Population-based Studies on the Natural History of Alzheimer's Disease and Vascular Dementia

Inauguraldissertation

zur

Erlangung der Würde eines Doktors der Philosophie

vorgelegt der

Philosophisch-Naturwissenschaftlichen Fakultät

der Universität Basel

von

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aus Lungern (OW)

Basel, 2012

Originaldokument gespeichert auf dem Dokumentenserver der Universität Basel
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Genehmigt von der Philosophisch-Naturwissenschaftlichen Fakultät

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To my wonderful wife

and our lovely daughter

ACKNOWLEDGEMENTS

Die vorliegend Arbeit entstand zwischen Februar 2009 und Juni 2012 am Institut für Klinische Pharmazie und Epidemiologie der Universität Basel unter der Leitung von Prof. Dr. Christoph Meier.

Mein Dank geht an alle, die in irgendeiner Form zum Gelingen dieser Arbeit beigetragen haben.

Speziell bedanken möchte ich mich aber in erster Linie bei Prof. Dr. Christoph Meier für seine grossartige Unterstützung, Motivation und Hilfsbereitschaft während der ganzen Dissertation. Ganz besonders geschätzt habe ich seine Offenheit, Kollegialität und seinen Humor.

Vielen Dank auch an Prof. Dr. Dr. Stephan Krähenbühl für die Übernahme des Korreferats und seine Inputs für die vorliegende Arbeit.

Ein herzliches Dankeschön auch an Prof. Dr. Kurt Hersberger für die Übernahme des Prüfungsvorsitzes.

Weiterer Dank geht an Dr. Markus Schürch und Dr. N. Jamie Robinson von der Firma F. Hoffmann-La Roche Ltd. für das Vertrauen und die gute Zusammenarbeit während des Alzheimer-Projektes.

Bedanken möchte ich mich auch herzlich bei Dr. Beat Disler von der Senglet-Stiftung für die finanzielle Unterstützung.

Vielen Dank auch an PD Dr. Michael Bodmer, Dr. Yolanda Brauchli Pernus und Prof. Susan Jick für die jeweils kritische Durchsicht der Manuskripte und die konstruktiven Beiträge.

Ein grosses Dankeschön geht auch an alle meine Kollegen und Kolleginnen aus der *Basel Pharmacoepidemiology Unit (BPU)*, namentlich Pascal Egger, Dr. Cornelia Schneider, Julia Spöndlin, Saskia Bruderer, Nadja Stohler, Delia Bornand, Daphne Reinau, Dr. J. Claire Wilson und Dr. Claudia Becker; der Pharmaceutical Care Research Group; dem „Markgräflerhof-Team“ der Klinischen Pharmakologie & Toxikologie und dem Team der Klinischen Pharmazie für die tolle Arbeitsatmosphäre und die vielen lustigen und unvergesslichen gemeinsamen Anlässe.

A very special thank goes to my friend and mentor Prof. Steve Hudson, who passed away the year before last. Thanks for everything you did for me, I'll never forget you.

Ganz herzlich danken möchte ich auch meinen Eltern Heinz und Vickie, sowie meinen beiden Brüdern Chris und Sascha. Ihr wart immer für mich da und habt es mir ermöglicht, dass ich diesen Weg gehen konnte. Vielen Dank für all eure Ermutigungen und eure treue Unterstützung.

Und nicht zuletzt möchte ich mich ganz besonders bei meiner wundervollen Frau Gaby für ihre grossartige Unterstützung während dieser ganzen Zeit bedanken. Du bist meine grosse Liebe und hast uns jetzt noch eine bezaubernde Tochter geschenkt. Ich könnte nicht glücklicher sein.

TABLE OF CONTENTS

SUMMARY

Pharmacoepidemiology is defined as the study of the utilization and effects of drugs in large human populations. Beside its classical role in the evaluation of drug safety after marketing, pharmacoepidemiology is increasingly gaining importance in the pre-marketing phase of the drug development process, where it can provide useful information on the natural history of the disease a drug is being developed to treat.

Alzheimer's disease (AD) is one of the most disabling and burdensome health conditions worldwide. It is the most common form of dementia with more than 26 million cases worldwide. Vascular dementia (VD) is the second most common dementia form, resulting from intracerebral vascular and circulatory pathology.

The aim of this thesis was to increase knowledge on the natural history of AD and VD, thereby focusing on the effect of certain drug therapies as potential risk or protective factors for these diseases or complications thereof.

The studies in this thesis were carried out using data from the United Kingdom (UK) based General Practice Research Database (GPRD), a large and well established physician-based primary care database. This database contains longitudinal records from several million patients representative of the UK population. The information recorded in the medical files includes patient demographics and characteristics (e.g. age, sex, height, weight, smoking status), symptoms, medical diagnoses, referrals to consultants, and hospitalizations.

In the first study (3.1) we identified patients aged ≥65 years with an incident diagnosis of AD or VD between 1998 and 2008 and assessed incidence rates (IRs) of AD and VD, stratified by age and sex. To each demented case patient we matched one dementia-free control patient and analyzed co-morbidities and drug use prior to the time of diagnosis. We identified 7,068 AD and 4,438 VD cases. For AD, IRs were higher for women than for men, but not for VD. Except for orthostatic hypotension, the prevalence of all cardiovascular (CV) co-morbidities and exposure to CV drugs was lower in patients with AD than in the corresponding controls, whereas the opposite was true for VD. We concluded that this may be a true finding or the result of diagnostic bias, i.e. that demented patients with CV diseases may be more likely to be diagnosed with VD than AD.

In the second study (3.2) we studied the influence of metformin or other antidiabetic drugs on the risk of developing AD. We performed a case-control analysis within the

population of AD cases and corresponding controls identified in the first study (3.1). We found that long-term users of metformin had a slightly increased risk of developing AD as compared to non-users, but there was no consistent trend with increasing duration of use. Use of other antidiabetic drugs such sulfonylureas, thiazolidinediones, or insulin was not associated with an altered risk of developing AD.

In the third (3.3) and fourth study (3.4) we followed the complete study population of the first study (3.1) forward in time to assess IRs of certain diseases (complications) of interest in patients with AD or VD and compared them to patients without dementia. We then performed a nested case-control analysis to identify potential risk factors for developing such diseases of interest. The diseases of interest in the third study were seizures/epilepsy and in the fourth study ischemic stroke, hemorrhagic stroke or transient ischemic attack (TIA). In the third study we found that seizures or epilepsy were substantially more common in patients with AD and VD than in dementia-free patients. Additionally, patients with longer standing (≥3 years) AD had a slightly higher risk of developing seizures or epilepsy than those with a shorter disease duration, while in patients with VD the contrary was observed. In the fourth study we found that patients with AD did not have a materially different risk of developing an ischemic stroke compared to patients without dementia, whereas patients with VD had an about twofold increased risk. AD patients receiving atypical antipsychotic drugs only had a higher risk of developing a TIA than AD patients not receiving any antipsychotic drug treatment, whereas for patients with VD there was no significant difference between users of atypical or typical antipsychotic drugs and those not receiving antipsychotic treatment.

The GPRD is a very useful tool to conduct pharmacoepidemiological research. Its strengths are the large size, the population-based character of the data, and the opportunity to have access to original medical records. On the other hand, data on important confounders such as dietary or exercise habits is largely missing.

ABBREVIATIONS

A*β*	*β*-amyloid
ACE	Angiotensin converting enzyme
AChEI	Acetylcholinesterase inhibitor
AD	Alzheimer's disease
ADL	Activities of daily living
ADRDA	Alzheimer's Disease and Related Disorders Association
AIDS	Acquired immune deficiency syndrome
AIREN	Association Internationale pour la Recherche et l'Enseignement en Neurosciences
ApoE	Apolipoprotein E
AT	Angiotensin
BMI	Body mass index
CAA	Cerebral amyloid angiopathy
CDT	Clock Drawing Test
CI	Confidence interval
CNS	Central nervous system
COPD	Chronic obstructive pulmonary disease
CPRD	Clinical Practice Research Datalink
CSF	Cerebrospinal fluid
CT	Computed tomography
CV	Cardiovascular
DM	Diabetes mellitus
GP	General practitioner
GPRD	General Practice Research Database
HIV	Human immunodeficiency virus
IR	Incidence rate
IRR	Incidence rate ratio
ISAC	Independent Scientific Advisory Committee
LBD	Lewy body dementia
MHRA	Medicines and Healthcare products Regulatory Agency
MMSE	Mini-mental state examination
MRI	Magnet resonance imaging

MS	Multiple sclerosis
NHS	National Health Service
NIN(C)DS	National Institute of Neurological (and Communicative) Disorders and Stroke
NMDA	N-methyl-D-aspartate
NP	Neuritic plaques
NSAIDs	Non-steroidal anti-inflammatory drugs
OR	Odds ratio
OTC	Over-the-counter
PET	Positron emission tomography
py	person-years
RCT	Randomized controlled trial
RR	Relative risk
SAS	Statistical analysis system
SPECT	Single photon emission computed tomography
UK	United Kingdom
US	United States
VD	Vascular dementia

CHAPTER 1

INTRODUCTION

INTRODUCTION

1.1 PHARMACOEPIDEMIOLOGY

1.1.1 General aspects

Pharmacoepidemiology is defined as the study of the utilization and effects of drugs in large human populations by applying reasoning, methods, and knowledge of epidemiology.[1] It is a relatively young scientific discipline bridging between clinical pharmacology and epidemiology.[2] The discipline has evolved against the background that drugs are not only beneficial, but occasionally can cause serious adverse events that were unexpected from pre-clinical studies or pre-marketing clinical trials.[3]

Pre-marketing clinical trials are designed to study the safety and efficacy of a new drug, however they have several limitations. First of all they are limited in size of the study population. If a rare but serious adverse event for example occurs only in one of 10,000 patients taking a new drug, inclusion of 1,000 participants in a phase III trial will not detect this event. Second, pre-marketing trials are limited in study duration, making it difficult to detect rare adverse events that develop after a long induction period or cumulative drug intake. Third, these trials often include a selected study population, which is usually not fully representative of subsequent users of the drug.[3]

One typical approach of addressing these limitations is the collection of spontaneous reports of adverse drug reactions during the post-marketing phase.[2] However, determining causation in spontaneous reports may be delicate because such reports often do not provide enough details on co-morbidities or other drugs to rule out other possible causes of the adverse drug reaction.[3] Pharmacoepidemiology uses a different approach, by performing controlled studies, which examine whether the adverse outcome under study occurs more often in the exposed population than in the non-exposed population.[2]

Beside its classical role in the evaluation of drug safety after marketing, pharmacoepidemiology is increasingly gaining importance in the pre-marketing phase. A valuable application is for example the retrospective analysis of data from clinical phase II or III trials to identify patient risk factors for a specific adverse event, thereby contributing to the safety profile of a drug. Another application is the estimation of so-called background incidence rates of serious adverse events in subjects not exposed to the drug under study. This can be helpful to assess whether

serious adverse events encountered during clinical trials are occurring at rates above the corresponding background incidence rates in subjects not exposed to the drug.[4] Additionally, epidemiological studies on the natural history of the disease a drug was developed to treat, performed early in the drug development process, can provide useful information on characteristics of the target population (e.g. in terms of co-morbidities or drug use) or the estimated market size and help prioritize drug development programs.[5]

1.1.2 Data sources

Many pharmacoepidemiological studies are conducted as field studies, using data that was purposely collected to answer a specific research question. These studies are sometimes conducted as multi-center studies to increase the number of cases.[3] Examples include a study about the use of appetite-suppressant drugs and the risk of developing pulmonary hypertension[6] or another study about the risk of developing Stevens-Johnson syndrome in association with use of different drugs.[7] Alternatively, already existing data sources, such as multipurpose cohorts or large health databases, are increasingly being used. Pharmacoepidemiological studies using such data, have the advantage that they can be conducted faster and are less expensive than field studies, as the data have already been collected.[3]

Multipurpose cohorts

Multipurpose cohorts are designed to study many different research hypotheses. The study population of such cohorts usually consists of a subset of a defined population that was not assembled by a specific exposure, but by other factors.[3] A typical example is the United States (US) Nurses' Health Study, where the study population (initially 121,700 registered female nurses aged between 30–55 years living in one of 11 US states) was assembled by demographic factors such age, sex, profession, and residence. Participants in this study were followed prospectively with follow-up questionnaires mailed every two years, asking them questions about different exposures (particularly hormone use), lifestyle factors (e.g. smoking status, exercise habits), and the development of chronic conditions (e.g. cancer, cardiovascular diseases). Later, questions about dietary habits and issues related to quality of life were added.[8] Although the study was initially designed to investigate the association

between oral contraceptive use and the risk of breast cancer, it has been the extensively used to study other pharmacoepidemiological research questions such as the association between use of non-steroidal anti-inflammatory drugs (NSAIDs) and the risk of Parkinsons' disease[9] or oral contraceptive use and the risk of multiple sclerosis (MS).[10]

Large health databases

Large health databases contain electronically recorded patient health care data and constitute another important data source for pharmacoepidemiological research. There are two main types: administrative databases and physician-based databases.

Administrative databases have been set up for the administration of reimbursement payments to health care providers.[3] In North America they have been used since 1980 for pharmacoepidemiological research.[11] Administrative databases usually contain patient information from two or more separate files, which are linked via a unique and anonymized patient-identifier (e.g. the social security number). These files usually contain information on patient's demographics, drug dispensations from pharmacies, hospitalizations, and ambulatory physician visits. Record linkage of these files enables to create person-based longitudinal files for a specific research question. Some databases such as the Canadian Saskatchewan's Health Databases allow record linkage with cancer registries and thus the study of potential carcinogen drug effects. Other examples of administrative databases include the US Group Health Cooperative databases, the Kaiser Permanente databases, or the Medicaid databases.[3]

Physician-based databases have been developed by researchers and consist of data entered by general practitioners (GPs) into their practice computers.[3,11] The best known example is the United Kingdom (UK) General Practice Research Database (GPRD). The GPRD was started in June 1987 under the name Value Added Medical Products (VAMP) research databank. At that time, VAMP provided GPs with practice computers and the corresponding software with the idea to gradually replace the written medical record. In return, GPs agreed to undertake a training in standardized data entry and to provide anonymized patient data to a central database for subsequent use in public health research. During the 1990, VAMP research databank underwent several organizational and management changes. In 1994 the database was donated to the UK Department of Health and renamed GPRD.[3,12]

Very recently, in April 2012 the GPRD has been transferred into the Clinical Practice Research Datalink (CPRD), the new English National Health Service (NHS) observational data and interventional research service, jointly funded by the NHS National Institute for Health Research (NIHR) and the Medicines and Healthcare products Regulatory Agency (MHRA).[13] A more detailed description of the characteristics of the GPRD is found in the methods section of the studies in this thesis. Other examples of physician-based databases include The Health Improvement Network (THIN) database, which also uses medical records from UK patients, or the Intercontinental Marketing Services (IMS) Disease Analyzer (previously known as MediPlus) databases, which contains patient records from the UK, Germany, and France.[14]

1.1.3 Study designs

Case-control studies

Case-control studies start with the outcome (e.g. the disease) and look backward in time for exposures that might have caused the outcome. The investigator defines a group of patients with a certain outcome of interest (e.g. myocardial infarction) (the cases) and another group of patients without the outcome (the controls). Then, through medical record review, interviews, or other means, the investigator compares the prevalence of a certain condition (e.g. hypertension) or the exposure to a certain drug (e.g. statins) between cases and controls and calculates a measure of association, the odds ratio (OR). If the OR is greater than 1, then the exposure represents a risk factor for the outcome, conversely if the OR is lower than 1, then the exposure is regarded as a protective factor. An OR of 1 signifies that the exposure is equally distributed between cases and controls. Case-control studies are especially useful for rare outcomes (e.g. autism) or outcomes that take a long time to develop (e.g. cancer). Such studies usually require less time, effort, and money than would cohort studies. On the other hand, a major concern in case-control studies is the choice of an appropriate control group. Controls should be similar to cases in all important respects except for not having the outcome of interest.[15,16]

Cohort studies

Cohort studies proceed in a logical sequence: from exposure to outcome. In cohort studies the investigator identifies two groups: one with the exposure of interest (e.g. use of antipsychotics) and another one without. He then follows both groups forward in time to determine the outcome of interest (e.g. stroke). If the exposed group develops a higher incidence of the outcome than the unexposed group, then the exposure is associated with an increased risk, otherwise the exposure has protective properties.[16,17] There are two types of cohort studies: prospective and retrospective ones. In prospective cohort studies the investigators assesses the exposure at baseline and follows individuals forward in time to study the outcome of interest, as described above. In retrospective cohort studies the investigator starts the study at the time follow-up has already been completed. Retrospectively, eligible individuals are identified, the cohort is composed and exposure is assessed at baseline. Subsequently, occurrence of outcome is studied during the historical observational period.[18] Cohort studies are useful to study rare exposures. Another advantage is that they allow investigating multiple outcomes after a single exposure (e.g. cigarette smoking and the development of chronic obstructive pulmonary disease (COPD), lung cancer, or ischemic heart disease). On the other hand, cohort studies have also limitations. Differential losses of follow-up between exposed and unexposed individuals can bias results. Another problem (particularly with longitudinal studies that continue for decades) is that exposure status of study individuals may change over time (e.g. switch to another antihypertensive agent).[17,19]

Nested case-control studies

The nested case-control study is a relatively new study design and can basically be regarded as a case-control study within a cohort study. It starts analogously to a cohort study with a defined cohort of individuals that is followed forward in time to study the occurrence of a certain outcome. But instead of analyzing person-time data for everyone in the cohort (as done in the classic cohort study) the analysis is conducted as a case-control study, where for each case (i.e. each individual who developed the outcome), a defined number of controls (i.e. individuals who did not develop the outcome during follow-up) is selected from the initial cohort. The number of selected controls per case is usually 4, but occasionally may go up to 10. Nested case-control studies have several advantages compared to classical cohort studies.

First, they allow better control for potential confounders (cf. chapter 1.1.4) such as age, calendar time or disease duration through matching. Second, they are less expensive to perform and the collection and analysis of data are less time-consuming Third, they allow better quantification of drug exposure with respect to time. This is important because the traditional (time-independent) Cox proportional hazard model (which is commonly used for the analysis of data from cohort studies) does not account for the time-dependent nature of drug use over time. [20,21]

Other study designs

Other, more recent study designs include the case-crossover and the case-time-control design. They are particularly useful for studying intermittent drug exposures with transient effects and are less susceptible to confounding by indication (cf. chapter 1.1.4). In case-crossover studies the exposure history of each case is used as his or her own control. Hence, cases and controls are comparable in most of their known and unknown confounders except for intermittent exposures. This eliminates the problem of between-person confounding by constant characteristics. The case-time-control design is a refinement of the case-crossover design. It uses exposure history from a conventional control group to estimate and adjust for the bias from temporal changes in prescribing.[22]

1.1.4 Bias

Bias in epidemiology refers to a systematic error which results in an incorrect estimate of the measure of association. Roughly, three broad categories of bias can be distinguished: selection bias, information bias, and confounding.

Selection bias

Selection bias is a systematic error that derives from procedures used to select subjects and from factors that influence study participation. It comes about when the association between exposure and outcome differs for those who are and those who are not included in the study. As the association between exposure and outcome among those who are not included in the study is usually unknown, the presence of selection bias must usually be inferred, rather than observed.[23] One example of selection bias is the ‘healthcare access bias’. This type of bias is introduced when

patients admitted to an institution do not represent the cases originated in the community. This may occur when a healthcare organization is organized in increasing levels of complexity (e.g. primary, secondary, and tertiary care) and complex cases are automatically referred to tertiary care or when patients by cultural, geographical, or economic reasons show a differential degree of access to an institution.[24] Another example of selection bias is the 'detection bias'. This type of bias is introduced when a specific outcome is diagnosed preferentially in individuals who are exposed to the drug that may be associated with that outcome.[25]

Information bias

An information bias in a study can arise when the information collected from study subjects is erroneous. If a variable (e.g. the exposure) is measured on a categorical scale and the error leads to a patient placed in a wrong category, then this information if often referred to as being misclassified. Misclassification of study subjects can be differential or non-differential. Differential misclassification bias is present when misclassification is different in the groups to be compared. Alternatively, non-differential misclassification bias is present when the misclassification is the same across the groups to be compared, for example, exposure is equally misclassified in cases and controls.[23-25] A common type of information bias is 'recall bias'. This type of bias occurs in case-control studies where a subject is interviewed to obtain exposure information after the outcome has occurred. For example in a case-control study that aims at studying the influence of different exposures during pregnancy on the risk of developing a birth defect, mothers of babies with a birth defect (cases) may be more likely to recall their exposure histories than mothers with a healthy baby (controls) because the birth defect serves as a stimulus for the mother to consider potential causes.[23] Another type of information bias is 'protopathic bias'. This type of bias occurs when a drug is inadvertently prescribed for an early manifestation of a disease that has not yet been diagnosed. When the disease is later discovered, a causal association between the drug and the disease may be incorrectly inferred. As an example, in a case-control study of estrogens and endometrial cancer, about 10% of the women exposed to estrogens specifically stated that the oral estrogen had been prescribed by their physician to treat an episode of uterine bleeding.[26]

Confounding

Confounding is a central issue for epidemiologic studies. Basically, confounding can be thought of as a mixing of effects. A confounding variable must have an effect and must be imbalanced between the exposure groups to be compared. In order for a variable to be considered as a confounder, it must meet three specific criteria: (1) it has to be associated with the outcome (either as a cause or a proxy for a cause but not as an effect of the outcome), (2) it has to be associated with the exposure and (3) it must not be an effect of the exposure.[23,25] As an example, a study in the 1960s showed a remarkable trend in prevalence of Down's syndrome with increasing birth order.[27] However, a third variable – the mother's age – was not taken into account. Mother's age is a confounding factor in so far as children with higher birth order tend to be born to older mothers and higher maternal age is an independent risk factor for Down's syndrome.[23] Confounding can be prevented at the design stage of a study by matching cases and controls on a potential confounding variable (in case-control studies), restriction of the study population to subjects who might have the same or nearly the same value for a potential confounder, or randomization, i.e. the random assignment of study subjects to experimental groups (in randomized controlled trials). In the analysis confounding can be controlled for by stratifying results at the level of the potential confounder or by performing multivariate analysis.[23,24] A particular type of confounding bias is 'confounding by indication'. This type of confounding bias is present if the indication for the prescription of a drug under study is also a determinant of the outcome of interest. Generally, a drug is more likely to be prescribed to a patient with more severe disease who, in turn, is more likely to experience an adverse outcome of the disease. Thus, patients prescribed the drug under study will have higher incidence rates of the outcome than those not prescribed the drug. This could simply be a reflection of the effect of disease severity, rather than of the drug itself.[3] As an example, in the study of the association between cimetidine and gastric cancer, the indication peptic ulcer is regarded as the potential confounder.[28]

1.2 ALZHEIMER'S DISEASE

Alzheimer's disease (AD) is a chronic progressive neurodegenerative disorder and one of the most disabling and burdensome health conditions worldwide. It is the most common form of dementia, accounting for about 60–80% of all cases.[29] The disease, which was firstly described by the German pathologist Alois Alzheimer more than 100 years ago (in 1906), is clinically characterized by a gradual decline in cognitive function, the presence of psychiatric symptoms, and increasing difficulties in performing activities of daily living (ADL).[30]

1.2.1 Epidemiology

In 2006, the number of people affected by AD was 26.6 million worldwide. By 2050 this number is expected to increase fourfold to 106.8 million.[31] China and its developing western-Pacific neighbors have the highest numbers of affected individuals, followed by western Europe, and North America.[32] In the United States approximately 13% of those aged ≥65 years have AD and it is estimated that every 68 seconds a new case is added. By 2050, there's expected to be one new case every 33 seconds, or almost 1 million new cases per year.[29] Generally, there are more women with AD than men. This is mainly explained by the fact, that women live on average longer than men.[33] The incidence of AD increases dramatically with increasing age and doesn't seem to level off after the age of 90.[34] In Switzerland, 107,000 people had a diagnosis of AD or another dementia form in 2010. It is estimated that this number will increase to approximately 200,000 by 2030 and 300,000 by 2050.[35]

1.2.2 Pathogenesis

The two core pathological hallmarks of AD are plaques, composed of *β*-amyloid (A*β*) peptides and neurofibrillary tangles, composed of hyperphosphorylated tau protein. A*β* peptides are natural products of metabolism consisting of 36–43 amino acids. They originate from proteolysis of the amyloid precursor protein (APP) by the sequential enzymatic actions of *β*-site APP-cleaving enzyme 1 (BACE-1), a *β*-secretase, and *γ*-secretase, a protein complex with presenilin 1 at its catalytic core. The so-called 'amyloid cascade hypothesis' suggests that an imbalance between

production and clearance, and aggregation of peptides causes A*β* to accumulate and this excess may be the initiating factor of synaptic dysfunction and neuronal cell death in AD.[36,37] Originally, only plaques and amyloid-fibrils were thought to cause toxicity, but recent research has shown that soluble oligomers (2–6 peptides) and intermediate amyloids (assemblies of coalesced peptides) are the most neurotoxic forms of A*β*.[38] The major constituent of neurofibrillary tangles is an abnormally hyperphosphorylated and aggregated form of tau. Tau is an abundant soluble protein in axons that promotes assembly and stability of microtubules and vesicle transport. Hyperphosphorylated tau is insoluble and aggregates into paired helical filament structures, the neurofibrillary tangles. Additionally, hyperphosphorylated tau destabilizes microtubule structure. Both procedures lead to impaired axonal transport and thus disruption of structure and function of neurons.[36,37] Similarly to A*β* oligomers, intermediate aggregates of hyperphosphorylated tau are cytotoxic and impair cognition.[37,39,40] The number of neurofibrillary tangles is a pathologic marker of the severity of AD.[37] Evidence from in-vitro studies suggests that A*β* accumulation triggers tau aggregation.[41,42]

1.2.3 Diagnosis

A definite diagnosis of AD can only be made post-mortem. Clinically, only a probable diagnosis is possible at present. For a clinical diagnosis of AD a detailed history of the symptoms is taken (either from the patient, partner or caregiver), and a clinical, neurological, and psychiatric examination is performed. Laboratory studies, such as thyroid-function tests, serum vitamin $B_{12,}$ or folate levels are recommended to identify secondary causes of dementia or common co-existing disorders. Neuroimaging plays an important role in the diagnosis of AD. Computed tomography (CT) or magnet resonance imaging (MRI) are useful to detect intracranial lesions or to exclude alternative causes of dementia (e.g. brain tumor or subdural hematoma). Neuroimaging is also helpful to measure cerebral atrophy or to detect cerebrovascular disease (e.g. cerebral infarcts or white matter lesions).[30,36,43] The clinical diagnosis of AD is made according to the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) and the Alzheimer's Disease and Related Disorders Association (ADRDA) criteria.[44] Recently, the National Institute on Aging (NIA) and the Alzheimer's Association released updated diagnostic

criteria for AD.[45] These new criteria establish that AD exists on a continuum and encompasses not only dementia but also a preclinical phase and a phase of mild cognitive impairment due to AD.[46] Additionally, these new criteria promote the incorporation of biomarkers into routine diagnosis of AD. The major AD biomarkers that have been widely investigated include (1) biomarkers of brain Aβ protein deposition: low cerebrospinal fluid (CSF) Aβ_{42} and positive positron emission tomography (PET) amyloid imaging; (2) biomarkers of downstream neuronal degeneration or injury: elevated CSF tau (both total tau and phosphorylated tau), decreased ^{18}fluorodeoxyglucose (FDG) uptake on PET in tempo-parietal cortex, and disproportionate atrophy on structural magnetic resonance imaging in medial, basal, and lateral temporal lobe, and medial parietal cortex.[45]

1.2.4 Treatment

At present, no curative treatment for AD exists. Currently available treatment options – acetylcholinesterase inhibitors (AChEI) and memantine – are symptomatic and do not halt or reverse disease progression. Tacrine was the first AChEI approved for treatment of AD in 1993, but due to the risk of serious hepatotoxicity and controversial efficacy it is rarely used in practice now.[47] The other AChEIs donepezil, rivastigmine and galantamine are licensed for the treatment of mild to moderate AD and constitute the mainstay of drug therapy in AD. AChEIs delay the degradation of acetylcholine released into the synaptic cleft and so enhance cholinergic neurotransmission. The efficacy of these drugs has been studied in more than 30 placebo-controlled randomized clinical trials (RCTs). Most trials had a duration of six months and included patients with mild to moderate disease (mini-mental state examination [MMSE] score of 10–26). Results were a modest positive effects on cognition (1.5–2 points on the MMSE over 6–12 months), with additional short-term (3–6 months) improvement in global outcome and stabilization of function over this period.[36] There's no evidence that these drugs differ in efficacy.[48] Memantine is an N-methyl-D-aspartate (NMDA)-receptor antagonist, which is licensed for the treatment of moderate to severe AD. It is believed to modulate the effects of pathologically elevated levels of glutamate that may lead to neuronal dysfunction. A pooled analysis of three RCTs showed modest positive effects on cognitive and behavioral symptoms and improved ADLs at six months in patients with moderate to severe AD.[49] Studies

comparing AChEI monotherapy with the combination of memantine and AChEIs showed that the combination is superior in slowing the progression of cognitive and functional decline[50] and delaying time to nursing home admission.[51] Behavioral signs, such as aggression, agitation, and psychosis (hallucinations and delusions) in patients with dementia are commonly treated with antipsychotic drugs, but benefits are moderate, and serious adverse events include sedation, parkinsonism, chest infections, ankle edema, and an increased risk of stroke and death.[36] Additionally, recent research suggests that use of antidepressant drugs to treat co-morbid depression in patients with AD may provide little benefit but increase the risk of drug-related adverse events.[52]

1.2.5 Risk and protective factors

Several risk factors have been linked to the development of AD, though with partially weak or controversial evidence. Well established risk factors are advancing age (which is certainly the most important one) and genetics (cf. chapter 1.2.6). Other potential risk factors include a history of head injury,[53] depression,[54] a low cognitive reserve (which depends on education, occupation, and mental activities),[55] low physical activity and exercise,[56] midlife obesity,[57] alcohol consumption,[58] and smoking.[59] Additionally, a number of cardiovascular (CV) diseases such as atrial fibrillation,[60] heart failure,[61] stroke,[62] midlife hypertension,[63] midlife hypercholesterolemia,[64] and diabetes mellitus (DM)[65] have also been associated with an increased risk of developing AD. On the other hand, there's some evidence that supplementary intake of vitamin B_{12} and folate,[66] antioxidants such as vitamin C and E,[67] ω-3 fatty acids,[68] or moderate wine consumption,[69] could reduce the risk of developing AD, but data so far are not conclusive to make any general recommendations. However, it has been shown that a Mediterranean diet has the potential to reduce the risk of AD.[70] Additionally, certain drugs such as non-steroidal anti-inflammatory drugs (NSAIDs), statins or estrogens (hormone replacement therapy) have been associated with a reduced risk of developing AD in observational studies but failed to show any benefit in large RCTs.[43] However, there's some promising evidence that certain anti-hypertensive drugs such as angiotensin (AT)-II receptor antagonists could lower the risk of developing AD.[71]

1.2.6 Genetics

Genetics play an important role as risk factors in both, early-onset (or familial) AD, which is characterized by a disease onset before the age of 65 years, and late-onset (or sporadic) AD with a disease onset after the age of 65 years. Early-onset AD is an autosomal dominant disorder. It is caused by mutations in three genes: the APP, presenilin 1, and presenilin 2 on chromosomes 21, 14 and 1, respectively.[30] However, early-onset AD accounts for less than 5% of all AD cases.[72] For late-onset AD, the only known genetic risk factor is apolipoprotein E (ApoE), located on chromosome 19. ApoE acts as a cholesterol transport protein in the brain. Three gene forms exist (ApoE ε2, Apoe E ε3, and Apo E ε4).[30,43] Homozygous carriers of the ε4 allele have a threefold increased risk of developing late-onset AD, heterozygous carriers a 15-fold.[73]

1.3 VASCULAR DEMENTIA

Vascular dementia (VD) is the second most common form of dementia in the elderly after AD, accounting for about 10–20% of all dementia cases.[74,75] Similarly to AD, the prevalence of VD increases continuously with increasing age and affects about 1.6% of those aged 65 years or more in Europe.[75] As the name implies the common cause of VD is the CVD lesion resulting from vascular and circulatory pathology. The primary lesions of VD are intracerebral hemorrhage, intracerebral ischemia, and combinations thereof. The ischemic forms of VD are generally divided into 'large-vessel' and 'small-vessel' disease, although some degree of overlap usually exists. Large vessel disease results from repeated strokes leading to multi-infarct dementia, or to a single strategic cortico-subcortical stroke affecting mainly anterior or posterior cerebral artery territories. Small vessel disease affects the small vessels of the brain and causes both lacunar strokes and Binswanger disease. The latter is characterized by incomplete ischemia of the periventricular white matter.[76,77] The clinical diagnosis of VD is made according to the National Institute of Neurological Disorders and Stroke (NINDS) and the Association Internationale pour la Recherche et l'Enseignement en Neurosciences (AIREN) criteria.[78] According to these criteria, three elements are required: (1) cognitive loss, (2) presence of cerebrovascular lesions as shown by brain imaging (or as inferred from a history of stroke and presence of focal neurological signs), and (3) onset of dementia within three months of a symptomatic stroke. (The latter condition does not apply for patients with subacute VD). Additionally, other causes of dementia such as AD must be excluded (although AD and VD often coexist[79]).[77] So far, no drug has been approved for the treatment of VD. However, AChEIs[80-82] and memantine[83] have been studied in patients with VD. Although these drugs were shown to produce some benefit on cognition, the effect size was rather small and of uncertain clinical significance.[84] Prevention strategies for VD should focus on the prevention of stroke and CV diseases with attention to control of risk factors such as hypertension, DM, hypercholesterolemia, and hyperhomocysteinemia.[77] Promising results have so far been demonstrated with the calcium channel blocker nitrendipine,[85] angiotensin converting enzyme (ACE) inhibitiors, and diuretics.[86] Additionally, AT-II receptor antagonists may be particularly effective because of their additional anti-ischemic effects in the brain.[87,88]

CHAPTER 2

AIMS OF THE THESIS

2 AIMS OF THE THESIS

The overall aim of this thesis was to contribute to the understanding of the natural history of the two most common dementia subtypes AD and VD, by using data from the GPRD, a large and well-established physician-based primary care database from the UK.

The aim of the first study (3.1) was to provide new data on the incidence of AD and VD in the UK and quantify the prevalence of co-morbidities and drugs used prior to the time of diagnosis. Current UK estimates of the incidence of AD or VD are based on diagnostic limitations of the 1990s and there's conflicting evidence on whether patients with AD or VD have more or less co-morbidities than non-demented individuals. Moreover, little is known about differences in drug use between patients with AD or VD and patients without dementia.

In the second study (3.2) we aimed at investigating the influence of the antidiabetic drug metformin on the risk of developing AD. Recent data from in vitro and animal studies suggest that this drug ameliorates typical AD pathology and thus could have a protective effect on the development of AD.

In the third and fourth study we followed patients with AD or VD forward in time to see whether they developed more or less often a certain disease (complication) of interest than patients without dementia. The diseases of interest in this case were seizures/epilepsy in Study 3.3 and ischemic stroke, hemorrhagic stroke or transient ischemic attack (TIA) in Study 3.4 Additionally, we aimed at studying the role of potential risk factors on the risk of developing such a disease of interest, in particular the role of anti-dementia drugs on the risk of seizures or epilepsy (Study 3.3) and the role of antipsychotic drugs on the risk of ischemic stroke, hemorrhagic stroke or TIA (Study 3.4). For both drugs there's limited or conflicting evidence from the literature on whether they increase the risk of the corresponding diseases or not.

CHAPTER 3

DEMENTIA PROJECT

3 DEMENTIA PROJECT

3.1 EPIDEMIOLOGY, CO-MORBIDITIES AND DRUG USE OF PATIENTS WITH ALZHEIMER'S DISEASE OR VASCULAR DEMENTIA IN THE UK

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J Alzheimers Dis 2012; submitted

3.1.1 Abstract

Background: Epidemiologic studies on age-specific incidence rates (IRs) separating Alzheimer's disease (AD) and vascular dementia (VD) in the UK are scarce. We sought to assess IRs of AD and VD in the UK and to compare co-morbidities and drug use between patients with AD, VD, or without dementia.

Methods: We identified cases aged ≥65 years with an incident diagnosis of AD or VD between 1998 and 2008 using the General Practice Research Database (GPRD). We assessed IRs, stratified by age and sex, matched one dementia-free control patient to each demented patient, and analyzed co-morbidities and drug use.

Results: We identified 7,086 AD and 4,438 VD cases. Overall, the IR of AD was 1.59/1,000 person-years (py) (95% CI 1.55–1.62) and the IR of VD 0.99/1,000 py (95% CI 0.96–1.02). For AD, IRs were higher for women than for men, but not for VD. Except for orthostatic hypotension, the prevalence of all cardiovascular (CV) co-morbidities and exposure to CV drugs was lower in patients with AD than in corresponding controls, whereas the opposite was true for VD.

Conclusions: The prevalence of CV diseases was lower in patients with AD. This may be a true finding or the result of diagnostic bias, i.e. demented patients with CV diseases may be more likely to be diagnosed with VD than AD.

3.1.2 Introduction

Dementia is one of the main causes of disability in elderly people.[89] In the UK, currently more than 820,000 people (about 1.3% of the population) have dementia, and that this number is estimated to increase to over 1,735,000 by the year 2051.[90,91] Dementia poses a heavy socioeconomic burden, generating annual costs of more than £23 billion in the UK.[91] The MRC CFA Study, a large population-based study assessing the prevalence and incidence of dementia in the UK, estimated some 180,000 new dementia cases in England and Wales each year.[92] However, UK data on the incidence of the most common subtypes of dementia, i.e. Alzheimer's disease (AD) and vascular dementia (VD), are based on only a few small studies from the 90s with little statistical power and diagnostic limitations of that time.[93,94]

Many older patients – whether demented or not – suffer from co-morbidities. Previous studies observed that patients with AD had generally less co-morbidities than non-demented patients, and it was suggested that patients with AD represent the healthiest group of demented patients.[95,96] More recent studies, however, reported significantly higher prevalence rates of co-morbidities for patients with AD.[97,98] Moreover, comparison of drug use between demented and non-demented patients revealed that demented patients use more central nervous system (CNS) active drugs, but fewer cardiovascular drugs than non-demented patients.[99] However, little is known about differences in drug use between patients with AD or VD and those without dementia.

We assessed incidence rates of AD and VD in the UK using primary care data, and we compared the prevalence of co-morbidities and drug use between patients with AD or VD and a comparison group without dementia.

3.1.3 Methods

Data source

We used the UK-based General Practice Research Database (GPRD) which was established in around 1987 and encompasses data on some 11 million patients who are or were registered with selected general practitioners (GPs).[100] The patients enrolled in the GPRD are representative of the UK population with regard to age, sex, geographic distribution, and annual turnover rate. The GPs have been trained to record medical information for research purposes in a standardized manner. The

information recorded includes patient demographics and characteristics (e.g. age, sex, height, weight, smoking status), symptoms, medical diagnoses, referrals to consultants, and hospitalizations. Since the doctors generate drug prescriptions directly with the computer using a coded drug dictionary, all recorded prescriptions include the name of the preparation, route of administration, dose of a single unit, number of units prescribed and, in most instances, intake regimen. The database has been described in detail elsewhere[101,102] and validated extensively.[103,104]

The study was approved by ISAC, the Independent Scientific Advisory Committee for Medicines and Healthcare products Regulatory Agency (MHRA) database research.

Case selection and validation

Based on Read codes, we identified patients aged ≥ 65 years with a first-time diagnosis of AD, VD, or any unspecified dementia recorded between January 1998 and September 2008, or who received a first-time prescription for an acetylcholinesterase inhibitor (i.e. donepezil, rivastigmine, galantamine, or tacrine) or the N-methyl-D-aspartate (NMDA)-receptor antagonist memantine, i.e. two treatments mainly used for AD. The date of the first-time diagnosis or the first-time prescription for one of the above-mentioned drugs, whichever came first, will subsequently be referred to as 'index date'. Patients with less than three years of active history in the database prior to the index date and those with a history of HIV/AIDS, alcoholism, drug abuse, multiple sclerosis, motor neuron disease, or Down's syndrome prior to the index date were excluded.

Since we intended to differentiate between the dementia subtypes AD and VD, we aimed at increasing the probability of including only well-defined cases of each subtype in the study population. We therefore manually reviewed 500 patient profiles and developed an algorithm which we applied to all potential AD, VD or unspecified dementia cases. To be included as an eligible AD case, a patient was required to have either (1) a diagnosis of AD followed by at least one prescription for an AD drug or vice versa, (2) a diagnosis of unspecific dementia followed by at least two prescriptions for an AD drug, (3) at least two recordings of an AD diagnosis, (4) an AD diagnosis after a specific dementia test (e.g. Mini Mental State Examination [MMSE], Clock Drawing Test [CDT], or Abbreviated Mental Test [7-Minute Screen]), a referral to a specialist (e.g. neurologist, geriatrician or psycho-geriatrician), or an assessment based on neuro-imaging technique (e.g. magnet resonance imaging

[MRI], computed tomography [CT], or single photon emission CT SPECT]), or (5) an AD diagnosis preceded or followed by any recorded dementia symptoms (e.g. memory impairment, aphasia, apraxia, or agnosia). In addition, cases with a recording of any other specific dementia diagnosis (e.g. VD, Pick's disease, or Lewy body dementia [LBD]) after the index date were not eligible, as well as those with a stroke diagnosis within two years prior to the index date. According to the NINDS-AIREN criteria[78] for the diagnosis of VD, patients who develop signs of dementia within three months following stroke are likely to have VD. However, as the diagnosis of VD in the UK is made by specialists, GPs often get this information with delay and therefore time of recording in the GPRD is often not consistent with the actual time of diagnosis; thus, we decided to expand our time window to two years. Analogously, to be included as an eligible VD case, a patient was required to have either (1) a diagnosis of VD or unspecified dementia within two years after a stroke, (2) at least two recordings of a VD diagnosis, (3) a VD diagnosis after a specific dementia test, a referral to a specialist, or an assessment based on neuro-imaging technique, or (4) a VD diagnosis preceded or followed by any recorded dementia symptoms. In addition, cases with a recording of any other subtype dementia diagnosis (e.g. AD, Pick's disease, or LBD) or a prescription of a specific drug to treat AD after the index date were not eligible.

This algorithm was a modified version of two case identification procedures from previous studies conducted using the GPRD.[105,106] To validate the algorithm, we sent a questionnaire to GPs for a random sample of 60 AD and 60 VD cases to get additional information on the clinical circumstances and the diagnostic steps taken. A copy of this questionnaire is provided in the appendix. In 79% of the AD cases the GPs confirmed the recorded AD diagnosis, whereas in the other AD cases the diagnosed dementia subtype was either different, not further specified, or the case did not have confirmed dementia. For VD, the corresponding confirmation rate was 74%.

Incidence rates

We estimated incidence rates (IRs) of AD and VD in the GPRD population for patients aged 65 years or more between January 1998 and September 2008, stratified by age (5-year age-groups) and sex. IRs were calculated as the number of

incident cases divided by the total number of persons-years (py) at risk with 95% confidence intervals (CIs).

Controls

From the base population we identified for each case with AD or VD one control patient without any type of dementia and without any prescription for a specific drug to treat AD at any time. Controls were matched to cases on age (same year of birth), sex, calendar time (same index date), GP, and number of years of recorded history in the database. We applied the same exclusion criteria to controls as to cases.

Co-morbidities and drug use

We assessed the prevalence of various co-morbidities recorded prior to the index date in cases with AD or VD as well as in the corresponding dementia-free controls. The co-morbidities of interest were congestive heart failure, atrial fibrillation, ischemic heart disease, hypertension, diabetes mellitus, hypercholesterolemia, orthostatic hypotension, chronic obstructive pulmonary disease (COPD), osteoporosis, inflammatory bowel disease, thyroid disorders, rheumatoid arthritis, epilepsy/seizures, and depression. We assessed the exposure to various drugs to treat these co-morbidities, whereby we focused on use during the last year prior to the index date.

Statistical analysis

We conducted conditional logistic regression analyses to compare co-morbidities and drug use between cases and controls using the statistical software SAS (version 9.2, SAS Institute Inc., Cary, NC, USA).

3.1.4 Results

Based on Read codes we identified 24,734 patients with a first-time diagnosis of AD, VD, unspecified dementia, or a first-time prescription for a drug used to treat AD. After applying the above described algorithm, a total of 7,086 AD cases (28.6%) and 4,438 VD cases (17.9%) remained. The characteristics are displayed in Table 3.1-1.

Incidence rates

The IRs of AD were higher for women than for men across all age categories, most pronounced in the higher ages. By contrast, the IRs of VD were similar for men and women in all age categories, except for those aged 70–74 or 85–89 years, where it was (slightly) higher for men. Overall, the IR of AD was 1.59/1,000 py (95% CI 1.55–1.62), and the IR of VD 0.99/1,000 py (95% CI 0.96–1.02). For both AD and VD, IRs increased with increasing age, with the highest age-specific IR for AD in those aged 85–89 years (3.99/1,000 py, 95% CI 3.79–4.20) (Table 3.1-2).

Co-morbidities and drug use

Except for orthostatic hypotension, the prevalence of all cardiovascular (CV) co-morbidities was lower in patients with AD than in the corresponding controls, whereas in patients with VD the contrary was observed. COPD and rheumatoid arthritis were also less prevalent among AD cases. Epilepsy/seizures or depression were both more prevalent among AD or VD cases than in corresponding controls, though the difference was more pronounced between patients with VD and their corresponding controls (Table 3.1-3).

A similar observation was made regarding the exposure to various drugs to treat these co-morbidities. CV drugs were less commonly prescribed in patients with AD than in the corresponding controls, whereas in patients with VD – except for some drugs that were similarly frequently prescribed – the opposite was true. Corticosteroids were also less commonly prescribed in patients with AD. In patients with VD the exposure to CNS drugs was distinctively higher than in the corresponding controls, whereas in patients with AD this was particularly true for antidepressants and antipsychotics/neuroleptics (Table 3.1-4).

Table 3.1-1: Characteristics of patients with Alzheimer's disease or vascular dementia and corresponding controls

	Alzheimer's disease						Vascular dementia					
	No. of cases (%) (n = 7086)		No. of controls (%) (n = 7086)		OR (95% CI)		No. of cases (%) (n = 4438)		No. of controls (%) (n = 4438)		OR (95% CI)	
Age [years]												
65–69	410	(5.8)	411	(5.8)	NA		157	(3.5)	156	(3.5)	NA	
70–74	895	(12.6)	895	(12.6)	NA		441	(9.9)	444	(10.0)	NA	
75–79	1639	(23.1)	1638	(23.1)	NA		882	(19.9)	880	(19.8)	NA	
80–84	2029	(28.6)	2034	(28.7)	NA		1254	(28.3)	1266	(28.5)	NA	
85–90	1477	(20.8)	1475	(20.8)	NA		1123	(25.3)	1114	(25.1)	NA	
≥90	636	(9.0)	633	(8.9)	NA		581	(13.1)	578	(13.0)	NA	
Sex												
Male	2198	(31.0)	2198	(31.0)	NA		1801	(40.6)	1801	(40.6)	NA	
Female	4888	(69.0)	4888	(69.0)	NA		2637	(59.4)	2637	(59.4)	NA	
Smoking status												
None	4182	(59.0)	4029	(56.9)	1.00	(Reference)	2370	(53.4)	2497	(56.3)	1.00	(Reference)
Current	597	(8.4)	669	(9.4)	0.85	(0.76–0.96)	522	(11.8)	382	(8.6)	1.48	(1.28–1.72)
Past	1626	(23.0)	1692	(23.9)	0.92	(0.84–1.00)	1145	(25.8)	1133	(25.5)	1.08	(0.97–1.20)
Unknown	681	(9.6)	696	(9.8)	0.94	(0.82–1.07)	401	(9.0)	426	(9.6)	0.97	(0.82–1.16)
BMI [kg/m^2]												
≤18.4	308	(4.4)	162	(2.3)	1.49	(1.21–1.82)	197	(4.4)	107	(2.4)	1.65	(1.29–2.10)
18.5–24.9	2907	(41.0)	2243	(31.7)	1.00	(Reference)	1663	(37.5)	1456	(32.8)	1.00	(Reference)
25–29.9	1762	(24.9)	2189	(30.9)	0.61	(0.56–0.67)	1106	(24.9)	1356	(30.6)	0.70	(0.63–0.78)
≥30	564	(8.0)	970	(13.7)	0.44	(0.39–0.50)	439	(9.9)	550	(12.4)	0.68	(0.59–0.79)
Unknown	1545	(21.8)	1522	(21.5)	0.79	(0.72–0.87)	1033	(23.3)	969	(21.8)	0.96	(0.85–1.09)

No. = Number; OR = Odds Ratio; CI = Confidence Interval; BMI = Body Mass Index; NA = Not Applicable

Table 3.1-2. Incidence rates of Alzheimer's disease and vascular dementia (per 1,000 person-years), stratified by age (5-year age-groups) and sex

			Alzheimer's disease		Vascular dementia	
	Age-group [years]	**Person-years at risk**	**No. of Cases**	**IR per 1,000 person-years (95% CI)**	**No. of Cases**	**IR per 1,000 person-years (95% CI)**
Men	65−69	558480	162	0.29 (0.25−0.34)	85	0.15 (0.12−0.19)
	70−74	490707	346	0.71 (0.63−0.78)	244	0.50 (0.44−0.56)
	75−79	393264	571	1.45 (1.34−1.58)	404	1.03 (0.93−1.13)
	80−84	253286	587	2.32 (2.14−2.51)	494	1.95 (1.79−2.13)
	85−89	120334	403	3.35 (3.04−3.69)	417	3.47 (3.15−3.81)
	≥90	45893	129	2.81 (2.37−3.34)	157	3.42 (2.93−4.00)
	Total	1861964	2198	1.18 (1.13−1.23)	1801	0.97 (0.92−1.01)
Women	65−69	650962	248	0.38 (0.34−0.43)	72	0.11 (0.09−0.14)
	70−74	606203	549	0.91 (0.83−0.98)	197	0.32 (0.28−0.37)
	75−79	544593	1068	1.96 (1.85−2.08)	478	0.88 (0.80−0.96)
	80−84	412040	1442	3.50 (3.32−3.68)	760	1.84 (1.72−1.98)
	85−89	249801	1074	4.30 (4.05−4.56)	706	2.83 (2.63−3.04)
	≥90	140967	507	3.60 (3.30−3.92)	424	3.01 (2.74−3.31)
	Total	2604566	4888	1.88 (1.82−1.93)	2637	1.01 (0.97−1.05)
All	65−69	1209441	410	0.34 (0.31−0.37)	157	0.13 (0.11−0.15)
	70−74	1096909	895	0.82 (0.76−0.87)	441	0.40 (0.37−0.44)
	75−79	937857	1639	1.75 (1.67−1.83)	882	0.94 (0.88−1.00)
	80−84	665326	2029	3.05 (2.92−3.19)	1254	1.88 (1.78−1.99)
	85−89	370136	1477	3.99 (3.79−4.20)	1123	3.03 (2.86−3.22)
	≥90	186860	636	3.40 (3.15−3.68)	581	3.11 (2.87−3.37)
	Total	4466529	7086	1.59 (1.55−1.62)	4438	0.99 (0.96−1.02)

No. = Number; IR = Incidence Rate; CI = Confidence Interval

Table 3.1-3: Prevalence of co-morbidities in patients with Alzheimer's disease or vascular dementia and corresponding dementia-free controls

Co-morbidities	Alzheimer's disease			Vascular dementia		
	No. of Cases (%) (n = 7086)	No. of Controls (%) (n = 7086)	OR (95% CI)	No. of Cases (%) (n =4438)	No. of Controls (%) (n =4438)	OR (95% CI)
Cardiovascular						
Congestive heart failure	448 (6.3)	677 (9.6)	0.63 (0.55–0.71)	600 (13.5)	465 (10.5)	1.35 (1.18–1.54)
Atrial fibrillation	517 (7.3)	741 (10.5)	0.67 (0.60–0.76)	814 (18.3)	503 (11.3)	1.76 (1.56–1.99)
Ischemic heart disease	1255 (17.7)	1630 (23.0)	0.72 (0.66–0.78)	1229 (27.7)	1099 (24.8)	1.17 (1.06–1.29)
Hypertension	2627 (37.1)	3345 (47.2)	0.64 (0.60–0.69)	2299 (51.8)	2079 (46.9)	1.23 (1.13–1.34)
Diabetes mellitus	570 (8.0)	747 (10.5)	0.75 (0.67–0.84)	655 (14.8)	474 (10.7)	1.45 (1.28–1.65)
Hypercholesterolemia	643 (9.1)	726 (10.3)	0.86 (0.77–0.97)	453 (10.2)	419 (9.4)	1.11 (0.95–1.28)
Orthostatic hypotension	206 (2.9)	131 (1.9)	1.59 (1.27–1.99)	198 (4.5)	105 (2.4)	1.96 (1.53–2.50)
Inflammatory, endocrine, metabolic						
COPD	333 (4.7)	505 (7.1)	0.64 (0.55–0.73)	363 (8.2)	335 (7.6)	1.09 (0.93–1.27)
Osteoporosis	657 (9.3)	660 (9.3)	1.00 (0.88–1.12)	397 (9.0)	375 (8.5)	1.07 (0.92–1.25)
Inflammatory bowel disease	68 (1.0)	74 (1.0)	0.92 (0.66–1.28)	56 (1.3)	48 (1.1)	1.17 (0.79–1.73)
Thyroid disorders	853 (12.0)	877 (12.4)	0.97 (0.87–1.07)	556 (12.5)	465 (10.5)	1.23 (1.08–1.41)
Rheumatoid arthritis	159 (2.2)	199 (2.8)	0.79 (0.64–0.98)	105 (2.4)	108 (2.4)	0.97 (0.74–1.27)
Central nervous system						
Epilepsy/seizures	144 (2.0)	112 (1.6)	1.29 (1.01–1.66)	215 (4.8)	84 (1.9)	2.62 (2.03–3.38)
Depression	1527 (21.6)	1080 (15.2)	1.57 (1.43–1.71)	1121 (25.3)	636 (14.3)	2.13 (1.90–2.39)

No. = Number; OR = Odds Ratio; CI = Confidence Interval; COPD = Chronic Obstructive Pulmonary Disease

Table 3.1-4: Exposure prevalence to various drugs in patients with Alzheimer's disease or vascular dementia and corresponding dementia-free controls

	Alzheimer's disease			Vascular dementia		
Drugs	**No. of Cases (%) (n = 7086)**	**No. of Controls (%) (n = 7086)**	**OR (95% CI)**	**No. of Cases (%) (n =4438)**	**No. of Controls (%) (n =4438)**	**OR (95% CI)**
Cardiovascular						
ACE inhibitors	1057 (14.9)	1561 (22.0)	0.58 (0.53–0.63)	1142 (25.7)	961 (21.7)	1.31 (1.18–1.45)
AT-II antagonists	261 (3.7)	547 (7.7)	0.44 (0.37–0.51)	307 (6.9)	330 (7.4)	0.92 (0.78–1.09)
Beta-blocking agents	1213 (17.1)	1626 (23.0)	0.66 (0.61–0.72)	1012 (22.8)	949 (21.4)	1.16 (1.05–1.29)
Calcium channel blockers	1121 (15.8)	1556 (22.0)	0.64 (0.58–0.70)	1085 (24.5)	1055 (23.8)	1.12 (1.01–1.24)
Diuretics	2305 (32.5)	3242 (45.8)	0.51 (0.48–0.56)	2135 (48.1)	2021 (45.5)	1.28 (1.17–1.41)
Vasodilators	727 (10.3)	1009 (14.2)	0.67 (0.61–0.75)	928 (20.9)	674 (15.2)	1.52 (1.36–1.70)
Anti-arrhythmics	128 (1.8)	211 (3.0)	0.60 (0.48–0.75)	130 (2.9)	142 (3.2)	0.91 (0.71–1.16)
Oral antidiabetics	344 (4.9)	413 (5.8)	0.82 (0.71–0.95)	404 (9.1)	297 (6.7)	1.42 (1.21–1.66)
Insulin	72 (1.0)	122 (1.7)	0.59 (0.44–0.79)	122 (2.8)	75 (1.7)	1.64 (1.23–2.20)
Statins	1200 (16.9)	1549 (21.9)	0.68 (0.62–0.75)	1241 (28.0)	902 (20.3)	1.69 (1.51–1.88)
Antiplatelets	585 (8.3)	712 (10.1)	0.79 (0.71–0.89)	883 (19.9)	420 (9.5)	2.67 (2.33–3.05)
Anticoagulants	252 (3.6)	390 (5.5)	0.62 (0.52–0.73)	395 (8.9)	276 (6.2)	1.51 (1.28–1.77)
Inflammatory, endocrine, metabolic						
Antiosteoporotics	494 (7.0)	508 (7.2)	0.97 (0.85–1.10)	305 (6.9)	294 (6.6)	1.06 (0.89–1.26)
Intestinal anti-inflammatory agents	51 (0.7)	64 (0.9)	0.79 (0.54–1.14)	44 (1.0)	29 (0.7)	1.51 (0.94–2.41)
Corticosteroids	444 (6.3)	668 (9.4)	0.62 (0.55–0.70)	371 (8.4)	416 (9.4)	0.88 (0.76–1.03)
NSAIDs	1257 (17.7)	1403 (19.8)	0.87 (0.79–0.96)	696 (15.7)	843 (19.0)	0.80 (0.71–0.91)
Thyroid gland therapeutics	675 (9.5)	718 (10.1)	0.93 (0.83–1.04)	431 (9.7)	379 (8.5)	1.17 (1.01–1.35)

Table 3.1-4 cont.

Drugs	Alzheimer's disease			Vascular dementia		
	No. of Cases (%) (n = 7086)	**No. of Controls (%) (n = 7086)**	**OR (95% CI)**	**No. of Cases (%) (n =4438)**	**No. of Controls (%) (n =4438)**	**OR (95% CI)**
Central nervous system						
Anticonvulsants	198 (2.8)	187 (2.6)	1.07 (0.87–1.31)	288 (6.5)	114 (2.6)	2.64 (2.11–3.29)
Antidepressants	1793 (25.3)	958 (13.5)	2.26 (2.06–2.48)	1371 (30.9)	550 (12.4)	3.44 (3.05–3.88)
Antipsychotics/neuroleptics	931 (13.1)	490 (6.9)	2.08 (1.85–2.34)	874 (19.7)	370 (8.3)	3.06 (2.66–3.52)
Benzodiazepines	1047 (14.8)	968 (13.7)	1.13 (1.03–1.25)	886 (20.0)	602 (13.6)	1.72 (1.53–1.94)

No. = Number; OR = Odds Ratio; CI = Confidence Interval; ACE = Angiotensin-Converting Enzyme; AT = Angiotensin; NSAIDs = Non-steroidal Anti-Inflammatory Drugs

3.1.5 Discussion

In this large epidemiological study we estimated IRs of AD and VD in the UK population, stratified by age and sex. Our finding of a higher IR of AD in women than in men, particularly at higher age, is supported by other European studies also describing higher IRs of AD in women than in men.[93,107-109] However, not all studies reported such a difference between men and women,[110-112] and it has been proposed that the higher number of women with AD may be due to the longer life-expectancy of women rather than sex-specific characteristics of the disease.[33] Regarding the sex-specific IRs of VD, our finding of a similar rate in men and women is supported by a large pooled analysis of eight European studies that also found no substantial difference in sex-specific IRs of VD.[74] Further support for our findings is given by another two European studies examining the effect of sex on the risk of developing VD and reporting no difference between men and women.[107,109] By contrast, a higher risk of developing VD in men than in women was found in the Rotterdam study[113] and in the Italian Longitudinal Study on Aging (ILSA).[108] However, both studies were based on relatively few VD cases and IRs in the various age strata were not statistically significantly different.

The increasing IR by age of both AD and VD in our study is consistent with findings of previous European studies.[93,108-110] However, in comparison with those studies, our average IR estimates of AD were between three to six times lower. There are several possible reasons for this difference. The percentage of AD cases among all initially identified dementia cases in our study (AD, VD, or unspecified dementia) was quite low (28.6%) in comparison to the Girona Cohort study[109] with 45.1% AD cases, the ILSA study[108] with 52.7% AD cases, or the study of Barmejo-Pereja *et al.*[110] with 71.4 % AD cases. Since AD is the most common form of dementia, accounting for about 62% of all dementia cases in the UK[90], a considerable proportion of the unspecified dementia cases in our study population may have been AD cases upon closer examination. However, in the MRC-ALPHA Study[93], in which the percentage of identified AD (27.8%) and VD (12.2%) cases was similar to our study (28.6% and 17.9%, respectively), the IR estimates of AD (4.9/1,000 py) and VD (2.6/1,000 py) were still about three times higher than ours (1.59/1,000 py and 0.99/1,000 py, respectively). This may be explained as follows: The MRC-ALPHA Study and the other above mentioned studies[108-110] were prospective studies, i.e. each individual in the study population was actively screened for dementia at baseline and during

follow-up. This is in contrast to our study, in which any dementia diagnoses were diagnosed and recorded as part of daily recording routine of the GP in the absence of any study hypothesis. Notably, a recent UK study applied established dementia prevalence rates to UK population estimates and compared these figures to the number of diagnosed dementia cases reported by the GPs. This analysis revealed that almost 60% of all dementia cases in the UK go undiagnosed.[114] Additionally, in our study dementia cases may not have been captured because elderly patients switch to nursing homes and may get lost from the GPRD. In this study we also compared the prevalence of co-morbidities between AD or VD cases and matched dementia-free controls. We found that, except for orthostatic hypotension, the prevalence of all cardiovascular co-morbidities was lower in patients with AD than in controls, whereas in patients with VD the opposite was true. A lower prevalence of cardiovascular co-morbidities in patients with AD as compared to non-demented patients was also observed in some previous studies.[95,96] On the other hand there are studies reporting significantly higher prevalence rates of cardiovascular co-morbidities in patients with AD than in dementia-free controls.[97,98] Since certain cardiovascular co-morbidities such as hypertension,[63] hypercholesterolemia,[64] or DM[65] are discussed as potential risk factors for AD, our finding of a lower prevalence of these disorders in patients with AD (as compared to dementia-free controls) may come as a surprise. However, this observation may be partially explained by diagnostic bias, i.e. the possibility that patients with a history of cardiovascular co-morbidities may be more likely to be diagnosed with VD than AD.[78] This notion is supported by the observation that the prevalence of cardiovascular co-morbidities was higher overall in patients with VD than in the dementia-free controls. Additionally, there is a possibility that certain diagnoses may be more likely to remain undetected in patients with dementia; in an elderly population of 1260 residents aged 64 years and above in Finland, patients with dementia had more undiagnosed hypercholesterolemia or hypothyroidism than non-demented controls.[115]

We also assessed the exposure prevalence to various drugs and found that the exposure to all cardiovascular drugs was lower in patients with AD than in the dementia-free controls, whereas in patients with VD for most of these drugs the contrary was observed. Notably, evidence from recent epidemiological studies suggests that use of angiotension (AT) II receptor antagonists may reduce the risk of developing AD.[71] However, since we observed a lower exposure prevalence to all

cardiovascular drugs in patients with AD than in the corresponding controls, and because these drugs are clearly linked to corresponding cardiovascular co-morbidities above, the observed lower exposure prevalence to antihypertensive drugs may be biased, at least to some degree, and may not reflect a causal association.

A limitation of our study is that the diagnosis of AD, VD, and other dementia types is not straightforward, and the recording of the diagnosis in a primary care record is by definition delayed, i.e. it does not occur until after a patient has had symptoms for a certain period of time prior to the actual recording date. Thus, as with many other slowly developing degenerative diseases, the disease onset (and therefore the index date) is not a precise point in time. This may affect some drug exposure estimates, particularly if early symptoms of the diseases of interest may affect the likelihood of beginning or stopping a given drug therapy prior to the actual index date. This can lead to spuriously low or high exposure estimates for drugs initiated or stopped within a few months prior to the recorded index date. Further, some degree of outcome misclassification is likely to occur as not all dementia diagnoses can be assigned to a certain subtype with certainty. It is, however, a strength of our study that we validated cases through use of a questionnaire and classified them by defining a sophisticated algorithm in the absence of any knowledge of the exposures of interest. The validity of this algorithm was corroborated by the fact that up to 80% of all our potential AD and up to 75% of all potential VD cases were confirmed by the GP using accepted diagnostic criteria for an AD or VD diagnosis.

In summary, we identified patients with an incident diagnosis of dementia in a large population-based observational study, classified them into dementia subtypes, assessed IRs stratified by age and sex, and quantified the prevalence of co-morbidities and drugs used prior to the index date. These data describe clinical characteristics of patients with an incident AD or VD diagnosis in a primary care setting in the UK. The risk estimates calculated to compare characteristics between patients with or without dementia are descriptive and are not intended to be interpreted as causal associations. Moreover, the relatively low IRs of AD and VD in this study indicate a certain degree of under-diagnosis of these disorders in the UK.

3.2 METFORMIN, OTHER ANTIDIABETIC DRUGS AND RISK OF ALZHEIMER'S DISEASE: A POPULATION-BASED CASE-CONTROL STUDY

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J Am Geriatr Soc 2012; 60(5):916-21

3.2.1 Abstract

Objectives: To explore the risk of developing Alzheimer's disease (AD) in patients with diabetes mellitus treated with metformin or with other antidiabetic drugs.

Design: Case-control study.

Setting: The UK-based General Practice Research Database (GPRD), a well-established primary care database.

Participants: Seven thousand eighty-six cases aged 65 years or more with an incident diagnosis of AD identified between 1998 and 2008 and the same number of matched controls without dementia. Matching criteria were age, sex, general practice, calendar time, and years of history in the database.

Measurements: Comparison of previous use of metformin or other antidiabetic drugs between cases and controls and calculation of corresponding odds ratios (ORs) with 95% confidence intervals (CIs), using conditional logistic regression. Risk estimates were stratified by duration of use and adjusted for potential confounders.

Results: As compared to non-users, long-term users of 60 or more metformin prescriptions were at an increased risk of developing AD (adj. OR 1.71, 95% CI 1.12–2.60), but there was no consistent trend with increasing number of prescriptions. Long-term use of other antidiabetic drugs such as sulfonylureas (adj. OR 1.01, 95% CI 0.72–1.42), thiazolidinediones (adj. OR 0.87, 95% CI 0.31–2.40) or insulin (adj. OR 1.01, 95% CI 0.58–1.73) was not related to an altered risk of developing AD.

Conclusions: Long-term use of sulfonylureas, thiazolidinediones, or insulin was not associated with an altered risk of developing AD. There was a suggestion of a slightly increased risk of AD in long-term users of metformin.

3.2.2 Introduction

Evidence from epidemiological studies suggests that patients with diabetes mellitus are at increased risk of developing Alzheimer's disease (AD),[65,116-118] although not consistently in all studies.[119-121] Studies on the association between antidiabetic medication and the risk of AD are scarce. In the Rotterdam study, diabetics treated with insulin had a substantially increased risk of developing AD.[117] By contrast, a more recent neuropathologic study reported that patients treated with both insulin and oral antidiabetic drugs had a significantly lower neuritic plaque (NP) density than non-diabetic patients.[122]

To our knowledge, data on metformin and the risk of AD only exist from *in vitro* studies or animal models. A recent study reported that metformin reduced phosphorylation of tau protein in cortical neurons of mice.[123] Additionally, metformin was found to improve impaired neuronal insulin signaling and AD-related neuropathological changes in another recent *in vitro* study.[124] These findings suggest that metformin may potentially play a role in reducing the risk of AD. However, the authors of another study found metformin to increase the generation of *β*-amyloid (A*β*) protein,[125] indicating that its use may even promote the development of AD.

The association between use of sulfonylureas or thiazolidinediones and the risk of developing AD has not been reported in published observational studies.

We studied the association between diabetes and use of antidiabetic drugs, in particular metformin, and the risk of developing AD in a large population-based case-control analysis.

3.2.3 Methods

Data source

We used the UK-based General Practice Research Database (GPRD) which was established in around 1987 and encompasses data on some 11 million patients who are or were registered with selected general practitioners (GPs).[100] The patients enrolled in the GPRD are representative of the UK population with regard to age, sex, geographic distribution, and annual turnover rate. The GPs have been trained to record medical information for research purposes in a standardized manner. The information recorded includes patient demographics and characteristics (e.g. age, sex, height, weight, smoking status), symptoms, medical diagnoses, referrals to

consultants, and hospitalizations. Since the doctors generate drug prescriptions directly with the computer using a coded drug dictionary, all recorded prescriptions include the name of the preparation, route of administration, dose of a single unit, number of units prescribed and, in most instances, intake regimen. The database has been described in detail elsewhere[101,102] and validated extensively.[103,104]
The study was approved by ISAC, the Independent Scientific Advisory Committee for Medicines and Healthcare products Regulatory Agency (MHRA) database research.

Case selection and validation

Based on Read codes, we identified patients aged 65 years or more who had a first-time diagnosis of AD or any unspecified dementia recorded between January 1998 and September 2008, or who received a first-time prescription for an acetylcholinesterase inhibitor (i.e. donepezil, rivastigmine, galantamine, or tacrine) or the N-methyl-D-aspartate (NMDA)-receptor antagonist memantine, i.e. two treatments specifically used for AD. The date of the first-time diagnosis or the first prescription to treat AD, whichever came first, will subsequently be referred to as 'index date'. Patients with less than three years of active history in the database prior to the index date, as well as those with a diagnosis of HIV/AIDS, alcoholism, drug abuse, multiple sclerosis, motor neuron disease, or Down's syndrome prior to the index date were excluded. Since we intended to focus the study on AD, we aimed at increasing the probability of including only well-defined AD cases by conducting a manual review of 500 patient profiles, and developing an algorithm which we applied to all potential AD or dementia cases. To be included as an eligible AD case, a patient was required to have either (1) a diagnosis of AD followed by at least one prescription for an AD drug or vice versa, (2) a diagnosis of dementia followed by at least two prescriptions for an AD drug, (3) at least two recordings of an AD diagnosis, (4) an AD diagnosis after a specific dementia test (e.g. Mini Mental State Examination [MMSE], Clock Drawing Test [CDT], or Abbreviated Mental Test [7-Minute Screen]), a referral to a specialist (e.g. neurologist, geriatrician or psychogeriatrician), a diagnostic test based on a neuroimaging technique (e.g. magnet resonance imaging [MRI], computed tomography [CT], or single-photon emission CT [SPECT]), or (5) an AD diagnosis preceded or followed by any recorded dementia symptoms (e.g. memory impairment, aphasia, apraxia, or agnosia). In addition, to reduce the likelihood of including patients with a dementia type other than

AD, cases were not eligible if they had a stroke prior to the index date (as this is more indicative of a diagnosis of vascular dementia [VD][78]) or a recording of any other specific dementia diagnosis (e.g. VD, Pick's disease, or Lewy body dementia) after the index date.

This algorithm was a modified version of two case identification procedures of previous studies done on the GPRD.[105,106] To validate the algorithm, we sent a questionnaire to GPs of a random sample of 60 AD cases to get additional information on the clinical circumstances and the diagnostic steps taken. A copy of this questionnaire is provided in the Appendix. The GPs of 79% of the AD case diagnoses confirmed the recorded AD diagnosis, whereas the other cases had either no dementia, were diagnosed with another dementia type, or the dementia type was not further specified.

Controls

From the base population we identified for each AD case one control patient without any evidence for any type of dementia and for any prescriptions for a specific drug to treat AD in their record at any time. Controls were matched to cases on age (same year of birth), sex, calendar time (same index date), GP, and number of years of recorded history in the database. We applied the same exclusion criteria to the controls as to the cases.

Exposure to metformin or to other antidiabetics

For both AD cases and dementia-free controls, we assessed exposure to metformin, sulfonylureas, thiazolidinediones, or insulin prior to the index date. We further categorized users of these drugs according to the number of recorded prescriptions prior to the index date (1–9, 10–29, 30–59, or ≥60 prescriptions for users of metformin, sulfonylureas, or insulin and 1–9, 10–29, or ≥30 prescriptions for users of thiazolidinediones. The exposure to other antidiabetic drugs (e.g. acarbose, glinides, gliptins, or exenatide) was not assessed due to the small numbers of users. Number of prescriptions is a proxy for exposure duration; an average prescription covers 45–90 days of treatment depending on whether the patient was prescribed one or two tablets per day.

Statistical analysis

We conducted conditional logistic regression analyses using the statistical software SAS, version 9.2 (SAS Institute, Inc., Cary, NC, USA). We calculated relative risk estimates as odds ratios (ORs) with 95% confidence intervals (CIs). For the main analyses we compared users of metformin, sulfonylureas, thiazolidinediones or insulin to non-users of the respective drugs. In a second model we categorized patients into mutually exclusive groups of users of metformin only, sulfonylureas only, insulin only, or thiazolidinediones only and assessed the risk of developing AD in comparison to patients without a diagnosis of diabetes mellitus.

Covariates

We controlled our analyses for the potential confounders age, sex, calendar time, GP, and years of recorded history in the database by matching, and we adjusted for body mass index (BMI) (≤18.4, 18.5–24.9, 25–29.9, ≥30 kg/m^2 or unknown) and smoking status (non, current, past, or unknown) in the multivariate model. For the main analyses (model 1) we adjusted the ORs for each antidiabetic drug for concomitant use of other antidiabetic drugs (metformin, sulfonylureas, thiazolidinediones, or insulin,). We did not control for acarbose, glinides, gliptins, or exenatide since exposure to these drugs was negligible. We further adjusted the ORs for a history of diagnosed hypertension or dyslipidemia, as well as for use of angiotensin converting enzyme (ACE) inhibitors or statins. Other potential confounders such as ischemic heart disease, heart failure, atrial fibrillation, depression, a history of head injury, use of angiotension (AT) II receptor antagonists, beta blockers, calcium channel blockers, diuretics, antiplatelets, anticoagulants, or non-steroidal anti-inflammatory drugs (NSAIDs) were also tested in multivariate analyses; however, as they had no material impact on the risk estimate for the association of interest, they were not included in the final model.

3.2.4 Results

We identified 20,753 cases with a first-time diagnosis of AD, dementia, or a first-time prescription for a drug used to treat AD. After applying the above described algorithm, a total of 7,086 AD cases and the same number of matched controls remained in the analysis. Table 3.2-1 displays the distribution of age and sex,

smoking status and body mass index (BMI), as well as the prevalence of hypertension and dyslipidemia in cases and controls. The mean age (± SD) of our study population at the index date was 80.7 (± 6.7) years and 69% were female. There were more underweight (BMI ≤18.4 kg/m^2) AD cases than controls, while the opposite was true for overweight (BMI 25–29.9 kg/m^2) or obese (BMI ≥30 kg/m^2) patients (Table 3.2-1).

Table 3.2-1: Characteristics of cases with Alzheimer's disease and controls

	No. of Cases (%) (n = 7086)	**No. of Controls (%) (n = 7086)**	**OR Unadjusted (95% CI)**	**OR Adjusted[*] (95% CI)**
Age [years]				
65–74	1305 (18.4)	1306 (18.4)	NA	NA
75–84	3668 (51.8)	3672 (51.8)	NA	NA
≥85	2113 (29.8)	2108 (29.8)	NA	NA
Sex				
Male	2198 (31.0)	2198 (31.0)	NA	NA
Female	4888 (69.0)	4888 (69.0)	NA	NA
Smoking status				
None	4182 (59.0)	4029 (56.9)	1.00 (Reference)	1.00 (Reference)
Current	597 (8.4)	669 (9.4)	0.85 (0.76–0.96)	0.78 (0.69–0.88)
Past	1626 (23.0)	1692 (23.9)	0.92 (0.84–1.00)	0.94 (0.86–1.03)
Unknown	681 (9.6)	696 (9.8)	0.94 (0.82–1.07)	0.88 (0.76–1.02)
BMI [kg/m^2]				
≤18.4	308 (4.4)	162 (2.3)	1.49 (1.21–1.82)	1.47 (1.20–1.81)
18.5–24.9	2907 (41.0)	2243 (31.7)	1.00 (Reference)	1.00 (Reference)
25–29.9	1762 (24.9)	2189 (30.9)	0.61 (0.56–0.67)	0.63 (0.58–0.69)
≥30	564 (8.0)	970 (13.7)	0.44 (0.39–0.50)	0.46 (0.41–0.52)
Unknown	1545 (21.8)	1522 (21.5)	0.79 (0.72–0.87)	0.78 (0.70–0.87)
Comorbidities[†]				
Hypertension	2627 (37.1)	3345 (47.2)	0.64 (0.60–0.69)	0.68 (0.63–0.73)
Dyslipidemia	643 (9.1)	726 (10.3)	0.86 (0.77–0.97)	0.95 (0.84–1.07)

[*]Adjusted for all variables in this table.

[†]Patients with a recorded diagnosis.

No. = Number, OR = Odds Ratio, CI = Confidence Interval, BMI = Body Mass Index, NA = Not Applicable

Overall, patients with diabetes mellitus did not have an altered risk of developing AD as compared to those without diabetes (adj. OR 0.99, 95% CI 0.87–1.12). However, there was a suggestion of a slightly increased risk with increasing diabetes duration

(adj. OR 1.33, 95% CI 1.09–1.63 in patients with diabetes duration ≥10 years. Patients with diabetes who did not receive any drug treatment (adj. OR 0.88, 95% CI 0.71–1.10) and patients who controlled their diabetes with antidiabetic drugs (adj. OR 1.03, 95% CI 0.90–1.19) were at a similar risk of developing AD as compared to patients without diabetes (Table 3.2-2).

Table 3.2-2: Relative risk estimates of developing Alzheimer's disease in patients with diabetes mellitus receiving various antidiabetic drugs

	No. of Cases (%) (n = 7086)	**No. of Controls (%) (n = 7086)**	**OR Unadjusted (95% CI)**	**OR Adjusted* (95% CI)**
Diabetes mellitus				
No	6516 (92.0)	6339 (89.5)	1.00 (Reference)	1.00 (Reference)
Yes	570 (8.0)	747 (10.5)	0.75 (0.67–0.84)	0.99 (0.87–1.12)
Diabetes mellitus duration				
<2 years	102 (1.4)	164 (2.3)	0.61 (0.47–0.78)	0.78 (0.60–1.00)
2–4.9 years	113 (1.6)	163 (2.3)	0.68 (0.53–0.87)	0.91 (0.70–1.17)
5–9.9 years	132 (1.9)	199 (2.8)	0.65 (0.52–0.81)	0.86 (0.68–1.09)
≥10 years	223 (3.2)	221 (3.1)	0.98 (0.81–1.19)	1.33 (1.09–1.63)
Diabetes mellitus treatment				
No	155 (2.2)	218 (3.1)	0.70 (0.57–0.86)	0.88 (0.71–1.10)
Yes	415 (5.9)	529 (7.5)	0.77 (0.67–0.87)	1.03 (0.90–1.19)
Metformin				
None	6802 (96.0)	6736 (95.1)	1.00 (Reference)	1.00 (Reference)
1–9 Rx	65 (0.9)	93 (1.3)	0.68 (0.49–0.94)	1.08 (0.75–1.56)
10–29 Rx	80 (1.1)	85 (1.2)	0.93 (0.69–1.27)	1.47 (1.03–2.09)
30–59 Rx	63 (0.9)	101 (1.4)	0.61 (0.45–0.84)	0.99 (0.68–1.44)
≥60 Rx	76 (1.1)	71 (1.0)	1.06 (0.77–1.46)	1.71 (1.12–2.60)
Sulfonylureas				
None	6779 (95.7)	6692 (94.4)	1.00 (Reference)	1.00 (Reference)
1–9 Rx	48 (0.7)	75 (1.1)	0.63 (0.44–0.91)	0.78 (0.53–1.16)
10–29 Rx	58 (0.8)	98 (1.4)	0.58 (0.42–0.81)	0.74 (0.51–1.06)
30–59 Rx	83 (1.2)	98 (1.4)	0.84 (0.63–1.13)	1.07 (0.75–1.52)
≥60 Rx	118 (1.7)	123 (1.7)	0.95 (0.74–1.23)	1.01 (0.72–1.42)
Insulin				
None	7008 (98.9)	6954 (98.1)	1.00 (Reference)	1.00 (Reference)
1–9 Rx	12 (0.2)	25 (0.4)	0.48 (0.24–0.95)	0.47 (0.22–1.01)
10–29 Rx	17 (0.2)	36 (0.5)	0.47 (0.27–0.84)	0.59 (0.32–1.10)
30–59 Rx	23 (0.3)	35 (0.5)	0.66 (0.39–1.11)	0.78 (0.44–1.36)
≥60 Rx	26 (0.4)	36 (0.5)	0.71 (0.43–1.18)	1.01 (0.58–1.73)

Table 3.2-2: cont.

	No. of Cases (%) (n = 7086)	No. of Controls (%) (n = 7086)	OR Unadjusted (95% CI)	OR Adjusted* (95% CI)
Thiazolidinediones				
None	7053 (99.5)	7029 (99.2)	1.00 (Reference)	1.00 (Reference)
1–9 Rx	14 (0.2)	25 (0.4)	0.54 (0.28–1.06)	0.89 (0.42–1.86)
10–29 Rx	12 (0.2)	21 (0.3)	0.57 (0.28–1.16)	0.97 (0.45–2.07)
≥30 Rx	7 (0.1)	11 (0.2)	0.64 (0.25–1.64)	0.87 (0.31–2.40)

*Adjusted for all antidiabetic drug classes in this table plus smoking, BMI, hypertension, dyslipidemia, use of angiotensin converting enzyme (ACE) inhibitors, and statins.

No. = Number, OR = Odds Ratio, CI = Confidence Interval, Rx = Prescriptions

In the main analysis, in which we compared users of metformin or other antidiabetic drugs to non-users of the corresponding drugs, long-term use of metformin of ≥60 prescriptions was associated with an increased risk of developing AD (adj. OR 1.71, 95% CI 1.12–2.60), although there was no consistent duration effect, i.e. no steady risk increase with increasing number of prescriptions. The risks of developing AD in long-term users of ≥60 prescriptions of sulfonlyureas (adj. OR 1.01, 95% CI 0.72–1.42) or ≥30 prescriptions of thiazolidinediones (adj. OR 0.87, 95% CI 0.31–2.40) were not materially altered as compared to non-users of the corresponding drugs. The same was true for long-term users of ≥60 prescriptions of insulin (adj. OR 1.01, 95% CI 0.58–1.73) (Table 3.2-2).

In the second model, in which we compared mutually exclusive groups of users of metformin only, sulfonylureas only, thiazolidinediones only, or insulin only with the reference group of patients without a diagnosis of diabetes, we did not observe an increased risk for AD in long-term users of either metformin or sulfonylureas (Table 3.2-3). As there were only small numbers of patients who were prescribed insulin only or thiazolidinediones only, no meaningful analysis was possible and the results are not displayed.

Table 3.2-3: Relative risk estimates of developing Alzheimer's disease in patients with diabetes mellitus receiving antidiabetic monotherapy with metformin or sulfonylureas only

	No. of Cases (%) (n = 7086)	**No. of Controls (%) (n = 7086)**	**OR Unadjusted (95% CI)**	**OR Adjusted[*] (95% CI)**
No diabetes mellitus	6516 (92.0)	6339 (89.5)	1.00 (Reference)	1.00 (Reference)
Metformin only				
1–9 Rx	27 (0.4)	31 (0.4)	0.83 (0.50–1.40)	1.24 (0.72–2.13)
10–29 Rx	25 (0.4)	25 (0.4)	0.98 (0.56–1.71)	1.57 (0.88–2.81)
≥30 Rx	20 (0.3)	29 (0.4)	0.67 (0.38–1.19)	1.00 (0.55–1.81)
Sulfonylureas only				
1–9 Rx	23 (0.3)	40 (0.6)	0.56 (0.33–0.94)	0.69 (0.40–1.20)
10–29 Rx	23 (0.3)	37 (0.5)	0.60 (0.36–1.03)	0.68 (0.39–1.17)
≥30 Rx	45 (0.6)	44 (0.6)	1.01 (0.67–1.54)	1.19 (0.77–1.84)
Others[†]	252 (3.6)	323 (4.6)	0.76 (0.64–0.90)	1.05 (0.88–1.26)

[*]Adjusted for smoking, BMI, hypertension, dyslipidemia, use of angiotensin converting enzyme (ACE) inhibitors, and statins.

[†]Further stratification into categories of users of thiazolidinediones only or insulin only was not meaningful due to low numbers of exposed patients. This category also includes patients with diabetes mellitus receiving prescriptions for two or more different antidiabetic drugs or switching between antidiabetic drugs.

No. = Number, OR = Odds Ratio, CI = Confidence Interval, Rx = Prescriptions

3.2.5 Discussion

The findings of this large case-control study do not provide evidence that use of metformin is associated with a reduced risk of developing AD. Our findings even suggest that long-term use of metformin may be associated with a slightly higher risk of developing AD than non-use of this drug, while such a finding was not seen for use of other antidiabetic drugs such as sulfonylureas, thiazolidinediones, or insulin. This finding supports evidence from the animal study by Chen *et al.* who observed that metformin increased the generation of A*β* protein, which is pivotal in the genesis of AD.[125] However, the findings regarding the effect of metformin have to be interpreted with caution, as this increased risk was not confirmed in a subgroup analysis of users of metformin only, and as there was no consistent trend towards an increased risk with increasing number of prescriptions.

In our study, short-term users of insulin had a substantially reduced risk of developing AD as compared to non-users of this drug, whereas in long-term users no risk alteration was observed. A possible explanation for this could be that diabetic

patients who show signs of cognitive impairment, but who are not yet diagnosed with dementia, are less likely to be started on insulin therapy than diabetics whose cognitive abilities are not impaired and who can comply with treatment.

Our findings are largely consistent with those of a recent study by Xu *et al.* who explored the risk of developing AD in a cohort of 1,248 dementia-free patients in association with diabetes mellitus and glycemic control. Patients with diagnosed diabetes mellitus at baseline did not have an increased risk of developing AD during follow-up, whereas patients with borderline diabetes were at a marginally increased risk of AD. A subgroup of patients with undiagnosed diabetes mellitus at baseline but elevated blood glucose levels ≥11 mmol/L during follow-up exhibited an increased risk of AD.[126] In contrast with our findings, patients with diabetes who were treated with insulin had the highest risk of developing AD as compared to patients without diabetes in the Rotterdam study.[117] However, the authors of this study stated that they could not rule out the possibility of having misclassified subjects with vascular dementia as patients with AD. Since diabetes mellitus has been clearly linked to a higher risk of developing vascular dementia,[120,127] this misclassification may have distorted the relative risk estimates for the association between diabetes and AD in the Rotterdam study.[117]

Our finding of a slightly increased risk of AD and metformin use in this large observational study is consistent with observations from a recent *in vitro* study, in which metformin was found to increase the biogenesis of Aβ protein.[125] By contrast, in other *in vitro* studies, metformin modified important steps in the biogenesis of neuritic plaques and neurofibrillary tangles, or improved impaired neuronal insulin signaling,[123,124] raising speculations about the potential to reduce the risk of developing AD. However, all these observations were made in cortical neurons of mice and the results may not be applicable to humans.

We also examined the role of thiazolidinediones on the risk of developing AD and found that diabetic patients treated with these drugs had no risk alteration as compared to non-users of these drugs. In animal models of AD, thiazolidinediones have been shown to ameliorate disease-related pathology and to improve learning and memory deficits.[128] Based on these observations, the efficacy of various thiazolidinediones (mainly rosiglitazone) in improving cognitive deficits in patients with AD has been tested in clinical trials, however with inconsistent findings. While Watson *et al.* reported cognitive improvement after six months of rosiglitazone

treatment in patients with mild AD as compared to placebo-treated controls,[129] Risner *et al.* found such an association only in individuals with apolipoprotein E (ApoE) ε4 negative status.[130] A recent phase III trial, in which subjects were stratified by ApoE ε4 status, extended-release rosiglitazone did not improve cognition in patients with mild-to-moderate AD neither in the ApoE ε4 negative nor in the other subgroups.[131]

A limitation of our study which needs consideration is that the diagnosis of AD and of other dementia types is not straightforward, and the recording of the diagnosis in a primary care record is by definition delayed, i.e. it does not occur until after a patient has suffered from symptoms for a certain period of time prior to the actual recording date. Thus, as with many other slowly developing degenerative diseases, the disease onset and therefore the index date in an observational study is not a precise point in time. This may affect some risk estimates, particularly if early symptoms of the diseases of interest may affect the likelihood of beginning or stopping a given drug therapy prior to the actual index date, potentially leading to spuriously low or high risk estimates for current short-term use, as may have occurred in short-term users of insulin in the present study. We looked at long-term use of each study drug in order to account for the unknown date of disease onset and found that long-term use was not associated with the risk of AD. Further, some degree of outcome misclassification is likely to occur as not all dementia diagnoses can be assigned to a certain subtype with certainty. It is, however, a strength of our study that we selected cases through use of a questionnaire and by defining a sophisticated algorithm to classify cases in the absence of any knowledge of the exposure of interest. The validity of this algorithm was corroborated by the fact that up to 80% of all our potential AD cases were confirmed by the GP using accepted diagnostic criteria for an AD diagnosis. This point is of great importance since diabetes mellitus is clearly associated with VD, and significant misclassification could have spuriously increased the risk in our study.

Diagnostic bias might have played a role in our study since diabetic patients may be more likely of getting an AD diagnosis as the result of a closer follow up by the GP than patients without diabetes. However, the reverse is also possible because patients with long-standing severe diabetes mellitus may be less likely to be investigated for AD.

We were not able to adjust for certain potential confounders such as ApoE ε4 allele,[73] level of education,[132] or certain lifestyle factors such as physical activity[133] or dietary habits,[68] since these factors are not regularly recorded in the GPRD. However, we

adjusted for BMI which is to some degree related to physical activity and dietary habits.

In summary, the findings of this large observational study do not provide evidence that use of metformin reduces the risk of developing AD. We even found that long-term use of metformin, as opposed to use of other antidiabetic drugs, was associated with a suggestion of an increased risk, but there was not a consistent trend with increasing number of prescriptions, and the result was not confirmed in a subgroup analysis of patients prescribed metformin only. Long-term use of sulfonylureas, thiazolidinediones, or insulin was not associated with an altered risk of developing AD in patients with diabetes mellitus.

3.3 SEIZURES IN PATIENTS WITH ALZHEIMER'S DISEASE OR VASCULAR DEMENTIA: A POPULATION-BASED NESTED CASE-CONTROL ANALYSIS

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Epilepsia 2012; submitted

3.3.1 Abstract

Purpose: Patients with Alzheimer's disease (AD) have an increased risk of developing seizures or epilepsy. Little is known about the role of risk factors and about the risk of developing seizures/epilepsy in patients with vascular dementia (VD). The aim of this study was to assess incidence rates (IRs) of seizures/epilepsy in patients with AD, VD or without dementia, and to identify potential risk factors of seizures or epilepsy.

Methods: We conducted a follow-up study with a nested case-control analysis using the UK-based General Practice Research Database (GPRD). We identified patients aged ≥65 years with an incident diagnosis of AD or VD between 1998 and 2008 and a matched comparison group of dementia-free patients. Conditional logistic regression was used to estimate the odds ratio (OR) with 95% confidence intervals (CIs) of developing seizures/epilepsy in patients with AD or VD, stratified by age at onset and duration of dementia as well as by use of anti-dementia drugs.

Key findings: Among 7,086 cases with AD, 4,438 with VD, and 11,524 matched dementia-free patients we identified 180 cases with an incident diagnosis of seizures/epilepsy. The IRs of epilepsy/seizures for patients with AD or VD were 5.6/1,000 person-years (py) (95% CI 4.6–6.9) and 7.5/1,000 py (95% CI 5.7–9.7), respectively, and 0.8/1,000 py (95% CI 0.6–1.1) in the dementia-free group. In the nested case-control analysis, patients longer standing (≥3 years) AD had a slightly higher risk of developing seizures or epilepsy than those with a shorter disease duration, while in patients with VD the contrary was observed.

Significance: Seizures or epilepsy were substantially more common in patients with AD and VD than in dementia-free patients. The role of disease duration as a risk factor of seizures/epilepsy seems to differ between AD and VD.

3.3.2 Introduction

Several epidemiological studies have consistently shown that patients with Alzheimer's disease (AD) are at a higher risk of developing seizures or epilepsy than patients without dementia,[134-138] a finding which is supported by mechanistic studies of seizures in models of AD.[139] However, relative risk estimates vary considerably between studies, ranging from a 6-fold higher risk in one study[135] to a 10-fold higher risk in another study,[134] depending – among other factors – on whether AD patients were recruited from a special care facility or from a population-based setting. Moreover, the role of different predictors of seizures or epilepsy in patients with AD is controversially discussed. While younger age at AD onset was found to be associated with an increased risk of developing seizures in one study,[140] others did not find such an association.[134,136] There is also conflicting evidence on whether a longer duration of AD is associated with an increased risk of seizures.[138,141,142] In addition, the role of specific anti-dementia drugs such as the acetylcholinesterase inhibitors (AChEIs) or memantine is also largely unclear. Limited evidence from case reports suggests that AChEIs such as donepezil[143] or tacrine[144] may provoke seizures in patients with AD. In animal studies, memantine was found to have both pro- and anticonvulsive properties.[145] However, large observational studies exploring a possible association between use of these drugs and an altered risk of developing seizures in patients with AD are lacking.

To our knowledge, there is only one study assessing the risk of incident seizures in patients with dementia forms other than AD;[135] however, in that particular study, the risk estimate was calculated for a mixed subgroup of 'other dementias' which contained all other possible dementia subtypes, such as vascular dementia (VD), Lewy body dementia, and other forms.

The aim of this study was to assess incidence rates of seizures or epilepsy in patients with AD or VD as well as in dementia-free patients, and to further explore the role of various predictors of seizures in these patients within a population-based setting.

3.3.3 Methods

Data source

We used the UK-based General Practice Research Database (GPRD) which was established in around 1987 and encompasses data on some 11 million patients who are or were registered with selected general practitioners (GPs).[100] The patients enrolled in the GPRD are representative of the UK population with regard to age, sex, geographic distribution, and annual turnover rate. The GPs have been trained to record medical information for research purposes in a standardized manner. The information recorded includes patient demographics and characteristics (e.g. age, sex, height, weight, smoking status), symptoms, medical diagnoses, referrals to consultants, and hospitalizations. Since the doctors generate drug prescriptions directly with the computer using a coded drug dictionary, all recorded prescriptions include the name of the preparation, route of administration, dose of a single unit, number of units prescribed and, in most instances, intake regimen. The database has been described in detail elsewhere[101,102] and validated extensively.[103,104]

The study was approved by ISAC, the Independent Scientific Advisory Committee for Medicines and Healthcare products Regulatory Agency (MHRA) database research.

Study population

The study population consisted of patients aged 65 years or more with a diagnosis of AD or VD between January 1998 and September 2008, identified through a validated algorithm described in detail in chapter 3.1.3, and a comparison group of dementia-free patients of the same number, matched to AD or VD patients on age (i.e. same year of birth), sex, GP, calendar time (i.e. the date when the case developed AD or VD), and number of years of recorded history in the database. Patients with less than three years of recorded history prior to the AD or VD diagnosis (or the corresponding date in the dementia-free comparison group), as well as those with a history of HIV/AIDS, alcoholism, drug abuse, multiple sclerosis, motor neuron disease, or Down's syndrome were excluded.

Follow-up and identification of incident seizures or epilepsy cases

In a first step we excluded all patients from the study population with a history of (diagnosed) epilepsy or seizures prior to the AD or VD diagnosis (or the corresponding date in the dementia-free comparison group). We then followed all patients until they developed a first-time diagnosis of epilepsy or seizures, died, or follow-up ended in the medical record, whichever came first. The date of the epilepsy/seizures diagnosis will subsequently be referred to as the 'index date'. Patients with more than three prescriptions for an anticonvulsant drug prior to the index date were excluded because they were considered to be prevalent rather than incident cases. As not all patients with diagnosed epilepsy or seizures need treatment with an anticonvulsant drug, the remaining patients with a recorded epilepsy or seizure code, but no treatment code ±90 days around the index date, were also included in the analyses. However, to verify the validity of our epilepsy or seizure cases, we ran a sensitivity analysis in those cases with a treatment code ±90 days around the index date, where a diagnosis of epilepsy may be more likely.

Nested case-control analysis

For each case patient with an incident diagnosis of epilepsy or seizures we identified at random up to four control patients from the study population who did not develop epilepsy or seizures during follow-up. We matched controls to case patients on age (i.e. year of birth, ±3 years), sex and calendar time (i.e. the date when the case developed epilepsy). For both cases and controls we assessed the prevalence of diagnosed AD or VD prior to the index date and stratified patients with AD or VD by age (65–79 and ≥80 years), age at dementia onset (65–79 and ≥80 years), and disease duration of diagnosed dementia (<1, 1–2.9, and ≥3 years). Patients with AD were additionally stratified by treatment, i.e. on the basis of whether they were treated with an anti-dementia drug (i.e. an AChEI and/or memantine) or not, taking into consideration the timing of the last prescription prior to the index date ('past', if last prescription ≥90 days, or 'current', if last prescription <90 days). Patients being treated with an anti-dementia drug were further stratified into those receiving AChEIs only, memantine only, or both.

Statistical analysis

In the follow-up analysis we assessed person-time for all patients in the study population from the date of first AD or VD diagnosis (or the corresponding date in the dementia-free comparison group) until a patient developed a first-time diagnosis of epilepsy or seizures, died, or follow-up ended in the medical record. We assessed crude incidence rates (IRs) with 95% confidence intervals (CIs) of epilepsy/seizures for patients with AD, VD or without dementia, stratified by age (65–79 and ≥80 years) and sex. We then calculated corresponding age- and sex-stratified crude incidence rate ratios (IRRs) with 95% CIs of epilepsy/seizures for patients with AD or VD, compared to the group of patients without dementia.

In the nested case-control analysis we conducted conditional logistic regression analyses using the statistical software SAS, version 9.2 (SAS Institute, Inc., Cary, NC, USA). We calculated relative risk estimates as odds ratios (ORs) with 95% confidence intervals (CIs). The analyses were controlled for the potential confounders age, sex, and calendar time by matching, and further adjusted for body mass index (BMI) (≤18.4, 18.5–24.9, 25–29.9, ≥30 kg/m^2 or unknown), a history of diagnosed stroke, transient ischemic attack (TIA) or of a head injury, as well as for current use (i.e. the last prescription ≤90 days prior to the index date) of antidepressants or antipsychotics in the multivariate model. Other potential confounders such as smoking status (non, current, past, or unknown), arterial hypertension, dyslipidemia, diabetes mellitus, current use of antiplatelet drugs, anticoagulants, or statins were also tested in multivariate analyses; however, as they had no material impact on the risk estimates for the association of interest, they were not included in the final multivariate model.

3.3.4 Results

The initial study population consisted of 7,086 patients with AD, 4,438 patients with VD, and 11,524 matched comparison subjects without a diagnosis of dementia. VD patients were on average slightly older at the time of diagnosis than the AD patients (mean age [±std.] 82.2 [±6.6] years vs. 80.7 [±6.7] years), whereas the proportion of females was higher among AD patients (69% AD vs. 59% VD). The proportion of underweight (BMI ≤18.4 kg/m^2) subjects was higher in both AD and VD patients than in the corresponding comparison group, while the opposite was true for the

proportion of overweight (BMI 25–29.9 kg/m^2) or obese (BMI ≥30 kg/m^2) subjects. Patients with VD were more frequently current smokers than the corresponding comparison subjects (Table 3.3-1).

Table 3.3-1: Characteristics of patients with Alzheimer's disease or vascular dementia and the corresponding matched comparison subjects without dementia

	No. of AD patients (%) (n = 7086)	**No. of comparison subjects (%) (n = 7086)**	**OR (95% CI)**	**No. of VD patients (%) (n = 4438)**	**No. of comparison subjects (%) (n = 4438)**	**OR (95% CI)**
Age [years]						
65–69	410 (5.8)	411 (5.8)	NA	157 (3.5)	156 (3.5)	NA
70–74	895 (12.6)	895 (12.6)	NA	441 (9.9)	444 (10.0)	NA
75–79	1639 (23.1)	1638 (23.1)	NA	882 (19.9)	880 (19.8)	NA
80–84	2029 (28.6)	2034 (28.7)	NA	1254 (28.3)	1266 (28.5)	NA
85–90	1477 (20.8)	1475 (20.8)	NA	1123 (25.3)	1114 (25.1)	NA
≥90	636 (9.0)	633 (8.9)	NA	581 (13.1)	578 (13.0)	NA
Sex						
Male	2198 (31.0)	2198 (31.0)	NA	1801 (40.6)	1801 (40.6)	NA
Female	4888 (69.0)	4888 (69.0)	NA	2637 (59.4)	2637 (59.4)	NA
Smoking status						
None	4182 (59.0)	4029 (56.9)	1.0 (Ref)	2370 (53.4)	2497 (56.3)	1.0 (Ref)
Current	597 (8.4)	669 (9.4)	0.9 (0.8−1.0)	522 (11.8)	382 (8.6)	1.5 (1.3–1.7)
Past	1626 (23.0)	1692 (23.9)	0.9 (0.8−1.0)	1145 (25.8)	1133 (25.5)	1.1 (1.0–1.2)
Unknown	681 (9.6)	696 (9.8)	0.9 (0.8−1.1)	401 (9.0)	426 (9.6)	1.0 (0.8–1.2)
BMI [kg/m^2]						
≤18.4	308 (4.4)	162 (2.3)	1.5 (1.2−1.8)	197 (4.4)	107 (2.4)	1.7 (1.3–2.1)
18.5–24.9	2907 (41.0)	2243 (31.7)	1.0 (Ref)	1663 (37.5)	1456 (32.8)	1.0 (Ref)
25–29.9	1762 (24.9)	2189 (30.9)	0.6 (0.6−0.7)	1106 (24.9)	1356 (30.6)	0.7 (0.6–0.8)
≥30	564 (8.0)	970 (13.7)	0.4 (0.4−0.5)	439 (9.9)	550 (12.4)	0.7 (0.6–0.8)
Unknown	1545 (21.8)	1522 (21.5)	0.8 (0.7−0.9)	1033 (23.3)	969 (21.8)	1.0 (0.9–1.1)

No. = Number, AD = Alzheimer's Disease, VD = Vascular Dementia, OR = Odds Ratio, CI = Confidence Interval, BMI = Body Mass Index, NA = Not applicable, Ref = Reference Group

Incidence rates of epilepsy or seizures

After excluding patients with a history of diagnosed epilepsy or seizures from the initial study population, 6,932 cases with AD, 4,205 with VD, and 11,321 dementia-free matched comparison subjects remained for follow-up. Within this study

population, we identified 207 cases with an incident diagnosis of epilepsy or seizures of which 180 (87%) met our predefined inclusion and exclusion criteria. The median follow-up time from the date of dementia diagnosis (or the corresponding date in the comparison group) to the index date was 1.5 years (interquartile range [IQR] 0.5–3.0 years). Of these 180 cases, 97 had a history of AD, 55 a history of VD, and 28 had no history of dementia.

Overall, the IR of epilepsy or seizures for patients with AD, VD, or no dementia was 5.6/1,000 person-years (py) (95% CI 4.6–6.9), 7.5/1,000 py (95% CI 5.7–9.7), and 0.8/1,000 py (95% CI 0.6–1.1), respectively. The corresponding crude IRR was 7.1 (95% CI 4.9–10.3) for patients with AD, and 9.3 (95% CI 5.3–16.5) for patients with VD with the no dementia group as the referent. Sex- and age-specific IRs and corresponding IRRs are displayed in Table 3.3-2. For patients with VD, but not AD, a higher age-specific IR and corresponding IRR was observed in those aged 65–79 years compared to those aged ≥80 years, although this difference was not statistically significant.

Table 3.3-2: Incidence rates of epilepsy/seizures in patients with Alzheimer's disease, vascular dementia, or no dementia, and corresponding incidence rate ratios, stratified by age and sex

	Person-years	Cases (n=180)	IR/1,000 person-years (95% CI)	IRR (95% CI)
No dementia				
All	35217	28	0.8 (0.6–1.1)	1.0 (Ref)
Men	12123	10	0.8 (0.4–1.5)	1.0 (Ref)
Women	23094	18	0.8 (0.5–1.2)	1.0 (Ref)
Age 65–79 years	11447	9	0.8 (0.4–1.5)	1.0 (Ref)
Age ≥80 years	23770	19	0.8 (0.5–1.2)	1.0 (Ref)
Alzheimer's disease				
All	17178	97	5.6 (4.6–6.9)	7.1 (4.9–10.3)
Men	5148	26	5.1 (3.4–7.4)	6.1 (3.0–12.4)
Women	12031	71	5.9 (4.7–7.4)	7.5 (4.9–11.7)
Age 65–79 years	6336	39	6.2 (4.5–8.4)	7.8 (4.3–14.0)
Age ≥80 years	10842	58	5.3 (4.1–6.9)	6.7 (4.1–10.8)
Vascular dementia				
All	7365	55	7.5 (5.7–9.7)	9.3 (5.3–16.5)
Men	2887	25	8.7 (5.9–12.8)	10.4 (4.5–24.1)
Women	4478	30	6.7 (4.7–9.5)	8.5 (4.0–18.4)
Age 65–79 years	2303	24	10.4 (7.0–15.5)	13.1 (5.3–32.6)
Age ≥80 years	5061	31	6.1 (4.3–8.7)	7.6 (3.7–15.8)

IR = Incidence Rate, IRR = Incidence Rate Ratio, CI = Confidence Interval, Ref = Reference Group

Nested case-control analysis

The analysis encompassed 180 case patients with an incident diagnosis of epilepsy or seizures, and 689 matched control patients (34% male patients). The characteristics of cases and controls are displayed in Table 3.3-3.

Table 3.3-3: Characteristics of cases with epilepsy or seizures and corresponding controls

	No. of cases (%) (n = 180)	**No. of controls (%) (n = 689)**	**OR unadjusted (95% CI)**	**OR adjusted[*] (95% CI)**
Sex				
Male	61 (33.9)	237 (34.4)		
Female	119 (66.1)	452 (65.6)		
Age [years]				
65–79	72 (40.0)	275 (39.9)		
≥80	108 (60.0)	414 (60.1)		
BMI (kg/m^2)				
12–18.4	4 (2.2)	15 (2.2)	1.0 (Ref)	1.0 (Ref)
18.5–24.9	71 (39.4)	237 (34.4)	0.9 (0.3–2.7)	1.2 (0.4–4.2)
25–29.9	46 (25.6)	184 (26.7)	0.8 (0.6–1.3)	0.9 (0.5–1.4)
30–60	15 (8.3)	81 (11.8)	0.6 (0.3–1.2)	0.6 (0.3–1.1)
Unknown	44 (24.4)	172 (25.0)	0.9 (0.6–1.4)	0.9 (0.6–1.5)
Comorbidities				
Stroke/TIA	76 (42.2)	119 (17.3)	3.6 (2.5–5.2)	3.2 (2.1–4.6)
Head injury	22 (12.2)	36 (5.2)	2.6 (1.5–4.6)	2.0 (1.1–3.8)
Drugs				
Antidepressants	49 (27.2)	108 (15.7)	2.4 (1.6–3.6)	1.7 (1.1–2.7)
Antipsychotics	33 (18.3)	55 (8.0)	3.5 (2.1–5.8)	2.9 (1.7–5.0)

[*]Adjusted for all covariates this table.

TIA = Transient Ischemic Attack , OR = Odds Ratio, CI = Confidence Interval, Ref = Reference Group

As compared to patients without dementia, the relative risk estimate (OR) of developing seizures or epilepsy in association with AD was 6.6 (95% CI 4.1–10.6), after adjusting for the potential confounders BMI, stroke or TIA, head injury, and current use of antidepressants or antipsychotics. Neither younger age at index date (65–79 years) nor younger age at AD onset (65–79 years) were related to an altered risk of developing seizures or epilepsy compared to those aged ≥80 years or to those with the AD onset at or after the age of 80 years, respectively. Patients with longer

standing (≥3 years) AD had a higher risk of developing seizures or epilepsy than those with a shorter duration of disease, although this difference was not statistically significant. The risk of developing seizures or epilepsy was not materially different among patients with AD receiving treatment with anti-dementia drugs compared to patients without drug treatment for AD (Table 3.3-4).

As compared to patients without dementia, the relative risk estimate (OR) of developing seizures or epilepsy in association with VD was 5.7 (95% CI 3.2–10.1), after adjusting for the potential confounders BMI, stroke or TIA, head injury, and current use of antidepressants or antipsychotics. Neither age at index date nor age at VD onset materially altered the risk of developing seizures or epilepsy. However, there was an increased risk of seizures or epilepsy in patients with shorter duration (<1 year) VD compared to cases with longer disease duration, though statistical significance was not reached (Table 3.3-4).

The sensitivity analysis in those patients with a prescription of an anticonvulsant drug ± 90 days around the index date revealed similar results (as the main analysis).

Table 3.3-4: Risk of developing epilepsy or seizures in patients with Alzheimer's disease or vascular dementia, stratified by age, age at dementia onset, duration of dementia, or specific Alzheimer's disease treatment

	No. of cases (%) (n = 180)		No. of controls (%) (n = 689)		OR unadjusted (95% CI)		OR adjusted* (95% CI)	
No dementia	28	(15.6)	448	(65.0)	1.0	(Reference)	1.0	(Reference)
Alzheimer's disease	97	(53.9)	164	(23.8)	7.0	(4.5–10.9)	6.6	(4.1–10.6)
Age [years]								
65–79	39	(21.7)	68	(9.9)	7.2	(3.8–13.8)	7.1	(3.5–14.4)
≥80	58	(32.2)	96	(13.9)	6.8	(4.0–11.5)	6.2	(3.5–10.9)
Age at onset [years]								
65–79	62	(34.4)	103	(15.0)	7.6	(4.5–12.9)	6.9	(3.9–12.1)
≥80	35	(19.4)	61	(8.9)	6.1	(3.3–11.3)	6.1	(3.2–11.8)
Duration [years]								
<1	27	(15.0)	60	(8.7)	5.0	(2.7–9.1)	5.3	(2.8–10.2)
1–2.9	35	(19.4)	64	(9.3)	6.4	(3.7–11.2)	5.7	(3.2–10.3)
≥3	35	(19.4)	40	(5.8)	11.7	(6.3–22.0)	10.7	(5.4–21.4)
Treatment								
No	48	(26.7)	89	(12.9)	6.6	(4.0–11.1)	6.2	(3.6–10.8)
Past	16	(8.9)	21	(3.1)	8.7	(4.0–19.0)	7.5	(3.2–17.6)
Current	33	(18.3)	54	(7.8)	6.9	(3.8–12.5)	6.7	(3.6–12.6)
AChEIs only	31	(17.2)	51	(7.4)	7.0	(3.8–12.7)	6.9	(3.6–13.1)
Memantine only	2	(1.1)	1	(0.2)	22.2	(1.9–256.5)	19.5	(1.6–237.1)
Both	0	(0.0)	2	(0.3)		–		–
Vascular dementia	55	(30.6)	77	(11.2)	8.9	(5.3–15.0)	5.7	(3.2–10.1)
Age [years]								
65–79	24	(13.3)	24	(3.5)	11.0	(5.1–23.8)	6.8	(2.9–16.4)
≥80	31	(17.2)	53	(7.7)	7.6	(3.9–14.8)	5.1	(2.5–10.2)
Age at onset [years]								
65–79	28	(15.6)	31	(4.5)	10.4	(5.3–20.5)	6.2	(2.9–13.2)
≥80	27	(15.0)	46	(6.7)	7.6	(3.8–15.2)	5.3	(2.5–11.0)
Duration [years]								
<1	35	(19.4)	34	(4.9)	12.5	(6.8–23.0)	8.1	(4.2–15.6)
1–2.9	17	(9.4)	35	(5.1)	6.3	(3.1–12.8)	3.7	(1.7–8.2)
≥3	3	(1.7)	8	(1.2)	5.5	(1.3–23.1)	3.4	(0.8–15.6)

*Adjusted for BMI, stroke/TIA, head injury, and current use of antidepressants or antipsychotics. AChEIs = Acetylcholinesterase inhibitors, OR = Odds Ratio, CI = Confidence Interval, Ref = Reference Group

3.3.5 Discussion

In the follow-up analysis of this large epidemiological study we estimated IRs of seizures or epilepsy among patients with AD, VD or without dementia, stratified by age and sex, and we calculated corresponding crude IRRs where those with no recorded diagnosis of dementia comprised the comparison group. For patients with AD we found an overall IR of 5.6/1,000 py and for VD we found an IR of 7.5/1,000 py. These were both higher than the IR of 0.8/1,000 py that we found for patients without dementia, and resulted in elevated IRRs and ORs in the nested case-control analysis.

The IR for AD was somewhat lower than the IR of 8.7/1,000 py reported in another study by Amatniek *et al.*, which assessed overall and age-specific IRs of seizures among 233 subjects with AD.[137] This difference could be explained by the fact that – in contrast to our study – younger AD patients were included in the Amatniek *et al.* study. In line with this interpretation, Amatniek *et al.* found age-specific IRs of 42.6/1,000 py and 15.5/1,000 py in those aged 50–59 years and 60–69 years, respectively. In patients aged 70–79 and in those aged ≥80 years, IRs of 5.7/1,000 py and 5.5/1,000 py were reported, findings which are closely similar to our results.

In the nested case-control analysis we calculated an adjusted OR of 6.6 (95% CI 4.1–10.6) of developing seizures or epilepsy in association with AD, which is somewhat lower than the relative risk (RR) of 10.0 (95% CI 4.3–19.7) found in an early study by Hauser *et al.*[134] or the hazard ratio (HR) of 8.06 (95% CI 3.23–16.61) reported in a more recent study by Scarmeas *et al.*[138] However, reported confidence intervals in these two studies were wide and included the point estimate reported in our study. In addition, in both these studies,[134,138] AD cases were selected from special care facilities or specialized diagnostic and treatment centers; thus, these patients were presumably at a more advanced stage of their disease compared to demented patients selected from the general population in primary care, as in our study. As more severe and advanced stages of AD have been reported to be associated with a greater risk of seizures or epilepsy,[136,137] these patients were probably more likely to have seizures or epilepsy than a sample of AD patients derived from the general population. Our findings are supported by another population-based study which assessed the relative risk of developing seizures in association with AD, reporting an approximately 6-fold increased risk (OR 6.2, 95% CI 2.2–17.0) as compared to patients without dementia.[135]

In our study, we found that neither younger age at index date, nor younger age at AD onset were materially associated with an altered risk of developing seizures or epilepsy. The latter finding is supported by the results from a prospective cohort study among 44 patients with mild AD and 58 healthy controls, where no difference in age at onset of AD between patients who developed seizures and those who did not was observed.[136] Additionally, in another retrospective analysis, there was no difference in age at onset of AD among 81 autopsy-confirmed AD cases between those who developed seizures and those who did not.[134] However, in a study among 446 autopsy-confirmed AD cases, patients who developed seizures were, on average, younger at age of dementia onset than those who did not develop seizures.[140] Contrary to our findings, younger age of AD was associated with an increased risk of seizures in two prospective cohort studies.[137,138] This could possibly be due to the fact that both prospective studies used a non-random sample of AD patients recruited from tertiary care university hospitals or specialized diagnostic and treatment centers, including those with more advanced/severe disease, whereas we used a population-based sample.

In this study, there was a suggestion that patients with a longer standing (≥ 3 years) history of diagnosed AD may be at a higher risk of developing seizures or epilepsy than those with a shorter duration of disease. However, available evidence from the literature is conflicting: While some studies in patients with AD found that seizures tended to develop late in the course of the disease,[141,142] another study examining predictors of new-onset seizures in patients with AD found no increased risk in association with longer duration of disease.[138] Of note, increasing evidence suggests that more severe AD and not primarily longer duration of AD is associated with an increased risk of developing seizures.[136,137,146]

In our study we did not observe a materially altered risk of seizures or epilepsy in patients using AChEIs. In comparison, in a small pilot study assessing the efficacy of donepezil to improve memory in patients with epilepsy, there was a small increase in frequency of generalized tonic-clonic seizures between the pre- and the post-administration period of donepezil, though the difference did not reach statistical significance.[147] In another small randomized controlled trial including 23 epilepsy patients there was also a statistically non-significant difference in seizure frequency between patients treated with donepezil and those treated with placebo.[148] However, since occurrence of seizures or epilepsy in AD is overall uncommon,[138] one would

require a much larger sample size (and/or a longer observation period) to detect a statistically significant difference among users of AChEIs compared to nonusers, if it exists.

A major limitation of our study is that we cannot rule out the possibility of AD and VD case misclassification as not all dementia diagnoses can be assigned to a certain subtype with certainty. It is, however, a strength of our study that we validated cases through use of a questionnaire and classified them by defining a sophisticated algorithm in the absence of any knowledge of the exposures of interest. The validity of this algorithm was corroborated by the fact that up to 80% of all our potential AD and up to 75% of all potential VD cases were confirmed by the GP using accepted diagnostic criteria for an AD or VD diagnosis. Moreover, there is the potential of seizure or epilepsy misclassification in our study, because only a small percentage (1%) of all cases was referred to a neurologist to confirm the diagnosis (according to GP's record). However, as the results of a sensitivity analysis in those cases who had a recording for an anticonvulsant drug ±90 days around the index date (making a diagnosis of epilepsy highly likely, 51% of all incident cases) were not materially different to those of our main analysis, we are confident that the potential of seizure or epilepsy misclassification could be kept to a minimum. Another limitation is that we could not assess the severity of AD (or VD) to verify whether severity rather than the duration of the disease was associated with an increased risk of developing seizures or epilepsy, because we had no information about patients' cognitive status from the GPs' record. However, as duration of symptoms has been related to dementia severity,[149] we used duration of the disease as a rough proxy for the severity.

Our study also has several strengths. First, we used a large, validated and well-established primary-care database to study the association between different dementia forms and the risk of developing seizures or epilepsy. Since occurrence of seizures or epilepsy is uncommon, though more likely in patients with a diagnosis of dementia, only use of a large database such as the GPRD allows inclusion of a substantial number of patients. In addition, we used a sophisticated and validated algorithm to identify only well-defined AD or VD cases in the database that formed our study population.

In summary, patients with AD or VD were at a much higher risk of developing seizures or epilepsy than dementia-free patients. Neither younger age, nor younger age at dementia onset, nor use of AChEIs were materially associated with an altered

risk of developing seizures or epilepsy. However, there was a suggestion that patients with longer standing (≥3 years) AD may have a higher risk of developing seizures or epilepsy than those with a shorter duration of disease, whereas in patients with VD the contrary was observed.

3.4 RISK OF INCIDENT STROKE IN PATIENTS WITH ALZHEIMER'S DISEASE OR VASCULAR DEMENTIA: A POPULATION-BASED NESTED CASE-CONTROL ANALYSIS

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Neurology 2012; submitted

3.4.1 Abstract

Background: Dementia has been associated with stroke, but the magnitude of the risk in patients with Alzheimer's disease (AD) or vascular dementia (VD) is largely unknown.

Objective: To explore the risk of ischemic stroke, hemorrhagic stroke, or transient ischemic attack (TIA) in patients with AD or VD.

Methods: We conducted a follow-up study with a nested case-control analysis using the UK-based Clinical Practice Research Datalink (CPRD). We included patients aged ≥65 years with an incident diagnosis of AD or VD between 1998 and 2008 and a matched comparison group of dementia-free patients. We estimated incidence rates (IRs) of ischemic stroke, hemorrhagic stroke, or TIA in patients with AD, VD, or without dementia, and we calculated odds ratios (ORs) with 95% confidence intervals (CIs) of developing such an outcome in patients with AD or VD, stratified by use of antipsychotic drugs.

Results: We followed 6,443 cases with AD, 2,302 with VD, and 9,984 matched dementia-free patients over time and identified 281 cases with incident ischemic stroke, 139 with hemorrhagic stroke, and 379 with TIA. The IRs of ischemic stroke for patients with AD, VD, and dementia-free controls were 4.7/1,000 person-years (py) (95% CI 8.8–12.0), 12.8/1,000 py (95% CI 23.2–33.5), and 5.1/1,000 py (95% CI 7.8–9.9), respectively. Compared to dementia-free patients, the OR of developing a TIA for AD patients treated with atypical antipsychotic drugs was 5.5 (95% CI 2.6–11.7).

Conclusions: Patients with VD, but not AD have a markedly higher risk of developing an ischemic stroke than those without dementia. In patients with AD, but not VD, use of atypical antipsychotic drugs was associated with an increased risk of TIA.

3.4.2 Introduction

Hospital- and population-based studies have indicated that patients with stroke have an about twofold increased risk of developing new-onset dementia as compared to patients without any history of stroke.[62] Conversely, 9–14% of all patients who develop a stroke have dementia.[150] Results from two population-based studies suggested that patients with severe cognitive impairment or with mild dementia had more than a twofold increased stroke risk compared to cognitively healthy subjects.[151,152] The mechanism by which dementia increases the risk of stroke is not fully understood. It has been hypothesized that cognitive impairment may be an early manifestation of vascular brain injury preceding stroke.[151,152] Consistent with this hypothesis, the authors from two recent studies found that patients with low cognitive test scores were at greater risk of developing a first-time stroke, independent of other major vascular risk factors.[153,154]

In addition to concerns that dementia itself increases the risk of stroke, concerns arose in recent years that use of risperidone or olanzapine, two atypical antipsychotic drugs which are used to treat behavioral symptoms in patients with dementia, may (also) be associated with an increased risk of stroke.[155,156] Subsequently, epidemiological studies investigated the association between use of atypical antipsychotic drugs and the risk of incident stroke, with controversial findings.[157-160] Recent studies suggest that the risk may not be limited to atypical antipsychotic drugs, but that all antipsychotic drugs are associated with an increased risk of stroke in demented patients.[161-163]

To our knowledge, no population-based study has yet been published that assessed the risk of developing stroke in patients diagnosed with specific subtypes of dementia, such as Alzheimer's disease (AD) or vascular dementia (VD), or that explored the role of antipsychotic drug use on the risk of developing stroke in patients with AD or VD.

3.4.3 Methods

Data source

We used the UK-based Clinical Practice Research Datalink (CPRD) which was established around 1987 and encompasses data on some 8 million patients who are or were registered with selected general practitioners (GPs).[100] The patients enrolled

in the CPRD are representative of the UK population with regard to age, sex, geographic distribution, and annual turnover rate. The GPs have been trained to record medical information for research purposes in a standardized manner. The information recorded includes patient demographics and characteristics (e.g. age, sex, height, weight, smoking status), symptoms, medical diagnoses, referrals to consultants, and hospitalizations. Since the doctors generate drug prescriptions directly with the computer using a coded drug dictionary, all recorded prescriptions include the name of the preparation, route of administration, dose of a single unit, number of units prescribed and, in most instances, intake regimen. The database has been described in detail elsewhere[101,102] and validated extensively.[103,104]

The study was approved by ISAC, the Independent Scientific Advisory Committee for Medicines and Healthcare products Regulatory Agency (MHRA) database research.

Study population

The study population consisted of patients aged ≥65 years with a diagnosis of AD or VD between January 1998 and September 2008, identified through a validated algorithm described in detail in the electronic appendix, and a comparison group of dementia-free patients matched one to one to AD or VD patients on age (i.e. same year of birth), sex, GP, calendar time (i.e. the date when the case developed AD or VD), and number of years of recorded history in the database. Patients with <3 years of recorded history prior to the AD or VD diagnosis (or the corresponding date in the dementia-free comparison group) or with HIV/AIDS, alcoholism, drug abuse, multiple sclerosis, motor neuron disease, or Down's syndrome were excluded.

Follow-up and identification of stroke or TIA cases

We excluded all patients from the study population with a history of stroke or transient ischemic attack (TIA) prior to the AD or VD diagnosis (or the corresponding date in the dementia-free comparison group). We then followed all patients until they developed a first-time diagnosis of stroke (defined as either ischemic stroke, hemorrhagic stroke, or unspecified stroke) or a TIA, died, or follow-up in the medical record ended, whatever came first. The date of the stroke or TIA diagnosis will subsequently be referred to as 'index date'.

To clearly differentiate between ischemic stroke, hemorrhagic stroke or TIA, we developed an algorithm using UK stroke/TIA management guidelines,[164,165] which

was applied to all potential cases with a recorded code of either ischemic stroke, hemorrhagic stroke, unspecified stroke or TIA at the index date. The algorithm was based on recordings of newly started or stopped pharmacological therapies (e.g. antiplatelet drugs, anticoagulants, or antihypertensive drugs), referrals (e.g. to special care units or rehabilitations clinics), brain imaging (e.g. CT or MRI scans), typical symptoms (e.g. contralateral hemiparesis, dysphasia, hemianopia, etc.), or death.

Nested case-control analysis

For each case with an incident diagnosis of ischemic stroke, hemorrhagic stroke, or TIA we identified at random up to four control patients from the study population who did not develop a stroke or TIA during follow-up. We matched them to case patients on age (i.e. year of birth, ±3 years), sex and calendar time (i.e. the date when the case developed a stroke or TIA). The exposure of interest was a diagnosis of AD or VD prior to the index date. Exposure was further stratified by age (65–79 and ≥80 years), sex, duration of the history of dementia (<1 and ≥1 year), and use of antipsychotic drugs. Use of antipsychotic drugs (in patients with AD or VD) was further stratified by timing of the last prescription prior to the index date ('past', if last prescription ≥90 days, or 'current', if last prescription <90 days), and by type of drug (only 'typical' antipsychotic drugs such as chlorpromazine, thioridazine, or haloperidol, only 'atypical' antipsychotic drugs such as olanzapine, quetiapine, or risperidone, or both).

Statistical analysis

In the follow-up analysis we assessed crude incidence rates (IRs) with 95% confidence intervals (CIs) of ischemic stroke, hemorrhagic stroke, and TIA for patients with AD, VD, and without dementia, stratified by age (65–79 and ≥80 years) and sex. We calculated corresponding age- and sex-stratified crude incidence rate ratios (IRRs) with 95% CIs of ischemic stroke, hemorrhagic stroke, or TIA for patients with AD or VD, compared to those without dementia.

In the nested case-control analysis, we conducted conditional logistic regression analyses using the statistical software SAS, version 9.2 (SAS Institute, Inc., Cary, NC, USA). We calculated relative risk estimates as odds ratios (ORs) with 95% confidence intervals (CIs). The analyses were controlled for the potential confounders age, sex, and calendar time by matching, and further adjusted for smoking status

(non, current, past, or unknown), body mass index (BMI) (≤18.4, 18.5–24.9, 25–29.9, ≥30 kg/m^2 or unknown), a history of diagnosed arterial hypertension, ischemic heart disease, congestive heart failure, atrial fibrillation, diabetes mellitus, dyslipidemia, and depression, as well as for current use (i.e. the last prescription ≤90 days prior to the index date) of angiotensin converting enzyme (ACE) inhibitors, diuretics, antiplatelet drugs, anticoagulants, or statins in the multivariate model. Other potential confounders such as epilepsy, current use of angiotensin (AT) II receptor antagonists, beta blockers, calcium channel blockers, or non-steroidal anti-inflammatory drugs (NSAIDs) were also tested in multivariate analyses; however, as they had no material impact (<10% change of the risk estimate) on the risk estimates for the association of interest, they were not included in the final multivariate model.

3.4.4 Results

The initial study population consisted of 7,086 patients with AD, 4,438 patients with VD, and 11,524 matched comparison subjects without dementia. VD patients were slightly older at the time of diagnosis than AD patients (mean age ± std.) 82.2 ± 6.6 years vs. 80.7 ± 6.7 years), whereas the proportion of females was higher among AD patients (69% AD vs. 59% VD). All cardiovascular co-morbidities were less prevalent in patients with AD than in the corresponding comparison subjects, whereas in patients with VD the contrary was observed (Table 3.4-1).

Table 3.4-1: Characteristics of patients with Alzheimer's disease or vascular dementia and the corresponding matched comparison subjects without dementia

	AD patients (n = 7086) n (%)	Comparison subjects (n = 7086) n (%)	OR (95% CI)	VD patients (n = 4438) n (%)	Comparison subjects (n = 4438) n (%)	OR (95% CI)
Age [years]						
65–69	410 (5.8)	411 (5.8)	NA	157 (3.5)	156 (3.5)	NA
70–74	895 (12.6)	895 (12.6)	NA	441 (9.9)	444 (10.0)	NA
75–79	1639 (23.1)	1638 (23.1)	NA	882 (19.9)	880 (19.8)	NA
80–84	2029 (28.6)	2034 (28.7)	NA	1254 (28.3)	1266 (28.5)	NA
85–90	1477 (20.8)	1475 (20.8)	NA	1123 (25.3)	1114 (25.1)	NA
≥90	636 (9.0)	633 (8.9)	NA	581 (13.1)	578 (13.0)	NA
Sex						
Male	2198 (31.0)	2198 (31.0)	NA	1801 (40.6)	1801 (40.6)	NA
Female	4888 (69.0)	4888 (69.0)	NA	2637 (59.4)	2637 (59.4)	NA
Smoking status						
None	4182 (59.0)	4029 (56.9)	1.0 (Ref)	2370 (53.4)	2497 (56.3)	1.0 (Ref)
Current	597 (8.4)	669 (9.4)	0.9 (0.8−1.0)	522 (11.8)	382 (8.6)	1.5 (1.3–1.7)
Past	1626 (23.0)	1692 (23.9)	0.9 (0.8−1.0)	1145 (25.8)	1133 (25.5)	1.1 (1.0–1.2)
Unknown	681 (9.6)	696 (9.8)	0.9 (0.8−1.1)	401 (9.0)	426 (9.6)	1.0 (0.8–1.2)
BMI [kg/m^2]						
≤18.4	308 (4.4)	162 (2.3)	1.5 (1.2−1.8)	197 (4.4)	107 (2.4)	1.7 (1.3–2.1)
18.5–24.9	2907 (41.0)	2243 (31.7)	1.0 (Ref)	1663 (37.5)	1456 (32.8)	1.0 (Ref)
25–29.9	1762 (24.9)	2189 (30.9)	0.6 (0.6−0.7)	1106 (24.9)	1356 (30.6)	0.7 (0.6–0.8)
≥30	564 (8.0)	970 (13.79	0.4 (0.4−0.5)	439 (9.90)	550 (12.4)	0.7 (0.6–0.8)
Unknown	1545 (21.8)	1522 (21.59	0.8 (0.7−0.9)	1033 (23.3)	969 (21.8)	1.0 (0.9–1.1)
Co-morbidities						
Ischemic heart disease	1255 (17.7)	1630 (23)	0.7 (0.7–0.8)	1229 (27.7)	1099 (24.8)	1.2 (1.1–1.3)
Congestive heart failure	448 (6.3)	677 (9.6)	0.6 (0.6–0.7)	600 (13.5)	465 (10.5)	1.4 (1.2–1.5)
Atrial fibrillation	517 (7.3)	741 (10.5)	0.7 (0.6–0.8)	814 (18.3)	503 (11.3)	1.8 (1.6–2.0)
Hypertension	2627 (37.1)	3345 (47.2)	0.6 (0.6–0.7)	2299 (51.8)	2079 (46.9)	1.2 (1.1–1.3)
Diabetes mellitus	570 (8.0)	747 (10.5)	0.8 (0.7–0.8)	655 (14.8)	474 (10.7)	1.5 (1.3–1.7)
Dyslipidemia	643 (9.1)	726 (10.3)	0.9 (0.8–1.0)	453 (10.2)	419 (9.4)	1.1 (1.0–1.3)
Depression	1527 (21.6)	1080 (15.2)	1.6 (1.4–1.7)	1121 (25.3)	636 (14.3)	2.1 (1.9–2.4)

AD = Alzheimer's disease, VD = Vascular dementia, OR = Odds Ratio, CI = Confidence Interval, BMI = Body Mass Index, NA = Not applicable, Ref = Reference Group

Incidence rates of stroke or transient ischemic attack

After excluding patients with a history of stroke or TIA from the initial study population, 6,443 cases with AD, 2,302 with VD, and 9,984 dementia-free matched comparison subjects remained for follow-up. Within this patient group, we identified 281 cases with an incident ischemic stroke, 139 cases with a hemorrhagic stroke, and 379 with a TIA. The median follow-up time was 1.7 years (interquartile range [IQR] 0.7–3.3).

The IRs of ischemic stroke for patients with AD, VD, or no dementia were 4.7/1,000 person-years (py) (95% CI 3.8–5.9), 12.8/1,000 py (95% CI 9.8–16.8), and 5.1/1,000 py (95% CI 4.3–5.9), respectively. The corresponding crude IRRs, stratified by sex and age, are displayed in Table 3.4-2.

The IRs of hemorrhagic stroke for patients with AD, VD, or no dementia were 2.7/1,000 py (95% CI 2.0–3.7), 9.3/1,000 py (95% CI 6.7–12.8), and 1.9/1,000 py (95% CI 1.5–2.5), respectively.

The IRs of TIA for patients with AD or without dementia were similar (8.2 and 6.2/1000 py, respectively with overlapping CIs), whereas for patients with VD the IR was significantly higher than for patients without dementia (IR 14.8/1,000 py) (Table 3.4-2).

Nested case-control analysis

The analysis encompassed 281 cases with ischemic stroke and 1,124 matched controls, 139 cases with hemorrhagic stroke and 556 matched controls, and 379 cases with TIA and 1515 matched controls; the respective characteristics are displayed in Table 3.4-3.

While rates of ischemic and hemorrhagic stroke and TIA varied among patients with AD and VD, patients with AD were at a similar risk of developing an ischemic stroke compared to patients without dementia (adjusted OR 0.9, 95% CI 0.7–1.3). Stratification by duration of AD or use of antipsychotic drugs did not materially change this association. The adjusted OR of developing a TIA in people with AD compared to people with no dementia was 1.4 (95% CI 1.1–1.8). Stratification by use of antipsychotic drugs revealed effect modification. Cases who were currently exposed to atypical antipsychotics were at high risk for TIA, adj. OR for TIA 5.5 (95% CI 2.6–11.7), while those not exposed to antipsychotic treatment had no materially elevated risk (adj. OR 1.3, 95% 0.9–1.8). The adjusted OR of developing a hemorrhagic stroke in association with AD was 2.0 (95% CI 1.2–3.3), which was higher in those exposed to typical antipsychotic drugs (adj. OR 7.1, 95% CI 1.9–26.9) than in those not receiving antipsychotic treatment (adj. OR 1.4, 95% CI 0.7–2.7), although the difference did not reach statistical significance because of small numbers (Table 3.4-4).

As compared with patients without dementia, patients with VD had an approximately twofold increased risk of developing an ischemic stroke (adj. OR 2.1, 95% CI 1.4–

3.1) or a TIA (adj. OR 1.8, 95% CI 1.3–2.6). The adjusted OR of developing a hemorrhagic stroke in association with VD was 4.7 (95% CI 2.5–9.0). Stratification by use of antipsychotic drugs revealed a markedly higher adjusted OR of 11.1 (95% CI 2.5–49.8) in patients receiving atypical antipsychotic drugs than in those not receiving antipsychotic treatment (adj. OR 4.2, 95% CI 1.6–11.0), although the difference did not reach statistical significance due to small numbers (Table 3.4-4).

Table 3.4-2: Incidence rates of ischemic or hemorrhagic stroke or transient ischemic attack in patients with Alzheimer's disease, vascular dementia, or no dementia and corresponding incidence rate ratios, stratified by age and sex

		Ischemic stroke			Hemorrhagic stroke			Transient ischemic attack		
	Person-years	Cases (n=281)	IR/1,000 person-years (95% CI)	IRR (95% CI)	Cases (n=139)	IR/1,000 person-years (95% CI)	IRR (95% CI)	Cases (n=379)	IR/1,000 person-years (95% CI)	IRR (95% CI)
No dementia										
All	30773	156	5.1 (4.3–5.9)	1.0 (Ref)	59	1.9 (1.5–2.5)	1.0 (Ref)	191	6.2 (5.4–7.1)	1.0 (Ref)
Men	10355	55	5.3 (4.1–6.9)	1.0 (Ref)	25	2.4 (1.6–3.6)	1.0 (Ref)	70	6.8 (5.4–8.5)	1.0 (Ref)
Women	20418	101	4.9 (4.1–6.0)	1.0 (Ref)	34	1.7 (1.2–2.3)	1.0 (Ref)	121	5.9 (5.0–7.1)	1.0 (Ref)
Age 65–79 years	10467	38	3.6 (2.6–5.0)	1.0 (Ref)	10	1.0 (0.5–1.8)	1.0 (Ref)	50	4.8 (3.6–6.3)	1.0 (Ref)
Age ≥80	20306	118	5.8 (4.9–7.0)	1.0 (Ref)	49	2.4 (1.8–3.2)	1.0 (Ref)	141	6.9 (5.9–8.2)	1.0 (Ref)
Alzheimer's disease										
All	15688	74	4.7 (3.8–5.9)	0.9 (0.7–1.2)	43	2.7 (2.0–3.7)	1.4 (0.9–2.2)	129	8.2 (6.9–9.8)	1.3 (1.0–1.7)
Men	4643	25	5.4 (3.7–7.9)	1.0 (0.6–1.6)	19	4.1 (2.6–6.4)	1.7 (0.9–3.2)	35	7.5 (5.4–10.5)	1.1 (0.7–1.7)
Women	11046	49	4.4 (3.4–5.9)	0.9 (0.6–1.3)	24	2.2 (1.5–3.2)	1.3 (0.8–2.2)	94	8.5 (7.0–10.4)	1.4 (1.1–1.9)
Age 65–79 years	5970	27	4.5 (3.1–6.6)	1.2 (0.8–2.1)	12	2.0 (1.2–3.5)	2.1 (0.9–5.0)	45	7.5 (5.6–10.1)	1.6 (1.0–2.4)
Age ≥80	9718	47	4.8 (3.6–6.4)	0.8 (0.6–1.2)	31	3.2 (2.2–4.5)	1.3 (0.8–2.1)	84	8.6 (7.0–10.7)	1.2 (0.9–1.6)
Vascular dementia										
All	3982	51	12.8 (9.8–16.8)	2.5 (1.6–3.8)	37	9.3 (6.7–12.8)	4.8 (2.6–9.0)	59	14.8 (11.5–19.1)	2.4 (1.6–3.5)
Men	1468	25	17.0 (11.6–25.0)	3.2 (1.6–6.1)	14	9.5 (5.7–15.9)	3.9 (1.5–10.1)	24	16.3 (11.0–24.2)	2.4 (1.3–4.4)
Women	2513	26	10.3 (7.1–15.1)	2.1 (1.2–3.6)	23	9.2 (6.1–13.7)	5.5 (2.4–12.5)	35	13.9 (10.0–19.3)	2.3 (1.4–3.8)
Age 65–79 years	1244	21	16.9 (11.1–25.7)	4.6 (2.0–10.4)	8	6.4 (3.3–12.6)	6.7 (1.5–29.8)	15	12.1 (7.3–19.8)	2.5 (1.1–5.5)
Age ≥80	2738	30	11.0 (7.7–15.6)	1.9 (1.1–3.1)	29	10.6 (7.4–15.2)	4.4 (2.2–8.6)	44	16.1 (12.0–21.5)	2.3 (1.5–3.6)

IR = Incidence Rate, IRR = Incidence Rate Ratio, CI = Confidence Interval, Ref = Reference Group

Table 3.4-3: Characteristics of cases with ischemic or hemorrhagic stroke or transient ischemic attack and corresponding controls

	Ischemic stroke								Hemorrhagic stroke								Transient ischemic attack							
	Cases (n = 281) n (%)		Controls (n = 1124) n (%)		Unadjusted OR (95% CI)		Adjusted* OR (95% CI)		Cases (n = 139) n (%)		Controls (n = 556) n (%)		Unadjusted OR (95% CI)		Adjusted* OR (95% CI)		Cases (n = 379) n (%)		Controls (n = 1515) n (%)		Unadjusted OR (95% CI)		Adjusted* OR (95% CI)	
Age [years]																								
65−79	105	(37.4)	420	(37.4)	NA		NA		58	(41.7)	232	(41.7)	NA		NA		129	(34.0)	516	(34.1)	NA		NA	
≥80	176	(62.6)	704	(62.6)	NA		NA		81	(58.3)	324	(58.3)	NA		NA		250	(66.0)	999	(65.9)	NA		NA	
Sex																								
Male	86	(30.6)	322	(28.7)	NA		NA		30	(21.6)	124	(22.3)	NA		NA		110	(29.0)	435	(28.7)	NA		NA	
Female	195	(69.4)	802	(71.4)	NA		NA		109	(78.4)	432	(77.7)	NA		NA		269	(71.0)	1080	(71.3)	NA		NA	
Smoking status																								
None	161	(57.3)	645	(57.4)	1.0	(Ref)	1.0	(Ref)	70	(50.4)	319	(57.4)	1.0	(Ref)	1.0	(Ref)	217	(57.3)	836	(55.2)	1.0	(Ref)	1.0	(Ref)
Current	34	(12.1)	111	(9.9)	1.2	(0.8−1.9)	1.4	(0.9−2.2)	18	(13.0)	48	(8.6)	1.7	(0.9−3.1)	2.7	(1.4−5.5)	38	(10.0)	144	(9.5)	1.0	(0.7−1.5)	0.9	(0.6−1.4)
Past	55	(19.6)	229	(20.4)	1.0	(0.7−1.4)	0.9	(0.7−1.3)	29	(20.9)	118	(21.2)	1.1	(0.7−1.8)	1.1	(0.6−1.9)	79	(20.8)	316	(20.9)	1.0	(0.7−1.3)	0.9	(0.7−1.3)
Unknown	31	(11.0)	139	(12.4)	0.9	(0.6−1.4)	0.8	(0.5−1.4)	22	(15.8)	71	(12.8)	1.4	(0.8−2.6)	1.8	(0.9−3.8)	45	(11.9)	219	(14.5)	0.8	(0.5−1.1)	0.8	(0.5−1.1)
BMI [kg/m^2]																								
≤18.4	5	(1.8)	15	(1.3)	1.3	(0.5−3.7)	1.4	(0.5−4.1)	1	(0.7)	15	(2.7)	0.3	(0.0−2.2)	0.2	(0.0−1.7)	8	(2.1)	32	(2.1)	0.9	(0.4−2.0)	0.8	(0.4−1.9)
18.5−24.9	99	(35.2)	396	(35.2)	1.0	(Ref)	1.0	(Ref)	47	(33.8)	198	(35.6)	1.0	(Ref)	1.0	(Ref)	135	(35.6)	493	(32.5)	1.0	(Ref)	1.0	(Ref)
25−29.9	76	(27.1)	343	(30.5)	0.9	(0.6−1.2)	0.9	(0.6−1.2)	33	(23.7)	141	(25.4)	1.0	(0.6−1.6)	0.9	(0.5−1.6)	107	(28.2)	426	(28.1)	0.9	(0.7−1.2)	0.9	(0.7−1.3)
≥30	31	(11.0)	101	(9.0)	1.2	(0.8−1.9)	1.1	(0.7−1.8)	16	(11.5)	56	(10.1)	1.2	(0.6−2.3)	1.0	(0.4−2.1)	32	(8.4)	165	(10.9)	0.7	(0.5−1.1)	0.7	(0.4−1.1)
Unknown	70	(24.9)	269	(23.9)	1.0	(0.7−1.5)	1.3	(0.8−1.9)	42	(30.2)	146	(26.3)	1.3	(0.8−2.0)	1.2	(0.7−2.2)	97	(25.6)	399	(26.3)	0.9	(0.7−1.2)	1.0	(0.7−1.4)
Co-morbidities																								
CHF	70	(24.9)	242	(21.5)	1.2	(0.9−1.7)	1.1	(0.8−1.6)	50	(36.0)	120	(21.6)	2.1	(1.4−3.2)	1.5	(0.9−2.6)	101	(26.7)	318	(21.0)	1.4	(1.1−1.8)	1.1	(0.8−1.5)
Atrial fibrillation	30	(10.7)	111	(9.9)	1.1	(0.7−1.7)	0.9	(0.5−1.4)	29	(20.9)	56	(10.1)	2.4	(1.5−4.1)	1.5	(0.8−2.8)	42	(11.1)	136	(9.0)	1.3	(0.9−1.8)	1.0	(0.7−1.6)
IHD	49	(17.4)	108	(9.6)	2.0	(1.4−2.9)	2.5	(1.6−3.8)	33	(23.7)	62	(11.2)	2.4	(1.5−3.8)	1.8	(1.0−3.3)	73	(19.3)	137	(9.0)	2.4	(1.7−3.2)	2.3	(1.6−3.3)
Hypertension	156	(55.5)	513	(45.6)	1.5	(1.2−2.0)	1.5	(1.1−2.0)	71	(51.1)	233	(41.9)	1.5	(1.0−2.2)	1.4	(0.9−2.4)	179	(47.2)	664	(43.8)	1.2	(0.9−1.5)	1.1	(0.8−1.5)
Diabetes mellitus	34	(12.1)	117	(10.4)	1.2	(0.8−1.8)	1.1	(0.7−1.8)	20	(14.4)	44	(7.9)	2.0	(1.1−3.6)	1.3	(0.7−2.6)	44	(11.6)	180	(11.9)	1.0	(0.7−1.4)	0.9	(0.6−1.3)
Dyslipidemia	38	(13.5)	108	(9.6)	1.5	(1.0−2.3)	1.5	(0.9−2.3)	10	(7.2)	43	(7.7)	0.9	(0.4−1.9)	0.6	(0.2−1.4)	41	(10.8)	138	(9.1)	1.2	(0.8−1.8)	1.0	(0.7−1.5)
Depression	56	(19.9)	211	(18.8)	1.1	(0.8−1.5)	1.1	(0.8−1.5)	39	(28.1)	95	(17.1)	1.9	(1.2−3.0)	1.7	(1.1−2.8)	85	(22.4)	275	(18.2)	1.3	(1.0−1.7)	1.2	(0.9−1.6)

Table 3.4-3 cont.

	Ischemic stroke								Hemorrhagic stroke								Transient ischemic attack							
	Cases (n = 281) n (%)		Controls (n = 1124) n (%)		Unadjusted OR (95% CI)		Adjusted* OR (95% CI)		Cases (n = 139) n (%)		Controls (n = 556) n (%)		Unadjusted OR (95% CI)		Adjusted* OR (95% CI)		Cases (n = 379) n (%)		Controls (n = 1515) n (%)		Unadjusted OR (95% CI)		Adjusted* OR (95% CI)	
Drugs																								
ACE inhibitors	43	(15.3)	203	(18.1)	0.9	(0.6−1.3)	0.7	(0.5−1.1)	38	(27.3)	97	(17.5)	2.2	(1.4−3.4)	1.5	(0.9−2.7)	78	(20.6)	276	(18.2)	1.2	(0.9−1.6)	0.9	(0.7−1.3)
Diuretics	113	(40.2)	393	(35.0)	1.5	(1.1−2.0)	1.2	(0.8−1.7)	57	(41.0)	184	(33.1)	2.1	(1.3−3.5)	1.1	(0.6−2.1)	149	(39.3)	566	(37.4)	1.3	(1.0−1.7)	1.1	(0.8−1.6)
Statins	48	(17.1)	187	(16.6)	1.0	(0.7−1.5)	0.9	(0.6−1.4)	34	(24.5)	87	(15.7)	2.0	(1.2−3.3)	1.3	(0.7−2.5)	72	(19.0)	265	(17.5)	1.2	(0.9−1.7)	1.0	(0.7−1.4)
Antiplatelets	27	(9.6)	86	(7.7)	1.3	(0.8−2.1)	1.2	(0.7−1.9)	19	(13.7)	46	(8.3)	1.9	(1.1−3.4)	1.6	(0.8−3.2)	61	(16.1)	130	(8.6)	2.1	(1.5−3.0)	2.0	(1.4−2.9)
Anticoagulants	9	(3.2)	42	(3.7)	0.9	(0.4−1.8)	0.5	(0.2−1.0)	17	(12.2)	11	(2.0)	7.2	(3.2−16.2)	4.3	(1.6−11.8)	20	(5.3)	63	(4.2)	1.3	(0.8−2.3)	0.8	(0.4−1.4)

*Adjusted for all covariates listed in this table. CHF = Congestive Heart Failure, IHD = Ischemic Heart Disease, ACE = Angiotensin Converting Enzyme , OR = Odds Ratio, CI = Confidence Interval, Ref = Reference Group

Table 3.4-4: Risk of developing ischemic or hemorrhagic stroke or transient ischemic attack in patients with Alzheimer's disease or vascular dementia, stratified by age, sex, duration of dementia, and current use of typical or atypical antipsychotic drugs

	Ischemic stroke								Hemorrhagic stroke								Transient ischemic attack							
	Cases (n = 281) n (%)		Controls (n = 1124) n (%)		Unadjusted OR (95% CI)		Adjusted* OR (95% CI)		Cases (n = 139) n (%)		Controls (n = 556) n (%)		Unadjusted OR (95% CI)		Adjusted* OR (95% CI)		Cases (n = 379) n (%)		Controls (n = 1515) n (%)		Unadjusted OR (95% CI)		Adjusted* OR (95% CI)	
No dementia	156	(55.5)	657	(58.5)	1.0	(Ref)	1.0	(Ref)	59	(42.5)	342	(61.5)	1.0	(Ref)	1.0	(Ref)	191	(50.4)	916	(60.5)	1.0	(Ref)	1.0	(Ref)
Alzheimer's disease	74	(26.3)	365	(32.5)	0.8	(0.6–1.1)	0.9	(0.7–1.3)	43	(30.9)	171	(30.8)	1.4	(0.9–2.2)	2.0	(1.2–3.3)	129	(34.0)	457	(30.2)	1.3	(1.0–1.7)	1.4	(1.1–1.8)
Sex																								
Male	25	(8.9)	119	(10.6)	1.0	(0.6–1.6)	1.0	(0.6–1.7)	19	(13.7)	70	(12.6)	1.6	(0.8–3.1)	2.8	(1.3–6.0)	35	(9.2)	141	(9.3)	1.1	(0.7–1.7)	1.1	(0.7–1.8)
Female	49	(17.4)	246	(21.9)	0.8	(0.5–1.1)	0.9	(0.6–1.3)	24	(17.3)	101	(18.2)	1.3	(0.7–2.2)	1.7	(0.9–3.1)	94	(24.8)	316	(20.9)	1.4	(1.1–1.9)	1.5	(1.1–2.1)
Age [years]																								
65–79	27	(9.6)	105	(9.3)	1.2	(0.7–2.1)	1.3	(0.8–2.3)	12	(8.6)	40	(7.2)	1.8	(0.8–4.2)	3.3	(1.2–9.1)	45	(11.9)	124	(8.2)	1.9	(1.2–2.9)	2.0	(1.3–3.1)
≥80	47	(16.7)	260	(23.1)	0.7	(0.5–1.0)	0.8	(0.5–1.1)	31	(22.3)	131	(23.6)	1.3	(0.8–2.1)	1.8	(1.0–3.0)	84	(22.2)	333	(22.0)	1.1	(0.8–1.5)	1.2	(0.9–1.6)
Duration [years]																								
<1	29	(10.3)	144	(12.8)	0.8	(0.5–1.3)	1.0	(0.6–1.5)	14	(10.1)	65	(11.7)	1.2	(0.6–2.3)	1.5	(0.8–3.0)	39	(10.3)	167	(11.0)	1.1	(0.7–1.6)	1.1	(0.7–1.6)
≥1	45	(16.0)	221	(19.7)	0.8	(0.6–1.2)	0.9	(0.6–1.3)	29	(20.9)	106	(19.1)	1.5	(0.9–2.5)	2.5	(1.4–4.4)	90	(23.8)	290	(19.1)	1.5	(1.1–1.9)	1.6	(1.2–2.1)
Antipsychotics																								
No use	41	(14.6)	212	(18.9)	0.8	(0.6–1.2)	0.9	(0.6–1.4)	17	(12.2)	100	(18.0)	0.9	(0.5–1.7)	1.4	(0.7–2.7)	65	(17.2)	251	(16.6)	1.2	(0.9–1.7)	1.3	(0.9–1.8)
Past use	16	(5.7)	90	(8.0)	0.7	(0.4–1.3)	0.7	(0.4–1.3)	12	(8.6)	42	(7.6)	1.6	(0.8–3.2)	2.0	(0.9–4.6)	28	(7.4)	142	(9.4)	0.9	(0.6–1.4)	0.9	(0.6–1.5)
Current use	17	(6.1)	63	(5.6)	1.1	(0.6–1.9)	1.1	(0.6–2.0)	14	(10.1)	29	(5.2)	2.7	(1.4–5.4)	4.0	(1.8–8.9)	36	(9.5)	64	(4.2)	2.7	(1.7–4.2)	2.9	(1.8–4.6)
Typical only	4	(1.4)	17	(1.5)	1.0	(0.3–2.9)	1.1	(0.3–3.3)	5	(3.6)	8	(1.4)	3.7	(1.1–11.8)	7.1	(1.9–26.9)	8	(2.1)	23	(1.5)	1.6	(0.7–3.7)	1.8	(0.8–4.2)
Atypical only	7	(2.5)	20	(1.8)	1.4	(0.6–3.4)	1.4	(0.6–3.5)	1	(0.7)	10	(1.8)	0.6	(0.1–5.2)	0.8	(0.1–8.5)	16	(4.2)	16	(1.1)	4.8	(2.3–9.8)	5.5	(2.6–11.7)
Both	6	(2.1)	26	(2.3)	1.0	(0.8–1.2)	1.0	(0.8–1.2)	8	(5.8)	11	(2.0)	1.3	(1.1–1.5)	1.3	(1.1–1.7)	12	(3.2)	25	(1.7)	1.2	(1.0–1.4)	1.2	(1.0–1.4)

Table 3.4-4 cont.

	Ischemic stroke								Hemorrhagic stroke								Transient ischemic attack							
	Cases (n = 281) n (%)		Controls (n = 1124) n (%)		Unadjusted OR (95% CI)		Adjusted* OR (95% CI)		Cases (n = 139) n (%)		Controls (n = 556) n (%)		Unadjusted OR (95% CI)		Adjusted* OR (95% CI)		Cases (n = 379) n (%)		Controls (n = 1515) n (%)		Unadjusted OR (95% CI)		Adjusted* OR (95% CI)	
No dementia	156	(55.5)	657	(58.5)	1.0	(Ref)	1.0	(Ref)	59	(42.5)	342	(61.5)	1.0	(Ref)	1.0	(Ref)	191	(50.4)	916	(60.5)	1.0	(Ref)	1.0	(Ref)
Vascular dementia	51	(18.2)	102	(9.1)	2.1	(1.5–3.1)	2.1	(1.4–3.1)	37	(26.6)	43	(7.7)	5.1	(3.0–8.8)	4.7	(2.5–9.0)	59	(15.6)	142	(9.4)	2.0	(1.4–2.8)	1.8	(1.3–2.6)
Sex																								
Male	25	(8.9)	41	(3.7)	2.9	(1.6–5.1)	2.9	(1.6–5.3)	14	(10.1)	12	(2.2)	7.2	(2.9–18.1)	8.3	(2.6–25.8)	24	(6.3)	60	(4.0)	1.8	(1.0–3.1)	1.7	(1.0–3.0)
Female	26	(9.3)	61	(5.4)	1.7	(1.0–2.8)	1.7	(1.0–2.8)	23	(16.6)	31	(5.6)	4.2	(2.2–8.2)	3.6	(1.6–7.8)	35	(9.2)	82	(5.4)	2.1	(1.3–3.3)	1.8	(1.2–2.9)
Age [years]																								
65–79	21	(7.5)	37	(3.3)	2.8	(1.5–5.3)	2.7	(1.4–5.2)	8	(5.8)	4	(0.7)	12.7	(3.2–50.2)	7.0	(1.4–35.2)	15	(4.0)	31	(2.1)	2.5	(1.3–4.8)	2.8	(1.4–5.5)
≥80	30	(10.7)	65	(5.8)	1.8	(1.1–2.9)	1.9	(1.2–3.1)	29	(20.9)	39	(7.0)	4.2	(2.4–7.6)	4.3	(2.1–8.7)	44	(11.6)	111	(7.3)	1.8	(1.2–2.7)	1.6	(1.0–2.4)
Duration [years]																								
<1	30	(10.7)	51	(4.5)	2.5	(1.5–4.0)	2.6	(1.6–4.3)	13	(9.4)	18	(3.2)	4.0	(1.9–8.8)	3.2	(1.2–8.4)	24	(6.3)	82	(5.4)	1.4	(0.9–2.2)	1.2	(0.7–2.0)
≥1	21	(7.5)	51	(4.5)	1.7	(1.0–2.9)	1.6	(0.9–2.9)	24	(17.3)	25	(4.5)	6.0	(3.1–11.8)	6.1	(2.8–13.5)	35	(9.2)	60	(4.0)	2.9	(1.8–4.7)	2.8	(1.7–4.6)
Antipsychotics																								
No use	28	(10.0)	54	(4.8)	2.1	(1.3–3.5)	2.3	(1.4–3.8)	13	(9.4)	20	(3.6)	4.0	(1.9–8.6)	4.2	(1.6–11.0)	24	(6.3)	78	(5.2)	1.5	(0.9–2.4)	1.4	(0.9–2.4)
Past use	19	(6.8)	25	(2.2)	3.4	(1.8–6.5)	3.1	(1.6–6.2)	11	(7.9)	9	(1.6)	6.7	(2.6–17.4)	4.7	(1.6–14.1)	17	(4.5)	33	(2.2)	2.5	(1.4–4.6)	2.1	(1.1–4.0)
Current use	4	(1.4)	23	(2.1)	0.7	(0.2–2.1)	0.7	(0.2–2.2)	13	(9.4)	14	(2.5)	5.8	(2.5–13.4)	5.3	(2.0–13.6)	18	(4.8)	31	(2.1)	2.8	(1.5–5.1)	2.5	(1.3–4.7)
Typical only	0	(0.0)	9	(0.8)		NA		NA	4	(2.9)	5	(0.9)	4.0	(1.0–15.4)	2.3	(0.5–10.7)	6	(1.6)	10	(0.7)	3.1	(1.1–8.7)	2.9	(1.0–8.6)
Atypical only	2	(0.7)	8	(0.7)	1.1	(0.2–5.2)	1.1	(0.2–5.7)	6	(4.3)	4	(0.7)	9.4	(2.6–35.0)	11.1	(2.5–49.8)	6	(1.6)	12	(0.8)	2.4	(0.9–6.6)	1.9	(0.7–5.5)
Both	2	(0.7)	6	(0.5)	1.4	(0.3–7.0)	1.4	(0.3–7.4)	3	(2.2)	5	(0.9)	4.2	(0.9–19.7)	5.2	(0.9–30.8)	6	(1.6)	9	(0.6)	3.1	(1.1–8.8)	3.0	(1.0–9.0)

* Adjusted for smoking, BMI, ischemic heart disease, congestive heart failure, atrial fibrillation, hypertension, diabetes mellitus, dyslipidemia, depression, and use of angiotensin converting enzyme (ACE) inhibitors, diuretics, antiplatelets, anticoagulants and statins. OR = Odds Ratio, CI = Confidence Interval, Ref = Reference Group

3.4.5 Discussion

We found that patients with AD did not have a materially altered risk of ischemic stroke compared to those without dementia, whereas patients with VD had an about twofold increased risk. We further found that patients with AD had a twofold higher risk of developing a hemorrhagic stroke than patients without dementia. Of note, cerebral amyloid angiopathy (CAA) is an important cause of sporadic hemorrhagic stroke in the elderly[166], and it has been suggested that presence of the apolipoprotein E ε4 allele – which has also been linked to the development of late-onset AD[73] – may accelerate the process that leads to CAA-related hemorrhagic stroke.[167]

A previous population-based cohort study of 1,551 subjects aged ≥75 years with no stroke history found similar results. The risks of incident stroke for patients with mild dementia or cognitive impairment in the study were 2.6 (95% CI 1.2–5.7) and 2.0 (95% CI 1.0–3.8), respectively.[152] Of importance, these authors did not stratify by dementia subtypes, as we did. They found that - within the group of patients with cognitive impairment - those who developed a stroke tended to have a higher prevalence of vascular risk factors (such as hypertension, heart disease, or diabetes mellitus) compared to those who did not.[152] This supports our findings that AD patients who had no increased risk of developing an ischemic stroke, had a lower prevalence of vascular risk factors than patients with VD, who in turn had an about twofold higher risk. Since VD by definition is associated with cerebrovascular disease[78] and, according to our data, VD patients have a higher prevalence of cardiovascular risk factors than patients without dementia, it may be that VD patients suffered from cerebral microangiopathy prior to developing an ischemic stroke and were therefore at a higher risk of ischemic stroke than non-demented subjects. In addition, since these authors[152] did not differentiate between ischemic stroke, hemorrhagic stroke or TIA, a direct comparison of the results is difficult. However, ischemic stroke is more common than hemorrhagic stroke[168] and thus may have accounted for the majority of stroke cases in that study.[152]

Regarding the role of antipsychotic drugs on the risk of developing stroke or TIA, we found that AD patients who received atypical antipsychotic drugs only, had a higher risk of developing a TIA than AD patients who did not receive antipsychotic drug treatment. For patients with VD there was no difference between users of typical or atypical antipsychotic drugs and those who did not receive antipsychotic treatment.

There are several observational studies[161-163,169] that examined the association between exposure to typical or atypical antipsychotic drugs in patients with dementia and the risk of cerebrovascular events, but to our knowledge there is only one study[170] that also stratified by different dementia types, i.e. AD vs. VD. In this particular cohort study of 14,029 US veterans aged ≥65 years, diagnosed with AD or VD, neither use of atypical nor typical antipsychotics in patients with AD was associated with an increased risk of developing a cerebrovascular event, compared to non-users of antipsychotic drugs; for patients with VD there was no significant difference in risk between users of atypical compared to typical antipsychotic drugs, but there was a suggestion of an increased risk of developing a cerebrovascular event associated with VD, which was not present in patients with AD. Although the latter finding largely supports our results of a significantly higher risk of developing a stroke in patients with VD, as compared to patients with AD, the study was limited by a relatively short follow-up period of 18 months (in which less than 4% of the study population developed a cerebrovascular event). Additionally, the authors of this study did not differentiate between stroke and TIA in their study. Since stroke itself is not a uniform condition, combining these conditions to one "cerebrovascular group" may have masked subtle differences in relative risk estimates, as found in our study.

Our finding of an increased TIA risk in AD patients exposed only to atypical antipsychotic drugs is supported by reports of adverse drug events in association with use of atypical antipsychotics from randomized controlled trials that aimed at studying the efficacy of these drugs to treat behavioral symptoms in patients with AD. In these trials, a TIA was found to be the only[171,172] or the most frequent[173] cerebrovascular adverse drug event.

The results of our study must be interpreted in the light of some limitations. First, we identified a large number of potential stroke or TIA cases based on recorded codes. As we were not able to review each patient's record to verify the stroke or TIA diagnosis, we used a stringent predefined algorithm to increase the likelihood of including cases with a valid diagnosis of stroke or TIA. However, some residual misclassification cannot be ruled out. Further, we could not assess the severity of AD or VD to test whether severity of dementia altered the risk of developing a stroke or a TIA, because we had no information on the patients' cognitive status from the record. However, as duration of symptoms has been related to dementia severity,[149] we used duration of the disease as a rough proxy for severity.

The major strength of our study is that we used a large and well-established primary-care database which has been validated numerous times in the past.[103,104] Since stroke and TIA are not common in patients with AD or VD (only about 4% of all AD patients and about 7% of all VD patients in our study developed a stroke or TIA during follow-up), a large database such as the CPRD was necessary to obtain an adequate number of patients to detect potential differences between users and non-users of (typical or atypical) antipsychotics. Furthermore, we used a sophisticated and validated algorithm to identify only well-defined AD or VD cases for inclusion in the study population.

In summary, we found that patients with AD did not have a materially different risk of developing an ischemic stroke compared to patients without dementia, whereas patients with VD had an about twofold increased risk. AD patients receiving atypical antipsychotic drugs only had a higher risk of developing a TIA than AD patients not receiving any antipsychotic drug treatment, whereas for patients with VD there was no significant difference between users of atypical or typical antipsychotic drugs and those not receiving antipsychotic treatment.

CHAPTER 4

DISCUSSION, CONCLUSIONS, OUTLOOK

4 DISCUSSION, CONCLUSIONS, AND OUTLOOK

4.1 DISCUSSION

The overall aim of this thesis was to contribute to the understanding of the natural history of the two most common dementia subtypes AD and VD, by using data from GPRD, a large and well-established physician-based primary care database from the UK. A detailed discussion of the main findings of this thesis is provided in the corresponding sections of the Studies 3.1–3.4. In this chapter some general strengths and limitations of the GPRD will be discussed and illustrated with examples from the different studies.

4.1.1 Strengths of the General Practice Research Database

Size

The GPRD encompasses data on over five million active research quality patients from the UK who are registered with selected GPs. This large number of patients translates into more than 45 million py of research quality data.[100] This large size of the database allows researchers to study rare outcomes with an incidence rate of less than one per 10,000 persons per year with enough statistical power.[174] As an example: based on limited evidence from case reports, AChEIs have been suspected to rarely provoke seizures in patients with AD.[143,144] This is supported by two small RCTs assessing the efficacy of donepezil to improve memory in patients with epilepsy that found a small but non-significant difference in seizure frequency between those treated with donepezil and those treated with placebo.[147,148] However, since occurrence of seizures or epilepsy in AD is overall uncommon,[138] one would require a much larger sample size (and/or a longer observation period) to detect a statistically significant difference among users of AChEIs compared to nonusers, if it exists. Notably, in our study (3.3) that included a relatively large sample of almost 7,000 AD patients observed over a median follow-up time of 1.5 years, we did not find a statistically significant difference.

Population-based data

The GPRD represents a defined population, which allows researchers to study all patients with a certain disease (i.e. the cases) and enables them to study control

patients from the same source population from which the cases were derived. This minimizes selection bias (cf. chapter 1.1.4) and improves the validity of the study.[12] Additionally, patients in the GPRD cover about 8% of the UK population[100] and are broadly representative of the general UK population in terms of age, sex, geographic distribution, and annual turnover rate. As an example: in Study 3.3 we estimated the relative risk of developing seizures in patients with AD. Our relative risk estimate (OR 6.6) was somewhat lower than the corresponding estimates reported in two previous studies (RR 10.0 and HR 8.06),[134,138] although reported confidence intervals in these two studies were wide and included the point estimate reported in our study. However, in both these comparison studies AD cases were recruited from special care facilities or specialized diagnostic and treatment centers; thus, these patients were presumably at a more advanced stage of their disease compared to demented patients selected from the general population in primary care, as in our study. As more severe and advanced stages of AD have been reported to be associated with a greater risk of seizures or epilepsy,[136,137] these patients were probably more likely to have seizures or epilepsy than a sample of AD patients derived from the general population.

Access to original medical records

Investigators who work with the GPRD have the opportunity to obtain anonymized photocopies of the patient's paper medical record. This allows investigators to verify the information recorded on death certificates or letters from specialists. Additionally, there's the possibility to send out questionnaires to the GPs asking them for additional patient information that has not been recorded in the electronic medical file. Sometimes it's even possible to have questionnaires completed by individual patients by working through their GP.[12,174] As an example: All the AD and VD cases that formed (together with their corresponding dementia-free controls) the study population in the studies of this thesis were identified through a specially developed algorithm. To validate this algorithm we sent out a questionnaire to GPs for a random sample of potential AD and VD cases to get additional information on the clinical circumstances and the diagnostic steps taken. The response rate of the GPs was almost 80%, a number which has also been confirmed by other studies.[175]

4.1.2 Limitations of the General Practice Research Database

Missing data

In fact the information recorded by the GP is expected to be complete. However, information from specialists as well as events that occur in the hospital may not be fully captured in the electronic patient record. Communications from specialists, discharge letters from hospitals, and laboratory test results are often received in hard copy and must be manually entered into the practice computer. Since this can be time-consuming, some practices may only enter information that will affect the future care of the patient. Therefore only abnormal test results may be entered into the computer. Additionally, information on treatments that are restricted by the National Health Service (NHS) to specialist care (e.g. chemotherapy in the hospital) may not be captured in the patient file. Information about over-the-counter (OTC) medication is not readily available in the GPRD. Furthermore, data on important confounders such as dietary or exercise habits is largely missing and information on other lifestyle factors such as smoking, BMI, or alcohol consumption is not recorded for all patients.[12,174] As an example: in Study 3.2, where we explored the risk of developing AD in patients with diabetes mellitus treated with metformin or with other antidiabetic drugs, we were not able to adjust for certain potential confounders such as ApoE ε4 allele,[73] level of education,[132] or certain lifestyle factors such as physical activity[133] or dietary habits.[68] However, we adjusted for BMI which is to some degree related to physical activity and dietary habits.

4.2 CONCLUSIONS

The aim of this thesis was to increase knowledge on the natural history of the two most common dementia forms AD and VD, thereby focusing on the effect of certain drug therapies as potential risk or protective factors for these diseases or complications thereof. In the following, the main findings are briefly summarized:

- The IR of AD was higher for women than for men, whereas for VD no difference in sex-specific IR was observed.
- The prevalence of all CV co-morbidities and exposure to CV drugs was lower in patients with AD than in those without dementia, whereas the opposite was true for VD. This may be a true finding or the result of diagnostic bias, i.e. demented patients with CV diseases may be more likely to be diagnosed with VD than AD.
- Long-term users of metformin had a slightly increased risk of developing AD as compared to non-users, but there was no consistent trend with increasing duration of use.
- Use of other antidiabetic drugs such as sulfonylureas, thiazolidinediones, or insulin was not associated with an altered risk of developing AD.
- Seizures or epilepsy were substantially more common in patients with AD and VD than in dementia-free patients.
- AD patients with longer standing (≥3 years) had a slightly higher risk of developing seizures or epilepsy than those with a shorter disease duration, while in patients with VD the contrary was observed.
- Patients with AD did not have a materially altered risk of developing an ischemic stroke compared to those without dementia, whereas patients with VD had an about twofold increased risk.
- AD patients receiving atypical antipsychotic drugs only had a higher risk of developing a TIA than AD patients not receiving any antipsychotic drug treatment, whereas for patients with VD there was no significant difference between users of atypical or typical antipsychotic drugs and those not receiving antipsychotic treatment.

4.3 OUTLOOK

There are currently two ongoing studies assessing incidence rates of new-onset diseases (complications) in patients with AD or VD and studying risk factors for the development of such complications. The first study focuses on fractures. Evidence from the literature suggests that AD patients have a higher risk of sustaining a fracture, particularly of the hip, as compared to non-demented elderly people.[176-178] Hip fractures represent about 50% of all fracture types in patients with AD,[176] and the association between AD and hip fractures has been found to be independent of other important risk factors for fractures such as osteoporosis or falling.[179] However, little is known about specific risk factors (e.g. age, sex, severity of dementia, etc.) of sustaining a hip fracture in patients with AD and specific risk estimates for patients with VD are lacking, too.

The second ongoing study focuses on depression. Depression is one of the most common psychiatric disorders observed in patients with AD. Many studies investigated the frequency of depression or depressive disorders in patients with AD and reported prevalence rates ranging between 30–50%.[180] By contrast, there are only few studies assessing the incidence of depression in patients with AD and estimates thereof vary considerably.[181-184]

Furthermore, there's an interesting study in preparation for submission that explored the risk of developing AD in association with a history of influenza infection(s). This against the background that several epidemiological studies suggest a potential involvement of viral pathogens in the development of AD.[185-188] However, while recent research focuses on herpes simplex virus type 1 (HSV-1),[189,190] the role of influenza infection is largely unknown.

CHAPTER 5

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5 REFERENCES

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CHAPTER 6

APPENDIX

6 APPENDIX

QUESTIONNAIRE FOR GENERAL PRACTITIONERS

Study into Dementia: Questionnaire for £

Please tick the appropriate box

1) Does the patient with the ID number ……have dementia?
   - ☐ Yes
   - ☐ No

2) Did you as GP perform any test(s) to assess the level of cognitive impairment?
   - ☐ Yes
   - ☐ No

   If 'Yes', which test(s)? (S*everal answers possible*)
   - ☐ Mini Mental State Examination (MMSE)
   - ☐ 6-Item Cognitive Impairment Test (6-CIT)
   - ☐ General Practitioner Assessment of Cognition (GPCOG)
   - ☐ Abbreviated Mental Test (7-Minute Screen)
   - ☐ Clock Drawing Test (CDT)
   - ☐ Other, **please specify** _____

3) Has the dementia diagnosis been confirmed by a specialist (e.g. geriatrician, psychiatrist, neurologist, psychologist, etc.)?
   - ☐ Yes
   - ☐ No

   If 'Yes', by which method? (S*everal answers possible*)
   - ☐ Neuropsychological assessment
   - ☐ Magnetic Resonance Imaging (MRI)
   - ☐ Computed Tomography (CT)
   - ☐ Single Photon Emission Computed Tomography (SPECT)
   - ☐ Cerebrospinal fluid (CSF)-biomarkers
   - ☐ Other, **please specify** _____

4) Has the subtype of dementia been further specified?

☐ Yes

☐ No

If 'Yes' what is the subtype of dementia?

☐ Alzheimer's disease

☐ Vascular dementia

☐ Mixed Alzheimer's disease/Vascular dementia

☐ Lewy body dementia

☐ Frontotemporal dementia (Pick's disease)

☐ Other, **please specify** _____

5) When was the dementia (including subtype) diagnosed?

_ _ / _ _ _ _ (MM/YYYY)

6) Does or did the patient receive regular pharmacological treatment (i.e. 3 or more prescriptions) for dementia which is not recorded in the electronic patient file (e.g. prescriptions issued by a specialized clinic)?

☐ Yes

☐ No

If 'Yes', which drug?

☐ Donepezil

☐ Rivastigmine

☐ Galantamine

☐ Memantine

☐ Other, **please specify** _____

Please also provide photocopies of all relevant hospital summaries, discharge letters and test results that can verify the diagnosis.

Many thanks for your time in completing this questionnaire.
Please now return it in the freepost envelope provided.

CHAPTER 7

CURRICULUM VITAE

7 CURRICULUM VITAE

Personal Data

Name	Patrick Alexander Imfeld
Date of Birth	30 September 1977
Place of Origin	Lungern (OW)
Marital Status	Married, 1 child
E-Mail	patrick_imfeld@gmx.ch

Education

02/2009–06/2012	**PhD** at the University of Basel *Title of PhD thesis:* 'Population-based studies on the natural history of Alzheimer's disease and vascular dementia' *Supervision:* Prof. Dr. Christoph Meier
09/2007–01/2009	Post-graduate Master's program in Clinical Pharmacy at the University of Strathclyde, Glasgow, UK *Degree:* **MSc in Clinical Pharmacy *with distinction*** (recognized in Switzerland as 'Fähigkeitsauweis FPH in Klinischer Pharmazie') *Title of Master thesis*: 'The pharmaceutical care plan in the continuity of care of older patients discharged to a nursing home' *Supervision*: Prof. Stephen Hudson, Dr. Markus Lampert
10/1998–04/2005	Study of Pharmacy at the Federal Institute of Technology (ETH), Zurich *Degree*: **Swiss Federal Diploma in Pharmacy** *Title of Diploma thesis*: 'Grundlagen für die Entwicklung eines miniaturisierten optischen Enzym-Assays für den Nachweis von Bakterien-Endotoxinen auf der Basis eines chromogenen LAL-Tests' *Supervision*: Prof. Dr. Ursula Spichiger-Keller, Dr. Gleb Zhylyak
08/1990–06/1997	**Matura, Type C** (main subject: mathematics) at the Kantonsschule Alpenquai, Lucerne

Continuing Education

2009-2012	**University of Basel:** Epidemiological Concepts, Biostatistics I, Scientific Writing, Seminars in Drug Discovery and Development, Key Issues in Drug Discovery and Development, various 'Advanced Studies' courses in Clinical Pharmacy **University Hospital Basel:** Montagsfortbildung der Medizinischen Poliklinik und der Klinischen Pharmakologie, Pharma-Update der Spitalpharmazie, Donnerstagskonferenz (DOKO) der Inneren Medizin, Pharmathemen
2005-2007	Various continuing education courses for pharmacists

Current position

Since 07/2012	Part-time **Research Associate** (50%) at the Basel Pharmaco-epidemiology Unit (BPU), University of Basel
Since 09/2011	Part-time **Clinical Pharmacist** (50%) at the University Hospital Basel

Professional Experience

02/2009–09/2011	Part-time **Pharmacist** (mainly two Sundays per month and additional days if required) at the Apotheke im Bahnhof, Uster (ZH)
	Assisting in spontaneous adverse drug reaction (ADR) reporting to health authority at the **Regional Pharmacovigilance Center Basel**
02/2006–09/2007	**Pharmacist** at the Park Apotheke-Drogerie, Winterthur (ZH) and at the Apotheke im Bahnhof, Uster (ZH). (Both belong to the Topwell-Apotheken AG, Winterthur (ZH)
07/2005–10/2005	**Pharmacist** at the Apotheke & Drogerie Oerlikon (ZH)
11/2002–02/2005	Part-time **Assistant-Pharmacist** (*cand. pharm*.) at different stores of the Letzi Apotheke und Drogerie AG, Lucerne
04/2001–06/2001	Temporary appointment at the **Cantonal Statistics Department Lucerne**
03/1998–08/2001	Several temporary appointments (between 2-6 months) at the SUVA Lucerne
12/1997–02/1998	Temporary appointment at the library of the Technikum Horw (LU)
08/1995–07/1997	Part-time appointment at the market research institute Demoscope in Adligenswil (LU)

Language Skills

German	Mother tongue
Spanish	Mother tongue
English	Very good oral and written skills Certificate: TOEFL (internet-based test) score in August 2007: 104 [max. score: 120]
French	Good oral and written skills

Computer Skills

Microsoft Office (Word, Excel, PowerPoint, Outlook)	Good knowledge
SAS Statistical Software	Basic knowledge
ProPharma Pharmacy Administration Program	Good knowledge

Publications

Imfeld P, Bodmer M, Jick SS, Meier CR. Metformin, other antidiabetic drugs, and risk of Alzheimer's disease: a population-based case-control study. J Am Geriatr Soc 2012;60(5): 916-21

Imfeld P, Brauchli Pernus YB, Jick SS, Meier CR. Epidemiology, co-morbidities, and drug use of patients with Alzheimer's disease or vascular dementia in the UK. J Alzheimers Dis 2012; submitted

Imfeld P, Bodmer M, Schuerch M, Jick SS, Meier CR. Seizures in patients with Alzheimer's disease or vascular dementia: a population-based nested case-control anaysis. Epilepsia 2012; submitted

Imfeld P, Bodmer M, Schuerch M, Jick SS, Meier CR. Risk of incident stroke in patients with Alzheimer's disease or vascular dementia: a population-based nested case-control analysis. Neurology 2012; submitted

Oral communications

Imfeld P. Anti-dementia drugs in patients with Alzheimer's disease and the risk of developing seizures or epilepsy: a population-based nested case-control analysis. 28th International Conference on Pharmacoepidemiology and Therapeutic Risk Management, Barcelona, E: 26 August 2012

Imfeld P. Risk of developing Alzheimer's disease in association with influenza infections. 1st GSASA-pharmaSuisse Congress, Interlaken (BE): 30 November 2011

Imfeld P. An epidemiologic study on Alzheimer's disease and other dementia forms. 1st Bürgenstock-Seminar (former: BCDSP Symposium on Drug Safety and Pharmacoepidemiology), Bürgenstock (NW): 8 June 2011

Imfeld P. Prevalence of co-morbidities and drug exposure in patients with Alzheimer's disease around the time of diagnosis. 26th International Conference on Pharmacoepidemiology and Therapeutic Risk Management, Brighton, UK: 22 August 2010

Imfeld P. The pharmaceutical care plan in the continuity of care of older patients discharged to a nursing home. ESCP-GSASA Symposium on Clinical Pharmacy, Geneva: 4 November 2009

Workshops

Imfeld P, Spöndlin J. Einen Infusionsplan verstehen und an einem konkreten Beispiel erstellen. Arzneimittelinformation – Advanced Study Centre, Basel: 21 Juni 2012

Iten S, Lattman C, Imfeld P. Therapiebeginn und -änderung durch den Apotheker: Wann und wie? 1st GSASA-pharmaSuisse Congress, Interlaken (BE): 1 December 2011

Hersberger KE, Imfeld P. Analgetika in besonderen klinischen Situationen (Leber-, Niereninsuffizienz, etc.): Diskussion von Fallbeispielen. Bruderholz-Seminar in Klinischer Pharmazie – Advanced Study Centre, Bruderholz (BL): 21 September 2011

Meier CR, Imfeld P. Reduzieren PPIs die Wirksamkeit von Clopidogrel? Eine kritische Analyse der Literatur. Bruderholz-Seminar in Klinischer Pharmazie – Advanced Study Centre, Bruderholz (BL): 14 September 2010

Hudson SA, Imfeld P. The pharmaceutical care plan in the continuity of care: case studies. Bruderholz-Seminar in Klinischer Pharmazie – Advanced Study Centre, Bruderholz (BL): 24 September 2009

Poster presentations

Imfeld P, Toovey S, Jick SS, Meier CR. Risk of developing Alzheimer's disease in association with influenza infections. Swiss Science Pharma Day, Berne: 29 August 2012

Imfeld P, Toovey S, Jick SS, Meier CR. Risk of developing Alzheimer's disease in association with influenza infections. 28th International Conference on Pharmacoepidemiology and Therapeutic Risk Management, Barcelona, E: 23-26 August 2012

Imfeld P, Toovey S, Jick SS, Meier CR. Risk of developing Alzheimer's disease in association with influenza infections. 40th European Symposium on Clinical Pharmacy, Dublin, IR: 18-21 October 2011

Imfeld P, Bodmer M, Jick SS, Meier CR. Metformin, other antidiabetic drugs and Alzheimer's disease: a case-control study. Swiss Science Pharma Day, Berne: 31 August 2011

Imfeld P, Bodmer M, Jick SS, Meier CR. Metformin, other antidiabetic drugs and Alzheimer's disease: a case-control study. 27th International Conference on Pharmacoepidemiology and Therapeutic Risk Management, Chicago, IL, USA: 14-17 August 2011

Imfeld P, Brauchli YB, Schuerch M, Robinson NJ, Jick SS, Meier CR. Alzheimer's disease and risk of subsequent stroke or transient ischemic attack: a population-based nested case-control analysis. 27th International Conference on Pharmacoepidemiology and Therapeutic Risk Management, Chicago, IL, USA: 14-17 August 2011

Imfeld P, Brauchli YB, Jick SS, Meier CR. Antihypertensive drugs and the risk of developing Alzheimer's disease. 39th European Symposium on Clinical Pharmacy, Lyon, F: 21-23 October 2010

Bodmer M, Brauchli YB, Imfeld P, Jick SS, Meier CR. Diabetes mellitus and risk of gallstone disease followed by cholecystectomy. 26th International Conference on Pharmacoepidemiology and Therapeutic Risk Management, Brighton, UK: 19-22 August 2010

Lectures

During my studies I followed courses of the following lecturers:

Altmann KH, Altorfer H, Amrhein N, Baltisberger M, Borschberg HJ, Boutellier U, Folkers G, Gander B, Gertsch J, Hächler H, Heilmann J, Helenius A, Hersberger KE, Kayser FH, Krähenbühl S, Lengeler C, Meier BH, Meier CR, Merkle HP, Möhler H, Müntener M, Pregosin PS, Rentsch K, Schibli R, Schubiger PA, Thurnheer P, Vonderschmitt D, Vounatsou P, Wolfer DP, Wunderli-Allenspach H