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A study of the link between cognitive decline and cost progression in the treatment of patients with Alzheimer's Disease

Abstract

In this three year longitudinal study we are able to learn more about the relationship between cognitive function and costs of care, following patients treated for Alzheimer's disease with the cholinesterase inhibitor donepezil. In our study sample of 435 patients we found that a cognitive decline, assessed with the ADAS-cog outcome score, induces a cost increase controlling for time. Furthermore, by differentiating between patients with respect to response to treatment we identified a group of responders, about one third of the sample, which showed an improved or stable cognitive function during the first 12 months of treatment. The difference in cost progression between these responders and the non-responders were estimated to cover the treatment costs for all patients. We found no predictors of treatment response other than men having a greater chance than women of being responders. We conclude that we are able to confirm previous findings of a link between cognitive decline and cost progression, and that treatment may lead to net cost savings.

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1. Introduction

Dementia is a great and growing problem for the modern world. The cognitive and functional impairment as well as the behavioral disturbances caused by dementia are associated with much distress for the afflicted and their families. Furthermore, it gives rise to substantial costs for public health care and social care systems. Wimo and Jönsson (2000) estimates the annual cost of dementia in Sweden to 38.4 billion SEK, which may be compared to for instance the total health care budget for Sweden of about 160 billion SEK the same year (Socialstyrelsen 2001). Costs are growing rapidly due to the ageing population. According to Wimo and Jönsson (2000), the number of demented will increase from about 130 000 cases in Sweden today to over 200 000 cases in 2025. Subsequently, costs are expected to increase dramatically unless there are significant changes in available therapies and systems of care for demented elderly. This makes dementia one of the most important challenges to our society, today and certainly also in the future. The aim of this paper is to gain more knowledge on how to alleviate the burden of the most common of dementing disorders, Alzheimer's disease (AD).

We know from previous studies (see section 3.1), that the cognitive function of patients with AD deteriorates over time. Furthermore, we know from cross-sectional studies that the average cost of care for patients with AD increases with cognitive impairment. That is, patients get worse over time and a patient with a severe impairment is more costly than a patient with a mild impairment. However, the relationship between changes in cognitive function and changes in costs of care over time has not been studied in equal detail. We are not sure that the cognitive decline in itself affects the progression of costs, even though this is intuitively satisfying. If there is such a link there would be possible cost savings to be made from therapies that prevents the deterioration in cognitive function. In order to examine the link between cognitive decline and cost progression, we need to follow patients over time, and look for a relationship between cognitive function and cost of care in panel data. Hence, our first objective is to *describe the relationship between cognitive decline and cost progression in a sample of AD patients*.

Also, from previous studies (see section 3.3) we know that the initial treatment response varies considerably between patients, but the long-term consequences for disease progression have not been widely studied. Therefore, we will study the relationship between treatment response and the development of costs of care in AD subjects treated with a cholinesterase inhibitor (donepezil, Aricept®, Pfizer). Hence, our second objective is to *study the relationship between costs of care and response to treatment and test if a positive response is associated with lower costs over time*.

In addition to these two objectives we will present a descriptive analysis of our study data including a model of how the disease and costs progress over time. The remaining sections are structured as follows. First we will describe some methods for economic evaluation (section 2) and conduct an overview of Alzheimer's disease (section 3). Thereafter, our contribution to research starts with materials and methods (section 4) where this study and its methods of analysis are presented. Then we have the results (section 5), followed by a sensitivity analysis (section 6) and a discussion on policy implications (section 7). The thesis ends with the conclusions from the study (section 8).

2. Economic evaluation

2.1. Definition and relevance

In recent time, health care technology has developed in many ways. Together with improvements in hygiene and overall living standards, the modern medical advances have improved both the length and the quality of life. However, these new opportunities increase the competition for resources at hand. In Sweden we have seen long queuing list to a lot of health care services the last decades. No matter how big amount of resources we would be able to gather there would always be demand for more. Thus, we would still have to deal with scarcity trying to allocate resources as to maximize our benefit. Our first task is to gather information. With the right information we stand a greater chance of making good decisions. This is the reason why we put interest in economic evaluation, since this is how we get information on how to allocate resources. The scarcity of resources sets the importance of economic evaluation.

Drummond et al. (2005 p. 9) defines economic evaluation as; "the comparative analysis of alternative courses of action in terms of both their costs and consequences". That is, we cannot evaluate a treatment without knowing both the costs and the consequences of that treatment. Nor can we evaluate a single treatment without any reference to compare with. The subsequent sections on economic evaluation are based on Drummond et al. (2005), unless otherwise stated. Note, we will not use all of the concepts described in this section, but they serve the purpose of putting the thesis in its context.

2.2. Measures of consequence

We usually distinguish between four kinds of analysis; Cost Minimization Analysis (CMA), Cost Effectiveness Analysis (CEA), Cost Utility Analysis (CUA) and Cost Benefit Analysis (CBA). The main difference between them is how the consequences are measured and valued.

CMA is the simplest form of analysis. It compares treatments that have the same consequences and therefore focuses on the differences in costs. The treatment with the lowest cost is preferred.

CEA measures consequences as units of effectiveness. These units could be various endpoints, for instance; number of days in nursing home avoided, number of points on a disease-specific measure improved or decrease in mortality rate. Dividing the difference in cost between two treatments with the difference in effectiveness of the same two treatments, i.e. $(C_a - C_b)/(E_a - E_b)$, we get the incremental cost-effectiveness ratio (ICER). This ratio depicts the marginal cost effectiveness for the more effective treatment compared to the less effective treatment. Low ICER indicates favorable cost-effectiveness.

CUA is actually a special case of CEA, but the two are usually separated. The measure of effectiveness in CUA is the utility of some subject(s) of interest, e.g. the patient or the caregivers. One of the most common measures in CUA is the Quality Adjusted Life Year (QALY). The advantage of the QALY concept is that it brings together the two different ways in which an intervention ultimately may affect us, i.e. the quality of life (morbidity) and the length of life (mortality). Some treatments are favorable at prolonging life and others at improving our health as we are still alive. The QALY enables us to compare these treatments with one single measure of effectiveness. The QALY concept is further presented in section 2.3.

In CBA, consequences are translated into monetary terms. As one can imagine, it is tricky to find the money value of a specific consequence, and there are a range of different approaches. Three from these are commonly used. The *human capital approach* values the consequences according to future production of an individual. The *revealed preference approach* looks at the trade off between health and money in the real market. For instance, jobs that have higher risk of injury have an extra risk

premium added to the wage. By comparing this wage premium with the risk of injury, a measure on the money value of health is revealed. Finally, in the *contingent valuation approach*, subjects are interviewed on how much money they would pay for a specific treatment programme if there was a market for it. The last two approaches are actually only two different methods to measure the same thing, why they should result in the same value. The human capital approach, however, may result in a different estimate of the money value of the specific consequence. The benefits of a treatment, measured by these different approaches, are reduced by the cost of treatment and all other effects on costs induced by the treatment, producing a net benefit. All treatments with a positive net benefit should be implemented, unless it excludes another treatment with a higher net benefit.

2.3. Measures of cost

The previous section presented four types of economic evaluation, all of them including a measure of cost. Naturally, this is no coincidence. Costs are central in all forms of economic analysis, since we always have a restriction on available resources. There are a range of aspects needed to be considered when measuring costs. In this section we will briefly go through the most important ones. This section is based on Drummond et al. (2005) and Wimo et al. (1998).

When considering how to allocate resources it is interesting to know the cost of a specific illness. We may measure the costs for a patient, with for instance Alzheimer's disease (AD), compile them and present a figure on how big is the cost for a patient with AD. However, we cannot only from this say anything about the cost of AD in itself. Many of these costs would be generated also by a subject without AD, for instance the cost of food and personal hygiene which is necessary for all people. Hence, if we want to estimate the cost of a disease, we need to compare with e.g. a matching healthy subject or with the same individual before onset of the disease. Any approach is associated with methodological issues and the costs of illness will always be a theoretical construct rather than a characteristic that can be directly measured, see also Jönsson (2003).

Choosing a perspective is crucial when considering costs. Different stakeholders are faced with different costs, not all of them being realized in money terms. In order to get the big picture we usually choose the so called societal perspective. From this perspective we consider all costs that are generated by the disease, no matter who has to bear them. However, transfer payments are excluded since a transfer cost for someone is a transfer benefit for someone else, while the net of the transaction is zero from a societal perspective. Examples of transfer payments include reimbursements from insurance companies and the out of pocket fee paid at the hospital. Another important aspect of this perspective is that of using opportunity cost, i.e. the value of the best forgone alternative use of this resource, instead of charges. If possible, the mark up should be considered as a transfer and not be included in the calculations.

We also distinguish between incidence-based costs and prevalence-based costs. The former is used when we want our cost measure to depend on at which point in time the patient was afflicted with the disease. This approach is useful when we want to evaluate a treatment, since disease progression and subsequently also costs of the disease will depend on the timing of the incidence. Prevalence-based cost, on the other hand, considers all patients at a specific point in time. This approach is useful when we want to measure the cost of a disease for a given time period.

When assessing costs we may start out by estimating total expenses of all diseases and then break them apart into disease categories. This is called a *top down* approach. Conversely, we could use a *bottom up* approach. Then we estimate the cost of each resource used by individual patients with a specific illness and then aggregate them into a total, multiplying with the total prevalence or incidence of the illness.

The time horizon is another important issue. First of all, we need to consider for how long we track our subjects, but then also to decide on a discount rate to assess future costs and benefits. This is sometimes of great importance as an intervention can be very costly initially, but also generate a lot of benefits for a long time afterwards. Vaccination is a good example of this, especially for diseases that we have managed to extinct.

We differentiate between prices and quantities as we assess costs. First we measure the amount of resources used, then we multiply with the price of each resource unit. By differentiating between prices and quantities, our calculations can more easily be altered, for instance when calculating the cost of the same resources in another country with different prices.

In addition to direct costs, such as the cost of medical care or drugs, there are indirect costs attributable to a disease. For instance, if patients are not able to work due to their illness, their loss of income is an indirect cost of the disease. Often patients are reimbursed through various insurance systems but these reimbursements are only transfer payments and do not change the fact that patients' lost productivity is an indirect cost to society as a whole. The *human capital approach* is the most common way of assessing indirect costs and measures the loss of income due to illness. In the case of a loss in leisure time, i.e. non-working hours (which very well could be household work), an estimated value of leisure time is used. Patients suffering from AD are in most cases already off their working age, why there is less importance of indirect costs due to loss of income.

Informal care is an important resource some times excluded from economic analysis. This is, for instance, the every day treatment performed by relatives which does not go into any health budget. These services constitute a complement to formal care and may amount to substantial size. Hence, informal care is important from the societal perspective, even though it is hard to calculate the cost of the resources used. One approach is to measure the opportunity cost of time given up in order to care for a family member, but there is no consensus on which method to use, see also Jönsson (2003).

2.4. QALYs

The QALY is based on a cardinal utility function, which means that twice as much QALYs yields twice as much utility, as opposed to a ordinal utility function which only orders the utility of the observed phenomena. The QALY ranges from 0 to 1, where 0 means dead and 1 means perfect health. There are several ways of measuring the utility of a specific health state, whereas two are more sophisticated; the standard gamble and the time trade-off method.

The standard gamble is a game where the subject chooses between the health state of interest (i) with certainty for (t) years and a gamble between full health and death. The probability of full health for (t) years followed by death is (p) and the probability of immediate death is (1-p). The value of (p) is altered until the subject is indifferent between the two alternatives. The resulting (p) is the QALY weight of health state (i).

In the time trade-off method the subject chooses between the health state of interest (i) for (t) years followed by death, and full health for (x) years followed by death. Now, (x) is altered until the subject is indifferent. The resulting (x/t) is the QALY weight of health state (i).

When we assume that patients are risk neutral, the standard gamble and time trade-off method will give the same utility weight.

2.5. Modelling

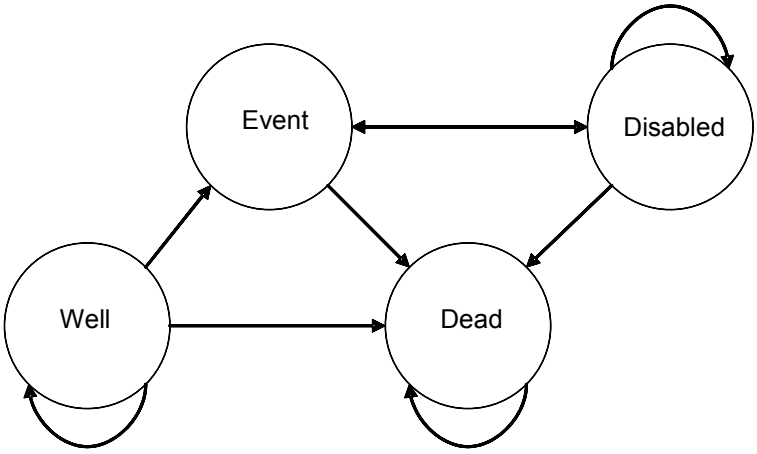
Some times, the conclusions we are able to draw from our study data is not sufficient as to serve as a basis for informed decisions. We often need to extend our analysis beyond what we can observe in the study, and for this purpose, we create a model. Modelling is about using the information at hand, putting it into a vehicle of assumptions and getting a lot more information at the other end. We use models when we want to combine data from different sources or when we want to extrapolate our data in order to reach outcomes that has not yet occurred under our follow-up period.

The decision tree is a common modelling technique used in decision analysis. By visualizing the choices of action, and the probability and value of each outcome corresponding to these choices, we are able to find the optimal strategy according to our expectations. However, as the number of choices and contingencies grow, the decision tree becomes complex and inaccessible.

For more complex studies we therefore need a different modelling technique. The Markov cohort simulation defines a set of health states over which a cohort of patients is distributed at baseline. From our data we are able to compute point estimates of the transition probabilities of each state, defined as the probability of a patient moving from state (i) to state (j) within a given period of time, called a cycle. At each cycle, all patients are redistributed over the states according to the transition probabilities. The cost and utility of spending a cycle in each state is multiplied with the share 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 cost and utility of the patient cohort is accumulated. As we end the simulation, we know the distribution of patients over the states and also their accumulated cost and utility. If we choose a terminate state, e.g. dead, we are able to run the model until all patients have died and get an estimate of total cost and utility of the remaining life of our study cohort.

Figure 2.1 shows a state transition diagram of an example 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 2.1 A Markov model



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. There are however reasons to believe that the probability of an event would depend also on previous events, that is, what happened in the previous cycles. For instance, if you have a hip fracture from which you recover and you go back to state well, you will be in the same state as all subjects that never had a fracture. Obviously, the probability that you will have another fracture is higher than the probability of the other subjects to have a first one. This issue could be overcome by adding a state, for instance a recovered from fracture state.

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) we follow one subject at a time which enables us to consider 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.

We may also take the uncertainty in underlying inputs into account, which is called the second-order uncertainty. Then inputs are presented as distributions instead of point estimates, and at each cycle inputs are randomly drawn from these distributions. Inputs may also change over time as patients grow older, which is intuitive since the risk of an event usually increases with age. Both the Markov cohort simulation and MCMC may be used with uncertainty in underlying inputs and time dependent inputs, see also Wimo et al. (1998 p.171-195).

2.6. Statistical methods

Considering the uncertainty in our estimates we need to use some statistical tools. This uncertainty arises since we want to say something about a larger population only looking at our sample data. Furthermore, as we extrapolate our study data as to model what will happen over a longer period of time our methods will again restrict the level of certainty.

2.6.1. Distribution of cost

Cost data are usually highly skewed. This is due to the non-existence of negative costs but also the special feature of most diseases that a small share (e.g. 20 percent) of the patients generate a lion's share of the costs (e.g. 80 percent). That is, most subjects have low cost, only a few have high costs and none have negative costs. This results in a distribution peak close to zero but positive and a long tail to the right. Another characteristic of cost data is that the variance of the observations increases with their mean, referred to as heteroscedasticity (Dunn et al. 2003).

2.6.2. The non-parametric bootstrap resampling method

We do not know the actual distribution of cost, only that it is not normal and that it is rightly skewed. Using a non-parametric bootstrap resampling method (Drummond et al. 2005 p.263) we do not need to make any assumptions about the distribution when we for instance want to calculate a confidence interval. With the non-parametric bootstrap resampling method the computer randomly draws an observation of cost, with replacement, from our study sample over and over again until the new sample is equally large as the study sample. The mean is then recorded for this new sample. The same procedure is done a large number of times which will produce an empirical estimate of the sampling distribution of mean costs. A 95 per cent confidence interval would then be given by removing the lowest and highest 2.5 per cent estimates.

2.6.3. The generalized linear model

Generalized linear models (GLM) (Dunn et al. 2003) are useful when we have heteroscedasticity and a non-normal distribution of our dependent variable, as in the case of our cost data. In GLM we assume that a *function* of our dependent variable is linear in the parameters of the explanatory variables. For instance, in a log-link GLM model we link the natural logarithm of our dependent variable and estimate the linear regression of this log-link, e.g. $\ln(Cost) = \alpha + \beta x + u$. This will produce stability in the variance alleviating the problem of heteroscedasticity, and by specifying the distribution of our dependent variable this will also affect the distribution of the error term u addressing the issue of non-normality. Costs are usually assumed to follow a gamma distribution. Note, the GLM method is not the same as the common approach of just calculating the logarithms of the cost and performing an ordinary least-squares regression (OLS), even though this is also used in order to alleviate the problem of a non-normal distribution and heteroscedasticity. In GLM we estimate the model on a function of the actual cost, not the log of cost, why our estimates should be more precise using the GLM. The GLM model is fitted using the maximum likelihood approach presented in the next section.

2.6.4. Maximum likelihood

When fitting a non-linear model, as for instance GLM, we use the maximum likelihood method (ML) (Gujarati 2003 p.633-635) instead of the ordinary OLS method. This since we cannot find the least square regression when our model is not linear and our function has multiple min and max points. Instead we use the computer to estimate the unknown parameters in our model as to maximize the likelihood of observing the given data. This is an iterative process, where the model is improved until the maximum likelihood is stable.

2.6.5. Panel data analysis

In clinical studies we usually follow a group of subjects over time, resulting in a set of data for each subject at each point in time. This combined form of cross-section and time-series data, called panel data, reveals more information why we get more knowledge from studying it compared to just cross-section or time-series data. When making an ordinary regression on cross-sectional (time-series) data we pretend that the intercept and the slope of the coefficients are the same for all sections (points in time). The deviance is then caught in the error term which is made as small as possible as the model is fitted. Now, having two dimensions the possibility of deviance from a fixed intercept and slope of the coefficients qualifies for both sections and time. If we would not take any of these deviances into account, the error term might become very large. In a *fixed effects model* (Baltagi 2001 p.11-15) we assume that the intercepts vary between different sections, but not over time. This is done by creating dummies with corresponding coefficients for every section we use. We then estimate the model with respect to the variance within each section, controlling for the variance between each section. The model would look like this;

$$Y_{it} = \beta_{1i} + \beta_2 x_{2it} + \beta_3 x_{3it} + u_{it},$$

where β_{1i} represents the individual dummies with coefficients and is individual for all sections *(i)*.

The way to interpret the fixed effects model is that we control for differences in underlying unknown characteristics between sections that will affect the dependent variable. Our estimate is then explaining the dependent variable given the explanatory variables, as if all sections started from the same point at baseline.

2.6.6. The logistic model

A logistic model (Gujarati 2003 p.595-600) may be used to predict the response of a binary variable, i.e. a dummy variable that takes the values 0 or 1. For instance, say we want to predict the response to treatment, i.e. our dependent variable is 1 if the patient is a responder (a positive response) and 0 otherwise. The probability of a positive response is P and thus the odds ratio of a positive response is $p/(1-p)$, i.e. the probability of a positive response divided by the probability of a negative response. Then we estimate our non-linear model $\ln(p/(1-p)) = \alpha + \beta x + u$ where x is our explanatory variable. We could extend the model to include more than one explanatory variable. Note, as the right hand expression goes from -∞ to +∞, $(p/(1-p))$ is bounded by 0 but $\ln(p/(1-p))$ also goes from -∞ to +∞.When fitting this model, we use the maximum likelihood method to estimate the parameters.

2.6.7. Survival analysis

We may estimate the time until various endpoints, such as nursing home placement, dropout or death in a survival analysis. Then we count the number of days until the event of interest. We also create a dummy which is set to 1 if the event is observed during the time of study and 0 otherwise. We may then produce a Kaplan-Meier diagram (Collett 2003 p.30-32) with time on the x-axis and share of the

sample that still have not experienced the event. This may also be done separating observations into relevant groups, for instance with respect to treatment response.

Furthermore, we may run a Cox proportional hazard model (Collett 2003 p.55-58) in order to try to explain which underlying variables may have an impact on the time to event. The model is given by;

$$h_i(t) = e^{\beta_1 x_{1_i} + \beta_2 x_{2_i}} h_0(t)$$

where $h_i(t)$ is the proportional risk of experiencing the event at time *(t)* for a subject with the characteristics x_i compared to the risk of a subject where all x_j are equal to zero. Note, when $\beta_1 x_{1i} + \beta_2 x_{2i}$ is positive, the proportional risk is positive, i.e. the risk of subject *(i)* is higher than the risk of subject with all x_j equal to zero and the proportional hazard is larger than unity. Vice versa, when $\beta_1 x_{1i} + \beta_2 x_{2i}$ is negative, the proportional risk is negative and the proportional hazard is between zero and one.

3. Alzheimer's disease

3.1. Definition and overview

Dementia originates from latin and would be translated into "out of ones mind". It is a cognitive disorder, different from amnesia and delirium in that it is progressive, i.e. subjects with dementia deteriorate over time. The symptoms are deterioration in cognitive functions (e.g. memory and language skills) and functional abilities (e.g. transportation and personal hygiene), but could also induce behavioral disturbances (e.g. aggressiveness and emotional lability) (Maj and Sartorius 2000 p.1-9). Alzheimer's disease (AD) accounts for 50 to 70 percent of all dementia cases, which makes it the single most prevalent of all cognitive disorders. Other types of progressive cognitive disorders are in order of prevalence; vascular dementia, Lewy body dementia and fronto-temporal dementia. The different types of dementia are hard to distinguish from each other, and mixed forms are highly prevalent. If a patient is diagnosed for dementia and none of the symptoms for other types are found, possible or probable Alzheimer's disease is the usual diagnosis (Jönsson 2003).

The prevalence of AD, (i.e. share of population afflicted), increases exponentially with age with almost a doubling every 5 years from the age of 65. At this age 0.6 per cent of all men and 0.8 per cent of all women are afflicted, while the prevalence rates at the age of 95 are 35.6 and 41.5, respectively. Note also that the prevalence is higher for women (Jönsson 2003). The progression of the disease may be slow in the beginning and hard to identify, why some years may go by from onset until diagnose. However, at the later stages the progression is more rapid and as the final stage of severe impairment is reached, the patient will usually die within short. The life expectancy from diagnosis is about 6 years on average (Ganguli et al. 2005).

The cognitive and functional impairments imply increasing dependence on caregivers and subsequently also increasing cost of care over time. As the demographic trends predict an older population in the future this implies an alarming rise in the number of demented, as well as the societal cost they generate. Costs increase with disease duration and are also higher for subjects with a worse cognitive impairment in cross-sectional analysis (Jönsson 2005).

3.2. Effects of cholinesterase inhibitor therapy

At present, there is no cure for AD but there are means to alleviate the burden of the disease. The cholinesterase inhibitors, the second generation of drug treatment on patients with AD, have been

successful in improving cognitive and global function in mild to moderate AD in the short run. A review on 27 studies, on the effect of treatment with the cholinesterase inhibitors donepezil, galantamine and rivastigmine, concludes that all three drugs “improve cognition and the global level of functioning in mild to moderate Alzheimer’s disease” (Olsen et al. 2005).

However, the benefits from treatment has been relatively small, why it has been debated if they warrant the costs of treatment (Jönsson 2005), not least since cholinesterase inhibitors are expensive; about 12 000 SEK per patient and year (FASS 2005). More studies are called for, especially long-term studies in clinical practice. These are needed since there are some methodological restrictions on studies in clinical trial.

Pivotal phase III (i.e. the third of four phases in the development of a new drug) clinical trials have strict inclusion criteria on subjects admitted in the study. Researchers choose their subjects carefully with respect to e.g. age and health, since they do not want their subjects to drop out due to other illnesses. Patients who are using medicines that could influence the outcome measures, living in institutions or lacking a caregiver are usually also excluded. These inclusion criteria generate a study sample that is not perfectly representative for the population as a whole. Furthermore, the clinical setting diverges from that of usual care in terms of the extended use of questionnaires and additional staff. These so called protocol driven costs could affect the study results and even if they were excluded from calculations, which usually is the case, there may still be divergence from clinical practice. This since the rate of unscheduled visits at the physician’s may be higher in clinical practice than in a clinical trial where you see your doctor as part of the trial. These issues together form some restrictions on the applicability of the results from clinical trial in the real setting, see further Wimo et al. (1998 p.507).

There is some evidence suggesting that drug treatment actually leads to net savings. Advances have been made to estimate the cost-effectiveness of drug treatment with models using consequence data from clinical trial and resource use data from observational studies. This is done by for instance Jönsson et al. (1999a), where treatment with the cholinesterase inhibitor donepezil was shown to lead to net cost savings of slightly above 15 000 SEK over five years including the cost of treatment. This due to the link between cognitive impairment and resource use and the assumption of subsequently lower costs as the deterioration in cognitive function is slowed down. Wimo et al. (2003) tested this assumption in a multinational clinical trial where donepezil was tested against placebo. They concluded that patients treated with donepezil had lower costs on average, including costs of treatment and informal care.

In a British longitudinal study, AD2000, a difference in cognitive function was found between patients on treatment with donepezil and placebo, but no significant difference in resource use was recorded. Hence, they concluded that the treatment was not cost-effective (Courtney et al. 2004). However, these findings have been widely criticized, mainly because of methodological problems with the study design (Holmes et al. 2004).

3.3. Treatment response

We know that the initial response to treatment varies between individuals. Some show improvements after being treated while others continue to progress at the same pace as before. Since AD is a progressive disease we expect cognitive function to deteriorate over time. A response to treatment would therefore be considered to be positive if the patient would avoid this deterioration, which would not have to mean that the patient’s cognitive function improves per se.

Wallin et al. (2004), studied the cognitive function and time until nursing home placement on patients treated with another cholinesterase inhibitor (tacrine, Cognex®). They differentiated between responders (i.e. improving in cognitive function), unchanged and deteriorated patients. They found that responders and unchanged patients had a prolonged time until nursing home placement compared to deteriorated patients. There was no difference in mortality rate between the groups and no predictors for treatment response were found at baseline. The treatment response was defined looking at the changes of 3 outcome scores; MMSE, ADAS-cog (further described below in section 3.4) and a global measure evaluating the patient’s overall progression. A responder patient had improved in at least 2 of the measures and had not changed in the third measure. An unchanged patient had improved in at

most one, deteriorated in at most one and had not changed in the other measure(s). A deteriorated patient had deteriorated in at least 2 of the measures and had not changed in the third measure. For those observations where the MMSE- or ADAS-cog score was lacking, the patient had been defined as deteriorated on basis of the global measure.

3.4. Cognitive function

Cognition, derived from the Latin word *cognoscere* which is translated into *to know*, includes a range of mental processes such as perception, attention, memory, communication and judgment. The deterioration in cognitive function is one of the main symptoms of AD, and probably also the most common disability to associate with dementia. Furthermore, cognitive function is the primary endpoint in most clinical studies on cholinesterase inhibitors where treatment has shown to be efficacious. For these reasons, maintained cognitive function is an important endpoint when treating patients with AD. This section is based on Caban-Holt et al. (2005).

Assessing cognitive function, there are two widely used measures; ADAS-cog and MMSE. ADAS-cog is the cognitive subscale of the Alzheimer's disease Assessment Scale and tests cognitive decline, memory, orientation, language and praxis. The most common version ranges from 0 to 70 points, where a higher score indicates a more severe cognitive impairment. In this study a refined version with a maximum of 85 points is used. However, for the purpose of comparability we will also make use of the 70 point version. It is simply produced by deducting two of the 13 questions in the 85 point version. The ADAS-cog measure takes 30 to 45 minutes to administer which, especially for patients with more severe cognitive impairment, may restrict appliance. For this reason, and also because of the scarce and valuable time of physicians, ADAS-cog has not been used as much in clinical practice as in clinical research studies.

MMSE, Mini-Mental State Examination, is a simpler measure. It takes only 5 to 15 minutes to administer, why it has dominated clinical practice. MMSE measures orientation, attention and concentration, immediate memory, language, delayed or recent memory, and constructional praxis. It ranges from 0 to 30 points, where a lower score indicates a more severe cognitive impairment.

An untreated subject deteriorates on average approximately 8 points per year on the 70 point version of the ADAS-cog and close to 4 points on the MMSE measure. Both measures may be sensitive to daily fluctuations in the patient's condition, which results in individual variability in outcome scores over time. Both measures also have a floor and ceiling effect, since neither is sensitive to changes in very mild or severe AD. However, these floor and ceiling effects are more articulate in MMSE, see also Wimo et al. (1998).

4. Materials and Methods

4.1. Study design

Data was collected from a cohort of AD patients within the Swedish Alzheimer Treatment Study (SATS). One of the objectives of this project is to collect data on AD patients in clinical practice, in order to study the treatment effects of cholinesterase inhibitors. The analysis of this thesis is based on a sample of 435 patients from the SATS project who were initiated on treatment with a cholinesterase inhibitor donepezil (Aricept®, Pfizer). There were no specific inclusion or exclusion criteria other than being diagnosed for Alzheimer's disease and beginning the treatment. If the treatment for some reason would end, the patient was excluded from the study. Informed consent to participate in the study was attained from all patients. Patients were included during the years of 1997 to 2001, and were each followed for three years. Data was collected every six months, which sum up to data on baseline and 6 follow-ups. The mean age at baseline was 75 years and 65 per cent were women.

4.2. Drop out

Attrition, i.e. failing to complete the study, is commonly high in longitudinal studies of AD patients, due to mortality, withdrawal of consent, moving to other accommodation, side-effects of treatment, protocol violations etc. At the 36th month check up, 166 of the initial 435 patients remained in the study which equals 38 per cent. The distribution of dropouts over time is shown in Table 4.1 and the causes are shown in Table 4.2. The drop out rate is fairly constant over time and “other living” is the most common cause, i.e. patients that has moved into a form of living, usually nursing home, where we are not able to follow them anymore. Almost half (16) of the cases noted as “suspicion of side effects” dropped out during the first 6 months and the cases of death are evenly distributed over time (4-6 cases every six months starting from 12 months).

Table 4.1 Distribution of dropouts over time

Months	0	6	12	18	24	30	36
Number of dropouts	0	39	41	58	39	48	44
Number of remaining subjects	435	396	355	297	258	210	166

Table 4.2 Causes of dropping out

Cause	Frequency
Other living	69
Change of treatment	18
Death	25
Other diagnosis	1
Withdrawn consent	25
Suspicion of side effects	35
Bad compliance	27
Other somatic disease	16
Bad outcome of treatment	24
Supplementing treatment, memantine (Ebixa®, Lundbeck)	4
Other cause	24

There is a risk of biased results unless the issue of dropping out is taken into account in the analysis. Looking at the dropouts due to “other living” for instance, we see this is the most common cause of dropping out. In all cases but one, these subjects have moved to nursing home which is the main cost driver in the late stages of AD. If the most costly patients drop out as they progress into worse stages of AD, this will affect the results in several ways.

First of all, the cost of AD will be underestimated as a relatively larger share of patients with lower resource use, as compared to patients with higher resource use, stay in the study. Secondly, if the risk of moving to a nursing home is higher for patients with low cognitive function, there will also be an under-estimation of the strength of the relationship between costs of care and cognitive function, as patients with worse outcome scores drop out to a larger extent. Thirdly, if more patients drop out of the non-responder group, this will result in an under-estimation of differences in both costs and outcomes between responders and non-responders.

At the end of the results section, in section 5.6, we will study the difference in dropouts between responders and non-responders. First we compare time until dropout with help from the Kaplan-Meier survival estimates. Then we do a Cox regression analysis, trying to explain the dropout rate with response to treatment.

4.3. Descriptive analysis

4.3.1. Outcome measures

The SATS study comprises measures of cognitive function (MMSE and ADAS-cog), functional ability (IADL, PSMS and FAST) and a global rating of the degree of dementia (GLOBAL). This thesis addresses cognitive function, why we will leave the other outcome scores aside.

From the measures of cognitive function we will mainly use ADAS-cog. The reasons for using ADAS-cog instead of MMSE are threefold. First of all, as discussed in section 3.4, ADAS-cog is a more comprehensive measure than MMSE and as a result is able to give a more precise measure of the cognitive function of the patient. Secondly, even though it is harder to use and therefore we drop observations along the way, we have ADAS-cog score data from almost all patients still in the study. Thirdly, ADAS-cog has not been used as much as MMSE in economic evaluation and might just for this reason add interest to the results.

As noted earlier we will mainly use the 85 point version of the ADAS-cog scale. However, since there are more studies made on the 70 point version we will use this one in our division into states of disease severity in section 4.3.3. From now on, when we write ADAS-cog we refer to the 85 point version, unless otherwise stated.

As discussed in section 3.1, we expect cognitive function to deteriorate over time. This relationship is presented in section 5.1.1.

4.3.2. Cost estimates

Data on resource use for accommodation, community care and outpatient care were collected from all participants at each point in time. In the dataset, dates for moving into each form of accommodation, number of home help visits per week, number of days per week with home delivered meals and number of days per week with day care, were covered. Accommodation data was expressed with dates of moving in and, where applicable, out. We counted the number of days attributable to each specific form of living for each cycle. Where a date on moving out was lacking, the subject was assumed to stay through out the study.

In order to calculate cost, we multiplied resource use data with the price of each resource unit. These resource unit prices were collected from Jönsson (2003) and are shown in Table 4.3. All prices are inflated with CPI (Oct 2005/ Jan 2003).

Table 4.3 Unit costs (inflated for Oct 2005)

Resource	Specification		Cost (SEK)
Accommodation	Block of service flats	per day	586
	Nursing home	per day	1507
	Temporal assistance	per day	1507
Community care	Home help	per visit	232
	Home delivered meals	per day	86
Outpatient care	Day care	per day	412

The accommodation resource group includes two forms of living, though this is an approximation. The block of service flats includes accommodation with some form of assistance but no staff with medical competence. The more expensive nursing home has nurses as part of the regular staff and access to physicians when required. The accommodation resource group also includes temporal assistance for patients staying in a nursing home temporarily. We expect accommodation costs to increase as the patient progress into worse stages of AD, due to the increasing need for assistance.

Community care services are usually performed in the patients' original home environment. Home help could be to do the everyday household work, like washing clothes and cleaning, but also

managing personal hygiene and dressing, while home delivered meals are exactly what it sounds like. These services usually enables a postponement of the more expensive, and often more distressful, forms of living. We expect costs for community care to be higher in early stages of AD, as patients still live in their original home environment.

Day care is the only form of outpatient care considered in this study. This is a service providing daytime medical care and activation, usually a few days per week, for patients residing in ordinary living.

The cost of the treatment drug, donepezil (Aricept®, Pfizer), is based on a flat rate used in Sweden; ~6000 SEK per every 6 months. This means that the price of the drug is the same no matter what dosage is administered. Since all patients were treated with donepezil and were all faced with the same cost for this drug, it is not included in the analysis but will be used for comparison in the discussion section. Hence, when we refer to total costs from now on we mean total non-drug costs.

A more important cost that is excluded from this study is that of informal care. Caring for someone with dementia can be very time consuming and the cost of informal care has been shown to represent a large part of the total cost of care for AD patients (Jönsson, 2003). Since no data on this resource is available in our dataset we will leave this cost aside for now. However, in the sensitivity analysis we will try to impute informal cost from another study in order to test our results.

We expect costs to increase over time, as discussed in section 3.1. The resource use over time is presented in section 5.1.2 and the development of costs over time is tabled in section 5.1.3.

Costs are expected to be skewed to the right as discussed in section 2.6.1. A histogram over total cost is shown in section 5.1.3, where values equal to zero are excluded in order to get an overview of data. In addition we show the distribution of logged cost. If logged costs have a more normal distribution this is an argument to use the logged cost in our regression analysis.

4.3.3. Definition of Markov states

Four states were defined with respect to the 70 point version of the ADAS-cog score. The score intervals were chosen according to the suggested intervals in Caban-Holt et al. (2005). In this states division scores below 10 indicate no impairment, scores between 10 and 25 indicate mild impairment, scores between 26 and 40 indicate moderate impairment and scores above 40 indicate severe cognitive impairment. The states were numbered from one to four with increasing cognitive impairment. Table 4.4 defines the states and shows number of observations in each state.

Note that there are several observations from each subject in this states division. As we have one observation per subject and cycle, we pool observations in order to make full use of the data.

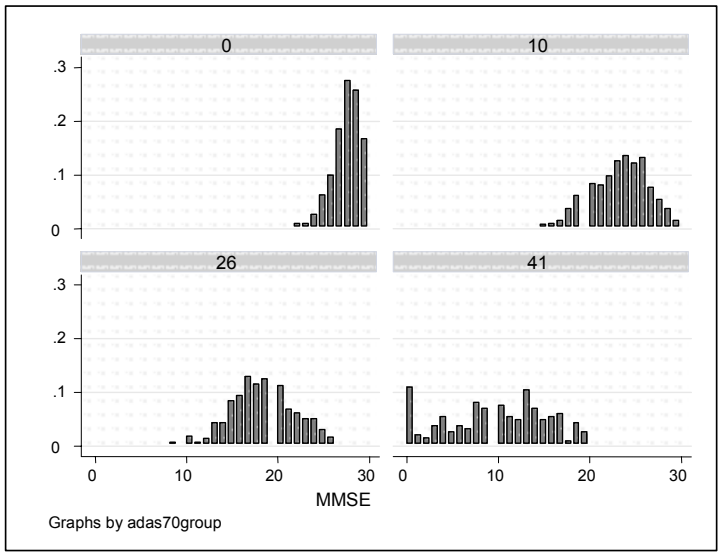
Table 4.4 Definition of ADAS-cog states

	State 1	State 2	State 3	State 4
	No impairment	Mild impairment	Moderate impairment	Severe impairment
ADAS-cog intervals (70 point version)	0-9	10-25	26-40	41-70
Number of observations	244	982	460	201

Later on we may need to know the distribution of MMSE over the states defined with help from the ADAS-cog measure. One would think that MMSE would easily be translated into ADAS-cog since they conceptually measure the same thing. However, the two measures sometimes yield very different results.

Figure 4.1 shows the distribution of MMSE scores sorted over the four states. The four groups of MMSE scores overlap each other, however we see a clear pattern where those observations with higher MMSE scores are located in lower states, defined by ADAS-cog. Remember that MMSE is inverse in relation to ADAS-cog, i.e. a high MMSE score indicates less impairment.

Figure 4.1 Distribution of MMSE scores



On basis of the distributions above we assign the MMSE intervals for each state according to Table 4.5. The mean MMSE score and standard deviations are also presented for each state.

Table 4.5 MMSE scores by state

	State 1	State 2	State 3	State 4
MMSE intervals	30-26	25-21	20-14	13-0
Mean MMSE score	27.8	23.4	18.3	9.9
Standard deviation	1.8	3.2	3.8	5.7

4.4. Markov model

As part of the descriptive analysis we present a Markov cohort evaluation where we show the progression of our study cohort. Since we have no data on mortality we have used data from the Kungsholmen project (KHP), which is a large longitudinal study on elderly in a specific area in Stockholm (Jönsson et al. 1999b). We did a survival analysis on the mortality data from KHP, using patients with dementia. From this we produced mortality probabilities with respect to state and age, on which we know that mortality depend. We did not have data on ADAS-cog in KHP why we used the MMSE to assign an observation from KHP to each state, according to the division of MMSE scores over states in the previous section.

Table 4.6 shows some examples of the mortality rates for each state, namely for a patient at the age of 60, 70, 80 and 90 years, respectively. The figures are interpreted as the risk of dying during a 6 months cycle.

Table 4.6 Mortality rates

	State 1	State 2	State 3	State 4
60 years	0.6%	1.1%	2.1%	2.6%
70 years	1.2%	2.2%	4.0%	5.0%
80 years	2.3%	4.2%	7.7%	9.6%
90 years	4.4%	8.1%	14.6%	18.1%

We know the initial distribution of patients over the states. This is simply given by the share of all subjects in each state at baseline. The transition probabilities are calculated on basis of the 6 cycles we have data on. We could make the transition probabilities dependent on time, but here we calculate the mean of transition probabilities over the whole study period. Both initial distribution and transition probabilities are shown in Table 4.7. For instance, the probability of a patient in state 1 remaining in the same state next cycle is 0.698 and the probability of moving to state 2 is 0.302. That is, given that the patient is still alive.

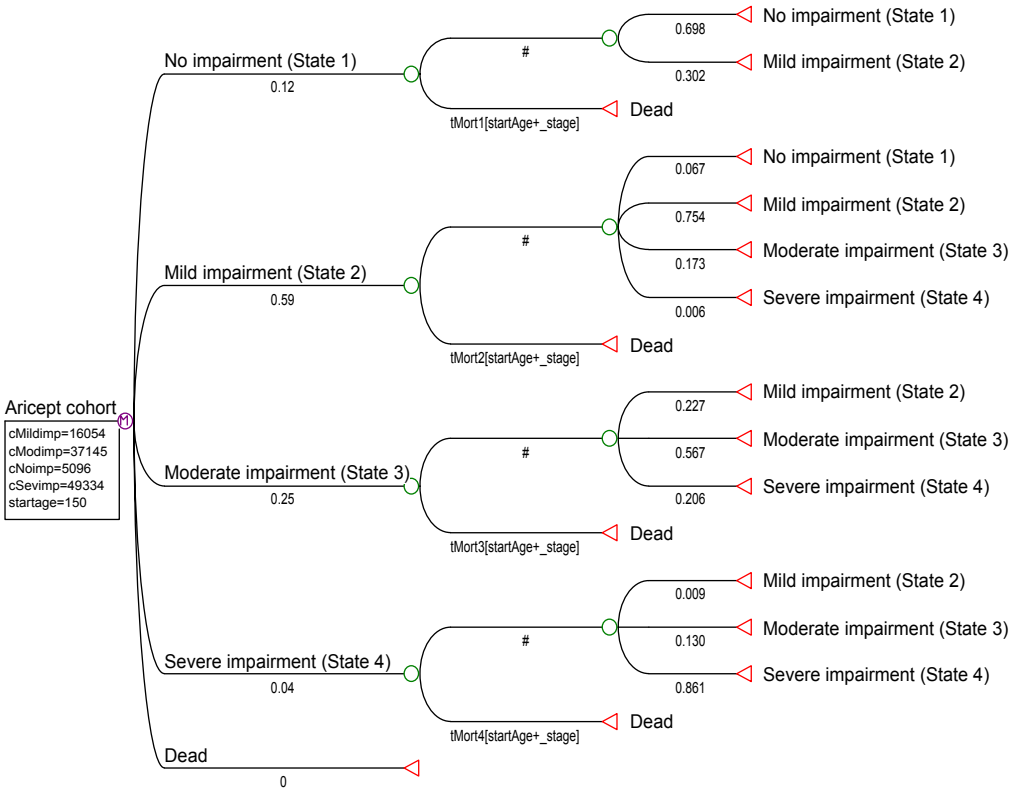
Table 4.7 Transition probabilities

	Initial distribution	Transition probabilities			
		State 1	State 2	State 3	State 4
State 1	0.12	0.698	0.302	-	-
State 2	0.59	0.067	0.754	0.173	0.006
State 3	0.25	-	0.227	0.567	0.206
State 4	0.04	-	0.009	0.130	0.861

Figure 4.2 shows our simulation in the form of a Markov tree. The initial distribution of patients over the states is seen at each state to the left in the figure. First, at each cycle, the share of the cohort that survived the cycle is given in each state by tMort, which is a function of the age of the patient (startAge + _stage). StartAge is the age of the patient at baseline and this is set to 150 cycles, which equals 75 years and the average age of the cohort at baseline. We have used the average age for the cohort for simplicity, but they could have been entered as the distribution of the age of all patients in the sample at baseline. _stage is the number of cycles, which in the tMort function will yield an increasing risk of dying as time elapses. # equals (1- tMort). Second, the survivals are redistributed over the states according to the transition probabilities.

The triangles at the end of the nodes are symbols of terminating the node and are followed by references saying in which state to begin the next cycle. At the very beginning of the tree is a box with the cost attributable to spending a cycle in each state. As we run the model we will get the accumulated cost for the cohort and their progression through the states. We will run the model for 30 cycles, i.e. 15 years in which time most patients will have died. Since we do not have any data on utility measures we exclude this aspect of the Markov model.

Figure 4.2 Markov model



4.5. Cost and cognitive function in cross-sectional analysis

In this section we want to study the generally accepted relationship between cognitive function and cost of care from cross-sectional analysis. For this we may use the pooled data from our states division in the previous section. We will also perform a GLM regression where we try to explain cost by ADAS-cog score.

We expect all costs to be higher in states with a more severe degree of cognitive impairment as discussed in section 3.1. This relationship between costs and the ADAS-cog states is examined in section 5.3.

The relationship between cost and a set of explanatory variables was estimated in a GLM model with a log-link, i.e. the natural logarithm. Costs were assumed to follow a gamma distribution and we cluster observations with respect to subjects, by which we specify that observations are independent across subjects but not necessarily within subjects over time. By this measure we control for collinearity in the covariates over time. For instance, if a subject has a relatively low ADAS-cog score relative to cost compared to other subjects at baseline, the same will probably be true also at the follow-ups. This does not say so much about the relationship between ADAS-cog and cost as it says about the relationship between time and ADAS-cog on the one hand and time and cost on the other. Hence, by clustering on subjects we control for this effect. Another way to think about the clusters is that we take advantage of having many observations from each subject but use this information in a cross-sectional analysis.

The covariates considered are in alphabetical order; ADAS-cog, age, alcohol consumption, debut age, disease duration, education, heredity, sex, and smoking habits. Education is a variable increasing with the level of education ranging from compulsory school (1) to doctoral studies (5). Covariates that were

not significant were removed stepwise, i.e. the one with the highest p-value was removed until all covariates used in the model were significant. The final estimation with explanatory variables significant on the 5 % level is presented in section 5.3. We will use the 5 % level of significance as a cut-off in all analyses.

4.6. Cognitive decline and cost progression

The previous section was the end of our analysis in which we studied relationships that are already generally accepted. Now we address the first main objective of our thesis, and move into the more innovative part of the study. That is, the possible relationship between cost progression and cognitive decline. In order to study this relationship we produce a fixed effects model on our panel data. Remember from section 2.6.5, that we in a fixed effects model control for differences in intercepts between our subjects. That is, we control for the fact that our subjects start off from different disease severities at baseline which would induce variations in costs according to the cross-sectional link between cognitive function and costs. Furthermore, if we include a variable that reflects the progress of time, e.g. duration, we should be able to get an estimate of the effect on cost from a change in cognitive function controlling for time. We use the natural logarithm of cost in order to get a more normal distribution of our dependent variable. Our fixed effects model is as follows;

$$\ln Cost_{it} = \beta_{1i} + \beta_2 ADAScog_{it} + \beta_3 duration_{it} + u_{it},$$

where $\ln Cost_{it}$ is the natural logarithm of cost for each individual (i) at cycle (t), $ADAScog_{it}$ is the cognitive function of each individual (i) at cycle (t), $duration_{it}$ is the number of years since diagnosis for each individual (i) at cycle (t), β_{1i} is the individual intercept for each individual (i), β_2 and β_3 are the estimated coefficients and u_{it} is the error term. The model is fitted with the maximum likelihood method and the results are presented in section 5.4.

4.7. Treatment response

4.7.1. Definition of response

If we early in the treatment process were able to distinguish non-responders from responders, we could replace the treatment of non-responders and avoid pointless waste of scarce resources. Finding the non-responders, though, is not an easy thing to do. This since we cannot be sure of how an individual patient on treatment would progress if not being treated.

However, we know that patients' cognitive function normally deteriorates over time. Hence, the absence of such deterioration could be used as an indication of response. Though we would not know for certain that this absence of deterioration would be due to the treatment, why our definition of response will only be approximate. Furthermore, the reliability would depend on where we draw the line between response and non-response with respect to the progression in cognitive function. If we use a threshold that is too high, some true responders will be defined as non-responders. Vice versa, if we use a threshold that is too low, some true non-responders will be defined as responders. Either way we do it, we will not get a perfect definition of treatment response.

As discussed in section 4.3.3, the two measures of cognitive function, ADAS-cog and MMSE, are not coherent. Some patients that improve in one measure deteriorate in the other. In order to avoid ambiguous results we have therefore chosen to use only the ADAS-cog measure in the definition of response. We rather use ADAS-cog than MMSE for reasons discussed in section 4.3.1.

We only use endpoints for cognitive function in the definition of response. If we manage to show that there is a difference in cognitive decline between responders and non-responders and also that the cost progression is lower for responders than for non-responders, then we have evidence on the link between cognitive disability and cost over time. This is one of the reasons not to mix in measures of

other outcomes. Another reason would again be to avoid unambiguous results. The drawback however, is that we rely on only one measure. If the patient had a bad day at that time, the ADAS-cog assessment would diverge from the true cognitive function which makes our results less robust.

First we define three groups; improved, unchanged and deteriorated patients. Each will be defined at two points in time, at 6 and 12 months, both compared to baseline. An improved patient has improved at least one tenth (0.1) of the standard deviation on the ADAS-cog measure. An unchanged patient has improved less then one tenth (0.1), or deteriorated less then one tenth (0.1), of the standard deviation on the ADAS-cog measure. A deteriorated has deteriorated at least one tenth (0.1) of the standard deviation on the ADAS-cog measure.

The one tenth of the standard deviation is not an obvious figure. When testing a patient, the ADAS-cog measure may vary a bit although there really is no substantial change in the patient's cognitive function. Therefore, we may allow the ADAS-cog score to vary slightly and still define the patient as unchanged. The choice of one tenth of the standard deviation equals one point on the ADAS-cog scale in both directions. It is chosen in order to get as an even amount of observations in each of the three groups as possible. In section 6.2, we redefine the groups at two point five tenths (0.25) of the standard deviation in order to test the robustness of our results.

Those patients that are not classified have either dropped out before they could be defined or lack the ADAS-cog score at 6 and 12 months respectively. The cognitive function and cost of care over time for the three defined groups are tabled in section 5.5.1.

The improved and unchanged patients are grouped and defined as responders. The deteriorated patients alone form the group non-responders, in accordance with the discussion in section 3.3.

4.7.2. Predictors of treatment response

When studying the relationship between cost and treatment response we would like to control for other explanatory variables. For instance, we know that cost increases with age, and if we would also find that treatment response tends to be positive if the patient is old, then a positive treatment response would induce higher cost just because of the age variable. To remove this effect we want to control for all variables that predict a specific treatment response. In section 5.5.2 we use a logistic model to test possible predictors of treatment response. The predictors tested were in alphabetical order; age, alcohol consumption, debut age, duration, education, head trauma, heredity, hypertension, instable blood pressure, sex, smoking habits, snus and stroke. Head trauma, hypertension, instable blood pressure and stroke are dummies for earlier experience of these specific illnesses. Snus is a dummy variable for using a Swedish form of wet tobacco. Non significant predictors were removed stepwise. If we would find predictors of treatment response this could be used as a screening process of who to put on which treatment in order to get optimal outcomes.

4.7.3. Comparison of responders and non-responders

In section 5.5.3, responders and non-responders are compared. First we calculate the difference in cognitive decline between the two groups. That is, the cognitive decline at each cycle compared to baseline. For instance, if a subject had an ADAS-cog score of 40 at baseline and deteriorated to 50 over the first year, the cognitive decline at 12 months would be equal to 10. The difference between the two groups may then be interpreted as how much more a non-responder has deteriorated from baseline at the end of each cycle. We present these differences in a block diagram with 95 per cent confidence intervals. These blocks will indicate a positive difference if the cognitive decline is larger for non-responders than for responders.

Next we move to cost where we calculate the difference in cumulative cost progression between the two groups. That is, the cumulative cost increase in every cycle from baseline. For instance, if a subject had cost amounting to 50 000 SEK per cycle at baseline, 80 000 during the first cycle and 150 000 during the second cycle, the cumulative cost progression would be equal to 130 000 (80 000-50 000 + 150 000-50 000) at 12 months. The difference between the two response groups may then be interpreted as how much more the cost of a non-responder has increased from baseline at the end

of each cycle. If we would assume that responders would experience the same cognitive decline and cost progression as non-responders if the responders were not treated, then the difference in cost progression would indicate how much we save by treating a responder in each cycle respectively. The difference in cumulative cost progression then shows how much we have saved so far at the end of each cycle.

Why do we control for costs at baseline? What we are interested in here is the consequences on cost of a difference in response to treatment. We divide our sample into two groups, one that has responded to treatment and one that has not. If these groups have differences at baseline, we should control for these since they are not attributable to the treatment, but will probably affect the level of cost also in the subsequent cycles. When controlling for these baseline costs, a positive difference in cost progression will indicate that a positive response to treatment leads to a lower increase in cost.

Since cost data are assumed to be skewed we use a non-parametric bootstrap resampling method with 300 repetitions to calculate the 95 per cent confidence intervals for the difference in cumulative cost progression between the two response groups.

5. Results

5.1. Descriptive statistics

5.1.1. Outcome measures

Table 5.1 shows mean ADAS-cog score over time. Patients progress into worse outcomes over time except for the last six month cycle. This could be due to the most severe patients dropping out.

Table 5.1 Mean ADAS-cog score over time

Month	0	6	12	18	24	30	36
Mean ADAS-cog score	29.77	29.90	30.65	34.21	35.01	36.18	35.12
Standard deviation	11.79	12.59	13.78	16.83	17.92	19.07	19.09
Number of subjects	420	362	318	251	221	169	147

5.1.2. Resource use

Table 5.2 shows resource use in each cycle. The first three rows show the share of patients that sometime during the cycle lived in each form of accommodation, respectively. Thus, the patient does not need to remain in the same form of accommodation the whole cycle to be included here. The final three rows show the resources used per patient in each cycle. All forms of accommodation become more common over time, as patients move out of their ordinary homes. The community care (home help and home delivered meals) and outpatient care (day care) resource use also increases over the 36 months compared to baseline, but there is some fluctuation.

Table 5.2 Resource use by state

Month		0	6	12	18	24	30	36
Temporary nursing home	share of patients	0.0%	0.0%	0.8%	0.3%	1.6%	1.9%	1.8%
Block of service flats	share of patients	0.5%	1.5%	2.8%	5.1%	5.0%	6.2%	7.2%
Nursing home	share of patients	0.0%	0.8%	3.1%	3.7%	5.0%	14.8%	20.5%
Home help	hours per week	0.93	1.44	1.65	1.39	1.94	1.58	1.88
Home delivered meals	meals per week	0.60	0.72	0.66	0.57	0.83	0.75	0.73
Day care	days per week	0.16	0.30	0.37	0.42	0.50	0.55	0.51

5.1.3. Costs of care

Looking at the cost of these resources we see that all cost measures increase over time. Table 5.3 shows the mean cost of each group at each cycle with the mean total cost to the right. The cost of community care peaks at 24 months and this is due to high use of home help and home delivered meals. As more patients move into accommodation with increased service, as seen in the later stages, these community care services are not needed as much as before and costs decrease again. The same way of reasoning can be applied for the drop in costs of outpatient care at 36 months.

Table 5.3 Mean cost over time (SEK, per 6 months cycle (SD))

Cycle	Accommodation	Community care	Outpatient care	Total cost
0	496 (7 306)	6 938 (20 283)	1 733 (8 002)	9 159 (24 331)
6	2 315 (17 415)	10 783 (25 586)	3 318 (10 517)	16 131 (35 839)
12	5 647 (26 551)	12 495 (28 159)	4 321 (11 855)	21 814 (44 551)
18	8 462 (39 042)	11 131 (24 836)	5 153 (12 411)	23 964 (49 366)
24	12 584 (48 861)	15 405 (31 312)	5 988 (13 312)	32 427 (59 716)
30	24 670 (64 290)	13 751 (28 701)	7 339 (13 740)	43 517 (71 030)
36	41 613 (90 088)	15 110 (34 119)	6 526 (13 489)	59 257 (93 105)

Costs are highly skewed. This is shown in the histogram on nonzero costs in Figure 5.1. The logged costs shown in Figure 5.2 are more normally distributed. Note that these distributions exclude a large number of observations with zero cost. Of 2 031 non-missing observations, as many as 1 318 have costs equal to zero.

Figure 5.1 Distribution of nonzero costs

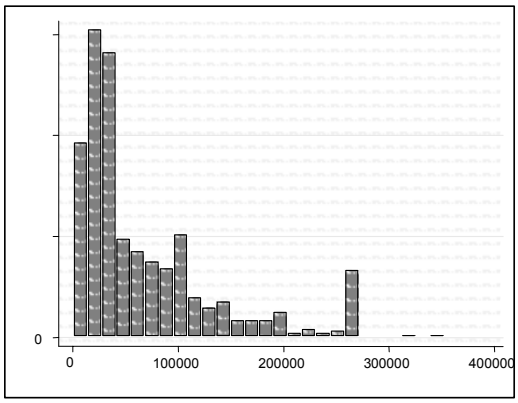
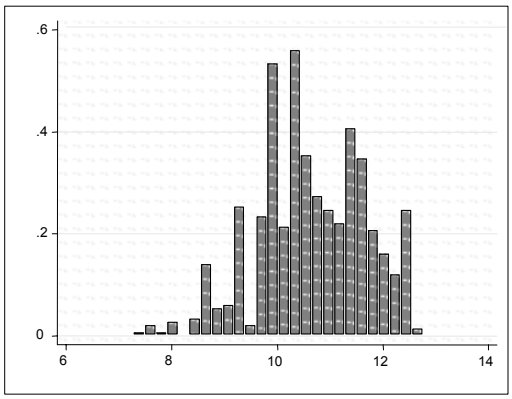


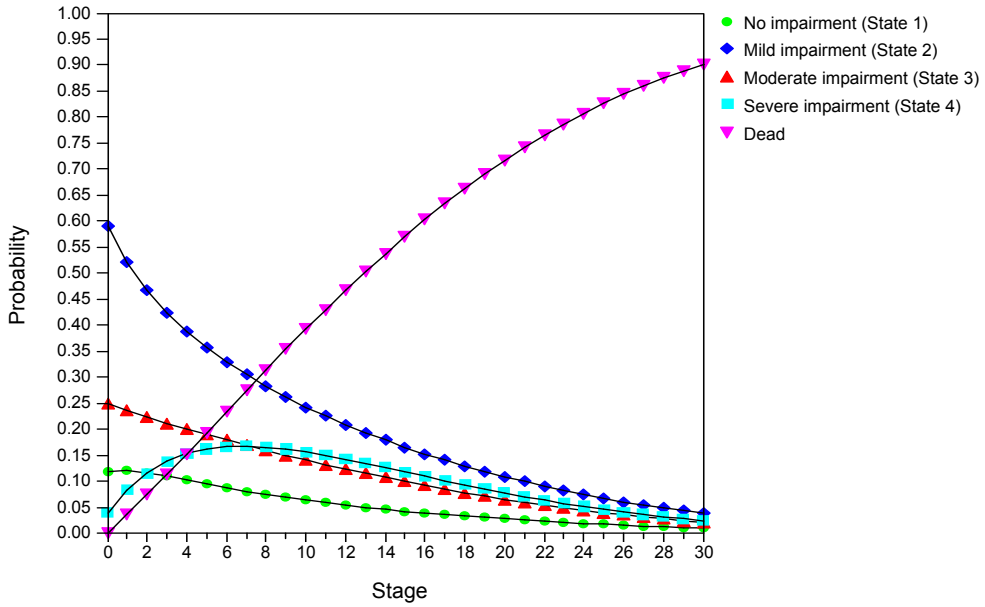
Figure 5.2 Distribution of ln(nonzero costs)



5.2. Markov model

Figure 5.3 shows the distribution of the states over time in our Markov model. After 30 cycles, 90 per cent of our patients have died and the accumulated cost of an average patient is about 311 000 SEK over these 15 years, using a yearly discount rate of 5 per cent. The median survival of the cohort is about 13 stages, i.e. 6.5 years which is consistent with findings in previous studies.

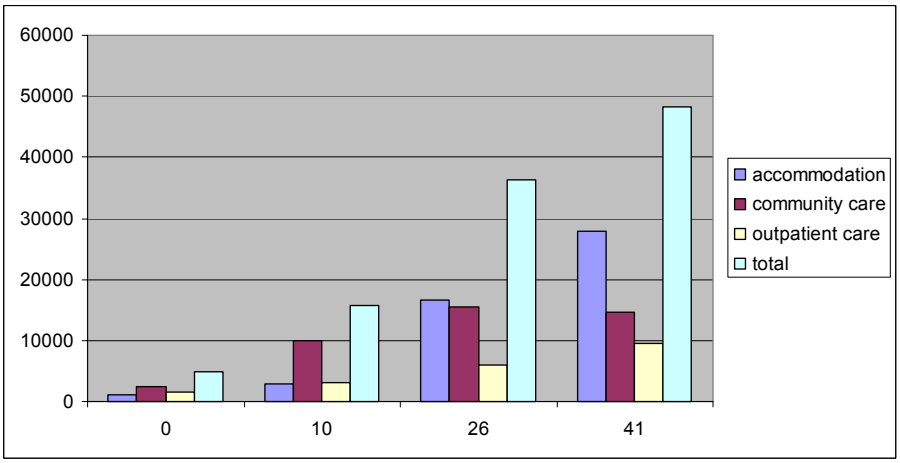
Figure 5.3 Simulated Markov state distribution



5.3. Cost and cognitive function in cross-sectional analysis

Figure 5.4 shows the mean cost, grouped by accommodation, community care, outpatient care and also the total, over ADAS-cog states from pooled observations. All cost measures increase with higher states, except for community care which decreases in state 4. At lower states community care constitutes the highest cost but as cognitive function declines, accommodation cost takes over as the number one cost driver. The way of reasoning is the same as discussed above. In lower states, patients are still able to live at home, however with help from community care services like home help and home delivered meals. As the patient's cognitive function declines, the patient can no longer live at home, but must instead move to the more costly service flat or nursing home where the community services are not needed.

Figure 5.4 Costs over ADAS-cog states from pooled observations, (SEK, per 6 months cycle)



The pooled observations in Figure 5.4 do not control for the effect on costs of explanatory variables other than ADAS-cog states. In order to address this issue we estimate a GLM regression where we

try to explain cost with a wide range of explanatory variables. We assume that costs follow a gamma distribution and we cluster our observations with respect to subjects. We started out with the explanatory variables; ADAS-cog, age, alcohol consumption, debut age, disease duration, education, heredity, sex, and smoking habits. By stepwise removal of non-significant explanatory variables at the 5 per cent level we finally ended up with ADAS-cog, debut age, duration and gender. The final regression is shown in Table 5.4. Our estimates show us that costs tend to increase with cognitive impairment, debut age, gender and disease duration. That is, a patient with a one point higher score on the ADAS-cog measure is estimated to have $\left(e^{0,0410346}-1\right)\cdot 100 = 4.2$ per cent higher costs than an in all other respects identical patient.

Table 5.4 GLM on total cost

	Coefficient	Standard Error	z	p-value	95% Confidence Interval	
ADAS-cog	0.0410346	0.009208	4.46	< 0.001	0.022988	0.059081
debutage	0.0670917	0.019763	3.39	0.001	0.028356	0.105827
duration	0.1736333	0.049443	3.51	< 0.001	0.076728	0.270539
male	-0.583934	0.240122	-2.43	0.015	-1.05456	-0.1133
constant	3.065132	1.668519	1.84	0.066	-0.20511	6.335368

5.4. Cognitive decline and cost progression

So far we have only confirmed findings that are already generally accepted, i.e. the relationship between cognitive function and costs looking at the difference between patients at a given point in time. As we move to study the relationship between cognitive function and costs over time, i.e. cognitive decline and cost progression, we move into a field that has not been studied in equal detail. Now we control for differences between patients and measure the effect of the cognitive decline of each patient on the development of costs for the same patient. Remember our fixed effects model from section 4.4;

$$\ln Cost_{it} = \beta_{1i} + \beta_2 ADAScog_{it} + \beta_3 duration_{it} + u_{it}$$

The estimates, presented in Table 5.5, are significant and indicate that a cognitive decline of one point on the ADAS-cog will induce a change in cost of $\left(e^{0,0438645}-1\right)\cdot 100 = 4.5$ per cent. For instance, using the cost of a typical patient with moderate impairment, this translates into a cost increase slightly above 1 600 SEK for every extra point on the ADAS-cog. The effect of disease duration is estimated to $\left(e^{1.33721}-1\right)\cdot 100 = 280$ per cent yearly, i.e. holding the cognitive function of a patient constant, cost will still increase by almost three times the cost of the previous year. However, we should be careful when interpreting the values of these coefficients. For instance, comparing the estimated change in cost due to disease duration to the cost development over time in section 5.1.3, we see that our fixed effects model overestimates the observed costs in Table 5.3. This is probably due to the skewness of our cost data and the large number of zero costs. Hence, while we conclude that costs tend to increase with time and cognitive decline, we leave the question of how much open.

The relationship between cognitive decline and cost progression is similar to the relationship between cognitive function and costs in the cross-sectional comparison in section 5.3. That is, one extra point on the ADAS-cog outcome score will induce 4.5 and 4.2 per cent higher costs, respectively. This is intuitively satisfying as it suggests that a patient who initially has a lower ADAS-cog outcome score and subsequently also lower costs, would have about the same costs as a patient with an initially higher ADAS-cog outcome score if their cognitive impairment would converge over time.

Table 5.5 Fixed effects model on ln(total cost)

	Coefficient	Standard Error	z	p-value	95% Confidence Interval	
ADAS-cog	0.0438645	.0113454	3.87	< 0.001	.0216094	.0661195
duration	1.33721	.0931419	14.36	< 0.001	1.154503	1.519917
constant	-3.659082	.403279	-9.07	< 0.001	-4.450153	-2.868011

5.5. Treatment response

5.5.1. Descriptive statistics

In this section we present the three defined groups; improved, unchanged and deteriorated. We look at the distribution of subjects over the three groups, the change in cognitive function and costs.

Table 5.6 shows the number of subjects over time in the 6 and 12 months defined groups respectively. Deteriorated patients constitute the largest group in both sets of defined groups, especially at 12 months where they constitute more than half of the classified subjects. There are also more dropouts from the deteriorated patients as a percentage of the baseline group. This will imply some complications; see section 4.2.

Table 5.6 Number of subjects grouped by treatment response

Months	0	6	12	18	24	30	36
Defined groups at 6 months							
Improved	125	125	111	99	88	68	59
Unchanged	81	81	76	56	53	43	41
Deteriorated	151	150	126	97	89	65	54
Unclassified	78	40	42	45	28	34	12
Total	435	396	355	297	258	210	166
Defined groups at 12 months							
Improved	99	96	99	75	79	66	54
Unchanged	57	54	57	51	42	32	29
Deteriorated	158	156	157	118	105	78	70
Unclassified	121	90	42	53	32	34	13
Total	435	396	355	297	258	210	166

Table 5.7 shows change in mean ADAS-cog from baseline in each cycle for 6 and 12 months defined groups respectively. The cognitive decline of the improved is slower than that of the deteriorated patients. The change for unchanged patients lies between those for improved and deteriorated in most cycles. The difference between improved and deteriorated patients is larger for the 12 months than for the 6 months group. This is an indication that the 12 months definition is better at distinguishing between patients that will improve and patients that will deteriorate in the long run. This also implies that 6 months may not be enough time to get a response to treatment.

Table 5.7 Changes in mean ADAS-cog over time compared to baseline (SD)

Months	6	12	18	24	30	36
Defined groups at 6 months						
Improved	-5.7 (1.9)	-2.1 (2.0)	2.4 (2.1)	3.5 (2.2)	3.3 (2.3)	5.6 (2.4)
Unchanged	0 (2.3)	1.3 (2.3)	3.6 (2.5)	4 (2.6)	5.8 (2.8)	3.4 (2.8)
Deteriorated	6.6 (1.7)	4.9 (1.8)	8.5 (2.0)	9.8 (2.0)	11.5 (2.3)	9.6 (2.5)
Defined groups at 12 months						
Improved	-2.9 (1.9)	-5.8 (1.9)	-1 (2.1)	-0.3 (2.1)	-1 (2.2)	-2.1 (2.3)
Unchanged	1.3 (2.5)	0 (2.5)	3.1 (2.6)	4.8 (2.7)	6.3 (3.0)	7 (3.1)
Deteriorated	2.6 (1.7)	7.3 (1.7)	10.4 (1.8)	11.9 (1.9)	13.9 (2.1)	12.8 (2.2)

In Table 5.8 the cost progression, i.e. the cost increase of each cycle compared to baseline, for the three defined groups is shown. The improved and unchanged have lower cost progression than deteriorated patients in all cycles. Furthermore, the unchanged have lower cost progression than improved patients in some cycles. This could be explained by an increase in the activity of improved patients which would result in higher costs, while unchanged patients have less interest in changing lifestyles. Again the difference between improved and deteriorated patients is larger for the 12 months than the 6 months group, which is consistent with the finding of a larger difference in the change in cognitive function.

Table 5.8 Total incremental cost over time compared to baseline, (SEK, per 6 months cycle (SD))

Months	6	12	18	24	30	36
Defined groups at 6 months						
Improved	2 172 (20 574)	13 654 (41 073)	14 695 (43 452)	21 532 (48 214)	37 380 (67 838)	50 813 (89 781)
Unchanged	8 761 (24 658)	10 736 (38 224)	11 480 (42 925)	21 584 (56 026)	26 551 (57 802)	29 339 (72 068)
Deteriorated	10 285 (26 794)	14 674 (35 438)	23 712 (49 166)	35 338 (61 038)	44 636 (72 529)	68 733 (99 139)
Defined groups at 12 months						
Improved	6 266 (29 821)	11 932 (39 093)	9 326 (35 808)	20 305 (53 003)	29 332 (62 635)	21 847 (70 333)
Unchanged	2 420 (15 252)	6 804 (20 599)	11 289 (23 054)	15 326 (42 461)	18 128 (32 656)	36 226 (71 914)
Deteriorated	7 984 (23 044)	15 969 (43 036)	23 615 (55 607)	30 538 (55 649)	47 540 (74 767)	78 617 (103 115)

5.5.2. Predictors of treatment response

We tested a wide range of variables; age, alcohol, debut age, duration, education, head trauma, heredity, hypertension, instable blood pressure, sex, smoke, snus and stroke, possibly predicting treatment response. Since we found in the previous sections that the 12 months definition was better at differentiating between treatment response, we will only make use of the 12 months response in this section. Non significant predictors were removed stepwise, which resulted in only the dummy variable for sex being significant at the 5 per cent level. Table 5.9 shows a logistic model with the significant p-value for the male dummy variable. Our estimate indicates that the chance of a man being a 12 months responder is almost 1.7 times the chance of a woman being a responder.

Table 5.9 Logistic model of predictors of 12 months treatment response

	Odds Ratio	Standard Error	z	p-value	95% Confidence Interval	
male	1.672644	0.3942117	2.18	0.029	1.053879	2.654704

5.5.3. Comparison of Responders and Non-responders

In this section we compare the groups; responders (improved or unchanged patients) and non-responders (deteriorated patients). In Table 5.10 we show the mean cognitive function and costs at baseline for responders and non-responders respectively. Responders have higher initial impairment than non-responders in the 6 months response but lower in the 12 months response. Also, responders have much lower costs than non-responders in the 12 months response, at baseline.

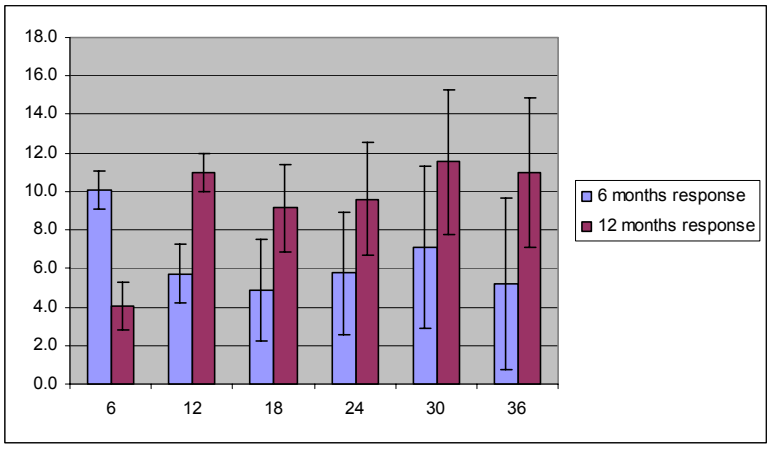
Table 5.10 Cognitive function and costs at baseline grouped by response at 6 and 12 months.

	6 months		12 months	
	Responders	Non-responders	Responders	Non-responders
ADAS-cog	29.6	28.4	27.9	29.3
Costs	7343	7280	4677	10698

The difference in cognitive decline, measured by the ADAS-cog increase from baseline to the end of each cycle, between non-responders and responders is shown in Figure 5.5 for 6 and 12 months response respectively. The 95 percent confidence intervals are included.

All differences are positive and significant, indicating that the decline in cognitive function is larger for non-responders in all cycles. For instance, after 18 months non-responders defined at 12 months have deteriorated 9 points more from baseline than responders, according to this estimate. The differences are lower for response defined at 6 months. Furthermore, the difference remains stable in the 12 months response group, whereas in the 6 months response group half of the difference is gone after 12 months.

Figure 5.5 Difference in cognitive decline between non-responders and responders

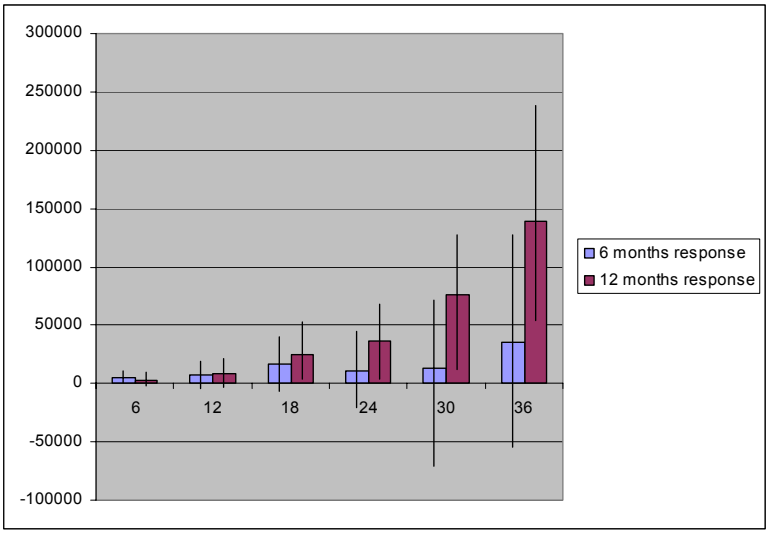


The difference in cumulative cost progression, i.e. the cumulative cost increase in every cycle from baseline, between non-responders and responders is shown in Figure 5.6. The 95 percent confidence intervals calculated by the bootstrap method are also included in the figure.

Differences are positive and significant from 18 months in the 12 months response comparison but in none of the cycles in the 6 months response comparison. After 36 months the cumulative cost progression from baseline for an average non-responder defined at 12 months is about 140 000 SEK higher than the cumulative cost progression for an average responder defined at 12 months. Or, another way of putting it, during the 36 months after baseline an average non-responder would cost 140 000 SEK more than an average responder with similar costs at baseline.

Again, the difference is more pronounced in the 12 months definition. In the subsequent sections we will mainly use the 12 months definition due to its favorable results.

Figure 5.6 Difference in cumulative cost progression between non-responders and responders. (SEK)

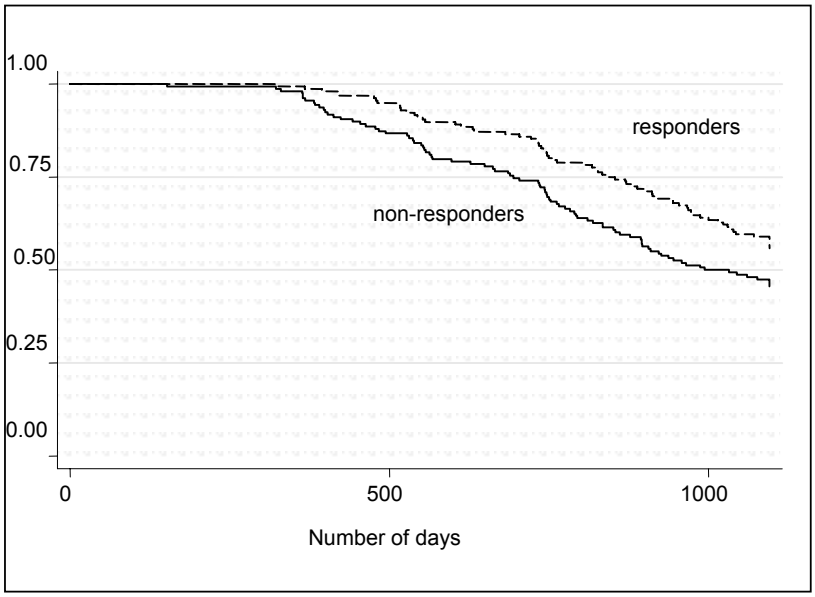


5.6. Drop out

In section 4.2 we discussed the possibility of our results being biased from subjects dropping out of the study. In this section we will present the results from our tests on dropouts.

Figure 5.7 shows the Kaplan-Meier survival estimates of time until dropout differentiating between response to treatment defined at 12 months. Non-responders (the lower line) tend to drop out before responders on average. After 1095 days, the three year follow-up period ends. By then about 44 per cent of the non-responders and about 53 per cent of the responders have remained in the study.

Figure 5.7 Share of 12 months response groups still in study over time.



We use a Cox proportional hazard regression model in which we try to explain who is likely to drop out of the study. In addition to the 12 months treatment response we use ADAS-cog states as covariates. The results, shown in Table 5.11, show that the responder12 ratio is not significantly different from one, i.e. we cannot claim that there is a significantly higher risk of dropping out if you are a non-responder. The p-values for the states are significant, saying that the risk of dropping out increases with increasing cognitive impairment. State 1 is used as a state of reference here, i.e. a non-responder in state 1 has a hazard ratio equal to 1, a non-responder in state 2 has a hazard ratio equal to 1.89 and a responder in state 2 has a hazard ratio equal to 0.73 * 1.89 and so on. These estimates tell us for instance; the risk of an early drop out of a non-responder in state 2 is 1.89 times higher than the risk of a non-responder in state 1.

Table 5.11 Cox-test on risk of early drop out

	Hazard Ratio	Standard Error	z	p-value	95% Confidence Interval	
responder12	0.7279484	0.121024	-1.91	0.056	0.525515	1.00836
state2	1.88907	0.500023	2.4	0.016	1.124453	3.173619
state3	2.038218	0.60263	2.41	0.016	1.141773	3.638492
state4	3.692875	1.434301	3.36	0.001	1.724887	7.906217

In Table 5.12 we remove the states and find that the responder dummy is now significant. These results suggest that non-responders have a significantly higher risk of dropping out but that the states are better at explaining some of this risk. That is, non-responders have a higher cognitive impairment on average and thus dominate the higher states. We conclude that non-responders tend to drop out earlier than responders.

Table 5.12 Cox-test on risk of early drop out removing states

	Hazard Ratio	Standard Error	z	p-value	95% Confidence Interval	
responder12	0.70	0.112896	-2.22	0.026	0.508458	0.958449

6. Sensitivity analysis

6.1. Informal cost

The data used in this study did not include informal cost, even though previous studies have shown that this resource is important when treating patients with AD, see section 2.3. In this section we therefore try to estimate the cost of informal care for each patient and cycle in our sample. This estimate is produced by finding a matching subject, from another study with data on informal cost, for each of our patients at each cycle. For this we have used data form 214 subjects in the Scandinavian Study of Cost and Quality of Life in Alzheimer's disease (SQUAD) which was conducted in the year of 2000 (data on file). We matched our study subjects with respect to the MMSE score (since there were no data on ADAS-cog), disease duration, age and gender.

Imagine a three dimensional coordinate system with MMSE, disease duration and age on each axis. Then we put all our study subjects (i) at each cycle (t), and all subjects of reference form the SQUAD study (j), into the coordinate system, differentiating between men and women. The closest subject of reference (j), according to the distance function below, is then chosen for each study subject (i) at each cycle (t). The cost of informal care is used from this match as an estimate of the informal cost of our study subject.

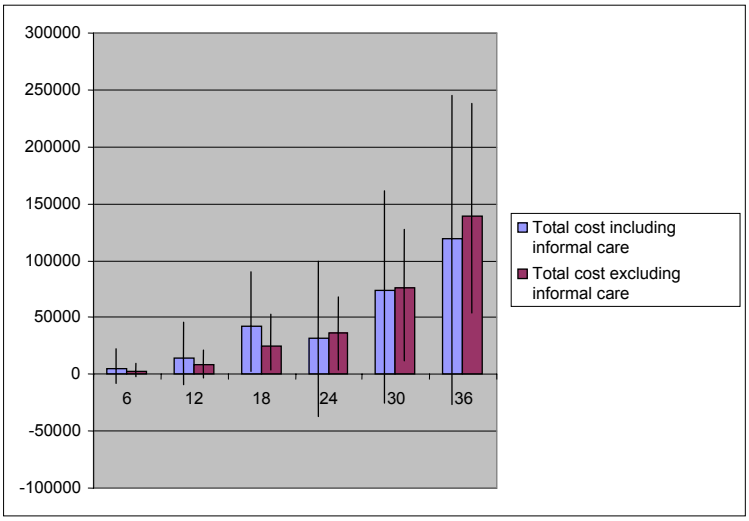
$$Dist_{ijt} = \sqrt{5\left(MMSE_j - MMSE_{it}\right)^2 + 2\left(duration_j - duration_{it}\right)^2 + \left(age_j - age_{it}\right)^2}$$

We believe that the MMSE score is of greater importance than both age and disease duration when finding a match for our study subjects. This we are able to take into account by giving MMSE extra weight in the distance function. The distance function above shows that the difference in MMSE is weighted 5 times greater than the difference in age, while the difference in disease duration is weighted 2 times greater than the difference in age. The differences are squared in order to get positive values. The root of the sum is the distance of interest. These calculations were made for all possible matches between our 435 study subjects at 7 points in time and the 214 subjects of reference, which yields 651 630 calculations. The smallest distance was located for each study subject at each point in time, and the informal cost of the match from the subjects of reference was recorded.

This imputed measure of cost of informal care was added to the total cost of each study subject at each point in time. Then we again calculated the difference in cost progression between non-responders and responders as in section 5.5.3. The results are presented in Figure 6.1, where the light blocks represent the recalculated total cost including the imputed cost of informal care and the dark blocks represent the old total cost without the cost of informal care, i.e. the same blocks as in Figure 5.6. Both refer to the difference in cumulative cost progression between response groups defined at 12 months.

The estimates are similar also when including cost of informal care. Though the confidence intervals are now wider and there are no longer any significant differences between the groups at 24 months and forward.

Figure 6.1 Difference in cumulative cost progression between 12 months non-responders and responders. (SEK)



6.2. Treatment response definition

In order to test the sensitivity to change in the treatment response definition we will use another cut off point between improved, unchanged and deteriorated patients as discussed in section 4.6. A quarter (0.25) of the standard deviation equals 3 points on the ADAS-cog score both ways. If we choose this cut off, all patients that have improved or deteriorated at most 3 points are defined as unchanged. This results in the distribution over groups shown in Table 6.1. Obviously, the increase in tolerance of fluctuation of a subject to be defined as unchanged results in a larger group of patients defined as unchanged.

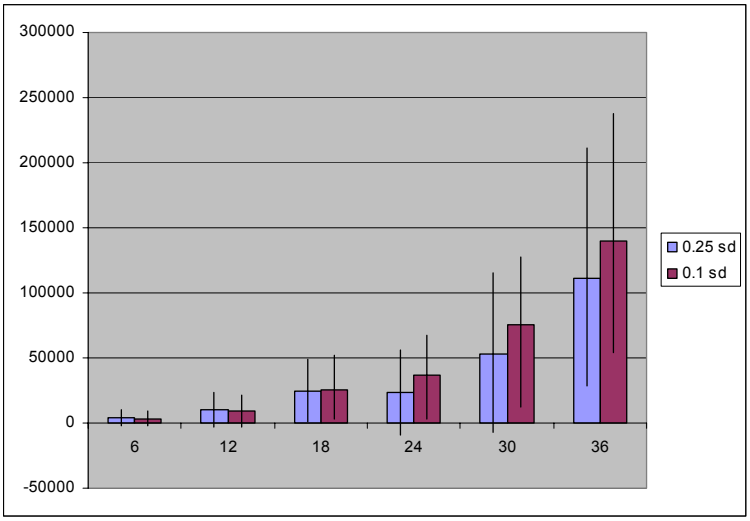
Table 6.1 Number of subjects grouped by treatment response

Months	0	6	12	18	24	30	36
Defined groups at 6 months							
Improved	80	80	74	65	56	47	39
Unchanged	175	175	157	123	115	80	80
Deteriorated	102	101	82	64	59	49	35
Unclassified	78	40	42	45	28	34	12
Total	435	396	355	297	258	210	166
Defined groups at 12 months							
Improved	65	65	65	50	53	43	35
Unchanged	121	115	120	100	87	71	64
Deteriorated	128	126	128	94	86	62	54
Unclassified	121	90	42	53	32	34	13
Total	435	396	355	297	258	210	166

More interestingly, how does this change in the definition affect our results? We move directly to the comparison between non-responders (i.e. deteriorated) and responders (improved or unchanged). Figure 6.2 shows the difference in cumulative cost progression between 12 months non-responders and responders. This time the two different sets of pillars represent the different definitions. The light pillars represent the new definition of response and the dark pillars represent the old one, i.e. the same blocks as in Figure 5.6.

The results are not that different comparing the two definitions, though the new definition results in a smaller difference between the response groups. This is due to some of the previous non-responders with higher costs shifting groups. Also, the differences in the new definition are no longer significant at 24 or 30 months.

Figure 6.2 Difference in cumulative cost progression between 12 months non-responders and responders. (SEK)



7. Discussion

We found that a cognitive decline induces a cost increase controlling for disease duration in our sample of patients on treatment for Alzheimer's disease. About a third of all patients were defined as responders after 12 months of treatment. In this responder group we noted a smaller decline in

cognitive function and also a smaller cost increase compared to non-responders. We did not find any predictors of treatment response apart from men having a greater chance than women of being responders. Furthermore, our findings suggest that 6 months may not be enough to get a response to treatment.

If we assume that responders would deteriorate at the same rate as non-responders on average and also have a similar development of cost if they were not treated, then the interpretation of the difference in cost progression is straight forward. That is, the difference in cumulative cost progression is an estimate of how much is saved by treating a responder. This assumption is intuitively satisfying since a non-response should not alter the path of the disease just as if the subject was not treated.

Since we are not able to predict who will be a responder in advance, we need to treat all patients. From our estimation on the difference in cumulative cost progression we note that treating all patients may still lead to a net saving even though these savings are only attributable to about a third of all patients treated. We use a yearly discount rate of 5 per cent in order to calculate the effect on cost from treatment. This equals 123 000 SEK per responder over three years, or about 44 000 per patient treated. The discounted cost of treatment is about 33 000 SEK per patient over three years, which results in a net saving of 11 000 SEK.

These findings are coherent with the findings of Jönsson (1999a). They used a model in order to estimate the effect on cost from treatment with donepezil, using consequence data from a clinical trial and cost data from an observational study on non-treated subjects. They found that treatment with donepezil lead to a net saving of slightly above 15 000 SEK over a five year period, including the cost of treatment. Our findings confirm this effect on cost from treatment, using cost data from the actual treated patients.

One could criticize this finding by saying that we are not sure what actually made some patients have lower costs than others. Costs are most likely correlated with behavioral differences, as for instance the care for ones hygiene. There might for instance be a bias in our response definition where our “responders” are patients more likely to enact a behavior that will induce lower costs. This would be true even if they were not treated, why then our estimate of potential cost savings from treatment is exaggerated. On the other hand we have already discussed a potential bias in the other direction, namely that of drop outs discussed in section 4.2. Even though all patients would be able to continue on treatment, those who do not benefit, i.e. non-responders, would to a larger extent end treatment by their own request.

Furthermore, it may be feasible to treat the whole population and after follow-up only continue to treat those who have shown a positive response. Then the net savings and the benefit from treatment would be even higher. This is the present recommendation from NICE (National Institute for Health and Clinical Excellence), which issues guidelines on which treatments should be included in the public health care of the United Kingdom (NICE 2001). However, there may be ethical and practical obstacles for such decision rules in practice, since it is hard to distinguish between those who benefit from treatment and those who do not.

The NICE guidelines for cholinesterase inhibitors are currently being revised and preliminary recommendations from this appraisal suggest that all cholinesterase inhibitors should be removed. NICE concludes, after looking at all research available, that the drugs have not been proven to be cost-effective and, hence, are not worth their cost. The final appraisal is expected in July 2006, and the future of these drugs is intensely debated. The first recommendation for further research of the NICE preliminary guideline proposal is that of identifying subgroups of patients for whom the cholinesterase inhibitors are cost-effective (NICE 2005). Attempts on advancements on this issue have been made in this study. We have identified a subgroup of responders in our sample and shown that cognitive decline and cost progression depend on response to treatment, and that treating responders may lead to net savings.

8. Conclusions

With respect to objective 1 we confirm previous findings of a link between cognitive decline and cost progression. Our estimate of the size of the effect on cost from a change in cognitive function should be read with caution, due to the risk of bias from the skewness in data and the large numbers of costs equal to zero. However, we estimate that every one point increase on the ADAS-cog measure induces a cost increase of about 4.5 per cent. This may be translated into about 1 600 SEK for a typical patient with moderate impairment.

With respect to objective 2 we find that the chance of a man being a responder is 1.7 times higher than that of a woman in our study sample. A positive response to treatment, i.e. absence of deterioration over the initial 12 months of treatment, has positive effects on both cognitive decline and cost progression for the entire 36 months period of study. Assuming that these differences between response groups mirror the consequences of treatment, there are enough cost savings from treating responders to cover the cost of treatment of all patients. If we even out these cost savings on all treated patients we have a net saving of 11 000 SEK per patient over the three years of study, including the cost of treating all patients.

In conclusion we confirm previous findings of a link between cognitive decline and cost progression and suggest that treatment of patients with Alzheimer's disease with the cholinesterase inhibitor donepezil may be cost effective due to its beneficial effects on the cognitive function of some of the treated patients. This effect may lead to cost savings large enough to cover the treatment cost of all patients.

9. References

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