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Abstract

Alzheimer's disease (AD) is a neurodegenerative disorder causing dementia, a syndrome of gradual loss of cognitive function causing impairment in social and occupational functioning. This leads to substantial loss in quality of life and premature death for persons with the disease, associated suffering for their families and large costs to society. In parallel to the aging of the population the world prevalence is predicted to threefold within the next 40 years, creating a challenge for researchers and decision-makers to make better treatments available. Further, improved methods for economic evaluation in AD are needed to identify the optimal treatment strategies. The overall objective of this thesis is to explore the application of cost-utility analysis in AD and address key methodological challenges and data needs.

In paper I, prediction functions for simulating disease progression and economic endpoints in a decision-analytic model were estimated. Three year follow-up data from the Swedish Alzheimer Treatment Study (SATS) on the natural course of AD of 435 patients commencing treatment with donepezil and their care setting and costs of care was analyzed. A simplified model in which cognition (representing the underlying course of disease) and the ability to perform activities of daily living (ADL) (representing patient care need) was assumed to predict the provision of care. According to the estimated statistical functions, cognition was found to be the key predictor of ADL-ability which itself was the main predictor of care setting and costs of care.

In paper II, we used contingent valuation methods to elicit caregivers' willingness-to-pay (WTP) for reductions in patient care need. In total, 517 caregivers of AD patients in four countries (Spain, Sweden, UK and US) were interviewed. The mean WTP for a one hour reduction per day was estimated at between £59 and £144 per month depending on country. The income of the caregiver was the only consistently significant determinant of WTP across all countries.

In paper III, we assessed predictors of the costs of care of 1,222 AD patients in four countries (Spain, Sweden, UK and US), both residing in the community and in residential care settings. Cognition, ADL-ability, behavioural symptoms and costs of care (RUD-Lite) were assessed via a patient and caregiver interview. Cost estimates ranged between £1,000 to £5,000 per patient and month, increasing with disease severity and higher in residential care settings. ADL-ability was the most important predictor of costs but part of the variation was also explained by cognition and behavioural symptoms.

In paper IV, the key components and drivers of costs of care in a clinical trial sample of 2,744 mild to moderate AD patients were identified. Costs were assessed with RUD-Lite at baseline and every 6 months over the 18 months trial. Informal care constituted 82-86 percent of total costs, whereas community care and patient accommodation constituted an equal share of 12-16 percent. Informal care also had the strongest correlation with disease severity measures including cognition, ADL-ability, global function and behavioural symptoms.

In conclusion, cognition, ADL-ability and behavioural symptoms are all important indicators of care need in AD and should be considered in economic modelling. Caregivers have a substantial willingness to pay for reductions in care need. Informal care is the key cost component in clinical trials in mild to moderate AD. Health utility estimates of AD patients are highly dependent on the methodology including choice of instrument, respondent and utility tariffs.

List of publications

I. Gustavsson A, Jonsson L, Parmler J, Andreasen N, Wattmo C, Wallin AK, Minthon L. Disease progression and costs of care in Alzheimer's disease patients treated with donepezil: a longitudinal naturalistic cohort. (Submitted to The European Journal of Health Economics)

II. Gustavsson A, Jonsson L, McShane R, Boada M, Wimo A, Zbrozek AS. Willingness-to-pay for reductions in care need: estimating the value of informal care in Alzheimer's disease. Int J Geriatr Psychiatry 2010;25:622-32.

III. Gustavsson A, Brinck P, Bergvall N, Kolasa K, Wimo A, Winblad B, Jonsson L. Predictors of costs of care in Alzheimer's disease – a multinational sample of 1,222 patients. (Accepted for publication in Alzheimer's & Dementia)

IV. Gustavsson A, Cattelin F, Jonsson L. Costs of care in a mild-to-moderate Alzheimer clinical trial sample - Key resources and their determinants (Accepted for publication in Alzheimer's & Dementia)

Contents

Abbreviations

15D	15 domains
AD	Alzheimer's disease
ADAS-cog	Alzheimer's Disease Assessment Scale- cognitive subscale
ADCS-ADL	Alzheimer's disease Cooperative Study- Activities of Daily Living inventory
ADLs	activities of daily living
AHEAD	Assessment of Health Economics in Alzheimer's Disease
Behave-AD	Behavioural Pathology in Alzheimer's Disease Rating Scale
CADTH	Canadian Agency for Drugs and Technologies
CBA	cost-benefit analysis
CDR	Clinical Dementia Rating scale
CDR-SB	CDR sum of boxes
CEA	cost-effectiveness analysis
CIBIC-plus	Clinician's Interview-Based Impression of Change plus caregiver input
CMA	cost-minimization analysis
CMAI	Cohen-Mansfield Agitation Inventory
CRA	Caregiver Reaction Assessment
CUA	cost-utility analysis
CV	contingent valuation
DAD	Disability Assessment for Dementia scale
DC	dichotomous choice
DES	discrete event simulation
DSM-IV	Diagnostic and Statistical manual of Mental Disorders – Fourth Edition
EGCg	Epigallocatechin-3-gallate
EQ-5D	EuroQoL – 5 domains
FAST	Functional Assessment Staging
FTC	full time care
HTA	health technology assessment

HUI	Health Utility index
IADL	Instrumental Activities of Daily Living scale
ICD-10	International Statistical Classification of Diseases and Related Health Problems – tenth edition
ICER	incremental cost-effectiveness ratio
MCMC	Markov Chain Monte Carlo simulation
mMMS	modified Mini-Mental State examination
MMSE	Mini-Mental State Examination
NHS	National Health Services
NICE	National Institute for Health and Clinical Excellence
NINCDS-ADRDA	National Institute of Neurological and Communicative Disorders and Stroke – Alzheimer's Disease and Related Disorders
NPI	Neuropsychiatric inventory
PBAC ESC	Economics Sub-Committee of the Pharmaceutical Benefits Advisory Committee
PRO	patient reported outcomes
PSMS	Physical Self-Maintenance Scale
QALY	quality adjusted life year
QoL-AD	Quality of life- Alzheimer's disease
RCT	randomized controlled trial
RUD	Resource Utilization in Dementia
SATS	Swedish Alzheimer Treatment Study
SG	standard gamble
SHTAC	Southhampton Health Technology Assessments Centre
SOS	National Board of Health and Welfare (Socialstyrelsen)
TLV	Dental and Pharmaceutical Benefits Agency (Tandvårds- och läkemedelsförmånsverket)
TTO	time-trade-off
WTA	willingness-to-accept
WTP	willingness-to-pay
ZBI	Zarit Burden Interview

1. Introduction

1.1 Alzheimer's disease

1.1.1 Definition and diagnosis

Alzheimer's disease (AD) is a neurodegenerative disorder causing dementia, a syndrome first described by a German psychiatrist and neuropathologist, Alois Alzheimer, in 1906. These symptoms include the gradual loss of cognitive function causing impairment in social and occupational functioning (1). The cause of the disease is not known, although there are several hypotheses being explored including beta-amyloid accumulation and neurofibrillary tangles in the brain, leading to cell death and brain atrophy (2).

A definite diagnosis of Alzheimer's disease can only be established after autopsy (3). In practice, a clinical diagnosis is set after examination based on the Diagnostic and Statistical manual of Mental Disorders – Fourth Edition (DSM-IV), International Statistical Classification of Diseases and Related Health Problems – tenth edition (ICD-10), or National Institute of Neurological and Communicative Disorders and Stroke – Alzheimer's Disease and Related Disorders (NINCDS-ADRDA) criteria (4-6). The DSM-IV criteria are as follows:

A. The development of multiple cognitive deficits manifested by both
   (1) memory impairment (impaired ability to learn new information or to recall previously learned information.)
   (2) one (or more) of the following cognitive disturbances:
      (a) aphasia (language disturbance)
      (b) apraxia (impaired ability to carry out motor activities despite intact motor function)
      (c) agnosia (failure to recognize or identify objects despite intact sensory function)
      (d) disturbance in executive functioning (i.e., planning, organizing, sequencing, abstracting)
B. The cognitive deficits in Criteria A1 and A2 each cause significant impairment in social or occupational functioning and represent a significant decline from a previous level of functioning.
C. The course is characterized by gradual onset and continuing cognitive decline.
D. The cognitive deficits in Criteria A1 and A2 are not due to any of the following:
   (1) other central nervous system conditions that cause progressive deficits in memory and cognition (e.g., cerebrovascular disease, Parkinson's disease, Huntington's disease, subdural hematoma, normal-pressure hydrocephalus, brain tumor)
   (2) systemic conditions that are known to cause dementia (e.g., hypothyroidism, vitamin B12 or folic acid deficiency, niacin deficiency, hypercalcemia, neurosyphilis, HIV infection)
   (3) substance-induced conditions
E. The deficits do not occur exclusively during the course of a delirium.
F. The disturbance is not better accounted for by another Axis I disorder (e.g., Major Depressive Disorder, Schizophrenia).

DSM-IV is mostly used in research while the Swedish system for medical records is built around ICD-10. There are new versions currently being developed for both systems: DSM-V (expected in May 2013) (7) and ICD-11 (8). The proposed revision for DSM-V includes removing the term

dementia and instead sort the dementias under a new category called Major Neurocognitive disorder (9).

Alzheimer's disease is the most common cause of dementia, accounting for 50 to 70 percent of all dementia cases (1). Other common causes include vascular dementia and dementia with Lewy bodies. Mixed dementia is also common, primarily cases with both Alzheimer pathology and vascular lesions (10).

1.1.2 Burden of dementia

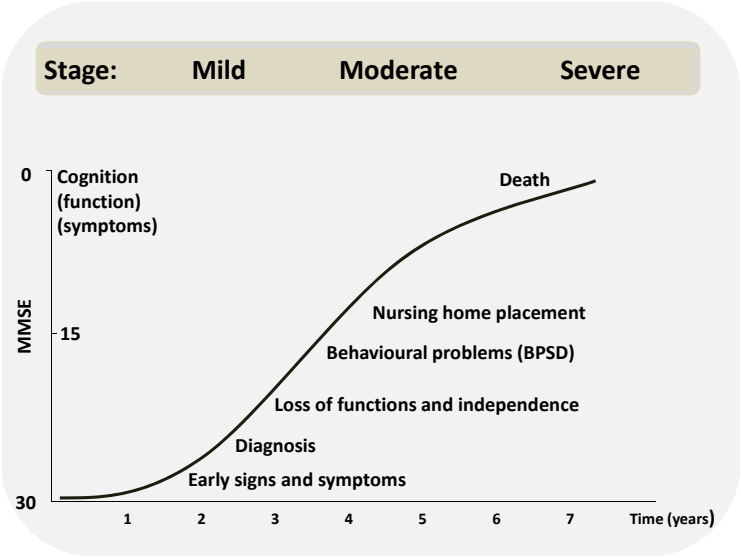
The worldwide prevalence of dementia was estimated at 34.4 million in 2009 (11) of which potentially 17-24 million have Alzheimer's disease (based on the 50-70 percent estimate). Alzheimer's Association estimates the US prevalence of Alzheimer's disease at 5.3 million (12). The world prevalence will increase over the next decades as a consequence of the aging population and the demographic transition in developing countries. A recent report predicted that 66 million people worldwide would be affected by dementia in 2030 and 115 million in 2050 (13).

Dementia affects society on several levels. Patients suffer from loss of function and quality of life as the disease progresses and ultimately premature death at the terminal stage. Their family and friends suffer from losing their loved ones but also from burden perceived from caring for the patient (14). Finally, the societal cost of dementia makes it one of the most costly disorders of our time. The worldwide societal costs were estimated at 422 billion US dollar in 2009 out of which a third ($142 billion) was costs of informal care from family and friends (11). In parallel to the aging of the population and increase in the prevalence of dementia, the economic burden of dementia is projected to increase rapidly over the next decades (13).

1.1.3 Staging of disease

The progressive nature of AD can be divided into three stages: mild, moderate and severe. The border between the three is diffuse and there are no strict criteria for progressing into a more severe stage. In general, in the mild stage, patients have impaired intellectual, social and occupational abilities, but are still capable of taking care of themselves. In the moderate stage, their cognitive impairment gets worse and they get dependent on care from others to carry out their activities of daily living (ADLs). In the severe stage they are dependent on constant care from others (15). The figure below is a reproduction from the literature describing the cognitive decline over time and its implications on patient dependence and care need (16, 17).

Figure 1 Staging the course of Alzheimer's disease (16, 17)



There are several instruments for assessing the severity of Alzheimer's disease. Many of them are used both to stage the disease and to serve as primary endpoints in clinical trials testing efficacy of novel treatments.

1.1.3.1 Cognitive function

The Mini-Mental State Examination (MMSE) (18), is a screening instrument for the assessment of cognitive impairment, and also a common tool for severity staging. It gives a score between 0 and 30 points, which can be stratified into mild (21 - 26), moderate (10 - 20), moderately severe (10 – 14) and severe (0 - 9) cognitive impairment (19). These cut-offs are not consistent across studies and alternative ranges have been reported in the literature (20). The MMSE is widely spread both in clinical practise and in research studies including randomized controlled trials (21). Another, and more comprehensive instrument for assessing cognitive function, is the Alzheimer's Disease Assessment Scale- cognitive subscale (ADAS-cog) ranging from 0 to 70 points with increasing impairment (22).

1.1.3.2 Function or ADL-ability

Function or ability to carry out ADLs, offer an alternative method for staging the disease course reflecting the independence of the patient and consequently their need for care. There are many instruments available for assessing function, most of them being administered to the primary caregiver of the patient as an informant. Some of the more common instruments include:

- The Physical Self-Maintenance Scale (PSMS) (23) includes 6 basic ADL domains (toileting, feeding, dressing, grooming, physical ambulation and bathing) forming a total score between 0 and 6 indicating in how many domains the patient is independent.

- The Instrumental Activities of Daily Living scale (IADL) (23) consists of eight instrumental ADL domains (using the telephone, shopping, preparing food, housekeeping, laundering, transportation, handling medications, and handling finances) forming a total score between 0 and 8 indicating in how many domains the patient is independent.

- The Disability Assessment for Dementia scale (DAD) (24) measures both basic and instrumental ADLs and gives a score ranging between 0 and 100 with increasing independence. The score reflects the proportion of tasks that the patient can perform.

- The Alzheimer's disease Cooperative Study- Activities of Daily Living inventory (ADCS-ADL) (25) assesses both basic and instrumental ADLs. The administration takes about 20 minutes and gives a score from 0 to 78 with increasing dependency.

- Functional Assessment Staging (FAST) (26) characterizes the functional course of AD in 7 steps with increasing disability.

1.1.3.3 Global assessment

Global clinical assessments, such as the Clinical Dementia Rating scale (CDR) (27), are also common and usually combine both cognitive and functional domains to stage the disease. These measures are more dependent on the rater as their aim is to assess their clinical impression of the severity of the patient (21).

1.1.4 Outcomes in clinical trials

Cognition, functional ability (or ADL-ability) and global assessments are usually primary endpoints in clinical trial. The global assessment is then more focused at the change of symptoms over time rather than staging the disease at each point in time. To this end, there are specific instruments for clinical trials including Clinician's Interview-Based Impression of Change plus caregiver input (CIBIC-plus) (28) and CDR sum of boxes (CDR-SB) (27, 29, 30).

Behavioural symptoms are not commonly used to stage the course of the disease but they are an important part of AD and an important endpoint in clinical trials. The most widely used instrument for their assessment is the Neuropsychiatric inventory (NPI) (31) which assesses the presence, frequency and severity of behavioural symptoms. It is also available in a shorter version (32). Other instruments include the Behavioural Pathology in Alzheimer's Disease Rating Scale (Behave-AD) (33) which assesses behavioural symptoms via an interview with the caregiver as well as direct observation of the patient, and the Cohen-Mansfield Agitation Inventory (CMAI) (34).

1.1.5 Patient care

As the disease progresses, patients become increasingly dependent on others. At first they usually need help with instrumental ADLs such as cleaning, shopping and cooking food. In later stages they also lose the ability to carry out basic ADLs such as eating, toileting and dressing. A family member or friend (a so called informal caregiver) commonly assists the patient with such tasks in early stages of the disease. In many health care systems there are also community

services available (e.g. home helpers, home-delivered food and day care centres) to alleviate the burden on the informal caregiver. As patients deteriorate into worse stages and the demand for care increases, many patients move into residential care settings with varying levels of nursing assistance available (35).

The National Board of Health and Welfare (SOS) is a Swedish governmental agency with one of its purposes to promote high quality health care provision in Sweden. They issued national guidelines on dementia care in 2010, with specific recommendations for optimizing the care of demented elderly. First, the establishment of a correct diagnosis is expected to result in improved care and a thorough diagnostic assessment should therefore be conducted whenever dementia is suspected. Second, the care should be organized with the needs of the individual patient at focus and carried out by multi-professional teams which should get adequate training in dementia care. Third, all patients should be re-assessed and their care re-evaluated at least annually. Fourth, the available pharmacological treatments should be offered to patients when indicated (including cholinesterase inhibitors and memantine). Fifth, dementia specific day care and specialized living should be offered to dementia patients. Sixth, support should be offered to the family of the patient education, respite care and psychosocial support (36).

1.1.6 Pharmaceuticals

1.1.6.1 Currently available treatments

There is no cure available for Alzheimer's disease, but there are four symptomatic drug therapies currently indicated for AD. Three of them are cholinesterase inhibitors for the treatment of mild to moderate AD: donepezil (Aricept®), rivastigmine (Exelon®) and galantamine (Reminyl®). All three compounds have shown efficacy on cognitive function and global endpoints in short-term (3-6 months) randomized controlled trial (RCT) in mild to moderate AD. Function, i.e. ability to carry out ADLs, has been assessed in placebo-controlled trials with duration up to 60 weeks with significant efficacy favouring active treatment while behaviour has only been assessed in donepezil and galantamine with some evidence of efficacy (37). Donepezil is also indicated for severe dementia in the US but not in Europe (38). The fourth symptomatic treatment, memantine (Ebixa®), is a NMDA receptor antagonist for the treatment of moderately severe to severe AD. Memantine have shown significant efficacy on cognition, function and global endpoints in 24 weeks randomized trials (39).

1.1.6.2 Current therapeutic targets

Memantine was the latest drug to receive approval for treatment of AD in 2002 in Europe, and 2003 in the US. Since then, many candidate compounds have failed due to lack of efficacy and/or unacceptable side effects. However, there are still many potentially capable drugs being explored and a handful of them have reached the third clinical phase and are currently tested in pivotal registration trials. These include bapinuzemab and solanezumab, two passive immunotherapies targeted at clearing Aβ from the brain that is believed to play an important role in the pathogenesis of AD. Another is Epigallocatechin-3-gallate (EGCg) which may inhibit toxic Aβ-aggregation. Other drugs with different modes of action are currently tested in smaller clinical samples in phase 2. These include active immunotherapies, drugs that prevent the production of Aβ (i.e. α-secretase activators and β-secretase and γ-secretase inhibitors), drugs that target tau proteins (a parallel hypothesis next to Aβ accumulation potentially causing the disease) and new cholinergic drugs. See Mangialasche for a recent review (2).

1.2 Methods for economic evaluation

1.2.1 Definition

Drummond et al. define economic evaluation as “the comparison of two or more alternative courses of action in terms of both their costs and consequences” (40). It is always comparative as the benefit of a potential intervention can only be measured if compared to an alternative, even if the alternative is doing nothing. The costs may constitute not only the costs of a specific intervention, but also the potential cost offsets in other parts of the health care system which are caused by the intervention. For instance, if a vaccination programme results in a lower care need in the future, this implies cost savings on coming budgets. Similarly, the outcomes of an intervention vary, may affect more people than the patient and can be measured with different endpoints.

1.2.2 Types of economic evaluations

There are different types of economic evaluations, differing mainly in the way the outcomes are measured. The following sections give an overview and comprehensive reviews are available elsewhere (40, 41).

1.2.2.1 Cost-minimization analysis

Whenever two interventions give the same outcome we would prefer the least costly of them. This is the principle of cost-minimization analysis (CMA). In practise, outcomes are rarely exactly the same which justifies some trade-off between a better outcome and a lower cost.

1.2.2.2 Cost-effectiveness analysis

In cost-effectiveness analysis (CEA) we allow two interventions to differ not only in their costs but also in their outcomes, or so called effectiveness. The effectiveness needs to be measured quantitatively, e.g. number of months of survival. We may then calculate the additional cost (the cost difference between the two interventions) of the additional effectiveness (in our example additional survival). This ratio is called the incremental cost-effectiveness ratio (ICER) defined as the difference in costs divided by the difference in effectiveness.

Our preferred intervention then depends on what our willingness-to-pay (WTP) is for the additional effectiveness. If we can identify a threshold for our WTP (e.g. £35,000 for every additional year of life) we may introduce a decision rule to invest in all interventions that result in a cost per every added year of life below or equal to this threshold.

1.2.2.3 Cost-utility analysis

A cost-utility analysis (CUA) is a special case of CEA in which all outcomes are translated into a common measure reflecting the individual’s relative preference for the different outcomes. This measure is often referred to as utility, also (incorrectly) in cases when the theoretical properties of utilities are not fulfilled. The expected utility theory rests on a set of assumptions first described by von Neumann-Morgenstern (42). In order for a preference measure to be a utility in its strict meaning, it needs to take the individual’s risk attitude into account. An individual may for instance prefer a certain outcome to a gamble between a better and a worse outcome, even if the expected value of the certain outcome and the gamble are equal. For this so called risk averse individual, the utility is therefore higher for the certain outcome than for the gamble. The opposite

is called risk seeking, i.e. a preference for risky gambles although the expected value of a certain outcome is equal. In many applications, preferences are measured when there is no uncertainty of the outcome in which case we should rather speak of the perceived value of an outcome than the perceived utility of the same.

In practise, the quality adjusted life year (QALY) is a commonly used preference outcome in economic evaluation. It is based on the assumption that people would be willing to trade between the length and quality of life, where each possible health state is associated with a quality of life value which can be depicted on an index scale. This scale is cardinal, meaning that there is an order of preference (i.e. the higher the scale value the more preferred is the outcome) and that the scale intervals have a meaning (i.e. an increment of 0.1 is equally preferred irrespective of location on the scale). The scale is usually anchored between 1 (perfect health) and 0 (dead). The QALY is then defined as the equivalent of one year of perfect health (e.g. 2 years in a health state with a scale value of 0.5 equals 1 QALY).

There are several methods for eliciting the quality of life of a certain health state. One of the more common methods is the time-trade-off (TTO) in which an individual is asked to choose between two scenarios: health state A for x years followed by death or perfect health for a fixed number of years followed by death. The number of years x is increased/decreased until a cut-off is reached. The ratio between the cut-off x and the fixed number of years is then assumed to be the quality of life or utility of health state A. Another common method which takes the respondent's risk attitude into account is the standard gamble (SG). The respondent is now asked to choose between health state A for t years, or a gamble with the probability p of perfect health for t years and the probability (1-p) of immediate death. The probability p is increased/decreased until a cut-off is reached and the probability p is then assumed to be the utility of health state A.

The TTO and SG are both direct methods to assess utilities in the study sample. However, the direct assessment is complex and time consuming. Indirect measures such as the EuroQoL – 5 domains (EQ-5D) (43) are therefore commonly used. The EQ-5D is a generic (i.e. applicable across multiple diseases) health indexing system developed for an easy and rapid estimation of the health utility of different health states. It contains five domains (mobility, self-care, usual activity, pain/discomfort and anxiety/depression) with three different levels, together forming 243 possible health states. Scoring algorithms or tariffs estimated from external sources are thereafter used to link each health state to a certain utility. One such tariff is available from a UK sample of about 3,000 individuals who elicited the utility of the EQ-5D health states using TTO methods (44). The utility derived with EQ-5D is thus determined by the preferences of an external population scoring the health state reported by the patient.

Other generic instruments to assess health utilities of different health states include the Health Utility index (HUI) (45) and the 15 domains (15D) (46). HUI Mark 2 includes seven domains with four to five levels within each domain. A later version, HUI Mark 3, includes eight domains with five to six levels within each domain. The 15D instrument assesses fifteen domains, each rated on a 5-point scale.

The use of cost-utility analysis (and QALYs in specific) is recommended for reimbursement submissions in many countries because they enable comparison of interventions across different disease area, irrespective of their outcome.

1.2.2.4 Cost-benefit analysis

In a cost-benefit analysis (CBA), all outcomes are translated into monetary values. The net benefit of an intervention is calculated by subtracting its incremental cost from the incremental monetary value of its outcomes. The decision maker should then invest in all interventions with a net benefit above zero.

1.2.3 Costing

1.2.3.1 Cost studies

Cost of illness studies do not by themselves offer any evidence of the value of a treatment. They are primarily used to explore the magnitude of the burden of a disease and draw the attention of policy makers and sponsors to particular needs for investment and research. However, data from cost of illness studies can be useful in economic models when combined with other sources on disease progression and treatment efficacy. Cost data should then be available for each of the relevant patient subgroups, i.e. defined by severity of symptoms, care setting and care need etc. This data can be collected with a bottom-up approach in which individual patients are assessed and estimates of the mean costs per patient are derived from a sample of patients with similar characteristics (the alternative top-down approach, in which aggregated data from e.g. national accounts are broken down to different subcategories, are generally not useful in this context).

Bottom-up cost studies can also be used to identify the important components of costs (i.e. how costs are distributed across different types of resources) and cost drivers (i.e. what determines the level of costs). This data is useful prior to the decision on what resources to capture in a study to ascertain that data on the most relevant costs are collected.

What costs to include in economic evaluation depends on the perspective of the analysis. In practice, the governmental agencies controlling or providing guidance on reimbursement decisions, set the standards for the economic evaluation of health care interventions in each country. In Sweden, the Dental and Pharmaceutical Benefits Agency (TLV), recommends a societal perspective, in which the costs of all stakeholders are considered (47). In England, the National Institute for Health and Clinical Excellence (NICE), requires a third party payer perspective which only takes into account the costs of the public health care system (and disregards e.g. private and indirect costs) (48).

1.2.3.2 Value of informal care

In economic evaluation, each resource should be valued at their opportunity cost which is defined as the value of their best alternative use on the market. Due to market imperfections, this may not be exactly reflected by the market price of the resource, but market prices are generally perceived to be close enough unless there are certain circumstances that merit adjustments (40).

Informal care (i.e. unpaid care, usually provided by a family member or friend) is not available on the market and the opportunity cost is therefore difficult to assess. There have been many alternative approaches proposed on how to estimate the value of informal care including the human capital, friction cost and replacement cost methods (49). The human capital method assumes that production is foregone while the informal caregiver provides care to the patient, and the opportunity cost should therefore be equal to this production loss. The friction cost method assumes that someone else covers the production loss due to the absence of the informal caregiver and the opportunity cost is therefore equal to the friction in which the responsibility and

knowledge is transferred to another person. The replacement cost method considers the value of informal care to be equal to the value of an alternative carer (e.g. a formal carer available on the market).

None of the above methods takes the caregiver's preferences into account and is therefore ignorant of the potential value or burden associated with the care giving as perceived by the caregiver. The revealed preference approach observes true transactions within the society which reveals peoples' preferences. The value of a reduction in waiting time may for instance be equal to the additional price people are willing to pay for moving ahead in the waiting line, which may be observable within the market. However, there are limitations in what preferences can be elicited this way as many scenarios do not occur in everyday life.

1.2.3.3 Contingent valuation methods

An alternative to revealed preference studies is contingent valuation (CV) methods (also known as the stated preference approach), which explores how people respond to hypothetical scenarios which are presented to them (49).

There are several ways of eliciting value in contingent valuation and the methods do indeed have impact on the results. The answers from the respondents are sensitive to what, when and by whom questions are asked and how they are formulated. Respondents may be influenced by the amount of material presented to them and too little information may lead to misinterpretation of questions (50). The payment vehicle (i.e. whether paid out of pocket, via a tax increase or an insurance premium) may affect the value expressed by the respondent. Another factor is what expectations the respondent has on the future, e.g. do they know that they will have use of the offered good or service or not. The reliability of the response may depend on the respondent's relationship with the interviewer and whether the respondent perceives certain incentives to respond in specific ways. For instance, if the patient of a caregiver is present during the interview, the caregiver's responses on questions relating to caregiver burden may be affected.

Willingness-to-pay (WTP) and willingness-to-accept (WTA) are two sides of the same coin but they commonly give different results. The price people are willing to pay to get something has been shown to be lower than the price people who have the same are willing to accept to give it away. One of the proposed causes of this difference is that WTP is limited by the available budget whereas WTA is not.

Four of the most frequently used elicitation methods in CV studies are: open-ended questions, bidding games, payment cards and discrete indicators. In open ended questions, the respondents are asked to state their maximum WTP which is simple, fast and straight forward but can also be demanding for the respondent. Bidding games may be easier as respondents are given an offer and then asked to either accept or reject it. Depending on the answer the offer is increased or decreased until a threshold (of maximum WTP) is reached. Payment cards provide a range of amounts in a single question from which the respondent is asked to select their maximum willingness-to-pay. The bidding game and payment cards are associated with biases related to the starting point (in the bidding game) (51) and range of values (payment card) (52). These biases can be avoided by the discrete indicator method (also referred to as dichotomous choice (DC) or take-it-or-leave-it-offers) in which the respondent is given one offer to accept or reject but without any bidding game following their response. The one offer is varied across respondents to explore how the proportion of accepts depends on the price, from which the mean WTP among all respondents can be estimated. This method is popular for its similarity to market transactions but may need a larger sample since we do not obtain the WTP from each respondent (53). Another

problem with the discrete indicator method is that respondents may want to express their appreciation of the good or service and accept an offer although the price is too high (in all three other methods, the respondent is given the opportunity to set a low price). Overestimation due to this so called yea-saying can be avoided by asking the respondent to state how certain they were of their response and only consider certain responses as accepts (54).

1.2.4 Patient-level data analysis

There are several sources of evidence in the economic evaluation of a new therapy. The randomized controlled trials (RCT), which are conducted prior to the registration of a new drug, offer a first opportunity to estimate the cost-effectiveness in a trial setting (so called within-trial cost-effectiveness) (55). These estimates have high internal validity (they are valid within the setting studied) but usually low external validity (the results are not necessarily applicable to the clinical practise setting). They are primarily designed to test efficacy and safety and therefore not optimal for cost-effectiveness analysis. The most important reasons for a low external validity are that patients are selected (e.g. less morbid than the overall patient population to alleviate risk of attrition), their care patterns are probably affected by the protocol (may have had no or additional visits if not enrolled into the study), and they are only followed over short periods of time (55). Most ongoing trials today include resource utilization as a secondary endpoint in their pivotal registration trials (56).

After registration, there may be opportunities to conduct experimental studies to test the cost-effectiveness in patients in a more realistic setting (so called phase 4 studies). However, such studies would need to recruit many patients and have long duration in order to capture effects on currently available endpoints considered of relevance to patients (e.g. institutionalization). This may not be feasible due to practical and ethical constraints in withholding potentially beneficial treatment for patients in the comparator arm of such a trial (56).

In comparison, registries and observational studies in clinical practise may have higher external validity to the general populations but the internal validity is lower because they lack a control group which is needed to identify a causal effect of the treatment (57). Instead, they can be used to study the natural course of the disease, treatment patterns and costs in a real life setting. They can also be used to follow time trends in the uptake of a new intervention and to explore whether there has been any change in health outcomes which may be linked to such intervention. Registries can also be used to validate findings from clinical trial and economic models, to evaluate treatment programmes and potentially inform risk sharing schemes by showing whether pre-specified outcomes have been reached.

1.2.5 Decision-analytic modeling

Drummond et al. suggests a number of rationales for the use of decision-analytic models (40). First, they allow for indirect comparison between all contingent comparators which may be unfeasible and costly in an experimental trial setting. Second, they allow for the combination of evidence e.g. linking intermediate endpoints assessed in trial with final endpoints that are more relevant to patients. Third, they allow for evaluating long-term outcomes, which would again be unfeasible, costly and delay decisions if assessed in experimental trials. Further, models allow for sensitivity analyses which are primarily performed to test the assumptions in the model but are also useful for exploring what uncertainties are important for the outcomes.

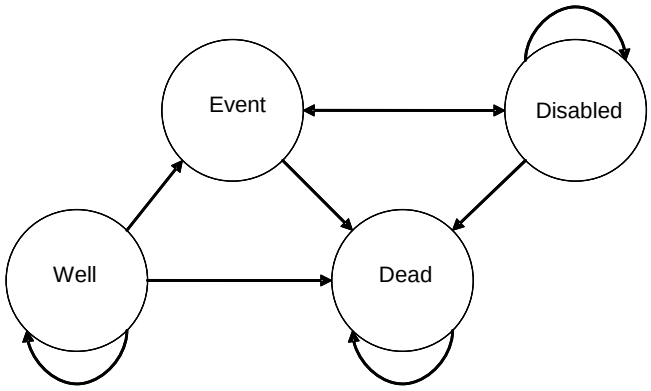
There are different types of modeling techniques and there is some debate on the optimal technique (58). Irrespective of the choice of modeling technique, input data is needed on disease progression over time and costs and outcomes related to specific health states or events.

1.2.5.1 Markov cohort simulation

One of the standard models in economic evaluation is the Markov cohort simulation. For this model, a set of health states are defined each associated with a certain cost and outcome and time is divided into preset time frames: so called cycles. At baseline, the patient cohort is distributed over the health states according to the characteristics of the studied population. Transition probabilities, defined as the probability of a patient moving from one state to another within a given cycle are derived from epidemiological data. At each cycle, the cohort of patients is redistributed over the states according to the transition probabilities. The costs and outcomes of spending a cycle in each state are multiplied with the proportion of patients in each state. As the model is run, cycles are added one by one and patients are moving from state to state, the costs and outcomes of the patient cohort accumulate. The model can be run with several arms with different assumed treatment effects (e.g. by altering the transition probabilities). Thereby, the accumulated costs and outcomes of different interventions can be compared, and their incremental cost-effectiveness calculated.

The figure below shows a state transition diagram of an exemplary Markov model. The arrows show the possible transitions. Patients are allowed to stay in three of the states more than one cycle, as is indicated by the bowed arrows. In the event state you are only spending one cycle at a time. In this example, either you enter the disabled state or you die. The dead state is a terminate state which is indicated by the absence of arrows to any other state. The double arrow between the event and disabled states indicates that there are possible transitions back and forth between these states. However, ones you have experienced an event you will never go back to the well state.

Figure 2 Markov state transition diagram



A special feature of the Markov cohort simulation is that future events are independent of what happened in previous cycles, also referred to as the *Markov property*. This since we cannot separate between patients who are in the same state. Thus, the transition probabilities depend on which state you are presently in, but not in which states you previously have been. This can be

overcome by adding more states, e.g. by adding a state for secondary events in the figure above and only let patients be in the primary event state once.

Another method to overcome the Markov property is to use another method for evaluating the Markov model. In the Markov Chain Monte Carlo simulation (MCMC), one subject is followed at a time which enables considering the events of previous cycles as the subject moves through the model. The simulation with a single subject is done a very large number of times, every time with new inputs, i.e. transition probabilities and cost etcetera. This will result in a random variation in individual outcomes, sometimes referred to as the first-order uncertainty. This cannot be done in a Markov cohort simulation since we study a cohort, consisting of subjects with various histories.

1.2.5.2 Alternative modeling approaches

Discrete event simulation (DES) offers an alternative approach to simulate the disease course (59). Instead of evaluating the model over fixed cycles, the DES estimates the time until next event for individual patients. This can be based on statistical functions in which the time to one event is dependent on patient characteristics and the occurrence of other events. Whenever an event has occurred, the model recalibrates and estimates the time to the next event. Costs and outcomes can then be linked to the events and accumulated over time, similar to the Markov cohort simulation.

A similar approach, the survival model, also estimates the time to the next event but multiple events have a hierarchical order (e.g. moving to the next severity levels). The resulting survival curves can be combined with data on costs and outcomes on each level to derive long-term outcomes (60).

1.2.6 Health policy application

The need for economic evaluation in health care has become evident as decision makers are faced with multiple alternatives for investments of their limited health care budgets. Simply selecting all interventions with a benefit for the patient until the resources have finished is not optimal, because alternative strategies may help more people with higher needs resulting in a healthier population overall.

The development of Health Technology Assessment (HTA) and economic evaluation as an instrument to inform decisions in health care started in the early 90-ies. The pioneering institutions were the Canadian Agency for Drugs and Technologies (CADTH) (61) and the Economics Sub-Committee of the Pharmaceutical Benefits Advisory Committee (PBAC ESC) in Australia (62), which were both established in 1993. Today, HTA is a centrepiece in health care decision making in most developed countries. In England, the National Institute for Health and Clinical Excellence (NICE), develops guidance on the use of pharmaceuticals and procedures to the National Health Services (NHS). NICE demands drug manufacturers to submit a thorough economic evaluation of drugs to be prescribed in England (48). In practise, the rationale for a negative opinion can be an ICER that is too high which results in the drug not getting reimbursed by public funds and therefore not being prescribed to English patients. In Sweden, the Dental and Pharmaceutical Benefits Agency (TLV), both evaluates the evidence of new drugs (as submitted by the drug manufacturer) and makes a decision whether it should get reimbursed by public funds. Their decision is based on three principles: 1) cost-effectiveness (cost should appear reasonable from the medical, humanitarian and economic aspects), 2) the principle of need and solidarity (those with the greatest medical needs should be prioritized) and 3) the principle of human value (respect for equal dignity of all human beings) (63).

1.3 Economic evaluation in Alzheimer's disease

1.3.1 Economic evaluation of AD drugs

The economic evaluation of the cholinesterase inhibitors and memantine has played a significant role in determining their availability to patients in many countries. Patient access to cholinesterase inhibitor and memantine treatment varies across countries. Even though they have been approved by regulatory agencies in most countries, many HTAs are sceptic of their benefits (especially in relation to the drug costs) (56). The clinical trials only show modest effects on short-term surrogate endpoints and the value for patients is uncertain. The drug manufacturers have presented evidence of reductions in informal care and institutionalization rates from treatment, causing cost offsets which are comparable to the cost of the drug (64-68). However, this data is largely built on assumptions of long-term effects and has not convinced all HTAs. For instance, NICE recommends only to prescribe the cholinesterase inhibitors in moderate AD (excluding mild AD) and not to prescribe memantine at all. The recommendations were based on estimates of poor cost-effectiveness in these indications (19).

1.3.2 Modeling in Alzheimer's disease

In the first models in AD, which were developed to estimate the cost-effectiveness of the cholinesterase inhibitors, the progression of the disease was represented by cognitive function alone. In a typical model, three disease severity states (mild/moderate/severe) were defined by MMSE scores and transition probabilities between the states over time indicated the rate of deterioration in cognitive function. A symptomatic treatment effect was applied by imposing a reduction in the probability of moving to a worse state for treated patients (data usually derived from RCT). As each state differed in terms of costs of care and health outcomes, the model simulation estimated the accumulated cost offsets from treatment and the difference in health outcomes between the treatment and comparator arms (69, 70).

A subsequent model, the Assessment of Health Economics in Alzheimer's Disease (AHEAD) model, utilized the patient's need for full time care (FTC) as surrogate endpoint to estimate cost-effectiveness (59). Prediction functions to simulate the proportion of patients in FTC over time were derived from a US sample of 236 patients (71). The cognitive function of the patient (measured by the modified mini-mental state examination, mMMS) was the main predictor together with presence of extrapyramidal symptoms, presence of psychotic symptoms, young age at disease onset and duration of illness. The AHEAD model was later modified by the Southhampton Health Technology Assessments Centre (SHTAC) as part of the HTA of all dementia treatments commissioned by NICE (72). SHTAC named a number of limitations of the AHEAD model, including the crude representation of the disease process with only two states (FTC and non-FTC) plus death, prediction functions being derived from a small sample of patients with high attrition over time, and statistical uncertainties in the prediction functions. They concluded that the AHEAD model could be used for illustrative purposes, in absence of any better model. In their recommendations for further research, SHTAC called for studies on other markers than cognitive function for the prediction of disease progression (especially ADL and functional outcomes).

1.3.3 Cost of AD

There are several studies available on the cost of AD patients in various countries and settings (20). They differ in their objectives, scope and methods which is ultimately reflected in large

differences in their results. Cost estimates for Europe range between €6,000 and €64,000 per patient and year, depending on country, study sample and methodology (20). We know from previous studies that costs increase with the severity of the disease, irrespective of what symptoms are at focus. Some evidence suggests that ADL-ability is the main cost driver (73-80), other that behavioural symptoms affects costs (81, 82), and potentially that these two domains together mediate the variance observed in costs by level of cognitive function (i.e. the cognitive function of a patient may not explain any additional variance in costs when controlling for ADL-ability and behavioural symptoms) (83). We also know that the costs of residential care settings (e.g. care homes, group livings or nursing homes) constitute a significant part of the life-time costs of an AD patient (82, 84). Studies showing delays in the need of such facilities also show important reductions in overall costs (84, 85).

1.3.3.1 Assessment of resource utilization in AD

There are several instruments for the assessment of resource utilization in dementia. The most widely spread is probably the Resource Utilization in Dementia (RUD) instrument which captures the health care resource utilization of the patient and their informal caregiver (86). RUD is also available in a short version (RUD Lite) which assesses the most important resources from a costing perspective, constituting 95% of the costs of the complete instrument (87). RUD is administered via an interview with the informal caregiver of the patient.

RUD includes an assessment of the time spent on informal care. The care provision is divided into three tasks: basic ADLs, instrumental ADLs and supervision. The caregiver is asked to consider a typical day during the past month when providing care to the patient and state how many hours they spent on basic ADLs. Thereafter, the caregiver is asked how many such days there were during the past month. The caregiver is then asked to consider the same (hours on a typical care day and number of such care days) for instrumental ADLs and finally supervision. With this data we may then calculate the mean care provision during the past month. We may especially be interested in the time spent on active care and then exclude the time spent on supervision.

The recall time is set to one month because caregivers are expected to be able to remember how much time they have spent on care during this time frame. Longer recall periods reduces the reliability of the responses.

These methods have been validated both in a sample of patients in group living cared for by professional staff (88) and in another sample of community dwelling patients with an informal caregiver (89). Still, many caregivers perceive they are caring for the patient around the clock which may lead to overestimations of the time spent on care. This can be avoided by asking the caregiver how much time they spend asleep on average and deduct this time from the available number of hours per day. A common method is also to cap the reported time at 18 hours per day to reflect the expected maximum (68).

1.3.4 Outcomes in AD

The primary endpoints to assess the efficacy of new drugs in Alzheimer's disease RCTs are set by regulators such as European Medicines Agency (90) and Food and Drug Administration (FDA) in the US (91). In Europe, the primary endpoints should include cognition and function (ADL-ability) (90).

The relevance of these efficacy endpoints to patients is uncertain and therefore less appropriate for HTA and reimbursement decisions. Guidelines on the economic evaluation of drugs from NICE and TLV suggests cost-utility analysis and the use of QALYs for measuring outcomes (47, 48). Because none of the existing pharmacological therapies have shown any effect on mortality, the main focus has been to show a benefit on the patient's quality of life from treatment. NICE recommends the use of the generic EQ-5D instrument to assess the health utility weights in cost-effectiveness analysis (48).

There are also disease specific quality of life instruments available, most notably the Quality of life- Alzheimer's disease (QoL-AD) (92) and DEMQOL (93, 94). QoL-AD contains 13 items with four levels per item and assesses the quality of life of the patient both by patient self-report and the caregiver as a proxy. DEMQOL is an interviewer-administered questionnaire which is specifically designed for use in people with probable dementia and has been validated in mild and moderate dementia, but is not suitable in severe dementia. DEMQOL-proxy is the 31 item version of the test and is designed for those caring of people with dementia.

Due to the cognitive impairment of patients in severe stages of AD, they commonly have difficulties in completing patient reported outcomes (PRO) such as the quality of life instruments. Instead, the caregiver has commonly been asked to complete the quality of life assessments as a proxy for the patient. This was done by Neumann et al. who showed that patient health utilities, assessed with HUI, decreased with increasing severity (95). Jönsson et al. let both patients and their caregivers complete the EQ-5D instrument to assess the health utility of the patient. The estimated utilities using the caregiver proxy-reports were higher than those based on the patient reports across all severities, and also more sensitive to the severity of cognitive symptoms as assessed by MMSE (96). Karlawish et al. further explored the relationships between quality of life, assessed with EQ-5D and HUI-II and reported by both the patient themselves and the caregiver as proxy, and other outcomes related to the health and perceptions of the patient and the caregiver (97, 98). They questioned the validity of patient-reported quality of life estimates based on limitations in their correlation with cognitive and functional impairment (as reported by the caregiver). Patients were also found to have limited awareness of their cognitive and functional impairment. In a second paper (98), they also found limitations in caregiver reported quality of life of the patient including the absence of a significant correlation between the caregiver ratings and patient subjective domains on self-reported quality of life. They also found that caregiver perceived burden had an impact on their ratings of patient quality of life.

Caregiver burden is another key outcome in Alzheimer's disease. It can be assessed objectively by measuring the time spend on care tasks (86) or subjectively by asking caregivers about their perceived burden from caring for the patient. There are multiple instruments for this assessment including the Zarit Burden Interview (ZBI) (99) and the Caregiver Reaction Assessment (CRA) (100). Caregiver burden may also have an effect on the quality of life of the caregiver (14).

2. Thesis objectives

The overall objective of this research is to explore the application of cost-utility analysis in Alzheimer's disease and address key methodological challenges and data needs. The four papers have the following specific objectives.

- Estimate prediction functions of Alzheimer's disease progression for economic evaluation (paper I)
- Estimate the value of informal care from a caregiver perspective (paper II)
- Assess predictors of costs of care of patients with varying severity of AD in a usual care setting (paper III)
- Identify the key components and drivers of costs in clinical trial (paper IV)

3. Summary of papers

3.1 Economic analysis of data from the Swedish Alzheimer Treatment Study (paper I)

3.1.1 Objective

We utilized data from a treatment registry, Swedish Alzheimer Treatment Study (SATS), which primary objective was to evaluate the long-term effects of cholinesterase inhibitor treatment in patients with AD in a routine clinical setting (101). The objective of paper I was to derive prediction functions for simulating disease progression and economic endpoints in a decision-analytic model.

3.1.2 Data

The first SATS cohort of 435 patients commenced treatment with donepezil and was followed semi-annually for up to three years. Data were captured via a patient interview collecting demographics, disease history, cognitive function, ADL-ability, global change and resource utilization. Cognitive function was assessed with MMSE and ADAS-cog, ADL-ability with PSMS and IADL and global change with CIBIC. Resource utilization was not captured with any standard instrument but included community care services (home help, home-delivered meals and day care) and dates of moves into an institutionalized care setting.

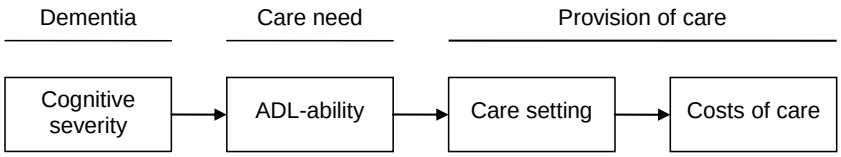
SATS also included other cohorts of patients commencing rivastigmine and galantamine treatment. The design and procedures in these treatment arms were identical to the donepezil arm, but only the donepezil cohort was considered in paper 1 because the data collection in the other arms had not finalized at the time of analysis.

We retrieved additional data on inpatient care resource utilization from the Swedish national patient register. Still, the resource data in the SATS study combined with what could be collected from Swedish registers does not give a complete picture on the resource use of the patients. Key components that were missing include informal care and outpatient visits. The main contribution from SATS was instead its unique data on the long-term progression of Alzheimer's disease progression, represented both by the gradual loss of cognitive function and ADL-ability of patients.

3.1.3 Prediction functions

We created an economic model based on the data available. We let the cognitive function of patients represent the underlying course of the disease which resulted in loss of ADL-ability over time. As patients lost their ability to care for themselves we assumed this would trigger a care need and consequently utilization of health care resources. Depending on the care setting this would give rise to various levels of costs of care. The model is depicted in the figure below.

Figure 3 Structure of economic model. The progression of dementia (represented by cognitive function) is assumed to cause loss of ADL-ability which determines the patient's need for care. The care need consequently translates into care provision and costs to society.



The level of costs of care was very different for patients residing in an institutionalized care setting compared to those living in the community, and many patients in the community had no costs at all. Therefore, we predicted costs in three steps. First, we estimated a prediction function for patients moving into an institution using survival analysis. Second, we estimated the probability of a community dwelling patient having a non-zero cost using logistic regression. Third, we predicted the actual cost of patients with a non-zero cost. This method aimed to be able to replicate the skewed distribution of costs as commonly seen in Alzheimer's disease, where many patients have zero costs, some have very high costs with small variation across subjects and over time (those residing in institutions), and the rest have costs in between with higher variance across subjects and over time.

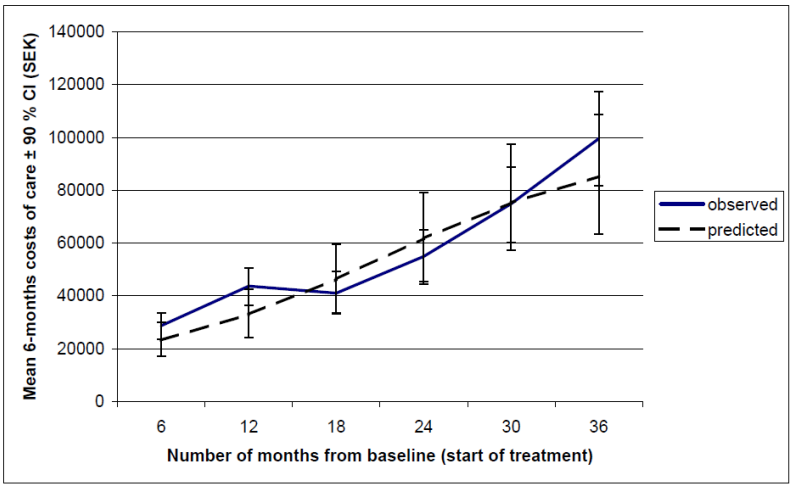
3.1.4 Cross-validation

The model was evaluated based on its ability to replicate the SATS study data. We did not want to validate it by replicating the same data as used for prediction (in-sample validation) so instead we sampled half of the study data for prediction and tried to replicate the other half combining the prediction functions with the baseline input from the replication half of the data. In order to explore the impact of what observations were included in each of the halves, we created an iterative process which was performed 1,000 times, each time randomly drawing a new half of the study sample for prediction to replicate the remaining half.

3.1.5 Results

The cross-validation process showed a good fit of our model predictions on observed data of costs over three years: the confidence intervals were overlapping for every 6 months period from baseline.

Figure 4 Comparison of predicted and observed mean 6-months costs of care and 90 % confidence intervals (SEK) over time. The 5th, 50th and 95th percentiles of 1,000 mean estimates are shown. (10 SEK ~ 1 Euro)



The mean cognitive decline per 6 months was ranging between 1.6 and 4.0 ADAS-cog points, increasing with disease severity. ADAS-cog was a significant predictor of ADL-ability (both PSMS and IADL) together with demographics (age and gender) and time from baseline. ADL-abilities (as measured by both PSMS and IADL) were (together with age and gender) significant predictors of the risk for institutionalization and non-zero costs. ADL-ability also correlated with the level of non-zero costs.

3.2 Willingness-to-pay for reductions in care need (paper II)

3.2.1 Objective

The objective of the study for paper II was to explore the value of informal care using contingent valuation methods. We wanted to learn how much caregivers would be willing to pay for reductions in the care need of the patient.

3.2.2 Data

The study was performed in four countries (Spain, Sweden, the UK and the US) and 517 caregivers were interviewed in total. Demographics of both the patient and the caregiver and the score of the latest MMSE assessment of the patient were captured. In a face-to-face interview with a study nurse, the caregiver was asked about their time spent on informal care, perceived caregiver burden (CRA), and the ADL-ability (DAD) and presence of behavioural symptoms (NPI) of the patient. The caregiver was then asked questions on their willingness-to-pay for a hypothetical scenario where the care need of the patient was reduced.

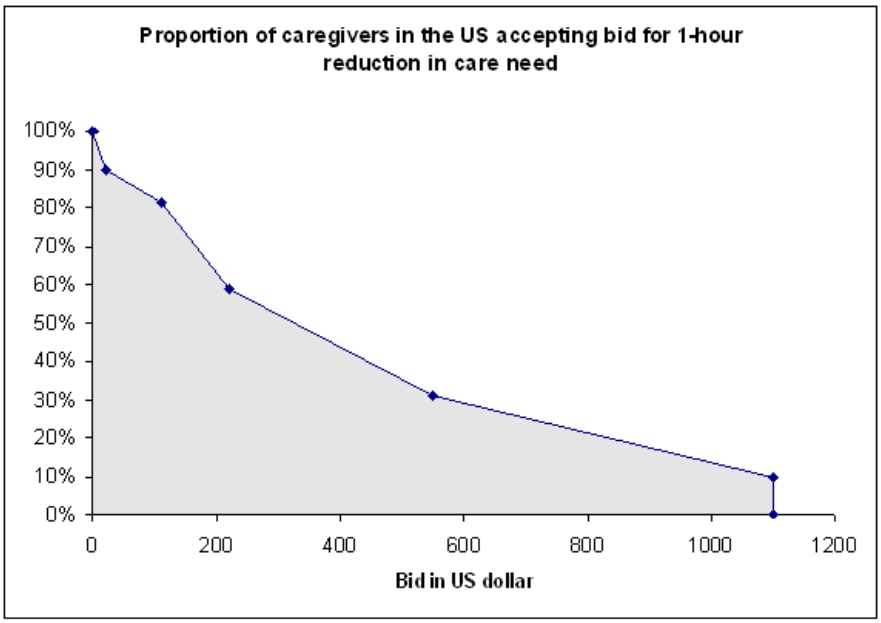
3.2.3 Contingent valuation questions

The caregivers were given two scenarios: first a reduction in the time needed to care for their patient by one hour per day and then a total elimination of the care need of their patient. For each scenario the reduction was offered at a price which they were asked to either accept or reject. If they accepted the price, they were asked about the certainty in their response. Then a bidding game followed to elicit their maximum WTP for the scenario. This way we combined the discrete indicator (also called dichotomous choice) and bidding game methods for separate analyses. The initial price differed across five groups to which the caregivers were randomly allocated.

3.2.4 Analysis

Maximum WTP for each scenario and country was estimated using three different methods. In a first parametric approach, a logistic regression function was estimated with the discrete indicator response as the dependent variable and the price as the independent variable. The resulting function was assumed to represent the demand curve for the scenario and the mean WTP was then given by the area under this curve. In the second approach, a non-parametric method was used to calculate the area under the curve by interpolation between the observed proportions of accepts by price on the x-axis. We assumed all caregivers would be accepting the reduction in care need at zero cost and none would be willing-to-pay more than the maximum bid (see figure below).

Figure 5 Demand curve for reduction in care need

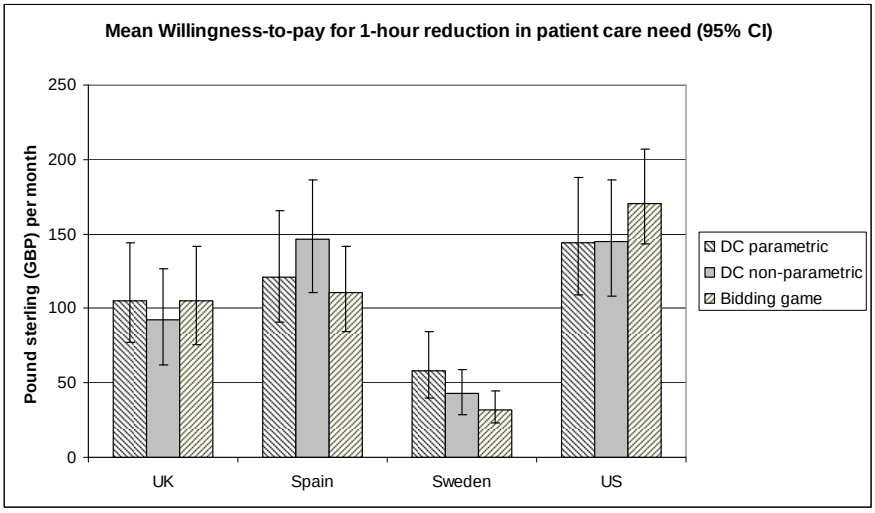


The third approach simply calculated the mean of the maximum WTP amounts resulting from the bidding game.

3.2.5 Results

A majority of caregivers were willing to pay to reduce the care need of their patient. Estimates ranged between £59 and £144 per month for a reduction of one hour per day, depending on country (estimated by parametric dichotomous choice methods). These estimates are comparable to the price of symptomatic treatment achieving this reduction in care need. Estimates were about four times higher for the total elimination of care need.

Figure 6 Mean WTP estimates for 1 h reduction in patient care need by country and estimation method (95% bootstrapped CI)



There was substantial variation in WTP within and between countries and they were highest in the US and lowest in Sweden. In the US, caregivers were more often the child of the patient whereas most Swedish caregivers were a spouse living with the patient. Spouses may recognize the care giving as their rightful responsibility whereas a child may be more prone to opting out if the opportunity comes. It is also reasonable to believe that there are cultural differences between countries resulting in different attitudes towards care giving and thus different willingness to pay for alternatives. In all countries, the stated willingness-to-pay increased with higher income. Otherwise there were no consistent predictors of WTP across all countries.

3.3 Cost of Alzheimer's disease patients in clinical practise (paper III)

3.3.1 Objective

The objectives of the study for paper III were to assess what measures of disease severity are the most important predictors of costs of care and whether these differed across countries. We also collected data on the burden perceived by caregivers and their quality of life which were the main topics of another publication from this study (14).

3.3.2 Data

The study was performed in four countries (Spain, Sweden, the UK and the US) and 1,222 patients and their caregivers were interviewed in total. Patients with a clinical diagnosis of Alzheimer's disease were recruited from memory clinics and primary care centres. An assessment of the cognitive function of the patient was conducted with MMSE. An interview with the caregiver assessed the ADL-ability (DAD), presence of behavioural symptoms (NPI) and resource utilization (RUD-Lite) of the patient. The caregiver also responded to a questionnaire including their perceived caregiver burden (ZBI) and their own and their patient's health utility (15D).

3.3.3 Disease severity stratification

We wanted to explore how costs and outcomes differed between patients across the whole spectrum of the disease. Therefore we defined six subgroups according to the disease severity of the patient (MMSE states: mild, moderate or severe) and their care setting (community or residential care setting). The study centres were encouraged to recruit patients into each of the subgroups and at the end of the study we closed the recruitment into large subgroups and asked the centres to focus on those with few patients. As this probably led to an over-recruitment into subgroups with relatively few patients, the overall sample should not be considered representative to the Alzheimer population as a whole.

3.3.4 Estimating costs of care

The resource utilization of the patient during the last 30 days prior to the study visit was collected via an interview with the caregiver using the RUD-Lite questionnaire. The informal care section included a question on how much time the caregiver spent asleep per night. Their time awake was assumed to set the limit of the maximum number hours they could care for the patient. The resource use was multiplied by a price vector collected for each country. The human capital method was used to value informal care. The time spent on care instead of working was valued at the average gross wage in each country and the remaining time spent on ADL care was valued at 35 percent of the average gross wage. Supervision was assumed to have a value equal to zero.

3.3.5 Results

Mean costs of care ranged between £1,000 per patient and month for mild patients living in the community to £5,000 for patients living in residential care settings. Cost estimates varied across countries and increased with the severity of disease for patients in community dwellings.

ADL-ability was the most important predictor of costs of care of community dwelling patients. A one-point decrease on the DAD scale resulted in a 1.4 to 2 percent increase in costs on average,

or a 45 percent increase from a standard deviation decrease on DAD. NPI-severity and MMSE also had a significant impact on costs but the effects sizes were smaller. The caregiver-reported health utility of the patient decreased with increasing severity of symptoms and was lower for patients in residential care settings. Mean estimates ranged between 0.52 (severe patients in residential care setting) and 0.76 (mild community dwelling patients).

Table 1. Determinants of costs of care in community dwellings

	Percentage change in costs of care from index change in determinant		Percentage change in costs of care from standard deviation change in determinant
DAD	-1.4%	***	-45%
MMSE	0.9%	*	6%
NPI-severity	1.0%	*	8%
Sweden	74%	***	
UK	ns		
US	28%		
Interaction DAD*Sweden	-0.6%	*	
Interaction DAD*UK	ns		
Interaction DAD*US	ns		

* p <0.05, ** p<0.01, *** p<0.001
ns = non-significant (p>0.1)

3.4 Cost of Alzheimer's disease patients in a clinical trial setting (paper IV)

3.4.1 Objective

We utilized the baseline and placebo follow-up data from two registration trials of a putative disease modifier in Alzheimer's disease. The purposes of our study (the objectives of paper IV) were to identify the key resource items in a RCT setting and assess how they are correlated with one another and with measures of disease severity.

3.4.2 Data

Data were retrieved from two multicenter, randomized, double-blind, placebo-controlled, parallel-group twin trials of Xaliproden and their double-blind 24 month extension trials. In total, 2,744 patients with a diagnosis of probable Alzheimer's disease according to the NINCDS-ADRDA criteria, MMSE score between 16 and 26 (inclusive), previously untreated of on stable AD treatment since 6 months, residing in the community and having a caregiver spending at least 4 hours times 4 days or 2 hours times 7 days per week were enrolled and used in analysis. Baseline data from both trial arms and follow-up data from the placebo arm were used in the analysis. Thereby, none of the observations in the data set were from a patient currently receiving the study drug. The data collected and used in our analysis included demographics, disease severity (CDR-SB), cognitive function (MMSE and ADAS-cog), ADL-ability (ADCS-ADL), behavioural symptoms (NPI) and resource utilization (RUD Lite).

3.4.3 Estimating costs of care

RUD-Lite was administered with a recall time of one month for all resources except hospitalizations which had a recall time of one month for baseline and 6 months for the follow-up visits. The time the caregivers reported spending at caring for their patient was capped at 18 hours per day to avoid overestimation of informal care provision. A common price vector from the UK was used for all patients as no comparisons across patients from different countries were made.

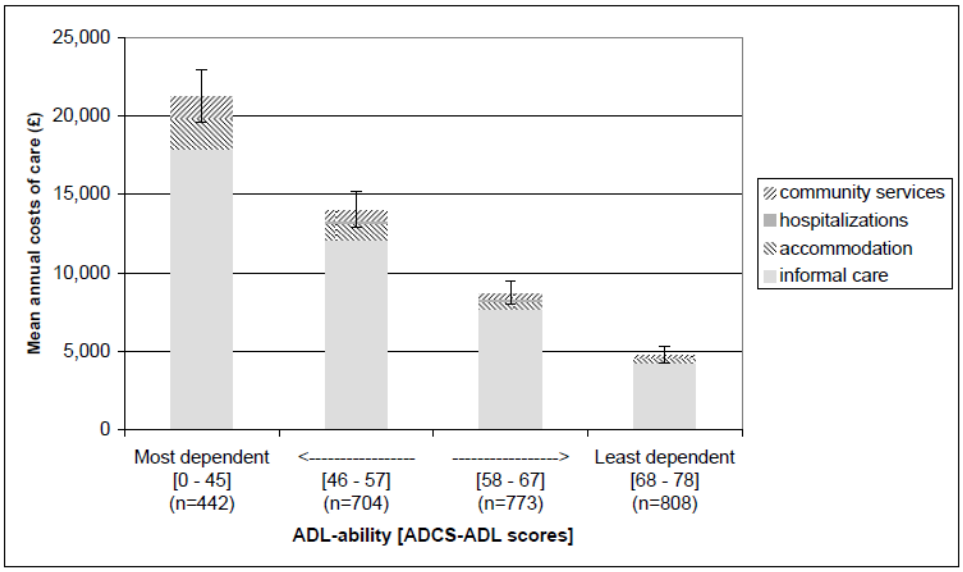
3.4.4 Analysis

Correlations between the measures of disease severity and resource utilization and costs at baseline were estimated. As resource utilization was collected retrospectively, the resource utilization and costs during the month preceding the actual assessments of disease severity were considered in the analysis.

3.4.5 Results

Informal care was the dominating cost in the randomized clinical trial, constituting over 80 percent of total costs. Informal care also had the strongest correlation, of all cost items, with the disease severity of patients. ADL-ability (measured with ADCS-ADL) was the strongest predictor of costs of care, of all disease severity measures.

Figure 7 Mean annual costs of care (£) by ADL-ability groups; all baseline observations with complete RUD and ADL-ability data (n=2,727), (1 GBP = 1.17 EUR = 1.43 USD)



4. Discussion

4.1 Role of cost-utility analysis in Alzheimer's disease

What is the role of cost-utility analysis in Alzheimer's disease in future economic evaluation? The difficulties in assessing patient preferences in Alzheimer's disease limit the usefulness of cost-utility analysis in this particular disease. It is questionable whether the estimates of utility derived by EQ-5D, 15D or HUI by the disease severity states in AD accurately reflect the preferences of patients. The estimates seem dependent on what instrument is used; proxy-rated 15D (paper III) and HUI-2 seem to give higher utility scores than EQ-5D (96, 98), and who the responder is; the reports by the caregiver and patient differ (98). A pivotal issue is whether to consider the patients' own preferences in different stages of the disease or whether to consider the preferences of the general public for descriptions of the same. Patients seem to have limited awareness of their own situation which may invalidate their own reports on their preferences. Caregivers can be used as proxy-raters but how do we know that their estimates accurately reflect the preferences of the patient? If we choose to consider the preferences of the general public, the validity of their estimates relies on the caregiver's accurate description of the relevant domains of the health of their patient. This is a classic catch 22 dilemma as the estimates derived from caregiver reports cannot be validated for the same reason we did not consider the patients' self-reported preferences in the first place.

We may also consider the own preferences of the primary caregivers because they are also highly affected by the disease, and an intervention that would help the patient may have important benefits also to the caregivers. If those benefits can be measured in terms of an increase in quality of life of the caregiver, they could be included in the denominator of the cost per QALY gained ratio. Alternatively, we may measure the monetary value of the benefit perceived by the caregiver and use in a cost-benefit analysis of the intervention. In our second paper, we showed that such analysis could support the investment in symptomatic treatment in Alzheimer's disease.

4.2 Modeling

Decision-analytic modeling has been found to be a useful tool in synthesizing the evidence base and informing decisions. They allow for combining inputs from multiple sources (e.g. RCTs, registries and observational studies), deriving from their comparative advantages, and studying complex scenarios which may be difficult to fully test in real life.

The design of economic models in Alzheimer's disease should be guided by the available data. The value of sophisticated modelling techniques is largely dependent on the data available to support them. This should be weighted against the transparency of the model which decreases with its increasing complexity. If the model is intended for informing decisions and the decision-makers don't understand it, they will most likely be sceptic of the results which will make the model useless.

If and when a new endpoint is discovered which is both meaningful to patients and possible to measure, this should be implemented into the economic models as well. In absence of this, we need to consider the surrogate endpoints at hand for modeling. This may include cognition, function, behavior and care setting. In paper 1 we assumed a linear causality from cognition (representing the underlying disease), determining ADL-ability (representing the care need),

which would determine the care setting and finally costs of care (representing care provision). The true causality in AD is uncertain and the correlations between the different endpoints are probably more complex than suggested in paper I. Still, we believe that our simplification is a useful model of reality and we also showed that we could use it to replicate costs of care in our patient sample. More research is needed on this topic.

We also found, in paper III, that function or ADL-ability is the key determinant of costs of care. Future models should therefore take this parameter into account in the prediction of costs of care over time. Cognition may not be necessary for prediction of costs or outcomes per se but it probably plays an important role in representing the underlying disease progression and also as the primary efficacy endpoint.

Alzheimer's disease leads to premature death but there is no evidence of any effect from the currently available treatments on mortality. For this reason, most economic models in AD have considered equal mortality irrespective of whether the patient gets pharmacological treatment or not. However, a treatment effect causing a delay in death may have perverse effects on the economic value of such treatment, depending on the severity of symptoms during the added years of life. If the life of a patient is extended while in great need of care the cost-effectiveness may worsen due to the reduction in mortality. The interpretation of this is not clear and needs to be explored further.

Any economic model in AD needs to reflect the progressive course of the disease. It will not be sufficient to differ only between patients with and without a need for full time care, because this ignores important changes to the well being of the patient and their costs of care before and after the need for full time care is reached. Further, there may be important differences between individual patients that need to be considered in economic modelling; e.g. differences in progression rates and treatment response. If the differences are too many it may be inefficient to model cohorts of patients because it would be difficult to keep track of the individual differences between patients within the same cohort. Instead, we can simulate individual patients (micro-simulation) each with a specific set of characteristics determining their predicted course of disease and response to treatment etcetera. By running many individual patient simulations we can estimate mean costs and outcomes of the target population.

4.3 Assessment and valuation of informal care

A recent review on the cost-of-illness literature in Alzheimer's disease shows that estimates of informal care costs as a proportion of total costs of care varies between 8 and 78 percent (20). Part of this variation may be explained by differences in the studied populations, not least since they come from different countries with different health care systems. However, the measurement and valuation of informal care time varies across the studies as well, and this probably explains most of the variation in cost estimates. There is need for standardization in measuring the time spent on informal care. The RUD instrument offers one validated method for this. The valuation is trickier as there is no clear opportunity cost of this non-marketed good. Sensitivity analyses should be considered to show how robust the results are to different valuation methods. Most importantly, authors need to be transparent in the way data has been collected and analyzed, what assumptions have been made and how their results compare with previous research.

Informal care may also play the key role in clinical trial. A full within-trial cost-effectiveness analysis may not be first priority when deciding what endpoints to measure in a pivotal registration trial. An alternative focus may be to accurately measure an economic endpoint of key importance

in the selected sample of patients. In paper IV, we showed that informal care constitutes more than 80 percent of the total costs of care. A treatment that would have an effect on informal care would therefore likely have an effect on total costs in this setting.

4.4 Limitations

The selection of patients into a study needs to be considered when interpreting the results. The study findings cannot be generalized to a different population than that from which the study subjects have been recruited. Recruiting subjects from a general population is preferred in epidemiologic studies because the results may then be inferred to that population. Depending on the objective of the study, the target population may be narrowed down, not to be representative to the whole population but instead to patients with a certain disease or treated with a certain drug etcetera. The SATS study (paper I) aimed to observe patients treated with cholinesterase inhibitors in a routine clinical setting. Because they were recruited from memory clinics they may not be valid for patients cared for in primary care settings. The sample selected for the cost study (paper III) was recruited from a mix of primary and secondary care centers and also recruited patients both living in the community and in residential care settings. The results from this study should therefore be more representative to the AD population in the countries studied. There may also be practical reasons to have more strict selection criteria for a study. In clinical trials the inclusion and exclusion criteria are commonly set to accommodate the measurement of efficacy e.g. by excluding patients without a knowledgeable informant that can accurately report outcomes, or patients with fatal co-morbidity potentially causing drop-out. The fourth paper was based on such a clinical trial and the findings are therefore not applicable to the general AD population.

Attrition is a common and inevitable problem of any longitudinal study. In experimental trials drop-outs are commonly caused by side-effects of the study drug or perceived lack of efficacy which may lead to the study subject withdrawing their consent to participate. Also in non-experimental studies, subjects drop out due to e.g. changes in their living situation or death. Sensitivity analysis should be performed at least comparing the baseline characteristics of subjects that have dropped out and those that have completed the study. The implications of the attrition in the SATS study (paper I) and the clinical trial analysis (paper IV) were discussed in each respective paper but not considered to have any significant impact on the study findings.

The cost of a patient with AD is not the same as their cost due to this disease. Part of the overall health care consumption of a patient may be caused by other morbidities. To assess the costs due to a disease we may ask a person what health care resources were used specifically due to that disease, or even better compare the costs of a sample of patients with the disease with a similar sample of subjects without the disease. In our cost study (paper III), we were interested in the cost differences between patients with different severities of AD, and we estimated a model to predict the additional costs of an increase in severity according to the key domains.

A similar issue affects the assessment of instrumental ADLs in elderly men. We are generally interested in the impact of Alzheimer's disease on the patients' ability to perform ADLs but in many cases they have never carried out certain ADLs (e.g. shopping, cleaning or washing) because their wife has taken care of this for them. In these instances, the instrumental ADL domains are not applicable because their dependence may not be due to their disease but instead caused by traditional family structures. The results of the SATS study (paper I) are therefore strictly not applicable to patients that have never carried of certain instrumental ADLs.

The statistical model estimated to predict disease progression in the SATS study was limited by the data available. Behaviour is an important determinant of costs of care in Alzheimer's disease but was not assessed within the SATS study. Further, the hypothesized link between cognition and ADL-ability is probably a simplification of reality. A longitudinal study assessing cognition, ADL-ability and behaviour over time as well as key economic endpoints is needed to explore the co-variance between the disease severity outcomes and their impact on economic outcomes over time.

There are a number of limitations to note with regard to assessing costs. First, the assessment of resource utilization in the SATS study (paper I) lacks important resources including informal and outpatient care. The other two studies assessing costs (paper III and IV) includes the RUD Lite instrument which should capture 95 percent of the total costs of care (87). Second, relatively large samples are required to estimate the mean cost of inpatient care because hospitalizations are infrequent but very costly once they occur which results in influential outliers where samples are too small. The studies included in this thesis are all too small to provide robust estimates of inpatient care costs. Third, the informal care costs are sensitive to both the methods for measuring care time and the subsequent valuation of the same.

The estimates of caregivers' willingness-to-pay for reductions in care need (paper II) have two important limitations. First, previous studies have shown a discrepancy between stated and actual willingness-to-pay, as respondents may say that they would accept an offer in a hypothetical scenario but change their minds once they got the opportunity in real life. We tried to control for this by only considering certain responses as accepts in the calculations. This method has been validated in previous research (54). Second, we expect that caregivers' perceived value of a reduction in care need is dependent of the cause of this reduction. We chose to state that the reduction in care need was caused by an improvement in the health of the patient, because we did not want to introduce any noise in the estimation related to uncertainty of the cause of the reduction in care need. How this affected the results is unknown and may be subject for further studies.

4.5 Future research

The natural course of Alzheimer's disease presents many challenges for the economic evaluation of AD treatment. These challenges may be overcome by more research into the field. The following are suggested needs for further research.

- The lack of biomarkers inhibits accurate diagnosis and staging of disease severity. Instead, surrogate endpoints are used to describe the severity of symptoms and they may be of little relevance to patients and have limited correlation with costs. More research is therefore needed on the identification of biomarkers and endpoints that are relevant to patients.

- The progressive nature of the disease prevents the use of traditional state transition models to describe the course of the disease, and multifaceted and inter-related symptoms further complicate an accurate description of the disease process. There are methods available to improve the economic models for evaluation of AD treatment, but the relevant applications need to be developed and there is need for further data to support them.

- The cognitive impairment of patients restricts their ability to complete self-reported outcomes and inform decision-makers on their preferences for different outcomes. There is need both for methods to accurately elicit patient preferences and alternative methods to determine the value of treatment in absence of valid patient-reported outcomes.

4.6 Health policy implications

Economic evaluation will be an important tool for decisions on the allocation of health care resources also in the future. The alternative, to neglect aspects of costs in decision-making, is simply not feasible because it will lead to suboptimal allocation of scarce health care resources. Economists may prefer cost-benefit analysis, i.e. the translation of all consequences from a given health care intervention into monetary values, because it enables direct comparison of costs and consequences. The decision rule that follows is simply to invest in all strategies with a positive net benefit (i.e. the monetary value of the benefits is larger than the costs). However, the monetary value of the consequences of a health care intervention can be difficult to assess, which limits the usefulness of cost-benefit analysis in practise.

NICE and TLV, among other key stakeholders in health care decision making, prefer cost-utility analysis because it enables the comparison of interventions across disease areas. By selecting interventions with the lowest cost per QALY gained until their budget is exhausted, decision-makers may optimize the allocation of the resources allotted to them. However, neither NICE nor TLV has a fixed budget to work from and cost-utility analysis does not provide any guidance on when to stop adding interventions with higher costs per added QALY. Still, they need to consider some threshold for what additional cost per added QALY they are willing to accept. Even in systems where the budget actually is fixed, how would policy makers know what the optimal size of the health care budget should be?

So what determines the threshold or size of health care budget in practise? The key to this discussion is that the benefits of any health care intervention indeed will be valued against its opportunity costs, be that other health care interventions, other investments by public funds, or

even lower taxes and insurance premiums. In many instances this valuation is made implicitly, without rigid analysis, as part of an overall policy, guided by public opinion or simply based on how things were done previously. Alternatively, the economic evaluation can be done explicitly by studying public preferences for different scenarios and thereby inform decisions that lead to optimal allocation of resources. This will likely be a key issue for future health policy.

Another key issue is how to handle the uncertainty of the outcomes of an investment into a new drug treatment. Traditionally, the drug developer bares the full cost of this uncertainty up until market launch where after the cost is shared with the payer. That is, the payer agrees to pay a certain price for the drug according to its expected outcomes. If the drug doesn't meet these expectations, the developer may lose from a low market penetration, or if the drug is widely used despite poor outcomes, the payer loses from the poor outcomes in relation to the agreed price. In practise, the actual outcomes of a new treatment may be difficult to monitor if post-marketing studies are not set up for this purpose. A recent development is for payers and drug developers to enter risk-sharing agreements in which the drug developer gets paid for performance based on post-marketing studies where the actual outcomes are assessed in the real life setting (102). This may be an efficient way of taking control over the cost of uncertainty in health care decision making.

Another important role of economic evaluation is to visualize cost offsets within different parts of the health care system. Some countries have a societal perspective in their decision-making process which increases the chance of making decisions that are beneficial to the society as a whole. Health care systems in other countries suffer from silo-effects where important investments risk not to get funding because the benefits and costs affect different sectors, each with their own independent budgets. In such systems there is a need to find ways to transfer benefits from one sector to another.

5. Conclusions

- Cognitive decline, gradual loss of ADL-ability and emergence of behavioural symptoms all play a key role in the development of care needs of AD patients. ADL-ability has the strongest correlation with costs of care.

- Caregivers have a substantial willingness to pay for a treatment that reduces patient care need. Mean willingness-to-pay was estimated at between £59 and £144, depending on country, per month for a reduction of one hour per day.

- The care provided by informal caregivers constitutes a substantial part of the total care for patients typically enrolled in clinical trials to assess the efficacy of a drug in mild to moderate AD.

- Health utility estimates of AD patients are highly dependent on the selected methodology including choice of instrument, respondent and utility tariffs.

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