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DEMENTIA AND USE OF DRUGS: ECONOMIC MODELLING AND POPULATION-BASED STUDIES

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Dementia and use of drugs: economic modelling and
population based studies
THESIS FOR DOCTORAL DEGREE (Ph.D.)

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ABSTRACT

ENGLISH

The overall aim of this thesis was to investigate epidemiological and health economic aspects of dementia and drug use in older people, through economic modelling and analyses of population-based studies. The major findings from the separate studies are summarized below.

Study I We aimed to investigate whether dementia was associated with higher drug costs in 4,108 participants aged ≥ 60 years from the Swedish National Study on Aging and Care in Kungsholmen and Nordanstig (SNAC-K and SNAC-N). Overall, the average crude cost of drug use was 6,147 SEK per year for people with dementia and 3,810 SEK per year for people without dementia. The cost of nervous system drugs was more than five times higher in persons with dementia than without. However, the higher crude costs for drug use in people with dementia were confounded by comorbidities and residential setting. In fact, the strongest drug cost driver was comorbidity followed by residential setting.

Study II We aimed to investigate inappropriate drug use (IDU) and risk of hospitalizations and mortality in older persons and in persons with dementia and to also estimate the costs of IDU-related hospitalizations. In this study, based on data from SNAC-K and SNAC-N, the National Patient Register and the Cause of Death Register, we used logistic and Cox regression models to analyse associations between IDU, hospitalizations and mortality in the whole study population and in the subpopulation of persons with dementia. We found a higher risk of hospitalization (adjusted OR=1.46; 95% CI 1.18-1.81) and mortality (adjusted HR=1.15; 95% CI 1.01-1.31) in the whole study population and with hospitalization (adjusted OR=1.88; 95% CI 1.03-3.43) in the subpopulation of persons with dementia, after adjustment for confounding factors. There was also a tendency for higher costs for hospitalizations with IDU than without IDU, although not statistically significant.

Study III We aimed to describe the costs of an incident cohort of persons with dementia through simulation modelling. With input from epidemiological data, the Markov model estimated approximately 24,000 incident cases of dementia in Sweden in 2005. The incident cohort was run in the model for ten cycles of one year each. State specific costs were used and defined by the Clinical Dementia Rating scale. Results of the simulation showed that the total costs of the cohort were 27.7 billion SEK. The average annual cost of one person with dementia was 269,558 SEK. The severe state of dementia accounted for the largest proportion of costs for incident dementia cases. Costs of drugs in dementia only accounted for about 2% of the costs in the model. The main cost driver was institutional care, even for mild dementia.

Study IV We aimed to introduce a hypothetical economic model of a disease modifying treatment (DMT) for Alzheimer's disease (AD). We created a Markov model built on Swedish conditions with two arms; one representing the hypothetical treatment and the other arm representing no treatment. States and progression of the disease were defined with Mini Mental State Examination. Epidemiological data of incidence, prevalence and costs of mild

cognitive impairment (MCI), studies of conversion from MCI to AD and official statistics were used as input in the model. The incremental cost effectiveness ratio was 293,002 SEK/Quality Adjusted Life Year. The treated persons showed increased survival (8.7 years) versus the non-treated persons (7.8 years). With a societal willingness to pay of 600,000 SEK, the hypothetical treatment can be considered as cost effective. The main reasons for the higher costs with DMT were the costs of DMT itself and the prolonged survival with DMT.

Conclusion: The observed higher crude drug costs in dementia were confounded by comorbidities and residential setting. We also found that IDU was associated with an increased risk of hospitalization and mortality among older persons. This underlines the need for cautious prescribing to elderly patients. However, further studies are needed to investigate the association between IDU and costs for hospitalizations.

The highest accumulated costs in dementia occur in severe dementia and the major cost driver is institutionalization, even in mild dementia. Drugs, on the other hand, constitute only a minor part of the total costs. Our study of a hypothetical DMT showed that DMT in AD is projected as not being cost saving if the treatment prolongs survival. Still, if a societal willingness-to pay level of 600,000 SEK is adopted, the treatment can be considered as cost effective.

Det övergripande syftet med denna avhandling var att undersöka epidemiologiska och hälsoekonomiska aspekter av demenssjukdom och läkemedelsanvändning hos äldre personer, genom ekonomisk modellering och analyser av populationsbaserade studier. De viktigaste resultaten från de separata studierna sammanfattas nedan.

Studie I Vi undersökte om demenssjukdom var associerad med högre läkemedelskostnader hos 4108 personer i åldern ≥ 60 år som deltog i den svenska nationella studien om åldrande och vård på Kungsholmen och i Nordanstig (SNAC-K och SNAC-N). I genomsnitt var den totala årliga kostnaden för läkemedelsanvändning 6147 kr för personer med demenssjukdom och 3810 kr för dem utan demenssjukdom. Kostnaden för läkemedel med påverkan på nervsystemet var mer än fem gånger högre hos dem med demenssjukdom jämfört med dem utan demenssjukdom. Dock var de ojusterade, högre kostnaderna för läkemedelsanvändning hos personer med demenssjukdom orsakade av samsjuklighet och boendesituation. I själva verket var den starkaste kostnadsdrivaren samsjuklighet följt av boendesituation (dvs. att bo i särskilt boende).

Studie II Vi undersökte olämplig läkemedelsanvändning, risken för sjukhusinläggningar och mortalitet hos äldre personer och personer med demenssjukdom. Dessutom beräknades kostnaderna för sjukhusinläggningar relaterade till olämplig läkemedelsanvändning. I denna studie, baserad på data från SNAC-K och SNAC-N, patientregistret och dödsorsaksregistret, använde vi logistisk och Cox regressionsanalys för att undersöka sambandet mellan olämplig läkemedelsanvändning, risken för sjukhusinläggningar och mortalitet i hela studiepopulationen och i subpopulationen med demenssjukdom. Vi fann en högre risk för sjukhusinläggning (justerad oddskvot = 1,46; 95 % konfidensintervall 1,18–1,81) och mortalitet (justerad Hazard kvot = 1,15; 95 % konfidensintervall 1,01–1,31) i hela studiepopulationen samt för sjukhusinläggning (justerad oddskvot = 1,88; 95 % konfidensintervall 1,03–3,43) i subpopulationen med demenssjukdom, efter justering för bakgrundsfaktorer. Det fanns också en tendens för att olämplig läkemedelsanvändning ledde till ökade kostnader för sjukhusinläggningar (dock inte statistiskt signifikant).

Studie III Vi ämnade beskriva kostnaderna för en simulerad kohort bestående av nyinsjuknade personer med demenssjukdom genom ekonomisk simulering. Med data om kostnader och antal insjuknade från epidemiologiska källor och statistik från officiella källor, användes en Markovmodell i tio cykler bestående av ett år vardera med 24 000 hypotetiskt, nyinsjuknade personer med demenssjukdom i Sverige år 2005. Stadiespecifika kostnader användes och definierades med hjälp av Clinical Dementia Rating scale. Resultaten av simuleringen visade att de totala kostnaderna för kohorten var 27.7 miljarder kronor. Den genomsnittliga årskostnaden för en person med demenssjukdom var 269 558 kr. Svår demens stod för den största andelen av kostnaderna vid demenssjukdom. Kostnader för läkemedel vid demenssjukdom stod för endast cirka 2% av kostnaderna i modellen. Den huvudsakliga kostnadsdrivaren var institutionsboende, även vid mild demens.

Studie IV Vi utvecklade en hypotetisk, ekonomisk modell för en sjukdomsmodifierande behandling vid Alzheimers sjukdom. Vi skapade en Markovmodell som bygger på svenska förhållanden med två armar där den ena representerar den hypotetiska sjukdomsmodifierande behandlingen och den andra representerar vård utan sådan behandling. Sjukdomsgrad och progression i sjukdomen definierades med hjälp av stadieindelning utifrån Mini Mental State Examination. Epidemiologiska data avseende nyinsjuknade, prevalens och kostnader för mild kognitiv svikt, studier av konvertering från mild kognitiv svikt till Alzheimers sjukdom och officiell statistik användes som data i modellen. Den inkrementella kostnadseffektivitetskvoten var 293 000 kr/vunnet kvalitetsjusterat levnadsår. De behandlade personerna hade en förlängd överlevnad (8,7 år) jämfört med de icke behandlade personerna (7,8 år). Med en samhällelig betalningsvilja på 600 000 kronor/ kvalitetsjusterat levnadsår, kan den hypotetiska sjukdomsmodifierande behandlingen betraktas som kostnadseffektiv. De främsta orsakerna till de högre kostnaderna med den sjukdomsmodifierande behandlingen var kostnaderna för behandlingen själv och för förlängd överlevnad.

Slutsats: De observerade, ojusterade högre kostnaderna för läkemedelsanvändning hos personer med demenssjukdom var i själva verket orsakade av samsjuklighet och boendesituation. Vi fann också att olämplig läkemedelsanvändning var associerad med en ökad risk för sjukhusinläggningar och mortalitet bland äldre personer. Detta understryker behovet av varsam förskrivning av läkemedel till äldre patienter. Sambandet mellan olämplig läkemedelsanvändning och kostnader för sjukhusinläggningar behöver dock undersökas i fler studier.

De högsta ackumulerade kostnaderna för demenssjukdom förekom vid svår demens och den främsta kostnadsdrivaren var institutionsboende, även vid mild demens. Läkemedel utgjorde endast en mindre andel av de totala kostnaderna. Vår studie av en hypotetisk sjukdomsmodifierande behandling vid Alzheimers sjukdom visade att denna behandling inte kan förväntas bli kostnadsbesparande om behandlingen förlänger överlevnaden. Men om en samhällelig betalningsvilja på 600 000 kronor antas, kan en sådan behandling betraktas som kostnadseffektiv.

LIST OF SCIENTIFIC PAPERS

- I. Sköldunger, A. Fastbom, J. Wimo, A. Fratiglioni, L. Johnell, K.
The impact of dementia on drug costs in older people: results from the SNAC study.
Submitted

- II. Sköldunger, A. Fastbom, J. Wimo, A. Fratiglioni, L. Johnell, K.
The impact of inappropriate drug use on hospitalizations, mortality and costs in older persons and in persons with dementia – findings from the SNAC study.
Manuscript

- III. Sköldunger, A. Wimo, A. Johnell, K.
Net costs of dementia in Sweden – an incidence based 10 year simulation study.
Int J Geriatr Psychiatry. 2012; 27(11): 1112-7

- IV. Sköldunger, A. Johnell, K. Winblad, B. Wimo, A.
Mortality and treatment costs have a great impact on the cost-effectiveness of disease modifying treatment in Alzheimer's disease – a simulation study.
Curr Alzheimer Res. 2013; 10(2): 207-16

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LIST OF ABBREVIATIONS

AD	Alzheimer's disease
ADL	Activities of daily living
ANOVA	Analysis of variance
ATC	Anatomical therapeutic chemical
CBA	Cost benefit analysis
CDR	Clinical dementia rating
CI	Confidence interval
CMA	Cost minimization analysis
COI	Cost of illness
CUA	Cost utility analysis
DALY	Disability adjusted life year
DES	Discrete event simulation
DMT	Disease modifying treatment
DDD	Defined daily dose
DRG	Diagnosis related group
DSM	Diagnostic and Statistical Manual of Mental Disorders
GLM	Generalized linear model
HR	Hazard ratio
HYE	Healthy years equivalent
ICD	International statistical classification of diseases and related health problems
ICER	Incremental cost effectiveness ratio
IDU	Inappropriate drug use
MCI	Mild cognitive impairment
MMSE	Mini Mental State Examination
MRI	Magnetic resonance imaging
NPR	National Patient Register
NSAID	Non-steroidal anti-inflammatory drug
OR	Odds ratio
OTC	Over the counter (drug)
PET	Positron emission tomography
PSA	Probabilistic sensitivity analysis
QALY	Quality adjusted life year
RUD	Resource utilization in dementia
SEK	Swedish krona
SNAC	Swedish National Study on Aging and Care
WHO	World Health Organization
WTP	Willingness to pay

1 INTRODUCTION

1.1 AGING POPULATIONS

Global aging is projected to increase at the end of this century as birth rates decline and life expectancy increases (1). The age structure of the population shifts when the median age and the proportion of older people increase worldwide (2, 3). Figure 1 shows that the total population worldwide is expected to increase in the future and the largest increase is expected among persons aged 60 years and over. It is apparent that the proportion of people aged over 60 years is expected to grow markedly until 2050.

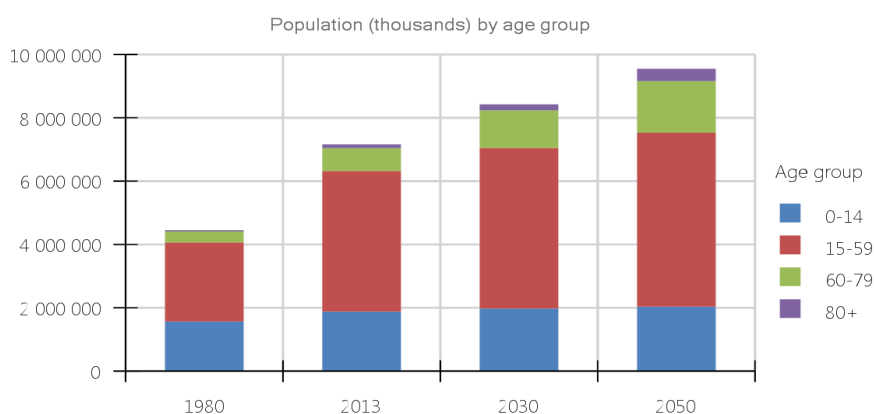


Figure 1. World population from 1980 to 2050 in different age groups. Source: <http://esa.un.org/unpd/popdev/AgingProfiles2013/default.aspx> (4).

In absolute numbers, more than 860 million inhabitants in the world were over the age of 60 years in 2010, which corresponds to a three-fold increase since 1950. Today, the highest proportion of older persons reside on the European continent, but trajectories of the world population estimates that in 2050 almost 80% of the older people in the world will live in developing countries (1).

It is often argued that the increase in population aging is driven by increasing longevity and this is indeed an important factor, but there are also other explanations (1). Decreasing fertility rates alter the age structure of the population and lead to higher median ages and demographic aging (5). This phenomenon is known as the demographic transition (6). This transition is characterized by a change from high levels to low levels of both fertility and mortality rates.

A higher proportion of people reaching old age is an achievement of society. However, health care utilization and other needs of the elderly population are likely to increase as a consequence of this achievement. Figure 2 shows the proportion of people in the ages 60+ years and 80+ years in 1980 and in 2050 in the world. The forecasts in Figure 2 shows a two-

fold increase in the proportion of people aged 60 years and over between the years 1980 and 2050.

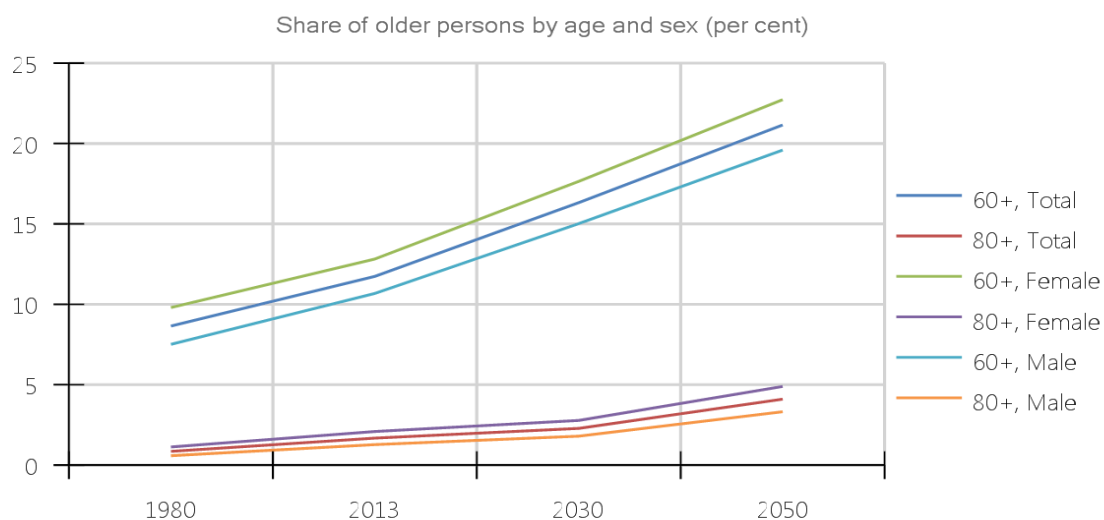


Figure 2. The share of older persons by age and sex. Source: <http://esa.un.org/unpd/popdev/AgingProfiles2013/default.aspx> (4)

The demands on health care systems will depend upon whether the added years of life are healthy or whether they are years with morbidity and disability; thus increasing needs for care (7-10). It is also difficult to predict how patterns of older peoples’ demand on care will change in the future (11).

As people live longer, many will suffer from age-related disorders, such as dementia, and many will use several drugs for their multiple conditions. These are major challenges for the society. Therefore, this thesis explored epidemiological and health economic aspects of dementia and drug use, through economic modelling and analyses of population-based studies.

1.2 DEMENTIA AND MILD COGNITIVE IMPAIRMENT

1.2.1 Dementia

Dementia is a syndrome with progressive deterioration in several cognitive domains that interfere with activities of daily living (ADL) (12). The cognitive deficits include mainly memory impairment and deterioration of at least one other cognitive domain, such as aphasia, agnosia or disturbances in executive functioning (13). Alzheimer’s disease (AD) is the most common dementia disorder and accounts for 60 – 70% of dementia cases (14, 15). There is currently no available cure for dementia, only symptom relieving drugs (16).

The worldwide occurrence of dementia was estimated to 36 million affected persons in 2010 (17). However, evidence of declining incidence is now emerging in high income countries around the world (18-22). Still, the number of people with dementia is expected to increase

over the next decades as the older population grows larger also in developing countries (1). It has been predicted that in 2030, 66 million people worldwide will be affected by dementia and in 2050 as many as 115 million (23).

Dementia is a disorder that affects many levels of society. Firstly, the individual suffers from impairments in cognition and functioning as well as impaired quality of life and shortened life expectancy (24, 25). Secondly, the relatives suffer from gradually losing a family member and in return receive a high care burden for the affected person. Indeed, the need for informal care increases when the dementia progresses with deteriorating cognition and functioning (26). Thirdly, dementia has a strong economic impact on the society. Care for persons with dementia is very costly and resource-demanding for both the formal and informal sector (17).

1.2.2 Mild cognitive impairment

Mild cognitive impairment (MCI) is a heterogeneous concept that includes self or informant-reported cognitive complaint, objective cognitive impairment, but being independent in ADL and not demented (27-29). There are suggestions of several subtypes of MCI; amnesic MCI and non-amnesic MCI where the discriminator is performance on neuropsychological tests of episodic memory. Amnesic MCI is characterized by poor episodic memory whereas non-amnesic MCI is characterized by poor performance in other domains, such as executive function, language and visuospatial ability (27).

The diagnosis of MCI is often difficult to determine, but use of biomarkers for AD may be helpful when setting a MCI diagnosis that is related to AD (30, 31). People with MCI are shown to convert to AD at a much higher rate than the general elderly population (28). In a review, the average conversion rate to dementia was about 10%, but showed great variability (32). However, not all people with MCI convert to dementia.

1.2.3 Diagnostics and treatment of dementia

Swedish national guidelines on care for dementia patients state that an investigation should be performed if cognitive decline is present and the underlying cause of the symptoms is not known (33). The investigation is divided into basic and expanded investigation. The basic investigation is based on patient history, simple cognitive tests, computed tomography scan and assessment of function (34). The expanded investigation includes, besides the basic investigation, neuropsychologic testing procedures, imaging techniques like positron emission tomography (PET) and magnetic resonance imaging (MRI) and the use of biomarkers in cerebro-spinal fluid (35-40). The underlying credential is that pathological changes in the brain may be present before the functional decline is observed (41-45).

Besides symptomatic treatment (46), drugs that are developed today for treatment of AD and other dementias aim to influence the progression of the disease and are, thus, disease

modifying treatments (DMT) (47-49). For AD, the main discussion is whether the underlying mechanism is related to pathological amyloid or tau aggregation (50-56).

1.3 PHARMACOEPIDEMIOLOGY

Pharmacoepidemiology is epidemiologic methods applied to studies of drug use in populations. It may be defined as the study of the utilization and effects of drugs in large numbers of people (57). Concepts from both epidemiology and pharmacology are used to build a bridge between the two.

This thesis is based on geriatric pharmacoepidemiology, which is becoming increasingly important as global aging proceeds (58, 59). Older people use more drugs than any other age group (60-63), and prescription of drugs is the most common form of medical treatment for older adults (64).

1.4 DRUG USE IN OLDER PERSONS

As a consequence of increasing longevity, people live longer with several diseases and are consequently treated with many drugs (65, 66). Drug treatment can reduce symptoms and morbidity, although there is a lack of evidence for treating frail older persons, as randomized clinical trials often exclude these patients (67, 68).

Since elderly people often have multiple diseases and impairments (e.g. kidney failure, cognitive impairment), they are often sensitive to drugs. Still, polypharmacy (i.e. concurrent use of several drugs, often defined as use of ≥ 5 drugs) (69) is common in old age (70-72). In Sweden, about 39% of community-dwelling and 76% of institutionalized people aged 65 years and older have polypharmacy (66).

Older persons are more likely than younger individuals to experience adverse drug reactions (73). These adverse events can lead to increased morbidity and mortality and also to increased costs for society (74-76). Indeed, it has been estimated that adverse drug events are involved in up to 30% of hospital admissions of older people (73).

Previous research has shown that the most commonly used drugs in the elderly population in Sweden are antithrombotic agents, cardiovascular drugs, analgesics and psychotropic drugs (61, 66). These drug therapies largely reflect the co-morbidity burden among older persons (77). There are, however, differences in drug use depending on age, sex, socioeconomic position and residential setting (78, 79). In extreme old age, analgesics, hypnotics/sedatives and anxiolytics are common, whereas use of antidepressants is less common (60). Older women use more psychotropic drugs than older men, but less antithrombotic agents (80, 81). Older individuals with a higher educational level are more likely to use newly marketed drugs (82), but less likely to be exposed to polypharmacy (83), than individuals who have a lower level of education. Also, older people in institutions are more prone to use antidepressants, laxatives and analgesics than their community-dwelling counterparts (66, 84).

1.4.1 Altered pharmacokinetics and pharmacodynamics

As a consequence of aging, the physical response to drugs is often altered (85). Physiological changes in the body can alter the drug effects in an undesirable way and prolong and/or increase the effect. The drug prescriber needs to be aware of these changes and balance the risk versus the benefits of the drug treatment (86).

1.4.1.1 Pharmacokinetics

Pharmacokinetics is often described as “what the body does to the drug”. It includes absorption, distribution, metabolism and excretion of the drug (87, 88). Absorption in itself is not age dependent, but surgery, some diseases and certain drugs (e.g. opioids and anticholinergic drugs) may delay absorption. The proportion of body fat increases in the aging body due to a reduction of the total volume of water. This results in a greater relative distribution volume of fat-soluble drugs, mainly centrally acting drugs, such as benzodiazepines, which may lead to prolonged effects. Drug metabolism is affected through a reduction of both blood flow and enzyme capacity in the liver (89). This may lead to increased drug concentrations, due to both increased bioavailability (i.e. the proportion of a given dose that reaches the bloodstream unchanged) and reduced metabolic clearance of the drug (90). This change can result in increased drug effects and adverse drug reactions (91, 92). The most important age-dependent pharmacokinetic factor is, however, the renal excretion of drugs. Reduced renal function is common in old age, and as a consequence, accumulation of water soluble drugs may cause adverse drug reactions. Hence, it is crucial to measure renal function in older persons in order to adjust their drug treatment appropriately (93, 94).

1.4.1.2 Pharmacodynamics

Pharmacodynamics is often described as “what the drug does to the body” (87). Many organs and organ systems are altered with increasing age, mostly resulting in increased sensitivity to the effects of drugs. The brain becomes more sensitive to centrally acting drugs, which can cause excessive sedation, cognitive disturbances and falls (85, 95, 96). The baroreflex, which controls the blood pressure during, for example, postural changes, is often impaired in old age, leading to increased sensitivity to blood pressure lowering drugs (88). Furthermore, age-related changes of the gastric mucosa increase the risk of gastrointestinal bleeding with certain drugs, mainly non-steroidal anti-inflammatory drugs (NSAIDs) and acetylsalicylic acid (97, 98).

1.4.2 Drugs and dementia

Due to pathological changes in the brain, people with dementia have a higher risk of adverse drug reactions when using central nervous system acting drugs (99-102). Yet, previous research has shown that persons with dementia often use psychotropic drugs and opioids (103-106). Prescription of these drugs can be problematic since they may cause cognitive

decline, falls and confusion (99, 107). Dementia patients are also sensitive to drugs with anticholinergic properties, which may negatively affect an already impaired cognition (108, 109).

Dementia often causes verbal difficulties which, in turn, can cause increased agitation and other behavioral symptoms when the affected individual is not able to communicate (110, 111). Ultimately this may lead to overtreatment with psychotropic drugs (105, 112, 113). In contrast, the dementia diagnosis may dominate the clinical assessment, leading to undertreatment of somatic conditions (114, 115). However, few studies have assessed the quality of prescribing in people with dementia (116).

Relatives and health care professionals may also have problems with identifying symptoms such as pain and depression in dementia (105, 117). This may lead to an undertreatment of, for example, depression, which has been reported to lead to morbidity and disability (118). On the other hand, a recent study shows that antidepressant use is three times more common in persons with AD than in persons without the disease (119), which may imply that the awareness and knowledge of depression in dementia have increased.

Currently, there are four drugs that are approved for the symptomatic treatment of AD in Sweden. Three of these drugs are acetylcholine esterase inhibitors (donepezil, rivastigmine and galantamine) and the fourth drug (memantine) has effects on the glutamatergic system (46). The efficacy, clinical effectiveness and cost effectiveness of these drugs have been analysed in a comprehensive report by the Swedish Council on Health Technology Assessment (SBU – Statens beredning för medicinsk utvärdering) (120). They conclude that there is evidence that symptomatic treatment with acetylcholine esterase inhibitors have effects on cognitive performance for mild and moderate states of AD and that memantine has effects on moderate and severe states of AD.

So far, there is no cure for AD or approved drugs that are labelled as disease modifying treatment (DMT) (47, 121). A DMT would not only have effects on symptoms but would also influence the underlying cause and the degeneration and death of neurons in AD. Many potential DMTs have been tested, but so far failed in phase III trials. However, there are still many such compounds in the pipeline (16, 122). Since there are great hopes that these drugs will result in decreased individual suffering and great cost savings, it is of great interest to analyse the potential cost effectiveness of DMT. Hence, we explored a hypothetical economic model of the cost effectiveness of DMT in AD in this thesis.

1.4.3 Inappropriate drug use

An important concept of drug therapy in old age is potentially inappropriate drug use (IDU), which has been defined in various ways in the literature. One common definition is “the use of medications for which the risks outweigh the benefits” (123-125). These drugs may be well tolerated in younger patients, but can, due to age-related changes, be regarded as

inappropriate among older patients. It is, however, important to note that treatment with these drugs may occasionally be justified for the individual patient (124, 126).

Principally, the concept comprises the choice of drugs, the dosage and length of therapy, inappropriate combinations of drugs (drug duplication and drug-drug interactions (127)), drug-disease interactions and under-prescribing of drugs (128-130). Common examples of IDU are long-acting benzodiazepines, drugs with anticholinergic properties and drug combinations that may lead to serious drug-drug interactions (124).

The prevalence of IDU has been reported to vary between 3 to 70 %, depending on the criteria used for defining IDU, the study populations and different settings (83, 123, 124, 131-136). The highest prevalence of IDU is found in nursing homes where about 30% are exposed to IDU in Sweden (124, 137, 138).

IDU is a well-recognized health problem in elderly persons and has been associated with adverse drug reactions, hospitalization, admission to nursing home and mortality (83, 116, 133, 139-143). However, previous research about outcomes of IDU has often been limited by lack of information about important clinical variables, such as dementia, or by analysis of small and selected samples. Cost analysis of IDU has so far been scarce (144-146), although these estimations are important from a stakeholder and resource allocation perspective.

Identifying IDU is of central importance in order to reduce the occurrence of drug-related problems in elderly patients. Therefore, several different criteria of IDU have been developed through expert consensus methods (134-136, 147), e.g. the Beers criteria from the US, the STOPP/START criteria from Ireland and the UK, the Laroche list from France and in Sweden a set of indicators developed by the National Board of Health and Welfare (128, 148-150). Because availability of drug therapies, prescribing guidelines and therapeutic traditions vary between countries (136, 147, 151), use of national indicators of IDU, as in this thesis, may be beneficial, although they may prevent comparisons between countries.

The Swedish indicators developed by the National Board of Health and Welfare include both disease- and drug specific indicators for evaluation of the quality of drug therapy in older people. The first version of the indicators was launched in 2003 and a revised version in 2010 (126, 128). These indicators are quantitative measures based on international literature and expert consensus. Several of the drug-specific indicators have previously been used in pharmacoepidemiological studies (124, 152, 153), for example showing that risk factors for IDU are female gender (133), institutionalization (138) and multi-dose drug dispensing (doseexpedition, 'Apodos') (154).

1.5 HEALTH ECONOMICS AND PHARMACOECONOMICS

In any society, resources in a wide context are limited. Economics is the science dealing with how limited resources are handled and managed to address potentially unlimited needs.

Health economics is the application of economy within the medical, and wider, the social care sector (155).

Any resource has an alternative use to which a certain cost for forgone benefits is attached. This cost is labelled as the opportunity cost which is recommended for use in economic evaluations (156). Although the opportunity cost concept may seem easy in theory where perfect market prices exists, it is not without problems when applying it to dementia, particularly regarding informal care (157, 158).

According to Drummond et al (156), health economic evaluation studies can be classified as in Figure 3.

	Only costs	Only outcomes	Both costs and outcomes
No comparator	Cost description	Outcome description	Cost outcome description
Comparator	Cost analysis	Efficacy or effectiveness evaluation	Cost effectiveness analysis (CEA) Cost utility analysis (CUA) Cost benefit analysis (CBA)

Figure 3. Different kinds of health economic studies (adapted from Drummond et al (156)).

In a cost effectiveness analysis (CEA), the consequences, or outcomes in terms of effects, are described in some kind of measurable physical units, such as survival, functional capacity or cognition. In a cost utility analysis (CUA), which may be regarded as a kind of CEA, the consequences are expressed in terms of utilities, such as quality adjusted life years (QALYs), see below. In a cost benefit analysis (CBA) both costs and consequences are monetary. In a cost minimization analysis (CMA), the consequences are assumed or shown to be similar and, thus, a cost analysis can be used. In this thesis, the application of health economics in terms of costs description (Study I, II, III) and cost effectiveness (Study IV) in dementia and drug use are explored.

Pharmacoeconomics is the application of pharmacology in health economics (159). All pharmacoeconomic studies can be described according to the classification outlined in Figure 3. Although use of drugs cannot be isolated from other aspects of care, pharmacoeconomics has a distinct focus on drugs, such as how large the costs of drugs are in relation to costs of other sectors of care (descriptive) or how cost effective drugs are (evaluations).

1.5.1 Cost of illness

Cost of illness (COI) studies are descriptive. Two approaches can be used: an incidence approach or a prevalence approach. With the incidence approach, the costs for new cases are estimated for both the annual costs and future (discounted) costs. In the approach, the costs for all cases during for example a year are estimated both for those who already have dementia as well as new cases occurring during the year under study (158, 160, 161).

Instead of aggregated costs, as with the prevalence approach, the COI can also be presented as the cost per person with a disorder during a specified time period depending on the approach. COI *per se* cannot be used for setting priorities of specific care approaches. However, by highlighting the economic burden and by showing how costs change over time and are distributed between different payers, COI studies can in an indirect way indicate which diseases and disorders should be of interest for allocation of resources for research and care (23, 158, 162).

1.5.2 Cost effectiveness

A complete cost effectiveness analysis (CEA; CUA; CBA) should include both the analysis of costs and outcomes together with a comparison between at least two caring or treatment approaches.

Cost effectiveness is often expressed as the Incremental cost effectiveness ratio (ICER):

$$\Delta C / \Delta E = (C_A - C_B) / (E_A - E_B).$$

Where C=costs, E=effects and A and B are different care or treatment options.

The ICER expresses the ratio between the change in costs and the change in consequences, outcomes or effects for two or more interventions.

A matrix for decision support is displayed in Figure 4. Cells 1 and 9 express complete dominance. For example in cell 1, the option A is both cheaper than B and has better effect. In cells 3 and 7, the ICER is particularly interesting since one option has better effect but at the same time is more expensive. In cell 5, either of the options can be chosen since both costs and effects are equivalent.

Cost ↓	Effect →	A better than B	A=B	A worse than B
A lower than B		1. Choose A	2. Choose A	3. ICER
A=B		4. Choose A	5. Neutral decision	6. Choose B
A higher than B		7. ICER	8. Choose B	9. Choose B

Figure 4. Decision matrix for cost effectiveness analysis (adapted from Drummond et al.(156).

1.5.3 Health economic viewpoint

Any economic evaluation must define its viewpoint. The viewpoint in this thesis is societal; thus aiming at reporting all included costs for society irrespective of payer. This approach may be regarded as the best option since it is possible to break down the costs into different payers. If, for example, only the payer of care is included in the analyses, the cost of informal care, which is a large cost in dementia, is neglected. This can be detrimental to the analyses (163, 164).

1.5.4 Outcomes and effects

The most frequently used utility concept in economic evaluations is Quality Adjusted Life Year (QALY) (165). QALYs are used in CUA and reflect both quantity and quality of life (166, 167). The key idea with QALYs is that this concept can be used for all kinds of diagnostic entities. Utilities are expressed as a figure with 0 representing death to 1 representing perfect health. The basic idea is shown in Figure 5. One year of perfect health gains 1 QALY which is similar to three years with QALY values of $0.5+0.3+0.2=1.0$.

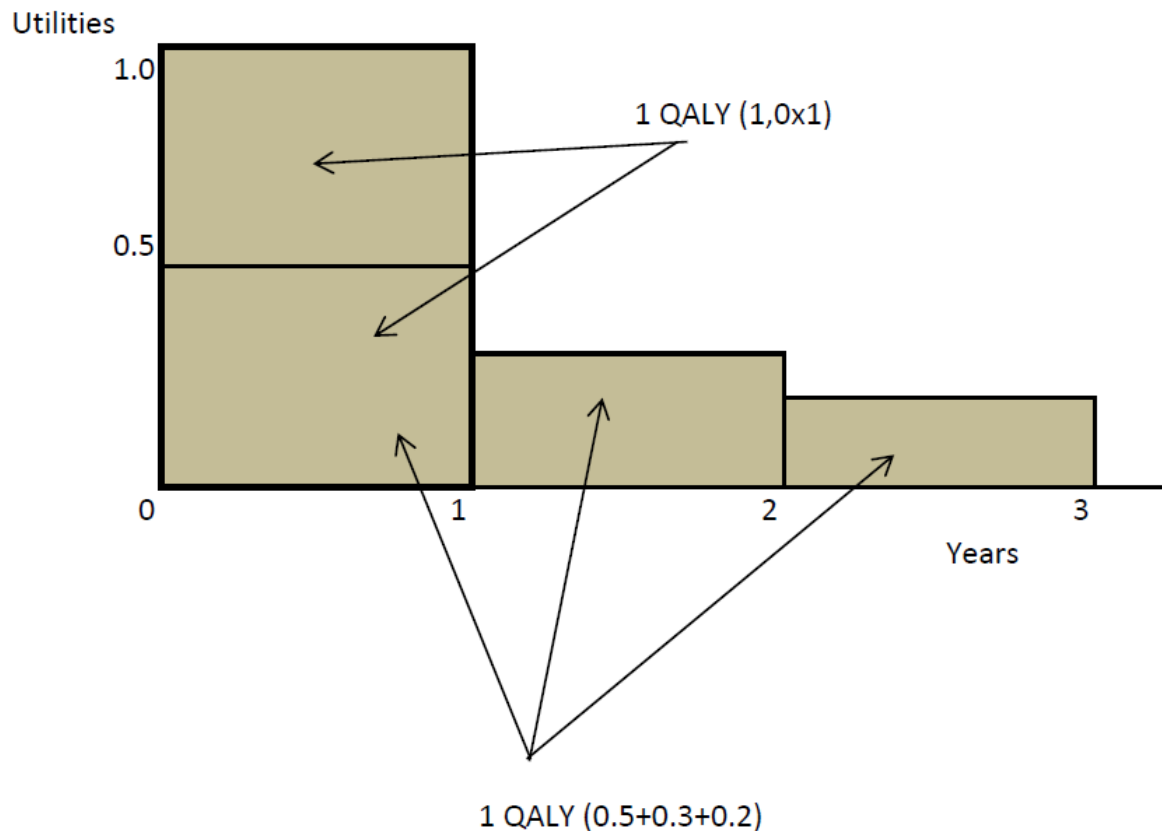


Figure 5. The basic idea of Quality Adjusted Life Years (QALYs).

However, the use of QALYs is not uncontroversial (168). Chronic incurable progressive disorders may be disfavored when compared with surgical treatments, such as cataract surgery or hip replacement surgery (158).

There are also other utility approaches, such as Disability Adjusted Life Years (DALYs) (169) which are used by the World Health Organization (WHO) and Healthy Years Equivalents (HYE) (170). However, DALYs focus on productivity and disability more than on quality of life and HYE require a great number of health scenarios (166).

Diagnosis specific utilities are also under development to serve as equivalents or proxies for QALYs. The idea with such an approach is to provide greater possibilities of studying utilities of a disorder than the generic utility instruments can. Such diagnosis specific instruments in the field of dementia are presented in papers by Ekman et al (171) and the group working with DEMQOL-U (172). Even if they are more sensitive in detecting intervention effects than the generic instruments, the disadvantage is that comparisons with other disorders are difficult or even impossible.

1.5.5 Long term effects

The major challenge in the evaluation of dementia care, both in terms of clinical effectiveness and cost-effectiveness, is the long duration of dementia disorders. There is no single design that can solve this problem. Several approaches can be used, as displayed in Figure 6. The

term external validity refers to how generalizable results are in the population the study aims to describe, while internal validity refers to how well the study fulfills criteria for a controlled experiment or a trial.

Most clinical studies last for 6-12 months while the progression and duration of for example AD may be several years to decades. Due to logistic and ethical issues, studies covering the whole disease period will probably never be accomplished. One option to determine long-term effects is to extend ongoing studies and perform open follow-up studies (158). Such studies have been published on acetylcholinesterase inhibitors (173-175). However, there are several drawbacks with this approach, such as selection bias, patients lost to follow-up and problems in defining controls (158). Another interesting option is to analyse register data and to merge databases, e.g. record-linkage of national registers (176) with quality registers (177) and population based studies, such as the Swedish National Study on Aging and Care (SNAC) (178). Another way of estimating long term effects, which has been used in this thesis (Study III and IV), is to use modelling techniques (179).

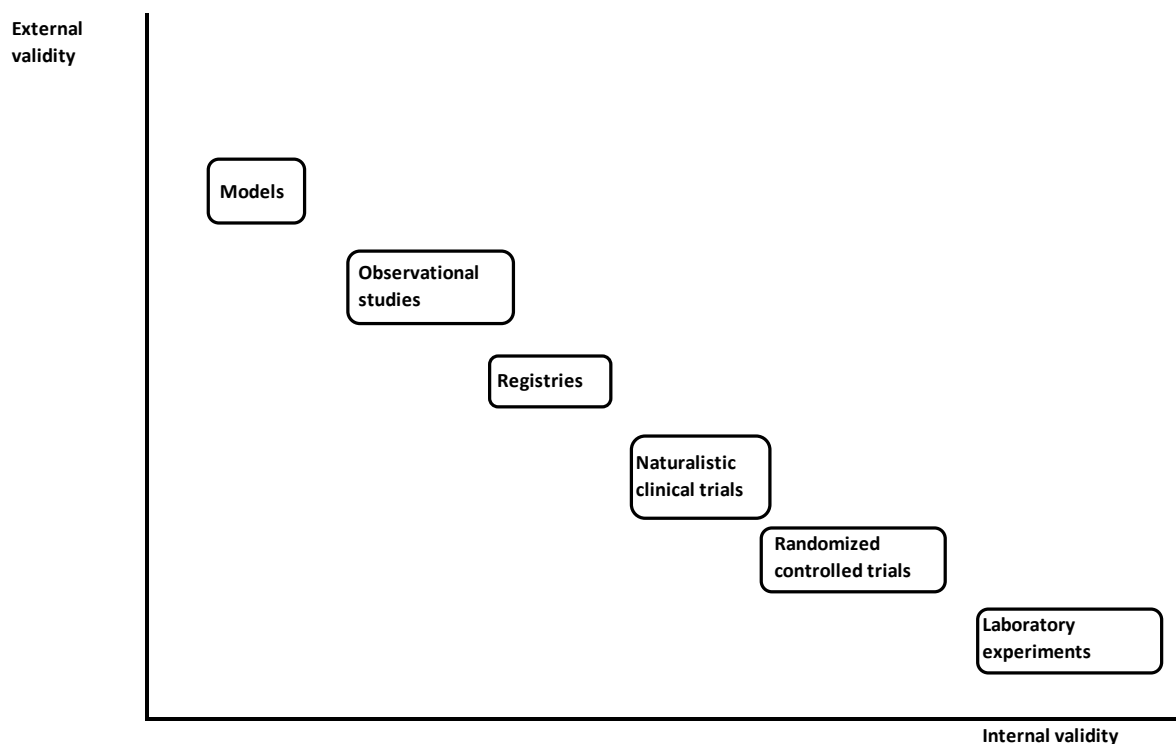


Figure 6. Schematic view of external and internal validity in different types of studies

1.5.6 Modelling/simulations

There are several different modelling techniques for analysing long-term disease progression and the associated costs, but in general they are based on the same concept (180-182). This is made through short term input on efficacy or similar and, depending on the research question, input for progression, costs, outcomes and survival, which are extrapolated to a longer time period (a fixed period or expected survival). Because it is possible to use an input that reflects the situation of the target population, such as dementia, the representativity of the target

population, and thus the external validity, may be high. However, besides the empirical core of efficacy as input, the internal validity is low since long term effects are simulated.

Frequently used modelling techniques are Markov models (183-185) (Study III and IV), decision trees, regression models, survival analysis and discrete event simulation (186). The basic concepts in a Markov cohort model (185) are states of a disease/disorder and transition probabilities between states and cycles (time, e.g. months, years).

Figure 7 illustrates the basic idea of a Markov model. Transitions between states are illustrated with arrows and the corresponding transition probabilities (the probability to remain or change from one state to another), during one cycle (e.g. one year). Example: The probability to remain healthy is 0.80 while the probability of getting a disease or die is 0.18 and 0.02, respectively (where 0.02 represents a risk of sudden death of a “healthy” person). The sum of transition probabilities for each state during one cycle are always 1.00 (0.80+0.18+0.02).

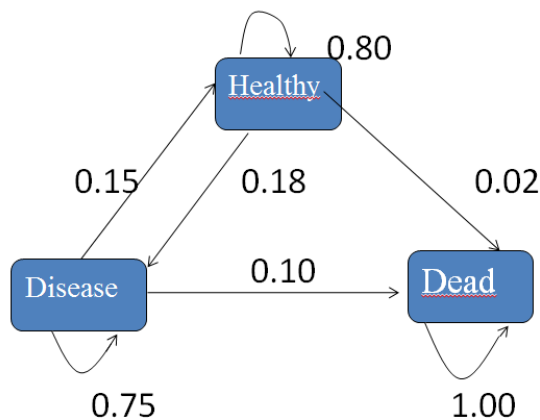


Figure 7. Principal overview of a Markov model

A model is usually run for several cycles to illustrate the course of a condition. To each state, there are inputs regarding transition probabilities, costs, outcomes and several arms can be compared (such as treatment vs. no treatment), making it possible to calculate the ICER. The models are often presented in a tree-form.

Since models have a rather long time horizon, the valuation of costs and consequences may differ. For example: if you have 1,000 SEK today and 1,000 SEK expected in 10 years, which option would you prefer? Probably the one of today. To adjust for these preferences over time, discounting is often used to give a future cost a present value (156). In short, discounting can be described as inverted interest rate calculations with a chosen discount rate. In the example above, with an annual discount rate of 3%, the present value of 1,000 SEK 10 years later would be around 750 SEK.

1.5.7 Sensitivity analysis

Any model consists of a set of input with an uncertainty for each input. Thus, the results of a model depend on the assumptions of the values of the different kinds of input. There are also different opinions about how to best estimate some of the input, e.g. costs of informal care (187, 188). Therefore, it is essential to test the robustness of a model by varying the different inputs (189).

Depending on the type of input, different methods to test uncertainty need to be used, such as statistical variability (e.g. confidence intervals) and fixed alternative values (e.g. unit costs and discount rates). The sensitivity analysis can be a *one way* sensitivity analysis, where one input is varied at each occasion, or a *probabilistic* sensitivity analysis, where several kinds of input are varied simultaneously with several iterations and based on statistic variability of each input (such as standard deviations) (189).

1.6 COSTS OF DEMENTIA

The worldwide societal costs for dementia were estimated to be 604 billion US dollars in 2010, of which 252 billion dollars in costs for informal care (17). These costs are expected to increase in the future because of population aging. It has even been questioned as to whether it will be possible to provide care and treatment for all persons with dementia in the future (190).

In Sweden, the societal costs for dementia were estimated to be 63 billion SEK in 2012 (191). About 78% of these costs occurred in the municipal sector, 17% in the informal care sector and only 5% occurred in the county council sector (191). The costs for the county councils refer to hospital care, primary care, diagnostic workup and costs for drug use. The costs of drugs only accounted for 2% of the societal costs(191). Consequently, the municipalities have undoubtedly the largest economic burden for the care of elderly people with dementia, but costs of drugs constitute a significant cost component for the county councils.

Also internationally, the main cost drivers in dementia have been reported to be informal care and institutional care rather than medical care (i.e. inpatient and outpatient care and drugs) (164). Previous research has also shown that disease severity needs to be considered in studies of economic impact of dementia, as costs more than double from mild to severe states of the disease (192).

However, longitudinal incidence-based COI studies of dementia are rare (193). Modelling approaches are useful in this context because of the long duration of dementia disorders that makes it difficult to collect empirical data (179).

Studies of costs of dementia should clearly define cost components and separate estimates by care setting and disease severity to make them useful for health policy planning (164). Thus, we aimed to include all these aspects in this thesis.

1.7 THE CARE SYSTEM FOR OLDER PEOPLE IN SWEDEN

In Sweden, about 90,000 elderly persons lived permanently in different kinds of institutional care and about 229,000 elderly persons received home help in 2013 (194).

The responsibility for the care of older people in Sweden is shared between the municipalities and the county councils. In general, the municipalities have the responsibility of care in the social sector (day care, home-care, respite care and nursing homes), while the county councils are responsible for the primary care and the specialist medical care. However a transition process is taking place; care in the home, previously provided by nurses from primary care, is being taken on by the municipalities.

Even if care is paid by these two main operators, care can also be organized by private companies using a care purchasing process (195). In 2012, 27% of the home help and 15% of the institutional care was carried out by private care providers in Sweden (196).

Both in social care and in medical care, the care receiver pays fees. However, the greatest part is financed by taxes.

2 AIMS

2.1 GENERAL AIM

To investigate epidemiological and health economic aspects of dementia and drug use in older people, through economic modelling and analyses of population-based studies.

2.1.1 Specific aims

2.1.2 Study I

To investigate whether dementia is associated with higher drug costs in older persons.

2.1.3 Study II

To investigate IDU and the risk of hospitalizations and mortality in older persons and in persons with dementia and to estimate the costs of IDU-related hospitalizations.

2.1.4 Study III

To describe the costs (including drug costs) of incident cases of dementia over time with a progression model based on Swedish conditions.

2.1.5 Study IV

To present a hypothetical economic model of the cost effectiveness of DMT in AD.

3 METHODS

3.1 DATA SOURCES

3.1.1 The Kungsholmen project (*Study III and Study IV*)

The Kungsholmen project was a longitudinal population-based study conducted in the urban area of Kungsholmen in Stockholm during the years 1987-2000 (197). All persons aged 75 years and older, including both institutionalized and community-dwelling persons, were invited and examined every third year (n=1,810 at baseline). Thorough medical and psychological examinations were performed as well as a structured interview by a trained nurse on health and social factors, including social network, education and functional status. Blood tests and measurements of physical performance were also gathered at every examination.

In 1995, a rural node was included and then the project was called the Kungsholmen-Nordanstig project (198, 199). Nordanstig is a municipality located in the county of Hälsingland, a coastal area in the middle part of Sweden. Nordanstig has no city or central area, only small villages. The same structured examination and test protocol were used in the rural area of Nordanstig as in the urban area of Kungsholmen.

3.1.2 The Swedish National Study on Aging and Care (*Study I and Study II*)

Building on the experiences from the Kungsholmen project, the Swedish National Study on Aging and Care (SNAC) was implemented in 2001 and is an ongoing longitudinal population-based multi-center study of aging and health conducted at four different sites in Sweden (178): the municipalities of Nordanstig and Karlskrona, four municipalities in the county of Skåne (Malmö, Eslöv, Hässleholm, Osby and Ystad) and Kungsholmen/Essingeöarna, a part of Stockholm city.

In this thesis, baseline data from Nordanstig (SNAC-N) and Kungsholmen (SNAC-K) were used (n=4,129). Each consists of a sample of eleven age cohorts of the ages of 60, 66, 72, 78, 81, 84, 87, 90, 93, 96 and 99 years and older. Baseline data were collected in 2001-2004. Persons over the age of 81 years are reexamined every third year and persons over the age of 60 years every sixth year.

The participants were examined extensively by using standardized protocols. The nurse's interview covered a wide range of domains including socioeconomic status, living habits and family history. The participants were also examined by a physician, neuropsychological tests were performed by a psychologist and laboratory tests were collected. Data about diseases and drug use were collected during the interview with the physician. If a participant was unable to perform the interview, a proxy (spouse or next of kin) was asked instead. If the person lived in an institution, the information was most often collected from medical records and staff.

3.1.3 The National Patient Register (*Study II*)

The National Patient Register (NPR) at the Swedish National Board of Health and Welfare was introduced in the 1960s and covers since 1987 all inpatient care in Sweden. The NPR contains, besides patient and medical data, also administrative and geographical data concerning every care episode. A validation of the NPR showed that over 99% of all psychiatric and somatic discharges are recorded (200).

3.1.4 The Cause of Death Register (*Study II*)

The Cause of Death Register at the Swedish National Board of Health and Welfare contains since 1961 data on all deceased persons registered as inhabitants in Sweden at the time of death. The register is updated annually and causes of death are coded according to international ICD codes (201).

3.2 MODELLING APPROACHES (*STUDY III AND STUDY IV*)

For the modelling approaches, many different sources of information formed the base for the models. This composite was collected both from epidemiological studies (i.e. the Kungsholmen project) as well as from demographic statistics and registers. Markov models were used to simulate the cohorts in Study III and Study IV (185).

There is currently no cure for AD. Consequently, there are no available empirical figures of efficacy or cost-effectiveness of this kind of treatment. In Study IV, a hypothetical DMT was assumed to lower the risk of progression from MCI to more severe forms of dementia, also affecting the subsequent progression in later states.

3.2.1 Clinical Dementia Rating (*Study III*)

Clinical Dementia Rating (CDR) (202) was used to describe dementia severity. The states 1, 2 and 3 were translated into mild, moderate and severe dementia. Study III used only states 1, 2 and 3. CDR state 0.5, rather similar to MCI, was not included in the model. The Kungsholmen project of people aged 75 years and older were used as empirical foundation (197, 199).

3.2.2 Mini Mental State Examination (*Study IV*)

In Study IV, states and progression of dementia in the model were defined by Mini Mental State Examination (MMSE) (203). MMSE is a screening instrument used for assessing cognitive impairment and can also be used as a tool for assessment of dementia severity. The scoring is 0-30, where a low score indicates worse cognitive impairment. A widely used stratification of MMSE scoring is: mild (18-23), moderate (10-17) and severe (0-9) cognitive impairment (204).

3.2.3 Resource Utilization in Dementia (Study III and Study IV)

Severity state specific costs were derived from the Kungsholmen project (205, 206) and were based on the Resource Utilization in Dementia (RUD) instrument (207, 208). RUD is a comprehensive instrument used to assess the resource utilization in dementia and aims at calculating costs from a societal viewpoint, also including costs of informal care (Table 1).

Table 1. Components of the RUD instrument (209)

Patient	Caregiver
Accommodation/long term care	Caregiver time (for patient)
Respite care	Work status
Hospital care	Hospital care
Out patient visits	Out patient visits
Social service	Social service
Home nursing care	Home nursing care
Day care	Day care
Drug use	Drug use
Work status	

For each resource, there is a unit cost applied and the resulting cost is based on the multiplication of the quantity of the resource and the unit cost, considering the time window.

3.3 OUTCOME VARIABLES AND EXPLANATORY VARIABLES

3.3.1 Outcome variables

3.3.1.1 Drug use (Study I and Study II)

Use of drugs was recorded by the physician through personal interviews and the participants were asked to bring current lists of medications, drug containers and prescriptions. If the participant was not able to answer, a proxy (spouse or next-of-kin) was asked to provide the information. Drug use was defined as use of a drug regularly at the time of the interview or as needed at any time during the preceding month. Data on both prescribed and over the counter (OTC) drugs were recorded. The drugs were classified according to the Anatomical Therapeutic Chemical (ATC) code, as recommended by the WHO (210).

3.3.1.2 Drug costs (Study I)

Drug costs were calculated based on a register of drug prices from the National Corporation of Swedish Pharmacies (Apoteket AB) from 2003, in a specialized computer software (Monitor[®]). Every drug used by each participant was sought out in the drug register. Thereafter, a matching preparation and strength was looked up and a suitable package was selected. For tablets or capsules, packages with 100 or close to 100 tablets/capsules were selected. For other preparations, such as mixtures, the largest package was selected. The price of the package was divided by the number of tablets, capsules or number of ml in cases of

fluid drugs. The price per unit was then multiplied with the number of units taken daily by the participant. For drugs taken as needed, we instead calculated the price per Defined Daily Dose (DDD), which is the average daily dose of a drug when used for its main indication in an average 70 kg adult, as established by WHO (210), and we assumed that drugs used as needed were taken in an average dose of half a DDD per day. For anti-infective drugs, we assumed a limited treatment period of 20 days per year.

3.3.1.3 Hospitalization (Study II)

The hospitalization data used in Study II were collected from the NPR. The data was collected from the time point of entrance of the participant into the study until one year after. Both acute and planned hospitalizations were included.

3.3.1.4 Costs of hospitalization (Study II)

To obtain the cost of the hospitalizations we used the ICD codes from the NPR. The ICD codes were translated into Nord-Diagnose Related Group (DRG) codes, which are a Swedish version of the original DRG codes (211, 212). The Nord-DRG database was developed to rationalize cost-finding and budgeting for practitioners. A DRG code has a specific weight and this weight was multiplied with the DRG cost of weight 1 to get a total cost for the actual hospital stay. For example, renal failure has DRG code 316 and in the year 2003 it had a weight of 1.2558 and the cost of 1 DRG was 43,661 SEK, resulting in a cost for the hospital visit of about 55,000 SEK.

3.3.1.5 Mortality (Study II)

Death certificates were retrieved from the national Cause of Death Register, from the date of inclusion of the participant until one year after.

3.3.1.6 QALYs (Study IV)

In study III, QALYs were used as outcome variable showing the effect of the hypothetical treatment for the simulated cohort. QALYs were accumulated for the cohort throughout the modelled period and allocated to the treated persons in the cohort.

3.3.2 Explanatory variables

3.3.2.1 Sociodemographic variables

Sociodemographic data covered age, gender, educational level and residential setting.

In the descriptive analysis, age was divided into age groups of 60-69, 70-79, 80-89 and 90 years and over, whereas in the regression models age was included as a continuous variable. Educational level was dichotomized into eight years or less (elementary) and nine years or more of schooling (additional). Residential setting was used as a dichotomous variable: living

in own home (community-dwelling) vs. living in an institution. Institutional living referred to all forms of sheltered housing, e.g. service-house, group-living and nursing homes.

3.3.2.2 *Comorbidity*

We used the Charlson comorbidity index (213), which is widely used to control for confounding effects of concurrent diseases. The index has been validated for both administrative databases (214) and institutional living (215, 216). We used an adapted version (139) based on the availability of data. The index consisted of nine diagnoses (weighted as below) resulting in the total sum of 11: myocardial infarction, congestive heart failure, cerebrovascular disease, dementia, chronic obstructive pulmonary disease, connective tissue disease, diabetes without complication, moderate or severe renal failure and any tumour. Moderate or severe renal disease and a diagnosis of tumour had the weight of two and all other diseases the weight of one. All diagnoses were based on information available in medical records and from the physician's examination, except for dementia and renal disease. The dementia diagnosis was made by the physician according to the DSM III-R criteria (217) and renal disease was estimated through calculations using the of Cockcroft-Gault formula (218). An estimated creatinine clearance $<25\text{mL}/\text{min}$ was assumed to indicate severe renal disease.

3.3.2.3 *Physical functioning*

We used the Katz ADL index as a measure of daily functioning (219). The Katz index is a hierarchical scale that measures physical dependence in six different basic daily activities; bathing, dressing, going to the toilet, transferring, continence and feeding. The level of dependency was expressed in grades from 0 to 6 with zero representing being totally independent in all of the activities and 6 being dependent in all six activities. Good reliability and construct validity have been reported for the Katz index when administered by nurses (220), which is done in both the Kungsholmen project and in the SNAC study.

3.3.2.4 *Dementia status*

The dementia diagnosis was made according to the DSM III-R (217), based on information obtained from patient history, medical examination and cognitive testing. If the participant was unable to answer questions, information was retrieved from a proxy, most often a spouse or next-of-kin. If the person lived in an institution, the information was most often collected from medical records and staff.

3.3.2.5 *Inappropriate drug use (IDU)*

The Swedish National Board of Health and Welfare has developed indicators for the evaluation of the quality of drug therapy in elderly people (128). These indicators are quantitative measures based on international literature and expert consensus. The indicators are divided into drug specific and disease specific. In this thesis (Study II), we used four of

the drug specific indicators (Table 2), which have previously been used in studies of IDU (124, 133, 138).

Table 2. Indicators developed by the Swedish National Board of Health and Welfare for analyses of IDU in elderly persons (Study II)*		
Indicator	Examples of drug /drug combinations	May cause (examples)
Anticholinergic drugs	Antihistamines, urinary antispasmodics, low-potency antipsychotics	Cognitive impairment, confusion and impaired functional status
Long-acting benzodiazepines	Diazepam, nitrazepam, flunitrazepam	Excessive sedation, cognitive impairment and falls
Concurrent use of three or more psychotropic drugs	Antipsychotics, anxiolytics, hypnotics-sedatives and antidepressants	Excessive sedation, cognitive impairment and falls
Potentially serious drug-drug interactions	Concurrent use of aspirin and warfarin	Attenuated/abolished therapeutic effects or severe side effects

*Adapted from Haasum (221).

3.4 STATISTICAL ANALYSIS

3.4.1 Statistical analysis (Study I and Study II)

Descriptive demographic statistics were made with cross-tabulations in both Study I and Study II. Cost data is often non-normally distributed with a skewed distribution. Accordingly, in Study I, the regression analysis of costs was performed by using a Generalized Linear Model (GLM) with the assumption of a gamma shaped distribution of the dependent variable (222). GLMs are generally well suited for statistical analysis of cost data, which often show a high degree of non-normality (223).

In Study I, a two-step procedure was adopted. Firstly, logistic regression with costs as binary outcome was performed in order to observe which factors were associated with high costs. Secondly, a GLM model was run to explore the magnitude of the cost-driving factors. In the GLM, the major cost drivers were dichotomized and first entered separately. All models were adjusted for age, gender and education. Then, all factors were entered in the joint analysis simultaneously. Dementia diagnosis is included in the Charlson Comorbidity Index, but in the

joint analysis, dementia was analysed as a separate variable and, thus, was removed from the index.

In Study II, we used logistic regression analysis to explore the association between IDU and hospitalizations within one year from assessment of IDU, after adjustment for covariates. We used Cox regression models for analysis of IDU and mortality within one year from assessment of IDU, after adjustment for covariates. Firstly, the outcomes of hospitalizations and mortality were analysed in the whole population. Secondly, we analysed the subpopulation of persons with dementia. The results are shown as odds ratios (ORs) and hazard ratios (HRs) with 95% confidence intervals (95% CIs). We used one way analysis of variance (ANOVA) to explore differences in mean cost of hospitalizations with and without IDU, after adjustment for age.

Inclusion of site (i.e. Kungsholmen and Nordanstig) did not affect the main results; therefore, this variable was not included in the analyses. A p-value of < 0.05 was considered statistically significant in both Study I and Study II.

All analyses in Study I and Study II were made with IBM SPSS Statistics version 22 (224).

3.4.2 Transition probabilities (*Study III and Study IV*)

Markov models were used to simulate the cohorts in Study III and Study IV. These models are based on the probability to make a transition between two or more states/events. The probability of transition between states of dementia, from mild to moderate and severe, was considered in the models. The transition probabilities between states also included mortality figures for mild, moderate and severe states of dementia. They were derived from the Kungsholmen project (197, 225). In both Study III and Study IV, there were no possibilities of back transition implicating that the progression of the disease was irreversible in the model.

3.4.3 Sensitivity analysis (*Study III and Study IV*)

In all modelling approaches, it is essential to test the model variation and robustness in order to investigate if the assumptions are reasonable. In a one-way sensitivity analysis, the mortality, transition probabilities between states, costs of informal care, discount rates and incidences were varied in the models.

In Study IV, additional sensitivity analysis of the hypothetical DMT on conversion rate to AD and proportion of responders of the treatment were varied. In addition, the cost of the hypothetical treatment and the possibility to enrich the target population through including persons with MCI-AD detected by using biomarkers was varied.

All analyses in Study III and Study IV were performed by using the software Treeage (226) and the extended analyses was performed in Microsoft Excel (227).

4 ETHICAL CONSIDERATIONS

4.1 KUNGSHOLMEN PROJECT AND SNAC

Study III and Study IV used data from the Kungsholmen project approved by the ethical board in Stockholm (Dnr: 94:122; 87:148; 87:234; 90:251). Study I and Study II used baseline data from the SNAC study conducted in Nordanstig and Kungsholmen which was approved by the ethical review boards in Stockholm (Dnr 01-114) and Uppsala (Dnr 01-123). Both studies collected informed consent from each participant and if not possible, proxy consent was requested from a close relative. The Kungsholmen and SNAC projects follow the ethical guidelines of the Swedish Council for Research in the Humanities and Social Sciences.

4.2 REGISTER DATA

Study I and Study II used data from the National Patient Register and the Cause of Death Register record-linked to baseline data from SNAC-K and SNAC-N, which was approved by the ethical review boards of Stockholm (Dnr 01-114, dnr 2009/595-32) and Uppsala (dnr 01-123). The register data were made anonymous prior to merging with the SNAC data and only non-identifiable data were analysed.

5 MAIN RESULTS

5.1 STUDY I

In Study I, drug use data and the associated costs were analysed for people with and without dementia. Of the 4,129 participants, 21 did not have information on drug use and were therefore excluded from the analyses (n=4,108; 319 with dementia).

The mean age for people without dementia was 73.2 (SD 10.6) years and for people with dementia 88.1 (SD 7.2) years. Community-dwelling participants had a mean age of 73.9 (SD 10.6) years and participants in institutions 88.6 (SD 7.5) years.

About 80% of all participants used drugs. The mean number of drugs was 5.4 in people with dementia and 3.5 in people without dementia ($p<0.001$). The mean number of drugs used among community-dwelling persons was 3.4 and in institutions 6.3 ($p<0.001$).

The overall annual drug costs for persons with and without dementia were 6,147 SEK and 3,810 SEK, respectively. Cardiovascular drugs (ATC group C), nervous system drugs (ATC group N) and drugs for the alimentary tract and metabolism (ATC group A) accounted for the majority of the drug costs; 55% in individuals without and 73% in individuals with dementia. The cost of nervous system drugs was more than five times higher in persons with dementia than without (3,202 SEK vs 585 SEK). This was explained by the higher use of virtually all types of nervous system drugs, including analgesics, antiepileptics, psychotropics and anti-dementia drugs, among the persons with dementia. Cardiovascular drugs were also more common among persons with dementia, but to a lower mean cost than among persons without the disease (514 SEK among persons with dementia and 1,009 SEK among persons without dementia). This was explained by the high use of high-ceiling diuretics, nitrates and cardiac glycosides among the individuals with dementia, whereas individuals without dementia had a higher use of beta blocking agents, calcium channel blockers, angiotensin II antagonists and lipid modifying agents.

The results of the GLM analysis revealed that, after adjustment for comorbidities and residential setting, dementia was not associated with higher overall drug costs. When the total costs of drugs were stratified by dementia status and residential setting, people living in institutions and without a diagnosis of dementia accounted for the highest costs of drugs (Figure 8).

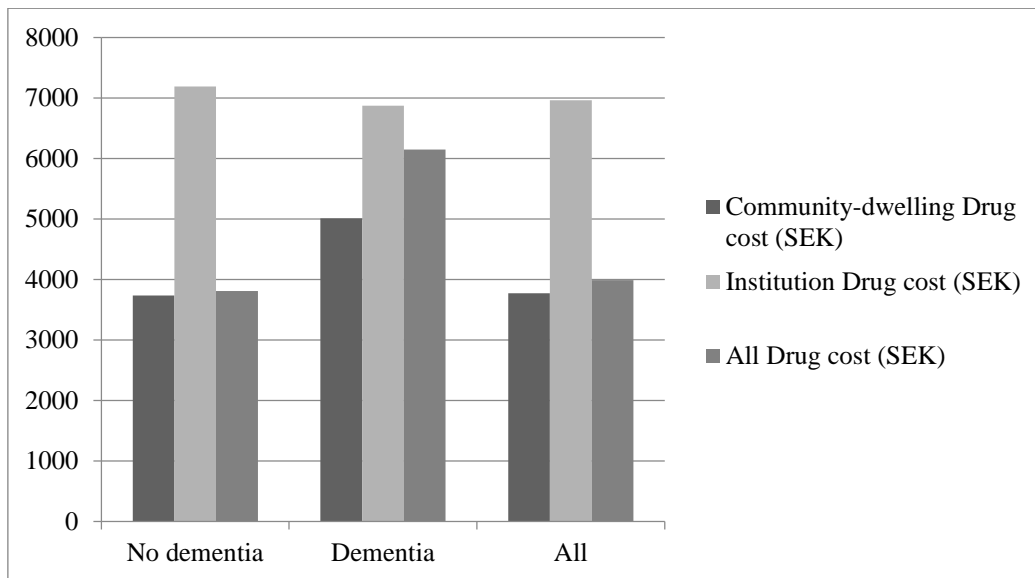


Figure 8. Total cost of annual drug use stratified by dementia status and residential setting.

The strongest drug cost driver was comorbidity followed by residential setting.

Thus, the GLM showed that after adjustment for age, gender, residential setting, physical functioning, comorbidity and dementia, the main drug cost drivers for elderly people are comorbidities and residential setting and not dementia *per se*.

5.2 STUDY II

In Study II, we analysed IDU – defined as exposure to at least one of four drug specific indicators according to the set developed by the Swedish National Board of Health and Welfare (Table 3) (138), and the risk of hospitalization and mortality in older persons and in persons with dementia. Of the 4,129 participants, 21 did not have information on drug use and were therefore excluded from the analyses (n=4,108; 319 with dementia).

The mean age of the study population was 74.8 years ranging from 60 to 105 years. Overall prevalence of IDU was 13%; 27% among persons with dementia and 12% among persons without dementia ($p < 0.001$). The prevalence of IDU in institutions was 34% and among community-dwellers 12% ($p < 0.001$).

IDU was associated with a higher risk of hospitalization within one year in the whole study population (adjusted OR=1.46; 95% CI 1.18-1.81), after adjustment for age, sex, dementia, residential setting, educational level, physical functioning and comorbidity (Table 3).

Table 3. Multivariate logistic regression analysis of the association between inappropriate drug use (IDU) and hospitalization within one year^a

	OR*	(95% CI)
Age, years (cont.)	1.04	(1.03, 1.05)
Sex		
Male	Reference	
Female	0.80	(0.67, 0.92)
Dementia		
No	Reference	
Yes	0.97	(0.68, 1.39)
Residential setting		
Community-dwelling	Reference	
Institution	0.25	(0.16, 0.38)
Education		
Elementary	Reference	
Additional	0.72	(0.61, 0.86)
Katz ADL		
Independent	Reference	
Dependent	2.15	(1.58, 2.92)
Co-morbidity		
No co-morbidities	Reference	
Co-morbidities	1.35	(1.15, 1.58)
IDU		
No	Reference	
Yes	1.46	(1.18, 1.81)

^a Data missing for 52 persons

* Adjusted for all variables in table

IDU was also associated with mortality within one year (adjusted HR=1.15; 95% CI 1.01, 1.31), after adjustment for age, sex, dementia, residential setting, educational level, physical functioning, comorbidity and hospitalization within 1 year (Table 4).

Table 4. Multivariate Cox proportional hazard regression analysis for inappropriate drug use (IDU) and risk of mortality within one year^a

	HR*	(95% CI)
Age, years (cont.)	1.07	(1.06, 1.08)
Sex		
Male	Reference	
Female	0.76	(0.68, 0.84)
Dementia		
No	Reference	
Yes	1.28	(1.08, 1.52)
Residential setting		
Community-dwelling	Reference	
Institution	1.09	(0.90, 1.52)
Education		
Elementary	Reference	
Additional	0.93	(0.83, 1.03)
Katz ADL		
Independent	Reference	
Dependent	1.18	(1.01, 1.39)
Co-morbidity		
No co-morbidities	Reference	
Co-morbidities	1.41	(1.27, 1.56)
Hospitalization within 1 year		
No	Reference	
Yes	1.37	(1.23, 1.53)
IDU		
No	Reference	
Yes	1.15	(1.01, 1.31)

^a Data missing for 52 persons

* Adjusted for all variables in table

We also performed the analyses only among the persons without dementia. However, the results of these analyses were similar to that of the whole study population.

Among the persons with dementia, IDU was associated with a higher risk of hospitalization within one year (adjusted OR=1.88; 95% CI 1.03-3.43), but not statistically significantly associated with mortality (adjusted HR=1.13; 95% CI 0.87-1.47).

Costs for hospitalizations, estimated based on data from the NordDRG, seemed higher in persons with IDU than without IDU, although not statistically significant (Figure 9).

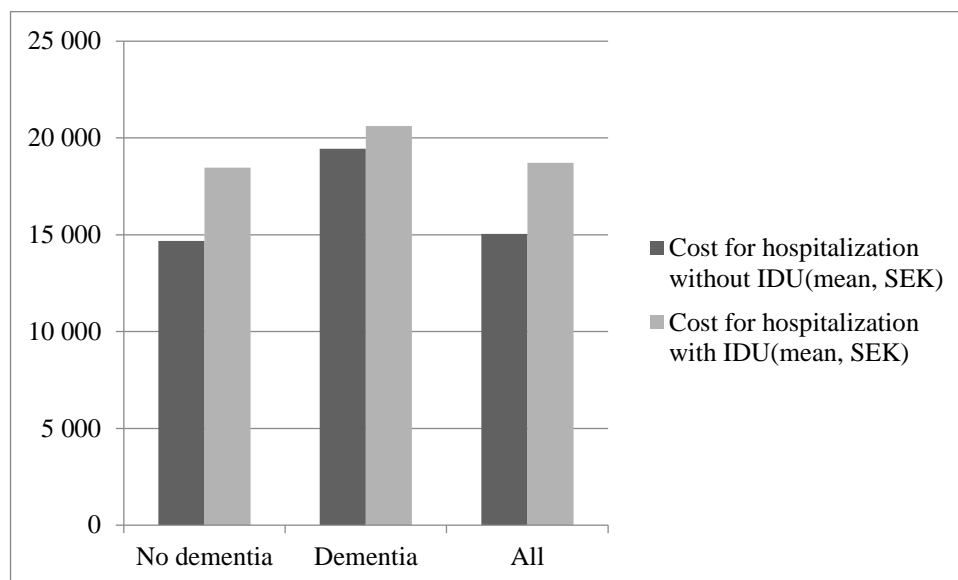


Figure 9. Costs of hospitalization in people with and without inappropriate drug use (IDU) stratified by dementia status

5.3 STUDY III

By conducting a 10-year simulation of a cohort of incident cases of dementia, we aimed to estimate the long term costs of dementia. Figure 10 shows the model used in Study III.

According to our calculations, we estimated approximately 24,000 incident cases of dementia in Sweden 2005. The simulation was run for 10 cycles of one year each. After three years in the base model, the simulated cohort had been reduced to only 45% of the original 24,000 incident cases due to mortality.

In total, the 10-year cost for the simulated cohort was about 27 billion SEK. Institutional care was the main cost driver and accounted for 51% to 91% of the total costs from year 1 to year 10. Total costs of drugs in dementia only accounted for about 2% of the costs in the model.

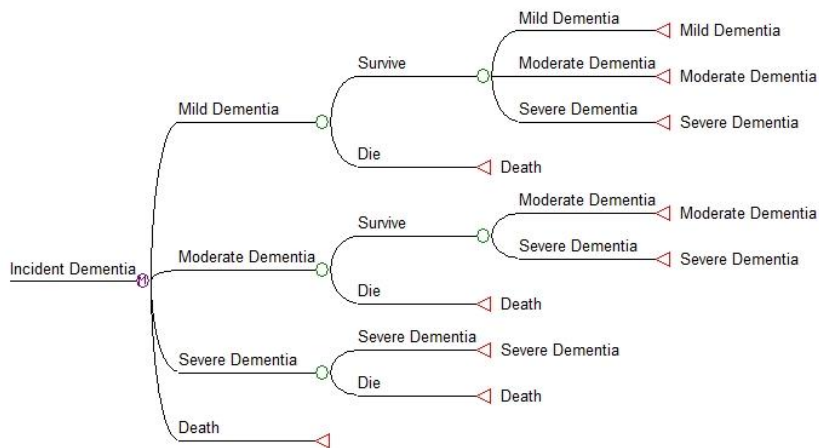


Figure 10. Base model for the incident dementia cohort

The states of mild and moderate dementia generated costs of about 12 billion SEK during the modelled period, constituting a proportion of almost 44% of the total costs. The severe state of the disease generated about 56% of the total costs, even though only about a third of the duration of the disease was spent with severe dementia. Thus, the severe state of dementia accounted for the largest proportion of costs for incident dementia cases.

By far, the highest costs were the costs of institutionalization, even as early as year 1 (Figure 11). Institutionalization accounted for 96% of the total costs in the case of the severe state and for 37% in the mild state of disease.

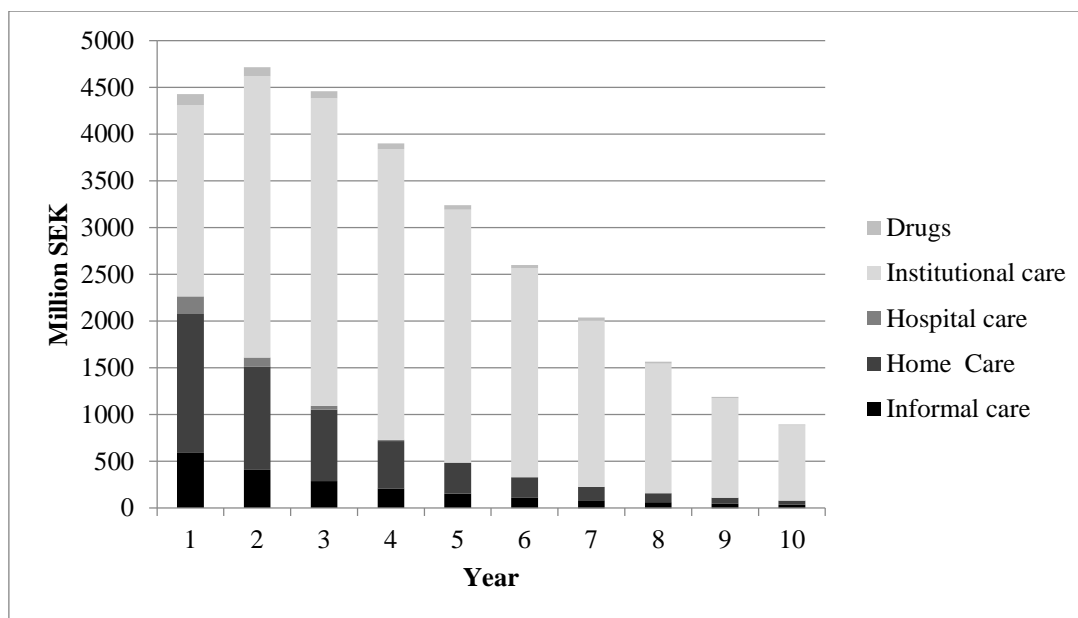


Figure 11. Total costs of incident dementia cohort stratified by type of cost.

When costs of informal care were varied in the sensitivity analysis from cost of leisure time of 91 SEK/hour to a replacement cost of 350 SEK/hour reflecting the change to a professional carer, the total cost increased with 27%. When testing different scenarios of

mortality, the option of high end 95% mortality confidence interval showed 26% decrease in total costs.

5.4 STUDY IV

In Study IV, a simulation was conducted in a Markov model of a hypothetical DMT aiming at treating MCI and mild states of dementia.

The simulation of DMT resulted in no societal cost savings when exploring the base case scenario for the whole cohort. In the base case, the incremental cost per person was 239,061 SEK. The higher cost was the result of the treatment itself and the fact that treated persons lived longer. The difference in survival was 0.9 years in favor of treated persons (Figure 12).

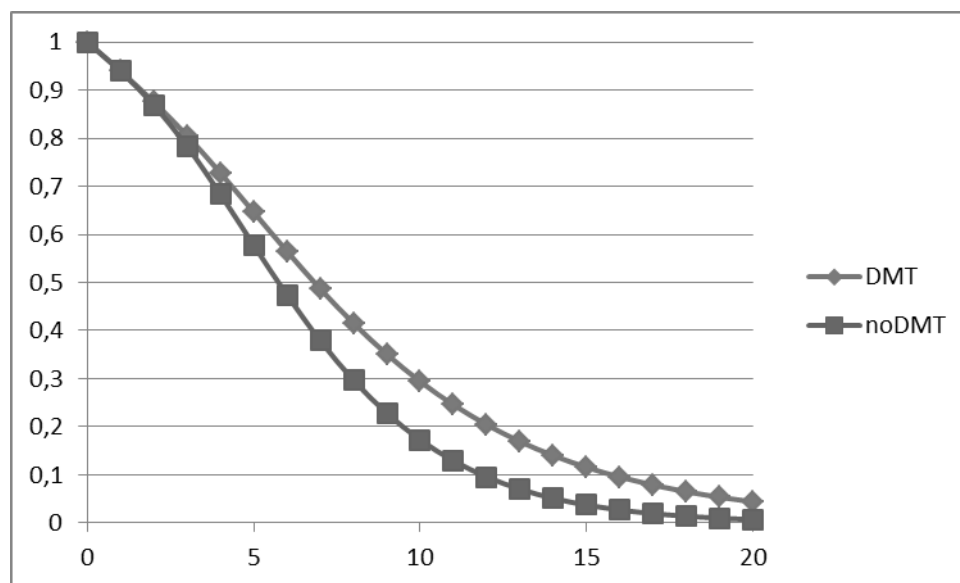


Figure 12. Survival curve of the model period

In terms of effect, the treated persons gained 0.82 QALYs and the resulting ICER was 293,000 SEK per gained QALY.

The sensitivity analysis showed that only one option was cost neutral and that was when the cost of the DMT was at the same level as for the acetylcholinesterase inhibitors (before these drugs became generic) and when the treatment did not affect mortality. With the assumption that DMT would have an effect, in all scenarios, the QALYs of the treated group exceeded the untreated group. If adopting a societal level of WTP of 600,000 SEK, all options of the treatment, except if cost for treatment was 300,000 SEK or more per annum, would be considered cost effective. A PSA was made with 1,000 iterations where distributions of transitions between states of AD and mortality and conversion to dementia were varied. The PSA (Figure 13) showed that in 99% of the simulations, the treatment option was in favour of DMT when adopting the above mentioned WTP, as shown in Figure 13.

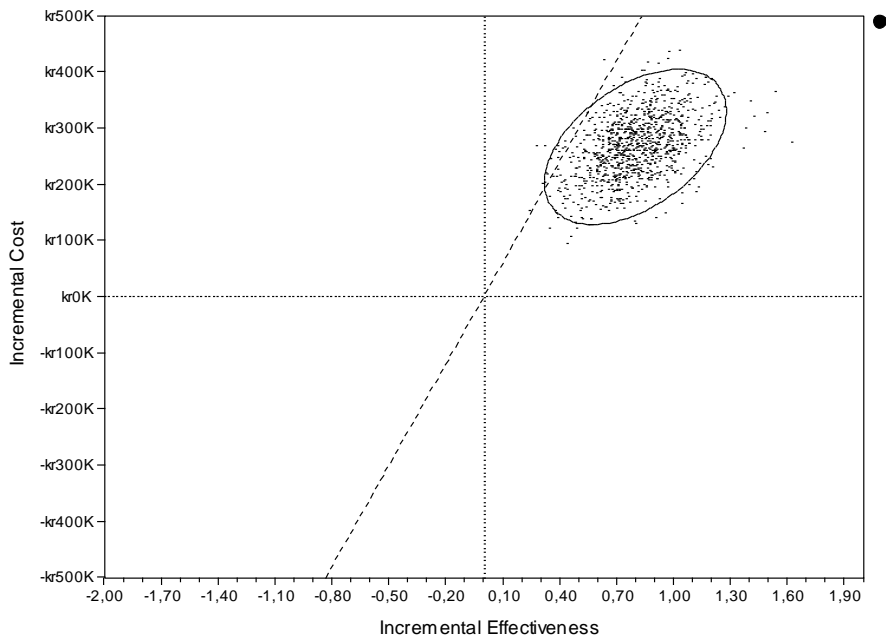


Figure 13. PSA Scatterplot of DMT treatment vs no treatment

6 DISCUSSION

6.1 MAIN FINDINGS

This thesis explored epidemiological and health economic aspects of dementia and drug use through analyses of population-based studies and economic modelling with a multi-disciplinary approach (228). As people live longer lives, many will suffer from age-related disorders, such as dementia, and many will use several drugs for their multiple conditions. These are major challenges for the society.

Drug use is extensive among older persons (66, 229). Indeed, about 80% of the older persons were found to use at least one drug (Study I). Drug treatment has its own costs (Study I) but there are also consequences of drug use in terms of IDU and adverse events (Study II), which are rarely given any economic value in COI and cost effectiveness studies. Costs of drug treatment in the elderly population is, as shown in this thesis, rather high and is expected to increase with the aging of the population (230).

If costs of hospitalization due to IDU (Study II) are added to the cost of the drugs, the total cost of drug treatment has a great impact on any health care budget (231). Thus, IDU may not only cause personal suffering and an increase in mortality (Study II) from suboptimal drug treatment, but also seems to lead to great expenditures for society (232).

The difference in hospitalization costs between people with and without IDU for the whole study population in Study II was around 3,700 SEK (although not statistically significant). If it is assumed that this gap is still valid in 2013 and the proportion of IDU patients is the same in the whole of Sweden (13%) for people aged 60 years and older, the aggregated extra hospitalization costs of IDU would amount to 1.2 billion SEK in 2013 ((18,718 SEK-15,045 SEK)* 2,444,102 (people 60+) *0,13). This figure is in line with a recent report by Fastbom (233), where the cost of hospitalizations due to adverse drug events among elderly people was estimated to be 900 million SEK.

However, not all costs related to IDU are avoidable. IDU may be a consequence of a necessary medical decision or part of a calculated risk where expected benefits were judged as greater than the estimated risks.

Costs of elderly care are extensive and particularly the cost of dementia care. In 2012, the societal costs of dementia in Sweden were estimated to be 63 billion SEK per annum (191). A wide economic approach can provide answers as to how societal resources may be allocated and give best value for money. Costs and effects can be measured and reported from different viewpoints. The viewpoint in this thesis is societal; thus aiming at reporting all included costs for society including informal care costs (Study III and Study IV).

To be able to give correct estimates of societal costs (Study III) and cost effectiveness of treatment (Study IV) in a broader sense, regarding a disorder such as dementia, it is crucial to

have input from population-based studies where non-users of care are included. If clinical or convenience study populations are used as input, there is a risk of overestimating the costs

Dementia generates costs in a complex manner and several payers are involved. These different payers are also involved at different time points in the course of the disease. There are transitions from care at home with informal family support in the early states, to long term care in the late state of dementia. When a modelling study (like Study III and IV) is performed, the sensitivity analysis is of great importance in order to show the robustness of the model. Inferences drawn from any health economic study rely on the validity of the many different kinds of input and since health economic studies are often a composite of different sources, evaluation of the different sources is even more crucial (234, 235).

6.2 THE IMPACT OF DEMENTIA ON DRUG COSTS

Economic studies of drug use in the elderly population have often focused on costs or cost-effectiveness of a single drug (236-241). Few previous studies have analysed both the magnitude of drug use at the level of drug classes and its costs. There is an extensive use of drugs among older persons and the associated drug costs are also high. We are, to our knowledge, among the first to compare costs for people with and without dementia in a population-based study, after adjustment for background factors in a regression model.

People with dementia used more drugs (5.4) than people without dementia (3.5) (Study I). Also the overall annual crude drug costs were higher for persons with than without dementia (6147 SEK vs. 3810 SEK). Moreover, the cost of nervous system drugs was more than five times higher in persons with dementia than without. Persons with dementia who are living in nursing homes often use psychotropic drugs (103, 242, 243), even though they are more likely to experience side effects of these drugs (99-102). However, there are now encouraging signs of a decline in the prescribing of these drugs to elderly persons (153, 244).

The cost for anti-dementia drugs was at the time frame of Study I very high and, thus, influenced the costs of nervous system drugs to a great extent. However, the prescription of these drugs was not very high at that time point (12% among persons with dementia). Today, the use of anti-dementia drugs is higher but the cost of these drugs is considerably lower. Since the patents have expired, costs for anti-dementia drugs have decreased to only about 5% of the cost at the time of Study I.

Costs for cardiovascular drugs were lower in the dementia group, even though the use was more frequent than among persons without dementia (Study I). These results are in concordance with previous findings showing that institutionalized elderly persons (of whom many have dementia or cognitive impairment) are less likely to use more expensive cardiovascular drugs (66). Persons with dementia were also older and their cardiovascular drug treatment may have been initiated a long time ago and then continued, although new and more expensive cardiovascular drugs were introduced on the market (60).

Drug costs in old age should be expected to be high given that elderly people often have many comorbid conditions (245-247). When comparing our results with a previous Swedish study (248), the costs for drug use had increased much more in the dementia group than in the group without dementia. This was partly explained by the introduction of the acetylcholine esterase inhibitors, but also by distinctly higher use of antidepressants, opioids and antipsychotics in the dementia group.

In the regression model, with adjustment for background factors, we found that the higher crude drug cost in persons with dementia was confounded by residential setting and comorbidities. One explanation for this confounding phenomenon could be that persons with dementia often live in nursing homes where use of drugs acting on the central nervous system is extensive (103, 242, 243).

6.3 INAPPROPRIATE DRUG USE IN OLDER PEOPLE AND IN PERSONS WITH DEMENTIA

IDU is common among older persons (91). We found an overall prevalence of IDU of 13% (Study II), which is lower than found in previous studies from the UK and Ireland (145, 249, 250), but similar to findings from Swedish national data (138).

We found that IDU was more common among persons with dementia and among persons in institutional care (Study II). These findings are in agreement with previous research from Sweden (131, 138, 251). Thus, IDU is most common among the frailest older people, which warrants more caution in prescribing to this vulnerable group of patients.

IDU was also found to be associated with an increased risk of both hospitalization and mortality, after adjustment for sociodemographic, functional and comorbidity factors. Hence, our study gives support to the growing body of literature on the negative outcomes of IDU and supports restrictive prescribing of these drugs in elderly patients (116, 124, 137, 139-141, 147, 252-255).

Moreover, we found a tendency for higher costs for hospitalizations with IDU than without IDU, although not statistically significant (Study II). Hospitalizations are likely to be the most costly outcome of IDU and may be, at least partly, preventable by more appropriate prescribing to older persons (144). The gap between hospital care costs for people with and without IDU in dementia was around 1,200 SEK. If this cost difference (although not statistically significant) is extrapolated to the whole Swedish dementia population, it represents a cost of about 185 million SEK per year. These costs could be added to the societal costs for dementia in COI estimates.

The results on IDU in this thesis show the importance of monitoring and reviewing drug therapy of elderly people both with and without dementia. Since the time of the baseline data collection in the SNAC-project, there has been a major focus on IDU in older people in Sweden and there are now encouraging findings of an improved quality of drug prescribing to this patient group (153).

6.4 COSTS OF DEMENTIA

Dementia is a long-term progressive disease and subsequently accounts for substantial societal costs (17), besides the burden of the disease itself for the affected persons and their families (256, 257). The long-term progressive nature of dementia disorders also entails a problem to collect all cost data during the course of the disease. In Sweden, the municipalities are faced with the majority of these costs while the county councils are responsible for a smaller share of the societal costs (258).

Study III shows that the highest costs for dementia occur in severe dementia and that long-term institutional care is the major cost driver, even in mild dementia. Even though many persons with dementia live at home, the costs of institutional care are so high that its proportion of the total costs for dementia is substantial. These findings are in line with recent findings from several European countries and may have implications for resource allocation and for strategies of long-term care placement (259-261).

Even though drug costs only accounted for 2% of the costs of dementia in Study III, its impact on the health care sector is high (191).

6.5 COSTS OF DISEASE MODIFYING TREATMENT AND PREVENTION IN DEMENTIA

The valuation of a DMT (Study IV), both in forms of efficacy and costs, is a hazardous task given that there is currently no such compound available on the market. Many trials so far have shown no efficacy or have been affected by safety issues (16).

Besides the disease modifying track, there are also great hopes of preventing AD through modifiable risk factors with up to as much 60% (262). The most influential risk factors identified today are the vascular risk factors (e.g. physical inactivity, smoking and midlife hypertension, obesity and diabetes) and depression (263-267). Interventions aimed at lifestyle factors have so far reported mixed results (268). One study focusing on prevention has also undergone complete health economic evaluation, i.e. of cost- effectiveness in a modelling approach, which showed that people in the intervention group gained QALYs and that the intervention cost less than usual care (269).

When, and if, a curable treatment for dementia enters the market, diagnosing the disease at an early stage may be necessary in order to change the course of the disease. New diagnostic criteria for AD have been suggested in this respect (270-273). However, the ethical implications concerning possible erroneous AD diagnoses are very important to consider.

According to our results (Study IV), developing a DMT for dementia will not lead to any cost-savings, mainly because of the prolonged survival with dementia and the cost of DMT. However, given that the societal WTP level is not exceeded, DMT could be considered cost effective. Even though our study showed no cost savings, a DMT can generate improved quality of life for the patient in gained QALYs. The higher cost for society is a consequence

of the treatment cost itself and the fact that it affects mortality. Hence, the prolongation of life with dementia will generate more costs to society. However, studies on this topic are rare. In a study without cost-effectiveness estimates, it was shown that time in long-term care was reduced and survival was prolonged with DMT (274).

6.6 LIMITATIONS

A general limitation of cross-sectional data is that no causal inference can be drawn. Simulation studies based on Markov models (Study III and IV) come with a set of limitations. A general limitation is the hypothetical nature of all simulations, i.e. a set of input values, taken from a fixed period of time, is used to calculate future scenarios. More specific to this thesis, dementia progression may alter with age, comorbid conditions and aggressiveness of the disease. Dementia is often associated with concurrent diseases and these diseases have their own costs, which we have not included (275, 276).

Other simulation techniques than those used in this thesis are available, such as discrete event simulation (DES) (277), but the most important aspect of any modelling approach is that the underlying assumptions are well-founded. When using hypothetical assumptions, as in Study IV, transparency is essential.

Our modelling approaches were based on Swedish conditions and may therefore have limited generalizability to countries with other care systems. We also used data from people aged ≥ 75 years (Study III and IV), which constitutes about 82% of the dementia population (205). Cost of informal care is controversial and often discussed (187, 188). Therefore, the informal care cost was varied in the sensitivity analysis to reflect different cost scenarios like the replacement cost and opportunity cost. Simulations can like other studies be biased and as a result potentially report incorrect numbers (278). For example, when a set of transition probabilities is estimated to be the same from mild dementia to moderate dementia as from moderate dementia to severe dementia, while in real life the transition probability of switching from mild to moderate dementia is lower than the probability of progressing from moderate to severe dementia (278), bias is introduced in the model.

6.6.1 Selection bias

An epidemiological study always runs the risk of selection bias. This is the case when distortions in the exposure-outcome association occur that is related to the procedure of selecting participants to a study and from factors related to study participation (279). However, both the Kungsholmen project and the SNAC study are in this respect well designed (178, 197). The participation rates were high in both studies with only small differences in the distribution of age, gender and education between participants and non-participants. Further, both the Kungsholmen project and the SNAC study include both community-dwelling and institutionalized persons, and proxy interviews when needed. This reduces the risk for systematic health differences between the participants and non-

participants (280). Thus, it is reasonable to think of the study population as representative of the source population.

6.6.2 Misclassification of outcome variables

Misclassification occurs when the collected information about an individual or group is erroneous. Both information on outcomes and exposures can be misclassified. It is important to consider whether the misclassifications are systematic or not. Non-systematic (non-differential) misclassification will, in most cases, lead to an attenuation of associations. However, systematic (differential) misclassification can lead to spurious associations (279).

6.6.2.1 Drug use and drug costs

There are several ways of collecting drug data, e.g. through interviews, using register data from pharmacies and medical records. Self-reported data, as used in this thesis, runs the risk of recall bias. Comparisons between self-reported data and other sources of drug use data have shown plausible under-reporting for self-reported data (281-283). However, unlike register data from pharmacies, which provide information about filled prescriptions, interview data also include information about OTC drugs and drugs that are actually taken and not only purchased.

Costs for the collected drug use are prone to the same risk of misclassification since the cost data are based on calculations from the underlying drug data. In the context of this thesis, the largest limitation would be if drug use and costs were systematically misclassified between persons with and without dementia. However, given the use of proxy interviews and that a trained physician was responsible for recording the drug use; the risk of systematic misclassification should be limited.

6.6.2.2 Hospitalization

All data on hospitalization were derived from the NPR. Validity of the data is high for almost all diagnoses (200). Misclassification is possible through diagnostic errors, translation errors and coding errors, but in total the errors are reported to be at a very low level (200).

6.6.2.3 Cost of hospitalization

When translating the ICD code of the NPR to costs derived from the Nord-DRG database, all of the above mentioned hospitalization errors can occur. Furthermore, the risk of erroneous underlying ICD codes may occur.

6.6.3 Misclassification of explanatory variables

Comorbidity was assessed by the Charlson comorbidity index (213) and included nine different diseases (i.e. myocardial infarction, congestive heart failure, cerebrovascular disease, dementia, chronic pulmonary disease, connective tissue disease, diabetes, renal failure and any tumour). However, the Charlson comorbidity index may not have completely

reflected the comorbidity burden among the participants. Further, there would have been a greater risk of bias if the index had relied on self-reported data only. Therefore, data on the diseases were collected through structured interviews by a physician, a clinical examination and blood testing.

Physical functioning was assessed by the Katz index of ADL (219) through interviews with trained nurses. If the participant was unable to answer, a next of kin was interviewed instead. It has previously been shown that assessments in a structured interview give higher validity than self-reported data (284). However, we cannot be certain that physical functioning has been completely accounted for in the analyses, given that this measure is difficult to estimate (285).

6.6.4 Confounding

In all pharmacoepidemiological studies, there is a risk of confounding by indication. This means that the association between drug use and outcomes can be confounded by the underlying disease that the drug is indicated for (286). We have tried to handle this in Study I and II by including a co-morbidity index (139) and hospitalization within one year as a proxy for disease severity in Study II (139).

Furthermore, we also took into account major known confounders in our data, such as age, sex, education, residential setting and physical functioning. However, residual confounding due to unknown factors cannot be excluded.

6.7 CONCLUSIONS

This thesis aimed at investigating dementia and use of drugs through analyses of population-based studies and economic modelling in a multi-disciplinary context.

The findings about drug therapy in persons with and without dementia revealed that the higher overall crude drug costs in dementia were confounded by comorbidities and residential setting. However, cost of nervous system drugs was more than five times higher in persons with dementia than without. Persons with dementia also used cardiovascular drugs to a higher extent but at a lower cost, indicating an older type of cardiovascular drug treatment in dementia patients. These findings may reflect differences in underlying disease patterns or differences in the care of persons with and without dementia.

We also found that IDU was associated with an increased risk of hospitalization and mortality among older persons. IDU might also lead to higher costs for society, although this needs to be investigated in further studies. This underlines the need for caution in the prescribing of these drugs to elderly patients. A large share of IDU is possible to avoid, which would benefit both society and elderly patients (233).

Our findings on net costs in dementia showed that the highest accumulated costs occur in severe dementia and that the major cost driver is institutionalization, even in mild dementia.

Drugs, on the other hand, constitute only a minor part of the total costs. It is essential to be transparent about all assumptions in a simulation model since costs are sensitive to assumptions concerning e.g. informal care, progression and mortality in dementia.

Finally, we found that DMT in dementia is projected to not be cost saving if the treatment prolongs survival. Still, if a societal willingness-to pay level of 600,000 SEK is adopted, the treatment can be considered cost effective. However, DMT would include very long treatment periods at high costs and with risks of adverse events.

6.8 FUTURE DIRECTIONS

Drug use in older people is a highly topical and timely research area. The implementation of the individual-based Swedish Prescribed Drug Register in 2005 provided new possibilities for advanced large-scale pharmacoepidemiological studies (287), including analyses of drug therapy in the elderly population. However, register data does not reveal all the information about an individual's drug treatment. On the other hand, older people may have more difficulties with self-reporting their complete drug use due to cognitive decline and polypharmacy. Therefore, validation studies of self-reported drugs vs. data from the Swedish Prescribed Drug Register are needed to disentangle the pros and cons of these different data sources among older persons.

Record linkage of population-based studies to register data is a valuable method for creating datasets that are rich in both clinical and self-reported variables as well as in objective and detailed data. This type of record-linkage is already done, but could be extended to also include the Swedish quality registers (e.g. the Swedish Dementia Registry).

There is also a need for longitudinal pharmacoepidemiological studies to provide valuable information about causal relationships and about changes in drug use over time.

The differences in drug treatment between persons with and without dementia merit further investigation. Future studies should aim to disentangle whether these differences reflect biomedical differences or if drug prescription is also affected by other factors such as communication problems and oversight of somatic conditions in persons with dementia.

The costs of IDU-related hospitalizations seemed high in this thesis. Further studies are needed to confirm our results and to assess to what extent these hospitalizations are avoidable through educational interventions and more cautious prescribing.

After the data for this thesis were collected, new treatment guidelines have been implemented, new drugs have reached the market and patents have expired. Therefore, the studies conducted within this thesis should be updated in order to investigate current conditions.

Simulations are well suited for describing long term progressive diseases and their associated costs. We have done analyses and projections based on Swedish data and our results may

mainly be applicable to our nearest neighbors (i.e. the Nordic countries). Hence, it would be of great interest to do the same kind of analyses in other countries or even globally in order to explore how costs are distributed in different health care systems with different payers. The hardest obstacle might be to find comparable and appropriate data sources.

Finally, it would be interesting to apply the same modelling techniques to other long term and progressive disorders like Parkinson's disease. There are also other interesting and suitable modelling techniques (e.g. discrete event simulation) that may have benefits when simulating diseases with long time perspectives and this has not yet been done under Swedish conditions.

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9 APPENDIX

List of dissertations from the Aging Research Center and the Stockholm Gerontology Research Center, 1991-2015

1991

Herlitz Agneta. Remembering in Alzheimer's disease. Utilization of cognitive support. (Umeå University)

1992

Borell Lena. The activity life of persons with a dementia disease.

1993

Fratiglioni Laura. Epidemiology of Alzheimer's disease. Issues of etiology and validity.

Almkvist Ove. Alzheimer's disease and related dementia disorders: Neuropsychological identification, differentiation, and progression.

Basun Hans. Biological markers in Alzheimer's disease. Diagnostic implications.

1994

Grafström Margareta. The experience of burden in care of elderly persons with dementia (Karolinska Institutet and Umeå University).

Holmén Karin. Loneliness among elderly – Implications for those with cognitive impairment.

Josephsson Staffan. Everyday activities as meeting-places in dementia.

Stigsdotter-Neely Anna. Memory training in late adulthood: Issues of maintenance, transfer and individual differences.

Forsell Yvonne. Depression and dementia in the elderly.

1995

Mattiasson Anne-Cathrine. Autonomy in nursing home settings.

Grut Michaela. Clinical aspects of cognitive functioning in aging and dementia: Data from a population-based study of very old adults.

1996

Wahlin Åke. Episodic memory functioning in very old age: Individual differences and utilization of cognitive support.

Wills Philippa. Drug use in the elderly: Who? What? & Why? (Licentiate thesis)

Lipinski Terzis Beata. Memory and knowledge in mild Alzheimer's disease.

1997

Larsson Maria. Odor and source remembering in adulthood and aging: Influences of semantic activation and item richness.

Almberg Britt. Family caregivers experiences of strain in caring for a demented elderly person. (Licentiate thesis)

1998

Agüero-Eklund Hedda. Natural history of Alzheimer's disease and other dementias. Findings from a population survey.

Guo Zhenchao. Blood pressure and dementia in the very old. An epidemiological study.

Björk Hassing Linda. Episodic memory functioning in nonagenarians. Effects of demographic factors, vitamin status, depression and dementia. (In collaboration with the Department of Psychology, University of Gothenburg, Sweden)

Hillerås Pernilla. Well-being among the very old. A survey on a sample aged 90 years and above. (Licentiate thesis)

1999

Almberg Britt. Family caregivers caring for relatives with dementia – Pre- and postdeath experiences.

Robins Wahlin Tarja-Brita. Cognitive functioning in late senescence. Influences of age and health.

Zhu Li. Cerebrovascular disease and dementia. A population-based study.

2000

Hillerås Pernilla. Well-being among the very old. A survey on a sample aged 90 years and above. (In collaboration with H.M.Quenn Sophia University College of Nursing, Stockholm, Sweden)

von Strauss Eva. Being old in our society: Health, functional status, and effects of research.

2001

Jansson Wallis. Family-based dementia care: experiences from the perspective of spouses and adult children.

Kabir Nahar Zarina. The emerging elderly population in Bangladesh: aspects of their health and social situation.

Wang Hui-Xin. The impact of lifestyles on the occurrence of dementia.

2002

Fahlander Kjell. Cognitive functioning in aging and dementia. The role of psychiatric and somatic factors.

Giron Maria Stella. The rational use of drugs in a population of very old persons.

2003

Jönsson Linus. Economic evaluation of treatments for Alzheimer's disease.

Yonker EJ. Hormones and Cognition: Testosterone and Visuospatial Ability, Estrogen and Episodic Memory. Stockholm University.

2004

Berger Anna-Karin. Old age depression: Occurrence and influence on cognitive functioning in aging and Alzheimer's disease.

Cornelius Christel. Drug use in the elderly: Risk or protection?

Larsson Kristina. According to Need? Predicting Use of Formal and Informal Care in a Swedish Urban Elderly Population.

Palmer Katie. Early detection of Alzheimer's disease and dementia in the general population. Results from the Kungsholmen Project.

Qiu Chengxuan. The relation of blood pressure to dementia in the elderly. A community-based longitudinal study.

2005

Derwinger Anna. Develop your memory strategies! Self-generated versus mnemonic strategy training in old age: maintenance, forgetting, transfer, and age differences.

Jones Sari. Cognitive functioning in the preclinical stages of Alzheimer's disease and vascular dementia.

Karp Anita. Psychosocial factors in relation to development of dementia in late-life: a life course approach within the Kungsholmen Project.

Nilsson Jan. Understanding health-related quality of life in old age. A cross-sectional study of elderly people in rural Bangladesh.

Passare Galina. Drug use and side effects in the elderly. Findings from the Kungsholmen project.

De Ronchi Diana. Education and dementing disorders. The role of schooling in

dementia and cognitive impairment.

2006

Jonsson Laukka Erika. Cognitive function during the transition from normal aging to dementia.

Klarin Inga. Drug use in the elderly – are quantity and quality compatible.

Ngandu Tiia. Lifestyle-related risk factors in dementia and mild cognitive impairment: A population-based study.

Nilsson Erik. Diabetes and cognitive functioning: the role of age and comorbidity.

2007

Batljan Ilija. Demographics and future needs for public long term care and services among the elderly in Sweden. The need for planning.

Ferdous Tamanna. Prevalence of malnutrition and determinants of nutritional status among elderly people. A population-based study of rural Bangladesh. (Licentiate thesis)

Beckman Gyllenstrand Anna. Medication management and patient compliance in old age.

Nordberg Gunilla. Formal and informal care in an urban and a rural elderly population. Who? When? What?

Rehman Jenny. The role of gender in face recognition.

Westerbotn Margareta. Drug use among the very old living in ordinary households. Aspects on well-being, cognitive and functional ability.

2008

Agahi Neda. Leisure in late life. Patterns of participation and relationship with health.

Gavazzeni Joachim. Age differences in arousal, perception of affective pictures, and emotional memory enhancement.

Haider Syed Imran. Socioeconomic differences in drug use among older people. Trends, polypharmacy, quality and new drugs.

Marengoni Alessandra. Prevalence and impact of chronic diseases and multimorbidity in the aging population. A clinical and epidemiological approach.

Meinow Bettina. Capturing health in the elderly population. Complex health problems, mortality, and the allocation of home-help services.

Rovio Suvi. The effect of physical activity and other lifestyle factors on dementia, Alzheimer's disease and structural brain changes.

Xu Weili. Diabetes mellitus and the risk of dementia: a population-based study.

2009

Atti Anna-Rita. The effect of somatic disorders on brain aging and dementia. Findings from population-based studies.

Livner Åsa. Prospective and retrospective memory in normal and pathological aging.

Paillard-Borg Stéphanie. Leisure activities at old age and their influence on dementia development.

Masud Rana AKM. The impact of health promotion on health in old age: results from community-based studies in rural Bangladesh.

Thilers Petra. The association between steroid hormones and cognitive performance in adulthood.

2010

Fors Stefan. Blood on the tracks: life-course perspectives on health inequalities in later life.

Keller Lina. Genetics in Dementia – Impact of sequence variations for families and populations.

2011

Caracciolo Barbara. Cognitive Impairment in the Non-demented Elderly. Occurrence, Risk Factors, Progression.

Rieckmann, Anna. Human aging, dopamine, and cognition. Molecular and functional imaging of executive functions and implicit learning.

Schön Pär. Gender Matters. Differences and Change in Disability and Health Among our Oldest Women and Men.

2012

Haasum Ylva. Drug use in institutionalized and home-dwelling elderly persons.

Lovén Johanna. Mechanisms of women's own-gender bias and sex differences in memory for faces.

Mangliasche Francesca. Exploring the role of vitamin E in Alzheimer's disease.

2013

Hooshmand, Babak. The impact of homocysteine and B vitamins on Alzheimer's disease, cognitive performance and structural brain changes.

Rizzuto, Debora. Living longer than expected: protective and risk factors related to human longevity.

2014

Sjölund, Britt-Marie. Physical functioning in old age: Temporal trends and geographical variation in Sweden.

Wastesson, Jonas. Unequal drug treatment: age and educational differences among older adults.