Population-based studies on the epidemiology of migraine and Parkinson's disease

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‘Keine Wirkung ist ohne Nebenwirkung’

(anonym)

‘No drug which is pharmacologically effective is entirely without hazard,
…, not all hazards can be known before the drug is marketed;
… these may only be known when the drug has been administered
to large numbers of patients over considerable periods of time.’

(Committee on Safety of Drugs, Medicines Act of 1968, UK)

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Summary

With epidemiologic analyses the effect of certain exposures on diseases can be studied in large population samples. Pharmacoepidemiology is a speciality which focuses on beneficial or harmful drug effects on the development of diseases. In my thesis I carried out different epidemiological studies in order to increase the knowledge on the natural history of migraine and Parkinson's disease. Another focus was to evaluate the effect of certain drug therapies on the risk of developing migraine or Parkinson's disease (PD) or complications of the diseases.

I used data from the General Practice Research Database (GPRD), which contains electronic records from primary-care of several million people in the United Kingdom (UK). Additionally, information on patient demographics (e.g. age, gender, body mass index, smoking status) is available for a large portion of the patients as well as data on hospital and specialist diagnoses. The GPRD has been the source for many important studies in epidemiology as well as in drug safety.

In my first project I identified 51'688 individuals of the GPRD with a first-time migraine diagnosis between 1994 and 2001 and an equal amount of control subjects without such a diagnosis. The incidence rates (IR) of first-time diagnoses of migraine by the general practitioners (GPs) were 2.5 times higher in women than in men and highest in puberty. The comorbid disorders of the migraineurs were also quantified in migraineurs and controls. By means of a case-control study design which included matching on several important confounders such as gender, age, general practice and index date, the odds ratios (ORs) for the comorbidities in migraineurs compared to non-migraineurs were investigated. This resulted in an increased OR for the migraineurs for most chronic diseases. Determination of the health resource utilisation (HRU) revealed that migraineurs with triptan prescriptions needed more health care, defined as visits to their GP or neurological specialists as well as prescriptions for headache related drugs.

In a second part of the migraine project I followed a cohort of migraineurs and their matched controls until they developed a stroke, a transient ischaemic attack (TIA), they died or until they were diagnosed with asthma for the first time. Again IRs were calculated and a nested case-control analysis performed. A previous history of

migraine was associated with an approximately twofold increased risk for stroke or TIA, however, residual confounding by migraine recency or severity could not totally be ruled out. Furthermore it is challenging to determine the stroke risk in association with prior triptan use because in the GPRD the actual timing of the drug intake is not recorded. The mortality of migraineurs was slightly decreased and no increased asthma risk was seen in migraineurs with or without triptan use.

In my second project I investigated the impact of prior drug use on the risk of being diagnosed with PD. During the study period from 1994 to 2005 3'637 individuals with idiopathic PD were identified from the GPRD. The majority of the cases with a first-time PD diagnosis were men older than 60 years of age. In two separate case-control studies, in which I used the same matching criteria as in the migraine project, I found a decreased risk of PD in patients with current use of calcium channel blockers. This finding is in accordance with a recent hypothesis regarding the involvement of calcium channels in the PD pathophysiology. After the assumption of an increased risk for PD associated with the use of statins, the results of the other case control study gave reassurance that in a large population sample from the GPRD the risk for a PD diagnosis was not increased for current or past use of statins.

To conclude, the GPRD data is very useful for the description of the natural history of diseases as well as for the investigation of particular drug safety questions. The potentials of the database could be further increased if genetic information was also available in future. Certainly, special diligence has to be exercised regarding the issue of data protection.

Abbreviations

ACE	Angiotensin converting enzyme
AD	Alzheimer's disease
AT	Angiotensin
BCDSP	Boston Collaborative Drug Surveillance Program
BMI	Body mass index
CBF	Cerebral blood flow
CGRP	Calcitonin gene-related peptide
CHF	Congestive heart failure
CI	Confidence intervals
COMT	Catechol-O-Methyltransferase
COPD	Chronic obstructive pulmonary disease
CoQ_{10}	Coenzyme Q_{10}
DNA	Deoxyribonucleic acid
DSRU	Drug Safety Research Unit
EPS	Extrapyramidal symptom
GP	General Practitioner
GPRD	General Practice Research Database
HMG-CoA	Hydroxymethylglutaryl-Coenzyme A
HMO	Health maintenance organisations
HRT	Hormone replacement therapy
HRU	Health resource utilisation
HSN	Health Service Number
IBD	Inflammatory bowel disease
ICD	International Classification of Diseases
ICHD	International Classification of Headache Disorders
IHD	Ischaemic heart disease
IR	Incidence rate
ISAC	Independent scientific advisory committee
ISPE	International Society of Pharmacoepidemiology
LDL	Low-density lipoprotein

MHRA	Medicines and Healthcare products Regulatory Agency
NC	North Carolina
NHS	National Health Service
NOS	Nitric oxide synthase
NSAIDs	Non-steroidal anti-inflammatory drugs
OCs	Oral contraceptives
OR	Odds ratios
OTC	Over-the-counter
OXMIS	Oxford Medical Information System
PEM	Prescription event monitoring
PD	Parkinson's disease
PPA	Prescription pricing authority
Py	Person-years
RA	Rheumatoid arthritis
RCT	Randomised controlled trial
RR	Relative risk
SAS	Statistical analysis system
SLE	Systemic lupus erythematosus
TCA	Tricyclic antidepressant
TIA	Transient ischaemic attack
UK	United Kingdom
US	United States (of America)

Chapter 1

Introduction

1 Introduction

1.1 Pharmacoepidemiology: a means of drug safety

1.1.1 Definition of pharmacoepidemiology

Epidemiology describes patterns of disease occurrence in human populations and identifies factors which influence the diseases [Hennekens et al. 1987]. If these factors are drugs, the discipline is called pharmacoepidemiology [Hennekens et al. 1987]. In other words, pharmacoepidemiology studies the risk and benefits of drugs in populations and analyses outcomes of drug therapies [Lawson 1984]. It thus applies the methods of epidemiology to the field of clinical pharmacology [Strom 2000].

This kind of research completes other methods of postmarketing surveillance and together they are important for the monitoring of drug safety after marketing authorisation. Premarketing clinical trials are primarily designed for assessing efficacy and risk-benefit ratio. However, due to the limited size and controlled nature of these studies, only the most common adverse effects will have been identified at the time of approval. The need for postmarketing surveillance is a direct result of these limitations which can only partially be addressed by spontaneous reporting of unexpected adverse drug effects [Kennedy et al. 2000]. A more systematic approach represent pharmacoepidemiological analyses of data available from large representative population samples.

Within the last decades pharmacoepidemiology has gained increasing importance. Serious adverse effects which were not detected before approval of the drug have been found in 51% of approved drugs as stated in a study by the United States (US) Government Accounting Office. Drug safety issues are frequently of public interest as shown by the recent examples of Lipobay® [Davidson 2002] and Vioxx® [McGettigan et al. 2006]. Pharmacoepidemiological studies can provide additional information on the suspected association between a drug and a disease. Side effects such as rhabdomyolysis or myocardial infarction which may occur only in a subgroup of patients with additional risk factors for the outcome are usually not detected and

quantified in premarketing clinical trials. Pharmacoepidemiology does not only provide the opportunity to detect such adverse events in large population samples but can also provide reassurance regarding the safety of drugs.

Pharmacoepidemiology also deals with economic aspects of drug use. In view of the increasing cost pressure in the public health sector, analyses of health care utilisation as well as comparisons of costs with effectiveness or benefit of the drug gain a lot of attention [Hagell et al. 2002; Silberstein et al. 2007].

1.1.2 Methods of data capturing

1.1.2.1 Spontaneous reporting

In Europe the awareness for the need of postmarketing surveillance increased largely after the occurrence of thalidomide-induced phocomelia in the 1960s [Speirs 1962]. Since then in many countries the governments established systems in which any suspicion of an unwanted drug effect needs to be reported [Wiholm et al. 2000]. Health care professionals as well as consumers inform the authority or the manufacturer of observed side effects. The manufacturers have to report directly to the authorities which collect the reports in national databases. Since 1970 the World Health Organisation (WHO) maintains an international database where all reports are collected [Olsson 1998]. Unusual accumulations of severe adverse events are sometimes detected and relevant action can be implemented by the authorities [Sigmund 1997]. Examples for limitations of spontaneous reporting are problems with the recognition of adverse events by health care professionals, which lead to a high degree of underreporting. Other restraints are a varying quality of the reports and difficulties in the estimation of the population exposure to the drug as a whole. Therefore valid statements regarding the scale of a detected problem are not possible. Nevertheless spontaneous reporting is a good source for signal generation and important to create hypotheses for further pharmacoepidemiological studies [Wiholm et al. 2000].

1.1.2.2 Intensive hospital-based cohort studies

The method of intensive hospital-based studies was first established in the 1960s in the US [Jick et al. 1970]. Demographic and clinical information on hospitalised patients were collected together with all "events" occurring in these patients. The data were analysed in cohort studies with the aim to detect the frequency of acute undesired drug effects during hospitalisation. This method was also useful for the evaluation of different subgroups of patients who were at greater risk for an adverse event (e.g. because of renal insufficiency or advanced age) [Jick et al. 1968; Lawson et al. 1982]. Later on the method was developed further and hospitalised patients were also questioned about their prior drug use in order to assess the risk of hospitalisation in association with drugs used in outpatients. This approach has some limitations as it covers only drugs frequently used in hospitals and the study population encompasses only hospitalised individuals. Thus, the results may not be applicable to the whole population [Borda et al. 1968] and monitoring of drug use in the general population is necessary in order to quantify the potential of associated serious diseases.

1.1.2.3 Prescription event monitoring

Prescription event monitoring (PEM) is a non-interventional, observational cohort technique first established in the United Kingdom (UK) [Inman 1981].Since the 1980s data on all prescription medicines dispensed within the National Health Service (NHS) are collected. PEM includes the majority of the UK population because the NHS encompasses practically all patients in the UK. The information is collected electronically by the Drug Safety Research Unit (DSRU) which contacts the responsible general practitioner (GP) within six months after the drug was dispensed. The DSRU sends a questionnaire to the GP asking for any adverse event that may have occurred while the patient was taking the drug. The aim is to collect information on approximately 10'000 patients taking the specific drug in order to conduct a cohort study with sufficient statistical power. Interim analyses are undertaken after information on every 2'500 patients has been accumulated. The time to achieve these limits may vary depending on the prescription rate of the drug. The advantage of PEM is its ability to monitor drug use in an everyday primary practice setting and the representative nature of the patient sample. Signals of serious events may be

generated which can be confirmed by other epidemiological methods. Since the data are solely collected in general practices, it is not possible to monitor drugs which are mainly used in hospital or by specialists [Mann 2000]. Furthermore, no valid statement of actual compliance with the drugs is possible as only the process of dispensing is recorded. Adverse events with a longer latency than the average six months may not be detected because the monitoring takes place at about six months after the drug was dispensed.

1.1.2.4 Automated databases

A main source of data for pharmacoepidemiological studies are large databases with drug prescription data and sometimes additional information on diagnoses. Up to now no such database exists in Switzerland or Germany.

1.1.2.4.1 Medicaid

In the US the Medicaid system is the national health insurance program providing health care mainly for persons with low income [Ray et al. 1989]. Therefore the information included is mainly on children, women and non-whites. Its advantage is its size of several millions of people which enables the study of rare outcomes. However, long-term effects are not suitable to study with Medicaid because frequent eligibility changes of the included individuals result in many persons losing Medicaid benefits which are therefore not included in the database any longer.

1.1.2.4.2 PharMetrics

The PharMetrics database covers 82 different health plans throughout the US with information on approximately 55 million lives. The earliest recordings date back to 1995. The average follow-up time of two years is rather short and therefore the database is more suited for the analysis of acute effects [Jick et al. 2006]. Patient demographics, diagnoses (ICD-9 codes) and drug use are included. The information on drug prescription encompasses the specific drug, the amount, the dose and the duration of supply. Medical information on hospitalisations is also covered. Access to original records is not possible and information on BMI and smoking status is scarce. Therefore the validation of the diagnoses and the adjustment of the analysis for important confounders (see chapter 1.1.4.3) are limited. A strength of PharMetrics is

its large size (up to 20 million people are included at one point in time) and the available information on newly marketed drugs.

1.1.2.4.3 Health Databases in Saskatchewan

In Canada the Health Databases in Saskatchewan cover a population of about one million people who receive universal health care [West 1988]. In contrast to Medicaid, eligibility is not based on socioeconomic status. The information is electronically recorded and includes data on drug prescriptions, vital statistics and hospital stays as well as physician services. For diagnoses and procedures a standard classification system is used. All data are linked by a unique Health Service Number (HSN). The database has been validated for a range of diagnoses [Ray et al. 1989; Raiford et al. 1996]. One limitation is the restriction to a drug formulary within Saskatchewan Health, thus not all marketed drugs can be studied. In addition, no information on factors such as smoking or alcohol use is available.

1.1.2.4.4 PHARMO database

In the Netherlands the PHARMO database links community pharmacy with hospital data on the basis of birth date and gender of the patients as well as the GP code [Herings et al. 1992]. It covers a population of approximately 500'000 persons. PHARMO is also linked to primary care, cancer and accident registries as well as to mortality data [Herings et al. 1992]. The data collection goes back to 1987. PHARMO data has been used together with genetic information to evaluate associations between drug exposure and the outcome with regard to genetic differences [Bloemenkamp et al. 1995; Kuivenhoven et al. 1998]. However, rare effects of recently released drugs are not likely to be detected within a certain period of time because prescription rates are too low in a population of the size of the Netherlands.

1.1.2.4.5 General Practice Research Database (GPRD)

In the UK the NHS provides a suitable medical environment to gather valid information on drug usage and related diagnoses. The GP acts as a gatekeeper to services within the NHS, recording extensive information on clinical events as well as prescribed medications and patient demographics (e.g. height, weight, smoking status, social factors and laboratory tests). Outpatient diagnoses, referrals and

hospital discharge letters are also recorded by the GP because within the NHS all consultants are required to forward the information on hospital services, outpatient as well as emergency treatment to the GP as the primary care giver.

In the late 1980s a computer system was established to record all the relevant information of patients on computers in GP offices [Lawson et al. 1998]. GPs have agreed to provide patient data for research purposes and were started to be trained to enter data in a standard manner. Information on recorded diagnoses and drugs are map ed to specific coding systems in order to efficiently derive information from the database. For the prescribed drugs details of individual products such as dose and route of administration are coded by the prescription pricing authority (PPA) coding system. Additionally, the date of a prescription, the amount prescribed and dosing instructions are recorded. Diagnoses are coded using the Oxford medical indexing system (OXMIS) [Perry 1978] or the READ coding system [Department of Health 1990]. The Boston Collaborative Drug Surveillance Program (BCDSP) conducted a broad range of studies to evaluate the quality and completeness of the recorded data [Jick et al. 1991; Jick et al. 1992; Jick et al. 2003]. Since 1991 most practices have been providing data of the required quality and completeness for pharmacoepidemiological studies [Garcia Rodriguez et al. 1998]. For a limited number of practices data is available from as early as 1987. Since 1994 the GPRD has belonged to the UK department of Health and is currently managed by the Medicines and Healthcare products Regulatory Agency (MHRA). Data for research can be obtained after review of research protocols by the Independent Scientific Advisory Committee for MHRA database research (ISAC), the ethical committee of the GPRD. All information is anonymised for research purposes. The GPRD now comprises more than 40 million patient-years worth of data which have been collected from approximately 6.2 million patients [GPRD 2007]. The number of different events included in the GPRD is shown in Table 1.1.1.

Table 1.1.1: Events captured in the Full Featured GPRD [Wood et al. 2004]

Event type	N° of events (million)
Clinical	251
Consultation	301
Immunisation	28
Referral	20
Tests	76
Prescriptions	305
Repeats	38

1.1.2.5 Others

There are a lot more attempts to use health care related data for (pharmaco-)-epidemiological studies: Data collected in health maintenance organisations (HMOs) such as the information from the Center for Health Research at Kaiser Permanente Medical Care Program [Friedman et al. 1971] or the Group Health Cooperative of Puget Sound [Fishman et al. 1998]; or the national prescription registers in Denmark [Frank 2000] and Finland [Klaukka 2001], to name a few. In these latter national prescription databases records of the purchase of all prescription drugs as well as information regarding emigration and vital status of the residents is collected primarily for refund purposes with legal permission for scientific use [Hallas 2001]. Unfortunately there is frequently no information on the indication for the prescriptions recorded.

1.1.3 Types of epidemiologic studies

1.1.3.1 Descriptive studies

Correlational studies, case reports or case series and cross sectional surveys belong to the group of descriptive studies [Grimes et al. 2002]. Described are aspects of the disease as well as characteristics of the affected population. If demographic data (e.g. age, health care utilisation or physical activity) of an entire population are collected and used to describe a disease, the study is called correlational or ecological. In contrast to the consideration of a whole population, case reports, case

series or cross sectional surveys describe an event in an individual patient or in a group of patients with a similar diagnosis. Case reports document unusual medical occurrences and can represent first clues in the identification of new adverse effects of exposures. Cross-sectional surveys assess exposure and disease status among individuals in a defined population at one point in time. Since exposure and disease status are assessed simultaneously, it is often difficult to determine whether the exposure preceded or resulted from the disease [Hennekens et al. 1987]. Descriptive epidemiology is mainly used to generate new hypotheses and identify further areas of research which can then be evaluated with more analytical study designs (see chapter 1.1.3.2, 1.1.3.3 and 1.1.3.4) [Grimes et al. 2002].

1.1.3.2 Case-control studies

Subjects of a case-control study are selected on the basis of whether they do (cases) or do not (controls) develop a particular disease under study [Jick et al. 1978]. The prevalence of certain exposures of interest is then compared between the two groups [Hennekens et al. 1987]. One advantage of case-control studies is their ability to study diseases with very long latency periods. They are carried out retrospectively by looking backwards in time to assess the exposure of interest in cases and controls. They are efficient in terms of time as well as costs because the investigators do not have to wait for years for the disease to develop. Because of their retrospective nature, case-control studies which use questionnaires or interviews to retrieve information on prior exposure are subject to *recall bias* (see chapter 1.1.4.2), whereas case-control studies using medical records are less prone to that problem. In case-control studies the selection of the control can possibly introduce bias into the study (see chapter 1.1.4.2). The analysis of case-control studies results in relative risks between the two exposure groups. Absolute risks can only be estimated if additional information is available.

1.1.3.3 Cohort studies

In a cohort study a group of individuals is identified based on an exposure to a suspected risk factor for a disease and then followed up together with a group of unexposed individuals until they develop the disease under investigation [Strom 2000]. Individuals must be free from the disease at the start of the follow up. With cohort

studies either c*umulative incidences* (i.e. number of events per number of exposed individuals per time) or incidence rates (i.e. number of events over a certain time of exposure) are calculated. The same cohort can be used to identify and evaluate a whole range of outcomes for a single exposure. If done prospectively, cohort studies are time-consuming and expensive. In a retrospective cohort study all relevant events (exposures as well as outcomes of interest) have already occurred when the study is initiated. Thus, cohort studies depend on the availability of relevant exposure data in adequate detail from preexisting records. A problem (also for case-control studies) may be the lack of information on potential confounding factors (see chapter 1.1.4.3).

An additional modification of the basic cohort design is the so-called *nested case-control study* [Liddell et al. 1977]. Therein exposed or non-exposed individuals of the study cohort without the outcome of interest form the controls for the cases with the outcome. The analysis is then carried out in matched sets of cases and controls. Cases are usually matched to up to four controls in order to increase the power of the analysis.

1.1.3.4 Intervention studies

The characteristic difference of intervention studies, which are also named clinical trials, is that the exposure status is allocated by the investigator [Hennekens et al. 1987]. Usually patients are randomly allocated to the case or the control group. This random allocation guarantees that potential (known as well as not measurable) confounders are equally distributed between the two study groups. Results from randomised controlled trials provide the highest credibility of detecting causal associations. However, they are expensive to conduct and carried out in an ‘artificial’ population, i.e. in persons with little comorbidity or no other drug therapies. Furthermore, because of the high costs, the premarketing clinical trials are usually carried out in some hundred to thousand individuals and last only several months until the efficacy of a new drug has been shown. Thus, rare (adverse) drug effects as well as effects long latency can not be identified.

1.1.4 Aspects of data analysis

A major objective of pharmacoepidemiology is to estimate the effects of drugs when they are prescribed after marketing authorisation. Because this does not happen in a controlled environment such as in clinical trials, many other factors (see chapter 1.1.3.4) can interfere with the effect under investigation. Epidemiologic analyses are carried out to obtain an accurate estimate of the true association between any risk factor (i.e. drug exposure or disease) and the outcome of interest.

1.1.4.1 Risk estimates

The relative risk (RR) quantifies the association between exposure and disease. It indicates the likelihood of developing the disease in the exposed group relative to those who are not exposed [Hennekens et al. 1987]. The RR is defined as the ratio of the incidence of a disease in the exposed group divided by the incidence of a disease in the non-exposed group [Hennekens et al. 1987]. The relative risk or rate ratio is used in cohort studies with person-time units of follow-up. In a case-control study the relative risk is estimated by calculating the ratio of the odds of exposure among the cases to that among the controls [Kirkwood et al. 2003]. This risk estimate is called the odds ratio (OR).

1.1.4.2 Bias

The observed relation may be true or caused by chance or by an erroneous analysis [Strom 2000]. There are two types of error which may occur during the assessment of the risk of a certain outcome associated with a drug exposure. The errors may explain the study results apart from causality or chance.

Bias is generally any systematic error in an epidemiologic study due to an incorrect estimate of the association between exposure and the risk of disease [Hennekens et al. 1987]. When interpreting the findings of pharmacoepidemiological studies it is important to consider the different types of bias that could be present in the study and the likely direction and size of the resulting effect (Figure 1.1.1).

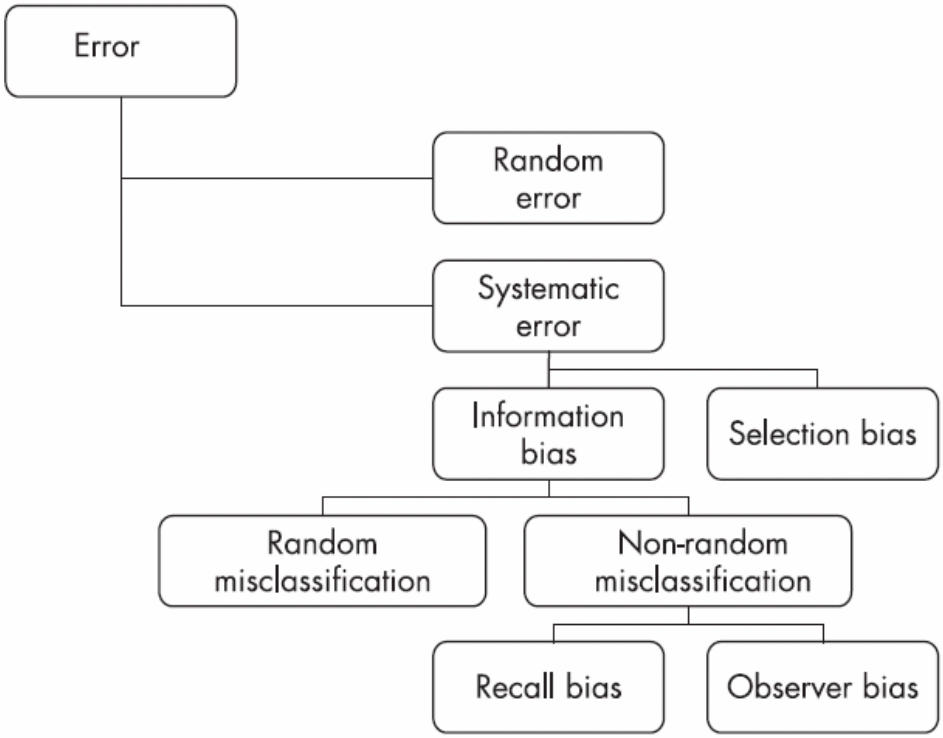

Figure 1.1.1: Types of bias [Henderson et al. 2007]

Selection bias, for example, can occur when there is a systematic difference between the characteristics of the selected cases and those who are not chosen [Hernan et al. 2004]. Selection bias can further occur if in a cohort study the individuals with the exposure are less likely to be followed up than those without the exposure (e.g. selective survival) [Henderson et al. 2007]. Additionally, the so-called *healthy user bias* is a sort of selection bias where the cases differ with regard to their adherence to preventive treatments and those with a good compliance may be systematically healthier than otherwise comparable patients. This may result in a falsely reduced risk related to the preventive use of a drug and an outcome [Brookhart et al. 2007]. *Information bias* is related to the accuracy of information regarding the exposure, the outcome or other covariates [Hennekens et al. 1987]. This type of bias may lead to *misclassification*. Another source of misclassification is the superficial analysis of drug effects without taking dose effects or different drug potencies into account. When the misclassification is random or equal between the study groups, any true association between the exposure and the outcome will be diluted. However, over- or underestimation will not arise [Strom 2000]. If systematic misclassification occurs, the results of a study may be invalid. Another concern is the *recall bias* which arises

when individuals with a particular adverse health outcome remember and report their previous exposure experience differently from those who are not similarly affected [Klemetti et al. 1967]. The term *observer bias* or *detection bias* refers to any systematic difference in recording or interpreting information from study participants, e.g. knowledge of the disease status may result in a different assessment of previous exposure history by an investigator in a case-control study which is based on an interview survey. The best strategy to avoid this is blinding, e.g. the exposure status should be unknown to the investigator who classifies the outcome. Still another type of bias is *protopathic bias* which is caused by an association of the outcome to an exposure that in fact results from the early symptoms of the outcome under investigation [Tamim et al. 2007].

1.1.4.3 Role of confounding

A confounding variable is related independently to the risk factor and the outcome variable and may not be an intermediate step in the causal pathway between the exposure and the outcome. This confounding source can create an apparent association or mask a real one (Figure 1.1.2) [Strom et al. 2000].

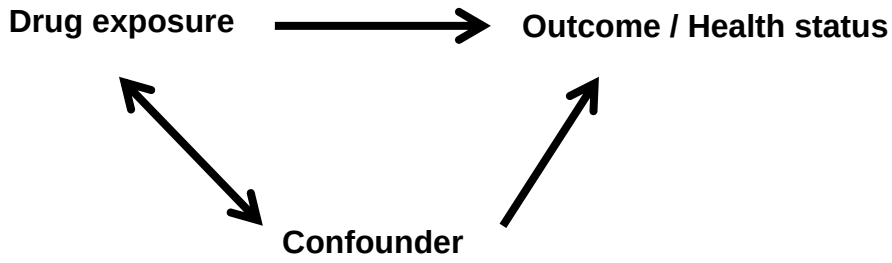

Figure 1.1.2: Mechanism of confounding [Strom et al. 2000]

Confounding occurs when the distribution of this variable is not the same in the groups being compared. In this instance the occurrence of the outcome may be partly or totally dependent on the confounding variable. It is therefore crucial for the validity of the results of an epidemiological study to have enough information on the additional risk factors for the outcome and to include this information in the analysis [Jick et al. 1998]. An example is c*onfounding by indication* where the reason for a

prescription (i.e. the underlying disease) actually influences the size of the effect on the outcome [Signorello et al. 2002]. Compared to the controls who are not receiving the particular drug (because they do not have the same comorbidity) the cases seem to have a higher risk of the outcome. The increased risk of the cases is then falsely attributed to the drug whereas the underlying comorbidity is responsible for the majority of the effect. The severity of the disease can also affect the outcome: If the likelihood for a therapy with a certain drug is higher in patients who are severely affected, the outcome is not only the result of the therapy with the drug but also depends on the degree of the severity of the disease [Garrett et al. 1996].

The effect of confounders can be reduced by a random selection of cases and controls out of a study population [Jick et al. 1998]. Additionally, for some factors such as age, gender, location of residence etc. cases can be matched to the controls in order to eliminate any differences in this respect. In the analysis of the data confounding can be controlled by *adjusting* the analysis for the presence of multiple confounding factors. Analyses capable of multivariate adjustments involve the construction of a mathematical model, e.g. multivariate linear regression (for continuous outcome variables) or multivariate logistic regression (for categorical or binary outcome variables) [Jick et al. 1998; Kirkwood et al. 2003].

If the risk estimate is not the same for different levels of a third variable (e.g. different gender or age groups) of the sample this is called *effect modification* or *interaction* [Kirkwood et al. 2003]. In this case a calculation of stratum-specific effects is necessary to show the influence of the effect modifier on the association between the exposure and the outcome [Normand et al. 2005].

1.2 Neurological disorders: migraine and Parkinson's disease

1.2.1 Migraine

1.2.1.1 Diagnosis

The term 'migraine' derives from the Greek expression 'hemikranion' which means a half skull [Silberstein 2004]. Migraine is a headache disorder with attacks of pulsating pain usually occurring on one side of the cranium. It is frequently accompanied by symptoms such as nausea, vomiting, sensitivity to light and noise and is aggravated by movement [Headache Classification Committee 2004]. In 20-60% of the migraineurs an aura occurs before the attack (i.e. classical migraine) [Silberstein 2004].

An aura can include visual, sensory or speech symptoms, preceding the attack by 1-2 hours. The diagnosis is based on the symptoms and the characteristics of the headache. For the diagnosis of common migraine (i.e. migraine without aura), the patient needs to have at least five attacks. However, a great part of the migraineurs does not search medical care and thus are never diagnosed with migraine.

1.2.1.2 Pathophysiology

The aura seems to be caused by a short excitation of the neurons and a subsequent prolonged depression of the cortical neuronal activity, a phenomenon which is called cortical spreading depression [Leao 1986]. After an initially decreased blood flow the aura symptoms develop in the opposite hemisphere [Olesen et al. 1990]. When the headache pain gradually develops the blood flow increases above usual levels [Olesen et al. 1990].

During the attack the trigeminal system is activated and the sensory neurons release polypeptides such as calcitonin gene-related peptide (CGRP), substance P, nitric oxide synthase (NOS) and other [Goadsby et al. 1990; Edvinsson 2001]. This leads to neuroinflammation, dilation of the blood vessels and platelet activation [Dimitriadou et al. 1992]. Besides the vasodilation, a generalised vasoconstriction occurs as reaction to the activation of the sympathetic nervous system. The sympathicus is activated as a result of the pain [Spierings 2003]. Genetic factors, possibly involving ion-channel

function, seem to influence the individual threshold and attacks occur with a higher frequency when this threshold is decreased or when certain triggers (hormonal fluctuations, stress) are present [Silberstein 2004].

1.2.1.3 Epidemiology

The prevalence of migraine in the western world is approximately 18% in women and 6% in men [Steiner et al. 2003; Lipton et al. 2007]. Chronic diseases with systemic inflammation such as systemic lupus erythematosus [Glanz et al. 2001], hypertension [Cirillo et al. 1999], glaucoma [Pradalier et al. 1998], depression [Breslau et al. 2000] or anxiety [Kowacs et al. 2003] have been linked to an increased risk of developing migraine. Additionally, diet may play a role as a trigger factor for migraine attacks [Millichap et al. 2003]. Individuals with a lower socioeconomic status or a positive family history of migraine also seem to have an increased risk for migraine [Bigal et al. 2007]. However, it is difficult to distinguish between a possible causal association and pure coincidence of these disorders. Patients with a history of migraine have been reported to have an increased risk of developing asthma [Davey et al. 2002], ischaemic stroke [Carolei et al. 1996; Merikangas et al. 1997], chest pain [Sternfeld et al. 1995] or psychiatric diseases [Lipton et al. 2000]. Migraine greatly affects quality of life and is ranked among the world's most disabling medical illnesses [Silberstein 2004]. Decreased productivity due to migraine is associated with a loss of US$ 13 billion per year to employers in the US [Hu et al. 1999].

1.2.1.4 Therapy

For the relief of the pain non-steroidal anti-inflammatory drugs (NSAIDs) or paracetamol are frequently taken together with prokinetic drugs such as metoclopramide or domperidone [Silberstein 2000]. Ergot alkaloids and triptans are used for severe migraine attacks [Goadsby 2006]. Triptans are effective against pain as well as against other vegetative symptoms. Prophylaxis is indicated when there are more than three attacks per month, when the attacks are very severe or prolonged or when a patient cannot tolerate regular treatment [Silberstein 2000]. Prophylactic approaches include first of all a well-balanced lifestyle and the avoidance of any triggers of migraine. Beta-blockers are the first choice for migraine prophylaxis [Goadsby 2006]. Other possible prophylactic therapies include flunarizine, a calcium

channel blocker with antidopaminergic, antiserotonergic as well as antihistaminergic properties, tricyclic antidepressants (TCAs) or antiepileptic drugs (e.g. valproic acid [Young et al. 2004], topiramate [Silberstein et al. 2007]).

1.2.2 Parkinson's disease

1.2.2.1 Diagnosis

Idiopathic Parkinson's disease (PD) is a common neurodegenerative disease of the central nervous system, characterised by the cardinal symptoms of rest tremor, bradykinesia, plastic rigidity, and impaired postural and righting reflexes [Hoehn et al. 1967]. The clinical diagnosis of PD requires the presence of at least two of these symptoms, the exclusion of potential causes for secondary parkinsonism, an asymmetric symptom onset and a good response to levodopa [Litvan et al. 2003]. However, an exact diagnosis of PD can only be obtained by post mortem autopsy [Hughes et al. 1992]. Underdiagnosis as well as misdiagnosis are common: 24% of the cases identified in a door-to-door survey were not known to have PD before [de Rijk et al. 1997] and in autopsy studies PD diagnosis has been incorrect in 25% of cases [Rajput et al. 1991]. Idiopathic PD should be distinguished from other parkinsonian syndromes, caused for example by certain drugs such as antipsychotics or by other diseases like vascular disorders, encephalitis, stroke, hydrocephalus or brain tumour [Stoessl et al. 1999].

1.2.2.2 Pathophysiology

PD is characterised by the loss of neurons in the substantia nigra and in other selective populations of neurons, e.g. in dopaminergic brain-stem nuclei, hypothalamic neurons in the olfactory bulb, sympathetic ganglia as well as para-sympathetic neurons in the gut [Jellinger 1990]. When clinical signs of the disease become evident, 80% of striatal dopamine and 50% of nigral neurons have already been lost [Fearnley et al. 1991]. The pathologic mechanisms underlying the progressive decline of dopamine-containing neurons are still largely unknown. Major processes involved seem to be oxidative stress, impairment in mitochondrial complex I activity and protein mishandling [Greenamyre et al. 2004].

Both genetic and environmental factors are considered important for the aetiology of PD [Schapira 2006]. For familial PD several single gene mutations have been identified [Schapira 2006] and the relative risk in first-degree relatives of PD cases is increased by approximately two- to threefold [Gasser 2001]. However, genetic factors explain only a minority of cases [Gasser 2001]. In patients with sporadic PD the same pathologic processes are induced by non-genetic factors. Environmental toxins such as pesticides or certain metals [Priyadarshi et al. 2001] have been linked to an increased risk of developing PD. Cigarette smoking is inversely related to the risk of developing PD [Morens et al. 1995; Tanner et al. 2002], and female hormones are possibly protective [Fernandez et al. 2000; Currie et al. 2004].

1.2.2.3 Epidemiology

The prevalence of PD has been assessed in various populations in Europe [de Rijk et al. 1997; von Campenhausen et al. 2005], the US [Strickland et al. 2004] and Asia [Kusumi et al. 1996; Tan et al. 2004]. Most of these studies were based on questionnaire surveys. The lifetime prevalence of PD has been reported to be around 0.1 to 0.3% in most studies. It increases sharply with age and reaches about 1% in people over 60 years [Nussbaum et al. 2003]. Many studies showed a 1.5- to 2-times greater risk for men [Baldereschi et al. 2000; Wooten et al. 2004]. Incidence rates are approximately 10-20 per 100'000 person-years [Van Den Eeden et al. 2003; von Campenhausen et al. 2005]. The reported prevalences as well as the incidence rates vary due to differences in study methodology such as the use of (or lack of) approved diagnostic criteria, or the restriction of the study population to a certain age range. Most investigations examined only a pre-selected population, whereas few were carried out within a large, unselected community-based population.

The overall frequency of cancer has been shown to be reduced in patients with PD [D'Amelio et al. 2004]. This effect was even more significant for smoking-related cancers [Olsen et al. 2005]. Patients with a history of PD have been reported to have an increased risk of developing dementia [Emre 2003], depression [McDonald et al. 2003], psychosis, sleep disturbances [Koller et al. 1989; Schrag et al. 2002], motor fluctuations and dyskinesias, symptoms of autonomic nervous system dysfunctions or falls with postural instability [Koller et al. 1989].

1.2.2.4 Therapy

For the pharmacotherapy of PD specific treatment standards and guidelines exist [Olanow et al. 2001]. However, data on how these standards are applied in practice are scarce [Leoni et al. 2002; Askmark et al. 2003]. Dopamine-replacement therapy with levodopa, in a fixed combination with a dopa-decarboxylase inhibitor, is the most common treatment for patients with advanced disease [Miyasaki et al. 2002]. But because of problems regarding the resistance to levodopa in patients with young onset PD as well as dopamine-induced dyskinesias, treatment alternatives are needed like dopamine agonists or indirect dopamine transmission enhancers [Muller 2002]. Medications unrelated to the treatment of PD have been associated with a potential neuroprotective effect. Among these are NSAIDs [Chen et al. 2003; Chen et al. 2005; Hernan et al. 2006], calcium antagonists [Rodnitzky 1999] and drugs used for oestrogen replacement therapy [Benedetti et al. 2001; Currie et al. 2004]. A therapy with HMG-Co-A-reductase inhibitors has been associated with the activation of PD in some patients [Muller et al. 1995; Muller 2003].

PD is an important economic factor for public health [Findley et al. 2003] and affects patients' quality of life [Gage et al. 2003; Quittenbaum et al. 2004]. Recent data indicate that health care utilisation due to PD may be increasing in the Western world as populations age [de Lau et al. 2006], possibly also due to new treatment options [Rubenstein et al. 2001; Muller et al. 2004].

Chapter 2

Aims of the thesis

2 Aims of the thesis

A major objective of this thesis was to contribute to the understanding of the natural histories of migraine and PD using data from primary-care in the UK recorded in the GPRD.

Migraine is a highly prevalent and disturbing disorder. The aim of the migraine project was to add relevant knowledge regarding the health burden of GP diagnosed migraine in the UK and the prevalence of comorbidities in migraineurs. The risk for possibly preventable complications of the disorder should be quantified compared to individuals without migraine. Furthermore, suspected risks associated with typical treatments for migraine should be investigated.

PD is the second most common neurodegenerative disease. The purpose of the project on PD was to increase the awareness for drugs as risk factors for the development of PD. With certain statistical approaches these risks were to be differentiated for subgroups of the population, e.g. men and women, several age groups or a subgroup with a particular comorbidity. Additionally, possible prophylactic (i.e. neuroprotective) treatments for PD should be identified.

Chapter 3

Migraine project

3 Migraine project

3.1 Migraine incidence, comorbidities and health resource utilisation in the UK

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3.1.1 Summary

Population-based data on migraine incidence and comorbidities are scarce. Therefore the aim was to quantify incidence rates and comorbidities of diagnosed migraine and health resource utilisation (HRU) in migraineurs in the UK primary care setting. We conducted a follow-up study with a nested case-control analysis on the GPRD. The study encompassed 51'688 patients with a first-time diagnosis of migraine between 1994 and 2001, and the same number of matched controls. The migraine incidence rate (IR) was 3.69 (95% CI 3.66-3.73) cases per 1'000 person-years (py). The IR was around 2.5 times higher in women. Most chronic diseases were slightly more prevalent in migraineurs than in controls. Triptan users had higher health resource utilisation than other migraineurs. This study shows that migraine is a common diagnosis in general practice and associated with a high prevalence of comorbidities. The increased HRU in triptan users suggests greater migraine severity.

3.1.2 Introduction

Migraine is a common, debilitating primary headache disorder, characterised by recurrent episodes of headache, associated with nausea, vomiting and sensitivity to light and sound. The prevalence has been reported to be around 14% in European countries [Stovner et al. 2006] including France [Henry et al. 2002], Sweden [Dahlof et al. 2001], England [Steiner et al. 2003] and Austria [Lampl et al. 2003] and similar in the US [Lipton et al. 2001]. Migraine is consistently reported to be more frequent in women (15-18%) than in men (about 7%). In Asia, the migraine prevalence has also been reported to be about 8-13% (11-14% in women and 4-7% in men) [Takeshima et al. 2004]. Data on age- and gender-specific incidence rates of migraine are scarce in the literature. Stewart and co-workers estimated the incidence rate by using the reported age of migraine onset in a prevalence study [Stewart et al. 1991]. However, this study sample only included persons 12 to 29 years of age. Another study, which again was restricted to young adults aged 21 to 30 years, found the migraine incidence to be 22.0 / 1'000 py in women and 5.0 / 1'000 py in men [Breslau et al. 1994]. In Denmark, the annual migraine incidence in a population aged 25-64 years was reported to be 8.1 /

1'000 py (male : female ratio = 1 : 6) [Lyngberg et al. 2005], while an US-based study using a linked medical record system reported the incidence of medically diagnosed migraine to be as low as 2.9 / 1'000 py in women and 1.4 / 1'000 py in men [Stang et al. 1992].

Migraine is a neuron-vascular disorder involving abnormal sensory processing, while the pathophysiology of migraine is not yet fully understood [Goadsby 2006]. A genetic disposition has been documented for familial hemiplegic migraine [Ophoff et al. 1996]. The prevalence of certain chronic diseases such as depression or anxiety disorders [Zwart et al. 2003], hypertension [Markush et al. 1975], or epilepsy [Ottman et al. 1994] has been reported to be higher in migraineurs than in individuals without migraine.

Many previous studies of migraine prevalence and comorbidities were based on questionnaire surveys, while population-based data on demographic and clinical characteristics of migraine patients in primary care are scarce, even though migraine is a disorder that is commonly diagnosed by GPs.

Migraine is associated with impaired quality of life [Lipton et al. 2003] and with a substantial socio-economic burden due to increased medical needs, referral to specialists, drug utilisation [Dueland et al. 2004], work absenteeism [Rasmussen et al. 1992] or reduced efficacy at work [Pop et al. 2002]. The introduction of $5HT_{1B/1D}$-agonists (triptans) for acute treatment of migraine attacks has improved the quality of life of many migraineurs, but it also increased costs for migraine therapy [Goldberg 2005].

The objective of this study was to characterise incidence rates of diagnosed migraine, a pattern of comorbidities, utilisation of prescription drugs and health resource utilisation in primary care in the UK.

3.1.3 Methods

3.1.3.1 Study design and data source

We performed a retrospective cohort study and utilised a nested case-control design. We used data from the large and well-validated UK-based GPRD which contains computerised medical records of approximately five million people who are enrolled with selected GPs [Walley et al. 1997]. In the UK, GPs are responsible for primary healthcare as well as for referrals to specialists. They record information on

demographics, diagnoses and drug prescriptions as well as referrals and hospital admissions. The recorded information on drug exposure and on diagnoses has been validated repeatedly and proven to be of high quality [Jick et al. 1992; Jick et al. 2003]. The GPRD is managed by the Medicines and Healthcare products Regulatory Agency (MHRA) in the UK. The patients enrolled in the GPRD are representative of the UK with regard to age, gender, geographic distribution and annual turnover rate.

3.1.3.2 Study base

The study base consisted of all patients in the GPRD who were 79 years or younger at the beginning of the study period from January 1, 1994 to December 31, 2001, and with at least three years of medical history in the GPRD computer record without a diagnosis of migraine.

3.1.3.3 Cases and validation of the migraine diagnosis

Cases were all persons in the study base with a recorded first time migraine diagnosis. The date of the first time migraine diagnosis will subsequently be referred to as ‘index date’. We identified GP-recorded migraine diagnoses from the computer. Since there are no objective indicators or diagnostic tests which clearly define migraine, the diagnosis should be based on medical history, clinical symptoms and on the ICHD criteria of the International Headache Society [Headache Classification Committee 2004]. To learn more about the diagnostic criteria which are used by GPs in the UK, and to validate the recorded diagnoses, a questionnaire was sent to the GPs of 200 randomly selected migraineurs, asking about the clinical manifestation of the disorder. These questions included time for first recorded migraine diagnosis and whether the patient had a medical history of headache problems. We also asked whether the patient had typical migraine-related symptoms according to the ICHD criteria [Headache Classification Committee 2004]. According to these criteria, a migraine diagnosis is likely if headache episodes are recurrent, associated with nausea and vomiting, one-sided and of pulsating character, last 4-72 hours, are accompanied by sensitivity to light, sound (or both) or by visual disturbances, and if a patient desires to lie down in a quiet and dark room during the attack.

3.1.3.4 Incidence analyses

IR of first-time GP-diagnosed migraine episodes in the GPRD population, stratified by age groups (<20, 20-29, 30-39, 40-49, 50-59, 60-69 and 70-79 years), gender and calendar year were calculated. The person years at risk were analysed individually for each person in the study population. The person time was assessed from the date of entry into the study until the patient had a migraine diagnosis, left the GPRD, died or the study ended in December 2001, whichever came first.

3.1.3.5 Case-control analyses to assess comorbidities and drug utilisation prior to the index date

A comparison group without migraine (i.e. controls) was selected, matched with respect to year of birth, gender, general practice and diagnostic index date of each case, and otherwise randomly from the study base. One control patient per case was selected. Cases and matched controls were compared with respect to prevalence of diagnosed diabetes mellitus, asthma, chronic obstructive pulmonary disease (COPD), cancer, depression, epilepsy, stroke, inflammatory bowel disease (IBD), diseases with severe systemic inflammation (e.g. systemic lupus erythematosus [SLE] or rheumatoid arthritis [RA]), hypertension or hyperlipidaemia prior to the index date. Smoking status (never, ex-smoker, current or unknown), and body mass index (BMI <25, 25-29.9, ≥30 kg/m^2) at the index date were also included. Additionally, the number of GP consultations in the year prior to the index date was assessed.

Prescriptions of acetaminophen or NSAIDs, antihypertensives (beta-blockers, calcium channel blockers, angiotensin (AT) II receptor antagonists, angiotensin converting enzyme (ACE)-inhibitors or diuretics), postmenopausal estrogens or hormonal contraceptives prior to the index date were all included in the assessment. We classified users according to the last prescription issued prior to the index date into ‘current’ (last prescription <90 days ago) or ‘past’ users (≥90 days ago).

3.1.3.6 Drug and health care utilisation following the diagnosis of migraine

The use of prescription drugs was assessed in migraineurs at or within the first week following the index date, whereby we identified the use of triptans, NSAIDs, other analgesics (i.e. codeine, propoxyphene), other drugs to treat migraine (e.g. anti-

histamines, ergot alkaloids) or prokinetic agents (i.e. domperidone, metoclopramide). In addition, a random sample of 500 triptan users and 500 migraineurs without triptan use was identified in the GPRD. These patients were followed for exactly three years after the index date. By manual review of the computer records the use of triptans and other relevant acute medication for migraine was quantified, as was the use of preventive medication including beta-blockers, antidepressants or antiepileptic drugs which were recorded in direct relation to a migraine diagnosis. Furthermore the frequency of GP consultations, referrals to specialists (e.g. neurologists) or hospitalisations directly related to migraine or headache-related complaints in the three years following the first-time diagnosis of migraine were assessed.

3.1.3.7 Statistical analysis

The incidence rates of a first-time migraine diagnosis stratified by age and gender were estimated. Incident cases of migraine were used as the numerator and the sum of person-years in the study population as the denominator within age- and sex-strata.

For the case-control analysis, conditional logistic regression analyses were conducted using the statistical software SAS (release 8.2, SAS Institute, Inc., Cary, NC, US). Relative risk estimates (ORs) are presented with 95% confidence intervals (CIs). The independent effects of potential confounders on the risk of developing a migraine were assessed, such as BMI (<25, 25-29.9, ≥30 kg/m^2 or unknown), smoking status, and the number of GP consultations in the year prior to the index date.

3.1.4 Results

We identified 51’688 cases and 51’688 controls of which 71.7% were women. Approximately two thirds of the cases had their first migraine diagnosis recorded before the age of 40 years.

Validation of data was done by sending a questionnaire to the GPs of 200 randomly selected migraine patients. One hundred seventy six (88%) questionnaires were returned, providing information on the duration of the disease prior to the first-time diagnosis and on the clinical characteristics of symptoms that led the GPs to record a

migraine diagnosis. GPs of 133 out of 176 migraineurs (76%) stated that they recorded the migraine diagnosis after a patient reported migraine symptoms for the first time, while the other group recorded the migraine diagnosis based on a patients' previous history of recurrent headache episodes. For 127 out of 176 (72%) migraineurs, the GPs reported that one or more of the symptoms mentioned in the ICHD criteria [Headache Classification Committee 2004] were present in their patients. Most GPs (152 out of 176; 86%) made a diagnosis based on their clinical judgement of medical history and symptoms, the remainder of patients were diagnosed following referral to a specialist. Based on the findings of these questionnaires it was determined that the migraine diagnosis in the computer records was in concordance with the ICHD criteria for a high proportion of cases, and all cases identified on the computer in our subsequent analyses were included.

3.1.4.1 Incidence rate analyses

Overall, the IR of first-time diagnosed migraine in the GPRD-population was 3.69 (95% CI 3.66-3.73) / 1'000 py. It was higher for women (5.21 [95% CI 5.16-5.26] / 1000 py) than for men (2.13 [95% CI 2.09-2.16] / 1'000 py). The IR was highest in the age range 10 to 19 years (6.43 [95% CI 6.32-6.56] / 1'000 py), and 4.5 / 1000 py for the age groups 20-29 and 30-39 years (Table 3.1.1).

Table 3.1.1: IRs of medically diagnosed migraine in the general population by age and sex

Age in years	Person-years	Migraineurs	IR / 1'000 py (95% CI)	IR / 1'000 py (95% CI)	IR / 1'000 py (95% CI)
By age			**Both sexes**	**Men**	**Women**
1-9	1'874'835.4	2'077	1.29 (1.24-1.34)	1.23 (1.16-1.30)	1.35 (1.28-1.43)
10-19	1'710'249.1	11'345	6.43 (6.32-6.56)	5.04 (4.90-5.19)	7.89 (7.78-8.08)
20-29	1'936'867.0	8'753	4.52 (4.43-4.61)	2.15 (2.06-2.25)	6.77 (6.61-6.93)
30-39	2'260'216.7	10'180	4.50 (4.42-4.59)	2.09 (2.01-2.18)	6.83 (6.68-6.98)
40-49	2'005'497.4	9'254	4.61 (4.52-4.70)	2.06 (1.98-2.16)	7.11 (6.95-7.28)
50-59	1'751'687.7	5'840	3.34 (3.25-3.42)	1.64 (1.56-1.73)	5.01 (4.86-5.16)
60-69	1'369'645.8	2'817	2.06 (1.99-2.14)	1.25 (1.17-1.34)	2.82 (2.70-2.95)
70-79	1'083'264.7	1'422	1.32 (1.25-1.39)	0.81 (0.73-0.89)	1.70 (1.60-1.81)
By sex			**All ages**		
Men	6'875'098.1	14'610	2.13 (2.09-2.16)		
Women	7'117'165.5	37'078	5.21 (5.16-5.26)		
Both sexes, all ages					
	13'992'236.7	51'688	3.69 (3.66-3.73)		

The IRs of migraine were constant over the time of calendar year during the study period (data not shown).

3.1.4.2 Case-control analyses to assess comorbidities and drug use prior to the index date

In the entire study population, comorbidity including hypertension (6.3% vs 5.6%, p = 0.06), hyperlipidaemia (2.0% vs 1.7%, p = 0.26), asthma / COPD (16.8% vs 13.1%, p <0.0001), a history of stroke (1.0% vs 0.6%, p <0.0001), renal diseases (2.0% vs 1.4%, p <0.0001), cancer (5.2% vs 4.4%, p <0.0001), epilepsy (1.7% vs 1.4%, p = 0.01), IBD (0.6% vs 0.5%, p = 0.01), RA / SLE (2.2% vs 1.6%, p <0.0001), depression / bipolar disorder (19.0% vs 12.8%, p < 0.0001), or anxiety / psychosis (13.4% vs 9.2%, p <0.0001) was slightly more prevalent in cases than in controls. Migraineurs visited the practitioner more frequently prior to the diagnosis than

controls (OR 2.31 [95% CI 2.23-2.39] for ≥30 practice visits in the year prior to the index date). The results from the multivariate analysis for all age-groups and both genders combined are presented in Table 3.1.2.

Current use of prescribed acetaminophen (adjusted OR 2.81, 95% CI 2.66-2.97) or NSAIDs (adjusted OR 1.22, 95% CI 1.10-1.35) was more frequent among migraineurs than in individuals without diagnosed migraine. Furthermore, the prevalence of use of oral contraceptives (OC) (adjusted OR 1.42, 95% CI 1.34-1.51) as well as use of other oestrogen containing products (hormone replacement therapy, HRT, adjusted OR 1.94 [95% CI 1.79-2.10]) were also higher in female migraineurs than in women without migraine (Table 3.1.2).

Table 3.1.2: Demographics and comorbidities of migraineurs and controls

Variable		Cases, No (%) (n=51'688)	Controls, No (%) (n=51'688)	OR* (95% CI)	p-value
Age (years)					
	<20	13'422 (26.0)	13'337 (25.8)	--	--
	20-39	18'933 (36.6)	19'166 (37.0)	--	--
	40-59	15'094 (29.2)	14'953 (28.9)	--	--
	≥60	4'239 (8.2)	4'282 (8.3)		--
Sex				--	--
	Male	14'610 (28.3)	14'610 (28.3)	--	--
	Female	37'078 (71.7)	37'078 (71.7)	--	--
Smoking status					
	Non	22'551 (43.6)	20'543 (39.7)	1.00 (referent)	--
	Current	9'713 (18.8)	9'331 (18.1)	0.89 (0.86-0.92)	<0.0001
	Ex	3'547 (6.9)	2'889 (5.6)	1.09 (1.03-1.15)	0.002
	Unknown	15'877 (30.7)	18'925 (36.6)	0.59 (0.56-0.62)	<0.0001
BMI (kg/m²)					
	<25	20'472 (39.6)	18'920 (36.6)	1.00 (referent)	--
	25-29.9	8'826 (17.1)	7'820 (15.1)	1.04 (1.01-1.09)	0.03
	≥30	4'351 (8.4)	3'932 (7.6)	1.00 (0.95-105)	0.96
	Unknown	18'039 (34.9)	21'016 (40.7)	0.88 (0.85-0.92)	<0.0001

Cont. Table 3.1.2

Variable	Cases, No (%) (n=51'688)	Controls, No (%) (n=51'688)	OR* (95% CI)	p-value
Comorbidities				
Diabetes mellitus	578 (1.1)	644 (1.3)	0.77 (0.69-0.87)	<0.0001
Asthma / COPD	8'693 (16.8)	6'760 (13.1)	1.26 (1.22-1.31)	<0.0001
Hypertension	3'268 (6.3)	2871 (5.6)	1.06 (1.00-1.12)	0.06
Hyperlipidaemia	1'053 (2.0)	880 (1.7)	1.05 (0.96-1.16)	0.26
Stroke / TIA	521 (1.0)	283 (0.6)	1.77 (1.52-2.07)	<0.0001
Renal disorders	1'034 (2.0)	718 (1.4)	1.36 (1.24-1.51)	<0.0001
Cancer	2'706 (5.2)	2'278 (4.4)	1.16 (1.09-1.24)	<0.0001
RA / SLE	1'119 (2.2)	847 (1.6)	1.24 (1.12-1.37)	<0.0001
Depression / bipolar disorder	9'821 (19.0)	6'593 (12.8)	1.52 (1.46-1.58)	<0.0001
Anxiety / psychosis	6'945 (13.4)	4'757 (9.2)	1.33 (1.28-1.39)	<0.0001
Epilepsy	897 (1.7)	740 (1.4)	1.14 (1.03-1.26)	0.01
IBD	325 (0.6)	239 (0.5)	1.25 (1.06-1.49)	0.01
Current drug use prior to index date**				
NSAIDs	1033 (2.0)	730 (1.4)	1.22 (1.10-1.35)	<0.001
Acetaminophen	5'618 (10.9)	2'577 (5.0)	2.81 (2.66-2.97)	<0.0001
OCs	3'772 (10.2)	3'022 (8.2)	1.42 (1.34-1.51)	<0.0001
Estrogens / HRT	2'366 (6.4)	1'427 (3.9)	1.94 (1.79-2.10)	<0.0001

* adjusted for the other variables in this table

** current use = at least one prescription within 90 days prior to the index date

Use of antihypertensives, adjusted for the diagnoses in Table 3.1.2, yielded relative risk estimates for use of ACE-inhibitors and AT II receptor antagonists around 1, while use of calcium channel blockers was associated with a lower migraine risk (OR 0.69, 95% CI 0.61-0.77). On the other hand, current use of beta-blockers was associated with an elevated relative risk of getting a migraine diagnosis (OR 1.70, 95% CI 1.57-1.84).

Furthermore patients taking beta-blockers were stratified into those with a recorded diagnosis of hypertension vs those without such a diagnosis. The adjusted OR across all age groups and both sexes was 1.31 (95 % CI 1.16-1.47) for individuals with hypertension vs 2.15 (95% CI 1.92-2.40) for those without hypertension. In the subgroup of young men taking beta-blockers without a diagnosis of hypertension, the OR was 6.26 (95% CI 4.40-8.91). Their computer records were reviewed and it was found that a large proportion (approx. 70%) had a previous medical history of chronic headache recorded.

3.1.4.3 Drug and health care utilisation after the first migraine diagnosis

On the day of the first migraine diagnosis or within the first week thereafter, 12.7% of migraineurs were prescribed a triptan (zolmitriptan, sumatriptan, rizatriptan, naratriptan or almotriptan). During the same period of time, 24.7% were prescribed NSAIDs, 15.8% other analgesics (e.g. propoxyphene or codeine-containing drugs), 16.4% prokinetic drugs, and 19.5% other drugs for acute treatment of migraine (i.e. prochlorperazine, trifluoperazine, promethazine, cyclizine, buclizine or cinnarizine). Only 1.0% of cases received a prescription for ergot alkaloids. The triptan prescription rate within the first week after migraine diagnosis increased during the study period from 8.5% in 1994 to 18.6% in 2001. A total of 19.5% of migraineurs were prescribed a triptan at least once during the time of the study. Based on the manual assessment of 1'000 patient records, triptan users had substantially more health resource utilisation than migraineurs without triptans in the three years following the first-time recorded migraine diagnosis; the mean (± standard deviation) number of GP-contacts (i.e. recorded diagnoses or drug prescriptions directly related to migraine or both) during the specified time period was significantly increased for migraineurs with triptan use compared to for migraineurs who did not utilise triptans (Table 3.1.3). Among migraineurs with triptan use, 16.0% were referred to a specialist or to a hospital or both during the three years following the first-time diagnosis of migraine, while this happened only to 9.6% of migraineurs without triptan use (Table 3.1.3).

Table 3.1.3: HRU in 500 triptan users and 500 migraineurs without triptan use in the 3 years after the first migraine diagnosis

	No triptan use			Triptan use		
	Mean (± std)	**Range**	**Median**	**Mean (± std)**	**Range**	**Median**
Number of GP-visits or prescriptions, or both	2.62 (5.71)	0-39	1	9.45 (12.63)	0-93	5

	Patients	**%**	**Patients**	**%**
Number of patients with ≥1 referral to a specialist or hospitalisation, or both	48	9.6	80	16.0

3.1.5 Discussion

This large UK primary care based observational study was done with the aim of generating additional information on migraine, comorbidities and health resource utilisation by migraine sufferers. It is based on longitudinal data in the GPRD, one of the world's largest databases of anonymised patient records. The overall IR was 3.7 cases of diagnosed migraine per 1'000 py and approximately 2.5-times higher in women than in men. First time diagnosis of migraine was frequently done during adolescence or young adulthood. These findings are consistent with previous published studies on migraine epidemiology [Stang et al. 1992; Lyngberg et al. 2005].

In this study, the IRs for boys and girls aged 1-9 years were similar. This is in concordance with a study involving Greek school children, reporting equal prevalences in this age group [Mavromichalis et al. 1999]. In other studies, however, the prevalence of migraine has been lower in girls than in boys [Mortimer et al. 1992; Abu-Arefeh et al. 1994], an observation that changes around puberty with the number of female migraine sufferers increasing throughout adulthood [Stewart et al. 1994].

IRs of migraine differ with study methodology; higher IRs are usually found in interview-based surveys [Stewart et al. 1991; Breslau et al. 1994; Lyngberg et al. 2005] whereas Stang *et al.*, who used a linked medical records system, reported lower incidence rates than our study [Stang et al. 1992]. Our results represent migraine

diagnoses made by primary care physicians rather than diagnoses based on self-assessment by patients through questionnaires. Therefore they are devoid of any recall bias associated with questionnaire-based surveys. However, the assessment of the migraine incidence or prevalence by using GP-records suffers from several limitations: First, there is no objective diagnostic procedure for migraine and the diagnosis is based on the medical history and patient-reported symptoms which can vary substantially between patients and sometimes even within a patient from one episode to another [Nachit-Ouinekh et al. 2005]. Second, migraine is a disease that is underdiagnosed to some degree in a primary care based assessment using GP-records since patients with mild or infrequent migraine may not see a doctor and just treat themselves with over-the-counter (OTC) analgesics [Lipton et al. 1998]. The percentage of patients never consulting a doctor for their headache has been as high as 68% in women and 57% in men in the study by Lipton *et al.* [Lipton et al. 1998]. This could be the reason that the IRs are lower than those found in questionnaire-based studies. Third, the likelihood that a GP will record a migraine diagnosis may depend on the frequency of medical care; it is likely that patients with more health problems will see their GP more often, thus for such patients with other comorbidities it is more likely that episodic headache will be reported to the GP and that a migraine diagnosis is recorded on computer. The last point is reflected in our study population by the observation that migraineurs had on average substantially more GP consultations prior to the first time migraine diagnosis than controls, suggesting the possibility of some diagnostic bias. However, certain comorbidities may also be causally associated with the risk of developing migraine, such as depression [Breslau et al. 2003] or other psychiatric diagnoses [Merikangas et al. 1990], as previously suggested. In the present study a significantly increased relative risk of migraine in persons with a diagnosis of depression, anxiety, psychoses, epilepsy and a variety of other metabolic or cardiovascular diseases was found.

The use of antihypertensives and the risk of migraine was also assessed since previous studies raised the possibility of a protective effect [Markley 1991; Schrader et al. 2001; Tronvik et al. 2003]. An increased relative risk of migraine was associated with use of beta-blockers. However, this is most likely the result of confounding by indication, rather than a causal effect, since the highest risk was seen in the subgroup of young

male beta-blocker users without diagnosed cardiovascular disease, a subgroup which most likely received beta-blockers to treat headache (some 70% in this group had a previous diagnosis of chronic headache). Beta-blockers are used to treat patients with chronic headaches or migraine to reduce the frequency and severity of migraine episodes. Although the first-time recorded diagnoses of migraine were analysed, there is always some imprecision in the timing of a first-time recording of a chronic disease without clear and well-defined onset, such as migraine. This also helps explaining the high migraine risk associated with beta-blocker use in young migraine patients. Furthermore, use of prescription analgesics / NSAIDs was also higher in migraineurs than in the control group, suggesting a higher prevalence of patients with pre-existing headache in migraineurs than in controls.

Migraine is linked with female gender. The prevalence of migraine is 2-3 times higher in women than in men, and for women the first migraine attack is common in puberty. The mechanism by which migraine is influenced by female hormones still remains unclear. In the present study a significantly increased migraine risk among women on OCs and HRT was found. Misakian and coworkers reported similar results in women using HRT (OR for migraine 1.94 [95% CI 1.79-2.10] for current users compared with never users) [Misakian et al. 2003]. The ICHD lists two entities related to the use of OCs and HRT, namely exogenous hormone-induced headache and oestrogen-withdrawal headache [Headache Classification Committee 2004]. Migraine attacks have been observed to occur often in the pill-free interval in women using OCs [Ryan 1978]. This observation corresponds to the oestrogen withdrawal that is supposed to be causally related to menstrual migraine, whereas sustained high sex hormone levels probably contribute to migraine attacks during HRT-treatment [MacGregor et al. 2003].

Within the migraine study population non-specific analgesics and NSAIDs were commonly prescribed, while triptans were used relatively infrequently. Over the entire study period, only 12.5% of migraineurs were prescribed a triptan as first-line treatment. This went up to around 20% of triptan prescriptions during subsequent months, when repeated migraine episodes occurred. It was not possible to precisely quantify use of OTC-available drugs to treat migraine attacks, such as NSAIDs containing ibuprofen, acetylsalicylic acid or naproxen. The assessment of triptan use,

however, is likely to be accurate since triptans were only available by prescription in the UK at the time of the study.

Based on the manual assessment of 500 triptan users and 500 migraineurs without triptan use, it was found that triptan users visited the GP more frequently for headache or migraine-related complaints after the first migraine diagnosis than those without triptan use, and they also had more referrals to specialists than non-users. This indicates that GPs prescribe triptans preferentially to patients with severe migraine who need closer monitoring.

In summary, this large primary care based migraine study quantifies migraine diagnosed by primary care physicians in the UK and it documents higher migraine incidence rates for women and for young people. Triptans have been used by approximately 20% of migraineurs during the study period, while non-specific pain medications were much more commonly used. Triptan users seem to have more severe migraine than non-users which is supported by the observation that they consulted their GP more often for headache related problems and had more referrals to specialists than triptan non-users. Migraineurs also suffer from psychiatric comorbidities more frequently than controls, making migraine management in primary care even more important and challenging.

3.2 Migraine and the risk of stroke, TIA or death

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3.2.1 Summary

Previous observational studies have reported a higher risk of stroke in migraine patients. The aim of this study was to estimate the risk of stroke, transient ischaemic attack (TIA), or death in migraineurs in the UK. A population-based follow-up study within the GPRD from 1994 to 2001 was conducted. The RR of stroke in migraineurs compared to non-migraineurs was 2.2 (95% CI 1.7-2.9). It was highest for patients with a migraine diagnosis recorded within 30 days prior to a stroke (OR 11.1 [95% CI 5.69-21.5]). The RR of TIA in migraineurs compared to non-migraineurs was 2.4 (95% CI 1.8-3.3), the mortality of migraineurs was slightly decreased. In the study the RR of developing a stroke or a TIA was doubled in migraineurs as compared to non-migraineurs, while that for death was close to unity.

3.2.2 Introduction

Several previous population-based studies reported an increased risk of stroke in association with migraine [Buring et al. 1995; Carolei et al. 1996; Merikangas et al. 1997; Schwaag et al. 2003]. Migraine with aura seems to be linked to an increased stroke risk [Stang et al. 2005], especially in women [Kurth et al. 2005]. The possibility that migraine and stroke share common pathogenetic processes in the central nervous system has been suggested [Agostoni et al. 2004]. Both disorders are characterised by release of inflammatory mediators such as vasoactive peptides [Gallai et al. 1995] and enhanced platelet reactivity [Zeller et al. 2004]. During an aura constriction of blood vessels is present [Olesen et al. 1990], reducing the cerebral blood flow (CBF) by approximately 27 % [Sanchez del Rio et al. 1999]. A reduced CBF in conjunction with vasoactive compounds may predispose for coagulopathies and arterial thrombosis [Moschiano et al. 2004]. Such vasoactive compounds for acute treatment of migraine attacks including 5-$HT_{1B/1C}$ receptor agonists and ergot alkaloids exert vasoconstriction as part of their pharmacological action [Villalon et al. 2003]. In theory, this may influence the risk of cerebrovascular events in migraine patients using triptans.

Following the introduction of triptans, costs of migraine-related therapy have increased [Goldberg 2005], while patient quality of life has improved substantially [Dahlof et al. 1997; Lainez et al. 2005]. Triptans are considered to be well tolerated and safe in

migraine patients without cardiovascular disorders, and the most frequent adverse events in clinical trials for triptans like naratriptan [Mathew et al. 1997], almotriptan [Pascual et al. 2001] or sumatriptan [Pfaffenrath et al. 1998] have been reported to be nausea, vomiting, somnolence and paraesthesia.

The aim of this large population-based study was to quantify incident stroke, a TIA, or death in migraineurs, as compared with non-migraineurs, and to explore the role of triptans in the risk of developing any of these outcomes.

3.2.3 Methods

3.2.3.1 Data Source

The large and well-validated UK-based GPRD was used which contains computerised medical records of some three million people who are enrolled with selected GPs [Jick 1997]. In the UK, GPs are responsible for primary healthcare as well as for referrals to specialists. They record information on patient demographics (age, gender), diagnoses, drug prescriptions, referrals and hospital admissions as well as some lifestyle information (e.g. smoking status). The recorded information on drug exposure and on diagnoses in the GPRD has been validated repeatedly and proven to be of high quality [Jick et al. 1991]. The GPRD is managed by the MHRA in the UK, and it is one of the world's largest databases of anonymised patient records. The patients enrolled in the GPRD are representative of the UK-population with regard to age, gender, geographic distribution and annual turnover rate [Wood et al. 2004], and GPRD data have been used in previous studies on stroke [Gibbs et al. 2001; Hall et al. 2004].

3.2.3.2 Study population and case definition

The study population consisted of all patients in the GPRD who were 79 years old or younger from January 1, 1994 to December 31, 2001. They had to have at least three years of medical history in the computer record prior to their first-time migraine diagnosis. From the study population patients with a recorded first-time diagnosis of migraine were identified as well as an equally sized comparison group of individuals without migraine, ascertained randomly from the study population, and matched to

migraineurs on age (year), gender, general practice (i.e. patients and controls had to be enrolled with the same GP), years of history on the GPRD and date of the first migraine diagnosis recorded.

Among migraineurs and controls, all persons were identified who had an incident diagnosis of thrombotic or hemorrhagic stroke, a TIA, or who died (of any cause) between the time of the first migraine diagnosis (or the corresponding date in the matched comparison group) and the end of the study period. All patients who had a history of stroke, or TIA, prior to their first recorded migraine diagnosis were excluded as well as patients with a history of cancer. Electronic records of potential cases were manually reviewed, blinded to exposure information (i.e. migraine diagnosis and prescription of a triptan) and included or excluded based on this manual assessment. Cases with stroke or TIA were included if they were referred to a specialist or to a hospital with a follow-up record confirming the diagnosis (e.g. by specific treatment, subsequent referrals for check-ups etc.). The cause of death in patients who died during the study period was further identified, as recorded by the GP.

3.2.3.3 Analysis (Follow-up study)

Cases and matched controls were followed from the date of first migraine diagnosis (of the case), until they developed a first-time diagnosis of stroke, TIA, or death, they reached 80 years of age, their follow-up in the GP-record ended, or the end of the study was reached (December 31, 2001), whichever came first.

Incidence rates of first-time diagnoses of stroke or TIA and mortality were assessed for the migraine population and the comparison group. Crude relative risk estimates with 95% CIs were calculated by comparing the incidence between migraineurs and control patients.

We also attempted to distinguish between migraine with or without aura. In the GPRD most migraine diagnoses have no further differentiation. However, there are diagnoses of ‘common migraine’, which is defined as migraine without aura, and of ‘classic migraine’, which is defined as migraine with aura or neurological symptoms, according to the criteria of the ICHD [Headache Classification Committee 2004]. Thus, the migraineurs were categorised into two groups, those with evidence for aura, and those with an unspecific diagnosis or with a diagnosis of common migraine.

3.2.3.4 Nested case-control analysis

Each case of stroke, TIA, or death was matched with four control patients from the entire study population (migraineurs and non-migraineurs) on age (± 3 years), gender, general practice and calendar time. Thus, controls were randomly selected from the population of migraineurs or from the comparison group, and the controls had to be alive at the index date, i.e. the date when the case had the first-time diagnosis of stroke, TIA, or death was recorded. All cases and controls were assessed for a history of migraine, prescriptions of triptans prior to the index date, and additional variables, including smoking status (non, current, ex, unknown), BMI (<25, 25-29.9, 30+ kg/m^2 or unknown), the number of recorded GP consultations in the year prior to the index date (<10, 10-19, 20+) as well as the recorded diagnosis of chronic disorders, including hypertension, dyslipidaemia, diabetes mellitus, rheumatoid arthritis, depression or bipolar disorder, anxiety or psychosis, or epilepsy. Conditional logistic regression analyses were conducted to explore the relative risk of developing an outcome of interest in association with a history of migraine and prescription of triptans, expressed as ORs with 95% confidence intervals. The association between diagnosed comorbidities or other potential confounders (i.e. smoking status, BMI, number of GP consultations in the year prior to the index date) and the risk of developing an outcome of interest was assessed in univariate analyses. Individual confounders were included in the final models if they were associated with the outcome in the univariate analysis with a p-value <0.1 and if they were statistically significantly associated (p-value <0.05) with the outcome in the multivariate model after applying a stepwise procedure. Since drugs affecting thrombocyte aggregation such as aspirin or NSAIDs may alter the risk of stroke or TIA we also adjusted the models for use of these drugs prior to the index date. Since some of these drugs are also available without prescription, not all use of aspirin and NSAIDs has been captured in the GPRD. However, most low dose aspirin use for the prevention of cardiovascular diseases will be recorded since it is most often prescribed by GPs and therefore documented in the GPRD profiles.

Separate analyses for thrombotic and hemorrhagic stroke were also conducted.

Adjusting the analysis for the presence of various comorbidities with a binary 0/1-variable may not adequately control for comorbidities since patients suffer from

diseases with a range of severities. In order to reduce the risk of residual confounding by these variables, a logistic regression analysis was conducted restricted to 'healthy' migraineurs (i.e. persons not diagnosed with hypertension, dyslipidaemia, diabetes mellitus, rheumatoid arthritis, depression, bipolar disorder, anxiety, psychosis, or epilepsy) and controls. We broke the matching for this analysis, conducted a logistic regression model and adjusted it for BMI, smoking, gender and age.

Additionally, health resource utilisation of migraine patients was quantified. For this purpose, computer records of migraineurs with stroke (cases) and migraineurs without stroke (controls) were reviewed and information for all headache-related GP consultations and drug prescriptions as well as referrals to specialist clinics or hospitalisations were collected for exactly three years after their first-time migraine diagnosis.

Since a recent prescription of a triptan is closely related to a recent migraine episode, and since a recent migraine episode is related to an increased stroke risk, we attempted to distinguish the effect of migraine from a possible triptan effect by conducting additional analyses: We compared the risk of developing a stroke among migraineurs with a recently recorded migraine episode (<30 days preceding the stroke date) and a recent prescription for triptans, or migraineurs with a recently recorded episode who were not recently prescribed a triptan, with the stroke risk of persons without migraine or triptans.

All statistical analyses were performed with SAS software, Version 8.1 (SAS Institute, Inc., Cary, NC, US).

3.2.4 Results

The study encompassed 103'376 individuals (51'688 migraineurs and 51'688 matched persons without a diagnosed migraine), of which 71.7% were females. Approximately two thirds of migraineurs had their first migraine diagnosis recorded below the age of 40 years, and some 26% were below the age of 20 years at the time of their first migraine diagnosis.

After individuals with a previous history of stroke, TIA, or cancer were excluded, we identified 200 patients with an incident diagnosis of stroke, 163 patients with a TIA and 458 who died during follow-up. They all met the inclusion criteria after the manual review of potential case records. The results of the person-time analyses are displayed in Table 3.2.1: for all outcomes, and the results of the nested case-control analyses are shown in Table 3.2.3 and Table 3.2.4.

3.2.4.1 Stroke

The group of 200 stroke cases comprised 87 cases with a diagnosis of thrombotic stroke, 47 with haemorrrhagic stroke, and 66 with a non-specified stroke diagnosis. In the follow-up analysis, the IR of all stroke events combined across all ages was 110.2 (95% CI 93.2-130.3) / 100'000 py among migraineurs, and 50.1 (95% CI 39.1-64.0) / 100'000 py among non-migraineurs, yielding a RR of 2.2 (95% CI 1.7-2.9).

In the nested case-control analysis, a previous history of migraine was associated with an increased risk of stroke for all stroke cases combined (OR 2.71, 95% CI 1.90-3.87), adjusted for age, gender, general practice and calendar time (by matching) and for BMI, smoking status, diabetes mellitus, hypertension and dyslipidaemia in the multivariate model. The stroke risk for migraineurs was slightly higher in males than in females (Table 3.2.1 and Table 3.2.3). The RR of stroke was much higher among patients with a migraine episode recorded within 30 days prior to the onset of stroke (adjusted OR 11.1, 95% CI 5.69-21.5). Among the 36 stroke cases with a migraine diagnosis recorded within 30 days prior to the stroke, 16 (44.4%) had seven or fewer days between the migraine attack and the stroke diagnosis. As compared to persons without migraine, the RR of stroke for migraineurs with aura was substantially higher (adj. OR 14.5, 95% CI 4.39-47.9) than for other migraineurs (OR 2.59, 95% CI 1.81-3.71).

For the 'healthy' migraineurs the relative risk estimate of developing stroke was 3.43 (95% CI 2.00-5.91) as compared to patients without migraine. The adjusted RR estimates of developing a thrombotic or hemorrhagic stroke associated with a previous diagnosis of migraine were 2.85 (95% CI 1.88-4.30) and 2.52 (95% CI 1.21-5.25), respectively.

Table 3.2.1: IRs of stroke, TIA or death, stratified by migraine and sex

Outcome	Group	Events	p-years	IR / 100'000 py (95 % CI)	RR (95% CI)
Stroke					
Migraine	All	137	124'320	110.2 (93.2-130.3)	2.2 (1.7-2.9)*
	Men	62	35'709	173.6 (135.5-222.5)	2.7 (1.7-4.1)**
	Women	75	88'611	84.6 (67.5-106.1)	1.9 (1.3-2.8)†
Non-migraine	All	63	125'849	50.1 (39.1-64.0)	1.0
	Men	24	36'770	65.3 (43.9-97.1)	1.0
	Women	39	89'079	43.8 (32.0-59.8)	1.0
TIA					
Migraine	All	115	124'320	92.5 (77.1-111.0)	2.4 (1.8-3.3)*
	Men	50	35'709	140.0 (106.2-184.5)	4.0 (2.4-6.5)**
	Women	65	88'611	73.4 (57.6-93.5)	1.9 (1.3-2.8)†
Non-migraine	All	48	125'849	38.1 (28.8-50.6)	1.0
	Men	13	36'770	35.4 (20.7-60.5)	1.0
	Women	35	89'079	39.3 (28.3-54.6)	1.0
Death					
Migraine	All	198	124'320	159.3 (138.6-183.0)	0.8 (0.6-0.9)*
	Men	81	35'709	226.8 (182.6-281.8)	0.9 (0.6-1.1)**
	Women	117	88'611	132.0 (110.2-158.2)	0.7 (0.6-0.9)†
Non-migraine	All	260	125'849	206.6 (183.0-233.3)	1.0
	Men	98	36'770	266.5 (218.8-324.7)	1.0
	Women	162	89'079	181.9 (156.0-212.1)	1.0

* as compared to all non-migraineurs

** as compared to male non-migraineurs

† as compared to female non-migraineurs

Table 3.2.2: Distribution of characteristics and comorbidities in cases and controls

	Stroke		Stroke ('healthy' migraineurs)		TIA		Death	
Variable	**Cases (%) (n=200)**	**Conts. (%) (n=737)**	**Cases (%) (n=76)**	**Conts. (%) (n=388)**	**Cases (%) (n=163)**	**Conts. (%) (n=605)**	**Cases (%) (n=458)**	**Conts. (%) (n=1684)**
Age (years)								
<30	13 (6.5)	53 (7.2)	9 (11.9)	35 (9.0)	4 (2.5)	16 (2.6)	30 (6.6)	122 (7.2)
30-59	90 (45.0)	347 (47.1)	40 (52.6)	200 (51.6)	54 (33.1)	230 (38.0)	187 (40.8)	694 (41.2)
≥60	97 (48.5)	337 (45.7)	27 (35.5)	153 (39.4)	105 (64.4)	359 (59.4)	241 (52.6)	868 (51.5)
Sex								
Male	86 (43.0)	300 (40.7)	39 (51.3)	184 (47.4)	63 (38.7)	221 (36.5)	179 (39.1)	626 (37.2)
Female	114 (57.0)	437 (59.3)	37 (48.7)	204 (52.6)	100 (61.3)	384 (63.5)	279 (60.9)	1058 (62.8)
Smoking								
Non	88 (44.0)	401 (54.4)	29 (38.2)	198 (51.0)	93 (57.1)	351 (58.0)	195 (42.6)	972 (57.7)
Current	61 (30.5)	141 (19.1)	20 (26.3)	73 (18.1)	35 (21.5)	105 (17.4)	141 (30.8)	269 (16.0)
BMI (kg/m²)								
<25	66 (33.0)	259 (35.1)	24 (31.6)	127 (32.7)	54 (33.1)	217 (35.9)	170 (37.1)	615 (36.5)
≥30	24 (12.0)	76 (10.3)	6 (7.9)	33 (8.5)	25 (15.3)	75 (12.4)	54 (11.8)	182 (10.8)
Comorbidities								
Diabetes mellitus	16 (8.0)	21 (2.9)	--	--	13 (8.0)	33 (5.5)	48 (10.5)	59 (3.5)
Hypertension	63 (31.5)	149 (20.2)	--	--	60 (36.8)	142 (23.5)	119 (26.0)	370 (22.0)
Dyslipidaemia	23 (11.5)	46 (6.2)	--	--	23 (14.1)	49 (8.1)	31 (6.8)	113 (6.7)

Table 3.2.3: Risk of stroke, TIA or death in the nested case control analysis

	Stroke			**Stroke** ('healthy' migraineurs)		
Parameter	**Cases (%) (n=200)**	**Conts. (%) (n=737)**	**OR* (95% CI)**	**Cases (%)**	**Conts. (%) (n=388)**	**OR* (95% CI)**
No migraine	63 (31.5)	395 (53.6)	1.0 (ref.)	27 (35.5)	239 (61.6)	1.0 (ref.)
Migraine	137 (68.5)	342 (46.4)	2.71 (1.90-3.87)	49 (64.5)	149 (38.4)	3.43 (2.00-5.91)
males	62 (31.0)	138 (18.7)	3.21 (1.82-5.66)	27 (27.3)	72 (18.6)	4.48 (1.98-10.14)
females	75 (26.9)	204 (27.7)	2.51 (1.57-4.02)	22 (22.2)	77 (19.8)	2.92 (1.35-6.33)
<30 ys	9 (4.5)	25 (3.4)	2.83 (0.37-21.92)	7 (9.2)	18 (4.6)	5.60 (0.34-92.88)
30-59 ys	65 (32.5)	163 (22.1)	2.77 (1.65- 4.66)	29 (38.2)	80 (20.6)	8.77 (2.65-29.06)
≥60 ys	63 (31.5)	154 (20.9)	2.67 (1.54- 4.61)	13 (17.1)	51 (13.1)	1.21 (0.39- 3.80)
<30 days**	36 (18.0)	22 (3.0)	11.1 (5.69-21.5)	17 (22.4)	10 (2.6)	18.0 (7.10-45.7)
with aura	10 (5.0)	6 (0.8)	14.5 (4.39-47.9)	4 (5.3)	2 (0.5)	22.1 (3.57-136)
other	127 (63.5)	336 (45.6)	2.59 (1.81-3.71)	45 (59.2)	147 (37.9)	3.20 (1.85-5.54)
	TIA			**Death**		
Parameter	**Cases (%) (n=163)**	**Conts. (%) (n=605)**	**OR* (95% CI)**	**Cases (%)**	**Conts. (%) (n=1684)**	**OR* (95% CI)**
No migraine	48 (29.4)	326 (53.9)	1.0 (ref.)	260	865 (51.4)	1.0 (ref.)
Migraine	115 (70.6)	279 (46.1)	2.76 (1.88-4.05)	198	819 (48.6)	0.84 (0.68-1.04)
males	50 (34.0)	97 (16.0)	4.97 (2.40-10.29)	81 (45.3)	324 (19.2)	0.86 (0.61-1.21)
females	65 (26.3)	182 (30.1)	2.06 (1.28- 3.32)	117	495 (29.4)	0.83 (0.63-1.09)
<30 ys	4 (2.5)	13 (2.1)	--	20 (4.4)	58 (3.4)	1.95 (0.76-5.00)
30-59 ys	39 (23.9)	111 (18.3)	2.55 (1.28-5.09)	79 (17.2)	342 (20.3)	0.84 (0.60-1.18)
≥60 ys	72 (44.2)	155 (25.6)	2.94 (1.79-4.82)	99 (21.6)	419 (24.9)	0.77 (0.57-1.04)
<30 days**	14 (8.6)	8 (1.3)	13.1 (4.69-36.5)	8 (1.8)	42 (2.5)	0.70 (0.32-1.55)
with aura	4 (2.5)	11 (1.8)	2.24 (0.61-8.23)	4 (0.9)	17 (1.0)	0.74 (0.24-2.30)
other	111 (68.1)	268 (44.3)	2.78 (1.89-4.10)	194	802 (47.6)	0.84 (0.68-1.04)

* adjusted for covariates from **Table 3.2.2** (for 'healthy' stroke: adjusted for smoking and BMI)

** last migraine attack was recorded <30 days prior to the index date

Table 3.2.4: Risk of stroke or TIA in association with triptan use in the nested case control analysis

	Stroke			
Parameter	**Cases (%) (n=200)**	**Conts. (%) (n=737)**	**OR* (95% CI)**	**OR** (95% CI)**
No migraine	63 (31.5)	395 (53.6)	1.0 (ref.)	1.0 (ref.)
Migraine <30 days, no triptan use	28 (14.0)	18 (2.4)	10.3 (4.96-21.3)	8.22 (3.87-17.4)
Migraine <30 days, recent triptan use†	7 (3.5)	2 (0.3)	18.7 (3.55-98.8)	12.8 (2.35-69.8)
Migraine <30 days, no triptan use	28 (14.0)	18 (2.4)	1.0 (ref.)	1.0 (ref.)
Migraine <30 days, recent triptan use†	7 (3.5)	2 (0.3)	1.82 (0.31-10.8)	1.56 (0.26-9.53)

	TIA			
Parameter	**Cases (%) (n=163)**	**Conts. (%) (n=605)**	**OR* (95% CI)**	**OR** (95% CI)**
No migraine	48 (29.5)	326 (53.9)	1.0 (ref.)	1.0 (ref.)
Migraine <30 days, no triptan use	11 (6.8)	7 (1.2)	9.89 (3.40-28.7)	9.22 (3.15-27.0)
Migraine <30 days, recent triptan use†	3 (1.8)	1 (0.2)	-- ‡	-- ‡
Migraine <30 days, no triptan use	11 (6.8)	7 (1.2)	1.0 (ref.)	1.0 (ref.)
Migraine <30 days, recent triptan use†	3 (1.8)	1 (0.2)	-- ‡	-- ‡

* adjusted for variables in Table 3.2.2 (plus aspirin and NSAID use), but not for HRU

** adjusted for variables in Table 3.2.2 (plus aspirin and NSAID use) and for HRU (0, 1, 2-4, 5+ contacts with health professionals due to migraine prior to the index date)

† ≥1 triptan prescription recorded <60 days prior to the index date

‡ ORs not available since numbers were too small

Migraineurs with ≥1 prescription for a triptan within 60 days prior to the index date had an increased RR of developing stroke (adjusted OR 2.51, 95% CI 1.10-5.71), as compared to migraineurs with no prescriptions for triptans. The adjusted OR for patients with recent migraine but without recent triptan use, as compared to no

migraine and no triptan prescription, was 10.3 (95% CI 4.96-21.3), while it was 18.7 (95% CI 3.55-98.8) for patients with recent migraine with recent triptan prescription recorded (Table 3.2.4). When the analysis was adjusted for health resource utilisation (0, 1, 2-4 or 5+ contacts with health professionals due to migraine prior to the index date), the ORs were reduced towards one (Table 3.2.4).

3.2.4.2 TIA

In the follow-up analysis, the IR of TIA among migraineurs was 92.5 (95% CI 77.1-111.0) / 100'000 py and 38.1 (95% CI 28.8-50.6) / 100'000 py for non-migraineurs, yielding a RR of 2.4 (95% CI 1.8-3.3) across all ages and both sexes.

In the nested case-control analysis, the RR of developing a TIA was also elevated for patients with a history of migraine (adjusted OR 2.76, 95% CI 1.88-4.05), with a higher risk for males than females ($p<0.01$ test for effect modification). In migraineurs, a prescription of a triptan was associated with an adjusted OR of 3.32 (95% CI 0.61-18.0) which was slightly reduced to 3.22 (95% CI 0.58-17.7) by further adjusting for migraine severity. In the subgroup of patients with a recent migraine attack, the number of migraineurs with a triptan prescription who developed a TIA was too small for further analyses (Table 3.2.4).

3.2.4.3 Death

The mortality rate in migraineurs was 159.3 (95% CI 138.6-183.0) / 100'000 py, while it was 206.6 (95% CI 183.0-233.3) / 100'000 py in non-migraineurs, resulting in a RR of 0.8 (95% CI 0.6-0.9). In the nested case-control analysis, the OR for overall mortality was 0.84 (95% CI 0.68-1.04) for migraineurs compared to patients without migraine, with statistically non-significant differences between genders.

Among migraineurs, a prescription of triptans within 60 days prior to death (as compared to non-use) resulted in an OR of 0.52 (95% CI 0.18-1.52).

3.2.5 Discussion

This population-based study compares the risk of developing an incident diagnosis of stroke, TIA, or death in patients with and without migraine. The key findings of this study were that a) a history of migraine was associated with a twofold increased risk

of an incident thrombotic or hemorrhagic stroke or a TIA, and b) the association was most pronounced in patients who had the last migraine event recorded within a month prior to the stroke date. The increased risk in this subgroup (OR 11.1) could be explained by a causal association, i.e. a severe migraine attack increases the risk of developing a stroke for a period of a few days or weeks, or alternatively a severe migraine attack and TIA or stroke share common symptoms which could lead to misdiagnosis. This was demonstrated by the fact that we identified 16 cases with a migraine attack and a stroke diagnosis recorded within a seven day period, suggesting that at least some of the strokes may first have been misdiagnosed as severe migraine headache, which was later corrected after referral or hospitalisation.

The association between a history of migraine (yes / no) and an elevated stroke risk has been investigated in several previous studies [Etminan et al. 2005], but to our knowledge there is only one study which accounted for the timing of the last migraine attack in relation to the stroke; the authors of a case-control study in young women reported that approximately 70% of migraineurs complained of headache in the three days immediately preceding the stroke [Chang et al. 1999].

In our study the risk for hemorrhagic stroke was almost as high as for ischaemic stroke. This is in contrast to other studies reporting risks for hemorrhagic stroke in migraineurs of 0.70 -1.57 [Chang et al. 1999; Jousilahti et al. 2003; Hall et al. 2004; Kurth et al. 2005]. In most of these studies the risk for ischaemic stroke was higher than for hemorrhagic stroke. Jousilahti *et al.*, however, reported even a higher risk for hemorrhagic stroke than for ischaemic stroke in women. All patient profiles were carefully reviewed by hand in order to distinguish between thrombotic and hemorrhagic stroke. However, it cannot be ruled out that there was some misclassification and that some of the hemorrhagic strokes may have been secondary transformations of initially thrombotic strokes.

We tried to distinguish between the risk of stroke in migraineurs with or without aura. Most migraine diagnoses in the GPRD are ‘migraine, non-specified’. Based on the documented READ-codes, we categorised migraineurs into ‘common’ or ‘unspecified’ migraine (i.e. likely without aura), vs. ‘classic’ migraine (i.e. with aura). This distinction is certainly not entirely precise, and some patients may have had mixed forms, i.e. one episode without aura and maybe later on another episode with aura, or vice

versa. It is also possible that patients with severe forms of migraine were more likely to get a diagnosis of 'migraine with aura', and that severity rather than the presence of aura may be associated with an increased stroke risk. In a previous meta-analysis the risk of ischaemic stroke was increased 2.9-fold in migraineurs with aura, and 1.6-fold in those without aura [Etminan et al. 2005]. Stang and coworkers also found a 2- to 3-fold increased stroke risk in migraineurs with aura of 55 years of age or older [Stang et al. 2005].

A prescription of a triptan was not associated with an elevated risk of death, while the data indicated an increased risk of stroke or TIA in the group of migraineurs prescribed triptans compared to other migraineurs. These results should be interpreted cautiously: First, it is difficult to study the safety of triptans since they are prescribed for acute treatment of migraine once the next attack occurs; thus, the date of a GP-recorded prescription may poorly reflect the actual timing of the drug intake. Second, a triptan prescription tends to correlate with the severity of migraine, according to a previous analysis of the current study population (Becker *et al.*, *Cephalalgia* 2007, in press), and thus migraineurs with a previous prescription of a triptan are more likely to be at higher risk of developing stroke. Therefore, an increased stroke risk in those migraineurs who received a prescription for a triptan may reflect confounding by indication and does not need to be causal.

A subgroup analysis was done in an attempt to distinguish a possible migraine effect on the risk of developing stroke from a possible triptan effect. This analysis indicated that a recent migraine attack was associated with an increased stroke risk with or without a triptan prescription. In order to assess how triptans influence the stroke risk in migraineurs, the total health resource utilization related to migraine was assessed manually from the computer records of migraineurs and added as a marker of migraine severity as well as frequency of attacks to the model. As a result, the association between triptans and stroke risk was reduced towards one, suggesting that migraine recency and severity are confounding factors, rather than triptans actually cause stroke. However, given these special circumstances, it is not possible to fully separate the effect of migraine from a potential effect of triptans on the stroke risk in an observational study.

Investigators of a previous observational study also explored the association between triptans and the risk of stroke by classifying triptan use into 'ever use' vs 'never use' [Hall et al. 2004]; in this study no evidence of an increased stroke risk for 'ever use' of triptans was found, but it is unlikely that any increased risk of triptans would be seen with exposure defined as 'ever use' since 'current use' of triptans is the exposure of interest in this instance. When we classified migraineurs into 'ever' vs 'never users' of triptans, the risk of developing stroke for 'ever' triptan users was also close to 1.0 (data not shown). Previous randomised clinical trials did not provide evidence for an increased risk of stroke by using triptans [Ferrari et al. 2002]. However, these trials lacked power and reliability to answer this question.

The mortality among migraineurs was slightly decreased compared to non-migraineurs in the present study although this result did not reach statistical significance (95% CI 0.68-1.04). Results from other studies regarding mortality of migraineurs are not consistent: a cohort study with some 3'000 women showed also a decreased overall mortality in migraineurs (OR 0.78, 95% CI 0.57-1.08) [Waters et al. 1983], whereas a recent evaluation of the Women's Health Study concluded that the risk of death due to cardiovascular disease was significantly increased in women with any history of migraine (OR 1.63, 95% CI 1.07-2.50), particularly in women with active migraine including aura features (2.33, 95% CI 1.21-4.51) [Kurth et al. 2006]. Another study found no increased risk for cardiovascular death in women with a history of any migraine (i.e. with or without aura) and a non-significantly increased risk for the aura-subgroup, although the study had only a low number of cases with an outcome of interest [Liew et al. 2007].

A strength of this study is that it was based on large population data derived from a well-validated and well-documented database. In addition, several associations between drug use or comorbidities and the risk of developing a study outcome (stroke, TIA, or death) were found that have been reported before and which lend credibility to the findings in this study population. For example, elevated stroke risks associated with diabetes mellitus, hypertension, dyslipidaemia, or current smoking were found, all associations which are well-documented in the literature [Goldstein et al. 2001].

But the study also has several limitations. Only GP-diagnosed migraine was included and it is well known, that not all migraine sufferers contact their physician. Thus, the study group of migraineurs probably does not encompass all patients with migraine in this population. Another limitation, as mentioned above, is the fact that it was not possible to reliably assess the timing of triptan exposure in this observational study, since the time of a triptan prescription and the actual intake of the drug may often not be the same. Furthermore, there may be some misclassification of the outcomes of interest, but to minimise this risk all computer records of cases with stroke, TIA, or death were manually reviewed without knowing whether these cases were migraineurs or not and without knowing the exposure status to triptans. The cases were classified according to a predefined algorithm. Cases with a previous history of stroke or TIA were excluded, thus only incident cases were included.

In summary, this population-based study provides further evidence for migraine as a risk factor for stroke and TIA with an approximately twofold increased risk for these outcomes. While there is a temporal association between migraine attacks and stroke, and between a prescription of a triptan and stroke, migraine severity and triptan use are closely related and difficult to separate in an observational study.

3.3 The risk of newly diagnosed asthma in migraineurs

(with or without previous triptan prescriptions)

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3.3.1 Summary

Previous observational studies reported an increased prevalence of asthma in migraine patients. Whether triptans affect the asthma risk has not yet been explored in an epidemiological study. The aim of the study was to estimate the risk of newly diagnosed asthma in patients with a GP-diagnosed migraine in the UK between 1994 and 2001. Therefore a population-based follow-up study and a nested case-control analysis were conducted using the GPRD.

The study encompassed 51'688 migraineurs and the same number of matched controls. In the follow-up analysis, the RR of developing asthma in migraineurs compared to non-migraineurs was 1.3 (95% CI 1.1-1.4). In the nested case-control analysis, the adjusted OR for asthma in migraineurs overall was 1.17 (95% CI 1.01-1.35), and for those with a recent triptan prescription 1.12 (95% CI 0.64-1.94). To conclude, the risk of developing asthma was not materially altered for patients with a GP-recorded migraine diagnosis, regardless of triptan use.

3.3.2 Introduction

There is reported evidence that migraineurs have a higher prevalence of asthma than individuals without migraine [Strachan et al. 1996; Davey et al. 2002; Von Behren et al. 2002; Aamodt et al. 2007]. To our knowledge, the risk of developing an incident asthma diagnosis associated with a prior migraine diagnosis has not been previously studied. Triptans are considered to be well tolerated and safe in migraine patients without cardiovascular disorders, and the most frequent adverse events in clinical trials for triptans have been reported to be nausea, vomiting, somnolence and paraesthesia [Mathew et al. 1997; Pfaffenrath et al. 1998]. However, 'chest-related symptoms' such as pressure, palpitations or shortness of breath have also been reported [Welch et al. 2000], not all of them associated with changes in the electrocardiography [Visser et al. 1996], and a direct effect of triptans on pulmonary vessels has been suggested [MacLean et al. 1996; MacLean et al. 1996].

Asthma and migraine share common pathophysiological characteristics, such as triggered release of vasoactive mediators. Migraine as well as asthma can be triggered by certain food, exercise or emotional stress [Fogarty et al. 2000; Millichap et al.

2003]. The platelet activating factor (PAF) is activated in a migraine attack [Sarchielli et al. 2004] as well as during bronchoconstriction [Vargaftig et al. 1980].

The aim of this study was to quantify incident asthma diagnoses in migraineurs in general practice and to compare them to non-migraineurs, as well as to explore a possible role of triptans on the risk of developing asthma.

3.3.3 Methods

The large and well-validated UK-based GPRD was used which has been described in detail elsewhere [Jick 1997]. In short, some GPs in the UK record all information on demographics (age, gender), diagnoses, drug prescriptions, referrals and hospital admissions as well as certain lifestyle parameters (e.g. smoking status) of their patients on a regular basis and provide the data in an anonymised form for research purposes [Wood et al. 2004]. GPRD data have been used in previous studies on asthma [Davey et al. 2002; Soriano et al. 2003; Watson et al. 2005].

The study population consisted of all patients in the GPRD aged 79 years or younger with a first-time migraine diagnosis between January 1, 1994 and December 31, 2001. A minimum of three years of medical history in the computer record prior to their first-time migraine diagnosis was required. An equally sized comparison group of patients without migraine was identified at random, matched to migraineurs on age, gender, general practice (i.e. patients and controls had to be enrolled with the same GP), years of history on the GPRD and index date (i.e. the date when first migraine diagnosis recorded for case patients). All patients with a history of asthma or COPD or cancer prior to their index date were excluded and all migraineurs and the comparison group were followed until they developed an incident asthma diagnosis, transferred out, died, or follow-up ended in the medical record, or the end of the study was reached. All electronic records of potential asthma cases, blinded to exposure information (i.e. migraine diagnosis and triptan use) were manually reviewed and included or excluded cases based on this manual assessment. Cases with an incident asthma diagnosis were included if the patient was referred, hospitalised or received pharmacological treatment with bronchodilators or corticosteroids. Crude asthma incidence rates were assessed in migraineurs and in

the comparison group and an incidence rate ratio between those two groups was calculated.

Additionally, a nested case-control analysis was conducted in which each incident asthma case was matched to four control patients from the entire study population (migraineurs and non-migraineurs) on age (± 3 years), gender, general practice and calendar time. Thus, controls were randomly selected from the population of migraineurs or from the comparison group. The controls had to be alive at the index date, i.e. the date when the case had the first-time asthma diagnosis. For all cases and controls a history of migraine, use of triptans prior to the index date, and additional covariates were assessed such as smoking status (non, current, ex, unknown), BMI (<25, 25-29.9, 30+ kg/m^2 or unknown), the number of recorded GP consultations in the year prior to the index date (<10, 10-19, 20+), use of NSAIDs or aspirin, as well as recorded diagnoses of hypertension, dyslipidaemia, diabetes mellitus, rheumatoid arthritis, depression or bipolar disorder, anxiety or psychosis, or epilepsy. Conditional logistic regression analyses were conducted to explore the relative risk of developing an outcome of interest in association with a history of migraine with or without use of triptans, expressed as ORs with 95% CI. All statistical analyses were performed with SAS software, Version 8.1 (SAS Institute, Inc., Cary, NC, US).

3.3.4 Results

The study encompassed 103'376 individuals (51'688 migraineurs and 51'688 matched comparison subjects without diagnosed migraine), of which 71.7% were females. A prevalent asthma diagnosis was present in 16.8% of the migraineurs and in 13.1% of the controls [OR 1.26 (95% CI 1.22-1.31)].

After exclusion of individuals with a previous history of asthma, COPD or cancer, 935 patients with an incident asthma diagnosis were identified during follow-up who met the inclusion criteria after manual review of patient records. The results of the person-time analysis are displayed in

Table 3.3.1, and the results of the nested case-control analyses are shown in Table 3.3.2 and Table 3.3.3.

Table 3.3.1: Incidence rates of asthma stratified by migraine and sex

Outcome	Group	Events	p-years	IR / 100'000 py (95 % CI)	RR (95% CI)
Migraine	All	520	124'320	418.3 (383.9-455.7)	1.3 (1.1-1.4) *
	Men	152	35'709	425.7 (363.3-498.7)	1.6 (1.2-2.0) **
	Women	368	88'611	415.3 (375.1-459.9)	1.2 (1.0-1.4) †
Non-migraine	All	415	125'849	329.8 (299.6-363.0)	1.0
	Men	98	36'770	266.5 (218.8-324.7)	1.0
	Women	317	89'079	355.9 (318.8-397.2)	1.0

* as compared to all non-migraineurs

** as compared to male non-migraineurs

† as compared to female non-migraineurs

The incidence rate of asthma in migraineurs was 418.3 (95% CI 383.9-455.7) / 100'000 py and 329.8 (95% CI 299.6-363.0) / 100'000 py among non-migraineurs, yielding a crude RR of 1.3 (95% CI 1.1-1.4).

In the nested case-control analysis, a history of migraine was associated with an OR of developing an incident asthma diagnosis of 1.17 (95% CI 1.01-1.35), adjusted for age, gender, calendar time and geography (by matching), and for smoking, BMI, diabetes mellitus, hypertension, dyslipidaemia, use of NSAIDs and use of aspirin in the multivariate model. When we adjusted the analysis for the number of GP consultations in the year prior to the index date to take to some degree medical awareness into account, the OR was further reduced to 1.07 (95% CI 0.92-1.25, p = 0.36).

Within migraineurs, a prescription for a triptan recorded within 60 days prior to the index date in migraineurs, as compared to no triptan use recorded, was not associated with a significant increase in the risk of developing an incident asthma diagnosis (OR 1.12, 95% CI 0.65-1.94).

Table 3.3.2: Characteristics, comorbidities and drug use in asthma cases and controls in the nested case-control analysis

Variable	Cases (%) (n=935)	Controls (%) (n=3'558)	Adjusted OR* (95% CI)
Age			
< 30 years	494 (52.8)	1'894 (53.2)	--
30-59 years	394 (42.1)	1'500 (42.2)	--
≥ 60 years	47 (5.0)	164 (4.6)	--
Sex			
Male	250 (26.7)	931 (26.2)	--
Female	685 (73.3)	2'627 (73.8)	--
Smoking status			
Non-smoker	344 (36.8)	1'332 (37.4)	1.0
Current	180 (19.3)	587 (16.5)	1.28 (1.03-1.58)
BMI			
<25 kg/m^2	324 (34.7)	1'270 (35.7)	1.0
≥30 kg/m^2	116 (12.4)	244 (6.9)	1.91 (1.45-2.51)
Diabetes mellitus	10 (1.1)	42 (1.2)	0.64 (0.30-1.34)
Hypertension	66 (7.1)	188 (5.3)	1.10 (0.79-1.54)
Dyslipidaemia	21 (2.3)	78 (2.2)	0.79 (0.46-1.37)
NSAIDs			
No use	894 (20.5)	3'460 (79.5)	1.0
Current use	15 (37.5)	25 (62.5)	1.83 (1.14-2.92)
Aspirin			
No use	649 (18.9)	2'793 (81.1)	1.0
Current use	28 (30.1)	65 (69.9)	2.38 (1.19-4.76)

* adjusted for age, sex, general practice and calendar time (by matching), for migraine and for all parameters in this table

Table 3.3.3: Migraine in asthma cases and controls in the nested case-control analysis

Migraine	Cases (%) (n=935)	Controls (%) (n=3'558)	Adjusted OR* (95% CI)
No	415 (44.4)	1'808 (50.8)	1.0 (ref.)
Yes	520 (55.6)	1'750 (49.2)	1.17 (1.01-1.35)
males	152 (29.2)	460 (26.3)	1.52 (1.15-2.03)
females	368 (70.8)	1'290 (73.7)	1.07 (0.90-1.28)
<30 years	276 (53.1)	930 (53.1)	1.20 (0.98-1.47)
30-59 years	221 (42.5)	728 (41.6)	1.21 (0.96-1.52)
≥60 years	23 (4.4)	92 (5.3)	0.78 (0.38-1.59)

* adjusted for age, sex, general practice and calendar time (by matching), and BMI, smoking, diabetes mellitus, hypertension, dyslipidaemia, NSAID and aspirin use

3.3.5 Discussion

This primary care based study compares the risk of developing an incident diagnosis of asthma in patients with or without a GP-diagnosed migraine. The risk of developing a first-time asthma diagnosis was not materially altered in migraineurs as compared to patients without diagnosed migraine. The slightly increased OR (OR 1.17, 95% CI 1.01-1.35, p = 0.04) could reflect an increased likelihood of getting an asthma diagnosis recorded if patients consult their physician more often due to migraine. Indeed, after adjusting the analysis for medical awareness, the OR was further reduced towards one.

Several studies demonstrated an increased prevalence of asthma in migraineurs compared to non-migraineurs [Strachan et al. 1996; Davey et al. 2002; Von Behren et al. 2002; Aamodt et al. 2007], but an increased asthma incidence has (to our knowledge) never been reported so far. In addition, the association between triptan use and incident asthma has not been studied before, and our analysis provides evidence that triptans do not materially alter the risk of developing asthma.

It is a strength of this study that it was based on large population derived from a well-validated and well-documented database. A potential limitation is the fact that

migraineurs who did not seek medical attention may have been missed since only individuals with a GP-diagnosed migraine were included. It is another limitation that the exact exposure status to triptans cannot be reliably assessed in an observational study because the time of a triptan prescription and the actual intake of the drug is often not the same. Furthermore, there may be some misclassification of the outcome diagnosis, but to minimise this risk all computer records of asthma cases were manually reviewed, blinded to disease status (migraine or not) and to triptan exposure status.

In summary, the current observational study provides evidence that migraineurs, with or without triptan use, do not seem to be at an increased risk of developing asthma.

Chapter 4

Parkinson’s disease project

4 Parkinson's disease project

4.1 Use of antihypertensives and the risk of Parkinson's disease

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4.1.1 Summary

Recent studies related ACE-inhibitors and calcium channel blockers to possible neuroprotective effects. Little is known about neuroprotection of AT II antagonists or beta-blockers. The aim of the study was to explore the association between antihypertensive drug use and the risk of developing a first-time diagnosis of idiopathic PD. Therefore a case-control analysis was carried out within the UK-based GPRD. Cases were ≥40 years of age with an incident PD diagnosis between 1994 and 2005. To each PD case one control was matched on age, sex, general practice, index date and duration of previous history in the database. Antihypertensive drug use was assessed by timing and by exposure duration. OR were calculated using conditional logistic regression, adjusted for BMI, smoking and' various cardiovascular, metabolic and psychiatric diseases and dementia. In total 3'637 cases with a first-time diagnosis of idiopathic PD were calculated as well as an equal number of matched controls. As compared to non-use of antihypertensive drugs, the adjusted OR for current use of ≥30 prescriptions was 1.08 (95% CI 0.85-1.37) for ACE-inhibitors, 0.91 (95% CI 0.41-2.00) for AT II antagonists, 1.16 (95% CI 0.95-1.41) for beta-blockers, and 0.77 (95% CI 0.63-0.95) for calcium channel blockers. Current long-term use of calcium channel blockers was associated with a significantly reduced risk of a PD diagnosis, while the risk was not materially altered for users of ACE-inhibitors or beta-blockers and, with less statistical precision, for users of AT II antagonists.

4.1.2 Introduction

Idiopathic PD is one of the most frequent neurodegenerative diseases. Selective dopaminergic cell death is thought to be caused by factors like oxidative stress with free radical production [Jenner 2003], excitotoxicity [Mytilineou et al. 1997], mitochondrial dysfunction [Schapira et al. 1990], protein aggregation [McNaught et al. 2003] and neuroinflammatory processes [Dawson et al. 2003].

In search for neuroprotective agents which may play a role in reducing the burden of PD, recent studies on ACE-inhibitors [Jenkins et al. 1999; Lopez-Real et al. 2005; Munoz et al. 2006] and calcium channel blockers [Kupsch et al. 1995; Kupsch et al. 1996; Chan et al. 2007]

in rodents and nonhuman primates showed promising results such as a significant reduction of experimentally induced dopaminergic cell loss and an increase in striatal dopamine levels. In addition, a double blind placebo-controlled crossover pilot study in seven patients with moderately severe PD demonstrated an improvement of motor functions after four weeks of treatment with perindopril [Reardon et al. 2000]. In Alzheimer's disease (AD), another neurodegenerative disease, patients with long-term use of ACE inhibitors crossing the blood-brain barrier had a significantly lower incidence of AD compared to users of other ACE-inhibitors (OR 0.25; 95% CI 0.08-0.75) [Ohrui et al. 2004] and a decreased rate of cognitive decline in mild to moderate AD [Ohrui et al. 2004], as compared to patients receiving other antihypertensive drugs. Little is known about possible effects of AT II receptor antagonists [Grammatopoulos et al. 2005; Grammatopoulos et al. 2007] or beta-blockers on the risk of PD. One recent population-based case-control study with 206 PD cases could not find any significant effects associated with the use of calcium channel blockers or beta-blockers on the risk of PD [Ton et al. 2007].

With the current large observational study the aim was to explore the association between use of various antihypertensive drugs and the risk of developing a first-time diagnosis of idiopathic PD.

4.1.3 Methods

4.1.3.1 Data source

A retrospective case-control analysis was performed using data from the GPRD. The GPRD provides health care information on more than 5 million people who are registered with GPs in the UK; it has been previously described in detail [Wood et al. 2004].

A group of specially trained GPs record information on demographics, diagnoses and drug prescriptions as well as referrals and hospital admissions. Drug prescriptions are generated directly from the computer and are recorded in each patient's computerised profile. Hospital discharge as well as referral letters are available on request for review to validate the recorded diagnoses. The recorded information on drug exposure and on diagnoses have been validated repeatedly and proven to be of

high quality [Walley et al. 1997; Jick et al. 2003]. The patients enrolled in the GPRD are representative of the UK with regard to age, gender, and geographic distribution [Wood et al. 2004]. GPRD data has been utilised in recent studies on PD [Hernan et al. 2004; Hernan et al. 2006]. The GPRD is managed by the MHRA in the UK. The study protocol was reviewed and approved by the Independent Scientific Advisory Committee for MHRA database research (ISAC). The investigators had only access to anonymised information.

4.1.3.2 Study base

The study base included all patients in the GPRD who were 40 years or older between January 1, 1994 and December 31, 2005.

4.1.3.3 Case ascertainment

Cases were all subjects in the study base with a code for idiopathic PD recorded for the first time during the study period and no previous diagnosis of a drug-induced parkinsonian disorder. A minimum of three years of medical history in the GPRD computer record prior to the first diagnosis of idiopathic PD was required.

The READ Clinical Classification [Chisholm 1990] and the Oxford Medical Information System (OXMIS) codes were used to classify medical diagnoses. The codes used to identify potential cases were OXMIS-codes 342 ('Paralysis agitans') and 342 D ('idiopathic parkinsonism') as well as READ-codes F12..00 ('Parkinson's disease'), F12z.00 ('Parkinson's disease NOS') and F120.00 ('Paralysis agitans'). GP-recorded PD diagnoses were identified from the computer. The date of the first recording of a code for idiopathic PD will subsequently be referred to as the 'index date'.

A validation of the PD diagnosis in the GPRD has been conducted in an earlier study [Hernan et al. 2004]. In that study GP-recorded PD diagnoses were confirmed in 90% of the cases who had received at least two prescriptions for the treatment of PD during follow up.

Because 28% of the cases in the present study had one or more prescriptions for an anti-PD-medication prior to the first recorded PD diagnosis, a random sample of 100 case profiles was manually reviewed to find out more about the validity of the index date. This profile review revealed that a substantial proportion of PD patients

received antiparkinson treatment due to early symptoms of PD, before the GP recorded the PD diagnosis at some later point in time. Therefore an algorithm for inclusion of cases into the analysis was set up; in order to be eligible as a case with a first-time diagnosis of idiopathic PD, patients had to have less than two prescriptions for any drug used to treat PD (levodopa, dopamine-agonists, selegiline, amantadine, apomorphine, anticholinergic drugs or Catechol-O-Methyltransferase [COMT] inhibitors) prior to the index date, the patients had to have received two or more prescriptions for levodopa, selegiline, dopamine-agonists or a COMT inhibitor after the index date, and they must not have had any prescriptions recorded for drugs known to cause parkinsonism (typical neuroleptics, metoclopramide or cinnarizine) within 180 days prior to the index date.

4.1.3.4 Controls

At random one control per PD case was identified from the base population, matched on year of birth, gender, general practice, index date and number of active years in the database prior to the index date

4.1.3.5 Exposure classification of antihypertensive drug use prior to the index date

Users were classified according to the date of their last prescription recorded prior to the index date into 'current' (last prescription <90 days ago) or 'past' (last prescription ≥90 days ago) users, and according to the number of prescriptions of the relevant study drugs (1-9, 10-29 and ≥30). In order to identify potential confounding, the prevalence of various diagnosed and recorded chronic diseases prior to the index date was also assessed such as diabetes mellitus, asthma, COPD, epilepsy, hypertension, ischaemic heart disease (IHD), congestive heart failure (CHF), arrhythmias, stroke or TIA, hyperlipidaemia, affective disorders, schizophrenia or neurotic and somatoform disorders. Other covariates such as smoking (never, ex-smoker, current or unknown), and BMI (<25, 25-29.9, ≥30 kg/m^2) were also considered and included in the analysis.

4.1.3.6 Statistical analysis

Conditional logistic regression analyses were conducted to explore the association between use of various antihypertensive agents and the risk of a first-time PD diagnosis using the statistical software SAS (release 9.1, SAS Institute, Inc., Cary, NC). Relative risk estimates (ORs) are presented with 95% CIs. The independent effects of potential confounders on the risk of developing PD were assessed, such as BMI (<25, 25-29.9, ≥30 kg/m^2 or unknown) and smoking status as well as various cardiovascular, metabolic and psychiatric diseases and dementia.

For the main analysis a model was created in which users of antihypertensive drugs were compared to non-users, whereby use of more than one antihypertensive drug group prior to the index date was possible. In the multivariate model the analyses were adjusted for such sequential or concurrent use of various antihypertensive drugs. In addition, a model was run in which subjects were categorised into mutually exclusive groups of users of ACE-inhibitors only, AT II receptor antagonists only, beta-blockers only, calcium channel blockers only, or any combination of these antihypertensive drug groups (switchers or combined use), and these groups were compared to non-users of any antihypertensive drugs.

4.1.4 Results

With this approach 3'637 cases and 3'637 controls (40% women) were identified. Approximately 90% of the cases had their first PD diagnosis recorded after the age of 60 years. Table 4.1.1 displays the age and sex distribution of cases and controls, their smoking status, BMI and the prevalence of comorbidities in cases and controls. Among the PD cases, 1'704 (46.9%) had ever used an antihypertensive drug prior to the index date: 629 (17.3%) had used an ACE-inhibitor, 89 (2.5%) an AT II receptor antagonist, 1'168 (32.1%) a beta-blocker, and 807 (22.2%) a calcium channel blocker (numbers do not add up to 46.9% due to combined use of study drugs).

Table 4.1.1: Characteristics of cases and controls and the multivariate effects on the risk of PD

Variable	Cases, No (%) (n=3'637)	Controls, No (%) (n=3'637)	Adjusted OR* (95% CI)	p value
Age, years				
<60	320 (8.8)	321 (8.3)	--	--
60-69	752 (20.7)	751 (20.7)	--	--
70-79	1'522 (41.9)	1'520 (41.8)	--	--
≥80	1'043 (28.7)	1'045 (28.7)		--
Sex			**--**	**--**
Male	2'167 (59.6)	2'167 (59.6)	--	--
Female	1'470 (40.4)	1'470 (40.4)	--	--
Smoking status				
Non	2'186 (60.1)	1'866 (51.3)	1.00 (referent)	--
Current	326 (9.0)	521 (14.3)	0.51 (0.43-0.60)	<0.0001
Ex	581 (16.0)	697 (19.2)	0.68 (0.59-0.78)	<0.0001
BMI (kg/m²)				
15 - 24.9	1'239 (34.1)	1'192 (32.8)	1.00 (referent)	--
25 - 29.9	1'121 (30.8)	1'104 (30.4)	1.01 (0.89-1.14)	0.88
≥30	364 (10.0)	399 (11.0)	0.90 (0.75-1.07)	0.23
Comorbidities				
Diabetes mellitus	291 (8.0)	308 (8.5)	0.95 (0.80-1.14)	0.58
Asthma / COPD	431 (11.9)	536 (14.7)	0.78 (0.68-0.90)	0.001
Hypertension	1'197 (32.9)	1'286 (35.4)	0.83 (0.74-0.92)	0.001
IHD	815 (22.4)	755 (20.8)	1.05 (0.93-1.19)	0.44
CHF	291 (8.0)	282 (7.8)	0.94 (0.78-1.14)	0.53
Stroke / TIA	541 (14.9)	349 (9.6)	1.65 (1.41-1.94)	<0.0001
Arrhythmia	385 (10.6)	370 (10.2)	1.01 (0.86-1.19)	0.88
Hyperlipidaemia	338 (9.3)	314 (8.6)	1.06 (0.88-1.26)	0.56
Epilepsy	91 (2.5)	62 (1.7)	1.30 (0.92-1.84)	0.14
Affective disorders disorder	786 (21.6)	527 (14.5)	1.48 (1.29-1.70)	<0.0001
Schizophrenia	30 (0.8)	24 (0.7)	1.00 (0.56-1.77)	0.99
Neurotic & somatoform disorders	692 (19.0)	442 (12.2)	1.55 (1.34-1.79)	<0.0001
Dementia	113 (3.1)	36 (1.0)	2.69 (1.81-3.98)	<0.0001

* adjusted for the other variables in this table

The relative risk estimates (ORs) of a first-time PD diagnosis for current use of ACE-inhibitors, compared to non-use and adjusted for the covariates in Table 4.1.1 as well as for use of diuretics and statins, was 1.00 (95% CI 0.84-1.19), for current use of AT II receptor antagonists 1.05 (95% CI 0.71-1.54), for current use of beta-blockers 1.19 (95% CI 1.02-1.39), and for current use of calcium channel blockers 0.78 (95% CI 0.67-0.92). The results of the analysis in which timing and duration of use were combined are displayed in Table 4.1.2.

Table 4.1.2: Antihypertensive drug use vs. non-use prior to the index date in PD cases and controls and associated risk estimates

Exposure	Cases, No (%) (n=3'637)	Controls, No (%) (n=3'637)	Unadjusted OR (95% CI)	Adjusted OR* (95% CI)	P value
ACE inhibitors					
Non-use	3'008 (82.7)	2'998 (82.4)	1.00 (referent)	1.00 (referent)	--
Current use	418 (11.5)	417 (11.5)	1.00 (0.86-1.16)	1.00 (0.84-1.19)	1.00
No. of prescriptions					
1-9 Rx	82 (2.3)	77 (2.1)	1.06 (0.77-1.45)	0.96 (0.68-1.36)	0.81
10-29 Rx	133 (3.7)	137 (3.8)	0.97 (0.76-1.24)	0.93 (0.71-1.23)	0.61
≥ 30 Rx	203 (5.6)	203 (5.6)	1.00 (0.81-1.22)	1.08 (0.85-1.37)	0.53
Past use	211 (5.8)	222 (6.1)	0.95 (0.78-1.15)	0.89 (0.70-1.13)	0.32
AT II antagonists					
Non-use	3'548 (97.6)	3'559 (97.3)	1.00 (referent)	1.00 (referent)	--
Current use	70 (1.9)	75 (2.1)	0.92 (0.66-1.30)	1.05 (0.71-1.54)	0.81
No. of prescriptions					
1-9 Rx	22 (0.6)	19 (0.5)	1.12 (0.61-2.08)	1.43 (0.73-2.79)	0.30
10-29 Rx	34 (0.9)	37 (1.0)	0.91 (0.57-1.46)	0.97 (0.58-1.64)	0.92
≥ 30 Rx	14 (0.4)	19 (0.5)	0.72 (0.35-1.48)	0.91 (0.41-2.00)	0.80
Past use	19 (0.5)	23 (0.6)	0.82 (0.45-1.51)	0.76 (0.40-1.46)	0.41

Cont. Table 4.1.2

Exposure	Cases, No (%) (n=3'637)	Controls, No (%) (n=3'637)	Unadjusted OR (95% CI)	Adjusted OR* (95% CI)	P value
Beta-blockers					
Non-use	2'469 (67.9)	2'646 (72.8)	1.00 (referent)	1.00 (referent)	--
Current use	553 (15.2)	519 (14.3)	1.16 (1.01-1.33)	1.19 (1.02-1.39)	0.03
No. of prescriptions					
1-9 Rx	114 (3.1)	67 (1.8)	1.84 (1.35-2.49)	1.79 (1.29-2.48)	0.001
10-29 Rx	132 (3.6)	150 (4.1)	0.94 (0.74-1.20)	0.91 (0.70-1.19)	0.48
≥ 30 Rx	307 (8.4)	302 (8.3)	1.12 (0.94-1.32)	1.16 (0.95-1.41)	0.14
Past use	615 (16.9)	472 (13.0)	1.42 (1.24-1.63)	1.36 (1.16-1.59)	<.0001
Calcium channel blockers					
Non-use	2'830 (77.8)	2'774 (76.3)	1.00 (referent)	1.00 (referent)	--
Current use	432 (11.9)	516 (14.2)	0.82 (0.72-0.94)	0.78 (0.67-0.92)	0.003
No. of prescriptions					
1-9 Rx	76 (2.1)	68 (1.9)	1.11 (0.79-1.54)	0.98 (0.68-1.40)	0.89
10-29 Rx	119 (3.3)	155 (4.3)	0.76 (0.59-0.97)	0.78 (0.59-1.02)	0.07
≥ 30 Rx	237 (6.5)	293 (8.1)	0.79 (0.66-0.95)	0.77 (0.63-0.95)	0.02
Past use	375 (10.3)	347 (9.5)	1.06 (0.90-1.25)	0.96 (0.80-1.16)	0.67

* adjusted for BMI, smoking status, comorbidities from Table 4.1.1, diuretics and statins

Since current use of ≥30 prescriptions for calcium channel blockers yielded an adjusted OR of 0.77 (95% CI 0.63-0.95), this group was further stratified into five categories of treatment duration (1-9,10-19, 20-29, 30-39 or 40+ prescriptions) to explore whether there was a trend towards decreasing ORs with increasing treatment duration; the results of this analysis are displayed in Table 4.1.3. The analysis of calcium channel blockers was also stratified by gender and by age (<80 vs. ≥80 years at the index date) and separate ORs for use of dihydropyridines (nifedipine, nimodipine, felodipine, amlodipine, lercanidipine, nicardipine, isradipine, lacidipine)

vs. non-dihydropyridines (verapamil, diltiazem) were assessed. The adjusted ORs of these various stratified analyses are also shown in Table 4.1.3.

Table 4.1.3: Risk of PD among current users of calcium channel blockers

Exposure	Cases, No (%) (n=3'637)	Controls, No (%) (n=3'637)	Unadjusted OR (95% CI)	Adjusted OR* (95% CI)
Calcium channel blockers				
Non-use	2'830 (77.8)	2'774 (76.3)	1.00 (referent)	1.00 (referent)
Current use	432 (11.9)	516 (14.2)	0.82 (0.72-0.94)	0.78 (0.67-0.92)
No. of prescriptions				
1-9 Rx	76 (2.1)	68 (1.9)	1.10 (0.79-1.53)	0.97 (0.68-1.39)**
10-19 Rx	65 (1.8)	82 (2.3)	0.78 (0.56-1.09)	0.81 (0.56-1.15)**
20-29 Rx	54 (1.5)	73 (2.0)	0.73 (0.50-1.05)	0.74 (0.50-1.10)**
30-39 Rx	46 (1.3)	61 (1.7)	0.73 (0.50-1.08)	0.77 (0.50-1.16)**
≥40 Rx	191 (5.3)	232 (6.4)	0.81 (0.66-0.99)	0.78 (0.62-0.98)**
Current long-term (≥30 Rx) use				
Men	156 (4.3)	174 (4.8)	0.89 (0.70-1.11)	0.88 (0.67-1.16)
Women	81 (2.2)	119 (3.3)	0.66 (0.49-0.89)	0.66 (0.47-0.93)
<80 years of age	174 (4.8)	187 (5.1)	0.94 (0.76-1.17)	0.93 (0.72-1.20)
≥80 years of age	63 (1.7)	106 (2.9)	0.52 (0.37-0.74)	0.52 (0.35-0.78)
Dihydropyridines	174 (4.8)	216 (5.9)	0.79 (0.64-0.97)	0.78 (0.62-0.99)
Non-dihydropyridines	63 (1.7)	77 (2.1)	0.80 (0.57-1.12)	0.76 (0.52-1.10)

* adjusted for BMI, smoking status, comorbidities from Table 4.1.1, diuretics and statins

** p-value test for trend = 0.33

While there was no materially altered PD risk for longer-term users of beta-blockers, a significantly increased risk was found for current use of 1-9 beta-blocker prescriptions (OR 1.79, 95% CI 1.29-2.48). Therefore beta-blocker users were stratified into those with a previously recorded diagnosis of a cardiovascular disease

(i.e. hypertension, stroke, TIA, arrhythmias, CHF or IHD), vs. those without such a recorded diagnosis. In the subgroup of patients with a recorded cardiovascular disease, the adjusted OR for current users with 1-9 beta-blocker prescriptions was 0.99 (95% CI 0.55-1.76), while it was 8.86 (95% CI 2.97-26.46) in those with no cardiovascular indication.

Though the risk estimate for current use of ACE-inhibitors was close to one, a stratification of the current users of ≥30 prescriptions by physico-chemical properties of the ACE-inhibitors was carried out. The ORs for users of hydrophilic (enalapril, ramipril, quinapril) or lipophilic (captopril, lisinopril, perindopril, trandolapril, cilazapril, fosinopril) ACE-inhibitors as well as for the individual agents were all close to one (data not shown).

In the analysis in which the effect of mutually exclusive exposure groups was explored, the adjusted ORs for current use of ≥30 prescriptions, as compared to non-users of any antihypertensive drugs, were 0.95 (95% CI 0.63-1.41) for ACE-inhibitor use only, 1.10 (95% CI 0.84-1.44) for beta-blocker use only, and 0.76 (95% CI 0.55-1.06) for calcium channel blocker use only. The exposure to AT II receptor antagonists only was too low for a meaningful analysis.

4.1.5 Discussion

The findings of this large primary care-based case-control study in the UK in subjects above the age of 40 years suggest that current long-term exposure to calcium channel blockers may slightly reduce the risk of developing PD, while no such association was found for users of ACE-inhibitors, AT II receptor antagonists or beta-blockers. This effect with the calcium channel blockers was seen in both models, in the one with adjustment for the use of other antihypertensive drugs as well as in the model in which exclusive use of calcium channel blockers was compared to non-users of any antihypertensive drugs.

PD is often associated with autonomic insufficiency and therefore hypotension [Goldstein 2006]. Thus, it is conceivable that PD cases receive fewer antihypertensive drugs than controls, leading to a potentially spurious low OR associated with the use of antihypertensives. In the population of the present study the prevalence of

hypertension was indeed substantially higher in controls than in cases (p = 0.001, Table 4.1.1). Therefore the controls would be expected to be treated with antihypertensives more frequently. However, a decreased OR was observed only in association with use of calcium channel blockers, but not with other antihypertensives. The same analysis was also carried out in a subgroup of cases and controls without diagnosed hypertension. In this subgroup who received calcium channel blockers for indications other than hypertension, the risk estimates for current calcium channel blocker use was 0.60 (95% CI 0.42-0.86).

There was a tendency towards a stronger risk reduction in women with current long-term use than in men, but not in those with less than 30 prescriptions. In addition, the risk reduction was most pronounced in individuals ≥80 years. This finding is interesting in light of a recent paper suggesting that with advanced age dopaminergic neurons rely increasingly on L-type $Ca_v1.3$-calcium channels for their activity which makes them more vulnerable to neurological damage, while neurons of younger people use different mechanisms [Chan et al. 2007]. If these calcium channels are blocked, neurons again make use of the less harmful mechanisms and cell damage may be decreased [Chan et al. 2007].

One previously published cross-sectional study reported a lower exposure prevalence to calcium channel blockers in prevalent PD patients with hypertension, as compared to another hypertensive patient group without PD [Rodnitzky 1999]. However, calcium channel blockers have also been related to potentially harmful effects with regard to PD; flunarizine and cinnarizine, which have dopaminergic receptor blocking properties [Daniel et al. 1995], and diltiazem have been reported to damage dopaminergic cells in vitro [Mena et al. 1995]. In a recent population-based case-control study prior use of calcium channel blockers was found to have no effect on the subsequent PD risk [Ton et al. 2007]. However, the two approaches of this and the present study are not directly comparable in terms of methodology. In the mentioned study ever use versus never use was analysed and all exposure within five years prior to the PD diagnosis was disregarded in order not to assess exposure occurring during already present subclinical PD. In our study the strongest risk reduction was seen in patients with 30 or more prescriptions who were still receiving prescriptions for the drug within 90 days prior to the PD diagnosis whereas, in

accordance with the results of the other group, there was no effect associated with past use of calcium channel blockers.

An increase of striatal dopamine synthesis and dopamine release in men after a four week treatment course with the ACE-inhibitor perindopril has been reported [Reardon et al. 2000], but in this study there was no evidence for a reduced PD risk for users of ACE-inhibitors in general or in the subgroup of users of ACE-inhibitors crossing the blood brain barrier.

An increased risk for a PD diagnosis in relation with current short-term use of beta-blockers was found. Since the PD risk was only increased for users of <10 beta-blocker prescriptions, and only in a subgroup of subjects without recorded cardiovascular diseases, this increased risk most likely reflects confounding by indication, i.e. patients with early symptoms of PD such as tremor received a beta-blocker to treat these symptoms, and shortly thereafter they received the PD diagnosis. In a review of a random sample of case records with current short-term beta-blocker use indeed symptoms such as tremor were found which were recorded for a high proportion of these patients.

Several limitations of this study need to be addressed. It was not possible to adjust the analysis for level of education [Frigerio et al. 2005], socioeconomic status or cholesterol level [de Lau et al. 2006], which themselves have been associated with PD. However, by matching on general practice it was possible to control at least to some degree for socioeconomic status since cases and controls came from the same area and therefore saw the same GP at the time of the study.

It is a strength of the study that it encompassed a large population sample, and that the GPRD is a validated and recognised database of high quality. The GPRD has already been used for two observational studies on PD [Hernan et al. 2004; Hernan et al. 2006]. The validation of the PD diagnosis for their cases resulted in a high proportion (90%) of confirmed computerised PD diagnoses for those who received two or more prescriptions for specific drugs to treat PD after the index date. Additionally, the finding of a strong protective effect of smoking on the PD risk is consistent with previous studies [Nefzger et al. 1968; Quik 2004; Hancock et al. 2007] and lends further credibility to the study results.

A known problem with epidemiological research on chronic diseases without acute and well-defined onset, such as PD, is the fact that the index date is difficult to define. This problem was addressed by restricting the analysis to a well-defined group of patients with a GP-recorded diagnosis of PD who were most likely idiopathic PD cases. There was no evidence for an increased risk in any exposure group (current as well as past drug use or an effect of treatment duration) for most antihypertensive drugs.

Cases and controls were matched on age, gender, general practice and calendar time (by using the same index date), and therefore it was controlled for these important confounders. In addition, the analyses were adjusted for a range of comorbidities to further reduce the risk of observing a spurious association between antihypertensive drug use and the risk of developing PD. The findings cannot be distorted by recall bias since all drug use was recorded before the PD diagnosis. All recordings of diagnoses and drug prescriptions were independent of any study hypothesis. Additionally, no bias could have arisen from the selection process of the controls as they were chosen at random from the same study base from which the cases were identified.

4.2 Statins and the risk of Parkinson's disease

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4.2.1 Summary

Low levels of cholesterol and low-density lipoprotein (LDL) have been found in subjects with PD, and case-reports have related HMG-CoA reductase inhibitors ('statins') use to PD. On the other hand, statins may have potentially beneficial effects on neurodegenerative diseases due to their anti-inflammatory properties. The aim of the current study was to explore the association between use of lipid-lowering agents and the risk of developing PD in the UK primary care setting. Therefore a case-control analysis was conducted using the GPRD. Cases were incident PD cases ≥40 years of age in 1994-2005. One control was matched to each case on age, sex, general practice and index date. Lipid-lowering drug use was assessed by timing (current vs. past use) and by exposure duration (1-9, 10-29 or ≥30 prescriptions). Ors were calculated using conditional logistic regression, adjusted for BMI, smoking and various cardiovascular, metabolic and psychiatric diseases. With this approach 3'637 cases with an incident idiopathic PD diagnosis and the same number of controls were identified. As compared to non-use, the adjusted OR for current use of ≥30 statin prescriptions was 1.07 (95% CI 0.75-1.52), for use of fibrates 1.34 (95% CI 0.55-3.29), and for use of other lipid-lowering agents 0.33 (95% CI 0.05-2.15). To conclude, long-term use of statins, fibrates or other lipid-lowering therapies was not associated with a substantially altered risk of developing PD in this large observational study.

4.2.2 Introduction

PD is a neurological disorder characterised by progressive loss of dopaminergic neurons in the substantia nigra pars compacta [Lang et al. 1998]. The aetiology is still largely unknown, with suggested involvement of oxidative stress [Jenner 2003], neuroinflammation [Hirsch et al. 2005], and mitochondrial dysfunction [Schapira et al. 1998]. In two recent observational studies low levels of cholesterol and LDL have been associated with PD [de Lau et al. 2006; Huang et al. 2007], raising the question whether pharmacological lowering of cholesterol may trigger PD. In addition, case-reports related use of statins to PD [Muller et al. 1995; Muller 2003]. On the other hand, statins have been shown to increase striatal dopamine concentration in animal models of PD

[Selley 2005], and they also have anti-inflammatory properties and decrease oxidative stress [Liao et al. 2005] which may be beneficial in reducing neuroinflammatory processes in PD. Observational studies have also found associations with statin use and a reduced risk of other neurodegenerative diseases [Jick et al. 2000; Stepien et al. 2005], although this effect was not seen in other studies [Rea et al. 2005]. Data on a possible effect of fibrates on PD are scarce.

It was the aim of the current study to explore the association between diagnosed hyperlipidaemia with or without use of lipid-lowering agents and the risk of being diagnosed with PD in a large patient sample within the UK primary care setting.

4.2.3 Methods

4.2.3.1 Data source

A retrospective case-control analysis was performed using data from the GPRD. The GPRD provides health care information on some 5 million people in the UK and has been previously described in detail [Jick 1997; Lawson et al. 1998; Wood et al. 2004]. Specially trained GPs record information on demographics, diagnoses and drug prescriptions as well as patient referrals and hospital admissions in the GPRD. Drug prescriptions are generated directly from the computer and recorded in each patient's computerised profile. Hospital discharge as well as referral letters are available on request to review and validate recorded diagnoses. The recorded information on drug exposure and on diagnoses has been validated repeatedly and proven to be of high quality [Walley et al. 1997; Jick et al. 2003]. The patients enrolled in the GPRD are representative of the UK with regard to age, gender, and geographic distribution [Wood et al. 2004]. The GPRD data has been used in recent studies examining PD [Hernan et al. 2004; Hernan et al. 2006; Schade et al. 2007]. The GPRD is managed by the MHRA in the UK. The study protocol was reviewed and approved by ISAC. The investigators had only access to anonymised information.

4.2.3.2 Study base, case identification and validation

The study base included all patients in the GPRD who were 40 years or older from January 1, 1994 to December 31, 2005. Cases were all persons in the study base

with a code for idiopathic PD recorded for the first time during the study period. The codes qualifying for case status were OXMIS-codes 342 ('Paralysis agitans') and 342 D ('idiopathic parkinsonism') as well as READ-codes F12..00 ('Parkinson's disease'), F12z.00 ('Parkinson's disease NOS') and F120.00 ('Paralysis agitans'). All cases were required to have a minimum of three years of medical history in the GPRD computer record prior to the first recorded diagnosis of PD. The date of the first code for PD will subsequently be referred to as the 'index date'.

A validation of the PD diagnosis was conducted in a recent study on the GPRD [Hernan et al. 2004] in which GP-recorded PD diagnoses were confirmed for 90% of PD cases who received at least two prescriptions for the treatment of PD during follow up.

Because 28% of the cases in the present study had received one or more prescriptions for an anti-PD-medication prior to the first recorded PD diagnosis, a random sample of 100 case profiles was manually reviewed to find out more about the reasons for PD medication use prior to the index date. This profile review revealed that a substantial proportion of PD patients received treatment due to early symptoms of PD, before the GP recorded the PD diagnosis at some later point in time. Therefore an algorithm for inclusion of cases into the analysis was set up; in order to be eligible as a case with a first-time diagnosis of idiopathic PD, patients had to meet the following three criteria: a) they had to have less than two prescriptions for any drug used to treat PD (levodopa, dopamine-agonists, selegiline, amantadine, apomorphine, anticholinergic drugs or COMT inhibitors) prior to the index date, b) the patients had to have received two or more prescriptions for levodopa, selegiline, dopamine-agonists or a COMT inhibitor after the index date, and c) they must not have had any prescriptions recorded for drugs known to cause parkinsonism (typical neuroleptics, metoclopramide or cinnarizine) within 180 days prior to the index date.

4.2.3.3 Controls

One control per PD case was identified at random from the base population, matched to the case on year of birth, gender, general practice, index date and number of years in the GPRD prior to the index date. Thus, controls also had to have a recorded history of at least 3 years prior to the index date.

4.2.3.4 Statistical analysis

Conditional logistic regression analyses were conducted to explore the association between the risk of PD and previous use of various lipid-lowering drugs, using the statistical software SAS (release 9.1, SAS Institute, Inc., Cary, NC). Relative risk estimates (ORs) are presented with 95% CIs.

Patients with no exposure to any lipid-lowering drugs formed the reference group. For the main analysis a model was created in which users of lipid-lowering drugs were compared to non-users, whereby use of more than one lipid-lowering drug prior to the index date was possible. The multivariate model was adjusted for such sequential or concurrent use of various lipid-lowering drugs. An additional model was run in which subjects were categorised into mutually exclusive groups of users of statins only, fibrates only, other lipid-lowering drugs (anion-exchange resins, derivates of nicotinic acid and omega-3-triglycerides) only, or any combination of these lipid-lowering drugs (switchers or combined use) and compared to non-users of any lipid-lowering drugs.

Users of lipid-lowering drugs were grouped, according to the date of their last prescription issued prior to the index date, into 'current' (last prescription <90 days) or 'past' (last prescription ≥90 days) users, and according to the number of recorded prescriptions (1-9, 10-29 and ≥30) for the study drugs prior to the index date. In order to identify potential confounding, the prevalence of various diagnosed and recorded chronic diseases prior to the index date was also assessed such as hyperlipidaemia, diabetes mellitus, hypertension, IHD, CHF, stroke or TIA, arrhythmias, asthma, COPD, epilepsy, affective disorders, schizophrenia, or neurotic and somatoform disorders. Other covariates such as smoking (never, ex-smoker, current or unknown) and BMI (<25, 25-29.9, ≥30 kg/m^2) were also considered and included in the analyses.

4.2.4 Results

With this approach 3'637 cases and the same number of matched controls were identified. Approximately 90% of the cases had their first PD diagnosis recorded after the age of 60 years, there were more males (60%) than females, and current

smoking was associated with a reduced risk of developing PD (OR 0.51, 95% CI 0.43-0.60). Table 4.2.1 displays the age and sex distribution, smoking status, BMI and the prevalence of comorbidities in cases and controls. Among the PD cases, 378 (10.4%) had ever used a lipid-lowering drug prior to the index date, 340 (9.4%) had used statins, 61 (1.7%) fibrates, and 24 (0.7%) another lipid-lowering agent (numbers do not add up to 10.4% because combined use was possible).

Table 4.2.1: Characteristics of cases and controls and the multivariate effects on the risk of PD

Variable	Cases, No (%) (n=3'637)	Controls, No (%) (n=3'637)	Adjusted OR* (95% CI)	p value
Age, years				
<60	320 (8.8)	321 (8.3)	--	--
60-69	752 (20.7)	751 (20.7)	--	--
70-79	1'522 (41.9)	1'520 (41.8)	--	--
≥80	1'043 (28.7)	1'045 (28.7)		--
Sex			--	--
Male	2'167 (59.6)	2'167 (59.6)	--	--
Female	1'470 (40.4)	1'470 (40.4)	--	--
Smoking status				
Non	2'186 (60.1)	1'866 (51.3)	1.00 (referent)	--
Current	326 (9.0)	521 (14.3)	0.51 (0.43-0.60)	<0.0001
Ex	581 (16.0)	697 (19.2)	0.67 (0.58-0.77)	<0.0001
BMI (kg/m²)				
15 - 24.9	1'239 (34.1)	1'192 (32.8)	1.00 (referent)	--
25 - 29.9	1'121 (30.8)	1'104 (30.4)	1.00 (0.89-1.13)	0.99
≥30	364 (10.0)	399 (11.0)	0.88 (0.74-1.05)	0.17
Comorbidities				
Diabetes	291 (8.0)	308 (8.5)	0.94 (0.79-1.13)	0.52
Asthma / COPD	77 (2.1)	116 (3.2)	0.70 (0.51-0.95)	0.02
Hypertension	1'197 (32.9)	1'286 (35.4)	0.84 (0.75-0.93)	0.001
IHD	815 (22.4)	755 (20.8)	1.06 (0.93-1.20)	0.39

Cont. Table 4.2.1

Variable	Cases, No (%) (n=3'637)	Controls, No (%) (n=3'637)	adjusted OR* (95% CI)	p value
CHF	291 (8.0)	282 (7.8)	0.93 (0.77-1.12)	0.44
Stroke / TIA	541 (14.9)	349 (9.6)	1.67 (1.43-1.96)	<0.0001
Arrhythmia	385 (10.6)	370 (10.2)	1.00 (0.85-1.18)	0.96
Hyperlipidaemi	338 (9.3)	314 (8.6)	1.06 (0.89-1.27)	0.50
Epilepsy	91 (2.5)	62 (1.7)	1.33 (0.95-1.88)	0.10
Affective	786 (21.6)	527 (14.5)	1.49 (1.30-1.71)	<0.0001
Schizophrenia	30 (0.8)	24 (0.7)	1.02 (0.57-1.80)	0.95
Neurotic & somatoform disorders	692 (19.0)	442 (12.2)	1.57 (1.35-1.81)	<0.0001

* adjusted for the other variables in this table

The relative risk (OR) of a PD diagnosis among those with an untreated, but recorded diagnosis of hyperlipidaemia compared to those with no such diagnosis was 0.96 (95% CI 0.72-1.27). Among subjects treated for hyperlipidaemia, the ORs of developing a first-time PD diagnosis, adjusted for the covariates in Table 4.2.1, were 0.92 (95% CI 0.73-1.16) for current statin use, 1.32 (95% CI 0.67-2.61) for current fibrate use, and 0.24 (95% CI 0.06-0.90) for use of other lipid-lowering drugs, as compared to non-use of these drugs. Since there were few subjects exposed to 'other lipid-lowering' drugs, this group was not further analysed. The results of the analysis in which timing and duration of use were combined are displayed in Table 4.2.2.

Table 4.2.2: Antihyperlipidaemic drug use vs. non-use prior to the index date in PD patients and controls and associated relative risk estimates

Exposure	Cases No (%) (n=3'637)	Controls, No (%) (n=3'637)	Unadjusted OR (95% CI)	Adjusted OR* (95% CI)	p value
Statins					
None	3'297 (90.7)	3'327 (91.5)	1.00 (referent)	1.00 (referent)	--
Current use	285 (7.8)	275 (7.6)	1.06 (0.88-1.28)	0.92 (0.73-1.16)	0.48
No. of prescriptions					
1-9 Rx	82 (2.3)	78 (2.1)	1.07 (0.77-1.47)	0.87 (0.61-1.25)	0.44
10-29 Rx	99 (2.7)	99 (2.7)	1.02 (0.76-1.37)	0.85 (0.60-1.19)	0.34
≥30 Rx	104 (2.9)	98 (2.7)	1.09 (0.81-1.45)	1.07 (0.75-1.52)	0.71
Past use	55 (1.5)	35 (1.0)	1.60 (1.04-2.46)	1.32 (0.82-2.13)	0.25
No. of prescriptions					
1-9 Rx	34 (0.9)	26 (0.7)	1.33 (0.79-2.24)	1.34 (0.75-2.40)	0.32
10-29 Rx	14 (0.4)	8 (0.2)	1.75 (0.74-4.18)	1.11 (0.44-2.83)	0.82
≥30 Rx	7 (0.2)	1 (0.1)	7.07 (0.87-57.38)	4.81 (0.51-45.18)	0.17
Fibrates					
None	3'576 (98.3)	3'589 (98.7)	1.00 (referent)	1.00 (referent)	--
Current use	23 (0.6)	17 (0.5)	1.36 (0.73-2.55)	1.32 (0.67-2.61)	0.42
No. of prescriptions					
1-9 Rx	4 (0.1)	4 (0.1)	1.00 (0.25-4.00)	0.56 (0.13-2.37)	0.43
10-29 Rx	7 (0.2)	3 (0.1)	2.33 (0.60-9.02)	2.26 (0.49-10.35)	0.29
≥30 Rx	12 (0.3)	10 (0.3)	1.22 (0.53-2.83)	1.34 (0.55-3.29)	0.52
Past use	38 (1.0)	31 (0.9)	1.23 (0.77-1.98)	1.06 (0.63-1.80)	0.83
No. of prescriptions					
1-9 Rx	17 (0.5)	14 (0.4)	1.21 (0.60-2.46)	1.16 (0.53-2.54)	0.71
10-29 Rx	8 (0.2)	8 (0.2)	1.00 (0.38-2.66)	0.68 (0.22-2.05)	0.49
≥30 Rx	13 (0.4)	9 (0.3)	1.46 (0.62-3.41)	1.16 (0.45-2.99)	0.76

Cont. Table 4.2.2

Exposure	Cases No (%) (n=3'637)	Controls, No (%) (n=3'637)	Unadjusted OR (95% CI)	Adjusted OR* (95% CI)	p value
Other lipid-lowering agents					
None	3'613 (99.3)	3'605 (99.1)	1.00 (referent)	1.00 (referent)	--
Current use	3 (0.1)	11 (0.3)	0.27 (0.08-0.98)	0.24 (0.06-0.90)	0.03
No. of prescriptions					
1-9 Rx	0	4 (0.1)	--	--	--
10-29 Rx	1 (0.1)	4 (0.1)	--	--	--
≥30 Rx	2 (0.1)	3 (0.1)	--	--	--
Past use	21 (0.6)	21 (0.6)	1.00 (0.55-1.83)	0.96 (0.51-1.81)	0.89
No. of prescriptions					
1-9 Rx	14 (0.4)	12 (0.3)	--	--	--
10-29 Rx	6 (0.2)	7 (0.2)	--	--	--
≥30 Rx	1 (0.1)	2 (0.1)	--	--	--

* adjusted for each other, BMI, smoking status, comorbidities from Table 4.2.1 and use of antihypertensive drugs

The analysis on statin was further stratified use by age and gender which did not provide evidence for effect modification (data not shown).

In the analysis of mutually exclusive exposure groups, the adjusted OR for current use of ≥30 prescriptions, as compared to non-use of any lipid-lowering drugs, was 1.14 (95% CI 0.79-1.65) for statins only and 1.52 (95% CI 0.53-4.36) for fibrates only.

The risk of a PD diagnosis was also separately analysed for the use of individual statins, stratifying the subgroup of subjects with current use of ≥30 statin prescriptions (104 cases and 98 controls) by the last statin prescribed prior to the index date. The results are presented in Table 4.2.3.

Table 4.2.3: Current long-term use of individual statins

Exposure	Cases, No (%) (n=104)	Controls, No (%) (n=98)	Unadjusted OR (95% CI)	Adjusted OR* (95% CI)	p value
Statins					
None	3'297 (90.7)	3'327 (91.5)	1.00 (referent)	1.00 (referent)	--
Current use of ≥30 Rx					
Simvastatin	53 (1.5)	51 (1.4)	1.06 (0.72-1.57)	1.02 (0.65-1.58)	0.94
Atorvastatin	31 (0.9)	35 (1.0)	0.91 (0.55-1.50)	0.88 (0.50-1.55)	0.67
Pravastatin	19 (0.5)	9 (0.3)	2.13 (0.96-4.72)	2.39 (1.01-5.68)	<0.05
Fluvastatin	1 (0.03)	2 (0.05)	--	--	--
Rosuvastatin	0	1 (0.03)	--	--	--

* adjusted for each other, BMI, smoking status, comorbidities from Table 4.2.1 and use of antihypertensive drugs

Since there was a suggestion of an increased risk associated with pravastatin use (OR 2.39, 95% CI 1.01-5.68), the group of pravastatin users was further divided into those with a prescription of a low to medium dose (10 or 20 mg) or users of a high dose (40 mg), yielding an adjusted OR of 4.46 (95% CI 1.38-14.38) for low to medium dose users, and of 0.85 (95% CI 0.22-3.36) for high dose users.

4.2.5 Discussion

The results of the present large observational case-control study suggest that neither current nor past exposure to a statin or any other lipid-lowering drug substantially alters the risk of developing a PD diagnosis. In addition, there was no association between duration of use of these study drugs and the risk of PD. To our knowledge, so far only one study has been published in the literature analysing statin use in prevalent PD patients [Lieberman et al. 2005]. The authors of this interview-based study concluded that statins did not seem to worsen PD in 173 patients with PD who used statins.

In theory statins may be able to protect glial cells from inflammation and subsequent neuronal cell death. Various pharmacological effects beyond inhibiting the cholesterol synthesis have been demonstrated for this drug class, such as neuroprotective and anti-inflammatory effects [Rajanikant et al. 2007]. Furthermore, positive effects of statins on dopamine metabolism have been shown in rodents such as prevention of striatal dopamine depletion [Selley 2005], reversal of down regulation of D_1 and D_2 receptors in the prefrontal cortex [Wang et al. 2005], or the enhancement of striatal dopamine concentrations [Wang et al. 2006]. However, these studies were carried out with doses clearly exceeding human therapeutic doses, and therefore these effects may not be reproducible with therapeutic doses in humans.

On the other hand, case reports related statin use to the onset of PD [Muller et al. 1995; Muller 2003]. Two patients with lovastatin therapy and one patient with fluvastatin therapy developed PD symptoms emerging three months to two years after starting a statin. In all cases the symptoms disappeared or at least improved after statin discontinuation. In addition, several case reports linked statins with other diseases of the central nervous system, such as depression [Duits et al. 1993; Tatley et al. 2007] or sleep disturbances [Sinzinger et al. 1994; Gregoor 2006], symptoms which are also highly prevalent in PD. Another argument supporting a possible association between statins and PD onset or progression of PD is that statins inhibit the endogenous production of coenzyme Q_{10} (CoQ_{10}, ubiquitine). This enzyme is important for the function of the mitochondrial electron chain [Ernster et al. 1995; Shults et al. 1997], and mitochondrial dysfunction is also discussed as one of the possible mechanisms of idiopathic PD [Schapira et al. 1992]. CoQ_{10} is generated by the same pathway as cholesterol [Ernster et al. 1995]. Thus, inhibiting the cholesterol synthesis may also decrease the amount of available CoQ_{10} necessary for certain physiological functions. Human plasma levels of CoQ_{10} have been shown to be inversely associated with statin use [Folkers et al. 1990; Ghirlanda et al. 1993; Laaksonen et al. 1994; Mortensen et al. 1997; Kaikkonen et al. 1999] and beneficial effects of orally administered CoQ_{10} on PD have been shown in trials in humans [Shults et al. 2002; Muller et al. 2003], whereby high doses of CoQ_{10} seemed to delay progression of early PD [Shults et al. 2002].

The findings of this study suggest that statins as a group do not substantially alter the risk of a first-time diagnosis of PD. There was a suggestion, however, that use of

pravastatin may be associated with an increased risk of a PD diagnosis. However, this finding was based on small numbers, and the increased risk was driven by users of a low daily dose (10-20 mg), but not seen in high-dose users, making a causal association rather unlikely.

Little is known about the effect of fibrates or other lipid-lowering agents in relation to the risk of PD. In a mouse model, fenofibrate exerted a neuroprotective effect, while bezafibrate did not [Kreisler et al. 2007]. In our study population the exposure to fibrates and other lipid-lowering agents was too low to allow meaningful conclusions.

Some limitations of this study need to be addressed. It was not possible to control for certain demographic factors in the study population such as level of education, socioeconomic status or cholesterol level, which themselves have been associated with PD [Frigerio et al. 2005; de Lau et al. 2006]. However, cases and controls were matched on general practice and therefore control to at least some degree on socioeconomic status was likely since cases and controls came from the same area and therefore saw the same GP at the time of the study. In addition, not all statin use may have been detected, since low-dose simvastatin (10 mg) became available as an over-the-counter drug in the UK in August 2004 [The Lancet 2004; Filion et al. 2007]. However, most PD diagnoses in the study population occurred before 2004, and one can expect that a high proportion of all statin use in the study population was captured.

It is a strength of the study that it encompassed a large population sample, and that the GPRD is a validated database of high quality. The GPRD has already been used for two observational studies on PD [Hernan et al. 2004; Hernan et al. 2006]. Their case validation resulted in a high proportion (90%) of confirmed computerised PD diagnoses for those who received two or more prescriptions for specific medication to treat PD after the index date. Furthermore, the finding of a substantially reduced PD risk for current smoking is consistent with previous studies [Nefzger et al. 1968; Quik 2004; Hancock et al. 2007] and lends further credibility to the validity of the results of this study.

It is difficult to define the index date for chronic diseases without acute and well-defined onset, such as PD. It has been tried to address this problem by restricting the analysis to a well-defined group of patients with a GP-recorded diagnosis of PD who

were most likely idiopathic PD cases and who had little or no drug use suggestive of previous PD symptoms. In addition, to address the uncertainty around the index date current as well as past use of study drugs was explored as well as duration of use; no evidence for an increased risk in any exposure group was found.

Cases and controls were matched on age, gender, general practice and calendar time (by using the same index date), and thus the analysis was controlled for important confounders. In addition, adjustment for a range of comorbidities was carried out to further reduce the risk of observing a spurious association between lipid-lowering drug use and the risk of developing PD. The findings cannot be influenced by recall bias because the drug use of interest was recorded prior to the PD diagnosis. Additionally, no bias could have arisen from the selection process of controls, since the controls were identified at random from the same study base as the cases.

To conclude, this large observational study based on UK primary care data provides evidence that use of statins (as well as use of fibrates or other lipid-lowering drugs, although based on a limited number of exposed patients) is not associated with a substantially altered risk of a first-time diagnosis of idiopathic PD.

Chapter 5

Discussion, conclusions and outlook

5 Discussion, conclusions and outlook

The main findings of each study are considered in detail in the respective chapters. In the following the study populations and methodologies utilised in the thesis will be discussed and subsequent suggestions for further research will be presented.

5.1 Discussion

5.1.1 Data source

The studies included in this thesis were conducted with data from the GPRD, one of the largest computerised databases of anonymised longitudinal clinical records in primary care [Wood et al. 2004] (see chapter 1.1.2). The GPRD is known for its high quality and completeness of information. The data are representative of the UK population. Because of the large number of included patients and patients-years, rare outcomes with incidence rates of less than one per 10'000 person years can be studied. With a complete recording of prescriptions and events dating back as far as 1987 for some practices, the analysis of effects with a long latency is also possible. Furthermore, the GPRD studies can be carried out in a 'real world' scenario with patients, who also have concomitant drug use and comorbid illnesses, are not forced to comply with clinical trials. With these comprehensive data it is also possible to study drug effects in very young or very old people as well as in pregnant women who are not usually included in RCTs for ethical reasons. Drug effectiveness (i.e. the benefits of the drug in a 'real life' setting) can be studied rather than just efficacy.

However, there are also certain limitations of the studies undertaken with data from the GPRD: It may sometimes be difficult to adjust for all potential confounders and therefore some residual confounding may remain. Additionally, for some life style related confounders (e.g. diet, physical exercise, and socioeconomic status) no information is available on the GPRD. Data on smoking, alcohol consumption, weight and height are not complete (information is available for approximately 70%), as is the recording of the dates of menarche or menopause.

Despite the high quality of the documented information on the primary medical care, the completeness of specialist diagnoses and care provided in hospitals is around 90-95% [Jick et al. 1991; Jick et al. 1992] which can represent a problem when studying certain rare outcomes which are usually treated in hospitals or by specialists. Information on drug use is derived from prescription data which does not clarify if the patient has actually ingested the drug. Additionally, the exact timing of drug intake is not recorded which is relevant for certain acute outcomes as for example stroke in association with triptan use (see chapter 3.2). Furthermore, OTC and in-hospital drug use is not necessarily recorded comprehensively for all patients.

In contrast to studies based on questionnaires or telephone interviews data from the GPRD is not subject to recall or interviewer bias because the medical events and prescriptions are recorded at a time when a particular study hypothesis is not known by the GPs. The costs of a study on the GPRD are relatively low (apart from expenses for the GPRD licence). There is the possibility of sending the GPs project-specific questionnaires with the objective to obtain additional information which are not recorded in the computer files. Another advantage of the GPRD is its availability which enables studies to be conducted rapidly, e.g. in response to a suspected harmful drug effect. In these circumstances timely decisions are expected from authorities and de novo data collection would require additional time. However, due to the retrospective nature of the GPRD there is usually limited information on newly marketed drugs.

5.1.2 Methodology

The thesis aimed at describing the natural history of migraine and PD for several population strata. The study populations were described in terms of demographic characteristics as well as the prevalence of comorbid disorders and prior drug use. In one study health resource utilisation was quantified for the cases and controls and discussed as a measure for the severity of the disease. The risk for further outcomes related to the underlying disease and possibly to the respective treatment were analysed by means of a cohort study with a nested case-control part.

For the assessment of an increased risk or possible beneficial effects associated with prior drug use two separate case-control studies were conducted.

In the case-control studies cases were matched 1:1 to a control, and in the nested case-control studies the matching was 1:4. Matching criteria were sex, age (+/- 3 years), the general practice attended by the patient, the time of recorded history on the database prior to the exposure or the event, and the index date. The controls were randomly selected from the database. For further potential confounders the analyses were adjusted in the statistical evaluation (see chapter 1.1.4.3).

The projects were conducted in close collaboration with the BCDSP. A computer programmer from the BCDSP extracted the relevant information on disease codes and drug prescription data of the patients with migraine or PD and of the respective control patients. Several approaches to assess the validity of the diagnoses were used: a) questionnaires were sent to a random sample of 200 GPs of the cases in order to find out more on how diagnoses were made and also about their validity, b) electronic patient profiles were manually reviewed and valid diagnoses subsequently selected after a predefined algorithm. The method of profile review was also deployed for the quantification of health resource utilisation. For the manual review the patient records were anonymised and blinded regarding any exposure or outcome of interest in order to avoid observer bias (see chapter 1.1.4.2).

The statistical analyses were conducted with the software program SAS (‘Statistical Analysis System’, releases 8.1 and 8.2 for the migraine project and 9.1 for the Parkinson project, SAS Institute, Inc., Cary, NC, US). Multivariate conditional logistic regression models were used in order to quantify the risk of an outcome of interest in association with a certain exposure, adjusted for several cofactors. Stratified analyses allowed the identification of potential effect modifiers such as sex, age or the presence of comorbid diseases which could affect the risk of the outcome of interest. However, as described above, it was not fully possible to adjust for all potential covariates as some data on demographic factors are not included in the GPRD. This point is addressed in the respective discussion sections of the projects.

5.2 Conclusions

In the five papers included in this thesis several (pharmaco-)epidemiological aspects of the two neurological disorders migraine and PD were addressed. Based on these findings it can be concluded that:

- Migraine is a common diagnosis in primary care in the UK, incidence rates are 2.5 times higher in women than in men and highest in young age.
- Migraineurs have an increased prevalence of most chronic diseases, and especially of depression.
- HRU is higher in migraineurs who have had a prescription for triptans, probably because their headache disorder is more severe.
- The risk of a stroke or TIA is doubled in migraineurs while mortality is not significantly increased, although it is difficult to evaluate this point in an epidemiologic study because of confounding by indication.
- It is not possible to quantify the risk of stroke in relation to prior triptan use in migraineurs with data from sources like the GPRD, because information on the actual timing of the drug use is lacking.
- The risk of asthma is not materially increased for migraineurs and a triptan prescription does not seem to be a risk factor for asthma in patients with a GP-recorded migraine diagnosis.
- In the UK a GP-recorded diagnosis of PD is found almost exclusively in cases after the age of 60 years, the prevalence of PD is twice as high in men as in women.
- Current use of calcium channel blockers seems to reduce the risk of developing a diagnosis of PD, especially in the elderly.
- Prescriptions of other antihypertensive medication are not associated with an altered risk for a PD diagnosis.
- Although PD is associated with low cholesterol levels, statins do not seem to increase the risk of a diagnosis for PD.

5.3 Outlook

5.3.1 Further epidemiologic studies on migraine and PD

As mentioned in chapter 3.2.5, it is not possible to completely address the effect of triptans on the stroke risk of migraineurs with a database such as the GPRD. In order to further clarify the association, a study on the acute effect of triptans would be helpful. This could possibly be done by questioning the patients about the drugs they had used immediately before their stroke. However, the uncertainty about the baseline risk of migraineurs for stroke without triptans still exists and is difficult to evaluate in an observational study.

Furthermore it would be interesting to study additional outcomes in migraineurs on the GPRD such as myocardial infarction or hypersensitivity related diseases (e.g. rhinitis). For both associations hints in the literature exist [Kurth et al. 2007; Levy et al. 2007].

The results of both studies of the PD project should be confirmed by further studies using other populations. The possible reduced PD risk associated with the current use of calcium channel blockers could be elucidated by a pilot clinical trial, preferably in patients with newly diagnosed PD. The neuroprotective effects of Q_{10} have been studied in this manner [Shults et al. 2002]. Additionally to the case-control design utilised in chapter 4.2, a cohort study could be carried out with GPRD or other data in order to analyse the absolute risk for a PD diagnosis in relation to prior use of statins.

5.3.2 Inclusion of genetic information into the GPRD

The response to a drug is also influenced by the genetics of the individual [Evans et al. 2003]. A different genetic setting may lead to altered activities of drug transporters, receptors or drug-metabolising enzymes responsible for pharmacologic action [Meyer 2000]. Within the last years genetic databases and DNA libraries have been established [Ollier et al. 2005; Kaiser 2006; Ronningen et al. 2006] which also collect information on patients demographics and on lifestyle, occupational and environmental factors [Jiang et al. 2006]. This information could be useful for epidemiologic research. One potential new application for GPRD data would be the

study of genetic difference in a huge population in primary care. Therefore access to genetic data of the patients would be required, either routinely gathered by the GP or, subject to ethical approval, for ad hoc studies in a restricted population identified in the course of a study.

Studying the impact of the genetic profile on susceptibility to clinical efficacy and adverse drug reactions will broaden the knowledge on drug efficiency and unwanted drug effects in special subsets of patients who are at an increased risk for adverse effects. There is evidence accumulating that both the efficacy of drugs [Bloemenkamp et al. 1995] and their safety [Kuivenhoven et al. 1998] have their genetic correlates.

It has been shown that DNA can reliably be extracted from buccal swabs and stored [Richards et al. 1993]. As this provides an inexpensive and feasible method for information on a large scale, it could be added to patient records in the GPRD for testing future hypotheses. Of course, an informed consent of the patients has to be obtained as well as a safeguard for confidentiality. Alternatively, GPRD data could be linked with genetic data from the UK biobank [UK biobank 2007].

Information on genetic genotyping could be used for example in assessing genetic differences in the risk of drug-induced Parkinsonism. Some smaller studies have already proposed an association between the genotype of the patient and the risk for extrapyramidal syndromes (EPS) after the use of relevant drugs [Schillevoort et al. 2002; Hedenmalm et al. 2006]. With that information, phenotypes could be determined prior to therapy with antipsychotics in order to prevent EPS in susceptible patients. The decreased rate of discontinuation with antipsychotic therapy may favourably affect the relapse rate in schizophrenia.

Additionally, it has recently been postulated that the response or non-response to triptans may be associated with a polymorphism of the gene encoding the dopaminergic D_2 receptor [Asuni et al. 2007]. The large population sample of the GPRD would provide a good possibility to increase the knowledge about these research questions.

Chapter 6

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6 Bibliography

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