Swiss Claims Data: Opportunities and Challenges for Observational Research

Inauguraldissertation

zur

Erlangung der Würde eines Doktors der Philosophie

vorgelegt der

Philosophisch-Naturwissenschaftlichen Fakultät

der Universität Basel

von

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aus Bonfol, JU

Basel, 2017

Genehmigt von der Philosophisch-Naturwissenschaftlichen Fakultät

auf Auftrag von

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Basel, den 13. Dezember 2016

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Dekan

„Was immer Du tun kannst

oder träumst es zu können,

fang damit an!“

Johann Wolfgang von Goethe

ACKNOWLEDGEMENTS

Die vorliegende Arbeit entstand zwischen September 2013 und November 2016 am Institut für Klinische Pharmazie und Epidemiologie der Universität Basel unter der Leitung von Prof. Dr. Christoph Meier.

Herzlichst möchte ich mich bei allen bedanken, welche mich auf meinem Weg unterstützt haben.

Ein besonderer Dank geht an meinen Chef Prof. Dr. Christoph Meier, dafür, dass er mir diese Dissertation ermöglicht, an mich geglaubt und mich immer unterstützt hat. Wann immer ein Problem während meiner Dissertation aufgetreten ist, nahm er sich die Zeit, dies mit mir anzuschauen, obwohl er mit vielen Aufgaben bereits sehr ausgelastet war. Zudem habe ich seine Geduld, seine Gelassenheit und auch seinen Humor immer sehr geschätzt.

Bedanken möchte ich mich auch bei Prof. Dr. Kurt Hersberger für die Übernahme des Korreferats sowie auch bei Prof. Dr. Alex Odermatt für die Übernahme des Prüfungsvorsitzes.

Vielen Dank auch an meine Co-Autoren Dr. Oliver Reich, PD Dr. Matthias Schwenkglenks, Dr. Alena M. Pfeil, PD Dr. Balthasar Hug und Prof. Dr. Susan S. Jick, für die jeweils kritische Durchsicht der Manuskripte und die konstruktiven Beiträge.

Ein grosses Dankeschön geht auch an mein Team aus der Basler ‘Pharmacoepidemiology Unit‘ für die tolle Arbeitsatmosphäre. Während meiner Dissertation haben viele Doktoranden neu begonnen und das Team belebt. Wir hatten gemeinsam eine wirklich gute Zeit, ob während der Arbeit, in den Pausen oder auch privat.

Und nicht zuletzt möchte ich mich bei meiner Familie, im Speziellen meinen Eltern, aber auch bei meinen Freunden aus Bern und Basel bedanken, dass sie mich bei gelegentlichen Tiefen moralisch unterstützt, aber auch die Höhen mit mir gefeiert haben.

Die Zeit als Doktorandin war eine wirkliche Bereicherung für mich. Ich habe mich fachlich weiter entwickelt, indem ich einen Einblick in die Pharmakoepidemiologie gewinnen und mich mit der Handhabung von grossen Datenbanken auseinandersetzen konnte. Nebenbei durfte ich den FPH in der klinischen Pharmazie absolvieren und habe an spannenden Patientenvisiten teilnehmen dürfen. Ich habe in dieser Zeit aber auch

gelernt mit Konfliktsituationen umzugehen, durchzubeissen, nicht aufzugeben, geduldig zu sein und Vertrauen in sich selbst zu haben.

Ein herzliches Dankeschön Euch allen!!!

INDEX OF CONTENT

LIST OF ABBREVIATIONS

AD	Alzheimer's disease
AIDS	Acquired immune deficiency syndrome
aOR	Adjusted odds ratio
ATC	Anatomic therapeutic chemical classification system
BMI	Body mass index
BzRAs	Benzodiazepine receptor agonists
CBD	Corticobasal degeneration
CH	Switzerland
CI	Confidence interval
CPR	Central Person Registration
CPRD	Clinical Practice Research Datalink
DNPR	Danish National Prescription Registry
DRG	Diagnosis-related groups
ECPM	European Center of Pharmaceutical Medicine
EHR	Electronic health records
GP	General practitioner
GPRD	General Practice Research Database
HDL	High-density lipoprotein
HIV	Human immunodeficiency virus
HMG-CoA	3-hydroxy-3-methylglutaryl-coenzyme A
HMO	Health maintenance organization
HRU	Health resource utilization
ICMJE	International Committee of Medical Journal Editors
ID	Iron deficiency
IDA	Iron deficiency anemia

IHD	Ischemic heart disease
IR	Incidence rate
ISAC	Scientific Advisory Committee for MHRA database research
LDL	Low-density lipoprotein
MHRA	Medicines and Healthcare products Regulatory Agency
mNCD	Major neurocognitive disorder
NHS	Nationals Health Service
OR	Odds ratio
OTC	Over-the-counter
PD	Parkinson's disease
PHARMO	Pharmaco-Morbidity Linkage
RCTs	Randomized controlled trials
RR	Relative risk
SES	Socioeconomic status
SD	Standard deviation
SwissDRG	Swiss Diagnosis Related Groups
TIA	Transient ischemic attack
UK	United Kingdom
WHO	World Health Organization

SUMMARY

Health care utilization databases such as claims data are frequently used in a variety of settings to analyze the outcome of drug treatments. Because of their large scale these data allow to study real-world effectiveness and utilization patterns at relatively low costs. The Swiss healthcare system is notable for its high degree of innovative capacity, which also involves new developments and improvements in the pharmaceutical industry. In collaboration with Helsana, we have recently used claims data for descriptive analyses of health resource utilization in Switzerland. The aim of this thesis was to contribute to the understanding of the Helsana claims data provided by the Helsana Group and to show the opportunities and challenges of these data with the following three projects.

Using claims data from the Helsana Group, **Project I** examined the association between statin use and the risk of cholecystectomy in a case-control analysis between 2013 and 2014. We applied conditional logistic regression analyses to calculate odds ratios (ORs) with 95% confidence intervals (CIs) and adjusted the analyses for history of cardiovascular diseases and for use of estrogens, fibrates and other lipid-lowering agents. The study supports the previously raised hypothesis that long-term statin use was associated with a reduced OR (adjusted OR [aOR] 0.77, 95% CI: 0.65-0.92). However, neither short-term current use nor past statin use affected the risk of cholecystectomy.

In a second case-control study, **Project II** examined the association between previous benzodiazepine use and the risk of developing Alzheimer's disease (AD) and identified 1,438 incident AD cases between 2013 and 2014. Because initiation of benzodiazepine use shortly before the AD diagnosis date may occur due to symptomatic treatment of prodromal symptoms of early major neurocognitive disorder, we introduced an induction period of two years before the AD diagnosis date. We applied conditional logistic regression analyses to calculate ORs with 95% CIs and adjusted for antidepressant use. After accounting for benzodiazepine use initiated during the prodromal phase, long-term benzodiazepine use was not associated with an increased risk of developing AD (aOR 0.78, 95% CI: 0.53-1.14).

In **Project III**, a retrospective descriptive study, we quantified use of oral and parenteral iron supplementation in Swiss data and compared it to data from the UK between 2012 and 2014. We further assessed the frequency of serum ferritin and hemoglobin tests prior to newly started iron therapy to see whether use was based on documented low iron levels or blood parameters, especially in the case of parenteral iron supplementation. The three-year prevalence of iron supplementation was 9.4% in Switzerland compared to 4.4% in the UK. Iron use increased slightly between 2012 and 2014 in both countries (CH +0.3%/UK +0.2%) and recorded parenteral iron administration was roughly a thousand times higher in Switzerland (1.9%) than in the UK in

2014. Hemoglobin values prior to a new parenteral iron therapy were relatively infrequent in Switzerland despite the required documentation of hemoglobin prior to therapy.

The Helsana claims data can be used for descriptive studies as well as to study pharmacoepidemiological hypotheses. Its strengths are the large size, the accurate documentation of the data and the low costs. On the other hand, data on important potential confounder's variables such as Body mass index (BMI), smoking status or alcohol consumption but also on clinical diagnoses is largely missing and leading to bias and confounding.

INTRODUCTION

1.1 Pharmacoepidemiology

1.1.1 Definition of Pharmacoepidemiology

Pharmacoepidemiology, including the two terms "pharmaco" and "epidemiology", is defined as the study of drug effects, both beneficial and adverse, in large human populations. Pharmacoepidemiology is a relatively young discipline; strongly correlated to the field of "clinical pharmacology" that observes drug effects in humans. The demand for pharmacoepidemiological studies raised in the 1960's during the "thalidomide disaster", when it came out that this drug causes phocomelia- a birth defect which is characterized by the absence of limbs or parts of the limbs. Most pharmacoepidemiological studies are undertaken after drug marketing to bridge the gap between the information generated during clinical pre-marketing trials and real world drug usage, since clinical trials may not provide an entire picture of drug effects. [1,2]

To test healthcare interventions, the British pioneer in clinical epidemiology, Archie Cochrane defined the following three concepts:

- Efficacy "Can it work?"
- Effectiveness "Does it work in practice?"
- Efficiency "Is it worth it?"

Efficacy is the ability that an intervention or drug does more good than harm under ideal circumstances while effectiveness studies an intervention under usual circumstances in healthcare practice. For testing efficacy randomized controlled trials (RCTs) are undertaken, while effectiveness is tested with pharmacoepidemiological studies. Efficiency assesses the effect of an intervention in relation to the resources it consumes and is tested by health economic studies. [3] Most of the clinical studies assess efficacy, which is mandatory for drug authorization, but this efficacy applies only to the specific indication it was tested for and to the small sample population it was tested in. It's important to close this gap between the pre-marketing clinical trials and the real-world drug use, since not all adverse drug reactions are known at the point of authorization. This gap his filled with post-marketing observational trials. [1–3]

1.1.2 Types of Observational Pharmacoepidemiological Studies

Pharmacoepidemiological studies can generally be divided into experimental or observational/non-experimental studies (Figure 1). Experimental trials can be subdivided into randomized and non-randomized trials; observational studies are further categorized into descriptive and analytical studies. Randomized controlled trials (RCTs) play mainly a role in pre-marketing research to assess efficacy, where the investigator prospectively controls the therapy. In observational studies the therapy is not controlled by the investigator, but data results of ongoing medical care which is analyzed. [1,4]

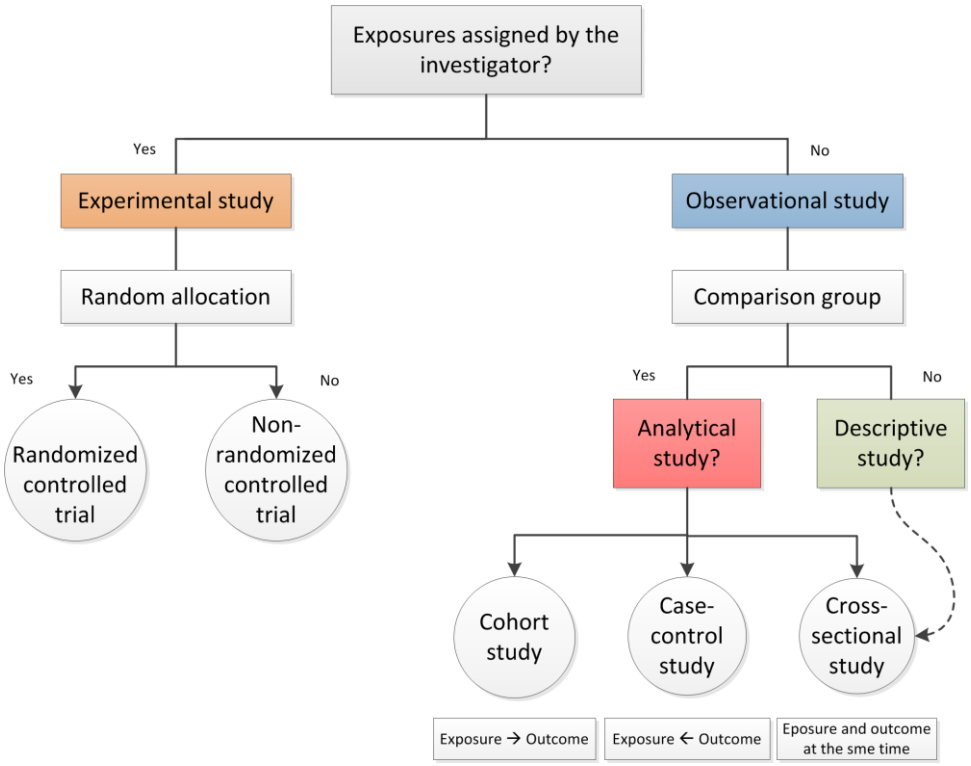

Figure 1: Classification of clinical research types. Figure adapted from Grimes et al. [4]

In terms of quality of evidence (Table 1), RCTs provide the highest level of evidence by the random allocation of patients to the drug under investigation or placebo. Analytical observational studies provide middle evidence, while descriptive observational studies provide only low evidence. [4,5]

Table 1: Rating of clinical evidence. Table adapted from US Preventive Services Task Force [5]

Quality of evidence	
I	Evidence from at least one properly designed randomized controlled trial.
II-1	Evidence obtained from well-designed controlled trials without randomization.
II-2	Evidence from well-designed cohort or case-control studies, preferably from more than one center or research group.
II-3	Evidence from multiple time series with or without the intervention (important results in uncontrolled experiments).
III	Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees.

Descriptive Studies

Descriptive studies (Figure 1) are observational studies that do not have a comparison/ control group. These studies give information about frequencies of disease distributions or they allow generating hypotheses about etiology ("what is the cause of this disease?") or risk factors ("why is a person affected and the other not?").

Examples of descriptive studies are cross-sectional or longitudinal studies. Cross-sectional studies examine the variables of interest at one point in time and therefore allow measuring the prevalence of a disease.

In longitudinal studies, a cohort of individuals is followed over time and new disease episodes are registered to calculate incidence rates. Public health authorities are often interested in trends of drug use, which is examined by longitudinal studies. [4,6,7]

Drug utilization research plays an important role in descriptive studies. The development of drug utilization research started in the mid-1960s in Northern Europe and in the United Kingdom and was defined by the WHO in 1977 as *"the marketing, distribution, prescription, and use of drugs in a society, with special emphasis on the resulting medical, social and economic consequences"* [7].

The aim of drug utilization research is to enable the rational use of drugs in populations in order to initiate a discussion on drug recommendations to further improve prescribing habits. It may be used for example to generate hypotheses and to describe utilization patterns and compare costs between different regions and/or at different times. [7]

Analytical Studies

Analytical studies are observational studies that have a comparison/control group. They can be categorized into cohort-, case-control, or cross-sectional studies (Figure 1) depending on how subjects are recruited. Cross-sectional studies may sometimes also be used to investigate the association between a presumed risk factor and a health outcome; however, as they are carried out at one specific point in time, they give no information about the sequence of events, i.e. whether the exposure occurred before, after or during the onset of the health outcome.

They can be further categorized into prospective and retrospective studies, depending on how data are collected. Within a prospective study, data are collected during the study, while within a retrospective study data collection is finished before the start of the study. [1,4]

Therefore, advantages of retrospective studies are that they are less time consuming, easier for rare outcomes, inexpensive, but because of missing variables also often problematic and incomplete. Compared to retrospective studies, prospective studies have the advantage that data collection is not yet finished and can be done in more detail. On the other hand, they are more time-consuming and more expensive. While prospective cohort studies are common, prospective case-control studies are scarce. For this thesis only retrospective case-control studies have been undertaken.

Case Control Studies

A case-control study is built up of cases with a certain outcome of interest (e.g. a disease) and controls without the specific outcome and looks back in time for specific exposures. While in cohort studies the relative risk (RR) of developing the specific outcome is defined as the frequency of outcome in the exposed group divided by the frequency of outcome in the unexposed group. In case-control studies the RR can be estimated with an

odds ratio (OR) that is a close approximation if the disease is rare. An OR is calculated by the ratio of the odds of the outcome in the exposed group to the odds of the outcome in the non-exposed, whereby the odds is defined as the probability that the event will occur divided by the probability that the event will not occur [1,4].

Analogue to the RR, an OR over 1.0 indicates an increased risk for the exposed subjects, while a value below 1.0 indicates a reduced risk for the exposed. ORs (also RRs) are reported with p-values and confidence intervals (CIs) to allow the determination of statistical significance. Case-control studies are especially useful for rare diseases and for diseases with a long latency period (e.g. cancer). As a rule, case-control studies are more efficient in settings in which the prevalence of exposure is higher than the incidence of outcome. Compared to cohort studies, case-control studies require less time and resources and they allow investigating more than one exposure at the same time. However, choosing an appropriate control group that is free of the outcome of interest but comparable to the cases is difficult and one disadvantage of the study design. At the point when the controls are selected, the investigator must predict all potential biases that could arise. [1,4,8] Therefore, case-control studies tend to be more susceptible to bias than other analytical study designs. [9]

1.1.3 Bias and Confounding

In epidemiology the systematic error can be categorized into the two forms bias and confounding. A study with a small systematic error is said to have a high validity; a study with high validity means that the findings correspond to the truth in a real population.

A bias refers to a systematic error, which leads to an incorrect assessment of the association between an exposure and an effect; an assessment in the study that is made unevenly in the groups to be compared; a lack of internal validity. Bias can be further classified into information bias and selection bias (Figure 2). Selection bias is an error that occurs while selecting the study population, when systematic differences in characteristics exist between those who were and those who were not selected. The information bias occurs during data collection and relates to misclassification of data.

If misclassification is different in the groups to be compared (e.g. cases and controls), it is regarded as differential misclassification. Otherwise, if the misclassification is the same across the groups to be compared, we call it non-differential. [10–13]

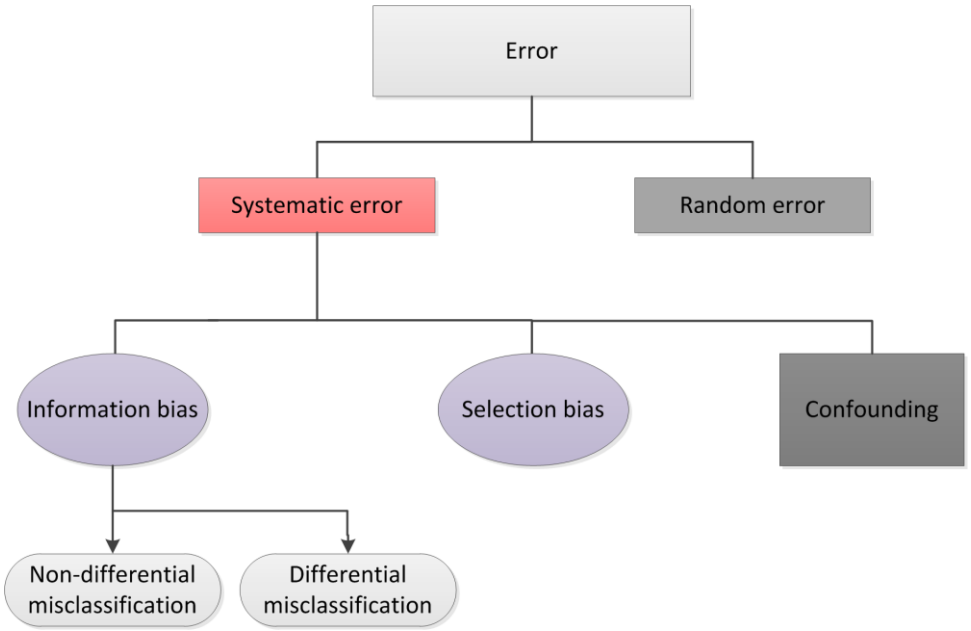

Figure 2: Types of bias. Figure adapted from Henderson et al. [11]

An example for the information bias is the protopathic bias. This type of bias occurs when a drug is inadvertently prescribed for an early manifestation of a disease that has not yet been diagnosed. As an example bias, in a case-control study that analyzed the association between exposure to estrogens and the risk of endometrial cancer, 10% of the women exposed to estrogens stated that estrogens had been prescribed to them for the treatment of uterine bleeding, which is an early manifestation of an endometrial neoplasm. Without excluding these 10% from the analysis, the risk of endometrial cancer would have been overestimated. [14]

To avoid biases, a careful study design is needed because bias can usually not be improved during the analysis.

Another form of systematic error is confounding. Confounding is present when a third variable, which is a risk factor for the outcome and is associated with the exposure but is

not an intermediate step in the causal pathway between exposure and outcome, is unevenly distributed between the two groups to be compared. Confounding can occur in every epidemiological study and can be avoided at the design stage of the study, e.g. by matching cases and controls on a potential confounder (in case-control studies), by restriction of the study population to subjects who are free of that potential confounder, or by randomizing (in RCTs). Confounding can also be controlled for later in the analysis by stratifying the results by the potential confounder or by adjusting for the confounder (by use of multivariate analysis). However, these statistical methods are only useful if the confounder is known and if the confounder can be measured. [10–13]

Confounding by indication is a special type of confounding where the disease forms the indication and acts as a confounder irrespective of its severity. In other words, a drug is more likely to be prescribed to a patient that suffers from more severe diseases who, in turn, is more likely to experience an adverse outcome. Thus, we can say that a patient who receives this drug is different from another patient not receiving this drug and the resulting higher incidence of the outcome in patients prescribed the drug could be due to the disease severity rather than an effect of the drug itself. This bias occurs mainly in retrospective observational studies. Sometimes confounding by indication is misidentified as protopathic bias. [10,15,16]

Bias and confounding provide alternative explanations for the observed differences between groups; a third alternative explanation is chance that belongs to the random error. In comparison to the systematic error, which is not controlled by increasing sample size, the random error occurs to the fact that studies are undertaken in a sample of the population, where different samples produce different outcomes. [10–13]

1.2 Automated Databases

Pharmacoepidemiological studies often use health databases, so called "automated databases" containing electronically recorded patient health care data. According to Brian Strom, the ideal health database would include records from inpatient and outpatient care, emergency care, mental health care, all laboratory and radiological tests, and all prescribed and over-the-counter (OTC) medications, as well as alternative therapies.

Moreover, the population covered would be large enough to identify rare events, would be stable over its lifetime and would provide information on lifestyle factors such as smoking status, body mass index (BMI) and alcohol consumption. These automated databases can be mainly divided into electronic health medical records and administrative health databases. [1,15] Notably health maintenance organizations (HMOs) deliver data from both sources, electronic health medical records and administrative health databases. [1]

1.2.1 Electronic Health Records

Electronic health medical records have originally been developed in Europe for use by researchers and similar databases have been established in the United States lately. They include patient data, generally entered by general practitioners (GPs) into their practice computers as part of their patient care. The Clinical Practice Research Datalink (CPRD) is considered to be the largest medical records database. [1,15]

Clinical Practice Research Datalink

The CPRD [17] has been established in 1987 as the General Practice Research Database (GPRD). This is a large UK-based General Practice Research Database providing health care information on over 11 million patients. The CPRD is one of the largest databases of longitudinal medical records from primary care in the world and has previously been described in detail. [18,19]

In the UK, GPs are responsible for primary healthcare as well as for referrals to specialists. They have been trained to record information on demographics, medical diagnoses, lab values, and drug prescriptions as well as patient referrals and hospital admissions, using standard coding systems. The medical diagnoses are recorded as READ codes. The GPs generate prescriptions directly with the computer and this information is automatically transcribed into the individual computerized patient record. Information on drug prescriptions contains the drug name, instructions for use, route of administration, dose, and number of tablets. For complete information, anonymized individual patient records can be obtained. Additionally, the CPRD holds information on lifestyle factors such as BMI, alcohol consumption, and smoking status. Recorded information on drug

exposure and diagnoses has been validated repeatedly and has proven to be of high quality. [20–22]

The active CPRD population currently covers about 7% of the total UK population, and enrolled patients are representative of the UK with regard to age, sex, and geographic distribution. [23] The CPRD is managed by the Medicines and Healthcare products Regulatory Agency (MHRA) in the UK. Study protocols need to be reviewed and approved by the Independent Scientific Advisory Committee for MHRA database research (ISAC). The investigators have access to anonymous information only. The CPRD data have been used in the UK and internationally to publish close to 2,000 research reports across all major therapeutic areas. [22]

Pharmaco-Morbidity Linkage

In the Netherlands, the pharmaco-morbidity linkage (PHARMO) database links community pharmacies with the national registry of hospital discharges on the basis of the date of birth, sex, and the individual GP number of a patient. [24] The data collection started in 1985 and enables the follow-up of more than 4 million (25%) residents. In 1999 the PHARMO Database Network has been founded and combines data from different healthcare settings in the Netherlands including general practices, in- and out-patient pharmacies, clinical laboratories, hospitals, cancer registries, pathology registries, and perinatal registries and links them all on a patient level. PHARMO is specialized in generating valid and reliable evidence by means of observational research and provides evidence on drug utilization, safety outcomes, effectiveness, burden of illness, patient journeys, and adherence/persistence. The database is used for research in different therapeutic areas including diabetes, oncology, respiratory diseases, cardiovascular diseases, women's health and, pediatrics. [25]

1.2.2 Administrative Health Databases

Administrative health databases exist and have been used since 1980 in North America. In contrast to the electronic health medical records, administrative health data are collected for billing purposes and have been developed for the administration of reimbursement to health care providers. Therefore, these databases were not implemented for research and contain usually patient-level information from two or more separate files

that, however, can be linked through a unique patient identifier. Usually, researchers who want to use these data for research purposes, have to receive approval by an ethics committee. [1,15]

Danish National Prescription Registry

In Denmark, information on all prescribed drugs has been recorded since 1994 in the Register of Medicinal Products Statistics (RMPS) and is provided by the Danish Medicines Agency. [26] All Danish pharmacies are obligated to record all dispensed prescriptions electronically for RMPS. In contrast to other databases, RMPS also contains information on OTC drugs as well as on drugs used in hospitals or nursing homes. The RMPS database has been made available for research since 2003 and is named The Danish National Prescription Registry (DNPR). [27]

The DNPR is tracking each Dane from birth to death by a ten-digit Central Person Registration (CPR) identification number. [27–29] Dispensed drug are identified by the Nordic article number that comprises trade name, pharmaceutical form, strength, and package size. Moreover, more than 30 additional categories of drug information are available, such as the dispensing date, number of packages, dosage form, and retail price. However not included in the DNPR are OTC drugs. They are only recorded if they are prescribed as a consequence of chronic disease which entitles the patient for reimbursement. Other drugs dispensed at the hospital for outpatient treatment or drugs prescribed but not reimbursed are not recorded. [27]

Nowadays each Nordic country has a nationwide prescription database. [30] In Finland the national prescription database is available since 1994 [31], in Norway since 2004 [32], in Sweden since 2005 [33], and in Iceland since 2006 [34]. All of these national prescription databases are similar in terms of the recorded information (Table 2). Potential linkages of the Nordic prescription databases to other registries are shown in Figure 3.

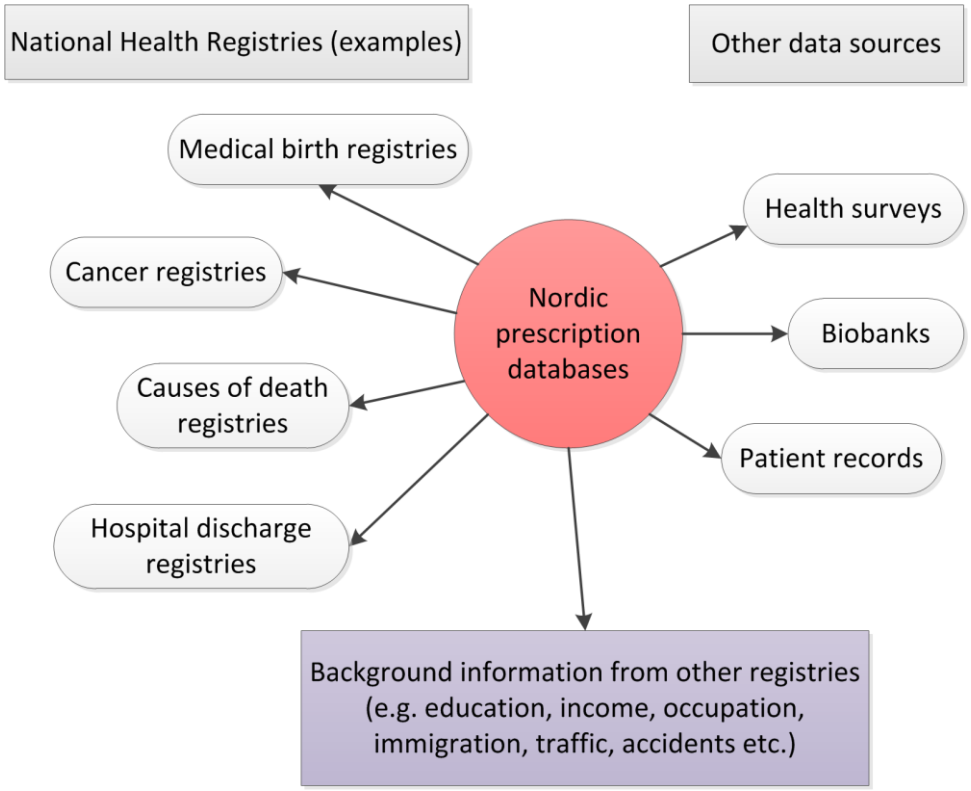

Figure 3: Potential linkages of the Nordic prescription databases. Figure adapted from Furu et al. [30]

Table 2: National prescription databases of the five Nordic countries. Table adapted from [30,35]

	Denmark	**Finland**	**Norway**	**Sweden**	**Iceland**
	Danish National Prescription Registry	The Finnish Prescription Registry	The Norwegian Prescription Database	The Swedish Prescribed Drug Registry	The Icelandic Medicines Registry
General					
Year data became available	1995	1994	2004	2005	2006
Patient					
Unique identifier	Yes	Yes	Yes	Yes	Yes
Age	Yes	Yes	Yes	Yes	Yes
Sex	Yes	Yes	Yes	Yes	Yes
Date of death	Yes	[1]	Yes	Yes	Yes
Emigration	Yes	[1]	[1]	Yes	Yes
Place of Residence	Yes	[1]	Yes	Yes	Yes
Dispensed drug					
Unique identifier	Yes	Yes	Yes	Yes	Yes
ATC code	Yes	Yes	Yes	Yes	Yes
DDD number	Yes	[1]	Yes	Yes	Yes
Number of packages	Yes	Yes	Yes	Yes	Yes
Prescribed dose	No	Free text	Free text	Free text	Free text
Reimbursed drugs	Yes	Yes	Yes	Yes	Yes
Non-reimbursed drugs	Yes	No	Yes	Yes	Yes
Date of prescription	No	Yes	No	Yes	Yes
Dispensing date	Yes	Yes	Yes	Yes	Yes
Diagnosis/ indication for use	No	Free text	Free text	No	No
Generic substitution done	Yes	Yes	Yes	Yes	Yes

	Denmark	Finland	Norway	Sweden	Iceland
	Danish National Prescription Registry	The Finnish Prescription Registry	The Norwegian Prescription Database	The Swedish Prescribed Drug Registry	The Icelandic Medicines Registry
Prescriber					
Unique identifier	Yes	Yes	Yes	Yes	Yes
Age	Yes	[1]	Yes	Yes	Yes
Sex	Yes	[1]	Yes	Yes	Yes
Profession [2]	Yes	Yes	Yes	Yes	Yes
Specialty	Yes	[1]	Yes	Yes	Yes
Practice/ clinic	Yes	[1]	Yes	Yes	Yes
Pharmacy					
Unique identifier	Yes	Yes	Yes	Yes	Yes
Location	Yes	[1]	Yes	Yes	Yes

ATC Anatomic therapeutic chemical classification system, *DDD* Defined daily dose

[1] Can be linked

[2] physician, dentist, nurse

In all of these databases the information is recorded with high accuracy and the size of the database allows studying rare exposures and outcomes. However, diagnoses or drug indications are missing and therefore only diseases identified by drugs or recorded procedures can be studied. Furthermore, information on lifestyle factors such as smoking habit or alcohol consumption is also missing. [30] Most studies undertaken with the Nordic databases were drug utilization studies but these databases have also been used for drug safety or drug effectiveness studies. [30,35] Besides, more than two thirds of the studies undertaken with the Nordic databases between 2005 and 2010 included record-linkage with health surveys and other registries. [30,35] The most frequently studied drugs were psychotropic drugs, antiepileptic drugs, analgesic, and drugs to treat Parkinson's (PD) or Alzheimer's disease (AD). Cardiovascular drugs and drugs acting on the alimentary system were also often studied. [35]

Claims Data

Health care utilization databases such as claims data are frequently used in a variety of settings to analyze the (adverse) effects of drug treatment. Because of their large size these databases allow to study real-world drug effectiveness and utilization patterns at relative low costs. Claims data result from an individual's use of the health-care system. When a patient goes to a pharmacy to fill in a prescription, the pharmacy dispenses the drug to the patient and claims the costs from the insurance. Analogously, when a patient goes to a GP, the GP bills the health insurance for the costs of the medical care. The insurance will later on reimburse the pharmacy and the GP. If there is a unique patient identification number, the pharmacy and medical claims data can be linked together. These linked data can provide information about compliance with treatment regimens based on the period between two prescription fill-ins, co-prescribing, duration of treatment and so on. [1,7,12]

An example for claims data is the Medicaid database, which was established in 1965. Medicaid is a funded health care service from the US, which has been used extensively for pharmacoepidemiological research since 1980. Medicaid is the largest US government founded program for medical and health-related services for people with low income in the United States. [1,36]

Helsana Claims Data

The Swiss healthcare system is notable for its high degree of innovative capacity, which also involves new developments and improvements in the pharmaceutical industry. The flip side to this is growing costs. Medication now accounts for around a quarter of the costs met by basic insurance – reason enough to look into this topic more closely. For these reasons the health insurance provider Helsana started publishing an annual drug report in 2014 in contribution with the university hospital of Basel and the European Center of Pharmaceutical Medicine (ECPM). With this drug report, the first of its kind in Switzerland, Helsana is actively contributing to raising awareness in this area. It gives a realistic insight into the supply of medication in Switzerland and critically analyzes the pharmaceutical market. It seeks to identify peculiarities and differences, and considers opportunities for improvement. [37]

In context with the Helsana drug report we received access to the Helsana claims database for research. The Helsana Group insures some 1.9 million inhabitants (1.2 million enrollees in the compulsory health insurance) in Switzerland. All health insurance companies in Switzerland are private, i.e. there is no national health insurance system, but health insurance is mandatory for everybody living in Switzerland. In collaboration with Helsana, we have recently used claims data for descriptive analyses of health resource utilization (HRU) in Switzerland. [37–39] The recorded data include patient demographics such as age and sex, postal code of residence, and drug prescriptions (including dose, galenic formulation, and package size). Patients' personal characteristics such as smoking habits or weight/BMI, as well as laboratory values, symptoms, ambulatory diagnoses, or medical resource use during hospitalizations are not recorded in the database. In 2012, Switzerland introduced a prospective payment system based on diagnosis-related groups (DRG) for acute-somatic inpatient care. The Swiss Diagnosis Related Groups (SwissDRG) system is based on the German G-DRG version of 2008 [40,41]; Swiss DRG codes are available from the database.

AIMS OF THE THESIS

A major aim of this thesis was to contribute to the understanding of the Helsana claims data provided by the Helsana Group. A further aim was to show the opportunities and challenges of using the Helsana claims data by conducting the following three projects as well as to show the limitations and weaknesses of the database in comparison to other automated databases, described in the introduction.

Project I, a case-control analysis, which aimed to examine the association between statin use and the risk of developing cholecystectomy according to a recently published study based on the CPRD *"Bodmer et al. Statin Use and Risk of Gallstone Disease Followed by Cholecystectomy. JAMA 302, 2001–2007 (2009)"*.

In **Project II**, another case-control analysis, the Helsana claims data were used to estimate the relative risk of developing AD in relation to previous benzodiazepine use in an outpatient setting in Switzerland, also according to a recently published study based on the CPRD *"Imfeld et al. Benzodiazepine use is not associated with an increased risk of Alzheimer's disease or vascular dementia: case-control analysis. Drug Safety. 38, 909–19 (2015)".*

Project III intended to quantify iron supplementation in Switzerland and compare it to Great Britain, using data from the CPRD. In a sensitivity analysis of patients with a new onset of oral or parenteral iron substitutions, it was studied if labor parameters as serum ferritin and/or hemoglobin were assessed before iron administration.

The annually **Helsana Drug Report** aimed to give a better understanding of the Swiss drug market and its development in terms of quantity and cost over the last few years. This drug report mainly focused on presenting drug utilization and drug costs covered by the Swiss health care system and to provide transparency of the Swiss drug market.

PROJECT I

Statin use and risk of cholecystectomy –

A case-control analysis using Swiss claims data

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Expert Opinion on Drug Safety 2016; 5 (12): 1577–1582

3.1 Abstract

Objectives: Using claims data from the Helsana Group, a large Swiss health insurance provider; we examined the association between statin use and the risk of cholecystectomy in a case-control analysis.

Methods: We identified 2,200 cholecystectomy cases between 2013 and 2014 and matched 4 controls to each case on age, sex, index date and canton. We categorized statin users into current or past users (last prescription ≤ 180 or > 180 days before the index date, respectively) and classified medication use by duration based on number of prescriptions before the index date. We applied conditional logistic regression analyses to calculate ORs with 95% CIs and adjusted the analyses for history of cardiovascular diseases and for use of estrogens, fibrates and other lipid-lowering agents.

Results: The adjusted OR (aOR) for cholecystectomy was 0.85 (95% CI: 0.74, 0.99) for current statin users compared to non-users. Long-term current statin use (5-19 prescriptions) was associated with a reduced OR (aOR 0.77, 95% CI: 0.65, 0.92). However, neither short-term current use nor past statin use affected the risk of cholecystectomy.

Conclusions: The study supports the previously raised hypothesis that long-term statin use reduces the risk of cholecystectomy.

3.2 Introduction

In Europe and the USA with a prevalence of 10-20% in adults, gallstones are the most common digestive disease leading to hospital admissions. [42] The disease with the second highest annual direct costs in the USA is gallbladder disease. [43–45] In the USA in 2004, diagnosis of gallstones was estimated to cause 1.8 million ambulatory care visits, mainly as first-line diagnosis. [46] In the same year, they caused the fourth highest total costs of all digestive diseases ($6.2 billion). [47] In Switzerland, direct costs for the treatment of gallbladder disease amounted to around 461 million Swiss francs in 2011. [48] As gallbladder disease is associated with complications such as gallstone formation and colic, more than 700,000 cholecystectomies are performed in the USA every year. [49,50] In Western countries, 80-90% of gallstones derive from cholesterol-supersaturated bile, formed as pigment stones, primarily from bilirubin and calcium. [50] Known risk factors for cholesterol gallstones are obesity, high-fat and high-carbohydrate diet, age, female sex, and estrogens in contraceptives or in postmenopausal hormone replacement therapies. [42,44,50] Besides, patients with gallstones suffered more often from diabetes or hepatic steatosis and were taking steroids more often than healthy controls. [42]

There is evidence from observational studies that statins, aside from its cardiovascular benefits, may reduce the formation of cholesterol gallstones and thereby the risk of cholecystectomy. [51–54] Furthermore, they may have positive effects in patients with gallstone complications by shortening the operation time of laparoscopic cholecystectomy. [55] Despite an increase in the prevalence of obesity, alcohol abuse and other comorbidities in the population, a Finnish study [56] reported a 10% decrease in the rates of all cholecystectomies; during the same time period, statin use increased significantly. On the other hand, other studies could not find an association between statin use and gallstone formation. [57,58] Statins are competitive inhibitors of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) and therefore effectively lower plasma low-density lipoprotein (LDL) cholesterol. They also lower triglycerides as well as increase high-density lipoprotein (HDL) cholesterol and therefore play an essential role in the prevention of cardiovascular events. [59,60] An explanation for the prevention of gallstone formation is the reduction of cholesterol biosynthesis [61] that may affect cholesterol gallstones. [62–64]

As to our knowledge no studies on the association between use of statins and risk of gallstone disease have been carried out in the Swiss population, which is why we conducted this study to add information to the body of knowledge on this issue. Furthermore, only few studies using claims data investigated this association before [54] and also controversial results on the effect of statins on gallstones have been previously reported. [57,58] For these reasons, we sought to examine whether statin use was associated with an altered risk for cholecystectomy in a sample of the Swiss population enrolled with the largest health insurance provider in Switzerland.

3.3 Methods

Study design and data source

We conducted a matched case-control study using claims data from the Swiss health insurance provider Helsana Group, covering the time span between 2008 and 2014. [65] The Helsana Group covers some 1.9 million inhabitants of Switzerland. All health insurance companies in Switzerland are private, that is, there is no national health insurance, but health insurance is mandatory for everyone living in Switzerland, and the conditions and benefit packages are tightly regulated by law and by the federal administration. Helsana's administrative claims data have recently been used for descriptive analyses of HRU in Switzerland. [37,38] The recorded data include patient demographics such as age and sex, postal codes and drug prescriptions (including dose, galenic formulation and package size). Not included are patients' personal characteristics such as smoking status, dietary habits or weight/BMI, as well as laboratory values, symptoms, diagnoses, or details on medical resource use during hospitalizations.

Cases with cholecystectomy

We included patients aged 20 years or older with an inpatient code for cholecystectomy in 2013 or 2014. We identified cases through SwissDRG hospital codes [66] H07A, H07B, H08A, and H08B. SwissDRG codes were introduced in Switzerland in 2012; they are based on and adapted from the German G-DRG Version of 2008. [40,41] The date of the patient's individual cholecystectomy will subsequently be referred to as the 'index date'. All cases were required to have been enrolled with the Helsana Group constantly from 2008 on (i.e. to have at least 6 years of active history in the database). We excluded patients with a diagnosis of cancer (except non-melanoma skin cancer) and/or a diagnosis of human immunodeficiency virus (HIV). We identified these patients by means of anatomic therapeutic chemical classification system (ATC) codes [67] of specific treatments as well as by SwissDRG hospital codes.

Controls

For each case, we identified at random four controls, matched on age, sex, and canton. We assigned the same index date of the case to the controls. All controls also had to be enrolled with the Helsana Group constantly from 2008 on. Controls had to be free of any evidence of cholecystectomy during the entire time in the database that we could overlook, and we applied the same exclusion criteria to controls as to cases.

Exposure to statins

We assessed exposure to statins in cases and controls prior to the individual index date. We categorized patients into current or past users of these drugs, if the last prescription was recorded no longer than 180 days, or more than 180 days prior to the index date, respectively. In previously published studies, an association between statin use and gallstone risk could only be seen for current long-term statin use; [51,52,68] we therefore categorized drug use prior to the index date by number of prescriptions into short-term (1-4 prescriptions), medium-term (5-19 prescriptions), or long-term (≥ 20 prescriptions) use.

Statistical analysis

We conducted conditional logistic regression analyses using Stata, Version StataMP 13, to calculate relative risk estimates as ORs with 95% CIs at a two-sided P value of 0.05.

We matched for the potential confounders age, sex, index date, canton, and years of history, and we further adjusted the multivariable model for history of diabetes, ischemic heart disease (IHD), ischemic stroke, transient ischemic attack (TIA), and for use of opposed or unopposed estrogens, fibrates or other lipid-lowering agents using ATC drug and SwissDRG hospital codes. As overweight has previously been associated with an increased risk for cholecystectomy, [51] we decided to adjust for diabetes, as patients' BMIs were not available in the data; diabetes can be seen as crude proxy for overweight, and current statin users tend to have a higher prevalence of diabetes [53]. For opposed and unopposed estrogen medications as well as for fibrates, and other lipid-lowering drugs, we classified patients into current (last prescription was recorded not more than 180 days before the index date) or past users (if the last prescription was recorded more than 180 days prior to the index date). We further categorized duration of drug use for these drugs into short- to medium-term (1-9 prescriptions), or long-term use (≥ 10 prescriptions).

3.4 Results

We identified a total of 2,220 cholecystectomy cases and 8,880 controls (Table 3). The mean age of the study population was 61.8 years (standard deviation, SD, 15.9 years) at the index date, and the majority of cases were female (59.2%). According to ATC and SwissDRG codes, we identified a total of 1,160 patients with diabetes (12.1% of cases; 10.1% of controls). A total of 2,746 patients had recorded prescriptions for statins (579 cases, 2,167 controls); fewer patients had a prescription for fibrates or other lipid-lowering drugs (Table 4). Compared with nonuse of statins, the aOR of undergoing a cholecystectomy was 0.85 (95% CI: 0.74, 0.99) for current statin users, regardless of exposure duration. After stratification by exposure duration, short-term current statin use was associated with a slightly, but statistically non-significantly elevated OR for cholecystectomy (aOR 1.34, 95% CI: 0.99-1.83), but longer-term use of statins (5-19 current statin prescriptions) was associated with a reduced aOR of 0.77 (95% CI: 0.65, 0.92).

Table 3: Characteristics of patients with cholecystectomy and controls in Switzerland, 2013-2014

	Cases (*n* = 2220)	Controls (*n* = 8880)	Crude OR [a]	Adjusted OR [b]
Age mean (%) y				
<40	224 (10.1)	896 (10.1)		
40-59	709 (31.9)	2836 (31.9)		
≥60	1287 (58.0)	5148 (58.0)		
Sex				
Male	905 (40.8)	3620 (40.8)		
Female	1315 (59.2)	5260 (59.2)		
Diabetes	268 (12.1)	892 (10.1)	1.24 (1.07-1.44)	1.12 (0.96-1.30)
IHD	1221 (55.0)	4093 (46.1)	1.55 (1.40-1.73)	1.45 (1.28-1.63)
Stroke or TIA	647 (29.1)	2118 (23.9)	1.40 (1.25-1.57)	1.12 (0.98-1.28)
No. of charges Opposed estrogens				
1-9	80 (3.6)	190 (2.1)	1.78 (1.35-2.34)	1.69 (1.28-2.23)
≥10	37 (1.7)	99 (1.1)	1.57 (1.07-2.32)	1.60 (1.09-2.37)
Unopposed estrogens				
1-9	239 (10.8)	878 (9.9)	1.16 (0.98-1.36)	1.10 (0.93-1.30)
≥10	81 (3.7)	228 (2.6)	1.53 (1.16-2.00)	1.49 (1.13-1.96)

IHD ischemic heart disease, *TIA* transient ischemic attack, *OR* odds ratio
[a] Adjusted for age, sex and canton by matching
[b] Further adjusted for the variables listed in this table
Opposed estrogens: estrogen with progestogen (progesterone and progestin)
Unopposed estrogens: estrogen only

Stratification yielded similar risk estimates for men and women as well as for those over or below 60 years of age (Table 4). Long-term use of more than 20 current statin prescriptions was associated with a statistically significantly decreased OR for patients below the age of 60 years (aOR 0.42, 95% CI: 0.18, 0.98), but not for the elderly. The relative cholecystectomy risk was not affected by past statin use, irrespective of the duration of exposure (Table 4).

Table 4: Use of statins and risk of cholecystectomy in Switzerland, 2013-2014

	Cases (*n* = 2220)	Controls (*n* = 8880)	Crude OR [a]	Adjusted OR [b]
Statin use				
No	1641 (72.7)	6713 (75.6)	1 [Reference]	1 [Reference]
Yes	579 (27.3)	2167 (24.4)	1.11 (0.99- 1.25)	0.90 (0.79- 1.02)
Current prescriptions				
Yes	396 (17.8)	1527 (17.2)	1.08 (0.94-1.23)	0.85 (0.74-0.99)
1-4 Current prescriptions	63 (2.8)	155 (1.7)	1.68 (1.24-2.27)	1.34 (0.99-1.83)
Men	34 (1.5)	77 (0.9)	1.80 (1.19-2.73)	1.50 (0.98-2.32)
Women	29 (1.3)	78 (0.9)	1.55 (1.00-2.39)	1.20 (0.77-1.88)
Age y				
<60	14 (0.6)	36 (0.4)	1.63 (0.87-3.04)	1.18 (0.61-2.27)
≥60	49 (2.2)	119 (1.3)	1.67 (1.19-2.36)	1.42 (1.00-2.02)
5-19 Current prescriptions	234 (10.5)	1005 (11.3)	0.96 (0.82-1.13)	0.77 (0.65-0.92)
Men	124 (5.6)	546 (6.1)	0.93 (0.74-1.16)	0.78 (0.61-1.00)
Women	110 (5.0)	459 (5.2)	0.98 (0.80-1.26)	0.77 (0.61-0.99)
Age y				
<60	34 (1.5)	101 (1.1)	1.43 (0.96-2.13)	0.91 (0.59-1.40)
≥60	200 (9.0)	904 (10.2)	0.90 (0.76-1.07)	0.76 (0.63-0.92)
≥20 Current prescriptions	99 (4.5)	367 (4.1)	1.12 (0.89-1.42)	0.88 (0.69-1.13)
Men	60 (2.7)	211 (2.4)	1.17 (0.86-1.59)	0.98 (0.70-1.37)
Women	39 (1.8)	156 (1.8)	1.05 (0.73-1.51)	0.79 (0.54-1.16)
Age y				
<60	7 (0.3)	42 (0.5)	0.72 (0.32-1.62)	0.42 (0.18-0.98)
≥60	92 (4.1)	325 (3.7)	1.16 (0.90-1.48)	0.96 (0.74-1.25)
Past prescriptions	183 (8.2)	640 (7.2)	1.18 (0.99-1.41)	0.99 (0.82-1.20)
1-4	95 (4.3)	339 (3.8)	1.16 (0.91-1.47)	0.98 (0.77-1.26)
5-19	83 (3.7)	284 (3.2)	1.21 (0.94-1.56)	1.00 (0.77-1.30)
≥20	5 (0.2)	17 (0.2)	1.22 (0.45-3.32)	1.06 (0.39-2.88)

OR odds ratio

[a] Adjusted for age, sex and canton by matching

[b] Further adjusted for diabetes status, history of ischemic heart disease, stroke or TIA, use of opposed or unopposed estrogens, fibrates or other lipid-lowering drugs, by conditional logistic regression

3.5 Discussion

In this case-control study based on Swiss health insurance claims data, long-term current use of statins was associated with a reduced risk of cholecystectomy, after controlling for sex, age, canton, and calendar time by matching, and after adjusting the multivariable analysis for history of diabetes, IHD, stroke, TIA, and use of opposed or unopposed estrogens, fibrates, and other lipid-lowering agents. Previous studies conducted in the UK and in Denmark using the same categories of statin exposure duration [51,52,68] found similarly reduced relative risk estimates of cholecystectomy for long-term users of statins. Another study [54], like ours based on claims data, also found a similarly reduced relative risk of cholecystectomy associated with long-term use of statins. In comparison with other studies [51,52,54,56] yielding possible protective effects of statins on gallbladder disease, the mean age of our statin users was higher (58% of the cases and controls were over 60 years old). In another study [51], only 36% of the study population was older than 60 years. The higher mean age in the present study could be an explanation for the fact that a relatively high proportion of patients in the current study had comorbidities such as IHD (Table 3). In general, cases tended to have more comorbidities such as diabetes, IHD, stroke, or TIA than controls, and women tended to take estrogens more frequently than the female populations of other studies. [51] We further observed an increased relative risk of cholecystectomy in patients with IHD, as has been previously described in a large prospective cohort of the Chinese population. [69,70]

As in all observational studies we clearly have to distinguish between statistical significance and clinical relevance. We consider the clinical relevance of this finding, as well as of findings of previous studies on this topic, relevant for two reasons: first, it is interesting from a pharmacological point of view to see that statins may have beneficial 'side effects' which are not the reason for prescribing them, but which are still good to now for both clinicians and patients. Second, from a public health point of view, already a rather small relative risk reduction may have a considerable impact for example on health costs, as both statin use and gallstone disease are highly prevalent in Western societies, and each gallstone operation potentially prevented by a beneficial side effects of a statin therapy would certainly be positive. However, without randomized studies and without an official extension of the indications by the drug authorities, doctors should not

prescribe statins with the primary goal to prevent gallstones, but it may still be good to know that mainly obese patients requiring a statin to lower cholesterol may profit from a statin therapy by slightly lowering their gallstone risk.

Our study has several limitations. Because we used claims data, we did not have information on some known risk factors for gallbladder disease such as overweight [51] or socioeconomic status (SES) [68]. Patients of low SES may have a higher gallstone risk since they are more likely to be obese and tend to have poor dietary habits. [68] As overweight and SES are in part related to diabetes, [71–74] and as we considered BMI to be an important factor and a potential confounder of the association between statin use and gallstones, we adjusted the analyses for diabetes as a proxy for BMI, albeit diabetes and BMI are not directly correlated.

Statins can be prescribed as a primary or as a secondary prevention for cardiovascular events; [75] the indication for statins as well as the temporal sequence between hyperlipidemia, cardiovascular diseases and statin use may not always have been entirely clear in all instances. It turned out that several cardiac diseases and diabetes were more prevalent in cases with gallstones than in controls free of gallstones, and we took these comorbidities into account in the adjustment of the association of interest. As we did not have access to diagnostic codes from ambulatory care, we could only use SwissDRG hospital codes to identify cholecystectomy cases, which we used as proxy for gallstone disease. We may therefore have only included the more severe end of the spectrum of gallstone diseases. Previous studies revealed that only 12% of patients with gallstones develop symptoms and that 15% develop severe symptoms. [76] However, including only the more severe cases of a given outcome of interest does not introduce distortion in a case-control analysis, but it is possible that a certain proportion of controls may have had yet undiagnosed subclinical gallstone disease. Another limitation of our study is the incomplete coverage of medical history in the database. Claims data were only available from 2008 on, and the insured persons in Switzerland are free to switch between health insurance companies every year. This limited the available number of cases and controls with long-term use of statins, but we still had enough statistical power to detect meaningful odds ratios. The restricted time period prior to the index date, however, also

leaves room for some misclassification, as we cannot rule out that we included some controls with a cholecystectomy prior to 2008.

The strengths of our study include the contribution of a large number of individuals from different regions of Switzerland. In addition, we were able to adjust for several known risk factors for gallbladder disease. An advantage of claims data is that the study drugs have been recorded with high comprehensiveness, as they were dispensed by a pharmacy or by a doctor to the insured person.

In conclusion, this large case-control study using health insurance claims data from Switzerland supports the previously raised hypothesis that long-term statin use reduces the risk of cholecystectomy.

PROJECT II

Benzodiazepine use and risk of developing Alzheimer's disease – A case-control study based on Swiss claims data

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CNS Drugs 2017; 31: 245–251

4.1 Abstract

Background: A possible association between benzodiazepine use and AD has been hypothesized in previous studies.

Objectives: Using claims data from the Helsana Group, a large Swiss health insurance provider; we examined the association between previous benzodiazepine use and the risk of AD.

Methods: We conducted a matched case-control study and identified 1,438 incident AD cases between 2013 and 2014 based on recorded first-time use of drugs used to treat AD [i.e., acetylcholinesterase inhibitors (donepezil, rivastigmine, and galantamine) and the N-methyl-D-aspartate receptor antagonist memantine] and matched one control to each case on age, sex, index date, and residence (canton). Because the initiation of benzodiazepine use shortly before the AD diagnosis date may occur as a result of symptomatic treatment of prodromal symptoms of early major neurocognitive disorder, we introduced an induction period of 2 years before the AD diagnosis date. Additionally, we categorized medication use by duration of use prior to the index date using prescriptions. We applied conditional logistic regression analyses to calculate ORs with 95% CIs and adjusted for use of antidepressants.

Results: The crude OR (95% CI) of developing AD for patients starting benzodiazepine treatment was 1.71 (1.17-2.99) in the year before diagnosis and 1.19 (0.82-1.72) in the third year before diagnosis. After accounting for benzodiazepine use initiated during the prodromal phase, benzodiazepine use was not associated with an increased risk of developing AD; long-term benzodiazepine use (≥ 30 prescriptions) yielded an aOR of 0.78 (0.53-1.14).

Conclusions: After taking into consideration a possible protopathic bias in the 2 years preceding the AD diagnosis date, benzodiazepine use was not associated with an increased risk of developing AD.

4.2 Introduction

In Switzerland, more than 100,000 people experience major neurocognitive disorder (mNCD), and it is assumed that this number will increase to about 300,000 by 2050. [77] The global prevalence of mNCD has been estimated in 2005 to be as high as 24 million people. [78] Use of benzodiazepines is high and is still increasing [38], and the prevalence of benzodiazepine use increases with age [79].

Benzodiazepines belong to the category of psycholeptic drugs. [67] By acting on the gamma-aminobutyric acid (GABA) system [80], they cause sedative, anxiolytic, anticonvulsant, and muscle relaxant effects. [81] Therefore, they are widely used in the treatment of anxiety, insomnia, schizophrenia [82], and epilepsy. [75,82] Abuse of benzodiazepines, also in combination with alcohol and/or other psychiatric medication, as well as benzodiazepine dependence are serious problems. [83–86] Furthermore, some benzodiazepines have a long plasma half-life in the elderly leading to prolonged sedation and subsequent adverse effects such as falls, drowsiness, cognitive impairment, fractures, and delirium. [87–90] Thus, benzodiazepines should be avoided in elderly patients or should only be given for a short time. [91,92] However, a recent US-based observational study revealed that the percentage of subjects using benzodiazepines increases with age, ranging from 2.6% in subjects aged 18 to 35 years to 31.4% in patients aged 65 to 80 years. [79]

A number of studies investigated whether the use of benzodiazepines is associated with an increased risk of mNCD. Most of these studies documented an increased risk of mNCD in benzodiazepine users, [93–99] but others did not confirm this relationship [100,101]. Because benzodiazepines are prescribed for anxiety, insomnia, and depression, which are also early symptoms of mNCD, [102–104] analysis of an association between benzodiazepine use and mNCD is delicate and has to be controlled for reverse causation, also known as protopathic bias [14]. Previous studies taking the prodromal phase into consideration yielded contradictory outcomes. [97,98,100,101]

To our knowledge, the association between use of benzodiazepines and risk of AD has not previously been studied in the Swiss population, and only a few studies using administrative claims data have investigated this heavily debated possible association

worldwide. [93,94,98,105] Therefore, we sought to examine the association between long-term benzodiazepine use and the risk of AD in Swiss citizens insured by the Helsana Group, one of the largest health insurance providers in Switzerland.

4.3 Methods

Study design and data source

We conducted a matched case-control study using claims data from the Swiss health insurance provider Helsana Group covering the time span between 2008 and 2014 [65]. The Helsana Group insures some 1.9 million inhabitants in Switzerland. All health insurance companies in Switzerland are private, i.e. there is no national health insurance system, but health insurance is mandatory for everybody living in Switzerland. In collaboration with the Helsana Group, we have recently used claims data for descriptive analyses of HRU in Switzerland [37,38]. The recorded data include patient demographics such as age and sex, postal code of residence, and drug prescriptions (including dose, galenic formulation, and package size). Patients' personal characteristics such as smoking habits or weight/BMI, as well as laboratory values, symptoms, ambulatory diagnoses, or medical resource use during hospitalizations are not recorded in the database. In 2012, Switzerland introduced a prospective payment system based on DRG for acute-somatic inpatient care. The SwissDRG system is based on the German G-DRG version of 2008 [40,41]; Swiss DRG codes are available from the database.

Case identification

We identified cases with an incident diagnosis of AD in 2013 or 2014 via recorded first-time use of acetylcholinesterase inhibitors or the N-methyl-D-aspartate receptor antagonist memantine using ATC codes N06DA02 for donepezil, N06DA03 for rivastigmine, N06DA04 for galantamine, or N06DX01 for memantine. [67] The date of the first prescription of one of these drugs is referred to as the 'diagnosis date'. All patients had to be continuously insured by the Helsana Group from 2008 onwards (i.e. to have at least 5 years of active history in the database). We excluded patients with an anytime diagnosis of cancer (except non-melanoma skin cancer), and/or a diagnosis of multiple sclerosis and/or HIV. We routinely exclude patients with cancer and/or HIV/AIDS in most studies as these patients undergo different medical care and are subject to bias and

confounding. Furthermore, HIV can lead to mNCD in 20-30%. As PD can also lead to mNCD, we excluded PD patients too. We additionally excluded patients with a diagnosis for multiple sclerosis because these patients can also experience cognitive difficulties. We identified HIV-positive patients and patients with cancer by ATC-codes for their treatment as well as by SwissDRG codes [66]; we identified multiple sclerosis patients on the basis of ATC codes only.

Controls

For each case patient, we randomly identified from the database one control subject with no prescriptions for one of the above-mentioned AD-specific drugs during the entire study period (i.e. between 2008 and 2014). We matched control patients to AD cases on age at diagnosis date, sex, diagnosis date, and residence (i.e. canton). Because all study participants had to have been insured by the Helsana Group without interruption since 2008, we indirectly also matched patients on years of recorded history. We applied the same exclusion criteria to control subjects and cases.

Induction time: Assessment of prodromal symptoms

We assumed that first-time prescription of a benzodiazepine shortly before the diagnosis date may be due to symptomatic treatment of prodromal symptoms of early mNCD. In the main analysis, we therefore ignored benzodiazepine prescriptions issued during the last 2 years preceding the diagnosis date and created an artificial 'index date', which was the diagnosis date minus 2 years.

Exposure to benzodiazepines

We assessed exposure to benzodiazepines (including the benzodiazepine receptor agonists [BzRAs] zolpidem, zopiclon, and zaleplon) prior to the index date by using ATC codes N05BA, N05CD, and N05CF. We categorized duration of use as 1-9, 10-29, or ≥ 30 prescriptions. Number of prescriptions is a widely used surrogate measure for exposure duration.

Statistical analyses

To assess the association between benzodiazepine exposure and the risk of AD, we conducted conditional logistic regression analyses using Stata, Version StataMP 13. We

determined ORs with 95% CIs at a 2-sided P value of 0.05. We compared users of benzodiazepines with the reference group of non-users of benzodiazepines.

We controlled for the potential confounders age, sex, index date, residency, and years of recorded history by matching, and we further adjusted for depression (use of antidepressants yes/no based in ATC drug codes) in the multivariate model as antidepressants and antipsychotics are often co-prescribed with benzodiazepines to treat mNCD-related insomnia, anxiety, depression, irritability, or agitation. [103]

4.4 Results

We identified 1,438 incident AD cases and 1,438 control subjects, of whom 742 (51.6%) were identified in 2013 and 696 (48.4%) in 2014 (Figure 4).

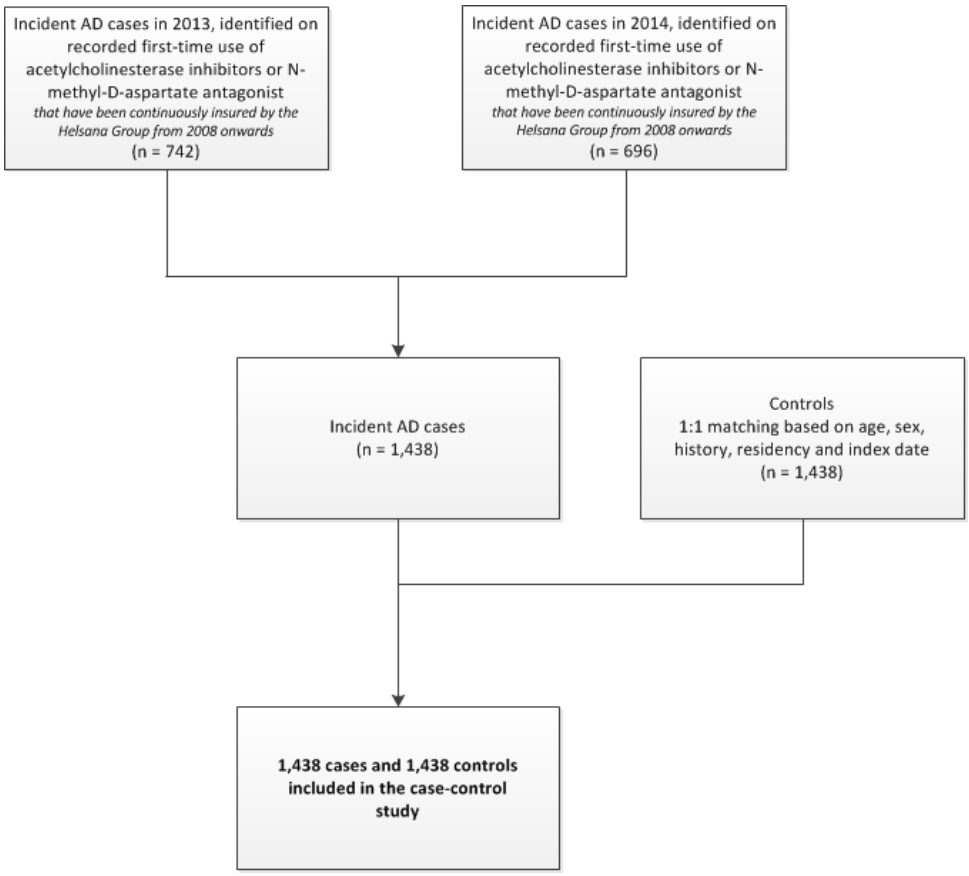

Figure 4: Flow chart of study population, *AD* Alzheimer's disease

The most frequent drug prescribed was donepezil (45.8%), followed by rivastagmine (27.2%) and memantine (22.7%). The mean (± SD) age of both the cases and controls was 80.6 (± 7.5) years and the study population encompassed more women than men (Table 5).

Table 5: Demographic characteristics of patients with AD and controls

	Cases (n = 1438)	Controls (n = 1438)	Crude OR [a]
Age mean (%) y			
31-76	336 (23.4)	336 (23.4)	
77-80	289 (20.1)	289 (20.1)	
81-85	445 (30.9)	445 (30.9)	
≥ 86	368 (25.6)	368 (25.6)	
Sex			
Male	513 (35.7)	513 (35.7)	
Female	925 (64.3)	925 (64.3)	
Region			
German part	1111 (77.3)	1111 (77.3)	
French part	223 (15.5)	223 (15.5)	
Italian part	104 (7.2)	104 (7.2)	
Antidepressant use			
No	732 (50.9)	1'032 (71.8)	1 [Reference]
Yes	706 (49.1)	406 (28.2)	2.42 (2.06-2.84)
Antidepressants, prescriptions			
1-19	544 (37.8)	306 (21.3)	2.46 (2.07-2.92)
20-39	126 (8.8)	80 (5.6)	2.20 (1.62-2.97)
≥ 40	36 (2.5)	20 (1.4)	2.89 (1.62-5.15)
*Benzodiazepine use			
No	653 (45.4)	717 (49.9)	1 [Reference]
Yes	785 (54.6)	721 (50.1)	1.19 (1.03-1.38)

AD Alzheimer's disease, *OR* odds ratio

[a] Adjusted for age, sex, and home location (region) by matching

[*] Benzodiazepine use/prescriptions without controlling for protopathic bias

Use of antidepressants was much higher in cases (49.1%) than in controls (28.2%). Use of benzodiazepines was statistically significantly ($p < 0.017$) higher in cases (54.6%) than in controls (50.1%), in an initial analysis. However, after correcting for the protopathic bias by shifting the diagnosis date, benzodiazepine use prior to the first prescription of an AD-specific drug was similar in cases (46.3%) and controls (44.3%).

Overall, the crude overall OR without correction for the protopathic bias of developing AD in association with benzodiazepine use was 1.19 (95% CI 1.03-1.38). The crude OR of developing AD for patients who started benzodiazepines in the first year before AD diagnosis was 1.71 (95% CI 1.17-2.99) and fell to 1.19 (95% CI 0.82-1.72) in those who started in the third year before the diagnosis (Figure 5). We therefore determined the induction time as 2 years prior to the AD diagnosis (Figure 5) and ran additional analyses based on the shifted index date.

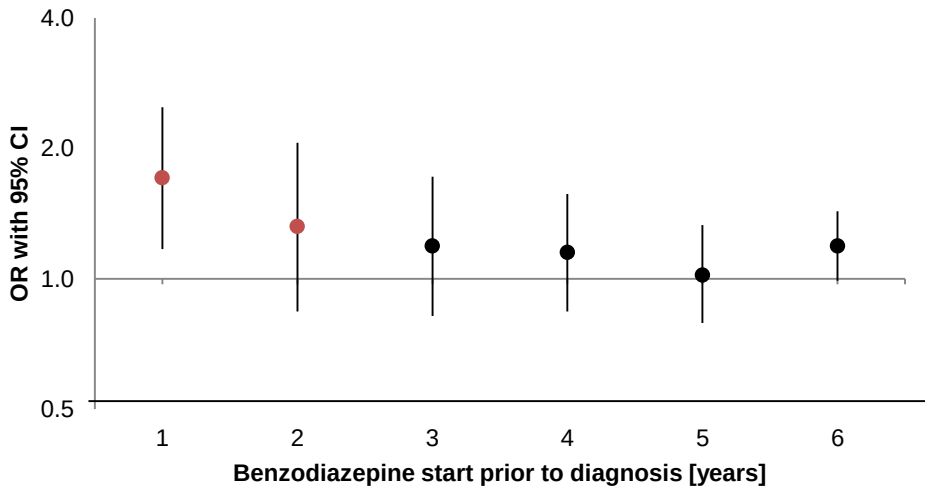

Figure 5: Crude ORs with 95% CIs of AD in relation to benzodiazepine start presented as whisker plot. *OR* odds ratio, *CI* confidence interval, *AD* Alzheimer's disease

Thus, after accounting for benzodiazepine use initiated during this potential prodromal phase, the overall risk of developing AD was no higher with prior benzodiazepine use (adjusted OR 0.82, 95% CI 0.70-0.97); the adjusted ORs were 0.86 (95% CI 0.71-1.03) for short-term use (1-9 prescriptions), 0.76 (95% CI 0.60-0.97) for medium-term use

(10-29 prescriptions), and 0.78 (95% CI 0.53-1.14) for long-term use (≥ 30 prescriptions) (Table 6).

Table 6: Use of benzodiazepines (prescriptions) and risk of AD, controlled for protopathic bias

	Cases (n = 1438)	Controls (n = 1438)	Crude OR [a]	Adjusted OR [b]
Benzodiazepines, prescriptions				
No	772 (53.7)	801 (55.7)	1 [Reference]	1 [Reference]
Yes	666 (46.3)	637 (44.3)	1.08 (0.94- 1.26)	0.82 (0.70- 0.97)
1-9	395 (25.0)	393 (27.3)	1.04 (0.88- 1.24)	0.86 (0.71- 1.03)
10-29	199 (13.8)	186 (12.9)	1.11 (0.89- 1.39)	0.76 (0.60- 0.97)
≥ 30	72 (5.0)	58 (4.0)	1.29 (0.90- 1.84)	0.78 (0.53- 1.14)
Classical benzodiazepines and BzRAs	128 (8.9)	127 (8.8)	1.04 (0.80- 1.36)	0.67 (0.50- 0.90)
1-9	100 (7.0)	106 (7.4)	0.99 (0.74- 1.32)	0.64 (0.47- 0.87)
10-29	22 (1.5)	17 (1.2)	1.34 (0.71- 2.55)	0.73 (0.37- 1.43)
≥ 30	6 (0.4)	4 (0.3)	1.68 (0.47- 6.07)	1.26 (0.33- 4.87)
Only classical benzodiazepines	449 (31.2)	435 (30.2)	1.07 (0.91- 1.26)	0.85 (0.71- 1.02)
1-9	369 (25.7)	364 (25.5)	1.05 (0.88- 1.25)	0.86 (0.71- 1.04)
10-29	68 (4.7)	56 (4.2)	1.26 (0.87- 1.81)	0.84 (0.57- 1.24)
≥ 30	12 (0.8)	15 (1.1)	0.82 (0.38- 1.77)	0.41 (0.18- 0.91)
Only BzRAs	89 (6.2)	75 (5.2)	1.24 (0.89- 1-71)	0.94 (0.66-1.33)
1-9	65 (4.5)	63 (4.5)	1.09 (0.76- 1.57)	0.82 (0.55- 1.21)
10-29	22 (1.5)	9 (0.6)	2.55 (1.17- 5.56)	2.06 (0.91- 4.68)
≥ 30	2 (0.1)	3 (0.2)	0.68 (0.11- 4.07)	0.49 (0.07- 3.22)
Only zolpidem	84 (5.8)	68 (4.7)	1.29 (0.92- 1.81)	0.99 (0.69- 1.42)
1-9	48 (3.3)	49 (3.4)	1.03 (0.69- 1.55)	0.81 (0.52- 1.24)
10-29	29 (2.0)	14 (1.0)	2.13 (1.12- 4.05)	1.54 (0.78- 3.03)
≥ 30	7 (0.5)	5 (0.3)	1.43 (0.45- 4.52)	1.22 (0.37- 4.08)

AD Alzheimer's disease, *OR* odds ratio, *BzRAs* benzodiazepine receptor agonists
[a] Adjusted for age, sex, and home location (canton) by matching
[b] Further adjusted for antidepressant use (yes/no)

There was no substantial difference in the relative risk of developing AD between users of classical benzodiazepines only or users of BzRAs only. Zolpidem was the most frequently used BzRA.

4.5 Discussion

Based on the fact that benzodiazepines can lead to drowsiness, cognitive impairment, and delirium [87–90], it has been postulated that long-term benzodiazepine use may also be associated with an increased risk of mNCD, in particular of AD. We did not detect any increase in the risk of AD in association with long-term benzodiazepine use after controlling for various potential confounders and for protopathic bias in this case-control study based on Swiss health insurance claims data. This is in contrast to some previous studies reporting an increased risk. [93–99] Only two of them considered that benzodiazepines may have been prescribed because of prodromal symptoms of mNCD and therefore corrected for the protopathic bias. [97,98] One of these studies, a cohort study conducted in 2012 [97], reported a multivariable adjusted hazard ratio of 1.62 (95% CI 1.08-2.45) in patients with new use of benzodiazepines. The other study, a case-control study conducted in 2014 [98] based on a Canadian insurance database, also reported a statistically significantly increased risk for AD in relation to benzodiazepine use expressed as cumulative daily doses (adjusted OR 1.43, 95% CI 1.28-1.60). However, our findings are consistent with two previous observational studies correcting for reverse causation bias, [100,101] which reported an overall adjusted OR of 0.69, (95% CI 0.57-0.85) [100] and an adjusted hazard ratio of 1.05 (95% CI 0.75-1.46) [101] for patients with long-term benzodiazepine use (≥ 121 defined daily doses).

Our study has several limitations. Because we did not have access to diagnostic codes from ambulatory care, we used ATC drug codes to identify AD cases. We may therefore have only included those patients who were thought to potentially profit from a pharmacological therapy. At the same time, it is possible that a certain proportion of controls may have had undiagnosed subclinical AD, which could lead to some outcome misclassification, which may dilute the relative risk towards a null finding if distributed non-differentially. As these drug used to identify AD cases could also have been used off-label to treat other forms of mNCD, there is also a possibility that we included not only AD cases. However, strictly speaking, AD can only be clearly and firmly diagnosed post-mortem.

With adjusting for antidepressant drugs, we tried to exclude the effect of depression. However, we may not only have excluded patients with depression, as antidepressants

can also be used for the treatment of pain. As mNCD is also associated with PD, [106] and as rivastigmine is also used in the treatment of mNCD associated with PD, [107,108] we excluded PD patients by identifying them via PD-specific treatment. PD is relatively rare in Switzerland; only about 15,000 patients are known to have PD. [109] However, mNCD is a frequent complication of PD with a yearly incidence of around 10% of patients with PD, often during later stages of the disease. [110] Lewy-body pathology is the most important factor in the development of PD dementia. [110] A previously published literature review on the prevalence and incidence of dementia with Lewy bodies reported a prevalence of 0.3-24.4% of all cases of mNCD. [111]

Another limitation of our study is the incomplete coverage of medical history in the database. Claims data were only available from 2008 onwards. Moreover, the limited time period prior to the index date prevented us from studying patients with very long benzodiazepine use, and it may leave room for some misclassification, as we cannot rule out with certainty that we included some controls with an AD diagnosis prior to 2008. Furthermore, we may have missed patients with depression, a potential confounder in our analysis, as we could only identify them by ATC drug codes for antidepressants. In addition, we may have misclassified patients taking antidepressants as patients with depression, because antidepressants can also be used as co-analgesics for other indications.

The strengths of our study include the substantial number of individuals with incident AD from different regions of Switzerland with several years of previously recorded drug history. As benzodiazepines as well as anti-mNCD drugs are only available upon prescription, we did not miss substantial amounts of exposure information in this study. Thus, an advantage of claims data is that the use of study drugs had been recorded comprehensively and that the medications had not only been prescribed, but actually been dispensed by a pharmacy or physician.

In conclusion, this large case-control analysis using health insurance claims data from Switzerland did not find evidence for a previously hypothesized association between benzodiazepine use and an increased risk of developing AD.

PROJECT III

Iron supplementation in Switzerland –

A bi-national, descriptive and observational Study

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Swiss Medical Weekly 2017; 147: w14444

5.1 Abstract

Background: Iron deficiency is the most common nutritional disorder in the world, and it is the only common nutrient deficiency in industrialized nations. It is thought to be the most common cause of anemia. Use of iron supplementation in Switzerland has not been previously quantified in detail.

Objectives: We quantified use of iron supplementation from Swiss data and compared it with data from the UK. We assessed the frequency of serum ferritin and hemoglobin tests prior to newly started iron therapy to see whether use was based on documented low iron levels or blood parameters, especially in the case of parenteral iron supplementation.

Methods: We conducted a retrospective descriptive study of prescription iron supplementation use, and compared use of oral or parenteral iron drugs between Switzerland (CH) and the UK. We retrieved Swiss data from the Swiss Health Insurance Helsana Group, and UK data were from the CPRD. The study period was 2012 to 2014.

Results: The 3-year prevalence of iron supplementation was 9.4% in Switzerland and 4.4% in the UK. Iron use increased slightly between 2012 and 2014 in both countries (CH +0.3%, UK +0.2%). Recorded parenteral iron administration was roughly a thousand times higher in Switzerland (1.9%) than in the UK in 2014. In Switzerland, iron supplements were mostly given to patients aged 20 to 49 years or older than of 80 years. In the UK, iron supplementation was less frequent in younger people, but more prevalent in the elderly. Prior to a first iron prescription, ferritin tests were done more frequently in Switzerland (oral 67.2%, parenteral 86.6%) than in the UK (oral 43.3%, parenteral 65.5%). Hemoglobin was measured before a new parenteral iron therapy rarely in Switzerland (oral 14.9%, parenteral 11.7%), but frequently in the UK (oral 77.4%, parenteral 85.6%).

Conclusions: Iron supplementation is more common in Switzerland than in the UK, particularly parenteral iron supplementation. Hemoglobin measurements prior to a new parenteral iron therapy are relatively infrequent in Switzerland despite the required documentation of hemoglobin prior to therapy.

5.2 Introduction

Iron deficiency (ID) is the most common nutritional disorder in the world and the only nutrient deficiency that is common in all industrialized nations. [11,112] The prevalence of ID in Europe has been reported to be around 12 to 40%. [114] In the UK, 21% of female teenagers between 11 and 18 years, and 18% of women between the ages of 16 and 64 years are iron deficient. [115,116] The prevalence of ID in Switzerland is not well known.

A recent study reported a prevalence of 50% (serum ferritin cut-off 22 µg/ l) in a sample of healthy female hospital employees in Switzerland; with a lower cut-off of 15 µg/ l, the prevalence was still 33%. [114] Another recent Swiss study assessed ID in hospitalized patients and found a prevalence of 4.9% (cut-off: ferritin < 15 µg/ l) [117], and a screening in young Swiss soldiers yielded a prevalence of 16.8% (cut-off: ferritin < 30 µg/ l) [118]. In 2013 the ID prevalence in Portugal was reported to be 16.7% (cut-off: ferritin < 15 µg/ l) in the total population, and 19.8% in females. [119] Serum ferritin is the most powerful test to detect ID and the best indicator of a response to an intervention to treat it. The cut-off level of serum ferritin varies between 12 and 15 µg/ l. [112,113]

ID is thought to be the most common cause of anemia. [112,120,121] The WHO defines anemia as a hemoglobin level below 13 g/ dl in men over 15 years, below 12 g/ dl in non-pregnant women over 15 years, and below 11 g/ dl in pregnant women. [112,122]

It is estimated that in the UK 3% of men and 8% of women suffer from iron deficiency anemia (IDA). [116] It is further estimated that in the developed world around 2 to 5% of adult men and postmenopausal women have IDA. [122] In Switzerland, 15% of a sample of healthy female hospital employees [114] and 1.0% of young Swiss soldiers [118] were diagnosed with IDA, and another Swiss study reported a high co-occurrence of ID and IDA [117]. The prevalence of IDA in Germany was reported to be 2.9% (cut-off: ferritin < 15 µg/ l) for the total population, and of 4.1% for females in 2011. [123] In 2013, a high IDA prevalence of 5.8% (cut-off: ferritin < 15 µg/ l) in the total population, and of 6.4% in the females was found in Portugal. [119] A large nationwide population-based study published incidence rates of IDA (cut-off: ferritin < 15 µg/ l) for Germany, Belgium, Spain and Italy. [123] The authors reported the highest incidence rate of IDA in 2011 in Germany and Spain with rates of 12.42 and 14.14 per 1000 person-years, respectively.

The incidence rates for females in Germany and Spain were reported to be 17.27 and 22.14 per 1000 person-years, respectively. Table 7 gives an overview of the ID/IDA prevalence. However, not all anemic people are iron deficient, and ID may occur without anemia. Iron supplementation is the most common therapeutic option currently used in developing countries to treat ID, as well as to treat existing IDA. It is important to correct ID in populations at high risk of ID and anemia, and to prevent anemia by providing iron supplementation. However, supplementation for the prevention of IDA and supplementation to correct it must be distinguished; the dose to prevent IDA in women of childbearing age in populations with a high prevalence of anemia (> 40%) is 60 mg/ day for 3 months; the dose of iron recommended to treat IDA for adults is 120 mg/ day for 3 months. [112] Women of childbearing age, not only pregnant women in whom the prevalence of IDA is 14% (12), are the target group for supplementation for the prevention of ID. Therapeutic supplementation should be covered by the healthcare delivery system. [112]

Table 7: Overview of ID/ IDA prevalence in different studies

Trial	ID prevalence	IDA prevalence	Serum ferritin cut-offs
Schuepbach et al. [114]	50% of female hospital employees	15% of female hospital employees	ID: < 22 µg/ l IDA: < 22 µg/ l
Heath et al. [115]	- 21% of females aged 11-18 years - 18% of females aged 16-64 years		< 15 µg/ l
Hug et al. [117]	4.9% of hospitalized patients		< 15 µg/ l
Schleiffenbaum et al. [118]	16.8% of young Swiss soldiers	1% of young Swiss soldiers	ID: < 30 µg/ l IDA: < 30 µg/ l
Fonseca et al. [119]	- 16.7% of total population - 19.8% of females	- 5.8% of total population - - 6.4% of females	ID: < 15 µg/ l IDA: < 15 µg/ l
British Society of Gastroenterology [122]		2-5% of adult men and postmenopausal women	
Ruston et al. [116]		- 8% of British females - 3% of British males	< 13 µg/ l
Levi et al. [123]		- 2.9% of German residents - 4.1% of German females	< 15 µg/ l

ID Iron deficiency, *IDA* Iron deficiency anemia

To date there are no data available on the correlation between IDA and iron supplementation in Switzerland. According to the Swiss Compendium [75], treatment with parenteral iron drugs (e.g. Ferinject®) is accepted for use restricted to the treatment of ID when oral iron preparations are ineffective or cannot be used. The diagnosis must be based on laboratory tests. Using claims data from the largest health insurance group in Switzerland and general practitioner-based data from the UK, we quantified iron drug use in Switzerland and described patterns of use of oral and parenteral iron supplementations (multivitamins are excluded) between 2012 and 2014 in the Swiss market and in the UK health system.

5.3 Methods

Study design and data source

We conducted a descriptive, bi-national study using claims data from the Swiss health insurance Helsana Group [65] and from the CPRD [17] covering the time span between 2012 and 2014. The Helsana Group insures some 1.9 million inhabitants in Switzerland. All health insurance companies in Switzerland are private, there is no national health insurance system, but health insurance is mandatory for everybody living in Switzerland. In collaboration with Helsana, we have used claims data for descriptive analyses of HRU in Switzerland. [37,38] The recorded data include patient demographics such as age and sex, postal code of residence, and drug prescriptions (including dose, galenic formulation, and pack size). Patients' personal characteristics such as smoking habits or weight/BMI, as well as laboratory data, symptoms, ambulatory diagnoses, or medical resource use during hospitalizations are not recorded in the database. In 2012, Switzerland introduced a payment system based on DRGs for acute-somatic inpatient care. The SwissDRG system is based on the German G-DRG version of 2008 [40,41]; SwissDRG codes are available from the database. The database is located at Helsana, and researchers had access to an anonymized dataset encompassing the relevant patients and the relevant parameters for this analysis.

The CPRD, formerly known as the GPRD [17], was established in 1987. It is a large UK-based database providing health care information on some 10 million patients in the UK; it is one of the largest databases of longitudinal medical records from primary care in the

world. The CPRD has previously been described in detail.[18,19] In the UK, GPs are responsible for primary healthcare and for referrals to specialists. They have been trained to record information on demographics, medical diagnoses, laboratory values, and drug prescriptions as well as patient referrals and hospital admissions, using standard coding systems. The medical diagnoses are recorded as Read-codes. The GPs generate prescriptions directly from the computer, and this information is automatically transcribed into the individual computerized patient records. They contain the drug name, instructions for use, route of administration, dose, and number of tablets for each prescription. For complete information, individual patient records may be assessed. Additionally, the CPRD holds information regarding lifestyle variables such as BMI, alcohol consumption, and smoking. We extracted the relevant patients and data parameters for this analysis from the fully anonymized database.

The study was approved by ISAC, the Independent Scientific Advisory Committee for MHRA database research (protocol number 15_080R).

Study population

We identified all individuals who received at least one prescription for a drug coded in the ATC as class B03A (oral and parenteral iron drugs; multivitamins are excluded) between 2012 and 2014. We then excluded all patients with a diagnosis of cancer (except non-melanoma skin cancer) at any time in the record. In the CPRD, drugs are identified by gemscript codes. The date of the first iron prescription during the study period was considered the index date. We quantified the number of oral and parenteral iron prescriptions as well as the number of ferritin and hemoglobin tests 12 and 24 months prior to the index date. We calculated the prevalence of iron drug use (oral/ parenteral/ both) for years 2012, 2013 and 2014, as well as the cumulative prevalence in 2012 to 2014. In addition, we assessed the time interval between the index prescription and the previous and subsequent iron drug prescriptions.

In a sensitivity analysis, we restricted the study population to ‘new’ users of oral or parenteral iron supplementations; new users must not have received another oral or parenteral iron prescription for at least 180 days before the index date. We assessed

whether these patients had any serum ferritin and/ or hemoglobin tests prior to the 'new' iron drug prescription.

An additional analysis distinguished between different parts of Switzerland according to language region (German, French or Italian). The list of cantons representing the three language regions is displayed as footnote in Table 8.

Statistical analysis

We additionally stratified the numbers and proportions of drug users by age group (0-9, 10-19… 90+) and sex (male/female). These analyses were pre-specified and planned *a priori*. We focused on women of childbearing age because of the higher prevalence of IDA in this subgroup.[124] We calculated frequency distributions using the software programs Stata MP 13.

5.4 Results

Within the Helsana claims database, the 3-year prevalence for ID was 9.4%, and the 1-year prevalence was 4.5% in 2014, which reflects a slight increase of 0.3% since 2012. In contrast, in the UK the 3-year prevalence for ID was 4.4% and the 1-year prevalence 2.6% in 2014, reflecting an increase of 0.2% since 2012. Women (CH 16.0%, UK 6.9%) had a substantially higher prevalence of diagnosed ID than men (CH 2.6%, UK 1.7%). We further observed a marked difference in the use of parenteral iron supplementation. In Switzerland around 1.9% of all insured persons received an infusion at some point in time during the study period in the ambulatory setting, whereas in the UK only 0.002% received iron intravenously, as recorded by the GPs. Since 2012, use of parenteral iron supplementation has slightly (+0.2%) increased in Switzerland, but remained stable at a low level in the UK. On the other hand, oral iron supplementation has increased both in Switzerland and in the UK by about 0.2% during the same time period. In Switzerland, iron supplementation tended to be slightly higher in the French-speaking part of Switzerland (5.4% in 2014) than in the German- (5.0% in 2014) or Italian- (5.0% in 2014) speaking parts, whereas use of parenteral iron supplementation tended to be slightly higher in the German-speaking part (2.1% in 2014) compared to the Italian- (1.9% in 2014) and the French- (1.6% in 2014) speaking parts (Table 8).

Table 8: Prevalence of oral and parenteral iron supplementation (% of insured)

Region	2012	2013	2014	Change since 2012
German part of Switzerland				
Oral iron supplementation	3.2	3.3	3.4	+0.2
Parenteral iron supplementation	2.0	2.1	2.1	+0.1
Total	4.8	4.9	5.0	+0.2
French part of Switzerland				
Oral iron supplementation	4.0	4.1	4.2	+0.2
Parenteral iron supplementation	1.3	1.5	1.6	+0.3
Total	5.0	5.2	5.4	+0.4
Italian part of Switzerland				
Oral iron supplementation	3.1	3.3	3.4	+0.4
Parenteral iron supplementation	1.5	1.8	1.9	+0.4
Total	4.3	4.7	5.0	+0.7
Overall Switzerland				
Oral iron supplementation	3.2	3.3	3.4	+0.2
Parenteral iron supplementation	1.8	1.9	1.9	+0.2
Total	4.6	4.8	4.9	+0.3

German part: Aargau, Appenzell Innerrhoden, Appenzell Ausserrhoden, Bern, Basel-Landschaft, Basel-Stadt, Glarus, Graubünden, Luzern, Nidwalden, Obwalden, St. Gallen, Schaffhausen, Solothurn, Schwyz, Thurgau, Uri, Zug, Zürich French part: Fribourg, Geneva, Jura, Neuchâtel, Vaud, Valais Italian part: Ticino

In Switzerland, the iron (III)-hydroxide polymaltose complex Maltofer® was the most frequent oral iron preparation used (11.7%). In contrast to other oral iron medications, it should be taken with food ingestion for better gastrointestinal tolerability. [75] Maltofer® was followed by iron (II) sulfate without folic acid (9.3%), and by a combination with folic acid (8.8%). Among parenteral iron preparations, iron carboxymaltose (Ferinject®) was the most commonly used preparation (86.3%).

In Switzerland (Figure 6), iron supplements were mostly given to patients between the ages of 20 and 49 years (prevalence 12.4%), and after the age of 80 years with peak prevalence of 14.1% between 30 and 39 years, and of 16.8% above 90 years. In the UK, iron supplements were less likely given to younger people, but more often to the elderly as compared to Switzerland. Compared with the UK (Figure 7), oral iron supplements were prescribed more to women (CH 11.0%, UK 6.9%) and less often to men (CH 1.7%, UK 1.9%) in Switzerland. Furthermore, children in Switzerland were more frequently treated with oral iron than in the UK (children up to the age of 9 years CH 3.8%, UK 1.3%).

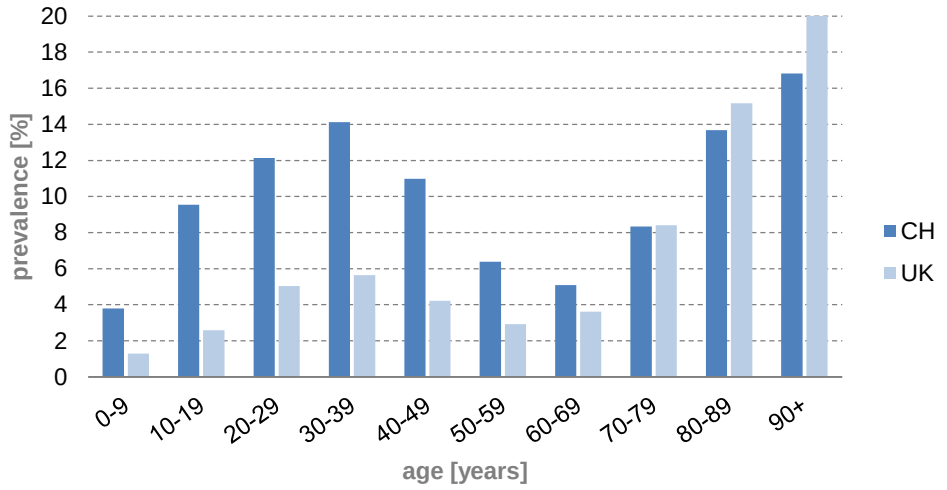

Figure 6: Prevalence of iron substitution in different age groups in Switzerland and the UK, 2012 to 2014

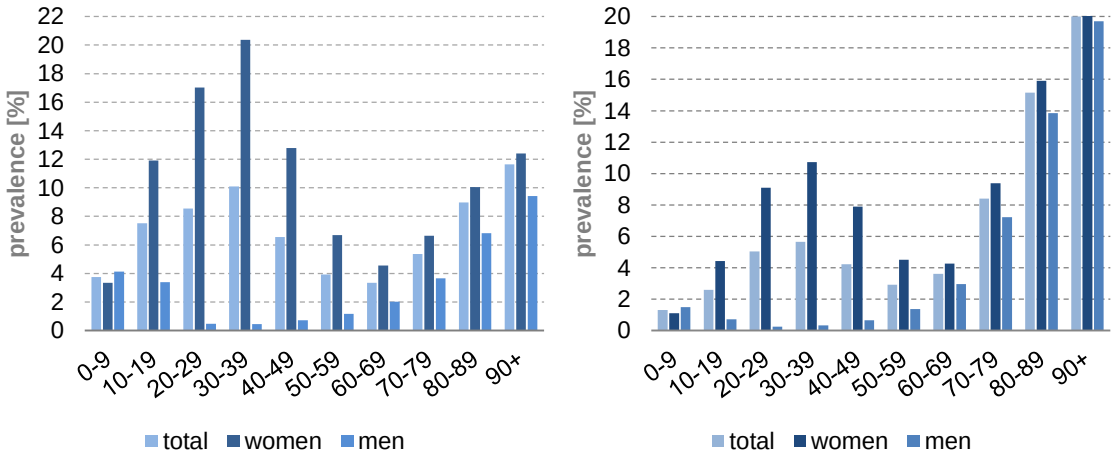

Figure 7: Prevalence of oral iron substitution in different age groups for both sexes in Switzerland (left) and in the UK (right), 2012 to 2014

In Switzerland, iron infusions were given less often than oral iron drugs (Figure 8). The age curves of parenteral and oral administration had similar shapes with a peak at age above 90 years (oral 11.6%, parenteral 5.2%). Intravenous iron applications were more likely to be given to the 40 to 49-year age group (4.5%); oral supplementation, was more common in the age range of 30 to 39 years (10.1%).

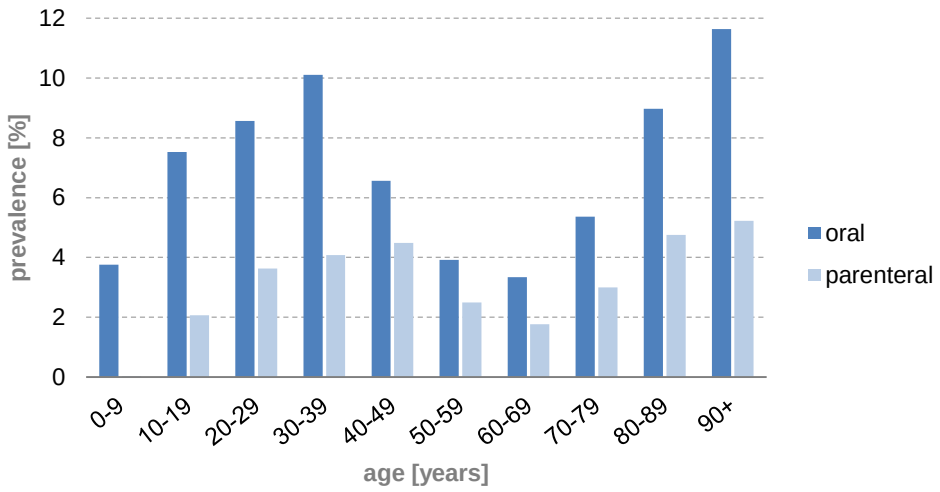

Figure 8: Prevalence of oral and parenteral iron substitution in different age groups in Switzerland, 2012 to 2014

In women (Figure 9) the peak prevalence of iron infusion was reached in the age group 40 to 49 years (8.8%), and in men the peak was in the group aged over 90 years (5.0%). In children up to the age of 9 years almost no iron infusions were administered in Switzerland, and none in the UK. Owing to lack of studies [75], parenteral iron supplementation is not recommended in children.

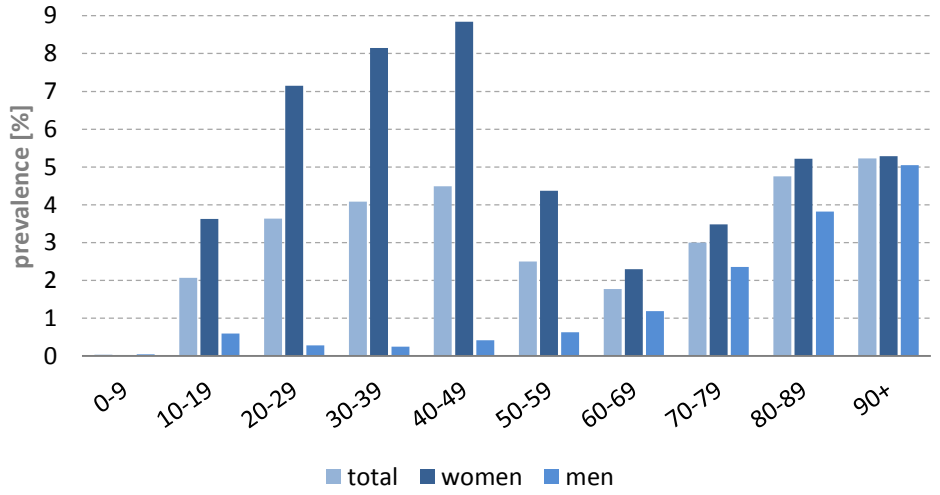

Figure 9: Prevalence of parenteral iron substitution in different age groups for both sexes in Switzerland, 2012 to 2014

In Switzerland and in the UK (Figure 10 and Figure 11), oral iron supplementation was given mainly to women of childbearing age (12-49 years) between 30 and 39 years old (prevalence CH 20.4%, UK 10.7%). On the other hand, parenteral iron supplementation was given mainly to women aged 40 to 49 years. However, iron infusions in the UK were rare, even in women of childbearing age (prevalence CH 8.8%, UK 0.005%).

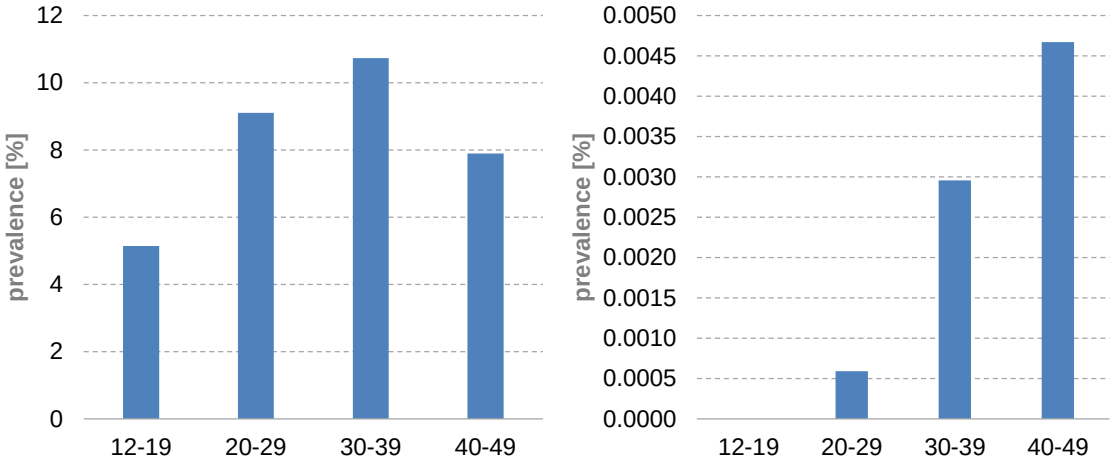

Figure 10: Prevalence of oral (left) and parenteral (right) iron substitution of women of childbearing age in the UK, 2012 to 2014

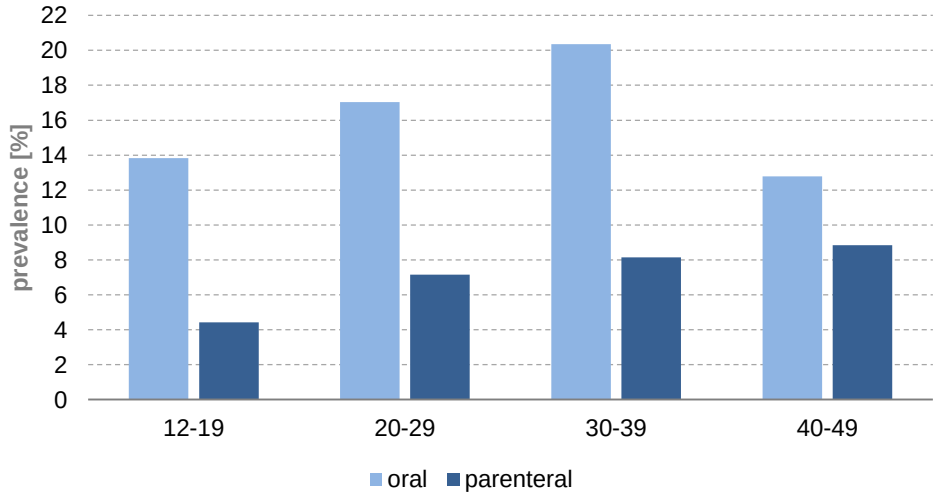

Figure 11: Prevalence of oral and parenteral iron substitution of women of childbearing age in Switzerland, 2012 to 2014

The sensitivity analysis of newly started oral and parenteral iron substitutions (Table 9) showed that in both Switzerland and the UK, laboratory parameters were measured more often before starting a new parenteral therapy (CH 87.9%, UK 87.1%) than before a new oral therapy (CH 73.8%, UK 78.2%).

Table 9: Lab parameters (ferritin, hemoglobin) measured within 180 days before iron substitution (percentage of patients treated)

Lab values	Switzerland (%)	United Kingdom (%)
Oral iron substitution		
Hemoglobin or ferritin	73.8	78.2
Ferritin only	67.2	43.3
Hemoglobin only	14.9	77.4
Hemoglobin and ferritin in combination	8.3	42.6
Parenteral iron substitution		
Hemoglobin or ferritin	87.9	87.1
Ferritin only	86.6	65.5
Hemoglobin only	11.7	85.6
Hemoglobin and ferritin in combination	10.3	64.0

Ferritin was in general measured more frequently in Switzerland (oral 67.2%, parenteral 86.6%) than in the UK (oral 43.3%, parenteral 65.5%), while hemoglobin tests before a new parenteral iron therapy were rare in Switzerland (oral 14.9%, parenteral 11.7%) and more frequent in the UK (oral 77.4%, parenteral 85.6%). Testing both ferritin and hemoglobin was more frequent in the UK (oral 42.6%, parenteral 64.0%) than in Switzerland (oral 8.3%, parenteral 10.3%).

5.5 Discussion

The practice of iron substitution is quite different in Switzerland and in the UK. In 2014, iron application overall was more frequent in Switzerland than in the UK. The prevalence of parenteral iron infusions was about 1,000 times higher in Switzerland than in the UK in the ambulatory setting. We cannot rule out the possibility that we missed infusions administered in hospitals in the UK; however, the same holds true for Switzerland. This observation of a substantially higher frequency intravenous application of iron in ambulatory care may be explained by the fact that GPs in the UK administer iron infusions rarely, and iron infusions administered in specialized clinics or hospitals are not comprehensively recorded in the CPRD. However, despite some possibly missing data in the CPRD, a substantial difference seems to exist in the frequency of iron infusions administered in Switzerland and in the UK in the ambulatory setting.

The overall prevalence of iron supplementation in Switzerland, 4.9% in our data, was consistent with the ID prevalence of 4.9% reported in a recent Swiss study [117], in which a cut-off of serum ferritin of < 15 µg/l was used.

The frequency of laboratory measurement of ferritin and hemoglobin for patients who were newly started on iron supplementation was lower in Switzerland than in the UK. In theory, assessment of hemoglobin is required to justify iron infusions and to find the appropriate iron dose, [75] but these results were not always available in Switzerland. Between 2006 and 2010, hemoglobin parameters were assessed more frequently than ferritin 90 days before iron treatment in Switzerland. [125]

To our knowledge, large studies assessing the prevalence of ID in Switzerland are lacking. [114,117,118] However, in relation to the ID prevalence reported in the international literature [114–116,119,123], the number of patients treated with iron seems to be low. A recently published study from Australia investigated whether people with IDA were more likely than 'healthy' people to get iron supplementations. [126] They concluded that there was a mismatch between the number of people who got iron supplementation and the number of people in need. They found evidence that iron supplementation is dependent on socioeconomic status, but less associated with risk factors for IDA, a pattern that was

similar in other studies [127–129]. Thus, estimating the prevalence of ID or of IDA in Switzerland by taking iron supplementation as a proxy may not be reliable.

Iron infusions in Switzerland are popular because administration is relatively quick and easy, the rate of adverse drug reactions, for carboxymaltose (Ferinject®), for example, is low, and intravenous application eliminates concerns over poor adherence, which may be a challenge where oral iron supplementation is associated with adverse gastrointestinal effects.

Strengths and limitations

The strengths of our study include the substantial number of individuals with iron supplementation from different regions of Switzerland, as well as from the UK, with several years of prior recorded drug history. Claims data tend to encompass drug use comprehensively; furthermore, medications had not only been prescribed, but actually dispensed by a pharmacy or physician. In the UK prescriptions are recorded by the GP, but it is not known whether the prescription was filled. In addition, it is intriguing to compare iron supplementation between two countries with different health systems - the Swiss health system with a mix of private and public characteristics versus the Nationals Health Service (NHS) in the UK.

Our study has several limitations. Because we used claims data, we identified only individuals who received prescriptions for the iron preparations of interest, but there is also use of OTC oral iron supplements. The same is also true for the analysis of UK data. However, such use is likely to be minimal compared with longer-term use prescribed by doctors, which occurs when IDA is diagnosed. Another limitation of the study is that although Swiss claims data do provide information on whether and/or when laboratory test was performed, they do not provide information on the actual laboratory value (e.g., ferritin, hemoglobin). Thus, we were not able to address the question of whether iron supplementation was justified in a given individual patient or not. Similar to the Swiss data, a limitation of the CPRD database is that we may have missed iron infusions administered in hospitals.

In conclusion, iron supplementation is more common in Switzerland than in the UK, particularly the application of parenteral iron infusions.

FINAL DISCUSSION, CONCLUSION, AND OUTLOOK

6.1 Discussion

The three projects presented within this thesis provide a multifaceted perspective on the use of Helsana claims data for pharmacoepidemiological research. The main results of each individual project have been discussed in detail in the respective discussion sections. In the following, more general aspects of the findings will be considered and the opportunities but also the limitations of the Helsana claims database will be discussed with examples from the different studies.

In the process of analyzing the data source, a number of factors must be taken into consideration, including the extensiveness and depth of data, the quality of database, the population covered, and the duration of information contained in the database. [130]

6.1.1 Strengths of the Helsana Claims Data

Documentation

In the Helsana claims data the information is recorded with high accuracy and is send for reimbursement to the health insurance in form of detailed, precise and complete claims. Drug identity, amount and dose are documented of extremely high quality in claims data since filling of an incorrect claim about drugs dispensed is fraud. Furthermore, claims data exactly show what was dispensed and not only what was prescribed, they are one step closer to the actual intake of medication than physician's prescriptions. This is an advantage compared to prescription databases such as the CPRD, because claims data tend to have less misclassification of medication exposure. [1,131] Thus, pharmacy dispensing information is considered to be the gold standard in drug exposure compared to outpatient medical records; they cannot be biased by the knowledge of study outcome. [12] Numerous validity studies confirm that the patient was dispensed exactly what the claims showed and this makes claims data providing some of the best data on drug exposure in pharmacoepidemiology. [1,12,22]

Another benefit of these data is that they include drug information dispensed from both the physician and the pharmacy, as long as the drug expenses are claimed back from the insurance. In Switzerland, people are free to choose their GPs and they can visit even several GPs at the same time, as well as they can visit numerous of pharmacies. But all

the insurances, in our case the Helsana claims data, are including a complete set of claims for each insured person, not depending on the source of prescriptions.

Size

With the amount of 1.9 inhabitants of Switzerland, the Helsana health insurance covers approximately 22.9% of the Swiss population [65,132], which is high compared to the CPRD database that covers only about 7% of the total UK population [23]. However, the PHARMO database covers approximately 25% of the residents [25]; the DNPR is tracking each Dane from birth to death [27–29] and covers therefore the entire Danish population.

The large size of the Helsana claims data allows studying rare events as well as utilization patterns at relatively low costs. In **Project II** that included a sample of almost 1,438 incident AD patients, the exposure of benzodiazepines as a potential cause of developing AD was observed. In Switzerland, more than 100,000 people suffer from mNCD [77] and AD is known to be the most common cause, but still it counts to rare disorders [133]. This study reported similar results compared to a previously published study carried out on the CPRD [100], namely that long-term use of benzodiazepines was not associated with an increased risk of developing AD. Both studies assumed that first-time prescription of a benzodiazepine shortly before the diagnosis date may be due to symptomatic treatment of prodromal symptoms of early mNCD and therefore they ignored benzodiazepine prescriptions issued during the last 2 years preceding the diagnosis date. The fact that we could reproduce the same results with our study let us assume that the Helsana claims data are suitable also for the analysis of rare diseases.

In **Project III,** we examined the use of oral and parenteral iron supplementation in Switzerland and compared it to the use in the UK. With this utilization study we further tried to estimate the prevalence of ID in Switzerland and the UK and additionally we focused on incident patients receiving iron supplements and checked whether these patients had any serum ferritin and/or hemoglobin tests prior to the 'new' iron drug prescription. To assess such basic information on the prevalence, incidence and duration of drug therapy is essential for health system planning and for evaluating the quality of prescribing. [12] Compared to records based on physician prescribing, these measures can be derived more accurately from pharmacy dispensing data as the Helsana claims data.

Low costs

The studies undertaken with claims data are retrospective because the data have been already recorded. Advantages of retrospective trials are the short time frame and the low costs. [6,134] For studies based on the Helsana claims data, no extra costs are generated because the data are collected for reimbursement anyhow.

6.1.2 Limitations of the Helsana Claims Data

Missing data

The lack of information on lifestyle factors as potential confounders in the Helsana claims data (e.g. smoking habits, BMI, alcohol consumption) may bias the association between drugs and the outcome. But also the missing of clinical diagnoses may lead to bias and confounding and is a general weakness of these data.

In **Project I** we could not adjust for some known risk factors for gallbladder disease such as overweight [51] or SES [68]. As overweight and SES are in part related to diabetes [71–74], and as we considered BMI to be an important factor and a potential confounder of the association between statin use and gallstones, we adjusted the analyses for diabetes as a proxy for BMI, albeit diabetes and BMI are not directly correlated. However, with this assumption we received similar results as a previously published study based on the CPRD [51].

The quality of the disease recording in claims data is inaccurate. [1] At hospital admission, hospital charges in Switzerland are claimed from the insurance according to the Swiss DRG system and they are based on accurate diagnoses. But outpatient diagnoses are assessed by the GP and do not have to be transferred to the health insurance. Thus, it has to be considered, that the observed outcome of analytical studies may have underlied the possible effect of misclassification. [12]

In **Project I** we identified the gallstone cases according to the SwissDRG procedure code for cholecystectomy. We therefore only included the more severe cases of patients with gallstones as previous studies revealed that only 12% of patients with gallstones develop symptoms and that 15% develop severe symptoms. [76] However, including only the more severe cases of a given outcome of interest does not introduce distortion in a case-control

analysis. Whenever an outcome can present with mild symptoms, with a moderate course or even as an acute and severe event, it is always difficult to draw a line and to decide which patient is a case and which one not. Gallstones can be mild and go undetected, they can be detected by chance upon ultrasound or other diagnostic means, they can lead to unspecific symptoms, or they can lead to a severe colic requiring a visit at the emergency room. It may often even be better to only include case patients with the most severe symptoms, as they are most likely those with the best documented and most valid outcome diagnoses, and they most likely differ most from controls who are not supposed to have gallstone disease. But the problem of potential misclassification in this study is that a certain proportion of controls may have had yet undiagnosed subclinical gallstone disease that could lead to considerable misclassification of the outcome, which may lead to a null finding.

The same problem of misclassification is also present in **Project II**, where AD cases were identified according to AD specific drugs. No sensitivity and specificity testing of using these medications to identify AD type of mNCDs has been previously done in the Swiss health-care system. We could therefore again not rule out that some of the controls may in fact have AD that were not identified with medication use. Furthermore, we may have included cases who were in fact not proper AD cases, but who were misclassified maybe due to other underlying conditions such as corticobasal degeneration (CBD), which is also associated with other forms of mNCDs.[106] Addressing these two points, we identified all cases, which suffered from PD (based on drugs used to treat PD) and excluded them from the cases but also from the controls. We additionally excluded all cases and controls with HIV as it can itself be an important risk factor for mNCDs in 20 to 30% and we excluded all patients with a diagnosis for multiple sclerosis because also these patients can experience cognitive difficulties.

Another issue is that we eventually have missed real AD cases who did not receive any AD treatment. However, as missing cases only reduced the power, this problem of misclassification is negligible.

The risk of misclassification is smaller in **Project I** compared to **Project II**. In **Project I**, only the more severe gallstone patients were included (low sensitivity), but the specificity is high, because the chance of having a cholecystectomy without gallstones is very rare.

In **Project II** we identified AD patients according to AD drug therapy. Here the same could have happened, that we included only the more severe or end of stage AD cases, but there is also a high chance that we included cases without AD but with other forms of mNCD (low specificity), even though AD is the most common form of mNCD [106]. In general, patients with a procedure code must have been undergone a surgery for sure; compared to patients with drug therapy, they did not must have taken the drugs or furthermore they could have taken them not in a correct dose or interval. But in both projects we cannot rule out that we potentially included cases in our controls; this might have diluted the association between explosion and outcome towards the null hypothesis.

To carry out such analytical studies as **Project I** and **Project II**, we had to find a solution for the lack of information on these clinical diagnoses as gallstones and AD. As discussed before, patients suffering from gallstones could be identified with a high specificity, but it has to be mentioned on the other hand that DRGs are in general very unspecific in their formulation and therefore opportunities of observing associations are limited. In comparison, patients suffering from AD could not be identified with high specificity, because AD treatment as most drug therapies, including treatments for cardiovascular or psychiatric diseases are unspecific too.

The lack of information on laboratory values is another limitation of missing data. In **Project III**, we tried to estimate whether iron supplementation in Switzerland is justified. Because of the missing hemoglobin and ferritin values we were not able to actually justify the higher supplementation in Switzerland compared to the UK. Thus, we could only examine whether use was based on previously applied blood tests, but we were not able to answer the question whether iron supplementation was justified in a given individual patient or not.

Another limitation of missing data in the Helsana claims data is that they do not contain OTC medication or drugs prescribed during hospitalization. [131] Furthermore, if the patient does not claim the expenses of prescribed drugs back from the health insurance by paying for them himself, the information about these drugs won't be in the database either. However, also if drugs are part of the database, we never know if they were in fact taken. This means that we cannot be sure that our exposed group was actually exposed. But, compared with other databases, based on medical records only (e.g. CPRD), we are able

to examine the frequency of patient's visits in the pharmacy and could therefore assume with a high degree of probability, whether he is taking his medication or not.

Confounding by indication

The Helsana claims data are generally depending on the prescriptions of physicians. The prescription of a drug itself is based on diagnostics but also on behavioral habits from the physician and the patient. In general, a drug is more likely to be prescribed to a patient that suffers from more severe diseases and this patient also is more likely to undergo adverse events from the disease. Thus, we can say that a patient who receives a certain drug therapy is basically different from another patient not receiving the therapy. [15,16]

In **Project I**, where we examined the risk of developing gallstones under statin exposure, we might have included statin users without elevated cholesterol levels. Therefore, we might have overestimated the negative association between statins and cholecystectomy based on the hypothesis that hyperlipidemia may affect cholesterol gallstones formation. [62–64] In general, patients can get prescriptions for statins because of their hyperlipidemia as primary prevention, or they can get statins as secondary prevention after a disease has already occurred.

Short follow-up

Helsana claims data are only available from 2008 on, and the insured persons in Switzerland are free to switch between health insurance companies every year. The restricted time period prior to the index date in **Project I**, however, also leaves room for some misclassification, as we cannot rule out that we included some controls with a cholecystectomy prior to 2008. In **Project II** this was not the case, as we included only incident AD cases. The fact that people can switch to another health insurance each year because of fluctuating insurance prices leads to an unstable data enrollment. But continuity of coverage is important to increase the likelihood of uninterrupted follow-up time. The opportunity for longitudinal analyzes is thereby hindered by the continual dis-enrollment of insured. [131]

Population-based data

The Helsana claims data do not fully represent the Swiss population (age, sex, canton), which was shown in previously published Helsana drug reports [37–39]. In these reports,

where medication costs and utilization were analyzed, the data were extrapolated to the entire Swiss population using expansion factors based on the Federal Office of Statistics considering age, sex and residency (canton) of the patients.

6.2 Conclusion and Outlook

Since the Helsana claims data exactly show what was dispensed and not only what was prescribed, these data are considered to be the gold standard in drug exposure as they cannot be biased by the knowledge of study outcome. Thus, these data are ideally suitable for drug utilization studies including the assessment of prevalence, incidence and duration of drug therapies. Furthermore, these data are very useful to study pharmacoepidemiological hypotheses in analytical studies in which the outcome is distinctly defined by a procedure or by drugs that clearly identify a disease.

However, the lack of information on lifestyle factors such as BMI, smoking status or alcohol consumption but also on clinical diagnoses is largely missing and leading to bias and confounding. Besides, diseases as outcomes clearly identified through procedure codes or drug treatments are rare.

Anyhow, the information within Helsana claims data is recorded with high accuracy and represents a full set of claims of each insured person. Having and analyzing data from the Swiss population is important as the population may not be entirely the same as for example the UK, the Scandinavian or the US population may vary with regard to dietary habits, lifestyle factors and medical care.

To optimize the Helsana claims data, the way of data collection should be expanded that more data including lifestyle factors could be collected. Further, linking claims data with EHR data including clinical diagnoses would be an implication for future research.

APPENDIX

Helsana Drug Report 2014-2016

7.1 Summary 2014

Medicines are considered a critical cost driver in the healthcare system. At the same time, they play an extremely important role in healthcare, as they cure diseases or make them more tolerable, enable patients to get back to the workplace, and reduce or even prevent costly hospitalizations. Hence, an isolated focus on costs, without examining and discussing medicine benefits, would certainly fall too short. In order to provide a basis for discussion and enable a better understanding of how the medicine market has developed in Switzerland in the last years, with regards to both amounts and costs, the authors of this report evaluated the administrative claims data of the largest Swiss provider of health insurance, the Helsana-Group. The data were analyzed according to therapeutic group, age, sex and canton of residence. They represent billing information from outpatient service providers that supplied patients with medicines in the years 2010 to 2013 and charged the insurer with these; that is, primarily from pharmacies, physician offices and outpatient services in hospitals. The data were extrapolated to the whole Swiss population using demographic information from the Swiss Federal Statistical Office.

In 2013, almost 100 million outpatient purchases of medicines occurred in Switzerland, generating direct costs of CHF 6.1 billion. Since 2010, the number of purchases (+16.6%) and the costs (+17.0%) have increased almost simultaneously. Patients in Switzerland purchased medicines for CHF 1,026 per person, which corresponds to a growth of 8.5% since 2010. In 2012, medicines were responsible for 9.2% of the total Swiss healthcare costs. If only those services are considered that were covered by the statutory health insurance, medicines contributed 23.0% of the total costs covered, in 2012.

The highest costs were generated by medicines of the anatomic main group "Cancer and Immune System" (Chapter 2.3.2). While only 1.5% of patients required such medicines, they generated 21.4% of the total costs. In 2013, among the ten most expensive individual preparations there were seven biologic agents which are predominantly applied in oncology, rheumatology and for other autoimmune disorders. The three ‘traditional’ medicines that entered the top-ten list of cost contributors were the gastric acid blocker pantoprazole, the lipid lowering medicine atorvastatin and the painkiller paracetamol. All

these medicines are available as generic medicines on the market. Their cost per patient is low but they are very widely used.

Expenditures for biologicals, which were responsible for more than a fifth of the total costs in the Swiss medicine market, increased by 54.2% from 2010 to 2013. An equally strong cost escalation was seen for medicines of the anatomic main group "Blood", in which individual, expensive coagulation factors and the change from coumarin-based coagulation inhibitors to new oral anticoagulants constituted a major cost factor. On the other hand, due to the rising use of generics, the costs for cardiovascular medicines sank, with a simultaneous growth in quantity.

Overall, many older medicines tended to become cheaper, partially due to government regulations and increasing use of generic medicines, although the amount of purchases increased (also owing to the rising resident population in Switzerland). However, these cost savings were overcompensated by the new, often very expensive biologicals, so that the cost of medicines in the period from 2010 to 2013 rose further. This trend can be expected to continue in the future due to broadening of indications for biologic agents and the launch of new products.

About 20% of all patients were responsible for approximately 80% of all medicine costs. The substance generating the highest costs in Switzerland in 2013 was Adalimumab (Humira®), which, in terms of frequency of purchase, occupied only the 332nd position among all medicines in the market. The biological agent with the second highest costs, Infliximab (Remicade®) ranked only 484th position in terms of effected purchases. In 2013, paracetamol was the medicine bought most frequently in Switzerland, with over 4 million purchases and total costs of about CHF 61 million.

Children and teenagers only accrued 3.5% of the total medicines costs, and had little weight. As expected, adults and, above all, elderly people generated the highest costs. Woman purchased 17.4% more medicines than men, although their costs were only 7.8% higher. Urban areas with a high density of medical service providers and the typical demographic characteristics of cities had distinctly higher costs than rural areas.

The pharmacies were most important distribution channel in 2013, responsible for 59.6% of all purchases. Physician offices were responsible for 29.6%, and the outpatient hospital sector for 10.8%. The increase in costs since 2010 was relatively low in the pharmacies (+8.8%); it was substantial in the physician offices (+15.3%) and in the outpatient hospital sector (+51.1%). The increase in the physician offices is probably related to the expansion of the self-dispensation in Switzerland, that is, direct sales of medicines by physicians. The increase in the outpatient hospital sector may be related to the application of more expensive, often intravenously or subcutaneously applied biologic and oncologic agents. However, the quantitative growth in the hospitals, by +44.3% since 2010, was also notable. Arguably, this might partially be because many individuals (young people, immigrants) have no family physician and are looking directly for an accident and emergency department or hospital outpatient service in the case of health problems.

Additional analyses specifically focused on the medicine market for patients with asthma or chronic obstructive pulmonary disease (COPD), the prescription behavior of Swiss physicians in the field of anti-infective agents, trends in the purchases of acid-blocking proton-pump blockers and of coagulation-inhibiting medicines for prevention and treatment of thrombosis, as well as the market in the area of immunologic agents. Data from Great Britain were additionally evaluated for some of these topics and compared to our observations for Switzerland.

About 45% of all medicine combinations for patients with asthma in Switzerland were in line with internationally recognized, evidence-based guidelines. In Great Britain, a largely governmentally regulated healthcare system, the proportion of guideline conform medicine combinations was substantially higher, at 83%.

Antiviral medicines against HIV play an important, growing role in Switzerland. These medicines are very effective, whereby patients live increasingly longer. Due to the high prices of these medicines, the costs rise ever more. Compared to southern countries, the application of antibiotics in Switzerland is generally more restrained, which is very important and correct in view of the worldwide issue of increasing bacterial resistance. However, it becomes apparent that the French-speaking and Italian-speaking parts of Switzerland compared to the German-speaking part, feature higher antibiotic purchases. Predominantly in the outpatient hospital sector, the consumption of reserve antibiotics

has increased in the last years. This indicates that, also in Switzerland, more and more bacterial strains become resistant against certain antibiotics, which is why reserve antibiotics have had to be administered.

Gastric acid blockers (PPI) are more and more administered prophylactically to avoid gastric bleeding in patients treated with non-steroidal antirheumatic agents (NSAIDs). Formerly, this was common practice predominantly in high-risk patients. Currently, a third of all patients receive a PPI along with a NSAID. The highest PPI use was observed in patients with long-term NSAID therapy, which is medically justified. We found very similar results for Great Britain.

In the field anticoagulation, new oral products which are easier to dose, require fewer laboratory controls, are less susceptible to interactions and possibly cause less bleeding complications, have seen a strong quantitative growth in the last years. This is reflected in an increase of the direct costs for this therapeutic group. The trend to shift more and more patients from traditional coumarin to the new anticoagulants is expected to continue in the foreseeable future.

The impressive cost growth of the new immunologic agents, which are predominantly used for autoimmune diseases, is expected to continue in the future. The compounds already available on the market are being tested for new indications and new products are in the research pipelines of pharmaceutical companies. The introduction of generic medicines that enter the market after the patent protection of the originals has expired is more complex here than in the case of traditional oral drugs. As the production of biologics is often very complex, generic products, called biosimilars, are often merely similar, but not analogous to the original. This implies a need for additional evidence of efficacy and safety studies, which increases development costs and reduces the cost-saving potential that is already being well-exploited in the "standard" generics market.

The total costs of healthcare increase year after year. While many factors contribute to this development, medicines do play an important role. New medicines are usually more expensive than those already on the market. In many cases this can certainly be justified by therapeutic breakthroughs and real innovation.

However, not all newly registered medicines show a distinct therapeutic superiority in comparison with older medicines already available on the market. In the future, sound cost-benefit calculations will have to be increasingly undertaken during the pricing process. Society and politics face the challenge, more than ever, to develop approaches that can limit the constant increase in costs, without compromising the attractiveness of the research activities pursued by the pharmaceutical industry, as in the end innovation and therapeutic progress arise from there.

We will continue to analyze the Swiss medicine market in the next years, based on the Helsana data. Trends regarding the usage and cost of the various groups of medicines will again be described. There will be complementary, focused analyses of relevant, 'hot' topics. The numerical data provided shall serve to make the Swiss medicine market more transparent. Health insurers, politicians, the public and other stakeholders will be provided with facts and figures to support sensible health policy decision making and well-founded discussion.

7.2 Summary 2015

A substantial part of the costs of the Swiss health care system is due to medication. In many cases, medication is an indispensable part of health care, as it can reduce the duration of illness, morbidity and in some cases mortality. Medication enables patients to have less or shorter hospital stays and to return to work quicker. This in turn leads to health care cost savings and increases economic performance. It would therefore be short sighted to criticize the high costs of medication without taking into consideration the benefits.

This report aims to contribute to a better understanding of the Swiss drug market and its development in terms of quantity and cost over the last few years. The data are based on administrative claims data provided by the Helsana Group – one of the largest health insurance providers in Switzerland. The data cover all medication costs for outpatients between 2011 and 2014, which were invoiced to Helsana. The bulk parts of the data have been supplied by pharmacies, physician practices and hospital outpatient departments. In order to reach conclusions for all of Switzerland, the results were extrapolated to the entire population using data from the Federal Office of Statistics. Analyses were carried out according to age, sex and canton of the patients, but also based on anatomic and therapeutic groups of medications, in order to obtain a detailed picture of the drug market.

The projected medication costs in the outpatient sector increased by 2.1% between 2013 and 2014, to almost CHF 6.3 billion. During the same period, 3.3% more medications were issued, but there was only a 1.0% increase in the number of persons obtaining medication. With around 6 million people being prescribed medication and around 103 million prescriptions during the year of 2014; the average cost per year amounts to CHF 1,039 per patient, or CHF 61 per prescription. Compared to 2011, the average costs per patient and per prescription increased, whilst the costs per prescription decreased slightly. Compared to the overall costs of the health care system of around CHF 72,894 million in 2014, the drug market represents a share of 8.6%. Medication costs were responsible for 21.9% of the expenses of the Swiss obligatory health care insurance. Medication costs for inpatient treatment were not taken into consideration.

In 2014, medications for the main anatomic group "cancer and immune system" continued to incur the highest costs of all main anatomic groups, of more than CHF 1.3 billion, implying a 4.3% increase compared to the previous year. This went along with a comparatively low number of 1.6 million prescriptions and less than 200,000 patients. Five active ingredients from this main anatomic group were amongst the top 10 of the most expensive individual drugs in 2014, as in 2013. The active ingredient infliximab led the chart for the first time, followed by adalimumab. The drug Gilenya® with its active ingredient fingolimod experienced the biggest relative cost increase of all immune suppressants, of over 750% since 2011. The only biological from another main anatomic group amongst the top 10 was ranibizumab, an eye medication. The active ingredient sofosbuvir, which has been available on the market since 2014, and which aims to treat hepatitis C, went straight to number 14 of the cost chart, with costs of around CHF 51 million. With a low number of prescriptions and patients, the per-capita-costs of sofosbuvir amounted to over CHF 66,000, with costs of CHF 22,241 per prescription. The anti-viral active ingredient combination tenofovir disoproxil/ emtricitabine became economically less important in the year 2014. It only reached rank 16 in terms of cost, with nearly equivalent prescription numbers.

Further top 10 active ingredients with higher prescription numbers (but lower prices) were the gastric acid blocker pantoprazole, the lipid-lowering agent atorvastatin, the psycholeptic quetiapin and the bronchodilating agent formoterol/budesonide. The latter two were previously only found amongst the top 20. The pain killer paracetamol only reached number 18 in the ranking of costs in 2014, compared to number 10 in the previous year and, despite its top rank in terms of prescriptions.

There were also substantial percentage increases in costs between 2011 and 2014 for the main anatomic groups "blood", "sensory organs" and "various." Most increases occurred in 2013. This was especially noticeable with respect to the "blood" group, due to the utilization of new, more expensive coagulation factors and many changes from coumarin to new oral anticoagulants during the relevant period. The only minor to moderate cost reductions between 2011 and 2014 occurred in medications for the nervous and cardiovascular systems and medications with an effect on breathing. Furthermore, there was a decrease in the costs for the main anatomic group "genitals" between 2013 and

2014. Due to an increased number of prescriptions in all main anatomic groups (apart from medications with an effect on breathing and anti-infectives since 2013), the cost reductions are most likely due to an increased number of prescriptions of cost-saving generic drugs. Only in the case of three main anatomic groups (anti-infectives, musculoskeletal system and sensory organs) did the percentage increase of prescriptions substantially exceed the increase in costs since 2013. This implies an increased number of prescriptions of less expensive medications within these groups.

As in previous years, around 20% of the patients caused around 80% of the medication costs. This was also reflected in the rankings in the most expensive and most prescribed active ingredients. Only three of the 20 most prescribed active ingredients (paracetamol, pantoprazole, atorvastatin) were amongst the top 20 of the highest cost drivers, whilst six of the eight active ingredients responsible for the highest costs (infliximab, adalimumab, ranibizumab, fingolimod, etanercept and trastuzumab) did not even belong to the 300 most frequently received active ingredients. For comparison, six of the 20 most common active ingredients (electrolyte solution, metamizole, metformin, cholecalciferol, levothyroxine-Na^+, mefenacide) were not included amongst the first 100 top cost drivers, and were therefore relatively low cost.

On average, female patients paid CHF 56 for each prescription in 2014, around CHF 13 less than male patients. The average number of prescriptions per head was 18.2 for women and 15.6 for men. Compared with 2013, the costs per prescription therefore decreased for female and male patients by around 70 or 60 centimes respectively, whilst the prescriptions per head increased by around 0.4.

There were major differences between the cantons in terms of medication costs and prescriptions. The number of prescriptions per head in Basel-Stadt and Neuchâtel was relatively high. In Appenzell-Innerrhoden, Uri and Zug, the number of prescriptions was relatively low, considering population size. Patterns for average costs per person were similar; however, Basel-Landschaft now also showed high costs, whilst Graubünden, Nidwalden and Obwalden showed low costs. Overall, urban areas tended to show higher costs than rural areas, probably due to their demographic structure and more medical services offered.

The medication costs and number of prescriptions in children and adolescents were low. In 2014, a prescription cost CHF 28 on average, and the costs per patient were around CHF 59. Most expensive in this age group were immunizations and systemic antibiotics. Medication costs and number of prescriptions increased with age. The costs for 19 to 64-year-old adults amounted to nearly CHF 3.5 billion, which represents an overall share of 55.1% of the total costs in the year 2014. The number of prescriptions amounted to 50 million. One prescription in this age group therefore cost around CHF 69 and the costs per patient were CHF 254. Obligatory health insurance providers incurred the highest costs for immune suppressants and antivirals. For persons above 65 years of age, the average cost per prescription was only CHF 58. Cancer and eye medications represented the biggest share of the costs for this age group. The costs per patient amounted to CHF 317.

Pharmacies remained an important channel of dispensation in 2013, both in terms of costs (with a share of 55.7% of the overall costs) and quantity of medication issued (with a share of 53.6% of the overall prescriptions). However, the cost increase for pharmacies was much lower than the cost increase for physician practices and hospital outpatient departments. For physician practices, the percentage increase in costs between 2013 and 2014 exceeded the percentage increase in the number of prescriptions.

An additional analysis in the specific part of this report looked at a protective effect of statins on the development of gallstones. The costs of statins (mainly atorvastatin) decreased substantially between 2011 and 2014 due to the introduction of generic drugs, even though there was an increase in the number of prescriptions. As demonstrated by our case control study, the relative risk of gall bladder removal in case of a long-term application of statins (at least 20 prescriptions during the examination period) was significantly lower. In contrast, patients who had used statins in the past (more than 180 days before the index date), or those who had not used them, did not experience an effect. A similar study in Great Britain reached similar conclusions.

Iron deficiency is the most common nutritional deficiency in the world. The actual extent of the problem in Switzerland is largely unknown. The measurement of serum ferritin is the first choice amongst the available diagnostic tests.

During an initial physician consultation, it should be combined with a hemoglobin measurement, as not all patients with an iron deficiency actually develop anemia. During anemia treatment, serum ferritin serves as a process parameter. Both oral and parenteral iron drugs are available for treatment. Parenteral drugs should only be utilized in Switzerland after unsuccessful (or unfeasible) oral treatment. Our study demonstrated that in more than 25% or 12% of the cases, respectively, there were no laboratory analyses before first-time oral or parenteral iron administration. Data from Great Britain indicate a similar pattern. In Switzerland, serum ferritin was often measured before treatment, while hemoglobin tests appeared to be the test of choice in Great Britain. There were hardly any combination tests in Switzerland. In the year 2014, around 4.9% of the population in Switzerland received iron prescriptions, in Great Britain the figure amounted to 2.6%. Parenteral iron administration was 1,000 times more common in Switzerland than in Great Britain (based on the British CPRD database). According to expert opinion, parenteral administration is more patient-friendly and more effective, especially because the compliance can be much better guaranteed for a one-off injection than for oral consumption over several weeks. Furthermore, parenteral administration of the currently available agents is fast and less prone to adverse effects. Despite this, the higher use of parenteral iron in Switzerland compared to England, in women during the age of fertility, should be scrutinized clinically, and studied further. It is at least questionable whether the use of parenteral iron substitution in Switzerland is medically justifiable in all cases.

A further analysis looks at the controversial active ingredient chondroitin sulphate, which is used in the treatment of osteoarthritis, but the benefits of which have so far not been unequivocally demonstrated. Despite this, an estimated 2.4% of the Swiss population received chondroitin sulphate in the year 2014, in comparison with 0.004% in Great Britain. Women and elderly persons received the medication much more often than men and those under 55 years of age. In the age group of 65-74 years, the number of persons who received chondroitin sulphate was highest (7%). The prevalence in the cantons varied between 1.4% and 3.4%, but it was not possible to discern a clear trend – not even regarding self-dispensation cantons. There was also no clear temporal trend between 2011 and 2014.

In Great Britain, however, the utilization substantially decreased in all age groups, despite the substantially lower initial level of utilization. Overall, chondroitin sulphate represented 0.5% of the medication costs of the Swiss obligatory health care insurance providers. Due to insufficient evidence, the utilization of the drug should be questioned. The potential of saving unnecessary costs should be explored.

A further case control study did not find an association between benzodiazepine use and the development of Alzheimer's disease. The analysis took into consideration that many patients with Alzheimer's disease are prescribed benzodiazepines before their diagnosis due to initial, yet unspecific symptoms of Alzheimer's disease. The occurrence of the disease in the case and control groups was not statistically significantly different. An apparent effect in persons taking large amounts of benzodiazepines disappeared when individual daily doses and the parallel consumption of anti-depressants were takin into account. This corresponds with findings in Great Britain.

The relatively new trend of mainly releasing new, innovative treatments in the indication areas of immunology and oncology will continue. We partially see completely new treatment approaches with excellent results for health problems which, so far, could not be satisfactorily treated. The downsides are very high costs, which will lead to a serious test of the health care system. The societal and political explosiveness of this development is partially due to the fact that only few patients require these expensive treatments, even though they represent a big share of the overall costs. The above-mentioned hepatitis C medication sofosbuvir, for example, reached number 14 in the 2014 ranking of costs, in the year of its release. In terms of number of prescriptions, however, the drug ranked number 1,004. Only 811 patients received a prescription. In the future, well-substantiated cost benefit calculations and cost analyses will be required as basis for decision making. Furthermore, new financing and pricing models need to be discussed. However, pharmaceutical development in general and in Switzerland may not be endangered, as it ultimately leads to the innovations and therapeutic advances which are desired by the entire society.

The above figures are intended to make the Swiss drug market more transparent. Sensible health care policy decisions can only be made based on a detailed knowledge of the relevant substance matter areas and meaningful data. This is why we provide data and facts to insurance providers, politicians, representatives of the health care system and interested members of the public on a regular basis, so that they may support meaningful health care policies and focused discussions.

7.3 Summary 2016

For the promotion of a rational use of drugs it is essential to have trustworthy data on the development of quantities and costs in the pharmaceutical sector. The aim of the analyses presented in this pharmaceutical drug report is to make such data available for the Swiss drug market. The electronic administrative claims database of the Helsana-Group, one of the largest providers of health insurance in Switzerland (1.2 million enrollees in the compulsory health insurance (*obligatorische Krankenpflege-versicherung*; OKP) in the year 2015) served as our basis.

The database contains all claims made to Helsana, within the limits of the OKP. Next to drug supplies, it covers amongst others, diagnostic assessments and surgeries. Outpatient diagnoses are unavailable, as these normally do not get transmitted to the insurer. The evaluations of drug utilization and costs depicted in this report refer to the period from 2012 to 2015, unless otherwise stated. They consider mainly the outpatient sector, since benefits from the inpatient sector are generally allocated in a lump sum, which makes a separate itemization of individual drugs impossible.

In order to be able to make statements about the whole Swiss population, based on Helsana's data, the data-sets were combined with year-specific expansion factors, which equalize the demographic differences between the Helsana enrollees and the population as a whole.

In Switzerland the cost of drugs in the OKP has risen by 714 million Swiss Francs since 2012 (+12.0%), and has reached more than 6.6. billion Swiss Francs in the year 2015. The yearly increase between 2014 and 2015 was +5.9 %, distinctly higher than in the previous years. Beside the number of people obtaining medication, the individual number of drugs obtained per patient also rose between 2012 and 2015 (2012: 16.3; 2015: 17.3), as did the costs per person (2012: CHF 1,023; 2015: CHF 1,078). In 2015, medication costs (without the costs of medications given to inpatients) contributed 9.1% to the total Swiss health expenditure and 22.1% to the services financed by the health insurers in the OKP. If one looks at the very high importance assigned to medication in our society and the undoubtedly crucial role played by pharmaceutical research and development in the rising life expectancy and well-being of our population, then a percentage of 9.1% of the

entire healthcare expenditure is a very low proportion of costs with a doubtlessly excellent cost-benefit assessment. Nevertheless, especially the newer, sometimes very expensive therapies in the areas of cancer and immunological treatment present a serious challenge to our health insurance system, which is financed on a basis of solidarity, especially in light of the fact that 20% of the patients cause 80% of the entire cost of medication.

Women claimed around 16.8% more drugs than men in the year 2015; on the other hand, the per capita costs were slightly lower for women (cost per woman: 1,042 Swiss Francs; costs per man: 1,120 Swiss Francs). Of the entire costs of medication and of the entire supplies 41.7% and 43.9%, respectively, were accounted for by persons over the age of 65. As already in the year before, the cantons of Basel-Stadt and Basel-Landschaft, Geneva, Neuchâtel, Waadt and the Ticino, showed claims and costs per person that were above average, while in the central and eastern part of Switzerland there were relatively few claims and low costs per person.

If one looks at medications by therapeutic groups (level 2 of the ATC- classification), then immunosuppressants, antivirals, and cancer medication were the most expensive drugs in 2015, with costs of around 1.8 billion. Thus, just three therapeutic groups are responsible for more than a quarter of the entire costs, even though their contribution to the total number of claims is relatively low at 1.7%. An extremely strong increase in cost of about +45.7% since 2014 was noted for antiviral drugs, which can be traced back to the market entry of very effective but highly expensive substances for the treatment of virus hepatitis C (sofosbuvir/ledipasvir). High increase of costs, of more than 10% since 2014, could also be noted for eye medications, immunosuppressants and medications to inhibit blood coagulation. Broken down to individual substances, a large amount of the costs is incurred by the antibodies infliximab and adalimumab (used for the treatment of auto-immune diseases such as rheumatoid arthritis, psoriasis and inflammatory bowel diseases), fingolimod (multiple sclerosis), aflibercept and ranibizumab (macular edema and macular degeneration), as well as rivaroxaban (therapy and prophylaxis of thrombosis). A very high cost per capita of 362,226 Swiss Francs was also generated by the drug Soliris® (eculizumab), belonging to the group of immunosuppressants and authorized for rare hereditary diseases, where a depletion of erythrocytes occurs.

When it comes to the amount of drug supplies, painkillers, psycholeptics, and anti-inflammatory and anti-rheumatic products are the front-runners. These three groups together were responsible for about a fifth of all supplies in the year 2015. Their cost amounted to 613.7 million Swiss Francs and was lower than the one of immunosuppressants alone. The substances most often procured included the painkiller paracetamol, electrolyte solutions, the gastric acid blocker pantoprazole and the anti-inflammatory drug ibuprofen.

Separating the analysis according to supply channels indicated that the highest costs (3.7 billion Swiss Francs) and supplies (57 million) were channeled through the pharmacies, far more than through physician's offices (2.0 billion Swiss Francs; 39 billion benefits supplied) and ambulatory hospital care (0.9 billion Swiss Francs, 11 billion benefits supplied).

The first additional analysis in the specific part of this drug report addressed the development of the market and the benefit assessment of new drugs, taking diabetes drugs as an example. Between 2010 and 2015 the supplies of diabetes drugs (+ 19.3%) as well as the number of patients treated with diabetes drugs (+19.7%) and the costs for diabetes drugs per patient (+ 14.4%) rose substantially. The latter can be explained by an increased use of new and more expensive substances that have gained market shares in recent years. The benefit assessments of different Health Technology Assessment (HTA) institutions of European countries attested only limited added value to these new drugs. In practice they can however mean a valid therapeutic step forward for certain patient groups. Weaknesses of the largely negative assessments of added benefit include rigorous assessment algorithms that give only little value to parameters relevant to patients, such as the treatment adherence, as well as lengthy processes, which may mean that assessments do not fully take into account the newest scientific evidence at the time point of publication.

The second additional analysis studied the relationship between the use of diabetes drugs (as a proxy for a diabetes diagnosis) and the implantation of either knee or hip endoprosthesis (as proxies for the presence of severe osteoarthrosis). This case-control study was conducted both with the Helsana data and data from a British General Practitioners' data base (Clinical Practice Research Datalink). The result showed that, in

Switzerland, overall, diabetes patients were slightly more likely to receive a hip or knee endoprosthesis than patients without diabetes. In Great Britain, on the other hand, all joint replacement surgeries were decidedly rarer in patients with diabetes than in patients without diabetes. A deeper analysis showed that the probability for a joint replacement in both countries decreased with increasing severity of diabetes. It is to be expected that, in Great Britain, patients with diabetes are operated on far less frequently than patients without diabetes, which could be related to economic considerations and rationing.

The third additional analysis, again a comparative case-control study, based on data from the Helsana database and the British Clinical Practice Research Datalink database, looked at the use of antidepressants with regard to a possibly increased risk of cataract. An increased risk of cataract due to therapy with selective serotonin reuptake inhibitors (SSRI) has been described in animal models as well as in an observational study of Canadian patients. Such an increased risk could not be confirmed in either the Helsana data or the British data. Thus, a long-term use of antidepressants (SSRIs as well as other types of antidepressants) seems not to have any impact on the risk of cataract.

The fourth additional analysis describes the development of the drug market in the field of oncology. The costs of oncology drugs rose by around 18% during 2012 to 2015, from about 494 million to 585 million Swiss Francs. Since the supplies only rose by around about 8% during the same period, it is mainly the price of the drugs that has risen. Targeted drugs such as monoclonal antibodies now account for about 75% of all oncology drug costs. This percentage has increased since 2007 but seems now to have reached a plateau for the time being.

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PUBLICATION LIST

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Biétry FA, Hug B. Eisensubstitution. Pharma-Update. University hospital Basel, Switzerland: 8 March 2016.

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POSTER PRESENTATIONS

FA Biétry, A Pfeil, O Reich, M Schwenkglenks, CR Meier. Benzodiazepine use and risk of developing Alzheimer's disease: A case-control study based on Swiss claims data. 32nd ICPE Conference. Dublin, Ireland: 25-28 August 2016.

FA Biétry, O Reich, M Schwenkglenks, CR Meier. Statin use and risk of cholecystectomy: A case-control analysis using Swiss claims data. 32nd ICPE Conference. Dublin, Ireland: 25-28 August 2016.

Fabienne A. Biétry, Oliver Reich, Susan S. Jick, Christoph R. Meier. Annual Research Meeting 2016. Prescribing patterns of proton pump inhibitors in patients with NSAID use: A comparison between Switzerland and the UK in primary care. Swiss pharma science day. University of Bern, Switzerland: 19 August 2015 & 31st ICPE Conference. Boston (MA), USA: 22-26 August 2015 & Annual Research Meeting. University of Basel, Switzerland: 10 February 2016.

Fabienne A. Biétry, Oliver Reich, Christoph R. Meier. Prescribing patterns of proton pump inhibitors in patients with use of NSAIDs in the Swiss ambulatory setting. Annual Research Meeting. University of Basel, Switzerland: 13 February 2015.