now known

to exert an antiinflammatory effect, as do the other two substances. Various other topical therapies are used as off-label treatments, such as clindamycin, erythromycin (+/- zinc), topical retinoids, permethrin 5% cream and others, often based on anecdotal evidence. [2, 47, 52, 58]

Systemic therapy mainly includes oral tetracycline and its second-generation derivatives minocycline and doxycycline, which hold antiinflammatory properties. A sub-antimicrobial dosage of doxycycline allows long-term application without causing pathogen resistances. Macrolide antibiotics (i.e. erythromycin, clarithromycin, and azithromycin), metronidazole, and isotretinoin have also been used to a lesser degree. Suggested off-label treatments, mainly to control flushing symptoms, include β-blockers (BBs), spironolactone, naloxone, ondansetron, aspirin, and clonidine, but clinical evidence for the use of such substances is extremely scarce. [2, 58, 59]

Daily sunscreen application may slow progression of the disease, and decorative cosmetics and education on avoidance of flushing triggering factors can mitigate the psychosocial impact of the skin disease.[2, 47, 51, 58]

Although sub-type-specific rosacea treatment has been described,[59] the frequent overlap of sub-types within patients requires a symptom oriented approach either way, whereby topical and systemic treatments may be combined. Most topical treatments and oral antibiotics are mainly effective against inflammatory symptoms such as papules and pustules, whereas laser therapy is used to remove telangiectases or persistent erythema.[2] Oral isotretinoin or laser interventions may be applied to treat rhinophyma. Mild ocular rosacea can usually be treated by lid hygiene, and lubricating eye drops, and in more severe cases with topical or systemic antibiotics or cyclosporine. More detailed information on sub-type or symptom specific rosacea treatment is found in recent literature.[2, 47-49, 51, 52, 59]

Within the UK, only topical metronidazole and azelaic acid, as well as oral oxytetracycline and doxycycline are officially indicated for the treatment of rosacea.[60]

Figure 1.2-2 shows a therapy guideline, suggested by the ROSIE Group (ROSacea International Expert Group) in 2011, in an attempt to introduce a rational, evidence-based, symptom oriented treatment approach for the skin disease.[2] Whether such schemes are applied in daily non-dermatologic clinical practice remains uncertain.

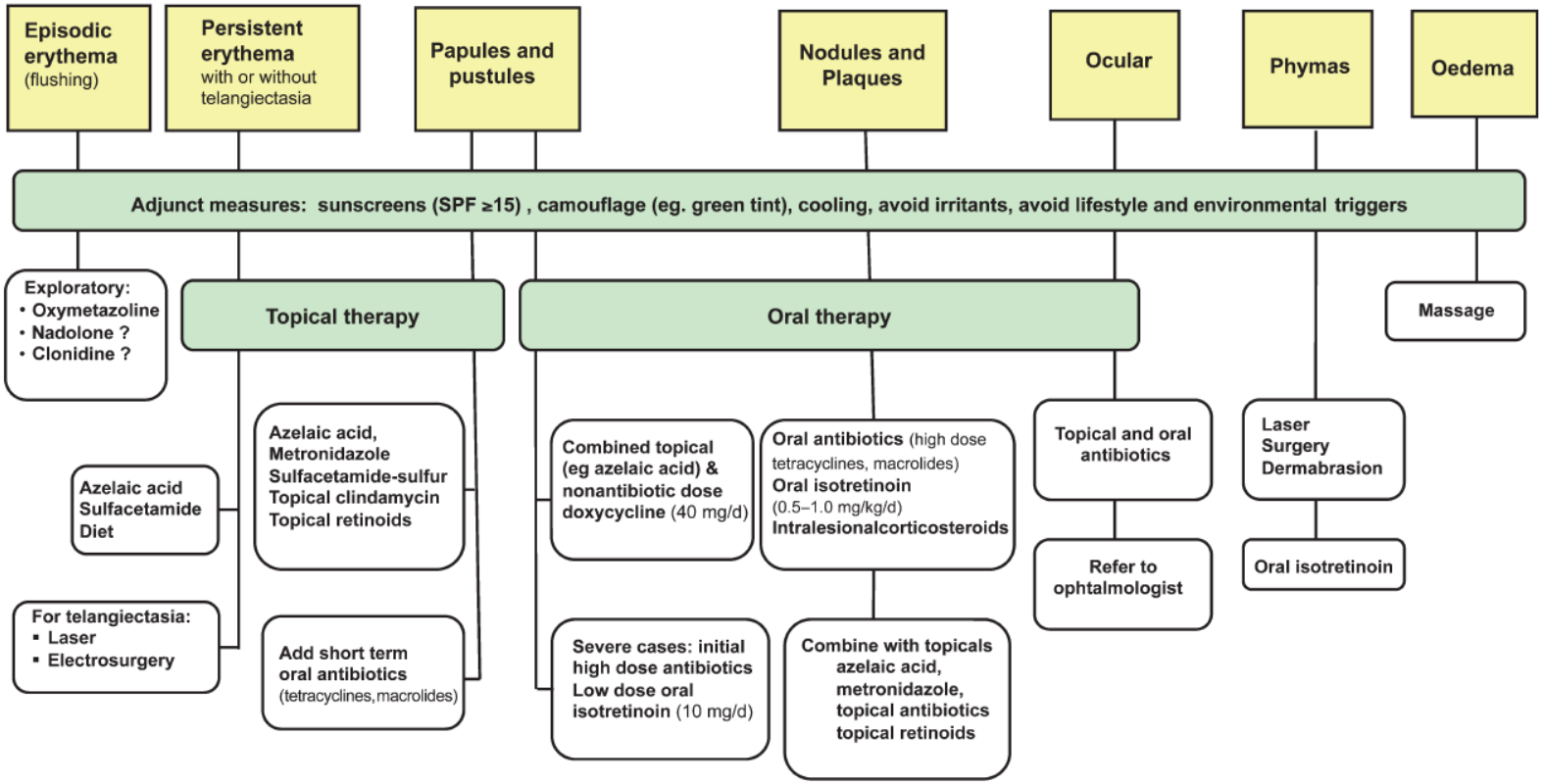

Figure 1.2-2: Suggested symptom-based treatment algorhythm for rosacea. From Elewski et al.[2] Rosacea – global diversity and optimized outcome: proposed international consensus from the Rosacea International Expert Group. Journal of the European Academy of Dermatology and Venereology. Copyright © 2011 by John Wiley & Sons, Inc. Reprinted by permission of John Wiley & Sons, Inc.

Chapter 2

Aims of the thesis

2 Aims of the thesis

The aim of this thesis was to contribute to the general understanding of rosacea in a comprehensive observational case-control study, using data from the GPRD, a large and well-established physician-based primary care database from the UK. Rosacea is a yet under-investigated field of research, haunted by an abundance of inconclusive hypotheses regarding its etiology, pathomechanism, and comorbidities.

Rosacea has not been studied on the GPRD before. Study 3.1 is the basis of the project and aims at describing the study population in terms of demographics, and lifestyle characteristics, including ocular symptoms and first-ever IRs.

Study 3.2 and 3.5 fathom some insufficiently supported notions regarding the association of rosacea with certain comorbidities. An association of migraine and rosacea has been discussed over years, based on inconclusive findings.[41, 61-63] Study 3.2 assesses the risk of incident rosacea in patients with migraine, stratified by age and gender. Within this context the impact of triptans on the risk of developing rosacea is assessed, which could be interesting from a mechanistic point of view. The rumor of a psychogenic origin of the skin disease has sustained over decades, but could neither be entirely established nor dismissed.[53, 54, 64, 65] Study 3.5 assessed the risk for rosacea in patients with depression, other affective disorders, or schizophrenia, stratified by use of antidepressant and antipsychotic drugs.

Based on weak evidence, spironolactone and BBs have been recommended as off-label treatments for rosacea, whereas a general advice not to apply calcium channel blockers (CCBs) in rosacea patients prevails in the literature.[47, 66-69] The objective of Studies 3.3 and 3.6 was to evaluate the effect of diuretics (focus spironolactone, Study 3.3), and of antihypertensive drugs (including BBs and CCBs, Study 3.6) on the risk of rosacea. Especially with abundantly used therapeutics (e.g. antihypertensive drugs) a basis of sound evidence is needed in order for healthcare professionals to make adequate decisions in clinical practice.

Finally, Study 3.4 introduces a novel aspect to rosacea research; i.e. the association of rosacea and diabetes mellitus (DM) / antidiabetic drugs (insulin and oral antidiabetic drugs [OADs]). The momentarily most credible pathomechanistic hypothesis on rosacea involves neurogenic vasodilation, whereas DM is known to inhibit vasodilation especially at an advanced disease stage and upon insulin exposure.[1, 56, 70, 71]

Chapter 3

Rosacea project

3 Rosacea project

3.1 A study on the epidemiology of rosacea in the UK (Study 3.1)

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3.1.1 Abstract

Background: Rosacea is a chronic facial skin disease of unclear origin. Epidemiological data are scarce and controversial, with reported prevalences ranging from 0.09% to 22%. To our knowledge, incidence rates have not been quantified before.

Objectives: In this observational study we quantified incidence rates of diagnosed rosacea in the UK and described demographic characteristics and the prevalence of ocular symptoms in patients with rosacea. We compared lifestyle factors such as smoking and alcohol consumption between rosacea patients and controls.

Methods: Using the UK-based General Practice Research Database, we identified patients with an incident diagnosis of rosacea between 1995 and 2009 and matched them (1:1) to rosacea-free control patients. We assessed person-time of all patients at risk and assessed incidence rates of rosacea, stratified by age, sex, year of the diagnosis, and region.

Results: We identified 60,042 rosacea cases and 60,042 controls (61.5% women). The overall incidence rate for diagnosed rosacea in the UK was 1.65 / 1,000 person-years. Rosacea was diagnosed in some 80% of cases after the age of 30 years. Ocular symptoms were recorded in 20.8% of cases at the index date. We observed a significantly reduced relative risk of developing rosacea among current smokers (odds ratio 0.64, 95% CI 0.62-0.67). Alcohol consumption was associated with a marginal risk increase.

Conclusions: We quantified incidence rates and characteristics of patients with rosacea diagnosed in clinical practice in a large epidemiological study using primary care data from the UK. Smoking was associated with a substantially reduced risk of developing rosacea.

3.1.2 Introduction

Rosacea is a chronic inflammatory facial skin disease characterised by flushing episodes, erythema, papules, pustules, and telangiectasia. Phymatous changes mostly of the nose, the rhinophyma, as well as inflammation of the eye and the eyelid can also be manifestations of the disease.[48, 52, 72, 73] Rosacea is not life-threatening, but affects quality of life.[52, 72-75] Official diagnostic guidelines do not exist, due to lacking measurable parameters and an official clinical definition of rosacea.[47, 52, 72, 73, 76, 77] In 2002, the American National Rosacea Society Expert Committee introduced a classification system which divides the disease into four subtypes: 'erythematotelangiectatic', 'papulopustular', 'phymatous', and 'ocular' rosacea.[48, 52]
The pathogenesis of rosacea remains unclear. Among various other factors, an altered innate immune response, neurogenic inflammation, neurovascular dysregulation, or sun damage have been hypothesised as possible causes.[1, 41, 47, 52, 55, 56, 72, 78-80]

Epidemiological data on rosacea are scarce, with reported prevalences between 0.09% and 22%.[41, 42, 44, 81-85] A study from Sweden screened 809 office employees and revealed a rosacea prevalence of 10%,[41] while a German and an Estonian study reported prevalences of 2.2% and 22%, respectively.[42, 43] Incidence rates (IRs) of rosacea, to our knowledge, have not been studied before. Rosacea is usually diagnosed after the third decade of life. Most studies reported the disease to be more common in women, but to develop into phymatous stages more frequently in men.[41-43, 72, 78, 82, 83, 86, 87] Rosacea seems to be diagnosed more often in fair-skinned people of Celtic origin. However, it is unclear whether pigmentation simply obscures detection of typical skin symptoms in darker skin.[41, 43, 44, 52, 72, 73, 76, 78, 85]
Ocular rosacea is most likely to be of inflammatory nature, but the exact aetiology remains unclear. Blepharitis, conjunctivitis, hordeola/chalazia, tear film insufficiency and foreign body sensation have been described as frequent ophthalmic symptoms, while sight-threatening corneal involvement may occur in rare cases.[72, 73, 88-91] Ophthalmic involvement in patients with rosacea has been observed in 6% - 72% of cases, depending on diagnostic methods and the population under study.[48, 52, 73, 88-93]
The association between cigarette smoking and the risk of developing rosacea has been explored in three studies: while one study found patients with rosacea to smoke less frequently than the general population,[94] two other studies associated cessation of smoking with an increased risk of developing this skin disease.[80, 95] Despite sparse

evidence, rosacea and in particular rhinophyma have been linked to excessive alcohol consumption.[47, 72, 78, 96] Alcohol can trigger flushing episodes, but previous studies did not find evidence for a materially altered rosacea risk associated with alcohol consumption.[47, 80, 96-98]

We conducted a large observational study to establish IRs of diagnosed rosacea in the UK, to characterise demographics of patients with rosacea, to quantify the prevalence of diagnosed ocular involvement, and to explore the impact of various lifestyle factors on the risk of developing the disease.

3.1.3 Materials and Methods

Study Design and Data Source

We conducted a retrospective case-control study using the UK-based General Practice Research Database (GPRD). This database is a large source of anonymised primary-care data comprising approximately 7 million active patients who are enrolled with selected general practitioners (GPs). Those GPs have been trained to provide clinical data in a standardised format. Participating practices provide information on patient demographics and characteristics (e.g. age, sex, height, weight, smoking status), symptoms or medical diagnoses, laboratory test results, referrals to secondary care and drug prescriptions, which are directly generated by the computer. The Medicines and Healthcare Products Regulatory Agency (MHRA) anonymises the raw data before release and performs quality control checks, to ensure that the standards are followed. The patients enrolled in the GPRD are representative of the UK population with regard to age, sex, geographical distribution, and annual turnover rate. Extensive validation of the GPRD [99, 100] has documented high case validity, especially for chronic conditions.[99] The database has been the source for numerous pharmacoepidemiological studies and for public health and disease epidemiology studies.[101] The study protocol was approved by the Independent Scientific Advisory Committee (ISAC) for MHRA database research.

Study Population

The study population consisted of all patients in the GPRD with a first-time recorded READ-code for rosacea[99] at a date between January 1995 and September 2009 (subsequently referred to as index date [ID]). We excluded patients with <3 years of

recorded active history on the database prior to their first-time rosacea diagnosis to increase the likelihood of including only incident cases. Patients with a diagnosis for rhinophyma only or ocular rosacea only were not included.

For the case-control analysis we randomly identified a rosacea-free control group of the same size and applied the same exclusion criteria as to cases. In addition, control patients were not eligible for inclusion if they had rhinophyma (without facial rosacea) or flushing symptoms recorded at any time. Controls were matched 1:1 to case patients on age (year of birth), sex, general practice, calendar time (ID), and number of years of recorded history in the database prior to the ID.

We assessed ocular symptoms in cases and controls within 1 year prior to and within 90 days after the ID. We further evaluated whether differential diagnoses of rosacea were recorded in cases and controls, in particular acne, perioral dermatitis, lupus erythematosus, atopic dermatitis, and seborrhoeic dermatitis.

We assessed the smoking status (non, current, ex, unknown), body mass index (BMI; <18.5, 18.5-24.9, 25.0-29.9, or 30+ kg m^{-2}), and alcohol consumption (0, 1-4, 5-9, 10-14, 15-24, or 25+ units per week, or unknown) for cases and controls, as well as the number of GP visits over a 1-year period prior to the ID as a marker for medical attention. Furthermore, we assessed the number of rosacea cases who had been referred to a dermatologist or an ophthalmologist within 1 year prior to or after the ID.

Statistical Analysis

We estimated IRs of diagnosed rosacea for all patients in the GPRD between 1995 and 2008, overall and stratified by age, sex and index year. Rates were calculated as the number of new cases divided by the total number of person-years (py) at risk. For rosacea-free patients, the number of py at risk was calculated by adding up person-time of all patients at risk in the GPRD between 1 January 1995 and the end of follow-up, which was the earliest of the following: a rosacea diagnosis, death, leaving the practice, or the end of the study period. In an additional analysis, we established IRs stratified into three geographical regions, i.e. the North (Scotland, Northern Ireland, North East England, North West England, and Yorkshire and the Humber), the Centre (Wales, East Midlands, West Midlands, East of England), or the South (South West, South Central, London, South East Coast) of the UK. We

age-standardised IRs stratified by geographical regions and by index year applying the direct method, using the European standard population as reference.
For the case-control analysis, we conducted conditional logistic regression analyses using SAS statistical software (version 9.2, SAS Institute, Inc., Cary, NC, US). Relative risk estimates were calculated as odds ratios (ORs) with 95% confidence intervals (CIs).

3.1.4 Results

The study population encompassed 60,042 rosacea cases and 60,042 controls, of whom 61.5% were female. The vast majority (80%) of patients with rosacea were at or above the age of 30 years at the ID (Table 3.1-1). Only 7.3% of the rosacea cases were referred to a dermatologist, and 4.1% saw an ophthalmologist within 1 year before or after the ID. A rhinophyma diagnosis was recorded in 422 (0.7%) of the cases, of whom 80.3% were male.

Incidence Rates

The overall IR of diagnosed rosacea in the GPRD population was 1.65 / 1,000 py (95% CI 1.63-1.66). It was higher in women (IR 1.92 / 1,000 py [95% CI 1.90-1.94]) than in men (IR 1.34 / 1,000 py [95% CI 1.32-1.36]), and peaked between the age of 40 and 59 years (Figure 3.1-1). The crude rate increased between 1995 and 2002 and then levelled off; the same was the case for the European-standardised rates over time, although slightly lower (Table 3.1-1). The crude IR was higher in the North with an IR of 1.93 / 1,000 py (95% CI 1.90-1.95) than in the South of the UK (IR 1.46 / 1,000 py [95% CI 1.44-1.48]). The age-standardised IR was 1.71 / 1,000 py (95% CI 1.69-1.73) in the North and 1.29 / 1,000 py (95% CI 1.27-1.31) in the South of the UK.

Demographics and Life-Style Characteristics

Current smokers had a significantly reduced relative risk of developing rosacea when compared with nonsmokers, yielding an OR of 0.64 (95% CI 0.62-0.67). The OR for ex-smokers, when compared with nonsmokers, was slightly increased (OR 1.14, 95% CI 1.10-1.18). The OR for rosacea increased slightly with increasing number of alcohol units consumed per week, with the highest OR of 1.51 (95% CI 1.41-1.63) for

patients consuming more than 25 units per week, as compared to those not drinking alcohol. Neither high nor low BMI was associated with an altered risk.
Rosacea cases had more GP visits in the year prior to the ID than controls, with the highest OR of 2.33 (95% CI 2.25-2.41) for those with 10 or more GP visits when compared with patients with 0-2 GP visits (Table 3.1-2).

Ocular Symptoms and Differential Diagnoses

In total, 12,480 (20.8%) of 60,042 rosacea cases had at least one ocular symptom recorded within a 1-year period prior to or up to 90 days after the ID, compared with 7,737 (12.9%) controls. Thus, the relative risk for cases to be diagnosed with ocular symptoms was 1.82 (95% CI 1.76-1.88). The prevalence of ocular symptoms was similar in men (19.8%) and women (21.4%). The most frequent ocular symptoms were hordeola / chalazia, followed by conjunctivitis and dry or watery eyes. The largest difference between cases and controls was seen for blepharitis, where the OR was 3.57 (95% CI 3.17-4.02).
We identified 23.2% of cases and 6.3% of controls with a recorded acne diagnosis prior to or up to 90 days after the ID, with most co-diagnoses in the age-group of <20 years. Seborrhoeic dermatitis was found in 10.9% of the cases and in 3.7% of the controls. The distribution of differential diagnoses of rosacea in cases and controls is displayed in Table 3.1-3.

Table 3.1-1: Incidence rates of diagnosed rosacea in the UK between 1995 and 2008

	Person-years at risk	Rosacea cases	IR per 1,000 person-years (95% CI)		IR per 1,000 person-years (95% CI)		IR per 1,000 person-years (95% CI)	
Overall	34,136,657	56,253	1.65	(1.63-1.66)				
By Sex								
Men	16,141,632	21,645	1.34	(1.32 - 1.36)				
Women	17,995,025	34,608	1.92	(1.90 - 1.94)				
By Age			**Men and Women**		**Men**		**Women**	
<20	7,179,962	6,367	0.89	(0.87 - 0.91)	0.83	(0.80 - 0.86)	0.95	(0.92 - 0.98)
20-29	3,948,312	5,147	1.30	(1.27 - 1.34)	0.91	(0.87 - 0.95)	1.68	(1.63 - 1.74)
30-39	4,776,305	8,657	1.81	(1.77 - 1.85)	1.05	(1.01 - 1.10)	2.47	(2.41 - 2.53)
40-49	5020,453	11,734	2.34	(2.30 - 2.38)	1.54	(1.49 - 1.59)	3.06	(3.00 - 3.13)
50-59	4,685,054	10,164	2.17	(2.13 - 2.21)	1.86	(1.81 - 1.92)	2.46	(2.39 - 2.52)
60-69	3,747,948	7,608	2.03	(1.98 - 2.08)	2.03	(1.97 - 2.10)	2.03	(1.96 - 2.09)
70+	4,778,621	6,576	1.38	(1.34 - 1.41)	1.59	(1.54 - 1.65)	1.23	(1.19 - 1.27)
By Year of Diagnosis					**Age-Standardised Rates***			
1995	1,734,936	2,428	1.40	(1.34 - 1.46)	1.29	(1.24-1.34)		
1996	1,934,725	2,929	1.51	(1.46 - 1.57)	1.42	(1.37-1.47)		
1997	2,081,764	3,123	1.50	(1.45 - 1.55)	1.41	(1.36-1.46)		
1998	2,200,167	3,467	1.58	(1.52 - 1.63)	1.48	(1.43-1.53)		
1999	2,315,649	3,504	1.51	(1.46 - 1.56)	1.41	(1.36-1.46)		
2000	2,429,796	4,139	1.70	(1.65 - 1.76)	1.58	(1.53-1.63)		
2001	2,502,051	4,408	1.76	(1.71 - 1.81)	1.61	(1.56-1.66)		
2002	2,564,020	4,591	1.79	(1.74 - 1.84)	1.63	(1.58-1.68)		
2003	2,622,215	4,276	1.63	(1.58 - 1.68)	1.48	(1.44-1.52)		
2004	2,686,549	4,716	1.76	(1.71 - 1.81)	1.58	(1.54-1.62)		
2005	2,722,527	4,581	1.68	(1.63 - 1.73)	1.50	(1.46-1.54)		
2006	2,760,846	4,568	1.65	(1.61 - 1.70)	1.46	(1.42-1.50)		
2007	2,779,225	4,625	1.66	(1.62 - 1.71)	1.46	(1.42-1.50)		
2008	2,802,186	4,898	1.75	(1.70 - 1.80)	1.54	(1.50-1.58)		

Abbreviations: IR, incidence rate; CI, confidence interval.

*Rates were age-standardised using the European standard population as reference.

Table 3.1-2: Distribution of patient characteristics and lifestyle factors in patients with rosacea and controls in the UK

	Rosacea cases, No (%) (n=60,042)		Rosacea-free controls, No (%) (n=60,042)		OR crude (95% CI)		OR adjusted* (95% CI)	
Age (years)								
<20	6,673	(11.1)	6,680	(11.1)	NA	NA	NA	NA
20-29	5,425	(9.0)	5,420	(9.0)	NA	NA	NA	NA
30-39	9,172	(15.3)	9,184	(15.3)	NA	NA	NA	NA
40-49	12,576	(21.0)	12,550	(20.9)	NA	NA	NA	NA
50-59	10,851	(18.1)	10,855	(18.1)	NA	NA	NA	NA
60-69	8,246	(13.7)	8,250	(13.7)	NA	NA	NA	NA
70+	7,099	(11.8)	7,103	(11.8)	NA	NA	NA	NA
Sex								
male	23,118	(38.5)	23,118	(38.5)	NA	NA	NA	NA
female	36,924	(61.5)	36,924	(61.5)	NA	NA	NA	NA
Alcohol Consumption (units/week)								
none/ex	7,622	(12.7)	7,874	(13.1)	1.00	(ref.)	1.00	(ref.)
current (units ?)	10,929	(18.2)	10,957	(18.3)	1.04	(0.99-1.08)	1.03	(0.99-1.08)
1-4	10,455	(17.4)	10,150	(16.9)	1.09	(1.04-1.13)	1.06	(1.02-1.11)
5-9	5,764	(9.6)	5,462	(9.1)	1.12	(1.06-1.18)	1.10	(1.05-1.16)
10-14	5,087	(8.5)	4,516	(7.5)	1.20	(1.14-1.27)	1.20	(1.14-1.26)
15-24	3,299	(5.5)	2,859	(4.8)	1.25	(1.17-1.33)	1.26	(1.19-1.35)
25+	2,668	(4.4)	2,032	(3.4)	1.43	(1.33-1.53)	1.51	(1.41-1.63)
unknown	14,218	(23.7)	16,192	(27.0)	0.81	(0.76-0.85)	0.95	(0.90-1.00)
Smoking Status								
Non	30,105	(50.1)	27,681	(46.1)	1.00	(ref.)	1.00	(ref.)
Current	8,972	(14.9)	12,274	(20.4)	0.66	(0.64-0.68)	0.64	(0.62-0.67)
Ex	11,863	(19.8)	9,657	(16.1)	1.17	(1.13-1.21)	1.14	(1.10-1.18)
Unknown	9,102	(15.2)	10,430	(17.4)	0.68	(0.65-0.71)	0.82	(0.77-0.86)
BMI (kg/m^2)								
12.0-18.4	995	(1.7)	1,070	(1.8)	0.85	(0.77-0.92)	0.90	(0.82-0.98)
18.5-24.9	21,038	(35.0)	19,556	(32.6)	1.00	(ref.)	1.00	(ref.)
25.0-29.9	15,116	(25.2)	14,233	(23.7)	0.99	(0.96-1.02)	0.97	(0.94-1.00)
30.0-60.0	8,020	(13.4)	8,235	(13.7)	0.91	(0.88-0.94)	0.89	(0.86-0.93)
Unknown	14,873	(24.8)	16,948	(28.2)	0.72	(0.70-0.75)	0.82	(0.78-0.86)
GP Visits (1 y prior to ID)								
0-2	10,290	(17.1)	16,888	(28.1)	1.00	(ref.)	NA	NA
3-4	7,332	(12.2)	7,440	(12.4)	1.67	(1.60-1.74)	NA	NA
5-9	14,834	(24.7)	12,922	(21.5)	2.03	(1.96-2.10)	NA	NA
10+	27,586	(45.9)	22,792	(38.0)	2.33	(2.25-2.41)	NA	NA

Abbreviatoins: BMI, body mass index; CI, confidence interval; GP, general practitioner; ID, index date; NA, not applicable; OR, odds ratio.

* Adjusted for BMI, smoking, alcohol consumption.

Table 3.1-3: Distribution of ocular symptoms and differential diagnoses in rosacea cases and controls in the UK

	Rosacea cases, No (%) (n=60,042)		Rosacea-free controls, No (%) (n=60,042)		OR crude (95% CI)	
Ocular Symptoms (1 year prior to and up to 90 days after the ID)						
Blepharitis	1,250	(2.1)	360	(0.6)	3.57	(3.17-4.02)
Hordeolum / chalazion	4,573	(7.6)	2,240	(3.7)	2.15	(2.04-2.26)
Conjunctivitis	2,471	(4.1)	1,443	(2.4)	1.75	(1.64-1.87)
Other inflammation	262	(0.4)	130	(0.2)	2.02	(1.63-2.49)
Other conjunctival disorders	193	(0.3)	144	(0.2)	1.34	(1.08-1.66)
Corneal disorders	416	(0.7)	308	(0.5)	1.35	(1.17-1.57)
Red eyes	1,358	(2.3)	958	(1.6)	1.43	(1.32-1.56)
Watery or dry eye	2,149	(3.6)	1,259	(2.1)	1.78	(1.66-1.92)
Itchy eye	1,157	(1.9)	709	(1.2)	1.67	(1.51-1.83)
Eye irritation / pain	1,928	(3.2)	1,320	(2.2)	1.49	(1.39-1.60)
Blurred vision	620	(1.0)	512	(0.9)	1.21	(1.08-1.37)
Eye involvement total	12,480	(20.8)	7,737	(12.9)	1.82	(1.76-1.88)
men	4,585	(19.8)	2,630	(11.4)	1.97	(1.87-2.08)
women	7,895	(21.4)	5,107	(13.8)	1.74	(1.67-1.81)
Differential Diagnoses (prior to or up to 90 days after the ID)						
Acne	13,921	(23.2)	3,772	(6.3)	6.13	(5.85-6.43)
<20 years	3,842	(6.4)	834	(1.4)	11.88	(10.50-13.44)
20-29 years	3,052	(5.1)	1,141	(1.9)	5.27	(4.76-5.83)
30-39 years	3,065	(5.1)	879	(1.5)	5.20	(4.73-5.71)
40-49 years	2,411	(4.0)	606	(1.0)	5.03	(4.54-5.57)
50-59 years	1,013	(1.7)	219	(0.4)	4.94	(4.24-5.76)
60-69 years	367	(0.6)	71	(0.1)	5.68	(4.35-7.42)
70+ years	171	(0.3)	22	(0.0)	7.68	(4.93-11.98)
Seborrhoea / seborrhoeic dermatitis	6,528	(10.9)	2,199	(3.7)	3.25	(3.09-3.42)
Perioral dermatitis	974	(1.6)	172	(0.3)	5.92	(5.01-6.99)
Lupus erythematosus	173	(0.3)	85	(0.1)	2.04	(1.57-2.64)
Atopic dermatitis	4,125	(6.9)	2,922	(4.9)	1.48	(1.40-1.55)

Abbreviations: CI, confidence interval; ID, index date; OR, odds ratio.

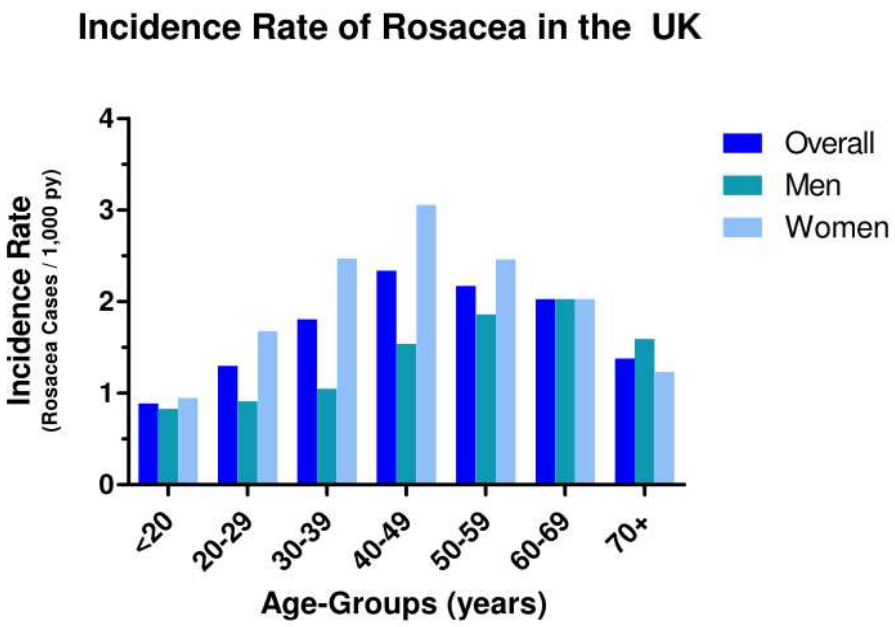

Figure3.1-1: Incidence rates of rosacea diagnosed in the UK between 1995 and 2008. py, person-years.

3.1.5 Discussion

In this large observational study we quantified IRs and assessed the demographic distribution of patients with rosacea in a primary care setting in the UK. Overall, the IR of GP-diagnosed rosacea in the UK was 1.65 / 1,000 py (95% CI 1.63-1.66), with higher IRs in females. Rosacea also tended to be diagnosed earlier in women than in men, a finding consistent with other studies, and usually developed after the age of 30 years.[41, 52, 72, 77, 78, 82, 86, 87] We further observed a slight increase in the crude and age-standardised IRs over the course of the study period until 2002, as was reported by the authors of a US-based publication from 2002.[79] A possible explanation for this rise is increased awareness of rosacea among GPs. In our study population, IRs were higher in the North than in the South of the UK. This observation was not changed after age standardisation. The Irish population has been reported to be predominantly fair-skinned,[102] so our findings may reflect an increased risk of rosacea with more fair-skinned populations.[41, 43, 44, 52, 78, 85]

We observed a significantly decreased OR for current smokers when compared with nonsmokers. Ex-smokers, on the other hand, yielded a slightly increased OR. It has been suggested that there is an immunosuppressive effect of cigarette smoking leading to potential beneficial effects in certain inflammatory diseases, such as ulcerative colitis and sarcoidosis.[103, 104] However, a negative impact on other inflammatory diseases, such as Crohn's disease or rheumatoid arthritis, has also been reported.[103] Further, neurovascular dysfunction causing vasodilatation has been implicated in the pathogenesis of rosacea.[1, 56] Cigarette smoking impairs peripheral microvascular relaxation and might thus decrease the risk of incident rosacea.[105] Three small studies of no more than 172 rosacea cases previously addressed the association between cigarette smoking and rosacea. One study found patients with rosacea to smoke less frequently than the general population,[94] and the other two found that cessation of smoking was associated with an increased risk of developing rosacea when compared to current or nonsmokers. The latter two hypothesised an immunosuppressive effect of cigarette smoking on rosacea, exerting a triggering or aggravating effect upon withdrawal, as has been described for ulcerative colitis.[80, 94, 95, 104] All three studies were based on self-reported smoking status. Current smoking status has been shown to be more reliably recorded than former skoking in the GPRD, with about 30% of 'ex-smokers' actually being current

smokers.[106] Thus, the risk of developing rosacea for ex-smokers may be somewhat higher than observed due to misclassification of smoking status. Regardless of some possible misclassification, our data suggest that cigarette smoking reduces the risk of developing rosacea.

A potential causal role of alcohol in the pathogenesis of rosacea has been discussed controversially for decades.[47, 97] However, most previous studies found a nonsignificant association between alcohol and the skin disease.[80, 96-98] In our study, ORs increased marginally with increasing number of alcohol units consumed per week, yielding an OR of 1.51 for patients drinking more than 25 units per week (4.4% of cases and 3.4% of controls). These data do not suggest that alcohol consumption plays a major role in the pathophysiology of rosacea.

We observed ocular symptoms in 20.8% of the cases within a year prior to or up to 90 days after the ID, implying an almost two-fold increased likelihood that patients with rosacea would be affected by ocular disorders when compared with controls. A study from 1953 reported that ocular symptoms preceded dermatologic findings in up to 20% of rosacea patients, whereas 27% of patients were diagnosed concomitantly.[48, 72, 107] We observed men and women to be similarly at risk, while previously reported male/female ratios were not consistent.[89, 90, 92, 107] Hordeola / chalazia were the most prevalent ocular symptoms in our study population, followed by conjunctivitis and dry or watery eyes. Although the reported frequencies of ocular symptoms of rosacea varied in the literature the overall distribution of observed symptoms in our study was consistent with most publications.[72, 73, 88-90] However, blepharitis was recorded in only 2.1% of rosacea cases in this study, while it has previously been among the most frequently reported ocular symptoms.[88, 91] It is possible that blepharitis usually occurs at a later stage of the disease and was therefore not yet present at the time of the diagnosis in our study population. Most ocular findings in our study were GP-diagnosed, with only 4.1% of cases referred to an ophthalmologist within the year prior to or after the ID. Diagnostic bias has been implicated before, suggesting that ocular rosacea may often go undetected in clinical practice.[48, 52, 73, 88-92]

As there are no strict guidelines for diagnosing rosacea, differential diagnostic criteria may have led to some misdiagnoses. Of all rosacea cases, 23.2% also had an acne diagnosis recorded before or up to 90 days after the ID, most of them in the age

group of <20 years. Rosacea is a common disease and can, just by coincidence, coexist with acne vulgaris.[86, 108] However, as rosacea does not typically manifest before the age of 20,[41, 78, 82, 87] it is unclear whether these results represent diagnostic uncertainty by the GP, or whether these two diseases actually coexisted in our sample. A study from the 1950's found acne to be present in about 7% of rosacea cases and controls.[98] On the other hand, young patients with rosacea were mentioned to often have a history of acne, although statistical evidence to back up this hypothesis was not found.[78, 108] The magnitude of the increase of co-diagnoses, however, suggests that diagnostic bias may play a certain role which needs to be considered when interpreting our results.

Seborrhoeic dermatitis has been referred to as a common feature of rosacea,[78, 86, 98, 109] although an increased sebum excretion in rosacea-affected skin was not observed.[110] We observed a three-fold increased OR of seborrhoeic dermatitis in patients with rosacea compared with controls. Again, we cannot establish whether these patients had seborrhoeic dermatitis as a feature of their rosacea, or whether they had been misdiagnosed. The results on atopic dermatitis (marginally elevated OR) as well as on lupus erythematosus or perioral dermatitis (low prevalence) do not imply major diagnostic bias within our study.

This study has several limitations that should be considered in interpreting our findings. First, mild rosacea may not necessarily cause patients to seek medical help; thus, a certain portion of cases may remain undetected, and our rates may be lower than the true rates in the UK population. Also, there is possible detection bias present since women might seek medical care more often than men.[76] Second, the likelihood of being diagnosed with rosacea may increase with increasing medical attention. To address this issue, we quantified the number of GP visits, and observed that patients with rosacea tended to see the GP more often prior to the diagnosis than controls. Thus, a certain degree of diagnostic bias cannot be ruled out. Third, due to lacking diagnostic guidelines or clinically measurable parameters, rosacea is diagnosed based on visible symptoms and by exclusion of other diseases. Such GP-diagnosed diseases are difficult to validate because most usual options for a case validation are not available, such as sending for referral letters, hospital discharge letters, or questionnaires. The observed overlap of rosacea and acne diagnoses around the ID might represent some degree of diagnostic uncertainty or misclassification of disease. However, a cross-sectional study analysing dermatology patient data from

South-East Scotland revealed a concordance of rosacea diagnoses of dermatologists and the referring GPs of 74%.[111] The fact that only 7.3% of all patients with rosacea were referred to a dermatologist, most probably those with an uncertain or more complicated diagnosis, allows us to assume an overall high validity of rosacea diagnoses in the GPRD. Finally, we could not control for ethnic background, skin pigmentation, socioeconomic status (e.g. income, education), or lifestyle factors such as sun exposure, profession or nutrition as these parameters are not recorded in the GPRD.[41, 47, 52, 72, 78-80] We were also not in a position to distinguish between erythematotelangiectatic and papulopustular rosacea, which may cause overdiagnosis of the disease as chronic actinic damage such as heliodermatitis is not always distinguishable from erythematotelangiectatic rosacea, in the absence of inflammatory lesions.[47, 85] Despite these limitations, this is - to our knowledge - the first epidemiological study on rosacea using UK-based primary care data, and by far the largest study to focus on the characteristics of patients with rosacea, including an analysis on the impact of alcohol consumption and cigarette smoking on the risk of incident rosacea.

In summary, this large observational study describes the epidemiology of rosacea in a large sample of the UK population and quantifies the presence of ocular involvement in this skin disease. Our findings suggest that smoking may substantially reduce the risk of developing rosacea, whereas alcohol consumption is associated with only a small increase in risk.

3.2 Migraine, triptans, and the risk of developing rosacea (Study 3.2)

A population-based study within the UK

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3.2.1 Abstract

Background: Rosacea is a common skin disease, involving neurogenic inflammation and neurovascular dysregulation. Migraine has been associated with vascular changes and sterile inflammation. The 2 diseases have been associated over decades, but evidence is scarce. Triptans have vasoconstricting and antiinflammatory properties, but a potential impact of this drug class on rosacea remains uninvestigated.

Objective: We sought to analyze the association between migraine or triptan exposure and the risk of developing rosacea within the UK.

Methods: We conducted a case-control study using the UK-based General Practice Research Database (GPRD). We identified patients with incident rosacea between 1995 and 2009 (cases), and matched one rosacea-free control subject to each case. We compared the prevalence of diagnosed migraine and exposure to triptans before the first-time rosacea diagnosis between cases and controls using multivariate conditional logistic regression.

Results: Among 53,927 cases and 53,927 controls, we observed a small overall association between rosacea and migraine in women (adjusted OR 1.22, 95% CI 1.16-1.29), but not in men. This effect was somewhat more distinct in female migraineurs aged 50 to 59 years (OR of 1.36, 95% CI 1.21-1.53). Female triptan users also revealed slightly increasing risk estimates with increasing age, with the highest OR of 1.66 (95% CI 1.30-2.10) in women of ≥60 years.

Limitations: This is a retrospective case-control study, for which a certain degree of bias and confounding cannot be ruled out.

Conclusions: We observed a slightly increased risk for female migraineurs to develop rosacea, particularly in women with severe migraine aged 50 years or older.

3.2.2 Introduction

Rosacea is a chronic facial skin disease, with neurovascular dysregulation and neurogenic inflammation as presumed pathophysiologic key components.[1, 47, 56, 70] Like rosacea, migraine is thought to involve neurovascular dysregulation and neurogenic inflammation.[112-114] Despite scarce evidence, the 2 diseases have been associated over decades,[41, 47] but previous results range from an overall strong association between rosacea and migraine to an association confined to postmenopausal women.[41, 61- 63, 115] Triptans, selective serotonin agonists, are indicated for treatment of acute migraine headache. Besides cerebral vasoconstriction, triptans are supposed to inhibit neurogenic inflammation, and transmission of nociceptive impulses.[112, 116-120] We were interested in assessing whether triptans or ergot derivatives may have a beneficial effect on the risk of developing rosacea by either mechanism, an association which, to our knowledge, has not been reported yet. We conducted a large population-based case-control study to explore the association between migraine, use of triptans and ergot derivatives, and the risk of developing rosacea within the UK.

3.2.3 Materials and Methods

Study design and data source

We conducted a matched case-control analysis using data from the UK-based GPRD. The GPRD was established in 1987 and is a large source of primary-care data comprising approximately 7 million patients who are enrolled with selected general practitioners (GPs) across the UK. In the UK, GPs hold a gatekeeper role within the National Health System (NHS). After referrals, consultants are required to send information on outpatient diagnoses and treatments to the GP who enters this information into the database and takes over long-term care. The GPs have been trained to provide clinical data in a standardized format. Participating practices provide information on patient demographics and characteristics (e.g. age, sex, height, weight, smoking status), symptoms or medical diagnoses, laboratory test results, referrals to secondary care, and drug prescriptions, which are directly generated by the computer, ensuring a complete and anonymous drug history. The Medicines and Healthcare Products Regulatory Agency (MHRA) checks the raw data

before release and performs quality-control checks on the comprehensiveness and validity of data recording by GPs. The patients enrolled in the GPRD are representative of the UK population with regard to age, sex, geographic distribution, and annual turnover rate. Extensive validation of the GPRD[99, 100] has documented its high validity, especially for chronic conditions.[99, 121] The database has been the source of numerous pharmacoepidemiologic studies and of public health and disease epidemiology studies.[101, 121] The study protocol was approved by the Independent Scientific Advisory Committee for MHRA database research.

Cases and controls

Cases were all patients with a first-time recorded medical Read-code for rosacea[99] at any age between January 1995 and September 2009. We excluded patients with less than 3 years of recorded active history in the database before the date of their first-time rosacea diagnosis (subsequently referred to as index date) to increase the likelihood of only including incident cases. Patients with a diagnosis for rhinophyma only or ocular rosacea only were not included. We also excluded all patients with a recorded specific Read-code for alcohol addiction or alcohol abuse, cancer (except nonmelanoma skin cancer), or HIV / AIDS before the index date. The same exclusion criteria were applied to rosacea-free controls as to cases. In addition, control patients were not eligible if they had rhinophyma (without facial rosacea) or flushing symptoms recorded at any time.

We randomly identified 1 control for each case patient matched on age (year of birth), sex, general practice, calendar time (index date), and number of years of recorded history in the database prior to the index date.

Exposure

Exposure was defined as a diagnosis of migraine (using Read-codes consistent with *International Statistical Classification of Diseases, 10th Revision* codes for migraine) at any time before the index date. The validity of migraine diagnoses in the GPRD has been shown to be more than 72% with diagnosed migraineurs presenting 1 or more symptoms mentioned in the *International Classification of Headache Disorders of the International Headache Society*.[122] Exposure to triptans was assessed irrespective of an underlying migraine diagnosis. Triptans are indicated in the UK for migraine exclusively, except for the subcutaneous application of sumatriptan, which

is also indicated for cluster headache. Only 84 of 1,590 triptan users had a record for cluster headache, of which 69 also had a migraine diagnosis. Drug exposure was defined as a minimum of one prescription for a triptan prior to the index date. The same was done to assess exposure to ergot derivatives.

Case-control analysis

We conducted 2 separate analyses using 2 different models. In 1 analysis we compared the likelihood of having a recorded diagnosis of migraine, and in the other we compared exposure to triptans as well as to ergot derivatives before the index date between cases and controls. Results are presented according to sex and different age groups. We further stratified use of triptans or ergot derivatives according to exposure duration, categorizing patients by the number of drug prescriptions into groups of 0, 1 to 3, or greater than or equal to 4 prescriptions. Because triptans are prescribed as stand-by drugs, timing of drug exposure could not be assessed, as the date of prescription rarely represents the actual date of drug intake. Finally, we compared the prevalence of tension-type headache, cluster headache, and unspecified headache between cases and controls before the index date.

Statistical analysis

We conducted multivariate conditional logistic regression analyses using SAS statistical software (version 9.2, SAS Institute, Inc., Cary, NC, US). Relative risk estimates were calculated as odds ratios (ORs) with 95% confidence intervals (CIs). We implemented several measures to account for potential confounding, bias, and effect modification. Our study population was matched on age, sex, general practice, calendar time (index date), and number of years on the database before the index date. To assess potential interactions we stratified drug use according to timing and duration of drug exposure. In the multivariate model, we adjusted all ORs for smoking (non, current, ex, unknown), alcohol consumption (0, 1-4, 5-9, 10-14, 15-24, or 25+ U/wk, or unknown), and for body mass index (<18.5, 18.5-24.9, 25.0-29.9, 30+ kg/m^2, or unknown). We further tested for potential confounding by drugs used in acute migraine (i.e. acetylsalicylic acid [except platelet aggregation inhibition dosage], paracetamol, nonsteroidal antiinflammatory drugs) or for migraine prophylaxis in the UK (i.e. CCBs, valproate, BBs, monoamine reuptake inhibitors, oral contraception, or

hormone replacement therapy [HRT]),[123] as well as for diseases previously associated with migraine (i.e. ischemic stroke / transient ischemic attack, myocardial infarction, diabetes mellitus, hypertension, depression, other affective disorders, epilepsy, or asthma).[112, 122, 124-127] Because none of these variables changed the relative risk estimates for the association between migraine and rosacea by more than 10%, we did not include them in the final multivariate model. As an exception, we also adjusted all female strata above the age of 50 years for exposure to HRT before the index date.

3.2.4 Results

We identified a total of 53,927 rosacea cases and the same number of matched controls. Of those, 62.8% were female, and 54.4% were diagnosed between 30 and 59 years of age. Table 3.2-1 provides the distribution of characteristics, lifestyle factors (smoking, body mass index, and alcohol consumption), comorbidities, and comedications of the study population.

We observed a significantly decreased OR of 0.63 (95% CI 0.61-0.66) for rosacea in current smokers, whereas neither alcohol consumption nor body mass index were associated with rosacea. We recently published a detailed description of the study population including lifestyle factors.[46] ORs for rosacea were slightly decreased in those with prior myocardial infarction (OR 0.88, 95% CI 0.80-0.97) and diabetes mellitus (OR 0.81, 95% CI 0.76-0.87), while opposed and unopposed HRT yielded ORs of 1.64 (95% CI 1.55-1.73) and of 1.48 (95% CI 1.39-1.57), respectively (females only).

The distribution of diagnosed migraine in cases and controls is displayed in Table 3.2-2, presented according to sex and age groups. In total, 4,803 patients with rosacea (8.9%) and 4,137 control subjects (7.7%) were given a diagnosis of migraine, resulting in an adjusted OR of 1.18 (95% CI 1.13-1.24). Of all identified migraineurs, 81.6% of cases were female. We calculated risk estimates for men and women within various age groups and observed ORs around 1 for men across all ages, and a marginal trend towards increasing ORs in women with increasing age, with the highest OR in women between 50 and 59 years of age (OR of 1.36, 95% CI 1.21-1.53).

Exposure to triptans was recorded in 1,590 cases (3.0%) and in 1,246 controls (2.3%), revealing an adjusted OR of 1.30 (95% OR 1.20-1.40). Stratification according to exposure duration did not change the effect, with an OR of 1.28 (95% CI 1.17-1.41) for patients with 1 to 3 prescriptions and of 1.31 (95% CI 1.16-1.49) for patients with 4 or more prescriptions. Again, we found ORs around unity for male patients across all ages, whereas ORs increased with increasing age in women, with the highest adjusted OR of 1.66 (95% CI 1.30-2.10) for women aged 60 years or older (Table 3.3-3). Further adjustment for use of HRT resulted in an OR of 1.51 (95% CI 1.19-1.93). Overall, use of ergot derivatives was associated with a small risk increase of developing rosacea (adjusted OR 1.26, 95% CI 1.04-1.52). Stratification according to duration of drug use (0, 1-3, ≥4 prescriptions) did not change this observation (data not shown). In total, some 250 cases received ergot derivatives, which did not allow extensive stratification as with triptans.

Finally, we observed 1,329 cases and 1,015 controls with a diagnosis for tension-type headache before the index date (adjusted OR 1.33, 95% CI 1.22-1.44). Cluster headache was diagnosed in 284 cases and 256 controls before the index date (adjusted OR 1.12, 95% CI 0.94-1.32), and 9,893 cases and 8,441 controls had ever been given a diagnosis of unspecified headache at any time before the index date (adjusted OR 1.23, 95% CI 1.19-1.27).

Table 3.2-1: Distribution of demographics, life-style factors, co-morbidities, and co-medications in rosacea cases and controls in the UK

	Rosacea cases, No (%) (n=53,927)		Rosacea-free controls, No (%) (n=53,927)		OR crude (95%CI)		OR adjusted* (95% CI)	
Sex								
male	20,048	(37.2)	20,048	(37.2)				
female	33,879	(62.8)	33,879	(62.8)				
Age (years)								
<20	6,630	(12.3)	6,626	(12.3)				
20-29	5,202	(9.7)	5,213	(9.7)				
30-39	8,586	(15.9)	8,576	(15.9)				
40-49	11,338	(21.0)	11,343	(21.0)				
50-59	9,410	(17.5)	9,403	(17.4)				
60-69	6,955	(12.9)	6,960	(12.9)				
70+	5,806	(10.8)	5,806	(10.8)				
Alcohol consumption (units/week)								
non/ex	6,918	(12.8)	7,162	(13.3)	1.00	(ref.)	1.00	(ref.)
current (units NA)	9,512	(17.6)	9,628	(17.9)	1.03	(0.98-1.07)	1.02	(0.98-1.07)
1-4	9,641	(17.9)	9,168	(17.0)	1.12	(1.07-1.17)	1.10	(1.05-1.15)
5-9	5,205	(9.7)	4,756	(8.8)	1.16	(1.10-1.23)	1.16	(1.10-1.22)
10-14	4,477	(8.3)	3,906	(7.2)	1.22	(1.15-1.29)	1.23	(1.16-1.30)
15-19	1,041	(1.9)	883	(1.6)	1.26	(1.15-1.39)	1.29	(1.17-1.42)
20+	3,421	(6.3)	3,123	(5.8)	1.17	(1.10-1.25)	1.22	(1.14-1.30)
unknown	13,712	(25.4)	15,301	(28.4)	0.84	(0.80-0.88)	0.96	(0.91-1.02)
Smoking status								
Non	27,475	(51.0)	25,031	(46.4)	1.00	(ref.)	1.00	(ref.)
Current	7,635	(14.2)	10,660	(19.8)	0.64	(0.62-0.66)	0.63	(0.61-0.66)
Ex	9,981	(18.5)	8,277	(15.4)	1.13	(1.09-1.17)	1.11	(1.07-1.15)
Unknown	8,836	(16.4)	9,959	(18.5)	0.69	(0.66-0.72)	0.80	(0.76-0.85)
BMI (kg/m^2)								
12.0-18.5	905	(1.7)	953	(1.8)	0.88	(0.80-0.97)	0.94	(0.85-1.03)
18.5-24.9	18,839	(34.9)	17,808	(33.0)	1.00	(ref.)	1.00	(ref.)
25.0-29.9	13,146	(24.4)	12,291	(22.8)	1.01	(0.98-1.05)	1.00	(0.97-1.03)
30.0-60.0	6,942	(12.9)	7,184	(13.3)	0.92	(0.88-0.95)	0.91	(0.87-0.94)
Unknown	14,095	(26.1)	15,691	(29.1)	0.76	(0.73-0.79)	0.86	(0.83-0.91)
Co-morbidities								
Myocardial infarction	824	(1.5)	923	(1.7)	0.88	(0.80-0.97)		
Ischemic stroke / TIA	897	(1.7)	973	(1.8)	0.92	(0.83-1.01)		
Diabetes mellitus	1,686	(3.1)	2,042	(3.8)	0.81	(0.76-0.87)		
Hypertension	7,235	(13.4)	7,411	(13.7)	0.97	(0.93-1.00)		
Depression	8,883	(16.5)	7,907	(14.7)	1.16	(1.12-1.20)		
Other affective disorders	1,624	(3.0)	1,424	(2.6)	1.15	(1.07-1.24)		
Epilepsy	1,102	(2.0)	1,152	(2.1)	0.96	(0.88-1.04)		
Asthma	8,264	(15.3)	7,722	(14.3)	1.09	(1.05-1.13)		
Co-medication								
CCB	4,409	(8.2)	4,427	(8.2)	1.00	(0.95-1.04)		
BB	8,978	(16.7)	8,319	(15.4)	1.11	(1.07-1.15)		
Acetylsalicylic acid	1,457	(2.7)	1,334	(2.5)	1.10	(1.02-1.19)		
Paracetamol	25,791	(47.8)	24,588	(45.6)	1.11	(1.09-1.14)		
NSAID	30,168	(55.9)	28,044	(52.0)	1.20	(1.17-1.23)		
Valproic acid	412	(0.8)	403	(0.8)	1.02	(0.89-1.17)		
Monoamine reauptake inhibitors	9,165	(17.0)	7,887	(14.6)	1.22	(1.18-1.26)		
COC (females only)	11,440	(33.8)	10,793	(31.9)	1.18	(1.13-1.23)		
HRT opposed (females only)	4,357	(12.9)	3,094	(9.1)	1.64	(1.55-1.73)		
HRT unopposed (females only)	3,193	(9.4)	2,341	(6.9)	1.48	(1.39-1.57)		

Abbreviations: BB, β-blocker; BMI, body mass indes; CCB, calicum channel blocker; CI, confidence interval; COC, comined oral contraception; HRT, hormone replacement therapy; NA, no answer; NSAID, nonsteroidal antiinflammaotry drugs; OR, odds ratio; TIA, transient ischemic attack

* adjusted for smoking, BMI, alcohol consumption

Table 3.2-2: Distribution of diagnosed migraine stratified by age and gender in rosacea cases and controls in the UK

	Rosacea cases, No (%) (n=53,927)		Rosacea-free controls, No (%) (n=53,927)		OR crude (95%CI)		OR adjusted* (95% CI)	
No Migraine	49,124	(91.1)	49,790	(92.3)	1.00	(ref.)	1.00	(ref.)
Migraine	4,803	(8.9)	4,137	(7.7)	1.18	(1.13-1.24)	1.18	(1.13-1.24)
By age (y)								
<40	1,868	(3.5)	1,665	(3.1)	1.14	(1.06-1.22)	1.14	(1.06-1.22)
40-49	1,214	(2.3)	1,046	(1.9)	1.19	(1.09-1.30)	1.20	(1.09-1.31)
50-59	951	(1.8)	757	(1.4)	1.29	(1.17-1.43)	1.29	(1.16-1.43)
≥60	770	(1.4)	669	(1.2)	1.17	(1.05-1.30)	1.15	(1.03-1.29)
Men by age (y)	886	(0.2)	861	(0.2)	1.03	(0.94-1.14)	1.04	(0.94-1.14)
<40	378	(0.1)	380	(0.1)	0.99	(0.86-1.15)	0.99	(0.85-1.14)
40-49	156	(0.0)	142	(0.0)	1.09	(0.86-1.38)	1.14	(0.89-1.45)
50-59	166	(0.0)	158	(0.0)	1.05	(0.84-1.32)	1.06	(0.84-1.33)
≥60	186	(0.0)	181	(0.0)	1.03	(0.84-1.27)	1.03	(0.83-1.27)
Women by age (y)	3,917	(0.7)	3,276	(0.6)	1.23	(1.17-1.29)	1.22	(1.16-1.29)
<40	1,490	(0.3)	1,285	(0.2)	1.18	(1.09-1.28)	1.19	(1.10-1.29)
40-49	1,058	(0.2)	904	(0.2)	1.20	(1.09-1.33)	1.21	(1.09-1.33)
50-59	785	(0.1)	599	(0.1)	1.36	(1.22-1.53)	1.36	(1.21-1.53)
≥60	584	(0.1)	488	(0.1)	1.22	(1.07-1.38)	1.20	(1.05-1.36)

Abbreviations: CI, confidence interval; OR= odds ratio.

* adjusted for smoking, body mass index, alcohol consumption.

Table 3.2-3: Distribution of triptan exposure stratified by age, gender, and exposure duration (number of prescriptions) in rosacea cases and controls in the UK

	Rosacea cases, No (%) (n=53,927)		Rosacea-free controls, No (%) (n=53,927)		OR crude (95% CI)		OR adjusted* (95% CI)	
No triptan Rxs	52,337	(97.1)	52,681	(97.7)	1.00	(ref.)	1.00	(ref.)
Triptan Rxs	1,590	(3.0)	1,246	(2.3)	1.29	(1.20-1.40)	1.30	(1.20-1.40)
By number of triptan Rxs								
1-3	980	(1.8)	776	(1.4)	1.28	(1.16-1.41)	1.28	(1.17-1.41)
4+	610	(1.1)	470	(0.9)	1.32	(1.17-1.49)	1.31	(1.16-1.49)
By age (y) and by number of triptan Rxs								
<40	471	(0.9)	392	(0.7)	1.22	(1.06-1.40)	1.25	(1.09-1.43)
1-3	356	(0.7)	311	(0.6)	1.17	(1.00-1.36)	1.20	(1.02-1.40)
4+	115	(0.2)	81	(0.2)	1.44	(1.08-1.91)	1.44	(1.08-1.92)
40-49	491	(0.9)	404	(0.7)	1.24	(1.08-1.42)	1.24	(1.08-1.42)
1-3	295	(0.5)	228	(0.4)	1.31	(1.10-1.56)	1.31	(1.09-1.56)
4+	196	(0.4)	176	(0.3)	1.14	(0.93-1.40)	1.14	(0.93-1.41)
50-59	392	(0.7)	291	(0.5)	1.37	(1.17-1.61)	1.36	(1.16-1.59)
1-3	206	(0.4)	156	(0.3)	1.33	(1.08-1.65)	1.31	(1.06-1.63)
4+	186	(0.3)	135	(0.3)	1.42	(1.13-1.78)	1.41	(1.12-1.77)
≥60	236	(0.4)	159	(0.3)	1.49	(1.22-1.83)	1.51	(1.23-1.86)
1-3	123	(0.2)	81	(0.2)	1.53	(1.15-2.02)	1.53	(1.15-2.04)
4+	113	(0.2)	78	(0.1)	1.46	(1.09-1.95)	1.48	(1.10-1.99)
Men by age (y) and by number of triptan Rxs	202	(0.4)	191	(0.4)	1.06	(0.87-1.29)	1.08	(0.88-1.32)
<40	65	(0.1)	44	(0.1)	1.48	(1.01-2.17)	1.50	(1.02-2.21)
1-3	50	(0.1)	37	(0.1)	1.35	(0.88-2.07)	1.38	(0.90-2.13)
4+	15	(0.0)	7	(0.0)	2.14	(0.87-5.25)	2.13	(0.86-5.27)
40-49	48	(0.1)	53	(0.1)	0.90	(0.61-1.34)	0.88	(0.59-1.33)
1-3	34	(0.1)	38	(0.1)	0.89	(0.56-1.43)	0.87	(0.54-1.41)
4+	14	(0.0)	15	(0.0)	0.93	(0.45-1.93)	0.91	(0.43-1.92)
50-59	47	(0.1)	52	(0.1)	0.90	(0.60-1.35)	0.94	(0.62-1.42)
1-3	27	(0.1)	35	(0.1)	0.77	(0.47-1.27)	0.80	(0.48-1.34)
4+	20	(0.0)	17	(0.0)	1.20	(0.61-2.38)	1.26	(0.63-2.52)
≥60	42	(0.1)	42	(0.1)	1.00	(0.65-1.53)	1.07	(0.69-1.65)
1-3	27	(0.1)	22	(0.0)	1.23	(0.70-2.15)	1.28	(0.72-2.27)
4+	15	(0.0)	20	(0.0)	0.75	(0.39-1.47)	0.83	(0.42-1.64)
Women by age (y) and by number of triptan Rxs	1,388	(2.6)	1,055	(2.0)	1.34	(1.23-1.45)	1.33	(1.23-1.45)
<40	406	(0.8)	348	(0.6)	1.19	(1.02-1.38)	1.21	(1.05-1.41)
1-3	306	(0.6)	274	(0.5)	1.14	(0.96-1.35)	1.17	(0.99-1.39)
4+	100	(0.2)	74	(0.1)	1.37	(1.01-1.84)	1.37	(1.01-1.86)
40-49	443	(0.8)	351	(0.7)	1.29	(1.12-1.49)	1.28	(1.11-1.49)
1-3	261	(0.5)	190	(0.4)	1.39	(1.15-1.68)	1.39	(1.15-1.68)
4+	182	(0.3)	161	(0.3)	1.16	(0.94-1.45)	1.16	(0.93-1.44)
50-59	345	(0.6)	239	(0.4)	1.48	(1.25-1.76)	1.44	(1.21-1.72)
1-3	179	(0.3)	121	(0.2)	1.51	(1.19-1.91)	1.46	(1.15-1.86)
4+	166	(0.3)	118	(0.2)	1.46	(1.15-1.85)	1.42	(1.11-1.82)
≥60	194	(0.4)	117	(0.2)	1.68	(1.33-2.12)	1.66	(1.30-2.10)
1-3	96	(0.2)	59	(0.1)	1.65	(1.19-2.28)	1.62	(1.16-2.25)
4+	98	(0.2)	58	(0.1)	1.71	(1.23-2.39)	1.70	(1.21-2.37)

Abbreviations: CI, confidence interval; OR, odds ratio; Rx, prescription.

* adjusted for smoking, BMI, alcohol consumption

3.2.5 Discussion

In this large case-control analysis we observed slightly increased ORs for incident rosacea among patients with diagnosed migraine, and in patients with previous exposure to triptans or ergot derivatives. We found ORs around unity across all age groups for men, whereas women, particularly those with exposure to triptans, were at a slightly increased relative risk of developing rosacea at older ages. Duration of triptan or ergot derivative exposure did not change the risk estimates.

Tan and Cunliffe[62] first described a strong overall association between migraine and rosacea in 1976 (44% in cases vs. 13% in controls) in a study including 137 cases. In 1994, Ramelet[61] reported an association of rosacea and migraine in women only in 48 patients with papulopustular rosacea (44% in women vs. 10% in men). Although we also observed slightly increased ORs among female migraineurs, the effect size was too small to suggest a clinically relevant association. Furthermore, we could not distinguish between papulopustular and erythematotelangiectatic rosacea on the GPRD. Female migraine patients aged 50 years or older, mainly those with exposure to triptans, yielded a somewhat increased rosacea risk. This finding is consistent with results of a cross-sectional study (809 office employees) by Berg and Liden, which described a significantly increased co-occurrence of rosacea and migraine in postemenopausal female rosacea patients only.[41, 63] The fact that the risk increase was stronger in female triptan users aged 50 years or older than in migraineurs of the same age overall, could either reflect an actual drug effect, or the severity of the underlying migraine (>80% of triptan users were previously diagnosed with migraine). Considering that patients with migraine using prescription medication tend to have more severe migraines, and that a previous GPRD study suggested triptan use as proxy for migraine recency and severity, such channelling bias seems likely.[128-130] In addition, a dose-response effect of triptans, a potential indicator for a drug effect, was not observed. Nevertheless, we cannot explain why ORs were increased in female triptan users aged 60 years or older, whereas female migraineurs overall yielded a slight trend in 50- to 59-year-old women only. The migraine subtype with aura has been associated with certain comorbidities (i.e. cardiovascular / psychiatric) and with all-cause mortality. Furthermore, migraine with aura has been shown to be overrepresented among patients with diagnosed migraine and to be more prevalent in women (10%) than in men (5%).[113, 125, 127, 131-133] Thus, although we could not

differenciate between the 2 migraine subtypes (>90% of migraine records fell on 1 unspecific Read-code), the aura subtype might contribute to the increased ORs in women. However, it does not explain why the effect was only observed at age50 years or older; while hormonal and vascular changes or some other factors might play a role,[134] we are also aware that such a small risk increase could be explained by chance, uncontrolled bias, confounding, or multiple comparisons in the analyses.

Use of ergot derivatives overall was associated with a slight risk increase, but causality remains uncertain considering potential residual confounding. In addition, it seems that ergot derivatives are not often used in the UK anymore, as about 80% of prescriptions dated back more than 2 years.

Although this observational study is based in a large and high quality primary-care database, several limitations have to be considered. First, we may be missing some migraine and rosacea patients due to underdiagnosis. Based on a study from the US, approximately half of all migraine patients remain without a diagnosis.[129, 131, 135] However, although we most likely included the more severe cases and still no effect was found, material bias is unlikely.[111, 113, 126, 129] While we may have missed some rosacea cases, a 74% concordance of rosacea diagnoses between dermatologists and the referring GPs has been shown in a study from South-East Scotland,[111] providing reassurance that the validity of rosacea diagnoses for included cases in the GPRD is sufficient. Second, we previously showed an overlap of rosacea and acne diagnoses around the index date among patients younger than 20 years, which might indicate diagnostic uncertainty.[46] Migraine has been reported to be underdiagnosed in children and adolescents.[136] This potential diagnostic bias has to be considered when interpreting our results. Third, the likelihood of being diagnosed with rosacea may increase with increasing medical attention. Previous GPRD studies showed that migraine patients saw the GP significantly more often than patients without migraine,[122] and that rosacea cases have a higher number of GP visits before the index date than control subjects.[46] However, as we only observed a weak association of rosacea and migraine, diagnostic bias seems unlikely to play a substantial role. Finally, we could not control for ethnic background, socioeconomic status (e.g. income, education), skin pigmentation, or lifestyle factors such as sun exposure, profession, or nutrition, as these parameters are not routinely recorded in the GPRD. We also were not in a position to account for severity of rosacea, or to distinguish between erythematotelangiectatic and papulopustular rosacea. The latter may cause

an overdiagnosis of rosacea, as chronic actinic damage such as heliodermatitis is not always distinguishable from the erythematotelangiectatic subtype in the absence of inflammatory lesions.[47, 85] Despite these limitations, this is – to our knowledge – by far the largest study on the association of rosacea and migraine, and the first study to assess a potential impact of triptans and ergot derivatives on the risk of developing rosacea.

In summary, this large case–control study provides evidence that the overall risk of developing rosacea is not materially increased in patients with migraine, an association which has been controversially discussed over decades. However, while ORs for men remained around 1.0 across all age groups, female migraineurs older than 50 years, particularly those with more severe migraine, had a slightly, but statistically significantly increased risk for incident rosacea. Exposure to triptans seems to represent a proxy for disease severity.

3.3 Spironolactone may reduce the risk of incident rosacea (Study 3.3)

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3.3.1 Abridged report

Rosacea is a chronic facial skin disease, with neurovascular dysregulation and neurogenic inflammation as presumed pathogenic key factors.[1] Spironolactone is recommended as an off-label treatment for rosacea, despite scarce evidence of efficacy [47, 137] (http://www.cks.nhs.uk/rosacea/management/scenario_rosacea#335449004, accessed 04 March 2013) Using the UK-based General Practice Research Database (GPRD[99]), we conducted a large population-based case-control analysis, including patients with a first-time diagnosis of rosacea (index date) between January 1995 and September 2009. We excluded patients with recorded alcoholism, cancer, or HIV, and patients with <3 years of recorded active history before the index date. Patients with diagnosed rhinophyma or ocular rosacea only were excluded. We randomly matched one control to each case on age, sex, general practice, calendar time, and number of previous years of recorded history in the database, and applied the same exclusion criteria to controls as to cases. The study protocol was approved by the Independent Scientific Advisory Committee (ISAC) for MHRA database research. We assessed use of diuretics (including combined products) before the index date, classified according to the WHO ATC index (http://www.whocc.no/atc_ddd_index/?code=C03, accessed 27 December 2012) into low-ceiling diuretics, high-ceiling diuretics, and potassium sparing agents (spironolactone vs. amiloride/triamterene). We stratified drug use by timing (last prescription ≤ or >180 days before the index date) and duration of use (number of prescriptions before the index date). To account for confounding by indication, we performed two sensitivity analyses; in the first model, we classified spironolactone users into those with or without a previous diagnosis of acne, seborrhea, hirsutism, or androgenic alopecia (dermatologic off-label indications for spironolactone), overall and stratified by exposure duration (further stratified by gender).[137] In the second model, we classified current spironolactone users into patients with or without concomitantly (≤180 days) prescribed cardiovascular drugs, such as ACE inhibitors, angiotensin receptor blockers, BBs, CCBs, thiazide- or loop diuretics, and nitrates (i.e. likely cardiovascular indication vs. likely dermatologic indication). We conducted multivariate conditional logistic regression analyses using SAS statistical software (version 9.3, SAS Institute, Inc., Cary, NC, US), and calculated odds ratios (ORs) with 95% confidence intervals (CIs). We adjusted all ORs for smoking (non, current,

ex, unknown), alcohol consumption (0, 1-4, 5-9, 10-14, 15-24, or 25+ units per week, or unknown), and body mass index (<18.5, 18.5-24.9, 25.0-29.9, 30+ kg m^{-2}, or unknown). Each diuretic drug class was adjusted for other diuretics and for drug classes contained in combined products, if applicable. Because other potential confounders, i.e. cardiovascular drugs (ACE inhibitors, angiotensin receptor blockers, CCBs, BBs and statins), anti-androgenic drugs, HRT, or cardiovascular comorbidities (hypertension, myocardial infarction, heart failure, ischemic stroke / transient ischemic attack, ischemic heart disease, diabetes mellitus, and hyperlipidemia) did not alter the relative risk estimates for the association between use of diuretics or spironolactone and rosacea by ≥10%, we did not include them in the final model.

The study population's demographics and methodology including limitations have been described in detail elsewhere.[46] Among 53,927 rosacea cases and the same number of controls, 8372 (15.5%) cases and 7926 (14.7%) controls had ≥1 recorded prescription for a diuretic drug before the index date (Table 3.3-1). While high-ceiling diuretics, low-ceiling diuretics, and amiloride/triamterene yielded ORs around 1.0 across all strata, spironolactone use (281 cases, 327 controls) revealed an overall adjusted OR of 0.83 (95% CI 0.70-0.98), which dropped to an OR of 0.47 (95% CI 0.35-0.63) in current users at the index date. At an α-level of 0.05 and a current spironolactone exposure prevalence of 0.5% among cases, the statistical power to detect an OR of 0.5 is 99%. We observed an OR of 0.39 (95 % CI 0.27-0.54) in current spironolactone users without a previous diagnosis for an androgenic skin disease (Table 3.3-2). This finding was consistent in men and women (Table 3.3-3, supplementary). We further observed an OR of 0.39 (95% CI 0.24-0.64) in current long-term spironolactone users with concomitant cardiovascular medication, whereas patients without such medication revealed an overall OR of 0.68 (95% CI 0.35-1.32).

While the decreased relative risks suggest that rosacea develops at a substantially decreased rate during spironolactone exposure, the mechanism remains unclear. As no other class of diuretics affected the risk estimate, a diuretic drug effect is an unlikely cause for the observed effect. Spironolactone is an aldosterone receptor antagonist with anti-androgenic properties (inhibition of androgen production and antagonism at the androgen receptor). Oral spironolactone has been proposed as

rosacea treatment, based on beneficial results of a small uncontrolled clinical trial in Japanese men. The authors hypothesized an inhibition of skin specific cytochromes underlying the observed effect.[66] Androgenic sebaceous stimulation has been discussed controversially with regard to rosacea.[47, 138, 139] Besides sebaceous activities, the androgen receptor has been linked to delayed wound repair, enhanced epidermal hyperplasia and collagen formation, pro-inflammatory properties, and an inhibitory effect on immune functions.[140, 141] Furthermore, activation of the aldosterone receptor (expressed in human skin) promotes inflammation, which is blocked by spironolactone.[142, 143] Evidence also emerged for a nonreceptor-mediated vasodilatory androgen effect.[144] Sensitivity analyses revealed decreasing ORs with increasing confidence of diagnostic accuracy and of unbiased indication (i.e. in patients with a likely cardiovascular context and in patients without certain dermatologic co-diagnoses). However, although we accounted for such bias, some residual confounding by indication or chance cannot be ruled out. To our knowledge, this is the largest study on the association between spironolactone and rosacea. We are not aware of previous studies reporting a spironolactone effect on rosacea in women or a potential association between other diuretics and rosacea. As a certain efficacy in treating dermatologic diseases with topically applied spironolactone has been shown, local spironolactone application might be a promising approach for the treatment of rosacea.[137, 145, 146]

Table 3.3-1: Distribution of diuretic exposure stratified by timing and duration of drug use in rosacea cases and controls in the UK

	Rosacea cases, No (%) (n=53,927)		Rosacea-free controls No (%) (n=53,927)		OR crude	(95% CI)	OR adj.*	(95% CI)
No high-ceiling diuretics	50,817	(94.2)	50,990	(94.6)	(1.0)	(ref.)	(1.0)	(ref.)
Use of high-ceiling diuretics	3,110	(5.8)	2,937	(5.5)	1.07	(1.01-1.13)	1.06	(0.99−1.13)
Duration (Nr of prescriptions)								
1-19	2,184	(4.1)	1,971	(3.7)	1.12	(1.05−1.19)	1.09	(1.02−1.17)
20-39	391	(0.7)	432	(0.8)	0.91	(0.79−1.05)	0.89	(0.77−1.03)
40+	535	(1.0)	534	(1.0)	1.02	(0.90−1.15)	0.98	(0.85−1.11)
Timing (180d)								
Current	1,331	(2.5)	1,444	(2.7)	0.93	(0.86−1.01)	0.88	(0.81−0.96)
Past	1,779	(3.3)	1,493	(2.8)	1.20	(1.12−1.29)	1.18	(1.09−1.27)
No low-ceiling diuretics	47,428	(88.0)	47,811	(88.7)	(1.0)	(ref.)	(1.0)	(ref.)
Use of low-ceiling diuretics	6,499	(12.1)	6,116	(11.3)	1.09	(1.04−1.13)	1.07	(1.02−1.12)
Duration (Nr of prescriptions)								
1-19	3,877	(7.2)	3,417	(6.3)	1.15	(1.10−1.21)	1.13	(1.07−1.19)
20-39	1,241	(2.3)	1233	(2.3)	1.03	(0.95−1.11)	1.00	(0.92−1.09)
40+	1,381	(2.6)	1466	(2.7)	0.96	(0.88−1.04)	0.93	(0.85−1.01)
Timing (180d)								
current	3,225	(6.0)	3,255	(6.0)	1.01	(0.96-1.07)	0.99	(0.94-1.05)
past	3,274	(6.1)	2,861	(5.3)	1.17	(1.11-1.23)	1.15	(1.09-1.22)
No Amiloride/Triamterene	52,128	(96.7)	52,278	(96.9)	(1.0)	(ref.)	(1.0)	(ref.)
Use of Amiloride/Triamterene	1,799	(3.3)	1,649	(3.1)	1.11	(1.03-1.19)	1.07	(0.99-1.16)
Duration (Nr of prescriptions)								
1-19	1,162	(2.2)	1,038	(1.9)	1.13	(1.04-1.23)	1.09	(0.99-1.20)
20-39	259	(0.5)	269	(0.5)	0.98	(0.82-1.17)	0.95	(0.79-1.14)
40+	378	(0.7)	342	(0.6)	1.12	(0.96-1.30)	1.08	(0.93-1.27)
Timing (180d)								
current	552	(1.0)	529	(1.0)	1.06	(0.94-1.20)	1.01	(0.88-1.15)
past	1,247	(2.3)	1,120	(2.1)	1.13	(1.04-1.23)	1.10	(1.00-1.20)
No Spironolactone	53,646	(99.5)	53,600	(99.4)	(1.0)	(ref.)	(1.0)	(ref.)
Use of Spironolactone	281	(0.5)	327	(0.6)	0.86	(0.73-1.01)	0.83	(0.70-0.98)
Duration (Nr of prescriptions)								
1-19	232	(0.4)	244	(0.5)	0.95	(0.79-1.13)	0.93	(0.77-1.12)
20-39	30	(0.1)	51	(0.1)	0.59	(0.37-0.92)	0.54	(0.34-0.85)
40+	19	(0.0)	32	(0.1)	0.59	(0.34-1.04)	0.57	(0.32-1.01)
Timing (180d)								
current	67	(0.1)	134	(0.3)	0.49	(0.37-0.66)	0.47	(0.35-0.63)
past	214	(0.4)	193	(0.4)	1.11	(0.91-1.36)	1.09	(0.89-1.33)

Abbreviations: adj., adjusted; CI, confidence interval; OR, odds ratio.

Percentages are rounded to the nearest tenth digit.

* adjusted for smoking, BMI, alcohol consumption, complementary diuretic drug classes, drug classes contained in combined products.

Table 3.3-2: Use of Spironolactone in rosacea cases and controls, after controlling for confounding by indication

	Rosacea cases, No (%) (n=53,927)		Rosacea-free controls No (%) (n=53,927)		OR crude	(95% CI)	OR adj.*	(95% CI)
No Spironolactone	53,646	(99.5)	53,600	(99.4)	1.00	(ref.)	1.00	(ref.)
Spironolactone with A/S/H/A	91	(0.2)	32	(0.1)	2.82	(1.89-4.22)	2.91	(1.94-4.37)
Spironolactone without A/S/H/A	190	(0.4)	295	(0.6)	0.64	(0.53-0.77)	0.65	(0.54-0.78)
Duration (Nr of prescriptions)								
1-19	153	(0.3)	217	(0.4)	0.70	(0.57-0.86)	0.72	(0.59-0.90)
20+	37	(0.1)	78	(0.1)	0.47	(0.32-0.70)	0.46	(0.31-0.68)
Timing (180d)								
current	47	(0.1)	123	(0.2)	0.38	(0.27-0.53)	0.39	(0.27-0.54)
past	143	(0.3)	172	(0.3)	0.83	(0.66-1.04)	0.85	(0.67-1.07)
Current spironolactone with cardiovascular co-medication	52	(0.1)	112	(0.2)	0.46	(0.33-0.64)	0.46	(0.33-0.65)
Duration (Nr of prescriptions)								
1-19	30	(0.1)	57	(0.1)	0.51	(0.33-0.80)	0.54	(0.34-0.85)
20+	22	(0.0)	55	(0.1)	0.40	(0.24-0.65)	0.39	(0.24-0.64)
Current spironolactone without cardiovascular co-medication	15	(0.0)	22	(0.0)	0.68	(0.35-1.31)	0.68	(0.35-1.32)

Abbreviations: adj., adjusted; A/S/H/A, acne/seborrhea/hirsutism/alopecia; CI, confidence interval.

Percentages are rounded to the nearest tenth digit.

* adjusted for smoking, BMI, alcohol consumption, complementary diuretic drug classes, drug classes contained in combined products

Table 3.3-3: Use of Spironolactone in rosacea cases and controls, after controlling for confounding by indication

Women	Rosacea cases, No (%) (n=53,927)		Rosacea-free controls, No (%) (n=53,927)		OR crude	(95% CI)	OR adj.*	(95% CI)
No Spironolactone	53,646	(99.5)	53,600	(99.4)	1.00	(ref.)	1.00	(ref.)
Spironolactone with A/S/H/A	79	(0.2)	27	(0.1)	2.91	(1.881-4.51)	2.97	(1.92-4.61)
Spironolactone without A/S/H/A	142	(0.4)	202	(0.6)	0.70	(0.56-0.87)	0.70	(0.56-0.87)
Duration								
1-19	113	(0.3)	146	(0.4)	0.77	(0.60-0.98)	0.79	(0.62-1.02)
20+	29	(0.1)	56	(0.2)	0.52	(0.33-0.81)	0.51	(0.33-0.80)
Timing (180d)								
current	31	(0.1)	83	(0.2)	0.37	(0.24-0.56)	0.38	(0.25-0.57)
past	111	(0.3)	119	(0.4)	0.93	(0.72-1.22)	0.95	(0.73-1.25)
Men								
Spironolactone with A/S/H/A	12	(0.1)	5	(0.0)	2.32	(0.82-6.60)	2.35	(0.81-6.78)
Spironolactone without A/S/H/A	48	(0.2)	93	(0.5)	0.51	(0.36-0.73)	0.53	(0.37-0.75)
Duration								
1-19	40	(0.2)	71	(0.4)	0.56	(0.38-0.83)	0.59	(0.40-0.87)
20+	8	(0.0)	22	(0.1)	0.36	(0.16-0.80)	0.36	(0.15-0.76)
Timing (180d)								
current	16	(0.1)	40	(0.2)	0.41	(0.23-0.72)	0.41	(0.23-0.74)
past	32	(0.2)	53	(0.3)	0.60	(0.38-0.93)	0.61	(0.39-0.96)

Abbreviations: adj., adjusted; A/S/H/A, Acne/Seborrhea/Hirsutism/Alopecia; CI, confidence interval; OR, odds ratio

* adjusted for smoking, BMI, alcohol consumption, complementary diuretic drug classes, drug classes contained in combined products

3.4 Risk of rosacea in patients with diabetes using insulin or oral antidiabetic drugs (Study 3.4)

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3.4.1 Abridged report

Rosacea is a chronic facial skin disease with a presumed key vasodilatory component,[1] whereas diabetes mellitus (DM) is associated with impaired vasodilation congruent with the degree of endothelial dysfunction. Insulin is a physiologic regulator of the vascular tone, but in the insulin-resistant state insulin increases vasoconstriction.[21, 71, 117, 147-149] Using the UK-based General Practice Research Database,[99] we conducted a large population-based case-control analysis, including patients with a first-time rosacea diagnosis (index date) between January 1995 and September 2009. We excluded patients with recorded alcoholism (explicit medical Read-code), cancer, or HIV, and patients with <3 years of recorded active history before the index date. Patients with diagnosed rhinophyma or ocular rosacea in the absence of another record of facial rosacea were excluded. We randomly matched one control to each case on age, sex, general practice, calendar time, and number of previous years of history in the database, and applied the same exclusion criteria to controls as to cases. The study protocol was approved by the Independent Scientific Advisory Committee (ISAC) for MHRA database research. Disease exposure was defined as a DM diagnosis (validity proven elsewhere[99, 150]) before the index date. Among DM patients, we captured the last $HbA1_c$ value before the index date, stratified into 4 categories (none, ≤7.5%, 7.6-10.9%, or ≥11%). DM duration was stratified into 6 categories by the number of years between the first recorded prescription of any antidiabetic drug and the index date (no treatment, <1, 1-3, 3-5, 5-10, 10+ years), sub-stratified by $HbA1_c$ levels (≤7.5% or >7.5%). We analyzed antidiabetic drug use (insulin vs. other antidiabetic drugs) stratified by timing (≤ or > 180 days before the index date) and duration of use (number of prescriptions before the index date). Within a mutually exclusive drug use model among diagnosed diabetics we assessed insulin exposure (irrespective of any OAD use) and OAD exposure alone (no insulin exposure at any time), stratified by timing and duration of drug use and by $HbA1_c$ levels. We conducted multivariate conditional logistic regression analyses using SAS statistical software (version 9.3, SAS Institute, Inc., Cary, NC, US), and calculated ORs with 95% CIs. We adjusted all ORs for smoking (non, current, ex, unknown), alcohol consumption (0, 1-4, 5-9, 10-14, 15-24, or 25+ units per week, unknown), and body mass index (<18.5, 18.5-24.9, 25.0-29.9, or 30+ kg m^{-2}, unknown). Because other potential confounders, i.e.

depression, cardiovascular diseases (hypertension, myocardial infarction, hyperlipidemia, heart failure, ischemic heart disease, ischemic stroke / transient ischemic attack), cardiovascular drugs (CCBS, BBs, ACE inhibitors, angiotensin receptor blockers, statins, acetylsalicylic acid (anticlotting dosage), vitamin K antagonists, and diuretics), systemic steroids, and NSAIDs did not alter the relative risk estimates for the association between DM or insulin and rosacea by ≥10%, we did not include them in the final model.

The study population's demographics and methodology including limitations have been described in detail elsewhere.[46] Of 53,927 rosacea cases and the same number of controls, 1,686 (3.1%) cases and 2,042 (3.8%) controls had a recorded DM diagnosis revealing an OR of 0.80 (95% CI 0.74-0.85), which further decreased with increasing $HbA1_c$ values (OR 0.57, 95% CI 0.41-0.79, $HbA1_c$ ≥11%) and with increasing disease duration (OR 0.64, 95% CI 0.54-0.78, disease duration ≥10 years, Table 3.4-1). At earlier disease stages, we observed decreased ORs in poorly controlled diabetics ($HbA1_c$ >7.5%), whereas a disease history of ≥5 years revealed decreased ORs irrespective of blood glucose control (Table 3.4-4, supplementary). Exposure to any antidiabetic drug was associated with a decreased OR of 0.76 (95% CI 0.71-0.83). The prevalence of insulin exposure was higher in controls (1.1%) than in cases (0.7%), yielding an OR of 0.75 (95% OR 0.65-0.85), unchanged across strata of timing and duration of insulin exposure. OAD exposure was also slightly more prevalent in controls (2.6%) than in cases (2.1%, OR 0.83, 95% CI 0.76-0.91), again independent of timing and duration of drug exposure (Table 3.4-3, supplementary). The mutually exclusive drug use model (Table 3.4-2) yielded significantly decreased ORs for insulin users, irrespective of $HbA1_c$ control. OAD use in the absence of insulin was associated with decreased ORs at $HbA1_c$ levels >7.5%, but non-significant results at $HbA1_c$ levels ≤7.5%.

Our findings suggest a decreased rosacea risk in DM patients at an advanced disease state, i.e. in patients with high $HbA1_c$ levels and / or long disease duration. The underlying mechanism remains to be clarified; we hypothesize a reciprocal link of the two diseases via the degree of endothelial dysfunction and thus impaired vasodilation. Extrinsic insulin exposure revealed significantly decreased ORs, irrespective of $HbA1_c$ control, whereas OAD use yielded decreased ORs in poorly controlled diabetics only. This might reflect an additional insulin effect on the rosacea

risk, but it could also depict a proxy for disease duration and / or severity. As insulin is used in diabetic patients only, we cannot disentangle the role of insulin from the underlying disease within this observational study. Most diabetic patients were coded with a DM-subtype-unspecific code (66.6% cases, 68.3% controls), but as ORs were decreased in insulin users and in poorly controlled OAD users, a subtype independent effect seems likely, especially since endothelial damage and diabetic microvascular complications are presumably driven by shared mechanisms caused by hyperglycemia in both DM subtypes.[118, 149, 151, 152] Our study provides evidence for a significantly reduced rosacea risk in diabetics at an advanced disease stage. This is, to our knowledge, a previously unreported finding, but some residual confounding or chance cannot entirely be ruled out. Whether insulin enhances this effect *per se* or whether it reflects a proxy for disease severity remains unclear.

Table 3.4-1: Distribution of diagnosed DM stratified by $HbA1_c$ values and disease duration

	Rosacea cases, No (%) (n=53,927)		Rosacea-free controls, No (%) (n=53,927)		OR crude	(95%CI)	OR adj.*	(95% CI)
No diagnosed DM	52,241	(96.9)	51,885	(96.2)	1.00	(ref.)	1.00	(ref.)
Diagnosed DM	1,686	(3.1)	2,042	(3.8)	0.81	(0.76-0.87)	0.80	(0.74-0.85)
Diagnosed DM by HbA1c (%)								
0-7.5	880	(1.6)	971	(1.8)	0.89	(0.81-0.98)	0.87	(0.79-0.96)
7.6-10.9	519	(1.0)	684	(1.3)	0.75	(0.67-0.84)	0.73	(0.65-0.82)
≥11	58	(0.1)	101	(0.2)	0.57	(0.41-0.78)	0.57	(0.41-0.79)
NA	229	(0.4)	286	(0.5)	0.79	(0.66-0.94)	0.78	(0.65-0.94)
Diagnosed DM by treatment duration (year)								
Untreated	444	(0.8)	439	(0.8)	1.00	(0.87-1.14)	0.96	(0.84-1.10)
<1	135	(0.3)	170	(0.3)	0.79	(0.63-0.99)	0.78	(0.62-0.98)
1-3	288	(0.5)	325	(0.6)	0.87	(0.74-1.02)	0.85	(0.72-1.00)
3-5	252	(0.5)	312	(0.6)	0.79	(0.67-0.94)	0.80	(0.68-0.95)
5-10	368	(0.7)	503	(0.9)	0.72	(0.63-0.82)	0.71	(0.62-0.81)
≥10	199	(0.4)	293	(0.5)	0.67	(0.55-0.80)	0.64	(0.54-0.78)

Abbreviations: CI, confidence interval; DM, diabetes mellitus; $HbA1_c$, Hemoglobin $A1_c$; NA, no answer; OR, odds ratio.

Percentages are rounded to nearest decimal.

*adjusted for smoking, body mass index, alcohol consumption.

Table 3.4-2: Mutually exclusive antidiabetic drugs use stratified by timing and duration of drug exposure and by $HbA1_c$ values

	Rosacea cases, No (%) (n=53,927)		**Rosacea-free controls, No (%) (n=53,927)**		**OR crude**	**(95%CI)**	**OR adj.***	**(95% CI)**
No DM	52,241	(96.9)	51,885	(96.2)	1.00	(ref.)	1.00	(ref.)
Diagnosed DM untreated	444	(0.8)	439	(0.8)	1.00	(0.88-1.14)	0.96	(0.84-1.10)
Diagnosed DM - $HbA1_c$≤7.5								
Current Insulin 1-39 (+/- OAD)	52	(0.1)	73	(0.1)	0.70	(0.49-1.00)	0.67	(0.47-0.96)
Current Insulin 40+(+/- OAD)	37	(0.1)	54	(0.1)	0.68	(0.44-1.03)	0.69	(0.45-1.05)
Past insulin use (+/- OAD)	9	(0.0)	16	(0.0)	0.56	(0.25-1.27)	0.55	(0.24-1.24)
Current OAD only 1-19	154	(0.3)	175	(0.3)	0.87	(0.70-1.08)	0.84	(0.67-1.04)
Current OAD only 20-39	125	(0.2)	143	(0.3)	0.86	(0.67-1.10)	0.85	(0.67-1.09)
Current OAD only 40+	184	(0.3)	195	(0.4)	0.92	(0.75-1.13)	0.92	(0.75-1.13)
Past OAD use only	20	(0.0)	32	(0.1)	0.59	(0.34-1.04)	0.62	(0.35-1.09)
Diagnosed DM - $HbA1_c$>7.5								
Current Insulin 1-39(+/- OAD)	118	(0.2)	160	(0.3)	0.72	(0.57-0.92)	0.72	(0.57-0.92)
Current Insulin 40+(+/- OAD)	119	(0.2)	160	(0.3)	0.73	(0.58-0.93)	0.69	(0.55-0.88)
Past insulin use (+/- OAD)	7	(0.0)	14	(0.0)	0.48	(0.20-1.20)	0.43	(0.17-1.07)
Current OAD only 1-19	103	(0.2)	138	(0.3)	0.74	(0.57-0.95)	0.72	(0.55-0.93)
Current OAD only 20-39	76	(0.1)	83	(0.2)	0.91	(0.66-1.24)	0.90	(0.65-1.23)
Current OAD only 40+	118	(0.2)	159	(0.3)	0.73	(0.58-0.93)	0.73	(0.57-0.92)
Past OAD use only	3	(0.0)	29	(0.1)	0.10	(0.03-0.33)	0.11	(0.03-0.36)
Treated DM - HbA1c not recorded	117	(0.2)	172	(0.3)	0.67	(0.53-0.85)	0.67	(0.52-0.85)

Abbreviations: CI, confidence interval; DM, diabetes mellitus; OR, odds ratio.

Percentages are rounded to the nearest decimal.

*adjusted for smoking, BMI, alcohol consumption.

OAD = oral antidiabetic drugs: include biguanides, sulfonylureas, thiazolidinediones, glinides, α-glucosidase inhibitors, and incretin-mimetics

Table 3.4-3: Distribution of diagnosed DM stratified by $HbA1_c$, sub-stratified by disease duration

	Rosacea cases, No (%) (n=53,927)		Rosacea-free controls, No (%) (n=53,927)		OR crude	(95%CI)	OR adj.*	(95% CI)
No diagnosed DM	52,241	(96.9)	51,885	(96.2)	1.00	(ref.)	1.00	(ref.)
Diagnosed DM	1,686	(3.1)	2,042	(3.8)	0.81	(0.76-0.87)	0.80	(0.74-0.85)
$HbA1_c$≤7.5 by DM treatment duration (y)								
Untreated	299	(0.6)	283	(0.5)	1.04	(0.88-1.22)	0.99	(0.84-1.17)
<1	60	(0.1)	68	(0.1)	0.87	(0.62-1.24)	0.87	(0.61-1.23)
1-3	169	(0.3)	188	(0.4)	0.89	(0.72-1.09)	0.85	(0.69-1.05)
3-5	124	(0.2)	127	(0.2)	0.96	(0.75-1.23)	0.96	(0.75-1.23)
5-10	159	(0.3)	207	(0.4)	0.76	(0.62-0.93)	0.75	(0.61-0.92)
≥10	69	(0.1)	98	(0.2)	0.69	(0.51-0.94)	0.69	(0.50-0.94)
$HbA1_c$>7.5 by DM treatment duration (y)								
Untreated	33	(0.1)	42	(0.1)	0.78	(0.50-1.23)	0.73	(0.46-1.16)
<1	50	(0.1)	80	(0.2)	0.62	(0.44-0.88)	0.61	(0.43-0.87)
1-3	91	(0.2)	104	(0.2)	0.86	(0.65-1.14)	0.86	(0.64-1.14)
3-5	98	(0.2)	157	(0.3)	0.62	(0.48-0.79)	0.62	(0.48-0.81)
5-10	182	(0.3)	221	(0.4)	0.81	(0.67-0.99)	0.79	(0.65-0.97)
≥10	123	(0.2)	181	(0.3)	0.67	(0.53-0.84)	0.63	(0.50-0.80)
No $HbA1_c$ record	229	(0.4)	286	(0.5)	0.79	(0.66-0.94)	0.78	(0.65-0.93)

Abbreviations: CI, confidence interval; DM, diabetes mellitus; $HbA1_c$, hemoglobin $A1_c$; OR, odds ratio; y, years.

Percentages are rounded to the nearest decimal.

* adjusted for smoking, body mass index, and alcohol consumption.

Table 3.4-4: Distribution of antidiabetic drug use (insulin and OAD) stratified by timing and duration of drug exposure

	Rosacea cases, No (%) (n=53,927)		Rosacea-free controls, No (%) (n=53,927)		OR crude	(95%CI)	OR adj*	(95% CI)
No AD	52,595	(97.5)	52,235	(96.9)	1.00	(ref.)	1.00	(ref.)
Any AD	1,332	(2.5)	1,692	(3.1)	0.78	(0.72-0.84)	0.76	(0.71-0.83)
OADs	1,134	(2.1)	1,405	(2.6)	0.80	(0.74-0.86)	0.83	(0.76-0.91)
Duration (Nr of p)								
1-19	439	(0.8)	558	(1.0)	0.78	(0.69-0.89)	0.80	(0.70-0.91)
20-39	268	(0.5)	309	(0.6)	0.86	(0.73-1.01)	0.89	(0.75-1.06)
40+	427	(0.8)	538	(1.0)	0.78	(0.68-0.89)	0.83	(0.73-0.96)
Timing (180d)								
current	971	(1.8)	1167	(2.2)	0.82	(0.75-0.90)	0.84	(0.77-0.92)
past	163	(0.3)	238	(0.4)	0.68	(0.55-0.83)	0.78	(0.63-0.97)
Insulin	399	(0.7)	564	(1.1)	0.70	(0.62-0.80)	0.75	(0.65-0.85)
Duration (Nr of p)								
1-39	230	(0.4)	319	(0.6)	0.72	(0.60-0.85)	0.77	(0.64-0.92)
40+	169	(0.3)	245	(0.5)	0.69	(0.57-0.84)	0.71	(0.58-0.87)
Timing (180d)								
current	373	(0.7)	513	(1.0)	0.72	(0.63-0.83)	0.78	(0.67-0.90)
past	26	(0.1)	51	(0.1)	0.51	(0.32-0.81)	0.54	(0.33-0.87)

Abbreviations: AD, antidiabetic drug; CI, confidence interval; d, day; OAD, oral antidiabetic drug; OR, odds ratio; p, prescription.

Percentages are rounded to the nearest decimal.

*adjusted for smoking, body mass index (BMI), and alcohol consumption. OAD use additionally adjusted for insulin use. Insulin use additionally adjusted for OAD use.

OADs include biguanides, sulfonylureas, thiazolidinediones, glinides, α-glucosidase inhibitors, and incretin-mimetics.

3.5 The association between psychiatric diseases, psychotropic drugs and the risk of incident rosacea (Study 3.5)

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3.5.1 Abstract

Background: Psychological conditions, such as traumatic events or stress, have been discussed controversially as aetiologic factors for rosacea.

Objectives: To assess the association between diagnosed depression, other affective disorders, and schizophrenia and subsequent incident rosacea. We further aimed at evaluating a possible role of different psychotropic drugs within this association.

Methods: We conducted a matched case-control study of psychiatric diseases and incident rosacea, stratified by exposure to various psychotropic drugs, using the UK-based General Practice Research Database (GPRD). Cases had a first diagnosis of rosacea recorded between 1995 and 2009. Each case was matched to one control on age, sex general practice, and years of history on the database.

Results: We observed a decreased rosacea risk (OR 0.71, 95% CI 0.60-0.91) for patients with diagnosed schizophrenia independent of lithium use, but not for patients with depression or other affective disorders. After stratification of these psychiatric diseases according to psychotropic drug treatment, lithium was the only drug that significantly affected the risk estimate. A sub-analysis of lithium users yielded a decreased OR of 0.58 (95% CI 0.38-0.88) for current long-term lithium use among people with no schizophrenia diagnosis (with or without affective disorders) compared to people not exposed to lithium.

Conclusions: Depression or other affective disorders did not affect the risk estimate of developing rosacea, whereas patients with schizophrenia were at a decreased risk of this skin disease in our study population. We observed a materially decreased risk of rosacea among people with chronic lithium exposure.

3.5.2 Introduction

Rosacea is a common facial skin disease encompassing four different clinical subtypes, i.e. 'erythematotelangiectatic', 'papulopustular', 'phymatous', and 'ocular' rosacea. The skin disease is characterized by vascular dysfunction (persistent erythema, flushing episodes, telangiectasia), inflammation (papules / pustules), and neuronal components (burning / stinging), but its pathology remains largely unclear. Fibrotic changes, such as the rhinophyma, or inflammatory ocular symptoms can be additional manifestations.[47, 48] Evidence points towards a pathogenic key role of neurovascular dysregulation and neurogenic inflammation.[1, 55, 56, 70] Despite scarce evidence, psychogenic factors have been discussed as aetiologic factors for rosacea, a notion that originated in a small and rather outdated body of anecdotal evidence that linked the onset of rosacea to emotional stress or traumatic events. The skin disease has even been associated with a specific personality structure that includes increased feelings of anxiety, guilt, and shame,[52-54, 65, 153-157] but more recent results do not support a general psychogenic aetiology of rosacea.[64] In 2011, a new rosacea subtype (neurogenic rosacea) was suggested for a small sub-group of therapy refractory rosacea patients, with a high degree of neurologic and neuropsychiatric conditions including depression.[158] Previous studies assessed rosacea with regard to depression mainly aimed at evaluating the psychological impact of facial disfigurement, but did not account for the chronological appearance of the two diseases.[156, 159] We are not aware of any studies that have assessed the association between rosacea and schizophrenia.

We are not aware of any evidence on a potential association between psychotropic drugs and the skin disease. We conducted a large population-based case-control analysis to explore the association between depression, other affective disorders, schizophrenia, and use of antidepressant and antipsychotic drugs, and the risk of developing rosacea.

3.5.3 Materials and Methods

Study Design and Data Source

We conducted a matched case-control analysis using data from the UK-based GPRD (General Practice Research Database, now known as the CPRD – the Clinical

Practice Research Datalink). This database is a large source of anonymous primary-care data comprised of approximately 7 million active patients who are enrolled with selected general practitioners (GPs). The GPs have been trained to provide clinical data in a standardised format. Participating practices provide information on patient demographics and characteristics (e.g. age, sex, height, weight, smoking status), symptoms or medical diagnoses, lab test results, and referrals to secondary care. Drug prescriptions are generated electronically via computer, ensuring a virtually complete drug history. The Medicines and Healthcare Products Regulatory Agency (MHRA) checks the raw data before release, and performs quality control checks. The patients enrolled in the GPRD are representative of the UK population with regards to age, sex, geographic distribution, and annual turnover rate. Extensive validation of the GPRD has documented its high validity, especially for chronic conditions.[99, 121] The database has been the source for numerous pharmacoepidemiological studies and for public health and disease epidemiology studies.[101, 121] The study protocol was approved by the Independent Scientific Advisory Committee (ISAC) for MHRA database research.

Study Population

The study population consisted of all patients in the GPRD with a first-time recorded Read code for rosacea[99] between January 1995 and September 2009. We excluded patients with <3 years of recorded active history in the database prior to the date of their first rosacea diagnosis ('index date') to increase the likelihood of only including incident cases. Patients with a diagnosis of rhinophyma or ocular rosacea only, in the absence of another code for facial rosacea, were not included. We also excluded patients with a recorded Read code for alcoholism / alcohol abuse, cancer (except non-melanoma skin cancer), or HIV / AIDS prior to the index date. The validity of rosacea diagnoses in the GPRD is high and has been reported in a previous study of our group.[46] We randomly identified one control patient for each case matched on age (year of birth), sex, general practice, calendar time (index date), and number of years of recorded history in the database prior to the index date. We applied the same exclusion criteria to controls as to cases. Controls were not eligible if they had rhinophyma (without facial rosacea) or flushing symptoms recorded at any time.

Case-Control Analysis

Exposure was defined as a Read code diagnosis of depression (ICD-10 F32-33), other affective disorders (ICD-10 F30,31,34,38,39) or schizophrenia (ICD-10 F20-29)[99, 160] at any time prior to the index date. Drug exposure was defined as a minimum of one prescription for a certain drug class prior to the index date, using single agent preparations only. We stratified antidepressants according to the WHO ATC drug index[161] into serotonin reuptake inhibitors (SSRI), tricyclic antidepressants (TCA), lithium, or other antidepressants. Antipsychotics were also stratified by WHO ATC drug-classes into phenothiazines, diazepines / oxazepines/ thiazepines, or other antipsychotics.[162]

We compared patients with diagnosed depression and/or other affective disorders to patients with neither of the two diagnoses, stratified by current drug exposure. Patients with diagnosed schizophrenia were compared to patients without a recorded schizophrenia diagnosis, divided into those with or without current drug treatment (≤ or > 180 days).

Statistical Analysis

We conducted multivariate conditional logistic regression analyses to evaluate the association of the various exposures in relation to rosacea using SAS statistical software (version 9.3, SAS Institute, Inc., Cary, NC, US). Relative risk estimates were calculated as odds ratios (ORs) with 95% confidence intervals (CIs). We established a mutually exclusive model, where we stratified patients with diagnosed depression and/or other affective disorders according to their psychotropic drug treatment into currently (≤ 180 days from last prescription to index date) untreated patients and into those currently treated either with SSRIs only, TCAs only, lithium only, another antidepressant only, or a combination of > 1 antidepressant drug class, and compared them to patients without any diagnosed affective disorder. Use of SSRIs, TCAs, and lithium was further sub-stratified according to timing (last prescription recorded ≤ or > 180 days before the index date) and duration of use (by assessing the number of prescriptions prior to the index date). Patients with diagnosed schizophrenia on current drug treatment were sub-stratified by pharmacologic drug classes. The small sample size did not allow stratification by timing and duration of antipsychotic drug therapy. In a sensitivity analysis we divided all lithium users into patients with a previous diagnosis for schizophrenia, irrespective of any co-

diagnoses, and into patients without a recorded schizophrenia diagnosis, sub-stratified by timing and duration of lithium use, and compared them to patients without lithium use at any time prior to the index date. We adjusted all ORs for smoking (non, current, ex, unknown), alcohol consumption (0, 1-4, 5-9, 10-14, 15-24, or 25+ units per week, or unknown), and body mass index (BMI, <18.5, 18.5-24.9, 25.0-29.9, 30+ kg/m^2, or unknown). We further adjusted the analyses on depression and/or other affective disorders for concomitantly recorded schizophrenia diagnoses and vice versa. Lithium use was additionally adjusted for the presence of seborrhea/seborrheic dermatitis. We separately tested for confounding by asthma, chronic obstructive pulmonary disease, diabetes mellitus, hypertension, ischemic heart disease, heart failure, myocardial infarction, stroke / transient ischemic attack, epilepsy, hyperthyroidism, hypothyroidism, rheumatoid arthritis, as well as for use of benzodiazepines or for other hypnotic agents. Since none of these variables individually altered the relative risk estimates for the association between the exposure variable and rosacea by ≥ 10%, we did not include them in the final multivariate model.

3.5.4 Results

Among 53,927 rosacea cases and the same number of controls, 62.8% were female, and 54.4% were diagnosed between 30 and 59 years of age. Table 3.5-1 provides demographics characteristics, and smoking and BMI for cases and controls; these have been reported in detail elsewhere.[46] Of all rosacea patients, 3086 (5.7%) cases and 2770 (5.1%) controls had a recorded referral to a psychiatrist / psychologist at some time before or after the index date, of which 637 (1.2%) cases and 594 (1.1%) controls were referred within 1 year before or after the index date.

We identified 9521 (17.7%) cases and 8528 (15.8%) controls with a diagnosis of an affective disorder (i.e. depression and/or other affective disorder) at any time before the index date, yielding an OR of 1.21 (95% CI 1.16-1.25) compared to patients without any recorded affective disorder. Of those, 93.3% of cases and 92.7% of controls were diagnosed with depression (OR 1.20, 95% CI 1.16-1.24 for depression compared to no recorded depression), and 17.1% of cases and 16.7% of controls had a record for other affective disorders (OR 1.13, 95% CI 1.05-1.22 for other affective disorders compared to no recorded other affective disorder). Stratification of

all patients with affective disorders according to their current treatment (stratified by exposure timing and duration) did not affect the relative risk estimates, revealing ORs around 1.0 for currently untreated patients as well as for patients treated with either antidepressant drug class. By contrast, patients with affective disorders currently treated with long term lithium had a decreased rosacea risk compared to patients without diagnosed affective disorders, with an OR of 0.59 (95% CI 0.34-1.02) for those who received ≥20 prescriptions, but the sample size was small (Table 3.5-2).

Recorded schizophrenia at any time before the index date (225, 0.4% cases and 318, 0.6% controls) yielded a statistically significantly decreased OR when compared to patients without a recorded schizophrenia diagnosis of 0.71 (95% CI 0.60-0.85). Of those, 101 cases and 143 controls were currently not under antipsychotic drug treatment (OR 0.70, 95% 0.54-0.91), whereas 124 cases and 175 controls received some antipsychotic therapy (OR 0.72, 95% CI 0.57-0.91). Although statistical power was low, a trend toward decreased ORs was present across all strata of antipsychotic drug classes (Table 3.5-3). The small sample size did not allow stratification by timing and duration of drug exposure.

Of all lithium users within our study population (125 cases, 194 controls), only 21% of cases and 20% of controls were diagnosed with schizophrenia before the index date (Table 3.5-4). We observed a significantly decreased OR of 0.58 (95% CI 0.38-0.88, ≥20 prescriptions) for current long-term lithium users without diagnosed schizophrenia (35 cases and 64 controls) compared to patients without lithium exposure at any time prior to the index date. Additional adjustment for seborrhea/seborrheic dermatitis did not substantially change the relative risk estimate (OR 0.54, 95% CI 0.35-0.82, for current long-term users without schizophrenia). Within the schizophrenic sub-group, the sample size was too small to yield meaningful results.

Table 3.5-1: Distribution of demographics, life-style factors, comorbidities, and comedications in rosacea cases and controls in the UK GPRD

	Rosacea cases, No (%) (n=53,927)		Rosacea-free controls, No (%) (n=53,927)		OR crude	(95% CI)
Sex						
male	20,048	(37.2)	20,048	(37.2)		
female	33,879	(62.8)	33,879	(62.8)		
Age (years)						
<20	6,630	(12.3)	6,626	(12.3)		
20-29	5,202	(9.7)	5,213	(9.7)		
30-39	8,586	(15.9)	8,576	(15.9)		
40-49	11,338	(21.0)	11,343	(21.0)		
50-59	9,410	(17.5)	9,403	(17.5)		
60-69	6,955	(12.9)	6,960	(12.9)		
70+	5,806	(10.8)	5,806	(10.8)		
Smoking Status						
Non	27,475	(51.0)	25,031	(46.4)	1.00	(ref.)
Current	7,635	(14.2)	10,660	(19.8)	0.64	(0.62-0.66)
Ex	9,981	(18.5)	8,277	(15.4)	1.13	(1.09-1.17)
Unknown	8,836	(16.4)	9,959	(18.5)	0.69	(0.66-0.72)
BMI (kg/m^2)						
12.0-18.5	905	(1.7)	953	(1.8)	0.88	(0.80-0.97)
18.5-24.9	18,839	(34.9)	17,808	(33.0)	1.00	(ref.)
25.0-29.9	13,146	(24.4)	12,291	(22.8)	1.01	(0.98-1.05)
30.0-60.0	6,942	(12.9)	7,184	(13.3)	0.92	(0.88-0.95)
Unknown	14,095	(26.1)	15,691	(29.1)	0.76	(0.73-0.79)
Referrals to psychiatrist						
No referral	50,841	(94.3)	51,157	(94.9)		
Referral to psychiatrist overall	3,086	(5.7)	2,770	(5.1)		
≤1 year prior to or after ID	637	(1.2)	594	(1.1)		

Abbreviations: BMI, body mass index; CI, confidence interval; OR, odds ratio.

Table 3.5-2: Distribution of diagnosed affective disorders stratified by exposure to antidepressant drugs (by timing and duration of drug use) in rosacea cases and controls

	Rosacea cases, No (%) (n=53,927)		Rosacea-free controls, No (%) (n=53,927)		OR crude	(95% CI)	OR adj.*	(95% CI)
No depression with or without other affective disorders	45,044	(83.5)	46,020	(85.3)	1.00	(ref.)	1.00	(ref.)
Diagnosed depression	8,883	(16.5)	7,907	(14.7)	1.16	(1.12-1.20)	1.20	(1.16-1.24)
No other affective disorders with or without depression	52,303	(97.0)	52,503	(97.4)	1.00	(ref.)	1.00	(ref.)
Diagnosed other affective disorders	1,624	(3.0)	1424	(2.6)	1.15	(1.07-1.24)	1.13	(1.05-1.22)
No depression or other affective disorder	44,406	(82.3)	45,399	(84.2)	1.00	(ref.)	1.00	(ref.)
Diagnosed depression and / or other affective disorder	9,521	(17.7)	8,528	(15.8)	1.16	(1.12-1.20)	1.21	(1.16-1.25)
Currently untreated	6,342	(11.8)	5,663	(10.5)	1.16	(1.12-1.21)	1.20	(1.15-1.25)
Current SSRI only	1,642	(3.0)	1,481	(2.8)	1.15	(1.07-1.24)	1.21	(1.13-1.31)
1-19	945	(1.8)	831	(1.5)	1.18	(1.07-1.30)	1.24	(1.13-1.37)
20-39	410	(0.8)	353	(0.7)	1.20	(1.04-1.38)	1.26	(1.09-1.46)
≥40	287	(0.5)	297	(0.6)	1.01	(0.85-1.19)	1.08	(0.91-1.27)
TCA only	876	(1.6)	746	(1.4)	1.22	(1.10-1.34)	1.26	(1.14-1.40)
Current 1-19	413	(0.8)	345	(0.6)	1.24	(1.07-1.43)	1.26	(1.09-1.46)
Current 20-39	192	(0.4)	143	(0.3)	1.39	(1.11-1.72)	1.45	(1.17-1.81)
Current ≥40	271	(0.5)	258	(0.5)	1.09	(0.92-1.29)	1.15	(0.97-1.37)
Lithium only	27	(0.1)	44	(0.1)	0.64	(0.40-1.03)	0.77	(0.47-1.25)
Current 1-19	7	(0.0)	2	(0.0)	3.62	(0.75-17.42)	4.43	(0.83-21.89)
Current ≥20	20	(0.0)	42	(0.1)	0.49	(0.29-0.84)	0.59	(0.34-1.02)
Other antidepressant only	291	(0.5)	314	(0.6)	0.95	(0.81-1.12)	1.04	(0.88-1.22)
Combination > antidepressant	343	(0.6)	280	(0.5)	1.27	(1.08-1.48)	1.39	(1.18-1.63)

Abbrevations: CI, confidence interval; OR, odds ratio; SSRI, selective serotonin reuptake inhibitors; TCA, tricyclic antidepressant.

* adjusted for smoking, BMI, alcohol consumption, disease additionally adjusted for complementary assessed diseases.

Table 3.5-3: Distribution of exposure to antiosychotic drugs stratified by timing and duration of drug use in rosacea cases and controls

	Rosacea cases, No (%) (n=53,927)		Rosacea-free controls, No (%) (n=53,927)		OR crude	(95% CI)	OR adj.*	(95% CI)
No schizophrenia	53,702	(99.6)	53,609	(99.4)	1.00	(ref.)	1.00	(ref.)
Diagnosed schizophrenia	225	(0.4)	318	(0.6)	0.70	(0.59-0.83)	0.71	(0.60-0.85)
Currently untreated	101	(0.2)	143	(0.3)	0.70	(0.54-0.91)	0.70	(0.54-0.91)
Currently treated	124	(0.2)	175	(0.3)	0.70	(0.56-0.89)	0.72	(0.57-0.91)
Phenothiazines only	37	(0.1)	42	(0.1)	0.88	(0.57-1.37)	0.90	(0.57-1.41)
Diazepine, oxazepine, thiazepine only	19	(0.0)	45	(0.1)	0.42	(0.25-0.72)	0.41	(0.24-0.72)
Other antipsychotic only	44	(0.1)	61	(0.1)	0.72	(0.49-1.06)	0.76	(0.51-1.12)
Combination >1 antipsychotic	24	(0.0)	27	(0.1)	0.88	(0.50-1.54)	0.88	(0.50-1.56)

Abbreviatoins: CI, confidence interval; OR, odds ratio.

* adjusted for smoking, BMI, alcohol consumption, depression, other affective disorders.

Table 3.5-4: Distribution of exposure to oral lithium stratified by underlying indication, sub-stratified by timing and duration of drug use in rosacea cases and controls

	Rosacea cases, No (%) (n=53,927)		Rosacea-free controls, No (%) (n=53,927)		OR crude	(95% CI)	OR adj*.	(95% CI)
No Lithium	53,802	(99.8)	53,733	(99.6)	1.00	(ref.)	1.00	(ref.)
Lithium with schizophrenia	26	(0.1)	39	(0.1)	0.64	(0.39-1.07)	0.73	(0.43-1.21)
By number of prescriptions								
current 1-19 presc.	3	(0.0)	3	(0.0)	0.90	(0.18-4.53)	0.94	(0.18-4.81)
current 20+ presc.	14	(0.0)	16	(0.0)	0.86	(0.41-1.80)	1.02	(0.48-2.17)
past use	9	(0.0)	20	(0.0)	0.44	(0.20-0.97)	0.48	(0.21-1.06)
Lithium with no schizophrenia (with or without other affective disorder)	99	(0.2)	155	(0.3)	0.64	(0.49-0.82)	0.69	(0.54-0.89)
By number of prescrtions								
current 1-19 presc.	14	(0.0)	18	(0.0)	0.78	(0.39-1.56)	0.80	(0.39-1.62)
current 20+ presc.	35	(0.0)	64	(0.1)	0.54	(0.36-0.82)	0.58	(0.38-0.88)
past use	50	(0.1)	73	(0.1)	0.68	(0.48-0.98)	0.76	(0.53-1.10)

Abbreviatoins: CI, confidence interval; OR, odds ratio.

*adjusted for smoking, BMI, alcohol consumption

3.5.5 Discussion

The findings of this large observational case-control study do not suggest a major association between diagnosed depression or other affective disorders and the risk of developing rosacea. Patients with diagnosed schizophrenia were at a substantially decreased risk of incident rosacea, but potential diagnostic bias cannot entirely be ruled out. Oral lithium was the only drug, among all psychotropic medications, that was materially associated with the risk of rosacea, yielding significantly decreased odds ratios in patients with long-term lithium exposure, irrespective of the underlying diagnosis (OR = 0.58, 95% CI 0.38-0.88 for ≥20 prescriptions)

Our results do not suggest an aetiologic association between pre-existing depression or other affective disorders and incident rosacea in general, though we cannot exclude the possibility of an association for a small subset of rosacea patients, as hypothesised for the neurogenic rosacea subtype.[158] It seems that the persistent belief in a potential psychogenic aetiology of rosacea is rooted in a rather outdated and small body of anecdotal evidence linking acute stressful life events, or other rather mild psychological conditions to the onset of the skin disease,[54, 153, 155] while more recent evidence does not support this hypothesis.[64] Since variables such as general stress or other mild psychological conditions are not reliably recorded in the GPRD, we did not assess these diagnoses in this study. To date, there is no specific evidence of an aetiologic effect of depression or other affective disorders on rosacea. One previous retrospective observational study assessed the concomitant manifestation of rosacea and depression based on the notion of a potential psychogenic origin of rosacea; the authors reported a relative over-representation of depression diagnoses in rosacea patients as compared to other psychiatric diagnoses. However, the overall rate of psychiatric comorbidities was very low (1.04%), and the question of the temporal sequence of the manifestation of the two diseases was not addressed.[97] Other studies on the association between depression and rosacea aimed to assess the impact of the facial disfigurement on the development of depressive symptoms.[156, 159]

We observed a significantly decreased risk of rosacea in patients with diagnosed schizophrenia, irrespective of drug treatment, a so far unreported association. While this is an interesting observation the association may not be causal and may rather reflect an under-diagnosis of the skin disease in patients with schizophrenia, due to

an altered disease perception of the patient or an altered diagnostic behavior on behalf of the GP.

We observed a decreased risk of rosacea with systemic long term lithium therapy, an effect which has also not been shown before. Oral lithium is indicated for the treatement of affective disorders, but may also be used as an add-on medication for schizophrenia.[163] However, as schizophrenia was only diagnosed in a minority of lithium users, and as ORs were significantly decreased in lithiums users without schizophrenia, confounding by underlying schizophrenia seems an unlikely explanantion for the result. Thus, our results are intriguing and suggest that lithium reduces the risk of rosacea. Although systemic lithium exposure might not be a desirable treatment approach for rosacea due to its toxicity and narrow therapeutic window,[164, 165] this finding might lead to new insights on the pathophysiology of the skin disease and should be followed up in further research.

This large observational study is based on a high quality, extensively validated and large primary-care database, but several limitations have to be considered when interpreting our findings. Firstly, we may be missing some rosacea patients since mild rosacea may not result in a visit to a doctor, especially in the case of erythematotelangiectatic rosacea.[159] Coding in the GPRD does not differentiate between erythematotelangiectatic and papulopustular rosacea, and our study population is likely to comprise an over-representation of more severe papulopustular rosacea patients.[159] Despite this potential for under-diagnosis and some degree of potential disease misclassification, a 74% concordance of rosacea diagnoses between dermatologists and the referring GPs has been shown in a cross-sectional study from South-East Scotland,[111] providing reassurance that the validity of rosacea diagnoses in the GPRD is sufficiently good. Second, the likelihood of being diagnosed with rosacea may increase with increasing medical attention, which is the case for patients with diagnosed psychiatric illnesses. We previously reported that rosacea patients tended to see the GP more often prior to the diagnosis than controls.[46] Thus, a certain degree of diagnostic bias cannot be ruled out, as it has been reported that patients with depressive symptoms have a stronger perception of mild skin symptoms.[159] Finally, we cannot rule out a certain degree of residual confounding and chance, since we could not control for ethnical background, skin pigmentation, socioeconomic status, or life-style factors such as sun exposure, profession, or nutrition, as these parameters are not recorded in the GPRD. Despite

these limitations, this is, to our knowledge, the largest study to assess the association between psychogenic factors and incident rosacea. It is also the first to analyze the impact of psychotropic drugs on the risk of rosacea.

In summary, this observational study suggests a potentially decreased risk of incident rosacea in patients with diagnosed schizophrenia, but we cannot rule out some diagnostic bias. Neither diagnosed depression nor other affective disorders were associated with an altered relative risk of developing rosacea in the current study population. Interestingly, we observed a materially decreased risk of rosacea in association with chronic oral lithium exposure independent of schizophrenia, which has not to our knowledge been reported before. His finding will have to be followed up in further research.

3.6 Antihypertensive drugs and the risk of incident rosacea (Study 3.6)

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3.6.1 Abstract

Background: Despite scarce evidence, use of calcium channel blockers is discouraged in rosacea patients, whereas beta-blockers are recommended as an off-label treatment for erythematotelangiectatic rosacea.

Objectives: To study the association between use of calcium channel blockers, beta-blockers, and other antihypertensive drugs and incident rosacea.

Methods: We conducted a matched case-control study of antihiypertensive drugs and incident rosacea, using the UK-based General Practice Research Database. Cases had a first diagnosis of rosacea recorded between 1995 and 2009. Each case was matched to one control on age, sex, general practice, and years of history on the database before the index date. Drug use was stratified by timing (≤ or > 180 days before the index date) and duration (number of prescriptions) of drug exposure, in a multivariate conditional logisitic regression model.

Results: Among 53,927 cases and 53,927 controls, we observed ORs around unity for calcium channel blockers across all strata, with a slightly decreased ORs of 0.77 (95% CI 0.69-0.86) for current users of dihydropyridine calcium channel blockers with ≥40 prescriptions. Among beta-blockers, atenolol and bisoprolol yielded slightly decreased ORs across all exposure strata, whereas propranolol revealed ORs around 1.0, irrespective of timing and duration of exposure. Neither ACE-inhibitors nor angiotensin receptor blockers altered the relative rosacea risk.

Conclusions: Our data contradict the prevailing notion that calcium channel blockers increase the risk of rosacea. Beta-blocker use was associated with a slightly decreased risk of rosacea, but the effect may be somewhat stronger in patients with erythematotelangiectatic rosacea.

3.6.2 Introduction

Rosacea is a common facial skin disease that has been categorised into four clinical subtypes, i.e. 'erythematotelangiectatic', 'papulopustular', 'phymatous', or 'ocular' rosacea. The skin disease is characterised by vascular dysfunction (persistent erythema, flushing episodes, telangiectasia), inflammation (papules / pustules), and neuronal components (burning / stinging), but its pathology remains largely unclear. Fibrotic changes, such as the rhinophyma, or inflammatory ocular symptoms can be further manifestations.[48] Besides various other suggested mechanisms, evidence points toward a key role of neurovascular dysregulation and neurogenic inflammation in the vasodilative pathomechanism of rosacea.[1, 55, 56, 70]

Beta-blockers (BBs, sub-type unspecified) are recommended as off-label treatment for erythematotelangiectatic rosacea.[2, 47, 59, 87] The evidence is, however, confined to a few small studies and case series showing limited effects.[68, 69, 166, 167] Use of calcium channel blockers (CCBs, again sub-type unspecified), on the other hand, is commonly discouraged in rosacea patients,[47, 168] as they supposedly trigger or exacerbate rosacea. Again, evidence to support this widespread belief seems to consist of one single small retrospective study from Italy.[54] As CCBs, BBs, ACE-inhibitors (ACEIs), and angiotensin receptor blockers (ARBs) are among the mainstays in the treatment of essential hypertension,[169-172] a more robust and valid risk-benefit assessment for these frequently used drugs in association with rosacea is required. We are not aware of any previous studies assessing a potential association of use of ACEIs or ARBs on the risk of developing rosacea. We therefore conducted a large population-based case-control analysis to explore the association between BBs, CCBs, ACEIs, and ARBs and the risk of developing a first-time rosacea diagnosis.

3.6.3 Materials and Methods

Study Design and Data Source

We conducted a matched case-control analysis using data from the UK-based GPRD (General Practice Research Database), now known as the CPRD (General Practice Research Datalink). This database is a large source of anonymous primary-care data comprised of approximately 7 million active patients who are enrolled with selected general practitioners (GPs). The GPs have been trained to provide clinical data in a

standardised format. Participating practices provide information on patient demographics and characteristics (e.g. age, sex, height, weight, smoking status), symptoms or medical diagnoses, lab test results, and referrals to secondary care. Drug prescriptions are generated electronically via computer, ensuring a virtually complete drug history. The Medicines and Healthcare Products Regulatory Agency (MHRA) checks the raw data before release and performs quality-control checks. The patients enrolled in the GPRD are representative of the UK population with regard to age, sex, geographic distribution, and annual turnover rate. Extensive validation of the GPRD has documented its high validity, especially for chronic conditions.[99, 121] The database has been the source for numerous pharmacoepidemiological studies and for public health and disease epidemiology studies.[101, 121] The study protocol was approved by the Independent Scientific Advisory Committee (ISAC) for MHRA database research.

Study Population

The study population consisted of all patients in the GPRD with a first-time recorded Read-code for rosacea[99] between January 1995 and September 2009. We excluded patients with <3 years of recorded active history in the database prior to the date of their first rosacea diagnosis (index date) to increase the likelihood of restricting the study to incident cases. Patients with a diagnosis of rhinophyma or ocular rosacea, in the absence of another code for facial rosacea, were not included. We also excluded all patients with a recorded Read-code for alcoholism / alcohol abuse, cancer (except non-melanoma skin cancer), or HIV / AIDS prior to the index date. Validity of rosacea diagnoses on the GPRD is discussed elsewhere.[46] We randomly identified one control for each case matched on age (year of birth), sex, general practice, calendar time (index date), and number of years of recorded history in the database prior to the index date. We applied the same exclusion criteria to controls as to cases. In addition, controls were not eligible if they had rhinophyma (without facial rosacea) or flushing symptoms recorded at any time.

Case-Control Analysis

Exposure to cardiovascular drugs was assessed irrespective of the underlying diagnosis, including single agents and combined products. Drug exposure was defined as a minimum of one prescription for a certain drug class prior to the index

date. We assessed all drug classes (i.e. ACEIs, ARBs, BBs, and CCBs) as separate groups, and compared patients with exposure to a certain drug class to patients without recorded use of the respective drugs at any time prior to the index date, stratified according to timing (last prescription recorded ≤ or > 180 days before the index date) and duration (number of prescriptions prior to the index date) of drug use. In addition, we stratified CCB use according to their pharmacodynamic properties into dihydropyridines (mainly vascular effects) or non-dihydropyridines (mainly cardiac effects), according to the WHO ATC index,[173, 174] and compared those patients to patients without CCB exposure at any time prior to the index date. Among BBs, we performed a sensitivity analysis for the three most frequently prescribed compounds (i.e. atenolol, propranolol, and bisoprolol, mutually exclusive by capturing the last recorded prescription before the index date), compared to non-use of BBs at any time prior to the index date.

Statistical Analysis

We conducted multivariate conditional logistic regression analyses to evaluate the association of different antihypertensive drugs in relation to rosacea using SAS statistical software (version 9.3, SAS Institute, Inc., Cary, NC, US). Relative risk estimates were calculated as odds ratios (ORs) with 95% confidence intervals (CIs). We adjusted all ORs for smoking (non, current, ex, unknown), alcohol consumption (0, 1-4, 5-9, 10-14, 15-24, or 25+ units per week, or unknown), and body mass index (BMI, <18.5, 18.5-24.9, 25.0-29.9, 30+ kg/m^2, or unknown). We further adjusted each analysis for use of statins and any of the other assessed cardiovascular drugs, including drugs contained in combination products. We separately tested the association between exposure to each assessed cardiovascular drug class and rosacea for confounding by diuretics (namely high-ceiling and low-ceiling diuretics, spironolactone, or other potassium sparing diuretics), as well as by hypertension, myocardial infarction, heart failure, ischemic stroke / transient ischemic attack, ischemic heart disease, diabetes mellitus, and hyperlipidemia. Since none of these variables individually altered the relative risk estimates for the association between the exposure variable and rosacea by ≥10%, we did not include them in the final multivariate model.

3.6.4 Results

Among 53,927 included rosacea cases and the same number of controls, 62.8% were female, and 54.4% were diagnosed between 30 and 59 years of age. The demographics of the study population, life-style factors (smoking, BMI), comorbidities, and comedication are displayed in Table 3.6-1, and are discussed in detail elsewhere.[46]

We identified 8977 (16.7%) cases and 8319 (15.4%) controls with one or more recorded BB prescription, revealing ORs around 1.0 in most strata, with a marginal trend toward decreased ORs in current users (OR 0.91, 95% CI 0.86-0.96) and in long-term users of 40+ prescriptions (OR 0.89, 95% CI 0.83-0.96, Table 3.6-2). This trend remained in a combined analysis of timing and duration of drug use, with slightly decreased ORs in current long-term users of BB, compared to non-users at any time prior to the index date (data not displayed). After stratification into the three predominantly prescribed BBs within the UK, we observed slightly decreased ORs during current use of atenolol across all strata of exposure duration (OR 0.83, 95% CI 0.74-0.94, 1-19 prescriptions], OR 0.80, 95% CI 0.70-0.90 [20-39 prescriptions], OR 0.82, 95% CI 0.74-0.91 [40+ prescriptions]), as well as for current long-term use of bisoprolol (OR 0.76, 95% CI 0.60-0.96), whereby strata of less than 40 prescriptions showed the same trend but did not reach statistical significance. Propranolol yielded ORs around unity across all strata of timing and duration of drug exposure, compared to non-users of any BB at any time before the index date (Table 3.6-3).

Among 4421 (8.2%) cases and 4441 (8.2%) controls with ever use of CCBs, we did not observe any statistically significantly altered ORs for current exposure across any strata of timing and duration of CCB use. ORs were marginally decreased in current users (OR 0.86, 95% CI 0.81-0.92) and in long-term users (OR 0.84, 95% CI 0.76-0.92, 40+ prescriptions, Table 2) when compared to non-users before the index date. After stratification by pharmacodynamic properties the same trend was present in patients with exposure to CCBs of the dihydropyridine type, with a slightly decreased OR of 0.77 (95% CI 0.69-0.86) in current users with 40+ prescriptions as compared to patients not using CCBs before the index date. Current short-term use of dihydropyridine CCB as well as use of non-dihydropyridine CCBs across all strata of timing and duration revealed ORs around unity (Table 3.6-4).

ACEIs as well as ARBs yielded ORs around 1.0 across all strata of timing and duration of drug exposure (Table 3.6-2).

Table 3.6-1: Distribution of demographics, life-style factors, co-morbidities, and co-medications in diagnosed rosacea cases and controls

	Rosacea cases, No (%) (n=53,927)		Rosacea-free controls, No (%) (n=53,927)		OR crude	(95% CI)
Sex						
male	20,048	(37.2)	20,048	(37.2)		
female	33,879	(62.8)	33,879	(62.8)		
Age (years)						
<20	6,630	(12.3)	6,626	(12.3)		
20-29	5,202	(9.7)	5,213	(9.7)		
30-39	8,586	(15.9)	8,576	(15.9)		
40-49	11,338	(21.0)	11,343	(21.0)		
50-59	9,410	(17.5)	9,403	(17.5)		
60-69	6,955	(12.9)	6,960	(12.9)		
70+	5,806	(10.8)	5,806	(10.8)		
Smoking Status						
Non	27,475	(51.0)	25,031	(46.4)	1.00	(ref.)
Current	7,635	(14.2)	10,660	(19.8)	0.64	(0.62-0.66)
Ex	9,981	(18.5)	8,277	(15.4)	1.13	(1.09-1.17)
Unknown	8,836	(16.4)	9,959	(18.5)	0.69	(0.66-0.72)
BMI (kg/m^2)						
12.0-18.5	905	(1.7)	953	(1.8)	0.88	(0.80-0.97)
18.5-24.9	18,839	(34.9)	17,808	(33.0)	1.00	(ref.)
25.0-29.9	13,146	(24.4)	12,291	(22.8)	1.01	(0.98-1.05)
30.0-60.0	6,942	(12.9)	7,184	(13.3)	0.92	(0.88-0.95)
Unknown	14,095	(26.1)	15,691	(29.1)	0.76	(0.73-0.79)
Comorbidities						
Hypertension	7,235	(13.4)	7,411	(13.7)	0.97	(0.93-1.00)
Hyperlipidemia	2795	(5.2)	2,822	(5.2)	0.99	(0.93-1.05)
Myocardial infarction	824	(1.5)	923	(1.7)	0.88	(0.80-0.97)
Ischemic stroke / TIA	897	(1.7)	973	(1.8)	0.92	(0.83-1.01)
Ischemic heart disease	2,462	(4.6)	2,405	(4.5)	1.03	(0.97-1.09)
Heart failure	518	(1.0)	552	(1.0)	0.93	(0.82-1.06)
Diabetes Mellitus	1,686	(3.1)	2,042	(3.8)	0.81	(0.76-0.87)
Co-medication						
Diuretic	8372	(15.5)	7926	(14.7)	1.08	(1.05-1.13)
OAD	1134	(2.1)	1405	(2.6)	0.80	(0.74-0.86)
Insulin	399	(0.7)	564	(1.1)	0.70	(0.62-0.80)
Statin	3718	(6.9)	3852	(7.1)	0.95	(0.90-1.00)

Abbreviations: BMI, body mass index; CI, confidence interval; OAD, oral antidiabetic drug; OR, odds ratio; TIA = Transient ischemic attack.

Percentages are rounded to the nearest decimal.

Table 3.6-2: Distribution of ACEI, ARB, BB, and CCB exposure, stratified by timing and duration of drug use in rosacea cases and controls

	Rosacea cases, No (%) (n=53,927)		Rosacea-free controls, No (%) (n=53,927)		OR crude	(95% CI)	OR adj.*	(95% CI)
No BB	44,950	(83.4)	45,608	(84.6)	1.00	(ref.)	1.00	(ref.)
Use of BB	8,977	(16.7)	8,319	(15.4)	1.11	(1.07-1.15)	1.11	(1.07-1.15)
Duration								
1-19	6,170	(11.4)	5,273	(9.8)	1.20	(1.15-1.24)	1.19	(1.14-1.24)
20-39	1,166	(2.2)	1,187	(2.2)	1.00	(0.92-1.09)	0.98	(0.90-1.07)
40+	1,641	(3.0)	1,859	(3.5)	0.90	(0.84-0.96)	0.89	(0.83-0.96)
Timing (180d)								
current	3,238	(6.0)	3603	(6.7)	0.92	(0.87-0.96)	0.91	(0.86-0.96)
past	5,739	(10.6)	4,716	(8.8)	1.25	(1.20-1.30)	1.25	(1.19-1.30)
No CCB	49,506	(91.8)	49486	(91.8)	1.00	(ref.)	1.00	(ref.)
Use of CCB	4,421	(8.2)	4,441	(8.2)	0.99	(0.95-1.04)	0.95	(0.90-1.00)
Duration								
1-19	2,542	(4.7)	2,344	(4.4)	1.08	(1.02-1.15)	1.03	(0.96-1.10)
20-39	811	(1.5)	878	(1.6)	0.92	(0.83-1.01)	0.87	(0.79-0.97)
40+	1,068	(2.0)	1,219	(2.3)	0.87	(0.79-0.95)	0.84	(0.76-0.92)
Timing (180d)								
current	2,534	(4.7)	2,780	(5.2)	0.91	(0.86-0.96)	0.86	(0.81-0.92)
past	1,887	(3.5)	1,661	(3.1)	1.13	(1.06-1.22)	1.09	(1.01-1.17)
No ACEI	49,629	(92.0)	49,622	(92.0)	1.00	(ref.)	1.00	(ref.)
Use of ACEI	4,298	(8.0)	4,305	(8.0)	1.00	(0.95-1.05)	0.93	(0.89-0.99)
Duration								
1-19	2,345	(4.4)	2,205	(4.1)	1.06	(1.00-1.31)	0.99	(0.93-1.07)
20-39	897	(1.7)	968	(1.8)	0.93	(0.84-1.02)	0.88	(0.79-0.97)
40+	1,056	(2.0)	1,132	(2.1)	0.93	(0.85-1.02)	0.91	(0.83-1.01)
Timing (180d)								
current	2,965	(5.5)	3,023	(5.6)	0.98	(0.93-1.04)	0.94	(0.88-1.00)
past	1,333	(2.5)	1,282	(2.4)	1.04	(0.96-1.13)	0.95	(0.86-1.04)
No ARB	52,716	(97.8)	52,822	(98.0)	1.00	(ref.)	1.00	(ref.)
Use of ARB	1,211	(2.3)	1105	(2.1)	1.115	(1.02-1.21)	1.08	(0.99-1.18)
Duration								
1-19	681	(1.3)	632	(1.2)	1.09	(0.97-1.22)	1.03	(0.92-1.16)
20-39	299	(0.6)	267	(0.5)	1.13	(0.96-1.34)	1.07	(0.90-1.27)
40+	231	(0.4)	206	(0.4)	1.14	(0.94-1.38)	1.13	(0.92-1.37)
Timing (180d)								
current	983	(1.8)	869	(1.6)	1.14	(1.04-1.26)	1.10	(0.99-1.23)
past	228	(0.4)	236	(0.4)	0.98	(0.81-1.17)	0.92	(0.76-1.12)

Abbreviations: ACEI, ACE inhibitor; ARB, angiotensin receptor blocker; BB = β-blocker; CCB, calcium channel blocker; CI, confidence interval; OR = odds ratio.

Percentages are rounded to the nearest decimal.

* adjusted for smoking, body mass index, alcohol consumption, other analyzed antihypertensives, drug classes in combined products.

Table 3.6-3: Exposure to the most frequently prescribed BBs within the UK stratified by timing and duration of use in rosacea cases and controls

	Rosacea cases, No (%) (n=53,927)		Rosacea-free controls, No (%) (n=53,927)		OR crude	(95% CI)	OR adj.*	(95% CI)
No BB	44,950	(83.4)	45,608	(84.6)	1.00	(ref.)	1.00	(ref.)
Use of propranolol	3,968	(7.4)	3,200	(5.9)	1.27	(1.21-1.34)	1.28	(1.22-1.35)
current 1-19	396	(0.7)	298	(0.6)	1.35	(1.16-1.58)	1.36	(1.17-1.59)
current 20-39	91	(0.2)	105	(0.2)	0.88	(0.66-1.17)	0.90	(0.67-1.19)
current 40+	171	(0.3)	170	(0.3)	1.01	(0.82-1.25)	1.02	(0.82-1.27)
past	3,310	(6.1)	2,627	(4.9)	1.30	(1.23-1.37)	1.30	(1.23-1.38)
Use of atenolol	3,803	(7.1)	3,898	(7.2)	0.99	(0.94-1.04)	0.95	(0.90-1.01)
current 1-19	572	(1.1)	672	(1.3)	0.86	(0.77-0.96)	0.83	(0.74-0.94)
current 20-39	475	(0.9)	573	(1.1)	0.84	(0.74-0.95)	0.80	(0.70-0.90)
current 40+	853	(1.6)	1010	(1.9)	0.85	(0.78-0.94)	0.82	(0.74-0.91)
past	1,903	(3.5)	1,643	(3.1)	1.18	(1.10-1.26)	1.14	(1.06-1.23)
Use of bisoprolol	510	(1.0)	539	(1.0)	0.96	(0.85-1.09)	0.94	(0.83-1.07)
current 1-19	113	(0.2)	133	(0.3)	0.85	(0.67-1.10)	0.85	(0.66-1.10)
current 20-39	79	(0.2)	90	(0.2)	0.88	(0.65-1.20)	0.88	(0.64-1.20)
current 40+	133	(0.3)	170	(0.3)	0.79	(0.62-0.99)	0.76	(0.60-0.96)
past	185	(0.3)	146	(0.3)	1.29	(1.04-1.61)	1.27	(1.01-1.58)
Use of other BB	696	(1.3)	682	(1.3)	1.04	(0.93-1.15)	1.00	(0.90-1.12)

Abbreviations: BB, β-blocker; CI, confidence interval; OR, odds ratio.

Percentages are rounded to the nearest decimal.

* adjusted for smoking, body mass index, alcohol consumption, other analyzed antihypertensives, drug classes in combined products

Table 3.6-4: Exposure to DH and non-DH CCBs stratified by timing and duration of drug exposure in rosacea cases and controls.

	Rosacea cases, No (%) (n=53,927)		Rosacea-free controls, No (%) (n=53,927)		OR crude	(95% CI)	OR adj.*	(95% CI)
No CCB	49,511	(91.8)	49,487	(91.8)	1.00	(ref.)	1.00	(ref.)
Use of DH	3,598	(6.7)	3,623	(6.7)	0.99	(0.94-1.04)	0.94	(0.89-1.00)
current 1-19	844	(1.6)	865	(1.6)	0.97	(0.88-1.07)	0.92	(0.82-1.01)
current 20-39	526	(1.0)	583	(1.1)	0.90	(0.80-1.01)	0.85	(0.75-0.96)
current 40+	693	(1.3)	847	(1.6)	0.81	(0.73-0.90)	0.77	(0.69-0.86)
past	1,535	(2.9)	1,328	(2.5)	1.15	(1.07-1.25)	1.11	(1.02-1.20)
Use of non-DH	818	(1.5)	817	(1.5)	1.00	(0.91-1.10)	0.97	(0.88-1.00)
current 1-19	140	(0.3)	143	(0.3)	0.98	(0.77-1.23)	0.97	(0.76-1.23)
current 20-39	108	(0.2)	130	(0.2)	0.82	(0.64-1.06)	0.77	(0.60-1.00)
current 40+	223	(0.4)	211	(0.4)	1.05	(0.87-1.27)	1.04	(0.86-1.27)
past	347	(0.6)	333	(0.6)	1.04	(0.89-1.21)	1.01	(0.86-1.17)

Abbreviations: CCB, calcium channel blocker; CI, confidence interval; DH, dihydropyridine; non-DH, non-dihydropyridine; OR, odds ratio.

Percentages are rounded to the nearest decimal.

* adjusted for smoking, body mass index, alcohol consumption, other analyzed antihypertensives, drug classes in combined products.

3.6.5 Discussion

The findings of this large observational case-control study do not support the current perception that CCBs trigger rosacea, a hypothesis which is based on a weak body of evidence mainly based on the fact that CCBs can trigger flushing reactions.[47] There was no material class effect of BBs, which are suggested as off-label treatment for erythematotelangiectatic rosacea.[2, 47, 59] Interestingly, atenolol and bisoprolol, for which no previous data were available, were associated with slightly decreased ORs, whereas propranolol, for which a beneficial effect on rosacea has been postulated,[68] was not associated with a decreased risk. Nor was there an association between either ACEIs nor ARBs and the risk of rosacea.

Natale et al.[67] previously reported a rosacea or pre-rosacea diagnosis in more than half of 62 patients following cessation of antihypertensive CCB treatment due to flushing side effects. In contrast to these results, we observed ORs of around 1.0 in current users of dihydropyridine CCBs, and even a slightly but statistically significantly decreased OR in current long-term users. Natale et al. did not provide their diagnostic criteria for either rosacea or pre-rosacea, and the proportion of diagnosed pre-rosacea vs. rosacea is not known. The adverse effects leading to CCB treatment cessation - i.e. flushing, peripheral edema, and tachycardia - suggest that most patients received their diagnosis based on flushing reactions and were thus likely diagnosed with pre-rosacea, which is not a well-defined diagnosis.[2, 48] It has previously been reported that many patients with flushing symptoms alone actually never develop rosacea.[47] These factors make a comparison between the previous study and ours difficult. A certain degree of confounding by indication cannot be ruled out within our study, as patients with a rosacea diagnosis might have had facial symptoms before the actual date of the first-time diagnosis, preventing GPs from prescribing CCBs to these patients. However, such confounding by indication would likely be strongest in short-term CCB users, as a time lag of several years between a first diagnostic suspicion and an actual rosacea diagnosis is rare. However, the fact that we observed the lowest OR in patients with long-term CCB exposure makes substantial confounding by indication unlikely. Thus, our results, which are based on a large study population from a well validated database, do not suggest a material association between use of dihydropyridine CCBs or non-dihydropyridine CCBs and the risk of developing rosacea. Based on these data we cannot determine whether the slightly decreased OR in current long-term users of dihydropyridine CCBs

represents a true effect, as the effect size is small and residual confounding and chance cannot be ruled out. We were not able to assess whether use of CCBs aggravates pre-existing rosacea with this study design.

Although BBs as a drug class have been recommended as an off-label treatment for erythematotelangiectatic rosacea,[2, 47, 59] we observed only marginally decreased ORs for current use of atenolol and bisoprolol. Propranolol, for which a beneficial effect on rosacea-associated flushing symptoms has been proposed,[68] yielded ORs of around unity across all strata. Two further small studies postulated a beneficial effect of carvedilol and nadolol on rosacea,[69, 166, 167] but no evidence was found on the effect of atenolol or bisoprolol. Interestingly, all previously reported allegedly beneficial effects of BBs involved non-cardio-selective BBs, whereas the only non-selective BBs within our study population (i.e. propranolol) yielded a null-result across all strata, while atenolol and bisoprolol, both cardio-selective BBs, revealed slightly decreased ORs.[176] We cannot rule out a certain degree of confounding by heterogeneity of BB subgroups, as propranolol holds a wider range of indications than each of the other substances (i.e. migraine prophylaxis, prophylaxis of variceal bleeding in portal hypertension, anxiety symptoms[177]), which has to be considered when interpreting our findings. The observed effect for current use of atenolol or bisoprolol was only small, but this effect might be somewhat diluted by the presence of papulopustular rosacea patients within our study population. The GPRD's Read codes do not allow a differentiation between papulopustular and erythematotelangiectatic rosacea, but previous results showed that papulopustular rosacea is overrepresented among diagnosed rosacea patients when compared to rosacea patients not seeking medical help.[159] Since the proposed beneficial effect of BBs has been hypothesised for the erythematotelangiectatic rosacea subtype exclusively, the effect found in this study may be stronger in an analysis restricted to this sub-group of patients. As in the case of CCBs, we cannot evaluate the potential effect of BBs on the course of pre-existing rosacea as this lies beyond the scope of our case-control study design. Thus, our results may partially support the recommendation of BBs as a possible rosacea treatment, but it remains to be clarified whether this effect differs between BB-substances. ACEIs and ARBs were not associated with the risk of incident rosacea.

This observational study is by far the largest of its kind and is based on a high quality, extensively validated, large primary-care database, which ensures a virtually

complete drug prescription history.[99] Nevertheless, several limitations have to be considered when interpreting our findings. First, we may have missed some rosacea patients, as patients with mild rosacea may not seek medical help.[159] Despite this potential under-diagnosing a 74% concordance of rosacea diagnoses between dermatologists and the referring GPs has been shown in a cross-sectional study from South-East Scotland,[111] providing reassurance that the validity of rosacea diagnoses in the GPRD is sufficient. Second, the likelihood of being diagnosed with rosacea may increase with increasing medical attention, which is the case for patients with cardiovascular medication. We previously showed that rosacea patients tended to see the GP more often prior to the diagnosis than controls.[46] Thus, a certain degree of diagnostic bias, masking a beneficial effect of a drug by skewing an OR toward 1.0, cannot be ruled out. Finally, we could not control for ethnical background, skin pigmentation, socioeconomic status (e.g. income, education), or life-style factors such as sun exposure, profession, or nutrition, as these parameters are not recorded in the GPRD. Despite these limitations, this is, to our knowledge, by far the largest study to assess the impact of various antihypertensive drugs on rosacea, an issue that has been discussed over decades based on a weak body of evidence.

In summary, our data contradict the prevailing impression that CCB use increases the risk of rosacea, a hypothesis that arose based on the fact that CCBs can induce flushing reactions.[47, 168] BBs, which are recommended as an off-label treatment for erythematotelangiectatic rosacea, were associated with slightly reduced risks, but only for atenolol and bisoprolol and not for propranolol. This effect might be stronger in patients with erythematotelangiectatic rosacea, as papulopustular rosacea is over-represented among diagnosed rosacea patients, possibly diluting an effect of unclear size of BBs in our study population.[159]

Chapter 4

Discussion and outlook

4 Discussion and outlook

4.1 Discussion

Although the understanding of rosacea has advanced over the past years, the skin disease remains a neglected area of research, haunted by an abundance of equivocal etiologic and pathomechanistic hypotheses.[48, 52, 53] Furthermore, epidemiologic research in the field of dermatology is scarce.[36] Therefore, this thesis aimed at contributing to the general understanding of rosacea by means of a comprehensive observational case-control study, using data from the GPRD,[b] a large and well-established physician-based primary care database from the UK.

Although pharmacoepidemiologic research originally focused on the field of post-marketing drug surveillance of rare ADEs, increasingly complex drug safety requirements augmented its importance across all stages of drug development. Pharmacoepidemiologic studies are applied in the assessment of disease burden (incidence, prevalence data), in the evaluation of previously undiscovered drug effects, in the analysis of drug utilization in clinical practice, and also to some degree in comparative effectiveness research.[3, 4, 6, 19] This rosacea project exemplifies the versatile applicability of pharmacoepidemiologic research covering three areas of focus; 1) the first part of the project (Study 3.1) describes demographics and characteristics of patients with rosacea in the UK, including first-ever IRs of rosacea. 2) Another part of the work brings the area of drugs as potential risk or protective factors for rosacea into focus, an area of rosacea research that has not received much attention in the past. 3) A further part of the study is concerned with the association of certain pre-existing co-morbidities and incident rosacea; again a largely unexplored field.

While some of the addressed research questions depict revisited hypotheses, others were newly raised. Table 4.1-1 schematically displays the six thematically ordered studies of this project with their objectives, main findings, research area, and the degree of novelty of the hypothesis.

[b] *Although the GPRD has been transferred into the CPRD in April 2012, the database is referred to as the GPRD throughout this thesis, as data collection was completed before the transfer.*

Table 4.1-1: Schematic description and classification of the six observational studies on rosacea presented within this thesis

Objectives	Main findings	Research area	Hypothesis	
			Revisited	*New*
Study 3.1 • *To describe demographics and characteristics of the study population, including ocular rosacea* • *To calculate first-ever IRs of rosacea.* • *To evaluate the impact of lifestyle factors on incident rosacea.*	• Overall IR of diagnosed rosacea in the UK: 1.65/1,000 py.	Disease burden		x
	• Significantly reduced rosacea risk in current smokers.	Lifestyle risk factor	x	
	• Marginal risk increase with alcohol consumption.	Lifestyle risk factor	x	
	• 20.8% of patients with pre-existing ocular symptoms at rosacea diagnosis.	Disease burden	x	
Study 3.2 • *To assess the association of migraine and incident rosacea.* • *To evaluate the impact of triptan use on the risk of developing rosacea.*	• No overall association of migraine and incident rosacea.	Associated disease	x	
	• Postmenopausal female migraine patients may be at a slightly increased rosacea risk.	Associated disease	x	
	• No impact of triptans on the risk of incident rosacea.	Non-established drug effect		x
Study 3.3 • *To analyze a potential protective effect of spironolactone on incident rosacea.* • *To analyze the effect of other diuretics on rosacea*	• Significantly reduced odds ratios under spironolactone.	Non-established drug effect	x	
	• Other diuretics were not associated with an altered rosacea risk.	Non-established drug effect		x
Study 3.4 • *To assess a potential association between DM and antidiabetic drugs (insulin or OADs) and incident rosacea.*	• Significantly reduced rosacea risk in diabetics at an advanced disease stage.	Associated disease		x
	• Unclear whether insulin enhances this effect.	Non-established drug effect		x
	• No effect of OADs on incident rosacea.	Non-established drug effect		x
Study 3.5 • *To evaluate the risk of developing rosacea in patients with depression, other affective disorders, or schizophrenia.* • *To analyze the role of psychotropic drugs in the risk of being diagnosed with rosacea.*	• No association between depression / other affective disorders and incident rosacea.	Associated disease		x
	• Decreased rosacea risk in patients with diagnosed schizophrenia?	Associated disease		x
	• Significantly decreased risk for rosacea during lithium exposure.	Non-established drug effect		x
Study 3.6 • *To analyze the role of antihypertensive drugs (BBs, CCBs, ACEIs, ARBs) in the risk of developing rosacea.*	• Rosacea risk not increased during CCB exposure.	Non-established drug effect	x	
	• Slightly decreased rosacea risk during BB use.	Non-established drug effect	x	
	• No association between ACEIs / ARBs and incident rosacea.	Non-established drug effect		x

Abbreviations: ACEI, ACE inhibitor; ARB, angiotensin receptor blocker; BB, β-blocker; CCB, calcium channel blocker; DM, diabetes mellitus; IR, incidence rate; OAD, oral antidiabetic drug; py, person-year.

The main findings, as well as a detailed evaluation of the results of the individual studies, are presented in the discussion section of the respective studies. In the following, the most intriguing findings and some general aspects are highlighted and discussed.

4.1.1 Study 3.1

A study on the epidemiology of rosacea in the UK.[46]

- The first-ever overall IR of rosacea was 1.65 / 1,000 py within the UK. This IR is confined to diagnosed rosacea patients, and cannot be arbitrarily extrapolated across geographic regions.
- Ocular symptoms were recorded in 20.8% of rosacea patients at the time of their first-time facial rosacea diagnosis.
- Current smokers revealed a significantly reduced rosacea risk (OR 0.64, 95% CI 0.62-0.67). This effect might be due to vasoconstricting and/or immunosuppressive effects of cigarette smoke and needs further investigation.
- The age-old misconception that rosacea was associated with an excessive drinking behavior was not supported; alcohol consumption was only associated with a marginal risk increase.

Study 3.1 is the basis of this rosacea project, describing the study population in terms of demographics and characteristics, including ocular symptoms that presented before the actual diagnosis of facial rosacea. Results are discussed in detail in the discussion section of Study 3.1. It is in the nature of the disease that epidemiologic results for rosacea cannot be extrapolated onto any other given population, as disease susceptibility varies across geographic regions, i.e. with the degree of skin pigmentation as well as with the degree of sun exposure.[44, 47] Thus, this study has to be regarded as an important entity within this project, conveying important information about the disease burden of rosacea within the UK. However, caution has to be applied when results are applied to other populations.

4.1.2 Study 3.2

Migraine, triptans, and the risk of developing rosacea.[178]

- In contrast to previous literature, incident rosacea was not overall associated with pre-existing migraine. However, the data do not allow inferences on rosacea as a triggering factor for migraine.
- Female migraine patients aged 50 years or older revealed slightly increased ORs, which is in line with one previous observational study from the 1980's.
- Although mechanistically conceivable, triptans did not exert an effect on the risk of developing rosacea. However, they might depict a proxy for migraine severity, suggesting a slightly increasing rosacea risk with increasing migraine severity.

Over the last decades, several studies reported an increased prevalence of migraine in patients with rosacea, albeit with inconsistent findings ranging from an overall association of the two diseases to an association confined to postmenopausal women.[41, 62, 63, 115] All of them applied a cross-sectional study design, which does not account for the chronologic manifestation of the variables of interest (i.e. migraine and rosacea), and is thus mainly useful in raising new hypotheses.[17] Study 3.2 aimed at assessing the association between pre-existing migraine and incident rosacea in a case-control analysis using the largest study population ever to address the association of the two diseases. Results do not indicate an increased risk of incident rosacea in migraine patients overall, but a slightly increased rosacea risk in postmenopausal females may exist.[185] Data do not allow an inference on whether or not pre-existing rosacea changes susceptibility to migraine. Thus, it remains to be clarified, whether the previously reported general association between migraine and rosacea was a spurious finding or whether rosacea favors the development of migraine.

One of the main drawbacks of large electronic health databases in the use of pharmacoepidemiologic research came into effect within this study, which is the failure to adequately capture time-varying factors such as disease progress or disease severity.[4] In this case of migraine. Triptans have been suggested as a proxy for disease severity in previous studies,[130] and are likely to be a good compromise to

infer upon migraine severity. However, as we were not able to entirely disentangle the drug effect from the disease effect by the given means, a final conclusion on this question will have to be achieved using another research approach.

4.1.3 Study 3.3

Spironolactone may reduce the risk of incident rosacea.[186]

- Current spironolactone exposure seemed to protect patients from developing rosacea across genders (OR 0.38, 95% CI 0.25-0.57, women / OR 0.41, 95 % CI 0.23-0.74, men). Although preventive effects were assessed in this study, this result justifies therapeutic off-label use of spironolactone in rosacea to some degree, as current drug use yielded the greatest effects.
- No other diuretic drug class had an impact on the risk of developing rosacea.

Bias and confounding can be a bottleneck in observational database research. If the drug under study has been associated with the outcome of interest beforehand, case patients might actually have received the drug to treat the disease under study before the diagnosis was recorded, causing ORs to be artificially increased.[3, 13, 17] In a sensitivity analysis, we accounted for confounding by indication in patients with previously recorded differential diagnoses, for which spironolactone is also used (i.e. acne, hirsutism, alopecia, seborrhea). However, we could not account for the fact that spironolactone has been suggested as an off-label rosacea treatment over several years. The significantly decreased ORs in current spironolactone users are thus all the more remarkable;[47, 59] If such bias was to play a role in these results, the rosacea risk would be even lower in the general population.

The common gender-unspecific recommendation for the use of spironolactone in the treatment of rosacea is attributed to its anti-androgenic properties, although a role of sex hormones in the skin disease could never be established.[47, 58] In contrast, the only study showing a beneficial effect of spironolactone on rosacea included male patients only, and hypothesized a cytochrome-inhibition confined to male skin.[66] Our study revealed a highly likely strong effect of spironolactone on incident rosacea in women and men, and a similar therapeutic effect of the drug on pre-existing rosacea

is likely, since patients with current drug exposure yielded the most prominent effects.[179] Thus, after the use of spironolactone in rosacea had found its way into clinical practice despite inexistent evidence to back it up, our study provides evidence that supports clinicians in their daily decisions. Such evidence is required more than ever, since spironolactone may cause severe side-effects, such as hyperkalemia or endocrine disorders, and should not be arbitrarily used in the treatment of a rather benign skin disorder.[180] Experimental research is now needed for a concluding efficacy and safety assessment of oral spironolactone in the treatment of rosacea, or to follow up on a potential topical application of the drug.

Today, rosacea is regarded as a mainly inflammatory skin disease. Most drugs that are used for rosacea therapy, such as metronidazole or tetracyclines, were originally used with a different intention (i.e. based on their antimicrobial effect), but are now known to be effective due to anti-inflammatory properties.[2] Recent evidence also indicates anti-inflammatory properties for spironolactone via blockage of the mineralocorticoid receptor.[142, 143] Another study observed that spironolactone stimulates the elastogenic effect, based on an as yet unclear mechanism.[181] It is thus thinkable that spironolactone joins other existing drugs in the group of anti-inflammatory drugs that were originally thought to act on the skin disease via a different mechanism. However, the conclusion on the underlying mechanism of the observed effect lies beyond the scope of an observational study, and will require further research.

4.1.4 Study 3.4

The risk of rosacea in patients with diabetes using insulin or oral antidiabetic drugs.[182]

- A decreased rosacea risk for patients with advanced DM was described for the first time.
- Poorly controlled hemoglobin $A1_c$ ($HbA1_c$) levels and the approximate disease duration correlated with the disease risk, yielding ORs around 0.6 in patients with a diabetes history of ≥10 years and / or $HbA1_c$ levels of ≥11%.
- Use of insulin might additionally decrease the rosacea risk, but it might also depict a proxy for DM severity. OADs did not affect the risk estimate.

Study 3.4 introduces an entirely novel aspect to the field of rosacea research, demonstrating that observational research merits acknowledgment in the field of exploratory research. The hypothesis behind this study is based on the idea that a recently highlighted vasodilatory key component in the pathomechanism of rosacea[1, 56, 70] may be prevented by the increased microvascular vasoconstriction inherent to DM, especially upon insulin exposure at an advanced stage of the disease.[71, 118] Admittedly, this is a rather vague hypothesis that does not fathom the pathomechanism of the two diseases on a molecular level. However, it is not uncommon that the exact biologic rationale behind an observation in epidemiology can only be explained many years later. In JP Vandenbroucke's[17] *'hierarchy of study designs that give the best chances of discovery and of studying new explanations',* observational study designs using pre-recorded data are described among the most desirable approaches to investigate new exploratory hypotheses in terms of cost and timeliness, which is clearly exemplified here. Thus, we were able to go about the evaluation of this question because the data was there, ready to be analyzed, and although such an observational study does not allow causal inference on the association of rosacea and diabetes, our study retrieved intriguing results, which will hopefully spark further research leading to future insights into the molecular mechanism of the observed association. In the case of insulin, it was impossible to entirely disentangle a potential drug effect from the effect of the underlying disease, but a hint towards an additional insulin effect on the risk of incident rosacea should be followed up in further research. Furthermore, it would be interesting to investigate a potential insulin effect on rosacea skin of non-diabetic patients, but to find an ethically acceptable study design for this might be challenging.

4.1.5 Study 3.5

The association between psychiatric diseases, psychotropic drugs, and the risk of incident rosacea.

- In answer to the prevailing controversy on a psychogenic origin of rosacea, depression and other affective disorders were found not to be associated with an increased risk of developing rosacea.

- On the other hand, patients with schizophrenia were at a decreased rosacea risk (OR 0.78, 95% CI 0.65-0.92), independent of underlying lithium use. This is an intriguing, previously unreported finding, which requires further investigation.
- Among all psychotropic drugs, chronic lithium exposure yielded a materially decreased risk of rosacea (OR 0.58, 95% CI 0.38-0.88), irrespective of the underlying diagnosis.

Precedent studies, such as the study conducted by the BCDSP in 1974[183, 184] about the effect of regular aspirin intake on the risk of myocardial infarction, taught us about the value of epidemiologic studies in the identification of new drug indications. Not only do we learn about a potential new treatment option for a certain disease, but such newly discovered associations can also reveal insights into potential pathologic mechanisms.[185]

Study 3.5 revealed intriguing results suggesting a significantly reduced rosacea risk during oral lithium exposure. Although the number of lithium users was proportionally small, the study was equipped with enough statistical power to detect these results, owing to the large size of the study population. The risk for confounding by indication is one of the most frequently denounced feature of pharmacoepidemiologic studies, since it is hard to control for if an association between a drug and an outcome has previously been described.[13, 19] In the case of lithium, such bias can be assumed to be minimal, since rosacea and oral lithium have never been associated.[17] Thus our study delivers highly relevant results, which could not have been achieved in experimental research, as exposure to a drug with such a narrow therapeutic window in an attempt to cure a rather benign skin disease would simply be unethical.[148] Although this study assessed the preventive effect of lithium on rosacea, a therapeutic effect of lithium on pre-existing rosacea seems likely, as the effect was most prominent during current exposure to the drug. However, due to the mentioned hazardous profile of oral lithium, this drug is an unfavorable approach for rosacea therapy. Nevertheless, follow-up projects on this finding may provide important insight in the pathomechanism of the skin disease, or may lead the way into new therapeutic options for rosacea.

4.1.6 Study 3.6

Antihypertensive drugs and the risk of incident rosacea.

- Results contradict the prevailing notion of an increased rosacea risk during CCB treatment, but they do not allow inference upon whether or not CCBs aggravate pre-existing rosacea.
- BBs, which have been suggested as an off-label treatment for ETR, were associated with a slightly decreased rosacea risk. The real effect is likely to be stronger in ETR patients only, as PPR is probably overrepresented in the GPRD.
- Neither ACEIs nor ARBs blockers affected the risk of rosacea.

The prevailing literature on rosacea consistently advises to abstain from CCBs in rosacea patients,[47, 59] whereas BBs are suggested as an off-label rosacea treatment,[2, 47, 59] both based on very scarce evidence.[67, 68, 184] Within Study 3.6, we could not confirm the postulated increased rosacea risk during CCB exposure, and even observed slightly decreased ORs in long-term users of dihydropyridine CCBs. This emphasizes the need for re-evaluation of insufficiently backed up hypotheses, even if they have already found their way into clinical practice. On the other hand, BBs revealed a slightly decreased rosacea risk, which would likely have been stronger had we been able to distinguish between PPR and ETR.

Considering the entire rosacea project, the inability to distinguish between ETR and PPR is most unfavorable in the case of this study (3.6). The association between BBs as well as CCBs and rosacea refers to a link via an altered flushing susceptibility upon drug intake. Per definition, flushing is mainly associated with ETR,[47, 59] whereas an overrepresentation of PPR of unknown proportion can be assumed among diagnosed rosacea patients, and thus on the GPRD.[159] However, a recent cross-sectional study showed that although more frequent in ETR, flushing was also present in 56% of PPR patients.[45] In the case of CCBs, it is unlikely that distortion of findings alone accounts for the results, since missing information would skew the OR towards 1.0 but would not cause decreased ORs in long-term users of dihydropyridine CCBs. However, for BBs we can only conclude a trend towards a beneficial effect of the drug class on the risk of developing rosacea, which will

hopefully trigger further investigation in this area of research. An actual reliable effect of BBs in ETR patients, which would be most valuable to clinicians in daily practice, could unfortunately not be displayed. This is a classical limitation of a database study employing pre-collected electronic data.[4] However, in consideration of the existing situation, in which clinicians are more or less left alone to manage refractory rosacea using trial and error, evidence to support clinicians' decisions on the use or non-use of important drugs, such as antihypertensives, is of great importance. Thus, the results of this study remain highly relevant.[59]

4.2 Limitations of the rosacea project

4.2.1 Incident rosacea and validation of the diagnosis

Rosacea has not been studied on the GPRD before, and validity of recorded rosacea diagnoses has thus never been assessed. Disease misclassification can be an issue in observational research, and the optimal measures to validate a recorded diagnosis on a database have to be defined individually based on a profound understanding of the database as well as of the disease under study. The validation of rosacea diagnoses on the GPRD, including challenges faced along the way, is discussed in detail in Study 3.1.[46] Rosacea is mainly diagnosed by the GP (7.3% referred to a dermatologist), based on its clinical picture alone. Therefore, most usual options to validate a recorded disease on the GPRD did not apply (i.e. sending for referral letters, hospital discharge letters, or questionnaires to GPs). However, a more or less contemporary cross-sectional study from South-East Scotland revealed a concordance of rosacea diagnoses of dermatologists and the referring GPs of 74%, implicating a rather high overall recording validity of rosacea on the GPRD.[111] Needless to say, an algorhythm including diagnostic and laboratory data would improve the confidence in the validity of rosacea diagnoses on the database, however this was not an option. The results from the cross-sectional study mentioned, combined with a demographic distribution of the study population that is congruent with previous studies, allowed us to assume a sufficient validity of rosacea diagnoses on the GPRD. After all, epidemiology is an approximate science by nature, and intractable uncertainties have to be discussed when interpreting study findings, such as a certain overlap of acne and rosacea diagnoses in the case of this project.[46]

The study population of this rosacea project consists of patients with an incident diagnosis for facial rosacea (i.e. ETR or PPR, not those with rhinophyma or ocular rosacea only), with at least three years of rosacea-free active history prior to their first rosacea diagnosis. However, as rosacea develops over years, presenting with usually mild (flushing)-symptoms at early stages, which might not prompt patients to seek medical help,[47, 76] we cannot entirely rule out that the disease has not actually existed in a mild stage before the date of the first diagnosis in some cases. In general, chronic diseases are gaining importance in pharmacoepidemiologic

research, and defining the onset of such chronic states imposes a general challenge in database studies, which has to be addressed when discussing the study findings.

4.2.2 Rosacea sub-type and disease severity

A major limitation of this rosacea project is the fact that the GPRD Read-coding system does not allow distinguishing between ETR and PPR. The two rosacea sub-types differ with regard to their symptoms and morphologic characteristics of skin lesions and thus, also in their treatment options and differential diagnoses.[47] A developmental march from one sub-type to another may be possible but has not been confirmed to date, and much has been speculated about potential differences in the basic pathology of the individual sub-types.[45, 48, 53] Recent gene profiling of rosacea sub-types revealed an overlap of the genetic structure between sub-types, but also suggested potential variations with regard to molecular pathways.[1] ETR is probably the most frequent rosacea sub-type in the general population,[41, 45, 47] but there is reason to assume an altered frequency distribution among diagnosed rosacea patients, probably resulting in an overrepresentation of PPR of an unknown proportion on the GPRD.[159] While PPR has a prominent inflammatory component, flushing and erythema are the prominent features in ETR.[2, 47] Most drugs on the market (e.g. metronidazole, tetracyclines) act on the inflammatory part of rosacea, and are mainly effective in PPR. It is possible, although not proven, that spironolactone and lithium act on the inflammatory part of rosacea and that the strong effect for these drugs shown in Studies 3.3 and 3.6 is due to a majority of PPR patients within our study population.[179] On the other hand, the use of BBs in rosacea patients is mainly attributed to their flushing-preventive action, and CCBs have been contraindicated in patients with rosacea as they may trigger flushing. The potential underrepresentation of ETR patients on the GPRD could have diminished the effect of these drugs on the skin disease.[2] The inability to account for such differences leaves somewhat of a grey area within the interpretation of the results of this project, and clearly demonstrates a typical limitation in observational studies using pre-collected data. This issue of missing information is discussed extensively in the respective studies, whenever it is assumed to play a role.

Furthermore, the GPRD coding system does not adequately capture time-trends, such as disease severity, which can introduce channeling bias into a study. At times,

disease severity can be accounted for by means of recorded treatment or diagnostic results, but lacking treatment or diagnostic guidelines for rosacea combined with inexistent confirmatory histologic or laboratory tests made this impossible within this study.[48] However, standardized grading of the skin disease does not seem to be routinely performed in daily clinical practice (inexistent official grading system), which is why an analysis on arbitrary severity levels of the skin disease using GPRD data would be of little value either way.[49] Capturing patients at the time when the disease is first brought to medical attention is a good and practical approximation in capturing patients with rosacea at a similar stage of disease; i.e. when it first prompted patients to seek medical help.

After taking into account the discussed limitations, the achieved results remain meaningful, providing strong evidence on a yet neglected field of research, using data from one of the largest health databases in use.

4.3 Strengths and limitations of database research

In database research, a profound understanding of the database in use is of utmost importance in order to adequately decide upon a study's feasibility and limitations.
Electronic health databases generally allow analyzing of hypotheses within large populations over a long period of time, in an efficient manner. Owing to the large size of the GPRD[c] (approx. 8% of UK population, seven million active patients) rare exposures, such as spironolactone (Study 3.3) or oral lithium (Study 3.6) were able to be studied with enough statistical power within this rosacea project. Furthermore, the results achieved within this rosacea project by means of GPRD data may be referred to as population-based, since the database is generally representative of the underlying UK-population. This is not possible in the case where a database holds an overrepresentation of a certain social class in terms of socioeconomic status, race, or education. This is the case for most existing claims databases. Additionally, the GPRD offers the opportunity to obtain anonymous photocopies of patients' paper medical records, or to send out questionnaires to the GPs asking them for additional patient information,[187] which, however, was not applicable within this project, as rosacea is a GP-diagnosed disease lacking confirmatory laboratory or histologic parameters; needless to say, it is also not usually a reason for hospitalization or death.[4]

The lack of randomization makes observational studies prone to bias and confounding; while some types of bias are more pronounced in database research, others are negligible. O*bservation bias,* which results from systematic differences in data collection between study groups, as well as *recall bias* (i.e. a patients' recall upon exposure) or *interviewer bias* (i.e. systematically different data recording on behalf of the interviewer) are minimized in database research, since data is captured as a by-product of daily clinical or administrative practice, irrespective of any study question.[4] Other types of bias, such as *selection bias* (differing enrolment criteria between cases and controls), *misclassification bias*, or *confounding* (especially residual confounding) can be of concern. In GPRD studies, however, selection bias

[c] *Although the GPRD has been transferred into the CPRD in April 2012, the database is referred to as the GPRD throughout this thesis, as data collection was completed before the transfer.*

can mostly be averted, as the database allows withdrawing of cases and controls from the same defined source population.

Missing data imposes another limitation upon database research. Data on important confounders such as dietary or exercise habits, socioeconomic status, race, or profession are incompletely captured on most electronic databases. In the case of rosacea, more comprehensive information on nutrition, sun exposure, skin pigmentation, or socioeconomic factors could have minimized residual confounding. Patients whose occupation or lifestyle involves extensive sun exposure may experience chronic actinic damage, which may be misdiagnosed as rosacea on the GPRD.[51, 85] Furthermore, fair-skinned people of Celtic origin are generally more susceptible to the skin disease than darker pigmented people.[44, 47, 48] Patients' race may be recorded on the GPRD, but until now the coverage of such information on the database is low. Also, certain foodstuff or beverages are commonly known as exacerbating factors of rosacea, and it would have been interesting to assess whether such aliments also increase the risk of actually developing the skin disease. Other lifestyle factors, such as smoking, BMI, or alcohol consumption are not recorded for all patients, and results of strata with missing data have to be interpreted cautiously.[4, 187] With regard to medication, information on over-the-counter (OTC) drugs, as well as on patients' compliance is lacking. Furthermore, in case of the GPRD, the tedious and time-consuming manual entry of information from specialists, in-hospital events, and laboratory tests may cause practices to only enter information that will affect the future care of the patient, such as abnormal test results. This however, does not affect GPRD-research on rosacea, as laboratory parameters or hospitalization data rarely apply to rosacea patients. For studies 3.1-3.6 different types of bias and confounding are discussed in the discussion sections of the respective manuscripts.

4.4 Outlook

In rosacea research, few questions have been sufficiently answered, while many more remain uninvestigated. This comprehensive rosacea project contributes to the general understanding of this under-investigated disease, revealing some intriguing and partly unreported findings. However, at the same time it has raised various new hypotheses that require further research and reproduction in studies using different study populations. Options using GPRD data have, for the most part, been exhausted within this project. Observational screening studies inquiring about previous drug use would allow follow-up investigations on the association of BBs or CCBs and the skin disease including a differentiation between PPR and ETR. Such a study design to assess different sub-types within the clinical picture of rosacea has recently been published, however drug exposure was not captured.[45] An RCT would be the optimal means to assess the efficacy of oral or topical spironolactone in the treatment of rosacea. Although RCTs are expensive, in this case it has the potential to lead to a new treatment for the skin disease, which is a declared need in clinical practice.[2] An observational cohort study could assess whether rosacea patients develop more migraine, whereas further observational studies of different designs should aim to reproduce the association between rosacea and schizophrenia, DM, and cigarette smoking, since these associations are insufficiently documented in previous literature.[17] Moreover, the observed reduced rosacea risk in current smokers and in patients with DM will hopefully trigger some basic investigations on the pathomechanistic aspects of these findings.

In April 2012 the GPRD was transferred into the Clinical Practice Research Datalink (CPRD), the new English National Health Service (NHS) observational data and interventional research service, jointly funded by the NHS National Institute for Health Research (NIHR) and the Medicines and Healthcare products Regulatory Agency (MHRA). This new research service is designed to maximize the population coverage as well as the data linkage to several datasets, such as disease registries, full mortality data, in-hospital and daycare drugs, mother-child linkage and many more.[188] Although this is a favorable development, it does not provide additional opportunities with regards to rosacea research, as rosacea is mostly neither a reason for referral to secondary care nor death. As an exception, Hospital Episode Statistics (HES) are available for patients who have been hospitalized within the UK, providing more

accurate and complete information about a patient's ethnic background. This could be interesting for observational rosacea research on the CPRD in the future, as disease susceptibility is greater in fair-skinned people.[188]

The research on the genetic background of rosacea is still in its infancy.[1] Endeavors are being made, also within the CPRD, to link pharmacoepidemiologic data to the latest genetic techniques.[188] However, it remains to be explored to what extent database studies may be used to include such molecular investigations. It is conceivable that in the near or distant future, CPRD data could be used to study drug effects at the level of a patients' genetic profile.[4]

Chapter 5

References

5 References

1. Steinhoff M, Buddenkotte J, Aubert J et al. Clinical, cellular, and molecular aspects in the pathophysiology of rosacea. *J Investig Dermatol Symp Proc.* 2011;15(1):2-11.
2. Elewski BE, Draelos Z, Dreno B et al. Rosacea - global diversity and optimized outcome: proposed international consensus from the Rosacea International Expert Group. *J Eur Acad Dermatol Venereol.* 2011;25(2):188-200.
3. Jick H. Thirty years of experience of the Boston Collaborative Drug Surveillance Program in relation to principles and methods of drug safety research. Side Effects of Drugs Annual 21: Elsevier 1998:xix-xxvi.
4. Garbe E, Suissa S. Pharmacoepidemiology. In: Ahrens W, Pigeot I, eds. Handbook of Epidemiology. Berlin Heidelberg: Springer; 2005:1225-66.
5. Etminan M, Gill S, Fitzgerald M et al. Challenges and opportunities for pharmacoepidemiology in drug-therapy decision making. *J Clin Pharmacol.* 2006;46(1):6-9.
6. Eichler HG, Pignatti F, Flamion B et al. Balancing early market access to new drugs with the need for benefit/risk data: a mounting dilemma. *Nat Rev Drug Discov.* 2008;7(10):818-26.
7. Strom BL, Kimmel SE, Hennessy S eds. Pharmacoepidemiology. 5th ed. Chichester: Wiley-Blackwell; 2012.
8. CEBM. Centre for Evidence-based Medicine. Available from: http://www.cebm.net/ [Accessed 18 May 2013].
9. Harris RP, Helfand M, Woolf SH et al. Current methods of the US Preventive Services Task Force: a review of the process. *Am J Prev Med*. 2001;20(3 Suppl):21-35.
10. Rothman KJ. Epidemiology: An Introduction. New York: Oxford University Press Inc.; 2002. 15-20 p.

11. Shakir SA, Layton D. Causal association in pharmacovigilance and pharmacoepidemiology: thoughts on the application of the Austin Bradford-Hill criteria. *Drug Saf.* 2002;25(6):467-71.

12. Concato J, Shah N, Horwitz RI. Randomized, controlled trials, observational studies, and the hierarchy of research designs. *N Engl J Med.* 2000;342(25):1887-92.

13. McMahon AD, MacDonald TM. Design issues for drug epidemiology. *Br J Clin Pharmacol*. 2000;50(5):419-25.

14. Hernan MA, Alonso A, Logan R et al. Observational studies analyzed like randomized experiments: an application to postmenopausal hormone therapy and coronary heart disease. *Epidemiology*. 2008;19(6):766-79.

15. Danaei G, Tavakkoli M, Hernan MA. Bias in observational studies of prevalent users: lessons for comparative effectiveness research from a meta-analysis of statins. *Am J Epidemiol.* 2012;175(4):250-62.

16. Danaei G, Rodriguez LA, Cantero OF et al. Observational data for comparative effectiveness research: an emulation of randomised trials of statins and primary prevention of coronary heart disease. *Stat Methods Med Res.* 2013;22(1):70-96.

17. Vandenbroucke JP. Observational research, randomised trials, and two views of medical science. *PLoS Med.* 2008;5(3):e67.

18. Grimes DA, Schulz KF. An overview of clinical research: the lay of the land. *Lancet.* 2002;359(9300):57-61.

19. Jick H, Garcia Rodriguez LA, Perez-Gutthann S. Principles of epidemiological research on adverse and beneficial drug effects. *Lancet.* 1998;352(9142):1767-70.

20. Euser AM, Zoccali C, Jager KJ et al. Cohort studies: prospective versus retrospective. *Nephron Clin Pract.* 2009;113(3):c214-7.

21. Grimes DA, Schulz KF. Descriptove studies: what they can and cannot do. *Lancet.* 2002;359:145-149.

22. Hill AB. The Environment and Disease: Association or Causation? *Proc R Soc Med.* 1965;58:295-300.

23. Schulz KF, Grimes DA. Case-control studies: research in reverse. *Lancet.* 2002;359(9304):431-4.

24. Grimes DA, Schulz KF. Cohort studies: marching towards outcomes. *Lancet.* 2002;359(9303):341-5.

25. Mann CJ. Observational research methods. Research design II: cohort, cross sectional, and case-control studies. *Emerg Med J.* 2003;20(1):54-60.

26. Etminan M. Pharmacoepidemiology II: the nested case-control study--a novel approach in pharmacoepidemiologic research. *Pharmacotherapy.* 2004;24(9):1105-9.

27. Ernster VL. Nested case-control studies. *Prev Med.* 1994;23(5):587-90.

28. Schneeweiss S, Sturmer T, Maclure M. Case-crossover and case-time-control designs as alternatives in pharmacoepidemiologic research. *Pharmacoepidemiol Drug Saf.* 1997;6 Suppl 3:S51-9.

29. Wang SV, Gagne JJ, Glynn RJ et al. Case-crossover studies of therapeutics: design approaches to addressing time-varying prognosis in elderly populations. *Epidemiology.* 2013;24(3):375-8.

30. Wang S, Linkletter C, Maclure M et al. Future cases as present controls to adjust for exposure trend bias in case-only studies. *Epidemiology.* 2011;22(4):568-74.

31. Delgado-Rodríguez M, Llorca J. Bias. *J Epidemiol Community Health.* 2004;58(8):635-41.

32. Rothman KJ. Epidemiology: An Introduction. New York: Oxford University Press Inc.; 2002. 223 p.

33. Etminan M, Samii A. Pharmacoepidemiology I: a review of pharmacoepidemiologic study designs. *Pharmacotherapy.* 2004;24(8):964-9.

34. Horwitz RI, Feinstein AR. The problem of "protopathic bias" in case-control studies. *Am J Med.* 1980;68(2):255-8.

35. Salas M, Hofman A, Stricker BH. Confounding by indication: an example of variation in the use of epidemiologic terminology. *Am J Epidemiol.* 1999;149(11):981-3.

36. Pocock SJ, Collier TJ, Dandreo KJ, de Stavola BL, Goldman MB, Kalish LA, et al. Issues in the reporting of epidemiological studies: a survey of recent practice. *Br Med J.* 2004;329(7471):883.

37. Walker AM. Confounding by indication. *Epidemiology.* 1996;7(4):335-6.

38. Seeger JD, Kurth T, Walker AM. Use of propensity score technique to account for exposure-related covariates: an example and lesson. *Med Care.* 2007;45(10 Supl 2):S143-8.

39. Rolleston JD. A Note on the Early History of Rosacea. *Proc R Soc Med.* 1933;26(4):327-9.

40. de Bersaques Jean. Historical Notes on Rosacea. *Eur J Dermatol.* 1995(5):16-22.

41. Berg M, Liden S. An epidemiological study of rosacea. *Acta Derm Venereol.* 1989;69(5):419-23.

42. Schaefer I, Rustenbach SJ, Zimmer L et al. Prevalence of skin diseases in a cohort of 48,665 employees in Germany. *Dermatology.* 2008;217(2):169-72.

43. Abram K, Silm H, Oona M. Prevalence of rosacea in an estonian working population using a standard classification. *Acta Derm Venereol.* 2010;90(3):269-73.

44. Doe PT, Asiedu A, Acheampong JW et al. Skin diseases in Ghana and the UK. *Int J Dermatol.* 2001;40(5):323-6.

45. Tan J, Blume-Peytavi U, Ortonne JP et al. An observational cross-sectional survey of rosacea: Clinical associations and progression between subtypes. *Br J Dermatol.* 2013 April: Epub ahead of print.

46. Spoendlin J, Voegel JJ, Jick SS et al. A study on the epidemiology of rosacea in the U.K. *Br J Dermatol.* 2012;167(3):598-605.

47. Powell FC. Clinical practice. Rosacea. *N Engl J Med.* 2005;352(8):793-803.

48. Wilkin J, Dahl M, Detmar M et al. Standard classification of rosacea: Report of the National Rosacea Society Expert Committee on the Classification and Staging of Rosacea. *J Am Acad Dermatol.* 2002;46(4):584-7.

49. Wilkin J, Dahl M, Detmar M et al. Standard grading system for rosacea: report of the National Rosacea Society Expert Committee on the classification and staging of rosacea. *J Am Acad Dermatol*. 2004;50(6):907-12.

50. Lehmann P. Rosacea. Clinical features, pathogenesis and therapy. *Der Hautarzt.* 2009;9:871-885.

51. Odom R, Dahl M, Dover J et al. Standard management options for rosacea, part 1: overview and broad spectrum of care. *Cutis.* 2009;84(1):43-7.

52. van Zuuren EJ, Kramer S, Carter B et al. Interventions for rosacea. *Cochrane Database Syst Rev.* 2011(3):CD003262.

53. Bamford JT. Rosacea: current thoughts on origin. *Semin Cutan Med Surg.* 2001;20(3):199-206.

54. Puchalski Z. Psychosomatic aspects in patients with alopecia areata, rosacea und lichen ruber planus. *Z Hautkr.* 1983;58(22):1648-54.

55. Yamasaki K, Gallo RL. The molecular pathology of rosacea. *J Dermatol Sci.* 2009;55(2):77-81.

56. Schwab VD, Sulk M, Seeliger S et al. Neurovascular and neuroimmune aspects in the pathophysiology of rosacea. *J Investig Dermatol Symp Proc.* 2011;15(1):53-62.

57. Yamasaki K, Di Nardo A, Bardan A et al. Increased serine protease activity and cathelicidin promotes skin inflammation in rosacea. *Nat Med.* 2007;13(8):975-80.

58. Pelle MT, Crawford GH, James WD. Rosacea: II. Therapy. *J Am Acad Dermatol.* 2004;51(4):499-512.

59. Odom R, Dahl M, Dover J et al. Standard management options for rosacea, part 2: options according to subtype. *Cutis.* 2009;84(2):97-104.

60. MIMS (2012). Available from http://www.mims.co.uk/search/Drugs/phrase/rosacea/sortby/therapeutic%20area/field/indications/ [Accessed 2 June 2013].

61. Ramelet AA. Rosacea: a reaction pattern associated with ocular lesions and migraine? *Arch Dermatol.* 1994;130:1448.

62. Tan SG, Cunliffe WJ. Rosacea and migraine. *Br Med J*. 1976;1(6000):21.

63. Berg M, Liden S. Postmenopausal female rosacea patients are more disposed to react with migraine. *Dermatology.* 1996;193(1):73-4.

64. Karlsson E, Berg M, Arnetz BB. Rosacea and personality. *Acta Derm Venereol.* 2004;84(1):76-7.

65. Whitlock FA. Psychosomatic aspects of rosacea. *Br J Dermatol.* 1961;73:137-48.

66. Aizawa H, Niimura M. Oral spironolactone therapy in male patients with rosacea. *J Dermatol.* 1992;19(5):293-7.

67. Natale F, Cirillo C, Granato C et al. Worsening of rosacea in patients treated with dihydropyridine calcium channel blockers: a clinical observation. *Hypertens Res.* 2011;34(6):790-1.

68. Craige H, Cohen JB. Symptomatic treatment of idiopathic and rosacea-associated cutaneous flushing with propranolol. *J Am Acad Dermatol*. 2005;53(5):881-4.

69. Wilkin JK. Effect of nadolol on flushing reactions in rosacea. *J Am Acad Dermatol.* 1989;20(2 Pt 1):202-5.

70. Aubdool AA, Brain SD. Neurovascular aspects of skin neurogenic inflammation. *J Investig Dermatol Symp Proc.* 2011;15(1):33-9.

71. Ko SH, Cao W, Liu Z. Hypertension management and microvascular insulin resistance in diabetes. *Curr Hypertens Rep.*12(4):243-51.

72. Crawford GH, Pelle MT, James WD. Rosacea: I. Etiology, pathogenesis, and subtype classification. *J Am Acad Dermatol.* 2004;51(3):327-41.

73. Oltz M, Check J. Rosacea and its ocular manifestations. *Optometry.* 2011;82:92-103.

74. Langenbruch AK, Beket E, Augustin M. Quality of Health Care of Rosacea in Germany from the Patient's Perspective: Results of the National Health Care Study RosaReal 2009. *Dermatology.* 2011;223(2):124-30.

75. Aksoy B, Altaykan-Hapa A, Egemen D et al. The impact of rosacea on quality of life: effects of demographic and clinical characteristics and various treatment modalities. *Br J Dermatol.* 2011;163(4):719-25.

76. Katz AM. Rosacea: epidemiology and pathogenesis. *J Cutan Med Surg.* 1998;2 Suppl 4:S4-5-10.

77. Bae YI, Yun SJ, Lee JB et al. Clinical evaluation of 168 korean patients with rosacea: the sun exposure correlates with the erythematotelangiectatic subtype. *Ann Dermatol.* 2009;21(3):243-9.

78. Jansen T, Plewig G. Rosacea: classification and treatment. *J R Soc Med*. 1997;90(3):144-50.

79. Blount BW, Pelletier AL. Rosacea: a common, yet commonly overlooked, condition. *Am Fam Physician.* 2002;66(3):435-40.

80. Abram K, Silm H, Maaroos HI et al. Risk factors associated with rosacea. *J Eur Acad Dermatol Venereol.* 2010;24:565-71.

81. Bamford JT, Gessert CE, Renier CM et al. Childhood stye and adult rosacea. *J Am Acad Dermatol.* 2006;55(6):951-5.

82. Kyriakis KP, Palamaras I, Terzoudi S et al. Epidemiologic aspects of rosacea. *J Am Acad Dermatol.* 2005;53(5):918-9.

83. Augustin M, Herberger K, Hintzen S et al. Prevalence of skin lesions and need for treatment in a cohort of 90 880 workers. *Br J Dermatol.* 2011;165(4):865-73.

84. Lomholt G. Prevalence of Skin Diseases in a Population; a Census Study from the Faroe Islands. *Dan Med Bull.* 1964;11:1-7.

85. McAleer MA, Fitzpatrick P, Powell FC. Papulopustular rosacea: prevalence and relationship to photodamage. *J Am Acad Dermatol.* 2010;63(1):33-9.

86. Wilkin JK. Rosacea. *Int J Dermatol.* 1983;22(7):393-400.

87. Culp B, Scheinfeld N. Rosacea: A Review. *P T.* 2009;34(1):38-45.

88. Lazaridou E, Fotiadou C, Ziakas N et al. Clinical and laboratory study of ocular rosacea in northern Greece. *J Eur Acad Dermatol Venereol.* 2011;25:1428-31.

89. Michel JL, Cabibel F. Frequency, severity and treatment of ocular rosacea during cutaneous rosacea [Article in French]. *Ann Dermatol Venereol.* 2003;130(1 Pt 1):20-4.

90. Starr PA, Macdonald A. Oculocutaneous aspects of rosacea. *Proc R Soc Med.* 1969;62(1):9-11.

91. Ghanem VC, Mehra N, Wong S et al. The prevalence of ocular signs in acne rosacea: comparing patients from ophthalmology and dermatology clinics. *Cornea.* 2003;22(3):230-3.

92. Browning DJ, Proia AD. Ocular rosacea. *Surv Ophthalmol.* 1986;31(3):145-58.

93. Bakar O, Demircay Z, Toker E et al. Ocular signs, symptoms and tear function tests of papulopustular rosacea patients receiving azithromycin. *J Eur Acad Dermatol Venereol.* 2009;23(5):544-9.

94. Mills CM, Marks R. Environmental factors influencing rosacea. *Clin Exp Dermatol.* 1996;21(2):172-3.

95. Breton AL, Truchetet F, Veran Y et al. Prevalence analysis of smoking in rosacea. *J Eur Acad Dermatol Venereol.* 2010;25(9):1112-3.

96. Curnier A, Choudhary S. Rhinophyma: dispelling the myths. *Plast Reconstr Surg.* 2004;114(2):351-4.

97. Gupta MA, Gupta AK, Chen SJ et al. Comorbidity of rosacea and depression: an analysis of the National Ambulatory Medical Care Survey and National Hospital Ambulatory Care Survey--Outpatient Department data collected by the U.S. National Center for Health Statistics from 1995 to 2002. *Br J Dermatol.* 2005;153(6):1176-81.

98. Sobye P. Aetiology and pathogenesis of rosacea. *Acta Derm Venereol.* 1950;30(2):137-58.

99. Khan NF, Harrison SE, Rose PW. Validity of diagnostic coding within the General Practice Research Database: a systematic review. *Br J Gen Pract.* 2010;60(572):e128-36.

100. Jick SS, Kaye JA, Vasilakis-Scaramozza C et al. Validity of the general practice research database. *Pharmacotherapy.* 2003;23(5):686-9.

101. Wood L, Martinez C. The general practice research database: role in pharmacovigilance. *Drug Saf.* 2004;27(12):871-81.

102. Gibson GE, Codd MB, Murphy GM. Skin type distribution and skin disease in Ireland. *Ir J Med Sci.* 1997;166(2):72-4.

103. Sopori M. Effects of cigarette smoke on the immune system. *Nat Rev Immunol.* 2002;2(5):372-7.

104. Abraham N, Selby W, Lazarus R et al. Is smoking an indirect risk factor for the development of ulcerative colitis? An age- and sex-matched case-control study. *J Gastroenterol Hepatol.* 2003;18(2):139-46.

105. Edvinsson ML, Andersson SE, Xu CB et al. Cigarette smoking leads to reduced relaxant responses of the cutaneous microcirculation. *Vasc Health Risk Manag.* 2008;4(3):699-704.

106. Lewis JD, Brensinger C. Agreement between GPRD smoking data: a survey of general practitioners and a population-based survey. *Pharmacoepidemiol Drug Saf.* 2004;13(7):437-41.

107. Borrie P. Rosacea with special reference to its ocular manifestations. *Br J Dermatol.* 1953;65(12):458-63.

108. Chamaillard M, Mortemousque B, Boralevi F et al. Cutaneous and ocular signs of childhood rosacea. *Arch Dermatol.* 2008;144(2):167-71.

109. Gupta AK, Bluhm R, Cooper EA et al. Seborrheic dermatitis. *Dermatol Clin.* 2003;21(3):401-12.

110. Burton JL, Pye RJ, Meyrick G et al. The sebum excretion rate in rosacea. *Br J Dermatol.* 1975;92(5):541-3.

111. Holme SA, Scott-Lang VE, Ooi ET et al. The South-East Scotland Dermatology Workload Study: 30 years analysis. *Br J Dermatol.* 2012;167(1):123-30.

112. Loder E. Triptan therapy in migraine. *N Engl J Med.* 2010;363(1):63-70.

113. Linde M. Migraine: a review and future directions for treatment. *Acta Neurol Scand.* 2006;114(2):71-83.

114. Brennan KC, Charles A. An update on the blood vessel in migraine. *Curr Opin Neurol.* 2010;23(3):266-74.

115. Ramelet AA. Rosacea: a reaction pattern associated with ocular lesions and migraine? *Arch Dermatol.* 1994;130(11):1448.

116. Barra S, Lanero S, Madrid A et al. Sumatriptan therapy for headache and acute myocardial infarction. *Expert Opin Pharmacother.* 2010;11(16):2727-37.

117. Asghar MS, Hansen AE, Amin FM et al. Evidence for a vascular factor in migraine. *Ann Neurol.* 2011;69(4):635-45.

118. Silberstein SD. Migraine pathophysiology and its clinical implications. *Cephalalgia.* 2004;24 Suppl 2:2-7.

119. Goadsby PJ. The vascular theory of migraine--a great story wrecked by the facts. *Brain.* 2009;132(Pt 1):6-7.

120. Ferrari MD, Roon KI, Lipton RB et al. Oral triptans (serotonin 5-HT(1B/1D) agonists) in acute migraine treatment: a meta-analysis of 53 trials. *Lancet.* 2001;358(9294):1668-75.

121. Walley T, Mantgani A. The UK General Practice Research Database. *Lancet.* 1997;350(9084):1097-9.

122. Becker C, Brobert GP, Almqvist PM et al. Migraine incidence, comorbidity and health resource utilization in the UK. *Cephalalgia.* 2008;28(1):57-64.

123. Scottish Intercollegiate Guidelines Network. Diagnosis and Management of Headach in Adults (CG107). Scottland: Scottish Intercollegiate Guidelines Network; 2008.

124. Robbins MS, Lipton RB. The epidemiology of primary headache disorders. *Semin Neurol.* 2010;30(2):107-19.

125. Bigal ME, Kurth T, Santanello N et al. Migraine and cardiovascular disease: a population-based study. *Neurology.*74(8):628-35.

126. Muzina DJ, Chen W, Bowlin SJ. A large pharmacy claims-based descriptive analysis of patients with migraine and associated pharmacologic treatment patterns. *Neuropsychiatr Dis Treat.* 2011;7:663-72.

127. Antonaci F, Nappi G, Galli F et al. Migraine and psychiatric comorbidity: a review of clinical findings. *J Headache Pain.* 2011;12(2):115-25.

128. Lipton RB, Scher AI, Kolodner K et al. Migraine in the United States: epidemiology and patterns of health care use. *Neurology.* 2002;58(6):885-94.

129. Lipton RB, Diamond S, Reed M et al. Migraine diagnosis and treatment: results from the American Migraine Study II. *Headache.* 2001;41(7):638-45.

130. Becker C, Brobert GP, Almqvist PMet al. Migraine and the risk of stroke, TIA, or death in the UK. *Headache.* 2007;47(10):1374-84.

131. Dahlof C, Linde M. One-year prevalence of migraine in Sweden: a population-based study in adults. *Cephalalgia.* 2001;21(6):664-71.

132. Kurth T, Slomke MA, Kase CS et al. Migraine, headache, and the risk of stroke in women: a prospective study. *Neurology.* 2005;64(6):1020-6.

133. Gudmundsson LS, Scher AI, Aspelund T et al. Migraine with aura and risk of cardiovascular and all cause mortality in men and women: prospective cohort study. *Br Med J.* 2010;341:c3966.

134. Sacco S, Ricci S, Degan D et al. Migraine in women: the role of hormones and their impact on vascular diseases. *J Headache Pain.* 2012;13(3):177-89.

135. Bigal ME, Ferrari M, Silberstein SD et al. Migraine in the triptan era: lessons from epidemiology, pathophysiology, and clinical science. *Headache.* 2009;49 Suppl 1:S21-33.

136. Winner P, Hershey AD. Epidemiology and diagnosis of migraine in children. *Curr Pain Headache Rep*. 2007;11(5):375-82.

137. Rathnayake D, Sinclair R. Use of spironolactone in dermatology. *Skinmed.* 2010;8(6):328-32.

138. Erkek E, Bozdogan O, Kocak M et al. Androgen receptor status in lesional and normal skin of patients with rosacea. *J Eur Acad Dermatol Venereol.* 2004;18(6):736-7.

139. Pye RJ, Meyrick G, Burton JL. Skin surface lipid composition in rosacea. *Br J Dermatol.* 1976;94(2):161-4.

140. Lai JJ, Chang P, Lai KP et al. The role of androgen and androgen receptor in skin-related disorders. *Arch Dermatol Res.* 2012;304(7):499-510.

141. Markova MS, Zeskand J, McEntee B et al. A role for the androgen receptor in collagen content of the skin. *J Invest Dermatol.* 2004;123(6):1052-6.

142. Chantong B, Kratschmar DV, Nashev LG et al. Mineralocorticoid and glucocorticoid receptors differentially regulate NF-kappaB activity and pro-inflammatory cytokine production in murine BV-2 microglial cells. *J Neuroinflammation*. 2012;9:260.

143. Odermatt A, Kratschmar DV. Tissue-specific modulation of mineralocorticoid receptor function by 11beta-hydroxysteroid dehydrogenases: an overview. *Mol Cell Endocrinol.* 2012;350(2):168-86.

144. Perusquia M, Stallone JN. Do androgens play a beneficial role in the regulation of vascular tone? Nongenomic vascular effects of testosterone metabolites. *Am J Physiol Heart Circ Physiol.* 2010;298(5):H1301-7.

145. Messina M, Manieri C, Musso MC et al. Oral and topical spironolactone therapies in skin androgenization. *Panminerva Med.* 1990;32(2):49-55.

146. Yamamoto A, Ito M. Topical spironolactone reduces sebum secretion rates in young adults. *J Dermatol.* 1996;23(4):243-6.

147. Barrett EJ, Eggleston EM, Inyard AC et al. The vascular actions of insulin control its delivery to muscle and regulate the rate-limiting step in skeletal muscle insulin action. *Diabetologia.* 2009;52(5):752-64.

148. Rask-Madsen C, King GL. Mechanisms of Disease: endothelial dysfunction in insulin resistance and diabetes. *Nat Clin Pract Endocrinol Metab.* 2007;3(1):46-56.

149. Browne D, Meeking D, Shaw K et al. Review: Endothelial dysfunction and pre-symptomatic atherosclerosis in type 1 diabetes - pathogenesis and identification. *Br J Diab Vas Dis.* 2003;3(1):27-34.

150. Van Staa TP, Abenhaim L. The quality of information recorded on a UK database of primary care records: A study of hospitalizations due to hypoglycemia and other conditions. *Pharmacoepidemiol Drug Saf.* 1994;3(1):15-21.

151. The Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl J Med.* 1993;329(14):977-86.

152. UKPDS Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet.* 1998;352(9131):837-53.

153. Klaber R. WE. The pathogenesis of rosacea: a review with special reference to emotional factors. *Br J Deramtol Syph.* 1939;51:501-24.

154. Higgins E, du Vivier A. Alcohol intake and other skin disorders. *Clin Dermatol.* 1999;17(4):437-41.

155. White JM, Jones AM, Ingham JG. A Rorschach study of the neurodermatoses. *J Psychosom Res.* 1956;1(1):84-93.

156. Su D, Drummond PD. Blushing propensity and psychological distress in people with rosacea. *Clin Psychol Psychother.* 2012;19(6):488-95.

157. Rebora A. The red face: rosacea. *Clin Dermatol.* 1993;11(2):225-34.

158. Scharschmidt TC, Yost JM, Truong SV et al. Neurogenic rosacea: a distinct clinical subtype requiring a modified approach to treatment. *Arch Dermatol.* 2011;147(1):123-6.

159. Abram K, Silm H, Maaroos HI, Oona M. Subjective disease perception and symptoms of depression in relation to healthcare-seeking behaviour in patients with rosacea. *Acta Derm Venereol.* 2009;89(5):488-91.

160. Nazareth I, King M, Haines A et al. Accuracy of diagnosis of psychosis on general practice computer system. *Br Med J.* 1993;307(6895):32-4.

161. World Health Organization. WHO Collaborating Centre for Drug Statitistics and Methodology. Available from http://www.whocc.no/atc_ddd_index/?code=N06A [Accessed 9 April 2013].

162. World Health Organization. WHO Collaborating Centre for Drug Statistics Methodology. Available from http://www.whocc.no/atc_ddd_index/?code=N05A [Accessed 23 April 2013].

163. Leucht S, Kissling W, McGrath J. Lithium for schizophrenia. *Cochrane Database Syst Rev*. 2007(3):CD003834.

164. Christodoulou GN, Siafakas A, Rinieris PM. Side-effects of lithium. *Acta Psychiatr Belg.* 1977;77(2):260-6.

165. British Medical Association and the Royal Pharmaceutical Society of Great Britain. British National Formulary / Lithium (2013). Available from http://www.medicinescomplete.com/mc/bnf/current/PHP2334lithium.htm?q=lithium&t=search&ss=text&p=4#_hit [Accessed 23 April 2013].

166. Hsu CC, Lee JY. Pronounced facial flushing and persistent erythema of rosacea effectively treated by carvedilol, a nonselective beta-adrenergic blocker. *J Am Acad Dermatol.* 2012;67(3):491-3.

167. Hsu CC, Lee JY. Carvedilol for the treatment of refractory facial flushing and persistent erythema of rosacea. *Arch Dermatol.* 2011;147(11):1258-60.

168. National Institute for Health and Care Excellence. Clinical Knowledge Summaries / Rosacea. Available from: http://cks.nice.org.uk/rosacea#!scenariorecommendation [Accessed 2 June 2013].

169. National Institute for Health and Care Excellence. Hypertension - clinical management of primary hypertension in adults (CG127). England: National Institute for Health and Care Excellence; 2011.

170. National Institute for Health and Care Excellence. MI: secondary prevention (CG48). England: National Institute for Health and Care Excellence; 2007.

171. National Institute for Health and Care Excellence. Chronic Heart Failure – national clinical guideline for diagnosis and management in primary and secondary care (CG108). England: Natoinal Institute for Health and Care Excellence; 2010.

172. National Institute for Health and Care Excellence. Stroke - National clinical guideline for diagnosis and initial management of acute stroke and transient ischaemic attack (CG68). England: National Institute for Health and Care Excellence; 2008.

173. World Health Organization. WHO Collaborating Centre for Drug Statitistics and Methodology. Available from http://www.whocc.no/atc_ddd_index/?code=C08 [Accessed 28 March 2013].

174. Grossman E, Messerli FH. Calcium antagonists. *Prog Cardiovasc Dis.* 2004;47(1):34-57.

175. Powell FC. What's going on in rosacea? *J Eur Acad Dermatol Venereol.* 2000;14(5):351-2.

176. Frishman WH, Saunders E. beta-Adrenergic blockers. *J Clin Hypertens*. 2011;13(9):649-53.

177. British Medical Association and the Royal Pharmaceutical Society of Great Britain. British National Formulary. Available from http://www.medicinescomplete .com/mc/ bnf/current/PHP944-propranolol-hydrochloride.htm?q=propranolol&t=search&ss= tex t&p=1#_hit [Accessed 12 April 2013].

178. Spoendlin J, Voegel JJ, Jick SS et al. Migraine, triptans, and the risk of developing rosacea: A population-based study within the United Kingdom. *J Am Acad Dermatol.* 2013 May; Epub ahead of print.

179. Spoendlin J, Voegel JJ, Jick SS et al. Spironolactone may reduce the risk of incident rosacea. *J Invest Dermatol.* 2013 Apr; Epub ahead of print.

180. Struthers A, Krum H, Williams GH. A comparison of the aldosterone-blocking agents eplerenone and spironolactone. *Clin Cardiol.* 2008;31(4):153-8.

181. Mitts TF, Bunda S, Wang Y et al. Aldosterone and mineralocorticoid receptor antagonists modulate elastin and collagen deposition in human skin. *J Invest Dermatol.* 2010;130(10):2396-406.

182. Spoendlin J, Voegel JJ, Jick SS et al. Risk of rosacea in patients with diabetes using insulin or oral antidiabetic drugs. *J Invest Dermatol.* 2013 May; Epub ahead of print.

183. Jick H. Regular aspirin intake and acute myocardial infarction. *Br Med J.* 1974;1(5905):440-3.

184. Jick H, Miettinen OS. Regular aspirin use and myocardial infarction. *Br Med J.* 1976;1(6017):1057.

185. Jick H, Elwood PC. Aspirin and myocardial infarction. *Am Heart J.* 1976;91(1):126.

186. Drummond PD. The effect of adrenergic blockade on blushing and facial flushing. *Psychophysiology.* 1997;34(2):163-8.

187. García Rodríguez LA, Pérez Gutthann S. Use of the UK General Practice Research Database for pharmacoepidemiology. *Br J Clin Pharmacol*. 1998;45(5):419-25.

188. Clinical Practice Research Datalink. Available from www.cprd.com [Accessed May 28 2013].

6 Index of Tables

Table 1.1-1: Hierarchy of clinical evidence according to the US Preventive Services Task Force (USPSTF). Table adapted from (9) 5
Table 1.1-2: ‚Hill criteria' on causality in medical research with their inherent problems. Table adapted from [10] 8
Table 3.1-1: Incidence rates of diagnosed rosacea in the UK between 1995 and 2008 38
Table 3.1-2: Distribution of patient characteristics and lifestyle factors in patients with rosacea and controls in the UK 39
Table 3.1-3: Distribution of ocular symptoms and differential diagnoses in rosacea cases and controls in the UK 40
Table 3.2-1: Distribution of demographics, life-style factors, co-morbidities, and co-medications in rosacea cases and controls in the UK 54
Table 3.2-2: Distribution of diagnosed migraine stratified by age and gender in rosacea cases and controls in the UK 55
Table 3.2-3: Distribution of triptan exposure stratified by age, gender, and exposure duration (number of prescriptions) in rosacea cases and controls in the UK 56
Table 3.3-1: Distribution of diuretic exposure stratified by timing and duration of drug use in rosacea cases and controls in the UK 65
Table 3.3-2: Use of Spironolactone in rosacea cases and controls, after controlling for confounding by indication 66
Table 3.3-3: Use of Spironolactone in rosacea cases and controls, after controlling for confounding by indication 66
Table 3.4-1: Distribution of diagnosed DM stratified by $HbA1_c$ values and disease duration 71
Table 3.4-2: Mutually exclusive antidiabetic drugs use stratified by timing and duration of drug exposure and by $HbA1_c$ values 72
Table 3.4-3: Distribution of diagnosed DM stratified by $HbA1_c$, sub-stratified by disease duration 73
Table 3.4-4: Distribution of antidiabetic drug use (insulin and OAD) stratified by timing and duration of drug exposure 74
Table 3.5-1: Distribution of demographics, life-style factors, co-morbidities, and co-medications in rosacea cases and controls in the UK GPRD 82
Table 3.5-2: Distribution of diagnosed affective disorders stratified by exposure to antidepressant drugs (by timing and duration of drug use) in rosacea cases and controls 83
Table 3.5-3: Distribution of exposure to antiosychotic drugs stratified by timing and duration of drug use in rosacea cases and controls 84
Table 3.5-4: Distribution of exposure to oral lithium stratified by underlying indication, sub-stratified by timing and duration of drug use in rosacea cases and controls 84
Table 3.6-1: Distribution of demographics, life-style factors, co-morbidities, and co-medications in diagnosed rosacea cases and controls 96
Table 3.6-2: Distribution of ACEI, ARB, BB, and CCB exposure, stratified by timing and duration of drug use in rosacea cases and controls 97

Table 3.6-3: Exposure to the most frequently prescribed BBs within the UK stratified by timing and duration of use in rosacea cases and controls 98
Table 3.6-4: Exposure to dihydropyridine and non-dihydropyridine CCBs stratified by timing and duration of drug exposure in rosacea cases and controls. 98
Table 4.1-1: Schematic description and classification of the six observational studies on rosacea presented within this thesis 106

“And then I thought that I had to be like Sherlock Holmes and I had to detach my mind at will to a remarkable degree so that I did not notice how much it was hurting inside my head.”

Mark Haddon, The Curious Incident of the Dog in the Night-Time