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## Long Term Outcome and Prediction Models of Cognition, Activities of Daily Living and Nursing Home Placement in Alzheimer's Disease with Cholinesterase Inhibitor Treatment

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# **Long Term Outcome and Prediction Models of Cognition, Activities of Daily Living and Nursing Home Placement in Alzheimer's Disease with Cholinesterase Inhibitor Treatment**

**Carina Wattmo, BSc, RN**



**LUND UNIVERSITY**  
Faculty of Medicine

DOCTORAL DISSERTATION

With due permission of the Faculty of Medicine at Lund University to be publicly defended on September 16, 2011 at 9:00 am, in the Main Lecture Hall at the Clinical Research Centre (CRC), Entrance 72, Skåne University Hospital, Malmö, Sweden

Faculty opponent

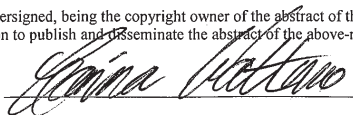
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Abstract  <b>Background</b> Prospective longitudinal studies in Alzheimer's disease (AD) that include cholinesterase inhibitor (ChEI) treatment in routine clinical settings are scarce. The patients vary in severity of the disease, clinical course, rate of progression and response to treatment. Knowledge about the predicted course of the disease, sociodemographic and clinical factors affecting the outcome and the impact of ChEI therapy, could be valuable for clinicians and the social services. This information is also essential for clinical research and for evaluating new therapies.  <b>Aims</b> Study aims are to investigate potential predictors of change, differences in long-term outcome and rates of decline, and the time to nursing home placement for ChEI-treated AD patients in clinical practice.  <b>Material</b> Swedish Alzheimer Treatment Study - outpatients with a clinical dementia diagnosis, and probable or possible AD, were recruited from memory clinics across Sweden. Cognitive, global and Activities of Daily Living (ADL) assessments were performed at the start of ChEI treatment and every 6 months during the following 3 years.  I. 435 donepezil-treated patients II. 843 patients treated with donepezil, rivastigmine or galantamine III. 790 patients treated with donepezil, rivastigmine or galantamine IV. 880 patients treated with donepezil, rivastigmine or galantamine  <b>Results</b> I. Regression models predicted 3-year cognitive outcome in ChEI-treated patients with high accuracy at the group level, but not individual patient responses. II. A higher dose of ChEI, male gender, older age, absence of the APOE ε4 allele or usage of NSAIDs/acetylsalicylic acid were predictors of improved cognitive response to ChEI treatment after 6 months, and of a more positive long-term outcome. III. Lower cognitive status at baseline, older age, higher education level, and solitary living were identified as risk factors for faster decline in functional ability, whereas a higher dose of ChEI, regardless of drug agent, was related to a slower instrumental ADL decline. IV. The rate of functional, but not cognitive, deterioration was a strong risk factor for nursing home placement. The males living alone, patients with a substantial increase in adult day care or those receiving a lower mean dose of ChEI during the study exhibited shorter time to institutionalization.  <b>Conclusions</b> Instrumental ADL ability is an essential measure for predicting longitudinal outcome and nursing home placement in AD. Patients with more cognitive impairment and older individuals exhibited a better response to ChEI therapy, stressing the importance of treating these groups as well. A higher ChEI dose, irrespective of drug agent, could possibly lead to more favorable cognitive and functional outcomes.  Key words Alzheimer's disease, cholinesterase inhibitors, cognition, activities of daily living, nursing home placement, longitudinal studies, disease progression, predictors, statistical models. Classification system and/or index terms (if any)		
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**Long Term Outcome and Prediction Models of  
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Nursing Home Placement in Alzheimer's Disease  
with Cholinesterase Inhibitor Treatment**

**Carina Wattmo, BSc, RN**



**LUND UNIVERSITY**  
Faculty of Medicine

Clinical Memory Research Unit  
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**CLIMATE  
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*Memory is a faculty by which we have an immediate knowledge of things past. The senses give us information of things only as they exist in the present moment; and this information, if it were not preserved by memory, would vanish instantly, and leave us as ignorant as if it had never been...* (Thomas Reid, 1785)



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# List of Original Publications

- I Predicting long-term cognitive outcome with new regression models in donepezil-treated Alzheimer patients in a naturalistic setting.**  
Wattmo C, Hansson O, Wallin Å K, Londos E, Minthon L.  
*Dementia and Geriatric Cognitive Disorders*. 2008; 26(3): 203-11.
- II Predictors of long-term cognitive outcome in Alzheimer's disease.**  
Wattmo C, Wallin Å K, Londos E, Minthon L.  
*Alzheimer's Research & Therapy*. 2011; 3(4): 23
- III Long-term outcome and prediction models of Activities of Daily Living in Alzheimer's disease with cholinesterase inhibitor treatment.**  
Wattmo C, Wallin Å K, Londos E, Minthon L.  
*Alzheimer Disease & Associated Disorders*. 2011; 25(1): 63-72.
- IV Risk factors for nursing home placement in Alzheimer's disease; a longitudinal study of cognition, ADL, service utilization and cholinesterase inhibitor treatment.**  
Wattmo C, Wallin Å K, Londos E, Minthon L.  
*The Gerontologist*. 2011; 51(1): 17-27.

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# List of Abbreviations

A $\beta$	$\beta$ -amyloid
ACh	acetylcholine
AChE	acetylcholinesterase
AD	Alzheimer's disease
ADAS-cog	Alzheimer's Disease Assessment Scale - Cognitive subscale
ADL	Activities of Daily Living
ANOVA	One-way Analysis of Variance
APOE	apolipoprotein E
APP	amyloid precursor protein
BuChE	butyrylcholinesterase
ChEI	cholinesterase inhibitors
CSF	cerebrospinal fluid
EEG	electroencephalography
FDA	Food and Drug Administration
IADL	Instrumental Activities of Daily Living Scale
MMSE	Mini-Mental State Examination
MRI	magnetic resonance imaging
NHP	nursing home placement
NSAIDs	non-steroidal anti-inflammatory drugs
PET	positron emission tomography
PSMS	Physical Self-Maintenance Scale
SATS	Swedish Alzheimer Treatment Study
SD	standard deviation
SPECT	single photon emission computed tomography
SPSS	Statistical Package for Social Sciences

# Abstract

## Background

Prospective longitudinal studies in Alzheimer's disease (AD) that include cholinesterase inhibitor (ChEI) treatment in routine clinical settings are scarce. The patients vary in severity of the disease, clinical course, rate of progression and response to treatment. Knowledge about the predicted course of the disease, sociodemographic and clinical factors affecting the outcome and the impact of ChEI therapy, could be valuable for clinicians and the social services. This information is also essential for clinical research and for evaluating new therapies.

## Aims

Study aims are to investigate potential predictors of change, differences in long-term outcome and rates of decline, and the time to nursing home placement for ChEI-treated AD patients in clinical practice.

## Material

Swedish Alzheimer Treatment Study - outpatients with a clinical dementia diagnosis, and probable or possible AD, were recruited from memory clinics across Sweden. Cognitive, global and Activities of Daily Living (ADL) assessments were performed at the start of ChEI treatment and every 6 months during the following 3 years.

- I. 435 donepezil-treated patients
- II. 843 patients treated with donepezil, rivastigmine or galantamine
- III. 790 patients treated with donepezil, rivastigmine or galantamine
- IV. 880 patients treated with donepezil, rivastigmine or galantamine

## Results

- I. Regression models predicted 3-year cognitive outcome in ChEI-treated patients with high accuracy at the group level, but not individual patient responses.
- II. A higher dose of ChEI, male gender, older age, absence of the APOE  $\epsilon 4$  allele or usage of NSAIDs/acetylsalicylic acid were predictors of improved cognitive response to ChEI treatment after 6 months, and of a more positive long-term outcome.
- III. Lower cognitive status at baseline, older age, higher education level, and solitary living were identified as risk factors for faster decline in functional ability, whereas a higher dose of ChEI, regardless of drug agent, was related to a slower instrumental ADL decline.
- IV. The rate of functional, but not cognitive, deterioration was a strong risk factor for nursing home placement. The males living alone, patients with a substantial increase in adult day care or those receiving a lower mean dose of ChEI during the study exhibited shorter time to institutionalization.

## Conclusions

Instrumental ADL ability is an essential measure for predicting longitudinal outcome and nursing home placement in AD. Patients with more cognitive impairment and older individuals exhibited a better response to ChEI therapy, stressing the importance of treating these groups as well. A higher ChEI dose, irrespective of drug agent, could possibly lead to more favorable cognitive and functional outcomes.

# Summary in Swedish / Populärvetenskaplig sammanfattning på svenska

Långtidsutfall och statistiska modeller för att förutsäga kognitiv och ADL-förmåga, samt tid till särskilt boende – vid behandling av Alzheimers sjukdom med kolinesterashämmare

## **Bakgrund**

Alzheimers sjukdom (AD) är den vanligaste formen av demenssjukdom och svarar för ca 60 % av dessa patienter. Sjukdomen har en smygande debut och den sjukliga processen i hjärnan börjar troligen decennier innan den ger kliniska symptom som försämrat minne och organisationsförmåga, språksvårigheter, problem med tidsuppfattning och orientering. Även förmågan att utföra vardagliga sysslor och aktiviteter (ADL) minskar. Orsaken till AD är inte känd men hög ålder och ärftlighet är vanliga riskfaktorer. Vid AD har hjärnan bl a brist på signalsubstansen acetylcholin och detta har beskrivits som en orsak till kognitiv försämring. Baserat på denna hypotes har acetylcholinesterashämmare (ChEI) införts som behandling för AD. Dessa läkemedel ökar mängden acetylcholin och förbättrar kommunikationen mellan nervcellerna. De ChEIs som för närvarande är godkända i Sverige är donepezil, rivastigmine och galantamine. ChEI har visat måttliga förbättringar i kognition, globalt allmäntillstånd och ADL jämfört med placebo för grupper med varierande svårighetsgrad av AD. Variationen mellan individer är dock stor avseende hur bra de svarar på behandlingen. Placebokon-

trollerade studier får av etiska skäl inte pågå längre än 6 månader. Därför jämförs ofta långtidsstudier med data från tidigare publikationer eller matematiska modeller som kan beräkna utfallet över tid för obehandlade patienter.

## Syfte

Avhandlingen syftar till att öka förståelsen av ChEI i klinisk rutin över lång tid. Förändras sjukdomsförloppet mätt med kognitiva tester och ADL förmåga i jämförelse med obehandlade kohorter? Är det möjligt att förutsäga detta förlopp för grupper av patienter? Finns det sociodemografiska och kliniska faktorer (t ex ålder, utbildning, sjukdomsgrad) som har betydelse för vilka patienter som svarar på behandling, har en bättre långtidsprognos, eller påverkar tiden till särskilt boende (NHP)? Har typ av ChEI eller dos någon betydelse? Det har gjorts mycket få studier av detta på behandlade patienter från en klinisk vardag.

## Metoder

SATS är en öppen, prospektiv, icke randomiserad, multicenter (Malmö huvudcentrum) studie för öppenvårdspatienter som uppfyllde de kliniska diagnoskriterierna för möjlig eller trolig AD. Totalt 1258 individer (varav 63 % kvinnor) har inkluderats från starten 1997 tom stoppdatum mars 2008. Patienterna, de flesta med mild till måttlig AD, behandlades med en av de tre ChEI i klinisk rutin under 3 år. De följdes upp i ett strukturerat program som bl a innefattade kognitiva och ADL-skattningar samt nyttjande av kommunal service vid behandlingsstart, samt var sjätte månad under studiens gång. Val av läkemedel och dosering för den enskilda patienten lämnades helt till läkarens omdöme. De statistiska metoder som främst har använts i manuskripten var avancerade multivariata regressionsmodeller och överlevnadsanalyser.

- I. 435 donepezil behandlade AD patienter, 38 % fullföljde 3 år, manus avser kognition
- II. 843 patienter behandlade med någon av de 3 ChEI, minst 3 kognitiva uppföljningar
- III. 790 patienter behandlade med någon av de 3 ChEI, minst 2 ADL uppföljningar
- IV. 880 patienter behandlade med någon av de 3 ChEI, varav 206 placerades på NHP

## Resultat

- I. Det gick att skapa modeller med hög förklaringsgrad för att förutsäga både 6-månaders behandlingsrespons, och det kognitiva långtidsutfallet för grupper av AD patienter. Kognitivt sämre individer vid behandlingsstart visade bättre svar på ChEI behandling efter 6 månader.
- II. Manligt kön, högre ålder, avsaknad av APOE  $\epsilon$ 4 allel, NSAID / acetylsalicylsyrabehandling eller högre medeldos av ChEI var prediktorer för kognitivt bättre behandlingsrespons efter 6 månader och för bättre långtidsutfall. De patienter som avbröt studien hade betydligt sämre kognitiv och ADL förmåga vid behandlingsstart samt fick en lägre medeldos av ChEI, jämfört med dem som fullföljde 3 år. Övriga variabler skilde sig inte mellan de individer som avbröt och de som slutförde studien.
- III. Snabbare försämring av ADL funktion uppvisade ett samband med lägre kognitiv förmåga vid behandlingsstart, högre ålder, bättre utbildningsnivå och ensamboende. De basala förmågorna "personlig hygien" och "tvättning" försämrades först medan "födointag" och "toalettbesök" var bäst bevarade efter 3 år. De individer som fick lägre medeldos av ChEI oavsett preparat, försämrades hastigare i instrumentella ADL funktioner (IADL). Ingen signifikant skillnad i ADL utfall sågs vid jämförelse av de 3 ChEI.
- IV. Försämringshastigheten i IADL, men inte i kognitiva funktioner påverkade tiden till NHP. Gruppen ensamboende män visade nästan 4 gånger högre risk att flytta till NHP jämfört med män som bodde med anhörig. De patienter som fick högre medeldos av ChEI, oberoende av läkemedel, visade en signifikant längre tid till NHP.

## Slutsatser

Sammanfattningsvis visades att statistiska modeller kan förutsäga kognitivt och funktionellt långtidsutfall med hög noggrannhet på gruppnivå, men inte för enskilda AD patienter. IADL förmågan har större betydelse för att förutsäga långtidsutfall och tid till NHP än kognitiva tester. Därför bör funktionella utvärderingar anses lika viktiga som kognitiva i framtida kliniska prövningar. Studier inkluderande patientgrupper med skilda sammansättningar av sociodemografiska och kliniska faktorer kan ha olika behandlingsrespons och långtidsresultat. Detta kan vara en förklaring till de heterogena utfall som observerats i olika studier. De patienter som hade en sämre kognitiv förmåga vid behandlingsstart visade bättre behandlingsrespons efter 6 månader, vilket poängterar vikten av att inte utesluta denna grupp från behandling. Vissa individer tolererade en högre dos av ChEI och hos dessa observerades en långsammare försämring av både



kognition och IADL, samt längre tid till NHP. Vilket läkemedel (donepezil, rivastigmine eller galantamine) som användes hade ingen betydelse för kortsiktig behandlingsrespons eller långtidsutfall över 3 år. Långsiktiga skyddande faktorer, som den möjliga effekten av NSAIDs kan ta år att utveckla. Därför är resultaten från denna avhandling där AD patienter i klinisk rutin får långtidsbehandling med ChEI viktig. Det är önskvärt att i framtiden fortsätta studera behandlingsrespons och longitudinellt utfall med avseende på patientgruppens demografiska och kliniska sammansättning.

# Introduction

## Historical perspective

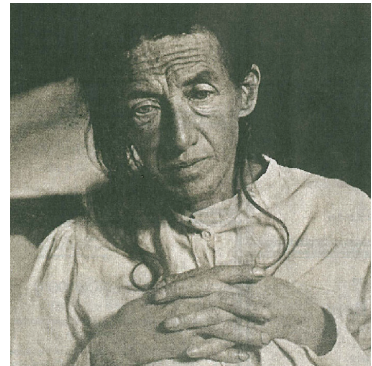
Alois Alzheimer was born in 1864 in Markbreit, Bavaria, Germany. He studied medicine in Berlin, Aschaffenburg, Tübingen and finally Würzburg, where he graduated with a medical degree in 1888. He began to work in the Städtische Anstalt für Irre und Epileptische (Municipal Asylum for the Insane and Epileptics) in Frankfurt am Main. Doctor Alzheimer became interested in research on the cortex of the human brain, and commenced education in psychiatry and neuropathology. In 1901, Dr. Alzheimer observed a 51-year-old patient named Auguste Deter, who early in her illness had told him, “Ich habe mich verloren (I have lost myself)”. Auguste had been a normal, healthy woman, but developed progressive memory lapses, disorientation, aphasia, strange behavioral symptoms and she had grown unable to care for herself [1].

In April 1906, Auguste died at the age of 55 and Dr. Alzheimer sent her patient records and brain to the Psychiatric Clinic in Munich where he was working in Dr. Emil Kraepelin’s laboratory. Post-mortem examination showed various abnormalities of the brain. The cerebral cortex was thinner than normal and senile plaques, previously only encountered in elderly people, had accumulated in the ordinarily empty spaces between



*Alzheimer*

Alois Alzheimer



Auguste Deter

the nerve cells. Tangles of string-like substances, now known to be one of the hallmarks of AD, were found in the brain. Having had access to a new nerve staining technique developed by Dr. Franz Nissl, a friend and colleague at the asylum, Alzheimer was able to identify these nerve tangles that had never previously been described. In 1904, he received his qualification as a university professor. A lecture, “*On a Peculiar, Severe Disease Process of the Cerebral Cortex*”, given in November 1906, made Dr. Alzheimer famous. That was the first time the pathology and the clinical symptoms of presenile dementia were presented together [1]. His observations of Auguste were published in 1907 [2]. Kraepelin first named the disease after Alois Alzheimer in the eighth edition of his book, “*Psychiatrie*”, issued in July, 1910. By 1911, his description of AD was being used by European physicians to diagnose patients in the US. Doctor Alzheimer died of heart failure after a time of illness in 1915, at the age of 51, in Breslau (now Wroclaw, Poland). He is buried in the Hauptfriedhof (main cemetery) in Frankfurt am Main, Germany.

The original microscope preparations on which Dr. Alzheimer based his description of the disease were made available through extremely fortunate circumstances, as these were rediscovered in 1997 in the Institute of Neuropathology, University of Munich. Thus, his findings could be reevaluated [3].

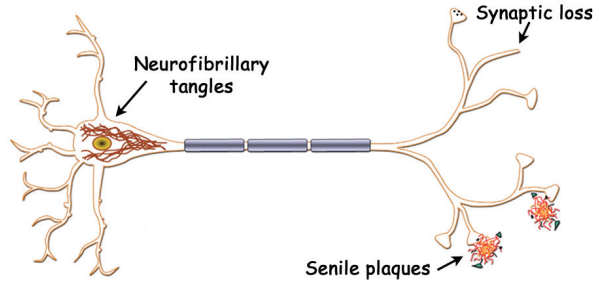
Doctor Kraepelin’s opinion that AD was equivalent to presenile disease with an onset before the age of 65 dominated the literature for many years. Dementia occurring later in life, “senile dementia”, was considered a natural part of the aging process or caused by arteriosclerosis. “*Senile*” means old, and dementia is derived from the Latin root “*de*” (out of) and “*mens*” (mind). In the late 1960s, Alzheimer pathology was also identified in senile dementia, and, meanwhile, arteriosclerosis was rejected as the major cause of dementia [4]. Furthermore, the focal phenomena (i.e., specific cognitive symptoms thought to originate from damage to certain cortical regions) of apraxia, aphasia, and agnosia were commonly observed in the senile cases [5]. The diagnosis of AD is now used for both early and late onset cases.

## Alzheimer’s disease (AD)

Alzheimer’s disease (AD) is the most common form of dementia among older people, accounting for 50% to 70% of the cases [6, 7]. Dementia is a broader term than AD and refers to any acquired brain syndrome resulting in deteriorating mental functions, severe enough to impair the individual’s normal daily life situation [8]. An insidious, progressive, neurodegenerative disease, the pathogenic process in AD starts probably decades before the clinical onset of symptoms [9, 10].

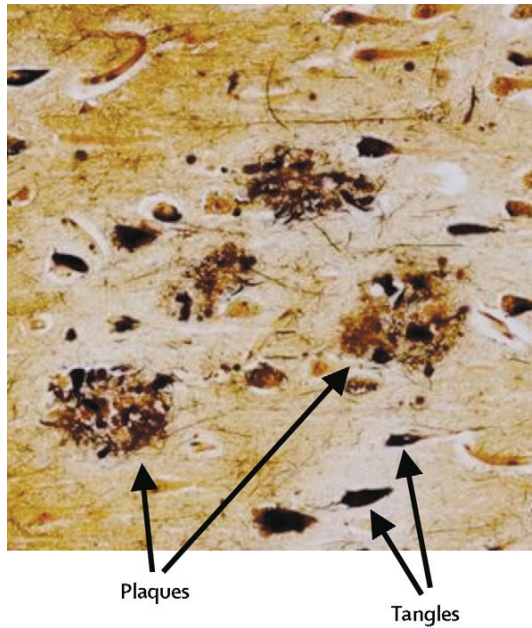
## Pathogenesis

### *Neuropathological changes*

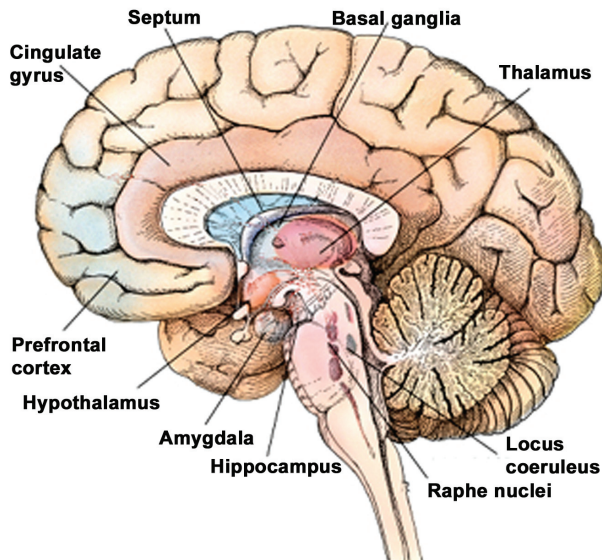


**Figure 1.** A neuron illustrating the major hallmarks of Alzheimer's disease, extra-cellular senile plaques containing deposits of  $\beta$ -amyloid, intra-cellular neurofibrillary tangles composed of abnormal hyperphosphorylated tau protein, and synaptic loss. *Modification of drawing by Kaj Blennow. With permission.*

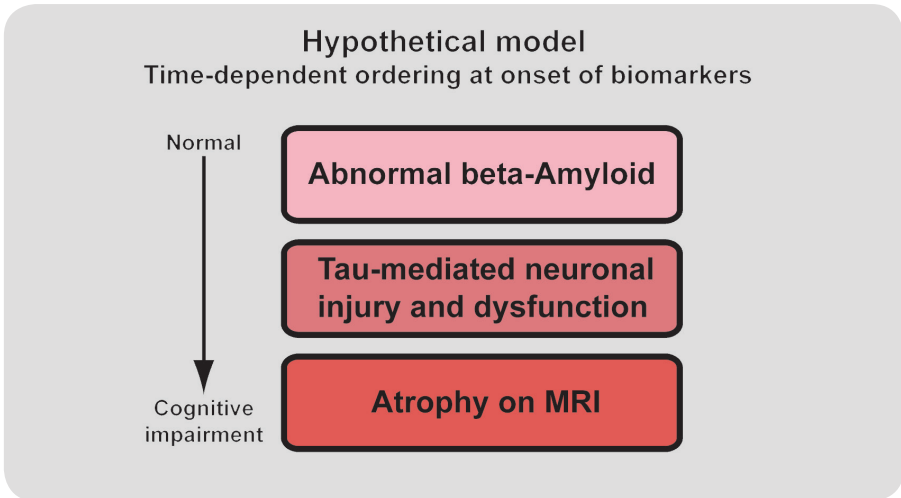
The pathogenic process that causes AD has not been fully explained, but is neuropathologically characterized by the major hallmarks, senile (neuritic) plaques, neurofibrillary tangles and synaptic loss (Figure 1). When present in sufficient number in the limbic and association cortices, those classical lesions allow a post-mortem diagnosis of "definite AD" [11]. Neuritic plaques are spherical, multi-cellular lesions containing extra-cellular deposits of mainly  $A\beta$  protein 1-42 [12]. Neurofibrillary tangles, primarily consisting of abnormally hyperphosphorylated tau protein [13], are intraneuronal cytoplasmic lesions causing disassembly of microtubules and impaired axonal transport, which generate poor neuronal and synaptic function, resulting in neuronal death [14] (Figure 2). Generally, tangles begin to develop in the entorhinal cortex, increase with the progression of the disease, accumulate in the hippocampus and amygdala and later in neocortical association areas [11, 15]. Figure 3 illustrates the anatomy of the brain. As more and more plaques and tangles form in the brain areas, a reduced function of several neurotransmitter systems occur [11]. In 1968, Blessed et al. [4] found a highly significant association between mean plaque counts in the cerebral cortex and dementia scores in psychological tests. More recent papers propose a stronger relation between cognitive severity and tangle load, than plaque formation [16]. Correlations between neuropathological changes, and global or functional performance were also reported [17]. A model that relates the stage of AD to biomarkers has been suggested, in which abnormal  $A\beta$  levels are observed first, followed by neurodegenerative biomarkers and cognitive symptoms [10] (Figure 4).



**Figure 2.** Senile plaques and neurofibrillary tangles in the cerebral cortex in Alzheimer's disease. The plaques contain  $\beta$ -amyloid, and the tangles consist mostly of hyperphosphorylated tau. *Reproduced with permission of Kaj Blennow and The Lancet Publishing Group.*



**Figure 3.** The anatomy of the brain. The hippocampus is essential in the memory process.



**Figure 4.** A hypothetical relationship between the developments of pathologies in Alzheimer’s disease. The pathogenic process starts probably decades before the clinical onset of symptoms. According to this theory by Jack et al. [10], abnormal  $\beta$ -amyloid levels are an early event in the pathogenesis, followed by phosphorylation of tau, which leads to neuronal dysfunction. Structural magnetic resonance imaging (MRI) measures of atrophy exhibit highly significant correlations with observed cognitive impairment.

However,  $A\beta$  deposits in quantities large enough to warrant a neuropathological diagnosis of AD have been described in 33% of the brains of aged, cognitively normal individuals [18]. Another study reported that only 57% of the participants without brain infarcts, but who showed sufficient Alzheimer-type pathology to receive a “definite AD” diagnosis, were demented [19]. This implies that the correspondence between clinical symptoms and the underlying pathology is not always consistent.

Whitehouse et al. [20] showed that neurons of the nucleus basalis of Meynert in the basal forebrain, which provides the major source of cholinergic input to the cerebral cortex, undergo selective degeneration in AD patients, causing the loss of a transmitter-specific neuronal population. Atrophy of the substantia innominata that reflects degeneration in the nucleus basalis of Meynert demonstrated a significant negative correlation with Mini-Mental State Examination (MMSE) [21] scores in AD patients [22]. The basal forebrain cholinergic pathways, predominantly those projecting to the hippocampus, are essential in the memory process [23]. Moreover, as AD progresses, the cells in the hippocampus start to degenerate and the atrophy is observed in the cerebral cortex, predominantly in the temporal and parietal regions bilaterally. Eventually, the brain tissue is reduced and the sulci and ventricles are enlarged [15].

## *Hypotheses of AD*

According to the prevalent *amyloid cascade hypothesis*, an imbalance between the production and clearance of A $\beta$  in the brain is the initiating event in AD pathogenesis. A $\beta$  accumulation and oligomerisation impair the synaptic function, as well as aggravate the inflammatory and oxidative stress caused by the aggregated and deposited A $\beta$ . These processes damage neuronal and synaptic function and generate neurotransmitter deficits, ultimately leading to neuronal degeneration [24, 25]. Another theory is that pathological *hyperphosphorylation of the protein tau* is critical to AD pathogenesis [13]. Phosphorylation leads to sequestration of tau and other proteins, destabilization of the axons, resulting in neuronal death [26]. More recently, the role of *inflammatory mechanisms* in the development of AD has gained much interest. Activated microglia and release of potentially neurotoxic substances such as cytokine were found around the amyloid plaques in human AD brains. Signs of altered immune response in AD patients have also been reported. Neuroinflammation is still considered to be a consequence in the amyloid hypothesis (for review see [27]). The inflammation theory is supported by the finding of lower AD prevalence among individuals on long-term NSAID therapy [28, 29]. Moreover, associations between AD pathogenesis and *cerebrovascular disease* have been observed. Current evidence suggests a decreased vascular density in aging and AD, and that cerebrovascular dysfunction precedes and accompanies cognitive impairment and neurodegeneration. Hypoperfusion may occur early in AD, inducing white matter lesions and correlating with dementia (for review see [30]). Additionally, *other hypotheses* for the cause of AD have been proposed, including: synaptic failure, mitochondrial dysfunction and oxidative stress (for review see [31]).

## **Symptoms**

People with AD exhibit different symptoms during the course of the disease. In general, it starts with mild changes in memory, communication patterns (dysphasia), or behavior. Common symptoms in the *mild stage* include misplacing important objects, and forgetting text that has just been read or not being able to name common objects. Functional difficulties in employment or social settings may be observed, and depression might be an early symptom in AD. At this stage the patient is often aware of a problem. Cognitive decline becomes more evident and other symptoms are apparent, including impaired mathematical ability (dyscalculia), moodiness, and social withdrawal. Executive ability, observed, for example, in planning and organizing a dinner, is diminished. Also, the ability to carry out complex Instrumental Activities of Daily Living (IADL) [32] tasks, such as, managing the finances and appropriate self-administration of medication.

Later, in the *moderate stage* of AD, difficulties in executing motor activities (dyspraxia) might occur and some assistance with daily tasks is required. Problems with memory and thinking become quite noticeable, including remembering key details about one's life history. Such symptoms as impaired ability to recognize objects (dysgnosia), disorientation to time and/or place, and decreased judgment and skills in regard to personal care are common. Moreover, as the disease progresses it, characteristically, is accompanied by personality and behavior changes, such as, agitation, wandering, or psychotic symptoms e.g. hallucinations and paranoid reactions. Assistance is required for most daily activities including personal hygiene and possible incontinence. This is often the most difficult stage for caregivers.

In the *final stage*, it is usually no longer possible to respond to the surrounding environment. The patient may be able to speak words or short phrases, but communication is extremely limited. Basic functions begin to shut down, such as motor coordination and the ability to swallow [33, 34].

## Diagnostic criteria

### *DSM-IV*

Modern diagnostic criteria for AD recognize that the disease is both a clinical and pathological entity. The Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) [35], outlines a detailed set of criteria for the diagnosis of AD. By definition, all patients with AD must have dementia, that is, an objective progressive loss of memory, and at least one other cognitive deficit such as problems with executive functioning, dysphasia, dyspraxia or dysgnosia. The deficits should be so severe as to interfere with the individual's working capacity, social relationships or daily function. The deficits must also represent a significant decline from the person's previous level of functioning, and consciousness should not be clouded. The clinical diagnosis of AD also requires a gradual onset, a progressive decline of symptoms, and other diagnoses that could account for the patient's clinical condition must be ruled-out, e.g., depression, cerebrovascular and thyroid diseases, and alcoholism.

Among proposed revisions for *DSM-V*, which is expected to be published in 2013, is replacement of the term "dementia" by "major neurocognitive disorder", a diagnosis that stands apart from its milder form, "mild neurocognitive disorder", made on the basis of evidence of minor objective cognitive decline from a previous level of performance, where the cognitive deficits would be considered insufficient to interfere with independence in Activities of Daily Living (ADL) [36].



### *NINCDS-ADRDA*

One of the more accurate and widely accepted definitions of dementia was produced by a work group of physicians and neuroscientists, the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association [37]. Their criteria are proposed to serve as a guide for the diagnosis of probable, possible, and definite AD. Clinical criteria for the diagnosis of AD include insidious onset and progressive impairment of memory and other cognitive functions (language, perceptual skills, constructive abilities, orientation, problem solving and functional abilities), on the basis of comparison with the patient's previous level of function. Neuropsychological tests provide confirmatory evidence of the diagnosis of dementia and help to assess the course and response to therapy. Brain scan, electroencephalography (EEG) or other laboratory instruments are important primarily in identifying other possible causes of dementia that must be excluded before the diagnosis of AD may be made.

*Definite AD* – A definite diagnosis can only be obtained post-mortem when histopathologic evidence obtained from a patient who had met the criteria for probable AD, confirms the diagnosis.

*Probable AD* – Dementia, established on the bases of clinical and neuropsychological examination information, includes progressing cognitive impairments in two or more of the forementioned areas of cognitive function. Deterioration of ADL ability is not required. The onset of the symptoms has to be between the ages of 40 and 90 years; consciousness must not be clouded; and, finally, there must be an absence of systemic or other brain diseases capable of developing a dementia syndrome. Supportive and unlikely features are also stated in the criteria.

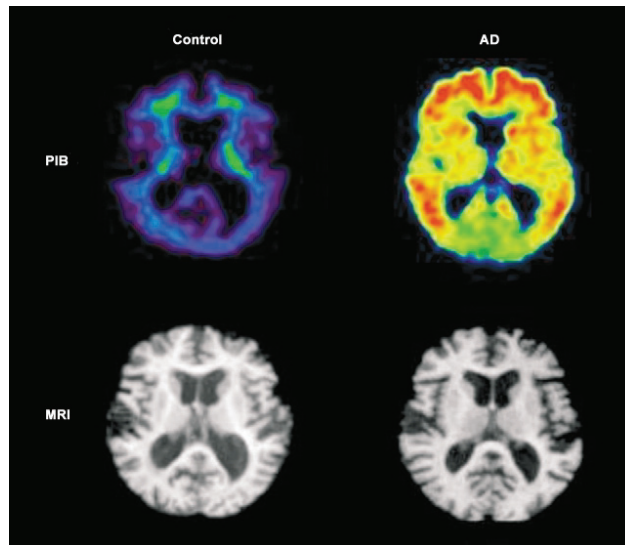
*Possible AD* – defined as a dementia syndrome with evidence of variation in onset, in presentation or clinical course; and absent other co-morbid diseases capable of producing dementia *or* another systemic or brain disorder sufficient to cause dementia but not considered to be a cause of the Alzheimer-type dementia.

These NINCDS-ADRDA criteria have shown good reliability and validity [38], and demonstrated a diagnostic accuracy of 66%–92% confirmed in neuropathological investigations [39-41]. The choice of neuropathological staging system could affect the assessment of AD pathology, and thus the final diagnosis [42].

After 27 years, revised clinical criteria for AD were published in April 2011 [43]. A new criterion "Probable AD dementia with increased level of certainty" was introduced. Evidence of progressive cognitive decline reported on follow-up assessments, when considered together with the old criteria, increases the likelihood that the condition is an ongoing pathologic process. This underlines the importance of our study because regular, well-structured clinical evaluations after the diagnosis were, indeed, performed on the patients included in this thesis.

### *The Dubois criteria*

According to the growth of scientific knowledge and technical skills, an international group of experts has suggested new revised criteria for the diagnosis of AD. These criteria are also based on early and significant episodic memory impairment, but at least one or more abnormal biomarker must be present from among the following: structural neuroimaging with magnetic resonance imaging (MRI), molecular neuroimaging with positron emission tomography (PET) (Figure 5) and cerebrospinal fluid (CSF) analysis of A $\beta$  or tau proteins. Many new drugs that are in development are aimed at changing the disease pathogenesis, such as A $\beta$  immunotherapy, and  $\gamma$ - or  $\beta$ -secretase inhibitors. It would be highly desirable to identify AD before irreversible pathological injuries aggravate the possibility of effective treatment. The proposed criteria should enable an earlier and more specific AD diagnosis [44, 45], but have been criticized for lack of accuracy in a naturalistic memory clinic sample [46].



**Figure 5.** Positron emission tomography (PET) images using Pittsburgh Compound-B (PIB) and magnetic resonance imaging (MRI) images, from a cognitively normal individual (left), and a patient with Alzheimer's disease (right). *Reproduced with permission of Kaj Blennow and The Lancet Publishing Group.*

### *National Institute on Aging – Alzheimer's Association criteria*

The clinical – pathological relationship in AD is not always consistent. The AD pathology may be present during a presymptomatic stage that may be absent clinically measurable symptoms of memory or cognitive impairment. Therefore, in the new revised diagnostic criteria, a distinction is made between pathological processes and clinically observable symptoms. The essential differences between

the new criteria and those published in 1984 are: 1) Incorporation of biomarkers of the underlying disease manifestations, such as A $\beta$  accumulation (decreased level of CSF A $\beta$ <sub>42</sub>, and abnormal tracer retention on amyloid PET imaging) and neuronal degeneration (increased levels of CSF T-tau and P-tau, and medial temporal lobe atrophy on structural MRI); 2) Formalization of three different stages of AD (asymptomatic preclinical phase, symptomatic predementia MCI phase and dementia phase) and the role of biomarkers in these stages [47].

## Implications of AD

### Epidemiology

In 2005, the total number of individuals with dementia in Sweden was approximately 142,000 people [48]. Ferri et al. [49] estimated that more than 24 million people worldwide had dementia in 2001, increasing by 4.6 million new cases every year. This implies that the number of affected people is expected to double every 20 years to 42 million by 2020 and 81 million by 2040, presuming no changes in mortality, and no effective prevention strategies or curative treatments. The incidence of AD displays an exponential increase up to the age of 90 years, with no sign of leveling off. Generally, no gender differences were found regarding incidence, but females tended to have a higher incidence in very old ages [50]. The prevalence of dementia is below 1% in individuals aged 60–64 years, and exhibits also almost an exponential increase with age, so that in people 85 years or older the prevalence is 24% to 33% in the Western countries. However, most individuals (60%) with dementia are estimated to live in the developing countries [49].

### Informal and formal care

Family caregivers experience substantial psychological distress, practical difficulties and financial dissatisfaction, as well as negative social reactions [51]. In 2008, the cost of informal care was estimated as 55% of the total cost of dementia disorders in Europe, ranging from 33% in northern Europe where institutional care is prominent, to 80% in southern Europe where the obligation to provide care within the family still exists [52] and institutionalization of elderly people is very low. Of those individuals with dementia in Sweden, 45% are estimated to live in special accommodations [48].

### Cost of dementia

AD imposes an immense economic burden to the society. The total worldwide societal cost of dementia, was estimated to be 422 billion USD (~323 billion

EUR, ~3,065 billion SEK) in 2009, 77% of these costs incurred in the developed countries [53]. A study from the UK demonstrated that the direct costs of AD were substantially greater than those of stroke, heart disease and cancer; noting however, that research expenditures on AD were disproportionately low compared with the other diseases [54]. In 2008, the total costs of dementia disorders in Europe were estimated to be 177 billion EUR (~1,677 billion SEK) [52], and in Sweden (2005) 50 billion SEK (~5.3 billion EUR) [48]. The annual cost in 2008 per person with dementia in Europe, on average, was approximately 17,500 EUR (~166,000 SEK), while the cost was remarkably higher, 36,000 EUR (~341,000 SEK), in Sweden and the other northern European countries [52]. Community-based services and nursing homes account for 85% of these costs in Sweden [48].

## Risk factors for AD

Epidemiological studies have led to the identification of several risk factors for sporadic AD. Aging is considered to be the primary risk factor [55, 56], and when age is 90 years or older approximately 40%-50% of those persons remaining alive will have dementia [57, 58]. Family history of dementia is associated with an increased risk of AD [59, 60]; a large twin study has reported that the extent of heritability for AD is almost 80% and does not differ by gender [61].

The  $\epsilon 4$  allele of the apolipoprotein E (APOE) genotype has been described as an important genetic risk factor for AD as well as for an earlier onset of the disease [62, 63]. The Rotterdam study showed that a single APOE  $\epsilon 4$  allele increases the risk of AD almost two-fold, whereas the homozygous configuration causes more than a six-fold increase in risk [64]. The most evident hypothesis is that the APOE allele may be involved in the production, distribution, or removal of  $A\beta$  [65]. In the familial forms of AD, the autosomal dominant inherited disease is associated with mutations of the genes encoding amyloid precursor protein (APP), presenilin 1 (PS-1), or PS-2, resulting in the overproduction of  $A\beta$  protein. However, these mutations with clinical onset sometimes as early as the third decade of life, account for only a small proportion of all patients with AD [65, 66].

Risk factors associated with vascular disease such as hyperlipidemia, hypertension, atherosclerosis, coronary heart disease, smoking, obesity, and diabetes, have been identified as potential antecedents to AD [67, 68]. The relation between AD and the cardiovascular factors may be strongest when they are present during mid-life, years before the onset of dementia [69, 70]. Whether they are true etiological risk factors remains uncertain, as cerebrovascular diseases are frequently concomitant illnesses among the elderly with AD [71]. Moreover, aging and vascular pathology might add to the AD pathology of tangles and plaques,

thus acting synergistically to cause neuronal degeneration and exceeding the threshold for dementia [68].

A decreased cognitive reserve, including smaller head size [72], poor linguistic ability during early life [73], lower educational level and occupational accomplishment [7, 74, 75], less social, mental and physical activity [76, 77], has been related to an increased risk of AD. The brain with a larger cognitive reserve contains more neurons and synaptic connections, providing a greater reserve against cognitive deterioration [78]. Some studies have shown that head trauma could be a risk factor for AD [79, 80]. A brain injury might cause neuronal degeneration in addition to AD pathology, thus reducing the reserve capacity.

A growing number of epidemiological studies suggest that there is a strong link between nutrition and AD, in which saturated fats and high serum cholesterol are associated with an increased risk of the disease [81, 82]. Dietary factors, such as regular consumption of fish and of omega-3 rich oils, intake of the antioxidants vitamin C and especially E, and moderate consumption of alcohol, particularly wine, may be related to a lower risk of AD (for reviews see [83, 84]). The studies investigating the homocysteine-related vitamins B12, B6, and folate on cognitive decline and AD have reported inconsistent results [84].

Furthermore, medications usage, that is, NSAIDs, estrogen by postmenopausal women and lipid-lowering agents has been associated with a decreased risk of AD in some studies (for review see [71]). Regular leisure activities, including physical, mental and social, are reported to reduce the risk, or postpone the onset, of dementia and AD [85, 86].

## Predictors of decline in AD

The progression rate of AD varies depending on numerous factors, such as considerable heterogeneity in the disease and its manifestations, concomitant somatic conditions and medications, as well as day-to-day level of patient ability. Statistical models that take into consideration individual differences in the assessments over time are of great importance, although more challenging to develop [87]. A vast number of earlier studies have examined various potential predictors of decline, and shown contradictory findings regarding the impact of demographic or clinical background variables on the rates of change in AD [88]. For example, disease severity, gender, age, age at onset, level of education and APOE genotype have all been examined as possible predictors and none has consistently been shown to affect the rate of cognitive decline (Appendix, Table A1-6).

Explanations of the divergent results would have to account for differences among studies in sample size, diagnostic criteria, selection and characteristics of subjects, test instruments, missing data, follow-up intervals and various statisti-

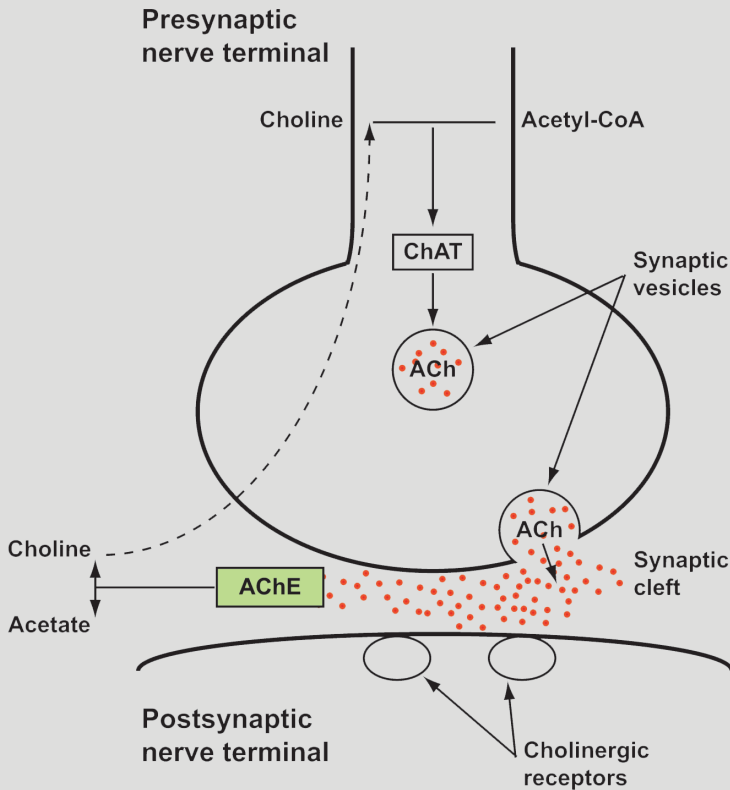
cal methods. Moreover, the demographic and clinical characteristics that were collected and made available for analyses in a particular study, the adjustment of and interaction between the variables in multivariate analyses, as well as the way each predictor is defined or grouped might affect the result [88]. A more stable pattern of predictor variables indicating decline appears among larger cohorts, for example, those with 100 or more participants [89]. The rates of change related to short intervals between tests are highly variable, while longer test intervals show fluctuations that approach the actual variation of disease progression [87, 90].

## The cholinergic hypothesis and treatment in AD

### Background

A systematic biochemical examination of the brains of AD patients began about 1970. The hypothesis was that a clearly defined neurochemical defect would be identified, like dopamine in Parkinson's disease, providing the basis for the development of pharmaceutical interventions [91]. In 1976, Bowen et al [92], reported finding a marked reduction of choline acetyltransferase (ChAT) in the cerebral cortex in patients with senile dementia compared with controls. This is the enzyme responsible for the synthesis of acetylcholine (ACh). Two years later, Perry et al. [93] observed that the cholinergic deficit correlated significantly with the amount of senile plaque formation and neurofibrillary tangles, and with the degree of intellectual impairment. Following these discoveries, impaired choline uptake and transport [94], and ACh release [95] were seen in AD patients' brain tissue. These findings and the loss of cholinergic neurons from the nucleus basalis of Meynert [20] that lead to decreases in ACh and the enzyme acetylcholinesterase (AChE), suggested a substantial cholinergic insufficiency. The wide range of cholinergic abnormalities in AD have led to the conclusion that ACh deficiencies may not be causative, but are a result of the widespread brain tissue damage. Furthermore, AChE is an important regulator of ACh activity, by degradation into acetyl and choline at the synapse (Figure 6), which shows the importance of finding low levels of AChE in postmortem AD brains. The greatest loss of cholinergic activity was seen in the parietal cortex and the hippocampus [96], the latter of which plays an important role in memory and learning [23, 97]. Postmortem examination of late-stage-AD brains showed that many more neurotransmitter systems were largely affected. For example, changes in serotonergic neurotransmission may be linked to behavioral disturbances, such as depression [98].

## The cholinergic synaptic transmission



**Figure 6.** The cholinergic transmission. Choline acetyltransferase (ChAT) is the enzyme responsible for the synthesis of acetylcholine (ACh). Acetylcholinesterase inhibitors affect preservation of ACh by inhibiting acetylcholinesterase (AChE), which is an important regulator of ACh activity by degradation into acetyl and choline at the synapse. This results in increased ACh levels in the synaptic cleft available for receptor absorption, and subsequently, enhances the cholinergic transmission and improves the communication between the neurons. *Drawing by Per-Åke Aronsson.*

## The cholinergic hypothesis

These studies led to the “cholinergic hypothesis” [99] which suggests that degeneration of ACh-neurons in the basal forebrain, and associated loss of cholinergic neurotransmission in the cerebral cortex and other areas, contributes substantially to cognitive decline in patients with AD. The forebrain cholinergic pathways serve important roles in, for example; working memory, conscious awareness, visual attention and behavioral activation [100, 101].

The “cholinergic hypothesis” prompted the search for potential treatment approaches designed to maintain and enhance the activity of the remaining cholinergic system. Randomized placebo-controlled trials were performed on several drug candidates, including: lecithin [102]; the cholinergic agonist, nicotine [103]; muscarinic agonists [104]; and the irreversible selective monoamine oxidase B (MAO-B) inhibitor, selegiline [105]; as well as of several cholinesterase inhibitor (ChEI) agents [106-108]. Some of these new drugs did not produce any clear clinical benefits or were withdrawn due to their severe side effects. The adverse hematologic (granulocytopenia) effect was reported with respect to eptastigmine [107], and neuromuscular dysfunction with life-threatening respiratory failure and death was reported for metrifonate [108]. The ChEI, tacrine, was the first drug agent to exhibit clinical efficacy as well as tolerable side effects [109].

### Cholinesterase inhibitor (ChEI) therapy

First- (tacrine) and second-generation (donepezil, rivastigmine, galantamine) acetylcholinesterase inhibitors work as anti-AD medications by affecting preservation of ACh by inhibiting AChE, the enzyme that breaks down ACh, resulting in increased ACh levels in the synaptic cleft available for receptor absorption (Figure 6). This enhances cholinergic transmission and improves the communication between the neurons [110, 111], which temporarily might counteract the associated cognitive deficits.

Cholinergic side effects of ChEIs include nausea, vomiting, dyspepsia, diarrhea and dizziness. They are usually mild, of short duration and responsive to dosage reduction [91, 111]. The incidence of adverse events was reported to be dose dependent [112, 113], and a longer titration schedule is estimated to reduce the side effects [112].

A general opinion is that ChEIs have a symptomatic effect but neuroprotective effects have also been discussed [114]. Post-treatment delays in symptom progression of approximately 6–12 months, on average, have been suggested [91, 110]. The response to treatment was described as heterogeneous, with some individuals responding considerably more than others. Patients responding to ChEI therapy report improved awareness and attention, better communication abilities and are more independent. The heterogeneity of AD at genetic, neurochemical, clinical and neuropathological levels may contribute to the various response rates [91].

*Tacrine* (Cognex<sup>®</sup>), tetrahydro-aminoacridine, an inhibitor of both AChE and BuChE was the first drug to receive Food and Drug Administration (FDA) approval for the treatment of AD [109]. In Sweden, it was approved in 1995; however, hepatic side effects were reported for about 50% of the patients in the tacrine trials [115]. Because of the hepatotoxicity, and the multiple daily dosages



due to the short half-life of 2-4 hours, the prescription of tacrine declined when the second-generation ChEI became available. Tacrine is no longer approved in Sweden.

### Current available ChEI drugs in Sweden

*Donepezil hydrochloride* (Aricept®) was the first of the second-generation ChEIs to be approved in Sweden in 1997. It is a potent and specific inhibitor of AChE with minimal effects on BuChE, and as a piperidine-based molecule, it is chemically distinct from other ChEIs. Donepezil has a long duration of action, with a half-life of about 70 hours, which allows once-daily administration. Clinical studies have shown that donepezil lacks the hepatotoxicity characteristic of acridine-based ChEIs [113].

*Rivastigmine* (Exelon®) is a “pseudo-irreversible” inhibitor of both AChE and BuChE, with a phenylcarbamate structure minimally metabolized by the hepatic cytochrome P450 enzymes, an effect which reduces the risk of interaction with other drugs. It was approved in Sweden in 1999, for the treatment of mild-to-moderate AD. Rivastigmine treatment is associated with a higher incidence of gastrointestinal adverse events than donepezil but no hepatic side effects have been reported [116, 117]. A transdermal patch is now available, which has the advantages of once-daily administration despite the short half-life of about two hours, as well as fewer reports of cholinergic side effects [118].

*Galantamine* (Reminyl®) can be isolated from several plants (greek; Galanthus, snowdrop), including daffodil bulbs, but is now synthesized. It is a specific, competitive, and reversible AChE inhibitor. Galantamine is also an allosteric modulator at nicotinic cholinergic receptor sites potentiating cholinergic nicotinic neurotransmission, giving this ChEI agent a dual mechanism of action [119]. It was approved in Sweden in 2000. The half-life of galantamine is 7-8 hours. Thus, to simplify dosing and enhance compliance, a once-daily prolonged-release capsule form of galantamine was developed [120]. The observed rates of gastrointestinal adverse events were similar to donepezil, except for diarrhea, which showed a lower frequency in galantamine-treated patients [111].

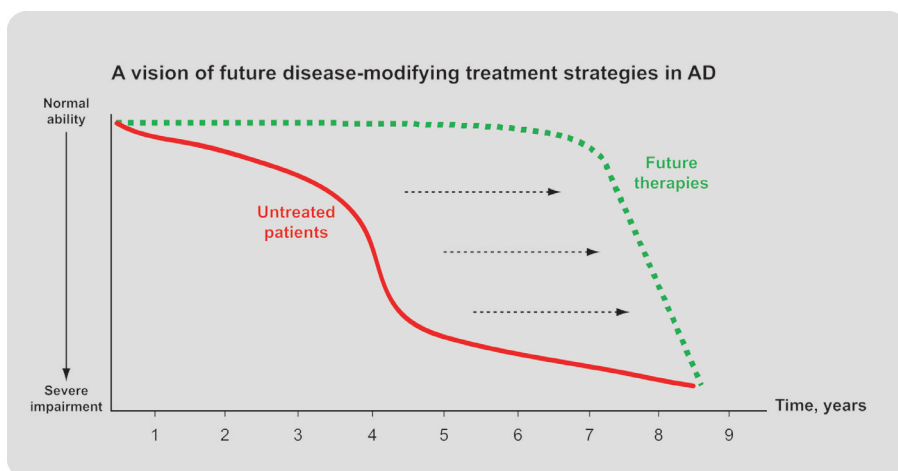
### Non-cholinergic treatment

*Memantine* (Ebixa®), apart from ChEIs, the only drug currently approved for AD treatment, available since 2002 in Sweden. Memantine is a non-competitive N-methyl-D-aspartate (NMDA) receptor antagonist believed to prevent neurons from glutamate-mediated excitatory neurotoxicity, without interfering with physiological NMDA-receptor activation, which is necessary for the memory and learning. The half-life is long, 60-100 hours. Memantine exhibited a small

beneficial effect at six months in moderate-to-severe AD [121]. Combination therapy, ChEI and memantine, showed significantly better response to treatment relative to ChEI alone [122, 123], and a longer time to nursing home placement (NHP) [124]. There is no evidence that memantine has any positive effect in mild disease. In general, the drug is well tolerated, with few adverse events [121].

## New potential therapeutic approaches for AD

Treatment, regardless of drug candidate, would be most useful if initiated early in the course of AD before widespread neurodegeneration occurs. Figure 7 illustrates a vision of how future disease-modifying therapies might alter the outcome of the disease. Below are mentioned several approaches intended to affect degenerative processes that probably begin decades before the clinical symptoms are observed. The main focus of new drug candidates has been the inhibition of A $\beta$  production and aggregation in the brain.



**Figure 7.** An illustration of how future disease-modifying therapies might alter the longitudinal outcome of Alzheimer’s disease (AD).

*Vaccines with active immunization* against the A $\beta$  peptide have been developed, and when used levels of A $\beta$  appeared to consequently decrease in human AD brains. However, one trial was interrupted because some patients developed meningoencephalitis [125].

*Passive immunization* with humanized monoclonal antibodies targeting portions of the A $\beta$  molecule offers another approach to reduce the level of brain A $\beta$ . Trials have shown it decreased cortical A $\beta$  load [126], but this also was associ-

ated with a serious adverse effect, reversible cerebral vasogenic edema. No clear significant improvement in cognitive or ADL abilities has yet been found [127]. Several new studies are ongoing.

*Inhibition of  $\beta$ -secretase*, which cleaves APP to produce  $A\beta$ , and  *$\gamma$ -secretase*, the final enzyme required for the generation of  $A\beta$  are additional therapeutic strategies [128, 129]. These enzymes have many functions in the body, thus requiring selective drugs to avoid unwanted side effects [130, 131].

The other hallmark of AD is the presence of neurofibrillary tangles containing tau protein. Some studied therapeutic approaches target tau, including trials of *inhibitors of glycogen synthase kinase-3* [132], though these have not reported any positive effects on cognition and ADL status in AD patients [132, 133].

*Direct-acting muscarinic agonists* act postsynaptically, in contrast to the effect of ChEI that requires intact cholinergic nerve terminals. In a selective muscarinic receptor 1 agonist trial, positive results were observed on cognitive ability, and particularly so on behavioral symptoms, but adverse cholinergic effects led to a more than 50% dropout rate [134]. Other immunotherapies with different types of anti- $A\beta$  monoclonal antibodies, drugs to prevent  $A\beta$  aggregation, neurotrophins, agents targeting tau protein, and drug candidates with cholinergic activity are in different stages of development and trials (for reviews see [135-137]).

Old drugs for other purposes, such as *non-steroidal anti-inflammatory drugs (NSAIDs)*, *lipid-lowering agents*, and *an antihistamine* have been suggested to be beneficial in manifest AD. However, no significant cognitive improvement was observed in clinical randomized trials using those agents [138-141].

*Non-pharmacological therapies*, for example cognitive and ADL training were described as useful and possibly cost-effective approaches to improve the AD patients' abilities, quality of life and delay institutionalization [142].

## Short-term studies with ChEI treatment

### Randomized clinical trials

Short-term randomized clinical trials with ChEI, usually less than 6 months, have shown modest improvements in cognition and global performance compared with placebo treatment in subjects with mild-to-moderate AD [112, 120, 143-145]. A meta-analysis demonstrated that larger ChEI doses were related to a better cognitive outcome [146], and an extension study suggested that effective dosages and sustained use might postpone the time to NHP [147]. In a recent randomized study of moderate-to-severe AD [148], donepezil 23 mg/d was related to greater cognitive benefit using the Severe Impairment Battery but not in global or ADL performance, compared with donepezil 10 mg/d. Adverse events were more frequently observed in the 23 mg/d group.

Only short-term AD treatment studies can be placebo-controlled, since placebo-controlled designs exceeding 3-6 months are no longer considered ethical. The Cochrane systematic review only includes randomized clinical trials of at least six months duration in AD [149]. Positive cognitive outcomes of ChEI treatment have also been reported for patients with mild cognitive impairment [150, 151], moderate to severe AD [152, 153], and severe AD [154, 155] in randomized trials. The peak of the cognitive response to treatment occurs about 6-12 weeks after initiation of ChEI therapy and returns to baseline level after 6-12 months. Persistent ChEI treatment seems to be required to maintain maximum drug effects, since 6-week washout periods or discontinuation of therapy are associated with regression from gains in cognitive ability, and therefore no significant benefits of treatment may be observed [156-158]. Placebo-controlled clinical trials have also shown that ChEIs are effective in slowing functional deterioration [113, 143, 159], and improving behavioral symptoms [152, 159]. In addition, some studies report that ChEI therapy delays the time to NHP [160, 161], while other studies do not [157].

Regarding short-term studies, the three ChEI agents were compared in two 12-week open-label trials [162, 163], and in naturalistic 6-month studies [164, 165]. All but one study found no differences in outcomes between the drugs. One 12-week open-label trial showed that donepezil was superior to galantamine [163].

However, not every individual benefits from ChEI therapy. A review of donepezil suggested that the proportion of AD patients showing significant improvement in cognition was less than 40% [166]. It is not possible to identify those who will respond to treatment prior to treatment [149]. Studies have questioned the efficacy of ChEI because due to small demonstrated clinical benefits and insufficient methods in the clinical trials [167]. Moreover, analyses suggest that patients are showing slower rates of cognitive deterioration in more recent trials compared with earlier, despite the participants being older and having more advanced AD and co-morbidity. The heterogeneity in cognitive outcome and response to ChEI therapy emphasizes the importance of identifying patients who respond positively to treatment, to enhance the drug efficacy and its cost benefits in AD [168].

## **Response to ChEI therapy**

Clinical trials for symptomatic ChEI agents, in which improvement in cognition, function, and global performance, or less decline over a short period, have been the principal outcomes of interest. The FDA has established criteria for efficacy of AD drug interventions. A cognitive rating scale has been recommended as a primary outcome measure, since the core symptoms of dementia are cognitive. However, the clinical significance of a change on a cognitive rating scale may not

be evident, therefore, a global scale has been recommended as a second primary outcome measure. Predominantly, the Alzheimer's Disease Assessment Scale - Cognitive subscale (ADAS-Cog) [169] and the Clinician Interview-Based Impression of Change-Plus have been the primary outcome scales. The FDA requires that evidence of superiority of the drug compared with placebo must be shown on each of these two measures in order for approval to be granted [170]. Many regulatory authorities, such as the FDA, recognize a four-point change on the ADAS-Cog at 6 months as indicating a clinically relevant difference [171].

The European Medicines Agency (EMA) guidelines recommend that symptomatic improvement be assessed in cognition and ADL, which reflect the two primary domains, and that global performance be assessed as a secondary outcome measure. The clinical trial and its duration should be methodologically capable to demonstrate significant differences in each of the two primary variables. In short-term AD treatment, responders may be defined at 6 months as improved, based on a relevant pre-specified level on the cognitive measure; and, at least, not worse on the two other domains (global and ADL) [172].

### **Predictors of response to ChEI therapy**

Some studies have focused on possible ways to identify which patients will respond to ChEI therapy. Subsequent analyses of data from large randomized placebo-controlled trials have reported an improved response to both rivastigmine and galantamine treatment in more cognitively impaired AD patients [173, 174], and in those with a faster rate of disease progression [175]. Greater reversible cholinergic deficit in the more severe stages of AD is a possible explanation, suggesting this subpopulation is more responsive to ChEI [176]. Naturalistic studies have also observed a better response to ChEIs in moderate dementia [168, 177], but one study found a more positive response to donepezil in mild compared with moderate AD [178]. Inconsistent results were found regarding gender [179, 180], age [181, 182], and APOE genotype [144, 183]. Moreover, occasional studies have shown that increased red blood cell AChE inhibition was associated with better effect of donepezil treatment [184], and increased plasma  $A\beta_{42}$  after two weeks of rivastigmine therapy predicted positive treatment response at 6 months [185]. However, the levels of selected CSF biomarkers did not change during a 6-month period of ChEI therapy [186].

Incorporation of a biomarker into randomized clinical trials would support the claim for a disease-modifying treatment effect. Such a marker should respond to and predict the clinical response to the intervention, and exhibit a strong relationship with the neurobiology of AD [187]. A discrimination rate of 70% between responders and non-responders to donepezil using a combination of MRI and single photon emission computed tomography (SPECT) examinations was reported. The responders had greater atrophy in the substantia in-

nominata, which reflects degeneration in the nucleus basalis of Meynert, but less prominent frontal cortical dysfunction [188]. Baseline SPECT profiles of AD patients might be used to predict a behavioral response to donepezil [189]. After 3 weeks of galantamine treatment, the cortical AChE activity was reduced by 30%–40% as measured by PET imaging, and the level of AChE inhibition correlated positively with performance on an attention test [190]. Other approaches suggested to measure response were quantitative EEG, postural blood pressure, platelet APP and pupillometry [191].

## Long-term outcome of ChEI treatment

The course of AD has a duration of several years, therefore, it is important to assess the potential of ChEIs over longer time periods than the usual 6-month randomized trials. Treatment success includes not only short-term improvement of symptoms but also less deterioration over the long term [192]. Four double-blind, randomized, placebo-controlled trials have investigated the efficacy of ChEI treatment over one year or longer [157, 193-195], and showed significant positive effects on cognition and function. Only Winblad et al.'s [193] study fulfilled the standards of the Cochrane Collaboration. The AD2000 study [157] was criticized for having a high number of dropouts, a complex design with multiple washout periods, and for attending physician uncertainty concerning the benefits of ChEI treatment for their patients who entered this study. The other studies were excluded due to small sample size [195] and because the patients left the trial when their function declined to a specified level and no further data was collected [194].

Nowadays, placebo-controlled trials longer than 3-6 months are not considered ethical due to the apparent drug efficacy shown, thus making it necessary to utilize open-label extensions of clinical trials or naturalistic cohort studies to investigate the longer-term effects of these drugs. Extension studies of placebo-controlled trials have shown that the effect of ChEI may last up to 5 years [156, 196-199], and a few long-term studies in routine clinical settings have also described benefits of ChEI in cognition [200, 201] and function [202]. A treatment that preserves the patients' abilities for a longer time is expected to reduce the caregiver burden and the use of social resources, and postpone NHP [161, 194].

Placebo-controlled trials and the subsequent open-label extensions are limited due to highly preselected clinical populations of patients with AD. Individuals participating in clinical trials tend to be younger, have a higher level of education and a better financial situation than patients not enrolled in trials [203, 204]. Moreover, they have fewer concomitant somatic diseases and medications, and experience fewer behavioral symptoms than those not included. The enrolled

patients might also decline more slowly and have lower mortality rates than the non-participants. From a large clinical AD database, less than 8% of the naturalistic patients would have been accepted in a randomized trial with typical inclusion and exclusion criteria [204]. In open label extensions, a substantial dropout often occurs between the randomized clinical trial and the subsequent extension. Of the original trial participants, 55%-76% elected to continue ChEI treatment in the open-label phase [199, 205, 206]. A selection bias in favor of individuals who could tolerate ChEI, or those with less cognitive decline, has been described for patients continuing the open-label extension study [205].

A naturalistic study enrolls ordinary patients from a routine clinical setting. By using wide inclusion criteria, acceptance of coexisting illnesses and concomitant medication, the results may more closely reflect effectiveness of ChEIs under conditions of usual clinical care. Long-term naturalistic studies from clinical practice are important, and complement and can potentially verify results of randomized trials [207].

In all long-term studies, the absence of a placebo group means that it is necessary to evaluate the treatment response by comparing with anticipated change obtained from various historical cohorts of AD patients, or by comparing with mathematical models of the rate of deterioration [208].

Long-term AD studies suffer from a large attrition rate, which is a complicating factor when evaluating treatment effect. Winblad et al. [199] showed a high completion rate of 39% in an open-label extension, whereas other studies [197, 198, 201, 206] report 20%-33% after 3 years. Assuming that the dropout is higher among the more impaired individuals and among those with less tolerance of treatment, this may contribute to a better cognitive and functional ability for the long-term completers, "survivorship bias" [198]. Nevertheless, the reasons for dropout may not always depend on the patient's adverse events or the worsening of AD, but also on concomitant somatic diseases or changes in the caregiver's health or situation.

## Statistical methods for investigating the longitudinal rate of change in AD

### Background

An adequate description of the natural history of AD is important for analyses and prediction of potential cognitive and functional changes in the longitudinal trajectory of the disease caused by ChEI therapy [209]. Thus, reliable models of how a cohort of patients can be expected to deteriorate using various assessment scales are needed. Models of decline can also be used to examine the role in-

fluencing the deterioration played by covariates, such as: severity of disease, age, gender, and years of education. Starting in the late 1980s, several efforts have been made to investigate the decline associated with AD. Early work examined simple change in scores of mental status tests, e.g. Blessed Information-Memory-Concentration (BIMC), in which change was usually measured by subtracting the initial score from the final score, then dividing by the length of time between the first and the last assessments [210-212].

### **Linear regression models**

Linear regression models were subsequently introduced, including the frequently used method of least-squares regression, which calculates the slope (an estimate of the average rate of decline) that best fits all points along time since baseline [213, 214]. The advantage of regression analyses over simple change scores is their ability to model the influence of associated factors (covariates), such as disease severity, age at onset and concomitant medications, on the decline pattern. In the early publications, it was assumed that decline in MMSE and BIMC scores was nearly linear [212, 215]. To improve the precision of the dependent variables in the multivariate linear regression models, Mortimer et al. [215] weighted each subject's estimated rate of decline by the inverse of the standard error of the slope. This method makes comparison with the results from non-weighted regression analyses difficult. However, it was observed in naturalistic studies, that measurement of change is complicated by the variable follow-up intervals and the possible non-linear pattern of change. Therefore, the 6- and 12-month intervals between pairs of visits were used as the unit of analysis in some models, assuming linearity of change over the interval, but not across all assessments in the dataset [216]. Another study [217] used a two-stage regression approach, first estimating for each subject the least squares slope and then weighting by the length of follow-up. The slopes are then used as the dependent variable in a second stage multivariate regression to find predictors of rate of decline. The advantages of subject-level regression are that the estimation of summary measures accounts for the intra-individual correlation between assessments, and that differing numbers of data points can be accommodated [218].

### **Non-linear regression models**

Several AD studies showed that decline rates in MMSE and ADAS-cog scores are not uniform across levels of cognitive severity [217, 219, 220], and that progression is heterogeneous, depending on several factors such as patient characteristics and clinical variables [88]. Stern et al. [219] analyzed linear, quadratic and higher-order polynomial effects and suggested the presence of a significant quadratic effect between baseline and the annual rate of cognitive change by us-



ing the ADAS-cog scale. Thus, a faster decline among individuals with a moderate level of cognitive severity, compared with those with milder or more severe impairment. This finding has been corroborated by other studies [217, 221]. The change in performance score by a certain test is expected to be larger at the level of function where the test most accurately measures the patient's abilities. In addition, most scales include items that are less sensitive during the mild stage of AD (ceiling effect). The slower progression of patients at the severe end might partly depend on the existing scales inability to assess severely impaired individuals adequately (floor effect) [87]. The selected test instrument can also affect the profile and the rate of deterioration [217].

These results lead to the motivation of examining and developing non-linear models. However, it might be complicated to fit a non-linear curve to prevalent cohort data in a longitudinal study design, particularly when the patients entered the study at different stages of disease severity and with uncertain times of onset [87]. Brooks et al. [222] suggested a tri-linear model with an initial period of stability, a period of detectable deterioration on a test score such as the MMSE, and a final period of stability with no further perceptible decline. This model may be an improvement over the simple linear regression model with respect to reproducing the underlying disease process. It can be used regardless of the individual's entry point, but it may not accurately reflect the patterns of deterioration for most patients, each of whom may have had several periods of decline and stabilization. In addition, the requirement of obtaining a minimum of five assessments per individual may limit the applicability of the model. Haxby et al. [223] described a biphasic trajectory of decline in patients with AD. After a single plateau, after which the non-memory functions began to decline, the deterioration was relatively stable in most individuals. Yet, the trajectories differed markedly among the patients in both the shape and the rapidity of decline.

### **Non-linear growth curves**

The observations have led to the adoption of more flexible non-linear methods. Liu et al. [87] used non-linear growth curves to model the conditional change in a global intellectual functional measure over the time interval since a given measurement. This method has the limitations of applying only to data collected on consecutive assessments with a constant time interval, and the assumption of uncorrelated conditional changes. An individual growth curve method specified by Francis et al. [224] uses hierarchical modeling methods, which enable the variance in outcome variables to be analyzed at multiple levels, such as individual and group levels. An advantage of this approach is that all available data for each patient can be used to estimate the growth curve parameters. This method takes into account differential weighting of data (more weight is given to individuals whose parameters have been estimated more precisely).

## **Mixed-effects models**

The well-known inter- and intra-patient variability led some authors [88, 123, 225] to apply the linear mixed-effects models by Laird & Ware [226], with a random intercept that allows a varying baseline level of disease severity [227]. The advantage of these models is their ability to analyze the interaction of the covariate on the outcome over time. Furthermore, to take into account the correlation within subjects, variations in the number of follow-up assessments available for the participants, and the actual time intervals between the collected data points [218, 228].

## **Latent class trajectory models**

An extension of mixed-effects models is latent class trajectory models, in which a given individual can follow a weighted mixture of several completely different trajectories. The weights correspond to a set of probabilities, containing one for each trajectory. These trajectories each represent separate classes of patients, the existence of which is inferred from the patterns in the data set. For some subjects the overall probability is accounted for mostly by a single trajectory, that is, the potential path these individuals are expected to follow. However, the subject's overall probability can also derive from two or more trajectories, each with substantial probability. Instead of a single path, this outcome may be considered as a mathematical approach to model heterogeneity. Subsequently, the classes can be used to identify underlying differences in disease trajectories, incorporating genetic, demographic or clinical factors [229, 230].

## **Generalized estimating equations**

Another more recently used approach [123, 231] for this type of longitudinal data is the method of generalized estimating equations (GEE), which represent an extension of linear and logistic regressions. This method also takes into consideration multiple measures per patient, that is, the correlation within subjects over time; and can handle varying numbers of data points among the individuals. Nevertheless, GEE derives from a different theoretical foundation and methodology than mixed-effects modeling. For example, the coefficients in a GEE model estimate the average effect across all patients (the repeated measures per patient are treated as a cluster), while the coefficients in a mixed-effect model estimate the effect for an individual patient [232].

## Analyses of endpoints

When the outcome measure is an endpoint (event), such as a pre-defined level of functional ability or NHP, the Kaplan-Meier method is often employed to obtain survival time estimates [194, 233, 234]. This approach accounts for variability during follow-up and accounts for those patients who do not reach the endpoint in the study period (censored data). Potential differences between representative survival distributions among groups can also be tested. However, the Kaplan-Meier method can only study the effect of one variable at a time and cannot be used for multivariate analysis. Cox proportional hazards regression model has the additional advantage of modeling the influence of characteristics that can affect the distribution of time, and to determine which predictors that are independently associated with time to the event [194, 234-236]. Logistic regression is another method that can be used if the endpoint is dichotomous, for example, dropout or NHP [237-239]. This analysis also takes into account the influence of associated factors, but does not consider the distribution of time to the event and the censoring of data if the event has not occurred.

## Practical statistical models and other methods of evaluating long-term AD therapy

### Background

Prior studies have suggested that three or more measurements per individual, during an average follow-up period of at least two years, are preferable when estimating regression slopes [215, 219]. The size of the cohort is another important factor, more than 100 subjects are needed to enable a more reliable pattern of change [89]. In addition, some studies of the rate of decline in AD reported that non-linear models proved to fit the data better compared with linear models [230, 240]. Findings from univariate analyses should be extended to more advanced multivariate models to reveal confounding factors, and examine possible interaction effects among the predictors [89]. A large dropout rate among AD patients in longer-term studies is commonly described [197, 198, 201], which could overestimate the outcome if the study is left with mainly less impaired individuals. By using the last observation carried forward (LOCF) approach to compensate for the dropout in analyses, involving a progressive disorder or when the missing data are non-random, one might exaggerate and bias the results [241]. It is important to develop more advanced models of AD progression that allow for the prediction of variations in disease course, and determine the sources of these variations as completely as possible.

## Practical statistical models

Different approaches to compensate for the lack of a placebo-group have been published earlier. A commonly used method in long-term open-label extensions and naturalistic studies [197, 200, 206, 242] is the Stern equation. Stern et al. [219] used the stepwise regression analysis to develop a non-linear model to predict the subsequent rate of cognitive change in untreated AD patients on the basis of ADAS-cog scores at study entry. The outcomes from the mathematical model corresponded well to the decline in a real placebo group [242]. The Stern equation was based on 72 patients that were followed for 12 to 90 months [ $35.3 \pm 20.2$ , mean  $\pm$  standard deviation (SD)]; with a reported baseline ADAS-cog score of  $35.1 \pm 3.8$  points (5–69, range). Observed change in the treated cohort can be compared with the predicted change using this formula.

The Stern model:

$$\text{Predicted ADAS-cog score at a time (T)} = -6.039689 + 1.329485 x_i - 0.005392 x_i^2 + (0.031974 + 0.036652 x_i - 0.000473634 x_i^2) \times T$$

In this equation: T = time from baseline in months,  $x_i$  = baseline ADAS-cog score for an individual.

Mendiondo et al. [221] showed that AD progression over time could be modeled using a cubic or logarithmic function of MMSE score. For each pair of MMSE scores they calculated the rate of change in points per year. The mean rate of change for each MMSE point (24 to 3) was then inverted to obtain an estimate (in years per point) of the time needed for the MMSE score to decrease by one point as a function of the average MMSE score. These equations were based on 719 patients that were followed from 0.5 to 7 years (mean 2.3). An adaptation of this model was used in a 5-year study of rivastigmine [198].

The Mendiondo model:

$$\text{AD progression in years} = -0.0011 \text{ MMSE}^3 + 0.0364 \text{ MMSE}^2 - 0.6012 \text{ MMSE} + 8.669$$

$$\text{AD progression in years} = -0.5157 \log(\text{MMSE}) + 4.2109 \log(30 - \text{MMSE}) - 5.906$$

Another equation derived from the same data set has also been described [90]:

$$\text{MMSE change, points per year} = 8.26 - 1.05 \text{ MMSE} + 0.17 \text{ MMSE}^2 - 0.01535 \text{ MMSE}^3 + 0.000647 \text{ MMSE}^4 - 0.00001046 \text{ MMSE}^5$$

In these equations: MMSE is the MMSE score at baseline ( $3 \leq \text{MMSE} \leq 24$ ).

Green et al. [243] developed a simple linear regression equation to describe the expected annual rate of functional change in untreated AD patients on the basis of IADL scores at study entry. Green's model was based on 104 patients that were followed from 12 to 66 months ( $30.75 \pm 15.9$ , mean  $\pm$  SD); with an observed baseline ADAS-cog score of  $37.4 \pm 18.6$  points (5–70, range) and IADL score of  $22.3 \pm 6.4$  points (9–30). This baseline-dependent equation has been used to calculate historical controls in a previous publication [244].

The Green model:

$$\Delta\text{IADL} = 10.124 - 0.332 \times \text{IADL}_{\text{Bas}}$$

in which  $\Delta\text{IADL}$  is the annual rate of decline of IADL and  $\text{IADL}_{\text{Bas}}$  is the IADL score at baseline.

Stern et al. [209] applied a growth curve model to prospective data and described the non-treated AD patients' progression over time. They used a modified MMSE test, which limits the applicability of the model, and the functional Blessed Dementia Rating Scale. The model was based on 218 patients that had at least 16 MMSE points at study entry, and were followed from 6 to 54 months. The changes in 6-month test scores between all visits for each subject were calculated. The next step was to compute the average change in a score, i.e. the growth rate, as a function of the present score. In the growth model, a starting score generates a prediction of the score at the next time interval, and the procedure is repeated until the score reaches its bound. The values of the model parameters determine the shape of the model and the point of maximal change. The authors also present an extended model including the age at onset, as an initial step towards a specific predictor profile, which can tailor the model better to an individual patient [87].

Amount of modified MMSE decline over the subsequent 6-month interval  
 $= -0.18Y_k \times \ln(57/Y_k)$ ,  $0 \leq Y_k < 57$

Amount of IADL decline using the Blessed Dementia Rating Scale over the subsequent 6-month interval  $= 0.145 \times (14 - Y_k)$ ,  $0 < Y_k \leq 14$

Amount of basic ADL decline using the Blessed Dementia Rating Scale over a 6-month interval  $= 0.46$ ,  $0 \leq Y_k < 9$

in which  $Y_k$  is the current score in each of the above-mentioned tests

Ashford et al. described a "Time Index" model, using measures of cognitive, global and ADL performance combined into an Average Global Clinical Scale (AGC), in which "days of illness" was estimated from the severity score. The three different domains, each consisting of a 50-point scale should yield comparable results. The rate of change (points/day) was calculated by dividing the AGC difference by the number of days between the assessments. For each pos-

sible AGC severity score, the average rate of change was calculated using all pairs of severity values with midpoint scores within 5 points of the severity score, i.e. a sliding average. The results were then inverted to obtain days per point. The model was based on 33 patients (27 females) who were evaluated on at least two separate occasions (mean  $\pm$  SD interval,  $263 \pm 97$  days, range 126-602); and a reported baseline mean age of  $75 \pm 7.7$  (55-85) years and a MMSE score of  $16 \pm 7.2$  (1-26) points. Using least-squares regression, the fitted cubic equation by Ashford et al. was:

$$\text{Time index} = 156.61 X - 3.9928 X^2 + 0.049654 X^3$$

where X is the AGC score, scored on a 50-point scale

A calculation was made to estimate time from the MMSE score:

$$\text{AGC} = 1.45 \times (29 - \text{MMSE score}), \text{ for AGC range } 5\text{-}42$$

An advantage of these models of untreated patients is that the patients' baseline score is considered when calculating the expected outcome for a cohort over time. Identical disease severity at baseline is assumed between the treated cohort and the calculated untreated cohort. The severity of AD has been described as an important predictor of the rate of cognitive and functional decline. When modeling a follow-up study, patients in the very early stage of the disease as well as in the moderate-to-late stages should have been included, to ensure that the observed measures from all the participants collectively comprise the entire course of AD.

## Historical controls

Another approach compares the change in the treatment groups to historical controls using earlier reported mean points of decline per year. The annual decrease of MMSE score in non-treated AD patients is, on average, estimated to 2–4 points/year [212, 217, 245], and the mean rate of deterioration using the ADAS-cog scale ranged from 5-8 points per year [219, 246, 247]. Several longitudinal studies have compared their results with previously reported amount of decline [196-198, 200].

A shortcoming using historical cohorts concern potential differences in clinical characteristics at baseline between the treated and historical groups. Cohort effects such as life conditions, the patients' state of health or different concomitant medications might influence the outcome [207]. Another concern is that untreated patients in placebo groups in more recent trials have shown less change over time compared with older trials [248]. Thus, the use of previous cohorts and subsequent mathematical models could overstate the treatment effect by increasing the drug-placebo difference.

## Open-label extension studies

In open-label extension studies, it is possible to compare the placebo group's amount of change in the double-blinded period with the amount of later change in the extension period [249]. Another approach is to compare changes in patients in an open-label extension to the projected change of the placebo group, as if the placebo had been continued through the extension study [205]. However, a disadvantage with these methods is that somewhat more deterioration in the later part of a longer trial than in the first months might be expected in untreated patients [250]. Thus, the results could slightly underestimate treatment effects. Investigators and clinicians must be aware of the effects of choosing any one of the analytic approaches on the interpretation of the data presented.

# Aims of the thesis

The longitudinal cognitive and functional abilities in AD patients are heterogeneous, depending on a multitude of factors, such as genetic, socio-demographic and clinical manifestations. The overall aim of this thesis was:

1. To investigate potential predictors of change, differences in long-term outcome, and rates of decline or time to NHP for groups of ChEI-treated AD patients in clinical practice.
2. To achieve optimal resolution for analyzing the complex association between the potential predictive factors over time, sophisticated multivariate statistical models were used.
3. To create regression models, that offer a high degree of explanation, and which predict longitudinal cognitive and ADL abilities in cohorts of ChEI-treated AD patients.

## Paper I

To create statistical models for prediction of the long-term (3-year) mean outcome of MMSE and ADAS-cog scores in AD patients in clinical practice, based on the patient's cognitive level at the start of ChEI treatment. An additional aim was, depending on the patient's cognitive level at baseline, whether the models could predict the mean cognitive change (response) after 6 months of treatment. Comparisons with previously published studies and a mathematical model of untreated patients were also performed.

## Paper II

To investigate whether socio-demographic and clinical factors had any impact on the response to ChEI therapy and longitudinal cognitive outcome using mixed-effects models. Moreover, a comparison of the ChEI drugs donepezil, rivastigmine and galantamine was included in the models.



### **Paper III**

To describe the long-term outcome levels of both instrumental and basic ADL in a cohort of AD patients treated with ChEI. In addition, to investigate if socio-demographic and clinical factors had influence on outcome over time. Other issues were addressed, including: to perform an in-depth analysis of the items in the ADL-scales, to study whether change in these abilities was homogeneous, and to create regression models for the longitudinal prediction of ADL outcome based on the functional level at baseline. Comparisons were made using previous publications of the untreated patients.

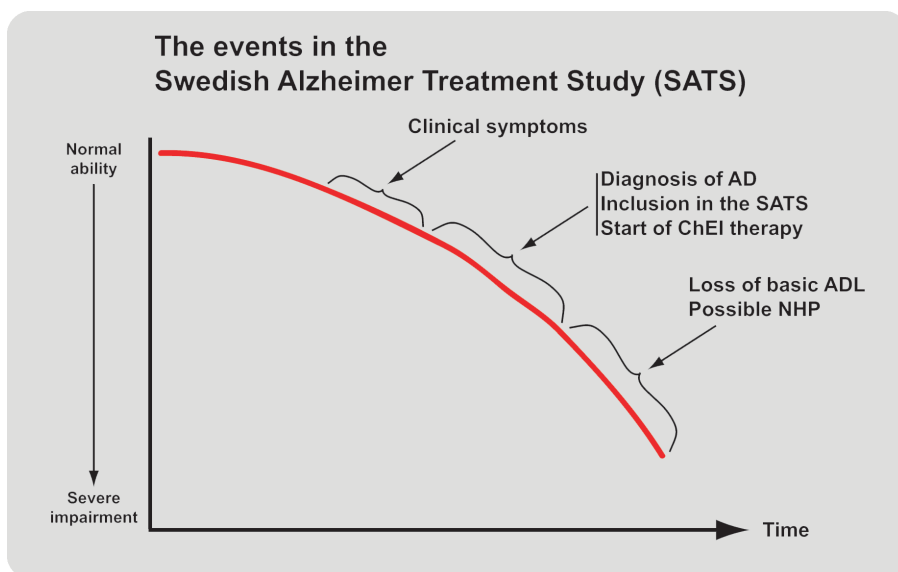
### **Paper IV**

To analyze the distribution of time from the start of ChEI treatment to the end-point NHP using survival analysis and Cox regression, focusing on the effects of long-term changes in cognition, ADL, service utilization and ChEI treatment. The possible impact of background variables on this outcome was also analyzed, as well as cognitive and functional level at the event NHP.

# Methods

## The Swedish Alzheimer Treatment Study (SATS)

The SATS was founded in 1997 to investigate the long-term effects of donepezil (Aricept<sup>®</sup>) treatment of AD patients in a routine clinical setting. The first patient treated with rivastigmine (Exelon<sup>®</sup>) was enrolled in 1998, and galantamine (Reminyl<sup>®</sup>) was started in 2000. In total, 1,258 subjects (donepezil n = 619, rivastigmine n = 269, galantamine n = 370) have been included in the study. Figure 8 illustrates the course of events in the SATS.



**Figure 8.** The course of events in the SATS. The patients, most in the mild-to-moderate stage of Alzheimer's disease (AD), had to be community dwelling at the time of diagnosis. After inclusion in the study, and after the baseline cognitive, global and functional evaluations, the patients started cholinesterase inhibitor (ChEI) treatment. The patients could be admitted to nursing homes (NHP) during the study and continue with the assessments, so long as they were able to visit the clinic. *Drawing by Per-Åke Aronsson.*

The SATS is a 3-year, prospective, open-label, non-randomized, multicenter study and the patients were recruited from 14 memory clinics located throughout Sweden. Malmö is the main center and the other clinics are from south to north: Göteborg, Falköping, Uddevalla, Södertälje, Stockholm (Handen, Huddinge and Danderyd), Uppsala, Sundsvall, Härnösand, Umeå, Piteå and Kalix. All centers had clinical and diagnostic experience with dementia. The participating physicians and staff at the different centers collected the data prospectively, and the results were continuously sent to the Clinical Memory Research Unit in Malmö for monitoring and data handling.

## Subjects

Prior to inclusion in the SATS, all patients underwent an extensive clinical investigation including medical history, somatic and neurological examination, cognitive, global and functional assessments, laboratory tests and computerized tomography (CT-scan) of the brain to rule out other causes of dementia. Outpatients from 40 years of age with a clinical dementia diagnosis defined by the Diagnostic and Statistical Manual of Mental Disorders, 4<sup>th</sup> edition (DSM-IV) [35], and probable or possible AD according to criteria of the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) [37] were considered for inclusion. In addition, the selected patients had to: be community dwelling at the time of diagnosis, have a responsible caregiver (in most cases the spouse or an adult child), and be assessable with the MMSE (i.e., had to have the capacity to communicate and sufficient visual and hearing abilities) at the start of ChEI treatment. Most participants are in the mild-to-moderate stages of AD. All patients and/or caregivers gave their informed consent to participate in the study, which was conducted according to the provisions of the Helsinki Declaration and approved by the Ethics Committee of Lund University, Sweden.

Individuals who did not meet the diagnostic criteria for AD, had already been treated with ChEI, or for whom ChEI therapy was contraindicated, were excluded from the study. By using wide inclusion criteria and the acceptance of concomitant illnesses and medications, a representative group of AD patients in clinical practice was enrolled. After inclusion and the baseline assessments, the patients were prescribed ChEI in accordance with the approved product labeling. The choice of ChEI and dosage for the individual patient was left entirely to the physician's discretion and professional judgment. All dose adjustments were documented during the study. Medications other than anti-dementia drugs were allowed and recorded as well.

The SATS patients were assessed during a structured 3-year follow-up program, which included evaluation using MMSE and global performance after 8 weeks. Cognition, global rating, ADL, and the amount of service utilization (home

help service, adult day care and NHP) were evaluated after 6 months and then semi-annually during 3 years. Trained dementia nurses obtained the ADL assessment and the amount of service per week from an interview with the caregiver.

Reasons for study withdrawal were, for example, admission to nursing home if the patient was not able to continue the visits to the clinic, initiation of concomitant memantine therapy, poor effect/deterioration, death, withdrawal of informed consent, compliance problems, side effects, switching to another study or to another ChEI agent, and somatic disease unrelated to ChEI treatment.

Table 1 describes the number of patients and the inclusion criteria for the selected patients in the papers in this thesis. The MMSE score limits of 10–26 (Paper II - IV) are often used when study designers intend to include a population of mild to moderate AD patients [160, 193, 251]. In the longitudinal regression models and the mixed-effects models (Paper I - III), only patients with at least three assessments per individual were included, as this gives more reliable estimates of the progression rate and more effectively models non-linearity in the trajectories [123, 215, 219]. Table 2 reports the baseline characteristics for the patients included in the papers.

Study	Start of ChEI treatment (last included patient)	Treatment	Number of assessments	Number of patients	MMSE at baseline, range	Statistical methods
I	2001-02-01	Donepezil	1-8 (3-8) <sup>a</sup>	435 (MMSE model, n=390; ADAS-cog model, n=330) <sup>a</sup>	30-6	Multivariate regression
II	2005-12-31	Donepezil Rivastigmine Galantamine	3-8	843	26-10	Mixed-effects models
III	2004-10-31	Donepezil Rivastigmine Galantamine	2-8 (3-8) <sup>a</sup>	790 (ADL models, n=694) <sup>a</sup>	26-10	Multivariate regression Mixed-effects models
IV	2004-10-31	Donepezil Rivastigmine Galantamine	1-8	880	26-10	Survival analysis Cox proportional hazards regression

<sup>a</sup>Numbers within brackets are numbers of corresponding assessments or patients included in the regression or mixed models.

Study	Number of patients	Females (%)	APOE ε4-carriers (%)	Solitary living (%)	Age at baseline <sup>a</sup>	Education, years <sup>a</sup>	MMSE at baseline <sup>a</sup>	ADAS-cog at baseline <sup>a</sup>	IADL at baseline <sup>a</sup>	PSMS at baseline <sup>a</sup>	Completion rate, 3-year (%)
I	435	65	66	37	74.6±6.5	9.6±2.6	22.0±4.6	20.7±10.0	15.9±5.8	7.4±2.2	38
II	843	63	68	34	75.0±7.1	9.4±2.5	21.4±3.8	20.6±8.9	15.9±5.4	7.4±2.1	44
III	790	63	69	34	75.0±7.1	9.4±2.5	21.4±3.8	20.8±9.0	16.0±5.5	7.5±2.1	43
IV	880	63	68	34	75.1±7.0	9.4±2.5	21.3±3.8	21.1±9.0	16.1±5.5	7.5±2.2	39

<sup>a</sup>Mean ± SD.

## Outcome measures

Rating scales are essential instruments for AD diagnosis, staging, and evaluation of symptoms as well as of potential treatment effects. An ideal assessment scale for AD should reflect all major abilities affected by AD, correlate these with the accumulation of neuropathology, demonstrate sensitivity over a range of disease levels, be valid and reliable, exhibit minimal floor and ceiling effects, and should be sensitive to long-term changes with negligible learning effects. With respect to comparisons between countries, the structure of the individuals' language and the cultural differences should not affect the outcome. The test must also work in clinical practice, that is, cannot be too time-consuming and exhausting for the patients [252, 253].

The observed pattern of deterioration in test scores can be associated with the psychometric properties of the scale as a function of the included items, and may not always measure the actual difference in the rate of progression of AD itself. Rating scales are made up of heterogeneous items that reflect different cognitive or functional abilities in the point of the disease at which specific domains are affected, and these domains might be unequally represented. The function will be greatest at the level of performance where the chosen scale most accurately measures the patients' abilities. Thus, some tests tend to be less sensitive to changes at the extremes of the scoring range and more sensitive to changes in scores in the midrange [90, 209]. Most instruments do not contain items that are responsive during the very early clinical stages of AD; therefore, the longitudinal scores on these tests may be rather flat during this period, i.e. the ceiling effect [218]. The floor effect can affect the observed rates of change when the disease continues to progress after a patient has reached the minimum score [209]. Alternatively, ADL scales can extend the range of possible evaluations in later, more severe

stages of the disease when the usual cognitive tests become less sensitive. The development of a new multi-domain scale is ongoing [253].

#### *Mini-Mental State Examination (MMSE)*

The MMSE [21] is a brief, structured, widely used cognitive screening test [207], which is easy to administer and takes about 10 minutes to complete. It includes items assessing memory (delayed word recall), orientation (time and place), attention, language abilities, and to a lesser extent visuospatial ability (copying pentagons); and it has a range of 0-30, a higher score indicating better function. In a large normative study, performance on the MMSE was mediated by socio-demographic variables, with scores decreasing with advanced age and fewer years of education [254]. On average, the MMSE score of an untreated individual with AD declined about 2-4 points each year [212, 217, 245], but the mean rate of deterioration could be greater in the moderate stage of the disease [221]. A MMSE change of 3 points has been suggested to indicate a clinically significant alteration in cognitive ability in patients with dementia [255, 256].

#### *Alzheimer's Disease Assessment Scale – Cognitive subscale (ADAS-cog)*

ADAS-cog [169] is the standard cognitive measure for clinical drug trials of AD [170]. The scale includes 11 items assessing memory, orientation, language and praxis. It is scored by number of errors, ranging from 0-70; the higher number the more cognitive impairment. Strengths of this instrument are its wide coverage of relevant cognitive domains (i.e., more thorough than the MMSE) and the availability of extensive longitudinal data [219], yet it is somewhat time-consuming to perform (approximately 45 min). Socio-demographic variables were also shown to influence the baseline performance on the ADAS-cog in AD, males and younger patients exhibited better cognitive ability [257]. The mean rate of decline in non-treated AD patients ranged from 5-8 points per year [219, 246, 247], to approximately 9-11 points/year in individuals with moderate AD [219]. The FDA has defined an improvement of at least 4 points in ADAS-cog score as clinically significant [144, 258].

#### *Instrumental Activities of Daily Living Scale (IADL)*

The IADL scale [32] was used to assess more complex daily activities, usually involving the use of an instrument. It consists of eight different items: ability to use telephone, shopping, food preparation, housekeeping, ability to do laundry, mode of transportation, responsibility for own medications, and ability to handle finances. Severity was scored per item (1 = no impairment to 3-5 = severe impairment), giving a total range of 8-31 points. A score of 5 (unable to participate in any housekeeping tasks) had been added to the item "housekeeping". Some of the activities are gender-dependent especially among the elderly, for example, women doing the laundry and men handling the finances. If an item was not applicable to the individual, that is, not performed in their premorbid state, the

score of this item was 0. To minimize the effect of gender-biased items in ADL scales, adjusting the effect of summed item scores was preferable compared with removing them, as the latter reduces the precision of the scale [259]. Therefore, a mathematical correction of the sum of the IADL scores was performed to correct for gender-bias. The transformation used the data from the rated items to estimate a total score within the range of the total IADL scale (8–31). The formula was adapted from Green et al. [243].

$$\text{Estimated IADL score} = 8 + (23(\text{IADL}_0 - \text{min}) / (\text{max} - \text{min}))$$

Where:  $\text{IADL}_0$  = original IADL score, i.e. the sum of the rated items, min = minimum possible score for  $\text{IADL}_0$ , max = maximum possible score for  $\text{IADL}_0$

### *Physical Self-Maintenance Scale (PSMS)*

The PSMS [32] includes assessment of essential basic ADL skills in typical self care and consists of 6 different items: toilet, feeding, dressing, grooming (e.g. brushing teeth, combing or shaving), physical ambulation and bathing. Each item was scored from 1 (no impairment) to 5 (severe impairment), allowing a total range of 6-30 points.

## Statistical analyses

The SPSS software (SPSS Inc., Chicago, IL, USA) was used to carry out the statistical analyses. Data were analyzed using standard statistical tests according to two-tailed  $p$ -values. Statistical significance was defined at the level of  $p < 0.05$  if not otherwise specified. Observed case analyses were performed to avoid overestimating the treatment effect by imputing higher, earlier outcome scores (Last Observation Carried Forward) in a long-term study of patients with progressive dementia. ANOVA with Bonferroni correction (*post hoc* test to adjust the significance level for multiple comparisons) was used to compare 3 or more independent groups, and independent sample  $t$  tests were used to compare the differences between the means for 2 groups. Chi-square test was computed for analyses of categorical variables. Paired-sample  $t$  test was performed to assess the mean difference at the different time intervals, between the observed scores in these studies and the predicted scores from the previous regression models of untreated patients (Paper I, III). Pearson's correlation coefficient was calculated to investigate any linear associations between changes during the course of the disease (Paper I, III). Friedman test was used to study possible differences in change among the individual items in the ADL scales (Paper III). Estimates of effect sizes were computed using Cohen's  $d$  (Paper II).

The procedures linear regression and curve estimation were used to find the regression models with the best fit (Paper I). Predicted scores in the models were

only calculated for patients still participating in the study. Collinearity analyses of the variables included in the regression models showed no sign of multicollinearity, that is, the undesirable situation when one independent variable is a linear function of other independent variables. Models assumptions were checked by residual analyses.

## Mixed-effects models (Paper II, III)

### *Background*

In a longitudinal study, researchers are usually interested in the pattern of change across time and how this change relates to individual characteristics. As time proceeds, they may encounter variations in the number of follow-up assessments available for the participants, and unequal time intervals between the collected data points. In most multivariate analyses, each individual must have complete data in all the included variables to perform the analysis. Otherwise, the automatic deletion of subjects with any incomplete data will lose important information. For example, the repeated measures analysis of covariance (ANCOVA) requires balanced designs in which subjects are observed exactly at the same time intervals, and each subject must have an assessment at each time point. These conditions complicate the usage of this analysis in naturalistic longitudinal studies [260].

### *Mixed models*

Mixed, linear and nonlinear, fixed and random coefficient regression models [218, 226, 228] solve these commonly described problems of missing data and non-fixed time intervals. The advantage of this method is the fit of “random coefficients” to the model, with individual paths assumed to follow the path of the group except for the random effects, which allow baseline level of disease severity to be higher or lower (random difference in intercept) and rate of decline to be faster or slower (random difference in slope) over time [227]. For example, if ADAS-cog scores were observed over time, a slope parameter in the fixed effects portion of the model would estimate the mean rate of decline in ADAS-cog over time for the total sample. A slope parameter in the random effects portion of the model (which is estimated for each subject) would quantify each subject’s deviation from the mean slope. Moreover, the mixed models takes into account observations of individuals that are not statistically independent (i.e., allow correlation within subjects). A lack of independence of observations, especially autocorrelated error across observations, violates assumptions of conventional significance tests, and the  $p$ -values might be inexact [228].



## Survival analysis and Cox regression (Paper IV)

### *Kaplan-Meier method*

Survival analysis was performed to study the distribution of time from baseline to the clinical endpoint, NHP. The nonparametric Kaplan-Meier method [261] generates life tables that describe the probability of reaching an endpoint as a function of the time patients were followed. The advantage of the procedure is that the survival function can be estimated directly from the continuous survival times (each time interval contains exactly one case, i.e. does not depend on grouping of the data). This approach takes into account variability in duration of follow-up and incomplete information (censored data), e.g. the patient's endpoint has not yet occurred or is lost to follow-up. Furthermore, the method assumes that the individuals who are censored have the same survival prospects, at any time, as those who continue to be followed.

### *Cox proportional hazards regression*

To analyze the possible influence of socio-demographic and clinical factors, and their hazard ratios, the Cox proportional hazards regression [262] was used. The proportional hazard model is the most general of the regression models because it is not based on any assumptions concerning the nature or shape of the underlying survival distribution. The model assumes that the underlying hazard rate (rather than survival time) is a function of the independent variables (e.g. demographic and clinical characteristics) and no assumption is made about the nature or shape of the hazard function. Parameter estimates are interpreted the same way as in parametric models, except no shape parameter is estimated. Thus, Cox's regression model may be considered to be a semi parametric method. In most situations, we are more interested in the parameter estimates than in the shape of the hazard; therefore, Cox model is a well-suited analysis [263].

### *Stepwise methods*

In stepwise method analyses, backward elimination was preferred. The analysis begins with a full model that included all potential explanatory variables. It then removes the least-significant variable, that is, the one with the highest  $p$ -value, at each step. The fit of the model is tested after eliminating each variable to ensure that the model still fits the data adequately. When no more variables can be eliminated from the model (i.e., only significant variables are left), the analysis has been completed and should contain the most important predictors. In contrast, forward selection starts with no variables in the model. It inserts the variables one by one and includes one only if it is statistically significant. In the forward method, one highly significant, previously included variable might prevent the inclusion of two or more other important predictors, which in combination ultimately have contributed to a better model [263].

As in other statistical analyses, to increase the predictive performance, it is important to choose the predictor variables carefully on the basis of previous research findings and well-educated hypotheses about what might affect the dependent variable. The models should always be stable; i.e., adding or deleting relatively few patients or any single variable should not unnecessarily change the selection of variables or essentially alter the  $p$ -values.



# Results and comments

## Main features of Paper I

### **Predicting long-term cognitive outcome with new regression models in donepezil-treated Alzheimer's patients in a naturalistic setting**

Measuring cognitive change over time is an important issue for clinical management and provides a critical measure in research studies of treatment for AD [89, 90]. In addition, statistical models of cognitive outcome might serve as models of phenotypic variability to validate new biological markers of progression [264]. Several studies have tried to create mathematical models of untreated patients to predict the course of the disease [90, 209, 219, 221]. Because placebo controlled designs are not allowed in long-term studies it is necessary to evaluate the treatment response and potential changes in the longitudinal trajectory using historical control groups or statistical models. Most published models are based on the patients' cognitive score at baseline and a time factor [219, 221]. Because of the insidious disease process, the patients come to medical diagnosis at variable intervals after the symptoms begin [265]. Furthermore, the severity of AD was described as a key predictor of the rate of decline [217]. No previous statistical prediction models of the ChEI-treated patients' cognitive outcome have been presented. The ability to model group progression of AD patients already treated with ChEI is essential for designing disease-modification long-term studies of new therapies [264].

#### *Hypothesis*

It is possible to accurately predict the long-term cognitive outcome for a group of ChEI-treated AD patients.

#### *Methods*

A total of 435 donepezil-treated patients, mostly in the mild-to-moderate stages of AD, were assessed with the MMSE and ADAS-cog scales at baseline and every 6 months during a period of 3 years. Multivariate regression models were fitted from the actual scores.

## *Results*

1. Regression models with a high degree of explanation (39%-63%) could be created for groups of donepezil-treated AD patients' both short and long-term predicted cognitive outcome, based on the cognitive ability at baseline measured by MMSE and ADAS-cog.
2. Patients with less cognitive ability at baseline showed a greater response to donepezil therapy after 6 months.
3. The patients had a mean 5-7-month cognitive improvement with donepezil treatment before the MMSE and ADAS-cog scores returned to baseline value.
4. The long-term cognitive outcome for the cohort of donepezil-treated patients was favorable compared with historical controls and a mathematical model of untreated AD patients.
5. The cognitive changes seen at 0-6 months did not predict later changes at 12-18 months or 30-36 months, for the individual patient.

## *Comments*

Feldman and Jacova address the results from Paper I in a commentary [266]. They concluded that the regression models accurately predict group mean MMSE and ADAS-cog scores over time, but not individual patient outcomes. A limitation of this study was the dropout rate of 62%, which might cause survivorship bias and overestimation of the benefits of therapy. Yet, the baseline-dependent models take the patients' initial ability into account when predicting the subsequent outcome over time. The long-term rate of cognitive decline in the multivariate regression analyses was not different between the completers and the noncompleters. Recent articles using mixed-effects models have also shown the importance of baseline scores and length of time when building predictive models [123, 264].

Analysis of the dataset in Paper I using the mixed-effects model approach, which takes into account intra-individual correlation, showed that the degree of explanation in the models slightly increased (ADAS-cog from 62.7% to 64.2%, and MMSE from 56.3% to 57.4%). The confidence intervals of the predicted mixed models became marginally greater than those of the regression models. However, the differences between the predicted ADAS-cog mean scores from the mixed model and the ADAS-cog mean scores from the baseline-dependent Stern regression model of untreated patients [219] were still significant from 6 months and onwards ( $p < 0.001$ ).

Medication usage data was obtained from all patients in Paper I. Those who fell into highest or lowest deciles based on ADAS-cog residuals (predicted – ob-

served values) were compared with the others. The individuals with the lowest residuals (i.e., lower observed cognitive ability than predicted) after 24 months of ChEI treatment had a larger number of medications (mean  $\pm$  SD),  $3.7 \pm 2.7$  vs  $2.3 \pm 2.1$  ( $p=0.005$ ). This difference was also observed after 36 months, although, due to the lower number of cases, was not significant. No difference was found when specific medications such as antihypertensive/cardiac therapy or antidepressants was examined, but most combinations of medication groups and deciles with highest/lowest residuals contained few individuals. Similar results were found using the MMSE scale.

The usage of the Stern equation [219], or historical untreated cohorts, assumes that the present day patients should have the same trajectory of decline as shown for those in the 1990s. A study of observations across a decade of clinical trials suggest that placebo-treated patients are showing slower rates of cognitive decline in more recent trials compared with older trials, although they also are found to have more comorbidities and medications [248]. This finding might correspond to an overestimation of the treatment effect. It would be interesting to compare the outcome for the early SATS cohort included in Paper I with that of the last enrolled patients in this study.

### *Conclusions*

Regression equations can predict 3-year cognitive outcome in donepezil-treated patients with high accuracy at the group level, but not individual patient responses.

## Main features of Paper II

### **Predictors of long-term cognitive outcome in Alzheimer's disease**

Three ChEIs available currently have demonstrated modest improvements in cognition and global performance compared with placebo treatment in patients with varying degrees of AD severity [149]. There may be a substantial variation in the expression of the disease [267], and the heterogeneity in response to ChEI treatment and long-term outcome among individuals with AD have proven to be large. To improve the management of patients and enhance the efficacy of ChEI therapy and its cost benefits, stress the importance of identifying individuals who respond positively to treatment [168]. Few studies have focused on possible socio-demographic and clinical characteristics that might lead to a different response to ChEI therapy [191]. An improved response was observed in patients who were more cognitively [168, 173] and functionally [268] impaired, but inconsistent results were found regarding gender [179, 180] and age [181, 182]. The divergent results of these studies suggest that the influence of these factors needs further investigation.

Studies on potential predictive characteristics that may affect the longitudinal outcome in naturalistic studies of ChEI-treated AD patients are scarce as well. The long-term cognitive and functional trajectories, including possible affecting factors, were analyzed in a study that focused on the comparison of three naturalistic AD cohorts (untreated, ChEI-treated, and treated with ChEI + memantine) [123], and in a recent study of predicting progression rate [264]. However, these studies did not address the potential impact of the different ChEI agents and dosages, and, furthermore, included a narrower selection of highly educated individuals. Tracking disease progression along with therapeutic effect in patients can be challenging due to the multitude of potential influences [267]. Advanced multivariate methods such as mixed-effects models including non-linear terms may provide a clearer pattern of the complexity associated with the impact of predictors [240].

### *Hypothesis*

At the group level, socio-demographic and clinical factors can influence the cognitive short-term response to ChEI treatment as well as the long-term outcome for patients with AD.

### *Methods*

A total of 843 AD patients with baseline MMSE scores ranging from 10 to 26, and for whom at least 3 assessments were available per individual, were evaluated using MMSE and ADAS-cog scales at baseline and every 6 months thereafter during a period of 3 years. Mixed-effects models were used in this longitudinal cognitive study of potential predictive characteristics.

### *Results*

1. Male gender, older age, APOE  $\epsilon 4$  non-carrier status, and NSAID/acetylsalicylic acid therapy or a higher mean dose of ChEI, were predictors of a better cognitive response after 6 months as well as of more positive long-term outcome of ChEI treatment.
2. Lower cognitive ability at baseline predicted an improved response to ChEI therapy after 6 months, but then a faster subsequent decline.
3. Slower longitudinal cognitive deterioration was associated with higher cognitive ability at baseline or with less-educated individuals.
4. The type of ChEI agent did not influence the short-term cognitive response or the long-term trajectory.
5. The completers exhibited significantly better cognitive and functional abilities at the start of the ChEI treatment compared with the noncompleters, and

received a higher mean dose of ChEI during the study. The other variables did not differ between the completers and those who discontinued.

### *Comments*

Paper II supports the finding from Paper I that patients with more cognitive impairment at baseline showed a better response to donepezil therapy after 6 months. In the current paper, the cognitive outcome was adjusted for several socio-demographic and clinical characteristics, a larger cohort including all three ChEI agents was enrolled and a more advanced statistical approach was performed.

Using a mixed models approach with an AD cohort, Wilkosz et al. [230] correspondingly observed that high initial MMSE score, male sex and older age were predictors of a slower longitudinal cognitive decline. Neither presence of the APOE  $\epsilon 4$  allele nor level of education influenced the trajectory. However, mean years of education was high in that cohort, as it has been in most American studies, indicating a narrower selection of individuals than in the SATS.

Davidson et al. [229] identified, using latent class analysis, a less cognitively impaired AD group at baseline that were younger, more educated, had a higher percentage of APOE  $\epsilon 4$  alleles and shorter duration of the disease. It had been interesting to know whether this group of patients also had a faster rate of deterioration, but no follow-up data was presented. Furthermore, that article suggested an interaction between male gender and a potential AD sub-phenotype that mainly affects attentional and constructional pathways. ChEI treatment was demonstrated to improve attention [269], which could be one explanation of the better response to therapy observed in men in our study.

A retrospective study of AD patients receiving donepezil for at least 2 years, demonstrated using univariate analyses that the non-responders were younger and had a longer duration of symptoms, although they found a similar mean MMSE score at baseline as the responders [270]. Duration of illness was not a significant predictor in our multivariate model. The caregiver's recognition of changes in the patient's performance, as well as other factors such as the level of education and APOE genotype could influence the estimated time from onset of symptoms to diagnosis, but these variables were not addressed in that study.

In contrast to our results, an observational 6-month study of donepezil-treated patients [178], suggested that the mild AD group exhibited more beneficial effect of therapy than the moderate. The gender difference in these two cohorts was large (mild 57.3% vs moderate 67.5% women), and not adjusted for in the multivariate models, which could have influenced the results. The presence of a larger percentage of males in the mild group might affect the outcome more positively, as was the case as male gender showed greater cognitive response to therapy in our study. In addition, the longer and more varying time intervals



from diagnosis to the start of study in the moderate group could bring a negative impact on those patients cognitive ability.

Jones et al. [248] showed that more recent randomized clinical trials included a larger percentage of older, more cognitively impaired patients in the placebo groups; those trials exhibited a slower rate of cognitive decline in comparison with the earlier ones. Our results suggested that individuals with these characteristics had significantly better ChEI treatment response after 6 months. These findings may hold important implications for future trial design and planning.

### *Conclusions*

A higher dose of ChEI, usage of NSAIDs/acetylsalicylic acid, absence of the APOE  $\epsilon 4$  allele, older age or male gender were predictors of better 6-month cognitive response to ChEI treatment and of a more favorable longitudinal outcome.

## Main features of Paper III

### **Long-term outcome and prediction models of Activities of Daily Living in Alzheimer's disease with cholinesterase inhibitor treatment**

In addition to increasing cognitive deterioration, patients with AD also experience a decline in their ability to perform daily activities. Progressive impairment in functional abilities is one of the most troubling aspects of dementia for patients and caregivers. The severity of disability is considered the most critical factor predicting NHP [236, 271]. Despite these facts, there has been appreciably less focus on the investigation of ADL ability than that of cognitive severity in previous long-term studies. Few prior studies have reported the impact of the potential predictive characteristics (sociodemographic and clinical factors) on the longitudinal functional outcome [123, 264]. Furthermore, the long-term change of the various items of the instrumental and basic ADL scales has rarely been analyzed and compared in ChEI-treated patients. Feldman and Jacova [266] have recommended analyses of ADL data from the SATS as a measure of daily functioning and, thereby, a clinically meaningful response to ChEI-treatment.

Functional decline in AD is progressive and once lost, the ability to carry out daily activities is rarely recovered. The effect of ChEI therapy on function is most likely to be observed as slowing down the deterioration rather than as an improvement over baseline [194]. Expected ADL decline has previously been analyzed using mathematical models in non-treated AD populations [215, 243, 250], but no functional models using ChEI-treated patients was presented earlier. In addition, no study of 3 years duration that compares the three ChEI agents has been published.

### *Hypothesis*

Socio-demographic and clinical patient characteristics may affect the functional longitudinal outcome in a cohort of ChEI-treated AD patients.

### *Methods*

A total of 790 AD patients with baseline MMSE scores ranging from 10 to 26, and treated with donepezil, rivastigmine or galantamine, were assessed with the IADL and PSMS scales at baseline and every 6 months for a period of 3 years. Mixed-effects models including non-linear terms were used in this study of possible predictors for ADL ability.

### *Results*

1. Faster deterioration of ADL ability was associated with lower cognitive ability at baseline, older age, a higher education level or solitary living.
2. More rapid decline on IADL scores was related to a lower mean dose of ChEI, irrespective of drug agent. No significant difference regarding the long-term ADL outcome was detected among patients treated with the three different ChEI agents.
3. The variables gender, APOE  $\epsilon 4$  status, and duration of AD showed no significant effect on functional ability over time. No differences were found between patients treated with antihypertensive/cardiac therapy, antidiabetics or lipid-lowering agents, compared with those not receiving these medications.
4. The basic ADL scale showed a significant difference in longitudinal outcome among the included items. The most impaired tasks after 3 years compared with the patients' baseline level were, on average, "grooming" and "bathing", whereas the items "feeding" and "toilet" were best preserved. The instrumental abilities showed a more homogeneous outcome over time.
5. Upon comparison with a historical group and a mathematical model of untreated AD patients, the ChEI-treated cohort indicated a slower deterioration in long-term ADL ability.

### *Comments*

A recent study by Doody et al., predicting progression in AD also used mixed-effects models to assess cognitive and functional long-term outcome, as well as the potential influence of socio-demographic and clinical covariates [264]. In contrast to our findings, age was not a significant covariate in the IADL and PSMS models in that study, and males exhibited a significantly slower IADL outcome. However, those patients were somewhat younger and had an appreciably higher education in comparison with our cohort. No attempt to correct for the gender-dependent activities was described in Doody's study. These are factors that could influence the results of multivariate models.

Correspondingly with our findings, the patients showing rapid functional decline exhibited significantly more cognitive impairment at diagnosis [178, 272]. In mild-to-moderate AD, a MMSE score of 16 was identified as the transition point at which was observed an accelerated decline in both instrumental and basic ADL [273], and another study reported that a MMSE score of  $\leq 14$  predicted a rapid decline of basic ADL [272].

In the present paper, the authors suggested that the faster deterioration in IADL performance observed for individuals living alone might depend on social isolation and apathy, associated with increased need of assistance to carry out routine daily tasks. Apathy is considered to be a characteristic of fronto-subcortical pathology. Patients with a significant burden due to this pathology, concomitant with a heavier load of AD pathology, may show a more aggressive course of disease [274]. Another study of how executive dysfunction predicts functional impairment showed that apathy scores explained 27% of the variance in IADL performance [275]. The rapidly declining AD patients, as measured by basic ADL ability, had higher levels of self-reported depressive symptoms at the initial evaluation [272]. Adding the independent variable antidepressant medications (no/yes) to our ADL mixed models showed a trend towards significance (IADL,  $p=0.080$ ; PSMS,  $p=0.063$ ), indicating that depression could increase the patients' rate of functional deterioration.

Our finding that a higher mean dose of ChEI, regardless of drug agent, was related to a slower instrumental ADL decline was corroborated in Paper II and IV, using different outcome variables (cognitive ability and NHP) and statistical methods (mixed models and Cox regression).

Although the outcomes of the individual tasks in the IADL scale were almost homogeneous in our study, the most preserved IADL item after 3 years of follow-up was "mode of transportation". The change in this task was significantly different from the other IADL items. This finding could be explained by the presence of difficulties in traveling independently already at baseline, as 56% had to be accompanied by another person; and, therefore, the longitudinal change in scores might be less in comparison with the other IADL items. Correspondingly, in a recent study by Razani et al. [276], patients with AD obtained relatively high scores on the transportation subscales compared with the other IADL items. Their scale only assessed the ability to identify road signs and driving rules, but not the actual driving ability. As described, to explain a particular outcome from different aspects might be complex.

### *Conclusions*

Lower cognitive status at baseline, older age, more years of education, and solitary living were identified as risk factors for faster deterioration in functional ability, whereas a higher dose of ChEI, regardless of drug agent, was related to a slower IADL decline.

## Main features of Paper IV

### **Risk factors for nursing home placement in Alzheimer's disease: a longitudinal study of cognition, ADL, service utilization and cholinesterase inhibitor treatment**

Many previous papers have focused on a large number of possible predictors that can affect the time to NHP for dementia patients generally [235, 277, 278] but fewer studies have analyzed this aim in patients with a specific dementia diagnosis such as AD [279, 280]. For example, the care recipient's age, gender, level of education, living arrangements, cognitive and functional status, behavioral and psychiatric symptoms and presence of comorbidity have been analyzed; as well as the caregiver's socio-economic characteristics, health status and burden. Most prior studies only take baseline predictors into account, which offer little information about the effect of potential longitudinal events that might change time to NHP [235]. In addition, sole predictors, but not their potential interactive effects between the critical predictors, have mostly been investigated earlier [278].

Studies regarding ChEI therapy in AD with NHP as an outcome measure are few and are inconclusive [278]. Some studies suggest that ChEI treatment postpones admission to nursing homes [160, 281], but not all [157]. Moreover, extension studies have reported that effective dosages and sustained use might delay institutionalization [147]. There are no previously published naturalistic AD studies that consider the effect of the different ChEI agents and dosages on the time to NHP.

#### *Hypothesis*

Assessed over longer study periods, changes in the individuals' cognitive and functional ability, and usage of community-based care, may influence time to NHP in ChEI-treated AD patients.

#### *Methods*

A total of 880 ChEI-treated AD patients with baseline MMSE scores ranging from 10 to 26, were assessed with cognitive and functional rating scales at baseline and every 6 months for 3 years. The amount of weekly assistance and the date of institutionalization were also recorded. Cox regression models were constructed to predict the risk of NHP.

#### *Results*

1. During the study, 206 patients (23%) were admitted to nursing homes. Median time from the estimated onset of AD to NHP was 4.7 years, and from the start of ChEI treatment to NHP 1.7 years.

2. The rate of change in IADL deterioration, but not in cognitive decline, was an important predictor of the time to NHP, after adjusting for multiple factors previously shown to be of importance.
3. An increase in  $\geq 3$  days per week in adult day care, and lower (0.25–3.5 hours) or higher ( $>7$  hr) increase in home help service/week predicted earlier institutionalization in the multivariate Cox regression models.
4. The hazard ratio for the time to NHP was 3.73 for men living alone compared with 1.0 for men living with their spouse or a relative. For women living solitary, the hazard ratio was 2.94 versus 1.69 for women not living alone.
5. The patients who received a high mean dose of ChEI, regardless of the specific drug agent, exhibited significantly longer median time to NHP, 23.5 months, compared with 16.5 months for those who received a lower dose.

### *Comments*

A recent follow-up study of AD patients who had previously participated in randomized placebo-controlled trials of galantamine, suggested that long-term ChEI therapy was related to significant delay in time to NHP. For each year of treatment with galantamine or other ChEI, the risk of institutionalization within a given period was reduced by 29%-31% [281]. Postponing NHP by only a few months can have a substantial effect on health care costs [282]. However, delaying institutional care and ignoring the increased burden of care on family caregivers, will negate that savings [283].

Correspondingly, the median length of time to NHP in our study (20 months) was similar to the results from a naturalistic AD study (19 months) [284], but ChEI usage was not addressed in that paper. A longer median time from start of ChEI therapy to NHP (42 months) was observed in Feldman et al.'s study [281]. One explanation of this difference could be that those patients originated from randomized trials; thus, were more selected and had fewer concomitant diseases and medications.

Research on how gender affects time to NHP has shown conflicting results in previous studies [235, 236, 285]. When analyzing only sole predictors in our models, female gender or solitary living were factors that precipitated NHP. However, when including the interaction effect, gender  $\times$  living status, the significant term indicated that men living alone were at high risk for early NHP. Consistent with our findings, a study of community-dwelling elderly persons showed that the spouse was most important in reducing the risk of institutionalization for men [237].

In a later sub-analysis not described in the manuscript, a measure of percent maximum dosage for the three ChEI agents, as calculated in Paper II and III, was included in the models instead of the dichotomous variable high versus low

dose. This measurement of dose was also highly significant in the Cox regression models ( $p=0.001$ ). The concomitant usage of medications at baseline, that is, antihypertensive/cardiac therapy, antidiabetics, lipid-lowering agents, estrogens, nonsteroidal anti-inflammatory drugs (NSAIDs)/acetylsalicylic acid, antidepressants, antipsychotics, or anxiolytics/sedatives/hypnotics were not significant when included in the models.

### *Conclusions*

The rate of functional but not cognitive deterioration was a strong risk factor for institutionalization. The males living alone, the patients with a substantial increase in adult day care or those receiving a low mean dose of ChEI during the study exhibited shorter time to NHP.



# Concluding discussion

These studies show that the SATS longitudinal data set can be used to calculate statistical models that offer a high degree of explanation for the prediction of cognitive and functional change in cohorts of ChEI-treated AD patients (Paper I, III). The coefficient of determination is greatest in the model with IADL as the dependent variable (Paper III), suggesting that this measure best predicts outcome over time. The rate of functional deterioration also provided a better predictive measure for time to NHP than cognitive decline (Paper IV), as is corroborated in other studies [235, 236].

The ability to model progression of AD, at the group level, is essential for clinical research. Such models are particularly useful, for example, when measuring the efficacy of new disease-modifying treatments that might alter the course of the disease. Prediction models can also be used as a measure of phenotypic variability to validate biological markers of progression rate, assuming they reflect the same underlying pathogenic process. Moreover, knowledge about the predicted course of AD and the impact of ChEI therapy would be a valuable tool for clinicians, caregivers and the social services to estimate disease prognosis, and to facilitate planning of the increased need for medical and social services [265, 286].

The individual self-care ADL items in the PSMS scale demonstrated different long-term rates of decline, whereas the outcomes of the individual instrumental ADL sub-tasks were more homogeneous (Paper III). The implication for clinical practice suggests that it is not necessary to evaluate all IADL items, in contrast to the basic PSMS. A few key questions regarding the ability to carry out instrumental tasks might reveal information about all IADL items. Dynamic predictors are scarce in studies of the time to NHP [235]. Paper IV showed that a low increase in home help service preceded NHP, indicating that the increased level of care was not sufficient to support the caregiver and prevent institutionalization [235]. The individuals living with a spouse or other relative received a smaller increase in home help service per week than did those living alone (Paper IV). This is the reverse of what might be expected. The active informal caregivers should be likely to report the patient's symptoms to the attending physician and request changes in treatment or services. However, the regular visits at the



clinic and the presence of an identified contact nurse for each participant in the SATS might represent better management of treatment, continuity and security for the patients. The care recipients who used more adult day care per week had an increased risk of NHP (Paper IV), which suggests that adult day care served more as a transitional period to institutionalization than a form of respite, and thus precipitated NHP [280].

There are few published long-term studies comparing the three ChEI-agents, and not one exceeds two years of follow-up. In papers II-IV using cognitive and functional outcome measures as well as NHP, and different statistical methods, the patients receiving a higher mean dose of ChEI exhibited a slower decline and a longer time to NHP. No difference was detected among the three drug agents, which is in agreement with most previous work [287-289]. Results of ours and others studies [146, 147] suggest the clinical importance of prescribing sufficient doses of ChEI to the individual patient. The incidence of adverse effects was slightly increased in individuals treated with higher doses, but could be mitigated when a longer titration schedule was employed [112].

The heterogeneity in outcome underlines the importance of identifying and treating patients with a better probability of response to ChEI, or those with a more aggressive course of AD; as early as possible to enhance the drug efficacy [290]. The patients who demonstrated more cognitive impairment in our study exhibited an overall better response to therapy after 6 months (Paper I, II), as did older individuals (Paper II), emphasizing the importance of not excluding patients in these groups from treatment opportunities. Knowledge and awareness of critical factors that may influence the response to, and outcome of, pharmaceutical trials are necessary to correctly interpret the results. Few studies have focused on patient characteristics that may affect this issue [191]. Using multivariate mixed models in paper II, we found that male gender, older age, NSAID/ acetylsalicylic acid therapy, and absence of the APOE  $\epsilon 4$  allele were predictors of a better cognitive 6-month ChEI-treatment response and of a more favorable long-term outcome. Individuals with a better cognitive status at baseline or a lower level of education showed a slower cognitive and functional decline over time (Paper II, III). Measuring cognitive ability, as a dependent variable, resulted in a finding that older patients exhibited better long-term outcome (Paper II). In contrast, higher age predicted more rapid functional deterioration (Paper III). A more pronounced decline in ADLs, as compared with cognition, might be expected in older individuals due to the aging process and general frailty.

The advantages of the SATS are the prospective, well-structured, follow-up assessments of large cohorts of ChEI-treated patients in a routine clinical setting. With the use of wide inclusion criteria, the acceptance of coexisting illnesses and concomitant medication, we were effectively defining a more ordinary, clinically realistic sample of patients than the highly selected individuals usually enrolled in randomized trials. The SATS design, within the context of offering individu-

alized care, has evolved into a clinical follow-up program, which is, nowadays, applied to all AD patients in our Memory Clinic. In Sweden, the health system is publicly funded and the income or insurance coverage of individuals is rarely an issue when seeking medical care, whether involving community-based care or NHP [291]. This implies a wider selection of patients in the SATS compared with American studies [123, 124, 264], taking into account socioeconomic status such as the level of education.

The 3-year completion rate of ~40% obtained for the SATS cohort is high compared with other AD extension or naturalistic studies. Most prior publications report 20%–39% completers after 3 years [197, 199, 201]. The high dropout rate in long-term AD studies may contribute to higher mean performance scores for patients remaining in the study, assuming that they benefit more from ChEI therapy. In the current study, when taking into account the patient's baseline cognitive score in both multivariate regression analyses and mixed-effects models, the slopes of change do not differ between the completers and the dropouts (Paper I, II). However, our results showed that the completers received a higher mean dose of ChEI during the study, suggesting a better tolerance of the treatment (Paper II).

A limitation of AD therapy studies longer than 6 months is that placebo-controlled designs are not permitted (because of ethical concerns); therefore, no control group was enrolled in the SATS. The presence of behavioral, psychotic, and extrapyramidal symptoms was not recorded in this study; these are factors that have been reported as affecting the rate of decline [215, 292]. The inclusion of additional candidate predictors might influence the multivariate models. Yet, our results are consistent with other studies and there are no indications that the significant predictors would be less important even if mediated by other variables.

In conclusion, the socio-demographic and clinical composition of the AD cohort under study may be one of the explanations for the heterogeneity of results observed in different studies. Future studies are warranted to investigate differences in cognitive and ADL response to treatment, as well as the longitudinal outcome, based on various patient characteristics. The statistical models presented need to be corroborated by other studies with data from other naturalistic cohorts. Functional ability is a key domain in predicting the outcome of AD and time to institutionalization; therefore, functional evaluations should be regarded at least as important as measures of cognitive abilities. Long-term protective effects, such as the potential impact of NSAIDs or other treatments, may take years to develop. The dosage of ChEI therapy, but not the drug agent, could possibly lead to different cognitive and functional outcomes. The knowledge gained from longitudinal, naturalistic ChEI treatment studies will continue to be important.



# Appendix, Table 1-6

<sup>a</sup>Mean  $\pm$  standard deviation.

<sup>b</sup>Multivariate – at least one sociodemographic variable such as gender, age or education was adjusted for. The number of variables and the specific variables that were adjusted for varied among the studies.

Abbreviations: ADAS cog+noncog – Alzheimer’s Disease Assessment Scale-cognitive and noncognitive subscales, APOE – Apolipoprotein E, BDS – Blessed Dementia Scale, BIMC – Blessed Information Memory Concentration test, CAMCOG – cognitive scale of the Cambridge Examination for Mental Disorders of the Elderly, DRS – Dementia Rating Scale, DSM – Diagnostic and Statistical Manual of Mental Disorders, MMSE – Mini-Mental State Examination, NINCDS-ADRDA – National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer’s Disease and related Disorders Association, nr - not reported

Table A1. Predictors of a faster rate of cognitive decline in AD

Predictor	Outcome effect	Reference	Number of patients	Diagnostic criteria	Outcome measure	Cognitive score at entry <sup>a</sup>	Length of study	Univariate/multivariate analysis <sup>b</sup>
<b>Severity of disease</b>	Moderate to severe	Salmon et al. 1990 [212]	92	NINCDS-ADRD	DRS	MMSE 17.4 ± 5.8	up to 2 years	Univariate
	Moderate	Burns et al. 1991 [293]	85	NINCDS-ADRD probable AD	MMSE	MMSE 10.0 ± 5.9	1 year	Univariate
	Moderate to severe	Morris et al. 1993 [217]	430	NINCDS-ADRD probable AD	MMSE	MMSE 18.7 ± 4.5	1–4 years	Univariate
	Moderate to severe	Teri et al. 1995 [220]	156	NINCDS-ADRD probable AD	MMSE	MMSE 20.7 ± 4.8	1–5 years (mean 2 yrs)	Multivariate
	Moderate to severe	Mendonso et al. 2000 [221]	719	nr	MMSE	nr	0.5–7 years (mean 2.3 yrs)	Multivariate
	No difference	Salmon et al. 1990 [212]	92	NINCDS-ADRD	MMSE	MMSE 17.4 ± 5.8	up to 2 years	Univariate
No difference	Stern et al. 1992 [216]	111	NINCDS-ADRD probable AD	modified BIMC (0-27)	nr	6-96 months (mean 30.5 mo)	Multivariate	
No difference	Rasmusson et al. 1996 [88]	132	NINCDS-ADRD probable AD	MMSE	MMSE 16.7 ± 4.0	up to 7.5 years (mean 2.5 yrs)	Multivariate	
Milder	Kramer-Ginsberg et al. 1988 [294]	60	NINCDS-ADRD probable AD	ADAS cog+noncog	ADAS 48.8 ± 22.0	1–2 years	Univariate	
Milder	Mortimer et al. 1992 [215]	65	NINCDS-ADRD probable AD	MMSE	MMSE 17.2 ± 4.8	up to 4 years (mean 2.3 yrs)	Multivariate	

Table A2. Predictors of a faster rate of cognitive decline in AD								
Predictor	Outcome effect	Reference	Number of patients	Diagnostic criteria	Outcome measure	Cognitive score at entry <sup>a</sup>	Length of study	Univariate/multivariate analysis <sup>b</sup>
<b>Gender</b>	Women	Lucca et al. 1993 [295]	56	DSM-III	BIMC	BIMC 17.1 ± 4.4	1 year	Multivariate
	No difference	Katzman et al. 1988 [211]	161	NINCDS-ADRDA prob. and poss. AD	BIMC	BIMC 13.2 ± 8.2	mean 2.2 years	Univariate
	No difference	Kramer-Ginsberg et al. 1988 [294]	60	NINCDS-ADRDA probable AD	ADAS cog+noncog	ADAS 48.8 ± 22.0	1-2 years	Univariate
	No difference	Burns et al. 1991 [293]	85	NINCDS-ADRDA probable AD	MMSE	MMSE 10.0 ± 5.9	1 year	Univariate
	No difference	Mortimer et al. 1992 [215]	65	NINCDS-ADRDA probable AD	MMSE	MMSE 17.2 ± 4.8	up to 4 years (mean 2.3 yrs)	Multivariate
	No difference	Stern et al. 1992 [216]	111	NINCDS-ADRDA probable AD	modified BIMC (0-27)	nr	6-96 months (mean 30.5 mo)	Multivariate
	No difference	Teri et al. 1995 [220]	156	NINCDS-ADRDA probable AD	MMSE	MMSE 20.7 ± 4.8	1-5 years (mean 2 yrs)	Multivariate
	No difference	Galasko et al. 2000 [89]	299	NINCDS-ADRDA prob. and poss. AD	MMSE, DRS	MMSE 19.1 ± 5.9	up to 8 years	Multivariate
	No difference	Mendiondo et al. 2000 [221]	719	nr	MMSE	nr	0.5-7 years (mean 2.3 yrs)	Multivariate

Table A3. Predictors of a faster rate of cognitive decline in AD

Predictor	Outcome effect	Reference	Number of patients	Diagnostic criteria	Outcome measure	Cognitive score at entry <sup>a</sup>	Length of study	Univariate/multivariate analysis <sup>b</sup>
Age at onset								
Younger		Lucca et al. 1993 [295]	56	DSM-III	BIMC	BIMC 17.1 ± 4.4	1 year	Multivariate
Younger		Jacobs et al. 1994 [296]	127	NINCDS-AD RDA probable AD	modified MMSE (0-57)	mMMSE 38 ± 5.8	2 years	Multivariate
Younger		Rasmusson et al. 1996 [88]	132	NINCDS-AD RDA probable AD	MMSE	MMSE 16.7 ± 4.0	up to 7.5 years (mean 2.5 yrs)	Univariate
Younger		Galasko et al. 2000 [89]	299	NINCDS-AD RDA prob. and poss. AD	MMSE, DRS	MMSE 19.1 ± 5.9	up to 8 years	Multivariate
No difference		Kramer-Ginsberg et al. 1988 [294]	60	NINCDS-AD RDA probable AD	ADAS cog+noncog	ADAS 48.8 ± 22.0	1-2 years	Univariate
No difference		Ortof & Crystal 1989 [213]	54	DSM-III	Blessed test	Blessed score mean 5.4 (range 3-10)	12-98 months (mean 32 mo)	Univariate
No difference		Burns et al. 1991 [293]	85	NINCDS-AD RDA probable AD	MMSE	MMSE 10.0 ± 5.9	1 year	Univariate
No difference		Stern et al. 1992 [216]	111	NINCDS-AD RDA probable AD	modified BIMC (0-27)	nr	6-96 months (mean 30.5 mo)	Multivariate
Older		Huff et al. 1987 [210]	77	NINCDS-AD RDA	BDS	BDS 20.7 ± 11.7	3 months or more	Univariate

**Table A4. Predictors of a faster rate of cognitive decline in AD**

Predictor	Outcome effect	Reference	Number of patients	Diagnostic criteria	Outcome measure	Cognitive score at entry <sup>a</sup>	Length of study	Univariate/multivariate analysis <sup>b</sup>
Age at entry								
Younger		Mortimer et al. 1992 [215]	65	NINCDS-ADRD probable AD	MMSE	MMSE 17.2 ± 4.8	up to 4 years (mean 2.3 yrs)	Multivariate
Younger		Teri et al. 1995 [220]	156	NINCDS-ADRD probable AD	DRS	MMSE 20.7 ± 4.8	1-5 years (mean 2 yrs)	Multivariate
Younger		Rasmuson et al. 1996 [88]	132	NINCDS-ADRD probable AD	MMSE	MMSE 16.7 ± 4.0	up to 7.5 years (mean 2.5 yrs)	Univariate
Younger		Mendiondo et al. 2000 [221]	719	nr	MMSE	nr	0.5-7 years (mean 2.3 yrs)	Multivariate
No difference		Katzman et al. 1988 [211]	161	NINCDS-ADRD prob. and poss. AD	BIMC	BIMC 13.2 ± 8.2	mean 2.2 years	Univariate
No difference		Burns et al. 1991 [293]	85	NINCDS-ADRD probable AD	MMSE	MMSE 10.0 ± 5.9	1 year	Univariate
No difference		Teri et al. 1995 [220]	156	NINCDS-ADRD probable AD	MMSE	MMSE 20.7 ± 4.8	1-5 years (mean 2 yrs)	Multivariate



Table A5. Predictors of a faster rate of cognitive decline in AD

Predictor	Outcome effect	Reference	Number of patients	Diagnostic criteria	Outcome measure	Cognitive score at entry <sup>c</sup>	Length of study	Univariate/multivariate analysis <sup>b</sup>
Level of education	Higher	Teri et al. 1995 [220]	156	NINCDS-ADRD probable AD	MMSE, DRS	MMSE 20.7 ± 4.8	1-5 years (mean 2 yrs)	Multivariate
	Higher	Rasmuson et al. 1996 [88]	132	NINCDS-ADRD probable AD	MMSE	MMSE 16.7 ± 4.0	up to 7.5 years (mean 2.5 yrs)	Multivariate
	Higher	Galasko et al. 2000 [89]	299	NINCDS-ADRD prob. and poss. AD	DRS	MMSE 19.1 ± 5.9	up to 8 years	Multivariate
	Higher	Mendiondo et al. 2000 [221]	719	nr	MMSE	nr	0.5-7 years (mean 2.3 yrs)	Multivariate
No difference	Katzman et al. 1988 [211]	161	NINCDS-ADRD prob. and poss. AD	BIMC	BIMC 13.2 ± 8.2	mean 2.2 years	Univariate	
No difference	Burns et al. 1991 [293]	85	NINCDS-ADRD probable AD	MMSE	MMSE 10.0 ± 5.9	1 year	Univariate	
No difference	Mortimer et al. 1992 [215]	65	NINCDS-ADRD probable AD	MMSE	MMSE 17.2 ± 4.8	up to 4 years (mean 2.3 yrs)	Multivariate	
No difference	Galasko et al. 2000 [89]	299	NINCDS-ADRD prob. and poss. AD	MMSE	MMSE 19.1 ± 5.9	up to 8 years	Multivariate	

**Table A6. Predictors of a faster rate of cognitive decline in AD**

Predictor	Outcome effect	Reference	Number of patients	Diagnostic criteria	Outcome measure	Cognitive score at entry <sup>a</sup>	Length of study	Univariate/ multivariate analysis <sup>b</sup>
<b>APOE genotype</b>	2 ε4 alleles	Craft et al. 1998 [297]	201	NINCDS-ADRDA probable AD, DSM-III-R	DRS	MMSE, mean 20.2-21.9	1-6 years (mean 2.5 yrs)	Multivariate
	2 ε4 alleles	Martins et al. 2005 [240]	218	NINCDS-ADRDA prob. and poss. AD	CAMCOG	CAMCOG, mean 64.5-72.7	mean 2.5-3.1 years	Multivariate
	No difference	Growdon et al. 1996 [298]	66	NINCDS-ADRDA probable AD	BDS	BDS, mean 9.5-11.2	up to 5.5 years (mean 2 yrs)	Multivariate
	No difference	Rasmusson et al. 1996 [88]	29	NINCDS-ADRDA probable AD	MMSE	MMSE 16.7 ± 4.0	up to 7.5 years (mean 2.5 yrs)	Multivariate
	0 ε4 alleles	Stern et al. 1997 [299]	99	NINCDS-ADRDA probable AD, mMMSE ≥ 30	modified MMSE (0-57)	mMMSE 38.2 ± 5.4	0.5-6 years	Univariate
	0 or 1 ε4 allele	Hoyt et al. 2005 [300]	151	NINCDS-ADRDA probable AD	MMSE	MMSE, mean 17.8-21.1	mean 3.2-3.6 years	Univariate



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# Paper 1



# Predicting Long-Term Cognitive Outcome with New Regression Models in Donepezil-Treated Alzheimer Patients in a Naturalistic Setting

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## Key Words

Alzheimer disease · Longitudinal studies · Cholinesterase inhibitors · Donepezil · Disease progression · Illness index, severity · Statistical models · Regression analysis · Psychiatric status rating scales

## Abstract

**Background/Aims:** To build and analyze regression models predicting (1) the long-term cognitive outcome in donepezil-treated patients with Alzheimer's disease, and (2) the short-term (6 months) cognitive impact of treatment depending on cognitive severity at baseline. **Methods:** The Swedish Alzheimer Treatment Study (SATS) is an open-label, non-randomized, 3-year, multicentre study in a routine clinical setting. A total of 435 patients, mostly in the mild and moderate stages of Alzheimer's disease, received the cholinesterase inhibitor donepezil. They were assessed with the Mini-Mental State Examination (MMSE) and Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-cog) at baseline and every 6 months for a total period of 3 years. Regression models were fitted from the actual scores at different intervals for the prediction of the cognitive outcome. **Results:** The ADAS-cog and MMSE scores during the 3-year treatment period could be predicted with a high degree of explanation using regression models ( $p < 0.001$ ). Moreover, there was a significant relation between the mean cognitive change after 6 months of treatment and the baseline scores

on MMSE ( $p < 0.01$ ) and ADAS-cog ( $p < 0.001$ ), respectively. **Conclusion:** Statistical models can be used to predict cognitive outcome in donepezil-treated cohorts of AD patients. These models can be clinically valuable, for example when assessing the efficacy of new therapies when added to cholinesterase inhibitor treatment.

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## Introduction

Alzheimer's disease (AD) is the most common form of dementia, accounting for more than half of the patients with dementia [1]. The pathogenic process of AD probably starts decades before the clinical onset of the disease [2]. The insidious onset sometimes makes it difficult to be certain that a cognitive disease has actually started and often complicates the initial diagnosis. As a consequence, AD is diagnosed at variable intervals after the first onset of symptoms [3].

Placebo-controlled clinical trials with a duration of up to 1 year have shown that cholinesterase inhibitors (ChEI) are effective in slowing down the apparent clinical progression of AD [4–7]. Furthermore, extension studies of placebo-controlled trials have shown that the effect of ChEI may last even longer [8–10], and a few long-term studies in a routine clinical setting have also described the effects of ChEI [11]. Nevertheless, there are studies

that have questioned the efficacy of ChEI because of small clinical benefits and insufficient methods in the clinical trials [12].

There are no investigations, however, predicting the long-term effects of ChEI in naturalistic settings and how they can alter the natural course of AD. In this study we therefore focus on the longitudinal outcome of cognitive ability in AD patients treated with ChEI. Mathematical models of expected cognitive decline in AD have previously been analyzed in non-treated populations. In these models different rates of decline in various stages of the disease have been described [13, 14].

The possibility of predicting progression rates in ChEI-treated AD patients could aid clinicians, patients and their families in decision-making. It would be important to know whether the patient is declining at a rapid or a slow rate and how long it might take before clinically meaningful deterioration occurs [3]. Further, the health and social services would have the opportunity to predict when more demanding care for the patient or nursing home placement is needed. It has previously been shown that estimations regarding the course of the disease are useful when comparing different populations for both clinical and research purposes [13].

The aim of this study was to build and analyze regression models for the prediction of the cognitive outcome during long-term (3 years) treatment with donepezil. We also studied the short-term (6 months) impact of donepezil treatment on cognition dependent on the patient's cognitive severity at baseline.

## Materials and Methods

### Study and Subjects

The Swedish Alzheimer Treatment Study (SATS) was started in order to investigate the long-term efficacy of ChEI treatment in naturalistic AD patients in a routine clinical setting. SATS is a 3-year, prospective, open-label, observational, non-randomized, multicentre study. Most patients are in the mild or moderate stages of the disease [the baseline Mini-Mental State Examination (MMSE) score was  $22.0 \pm 4.6$ ; table 1]. The 435 donepezil-treated subjects included in this study were the first AD patients who had the opportunity to complete the full 3-year SATS programme. They were prospectively recruited from 10 memory clinics specializing in dementia care in different parts of Sweden. The demographic and clinical characteristics are displayed in table 1.

The full SATS protocol and other results from this set of patients have been described in a previous publication [11]. Briefly, all patients underwent a thorough clinical investigation including medical history, physical and neurological examination, laboratory tests and a cerebral computerized tomography in order to rule out other causes of dementia. Outpatients aged 40 years and

**Table 1.** Demographics and clinical characteristics (n = 435)

### a Demographics

Variable	Number	Percent	n
Gender, males/females	153/282	35/65	435
Education level, compulsory/higher	294/139	68/32	433
APOE $\epsilon 4$ carrier, no/yes	143/278	34/66	421

### b Clinical characteristics

Variable	Mean $\pm$ SD	Range	n
Estimated age at onset of dementia, years	71.5 $\pm$ 6.9	48–86	433
Age at baseline, years	74.6 $\pm$ 6.5	50–87	435
Estimated duration of dementia at baseline, years	3.1 $\pm$ 2.3		433
MMSE at baseline	22.0 $\pm$ 4.6	30–6	435
ADAS-cog (0–70) at baseline	20.7 $\pm$ 10.0	3–59	420
Donepezil mean dose during the entire follow-up period, mg/day	6.7 $\pm$ 1.7	3.4–9.4	435
Follow-up visits per subject	5.6 $\pm$ 2.2	1–8	435

Education level: compulsory = 9 years or less, higher = more than 9 years. Donepezil: after 1 year of treatment the mean dose  $\pm$  SD was  $7.4 \pm 2.6$  mg, after 2 years  $8.1 \pm 2.4$  mg and after 3 years  $8.3 \pm 2.4$  mg per day.

older who received the clinical diagnosis of dementia as defined by the Diagnostic and Statistical Manual of Mental Disorders, 4th edition [15] and probable or possible AD, according to the criteria of the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association [16], were considered for inclusion. Moreover, the selected patients had to live at home at the time of diagnosis, had to have a caregiver and had to be assessable with the MMSE [17] at baseline. Medication other than anti-dementia drugs was allowed and recorded during the study. Patients not fulfilling the diagnostic criteria for AD and those already on active treatment with other ChEI or patients with contraindications to donepezil treatment were excluded from the study.

All patients gave informed consent to participate in the study which was conducted according to the provisions of the Helsinki Declaration and approved by the ethics committee of Lund University, Sweden.

The SATS patients were assessed in a structured follow-up programme over the course of 3 years with the purpose of evaluating cognition, global functioning and activities of daily living. In this paper we focus on the long-term effect of treatment on cognition evaluated using the MMSE and the Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-cog) [18]. The subjects were assessed at baseline and after 8 weeks (MMSE only) and then every 6 months after baseline during the 3-year period.

Following inclusion and baseline assessments, the patients received treatment with donepezil according to the approved prod-

uct labelling as in routine clinical practice. They started with 5 mg per day and most of them increased their dose to 10 mg per day after 4 weeks of treatment.

Reasons for study withdrawal were for example nursing home admission, change of therapy to another ChEI, death or withdrawal of consent. In general, the reasons for dropout in this naturalistic study are varied and sometimes complex and may not always be related to the patient or their dementia. For example, concomitant somatic disease can contribute to withdrawal of informed consent, compliance problems or nursing home placement, as can changes in the caregiver's health status or situation. Withdrawal of consent and switch to other ChEI are factors related to this study and not ordinary dropout reasons in an everyday clinical setting. A thorough dropout analysis has been presented in a previous article [11].

#### Data and Comparative Analyses

In the study reported here, we model the cognitive outcome in the donepezil-treated patients as follows. The 95% confidence interval (CI) is presented in the figures as a measure of dispersion in the regression models, i.e. this interval with 95% certainty contains the true mean cognitive score for a cohort of patients. The 95% prediction interval for the individual patient is too wide to specifically predict an individual patient's cognitive outcome and is therefore not presented. To facilitate comparisons of rates in MMSE and ADAS-cog scores, change of score is converted to positive values indicating improvement and negative values worsening.

#### ADAS-cog, Prediction of Outcome during 3 Years of Treatment

The actual ADAS-cog scores at each assessment were used in building the regression models. The time in months was defined between baseline and the exact number of months when the visit was performed. This method has the advantages of considering all data points and the correct time intervals. Stepwise multiple regression analysis was used to predict the ADAS-cog scores. The independent variables included in the analysis were: ADAS-cog score at baseline, time in months from baseline, baseline score by time interaction and the squares of these variables.

To predict the subsequent rate of cognitive change in untreated AD patients on the basis of ADAS-cog scores at study entry, Stern et al. [14] developed a multiple regression equation:

$$\begin{aligned} \text{Predicted ADAS-cog score at a time } t = & \\ -6.039689 + 1.329485 x_1 - 0.005392 x_1^2 & \\ + (0.031974 + 0.036652 x_1 - 0.000473634 x_1^2) t & \end{aligned}$$

In this equation,  $t$  = time from baseline and  $x_1$  = baseline ADAS-cog score for an individual.

#### MMSE, Prediction of Outcome during 3 Years of Treatment

As with ADAS-cog scores similar calculations and regression analysis were performed.

As a comparison, a meta-analysis of 37 studies of non-treated AD patients described an annual MMSE mean rate of 3.3 points decline (95% CI: 2.9–3.7) [19]. A large sample follow-up study of untreated AD patients showed an annual mean MMSE decline between 2.2 and 4.1 points during the 4-year study [20]. Hence, the annual decrease of the MMSE score in untreated patients was estimated at 2–4 points/year.

#### ADAS-cog Change after 6 Months of Treatment

The ADAS-cog change in score between baseline and the 6-month assessment was calculated ( $n = 353$ ). If the number of months between baseline and the 6-month visit differed from 6, the figure was adjusted:

$$\text{Change of score}_{\text{ADAS}} = \frac{(\text{baseline score}_{\text{ADAS}} - 6\text{-month score}_{\text{ADAS}})}{(\text{actual time in months between visits}/6)}$$

For each baseline score the mean of all 6-month change scores was calculated before building the regression models. The advantages of this method are that it uses all data points and does not assume linearity. Linear, quadratic and cubic regression models were built to assess the amount of variation explained by the model, i.e. the best fit.

To predict the rate of decline in non-treated patients with AD the Stern model was used [14]. The equation shows a quadratic relationship between cognitive severity at baseline measured by ADAS-cog and the annual rate of cognitive change. To obtain the 6-month rate of change in untreated patients, the equation was divided by 2:

$$\begin{aligned} \text{Annual rate of cognitive change} = & \\ -6.357 + & \\ (1.022 \times \text{baseline score}) - (0.01339 \times \text{baseline score}^2). & \end{aligned}$$

#### MMSE Change after 6 Months of Treatment

Similarly, as with ADAS-cog, the MMSE change in score was calculated ( $n = 378$ ) and the stated models were tested:

$$\text{Change of score}_{\text{MMSE}} = \frac{(6\text{-month score}_{\text{MMSE}} - \text{baseline score}_{\text{MMSE}})}{(\text{actual time in months between visits}/6)}$$

Annual mean changes in MMSE score ( $\pm$  standard error) for different values of baseline MMSE between 3 and 24 in untreated AD patients have been presented previously by Mendiondo et al. [13]. These values divided by 2 to obtain the 6-month changes have been used as a comparison to our model. The standard errors were computed to CI.

#### Statistical Analyses

The SPSS program version 15.0 was applied to perform the statistical analyses. The level of significance was defined as  $p < 0.05$  if not otherwise specified.

Observed case analyses were performed to avoid over-estimating the treatment effect by imputing higher, earlier outcome scores over a long-term study of patients suffering from a progressively deteriorating disease.

The procedures linear regression and curve estimation were used to find the regression models with the best fit. Predicted scores were only calculated for patients still participating in the study. Collinearity analyses of the variables included in the regression models showed no sign of multicollinearity, i.e. the undesirable situation when one independent variable is a linear function of other independent variables.

The independent-samples t test was used to compare the mean differences between the completers and the dropouts. Pearson's correlation coefficient was calculated investigating any linear associations between changes during the course of the disease. The possible deviation in slopes of cognitive change between completers and dropouts was analyzed using a random coefficient model.

## Results

### *ADAS-cog, Prediction of Outcome during 3 Years of Treatment*

For patients with at least 3 assessments each (330 patients, 1,402 observation points) we predicted a longitudinal regression model for the dependent variable ADAS-cog score (fig. 1). The multiple linear regression analysis had most of the variation explained by the model, i.e. showed the best fit ( $R^2 = 0.627$ ,  $R = 0.792$ ,  $p < 0.001$ ). All coefficients were significant at the  $p < 0.001$  level.

Predicted ADAS-cog score in ChEI-treated patients at a time  $t$ :

$$\hat{Y} = -3.966908 + (0.287507 \times t) + (1.124336 \times x_i)$$

where  $t$  = time in months between the first score (baseline) and the actual visit and  $x_i$  = baseline (time 0) ADAS-cog score for patient  $i$ .

The model presented in figure 1 shows a favourable effect on cognition in ChEI-treated patients compared to the Stern model of untreated patients [14], with significant differences between the ADAS-cog mean scores from 6 months and onwards ( $p < 0.001$ ). In the present study with an ADAS-cog mean score of 20.7 at the start of treatment the model indicates almost 5 months of improvement in cognition before again reaching the baseline mean score.

### *MMSE, Prediction of Outcome during 3 Years of Treatment*

We predicted a longitudinal regression model for the dependent variable MMSE score (fig. 2) for patients with at least 3 assessments each (390 patients, 1,955 observation points). This multiple non-linear regression analysis showed the best fit ( $R^2 = 0.563$ ,  $R = 0.750$ ,  $p < 0.001$ ). All coefficients were significant at the  $p < 0.001$  level).

Predicted MMSE score in ChEI-treated patients at a time  $t$ :

$$\hat{Y} = 4.913161 + (-0.377400 \times t) + (0.826765 \times x_i) + (0.010307 \times tx_i)$$

where  $t$  = time in months between the first score (baseline) and the actual visit and  $x_i$  = baseline (time 0) MMSE score for patient  $i$ .

The regression model in figure 2 shows a positive effect on cognition in ChEI-treated patients. It indicates 7 months of improvement in cognition before reaching the MMSE mean score at the start of treatment.

### *ADAS-cog Change after 6 Months of Treatment*

The short-term (6 months) cognitive impact of donepezil treatment dependent on the patient's cognitive severity at baseline was also investigated. There was a significant quadratic and cubic component between baseline scores on ADAS-cog versus 6-month mean cognitive change. We present the cubic model that has most of the variation explained by the model, i.e. the best fit (fig. 3a, b). The first 6-month rate of ADAS-cog change after the start of donepezil treatment was strongly dependent on the baseline score ( $R^2 = 0.389$ ,  $R = 0.624$ ,  $p = 0.0002$ ).

Predicted ADAS-cog change after 6 months of ChEI treatment:

$$\hat{Y} = -1.897176 + (0.156200 \times x_i) + (-0.007530 \times x_i^2) + (0.000133 \times x_i^3)$$

where  $x_i$  = baseline (time 0) ADAS-cog score for patient  $i$ .

The predicted mean rate of change was more rapidly improved for the more severely affected patients with 30 and above on the ADAS-cog scale (fig. 3a). The expected ADAS-cog mean rate of change varied from a 1.5-point decline at 6 months in the group of patients with a baseline score of 5 to as much as a 2.3-point improvement at 6 months in the group with a baseline score of 45 (fig. 3a). Figure 3b shows examples of how to interpret the figure. The expected mean rate of change in ADAS-cog after 6 months of treatment will be approximately a 1-point improvement in a group of patients with a baseline score of 40 and a 1-point decline in a group with a baseline score of 20.

### *MMSE Change after 6 Months of Treatment*

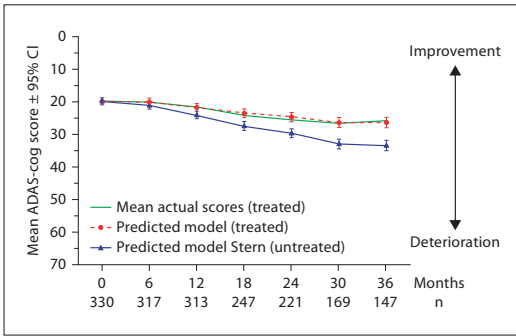
As with ADAS-cog, there was a significant quadratic and cubic component between MMSE baseline scores versus 6-month mean cognitive change. In figure 4a, b we present the cubic model that has the best fit. The first 6-month rate of MMSE change after the start of donepezil treatment also showed a strong dependence on the baseline score ( $R^2 = 0.482$ ,  $R = 0.695$ ,  $p = 0.0069$ ).

Predicted MMSE change after 6 months of ChEI treatment:

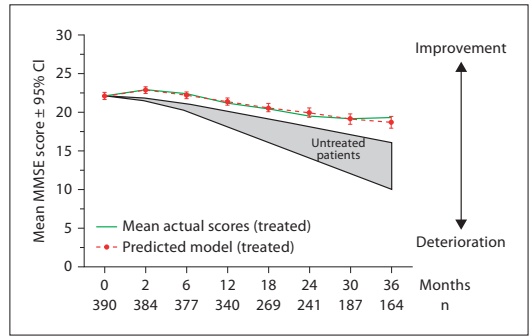
$$\hat{Y} = 9.210926 + (-1.293101 \times x_i) + (0.067108 \times x_i^2) + (-0.001188 \times x_i^3)$$

where  $x_i$  = baseline (time 0) MMSE score for patient  $i$ .

Further, the more impaired patients with 17 and below on the MMSE scale appeared to obtain more rapid improvement (fig. 4a). The expected mean rate of change in MMSE after 6 months of donepezil treatment varied



**Fig. 1.** Predicted ADAS-cog mean scores with 95% CI from our regression model regarding donepezil-treated patients.  $\hat{Y} = -3.966908 + (0.287507 \times t) + (1.124336 \times x_i)$ , where  $t$  is the time in months between the first score (baseline) and the actual visit, and  $x_i$  is the baseline score on the ADAS-cog scale at time 0 for patient  $i$ . The individuals' actual mean scores are also presented. The mean predicted scores with 95% CI from the Stern equation [14] calculated from untreated patients are also included in the figure for comparison.



**Fig. 2.** Predicted MMSE mean scores with 95% CI from the multiple non-linear regression model calculated from donepezil-treated patients.  $\hat{Y} = 4.913161 + (-0.377400 t) + (0.826765 \times x_i) + (0.010307 \times tx_i)$ , where  $t$  is the time in months between the baseline score and the actual visit, and  $x_i$  is the baseline score on the MMSE scale at time 0 for patient  $i$ . The subjects' actual mean scores are presented in the figure as well. The shaded area shows the decline of 2–4 MMSE points/year based on historical untreated patients [19, 20].

from a 1.3-point improvement in the group of patients with a baseline score of 12 to a 0.2-point decline in those with a baseline score of 27, although predicting the high scores can be uncertain due to the ceiling effect (fig. 4a). Figure 4b shows some examples. The expected mean rate of change in MMSE after 6 months of treatment will be approximately a 1-point improvement in a group of patients with a baseline score of 15 and a 0.5-point improvement in a group with a baseline score of 23.

Moreover, we studied whether the initial change of cognition during the first 6 months of donepezil treatment has any linear association with cognitive change in later stages of the disease in the same patient. When ADAS-cog and MMSE changes during 0–6 months were compared with the changes during a period halfway in the study (12–18 months) and with the last period (30–36 months), no significant correlations were found.

#### Dropout Analyses

A comparison of the baseline characteristics for the completers and the dropouts showed that the dropouts were older at baseline ( $75.2 \pm 6.2$  vs.  $73.8 \pm 7.0$  years,  $p = 0.016$ ), had higher ADAS-cog scores at baseline ( $22.1 \pm 10.3$  vs.  $18.5 \pm 9.2$ ,  $p < 0.001$ ) and lower MMSE scores ( $21.5 \pm 4.6$  vs.  $22.9 \pm 4.3$ ,  $p = 0.002$ ). The 2 groups did not differ in gender, ApoE type or duration of the disease.

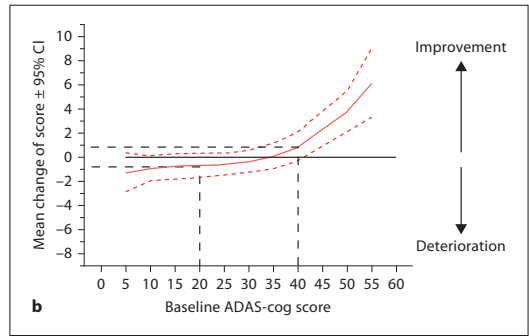
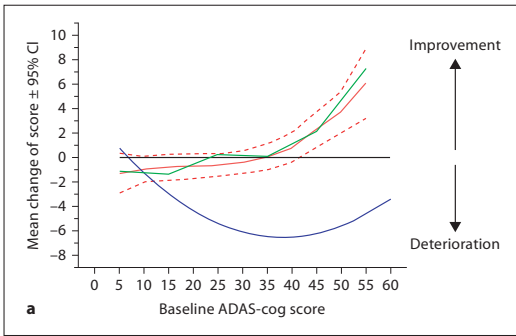
By using the cognitive score at baseline as a predictor (independent) variable, the regression model takes the lower mean cognitive ability at baseline in the dropout cohort into consideration. Age at baseline was not a significant variable when included in the regression models.

Residual analysis was used to study if there were any mean differences between the regression residuals [observed values ( $Y$ ) – predicted values ( $\hat{Y}$ )] in the 2 groups, dropouts and completers. No significant differences in ADAS-cog residuals ( $p < 0.237$ ) and MMSE residuals ( $p < 0.493$ ) were found. Figures illustrating the distribution of completers and dropouts in relation to the predicted and the observed values from the regression models have also been analyzed (not presented in the article), and no systematic bias was identified.

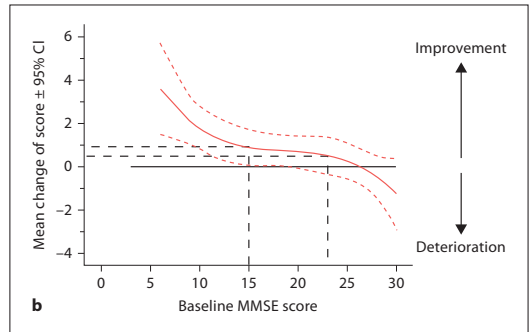
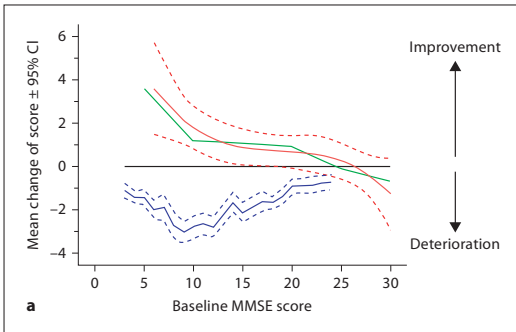
Random coefficient models were applied to compare the slopes of cognitive change between the 166 patients (38%) who completed the study and those who dropped out for any reason ( $n = 269$ , 62%). The models analyzed possible deviations between the 2 groups using the difference between the last 2 measurements of ADAS-cog ( $p < 0.137$ ) and of MMSE ( $p < 0.843$ ), thus demonstrating that the slopes of cognitive change between the completers and dropouts were not statistically different.

The main reasons for dropout from the study were: admission to nursing home in 26% of the dropout cohort





**Fig. 3. a** Predicted ADAS-cog mean change with 95% CI after 6 months of donepezil treatment as a function of the baseline score (red line), compared to mean change in untreated patients according to the Stern equation [14] (blue line). The patients' actual ADAS-cog mean changes grouped according to their baseline scores are also presented (green line). **b** Examples of how to interpret the figure. The expected mean rate of change in ADAS-cog after 6 months of donepezil treatment will be approximately a 1-point improvement in a group of patients with a baseline score of 40 and a 1-point decline in a group with a baseline score of 20. Predicted model:  $\hat{Y} = -1.897176 + (0.156200 \times x_i) + (-0.007530 \times x_i^2) + (0.000133 \times x_i^3)$ , where  $x_i$  is the baseline score on the ADAS-cog scale at time 0 for patient  $i$ .



**Fig. 4. a** Predicted MMSE mean change with 95% CI after 6 months of donepezil treatment as a function of the baseline score (red line), compared to mean change with 95% CI from a previous study of untreated patients [13] (blue line). The actual MMSE mean changes grouped according to baseline score are shown as well (green line). **b** Examples. The expected mean rate of change in MMSE after 6 months of treatment will be approximately a 1-point improvement in a group of patients with a baseline score of 15 and a 0.5-point improvement in a group with a baseline score of 23. Predicted model:  $\hat{Y} = 9.210926 + (-1.293101 \times x_i) + (0.067108 \times x_i^2) + (-0.001188 \times x_i^3)$ , where  $x_i$  is the baseline score on the MMSE scale at time 0 for patient  $i$ .

(i.e. 16% of the initial cohort), switch to other ChEI in 7% (4%), death in 9% (6%), withdrawal of informed consent in 9% (6%), side-effects in 13% (8%), compliance problems in 10% (6%), poor effect/deterioration in 9% (6%) and somatic disease unrelated to donepezil treatment in 6% (4%).

## Discussion

In this study we found that it is possible to predict both the short- and long-term cognitive outcome for donepezil-treated patients with a substantial degree of explanation of the variance in the data set. Further, the predicted

models for changes in ADAS-cog and MMSE scores are similar, which gives creditability to the results.

The course of the disease in 95% of the donepezil-treated groups of naturalistic AD patients will follow within 2 standard deviations, i.e. the 95% CI of the presented models, assuming the population is normally distributed. The 95% prediction interval for the individual case is too wide to specifically predict an individual patient's cognitive outcome; therefore the regression models are not adapted to predict the outcome for the individual patient. Nevertheless, the models might serve as an approximation of the development of the disease course over time in ChEI-treated patients. It could be possible to notice if the individual's disease progresses at a fast or slow rate and might aid the physician in detecting clinical developments during the disease course that are atypical and merit evaluation of superimposed problems [21]. Moreover, knowledge about the predicted course of AD might help caregivers and the social services to facilitate planning in response to the increased demands for medical and social resources.

Staging and monitoring the disease is important while recruiting patients for studies at definable levels of disease severity [22]. The changes in progression rate in our models can be used in clinical research, e.g. when measuring the efficacy of new disease-modifying therapies that might alter the course of the illness. Due to ethical reasons, trials investigating the effects of new drugs are at present being performed in patients already treated with ChEI. Hence, future research would benefit from access to stable models of expected change in ChEI-treated patients.

The advantages of the SATS 3-year treatment study are the prospective, well-structured follow-up assessments of large cohorts of ChEI-treated patients in a routine clinical setting. With the use of wide inclusion criteria, the acceptance of coexisting illnesses and concomitant medication we sought for more ordinary patients than the highly selected ones usually included in clinical trials. Consequently, the results can be applied to the everyday patient in a memory clinic.

The residual analysis and the slopes of cognitive change between the completers and dropouts were not statistically different. The regression models take the difference in cognitive ability at baseline between the 2 groups into consideration. Moreover, any systematic bias between the groups could not be detected in the models, which is an indication that they can be applied to both groups. Thus, in a naturalistic setting, the patients who stay on the drug and continue their assessments at the

clinics are those who will be the focus of evaluation. Compared to 3-year ChEI treatment open-label extensions [9, 10, 23, 24], or other open studies from naturalistic settings [25], this study has one of the highest completion rates.

A limitation of long-term studies is, however, that they cannot be placebo controlled, since placebo-controlled designs in AD treatment studies exceeding 3–6 months are no longer considered ethical. Hence, we are restricted to evaluating the long-term response to treatment using ADAS-cog and MMSE data derived from historical cohorts of AD patients or mathematical models. There are important methodological limitations to these kinds of comparisons, such as lack of randomization and open-label administration of ChEI. In particular, differences in clinical characteristics at baseline between the treated and historical groups may invalidate comparisons.

To minimize this discrepancy, the regression models in the present study, as well as in the Stern model predicting cognitive decline in untreated patients [14], take into consideration the cognitive scores at baseline. The Stern equation is often used in long-term treatment studies as a substitute for a placebo group [23, 26]. The cognitive status at baseline is one aspect that can serve as an indication of the level and extent of AD [27], therefore assuming an identical cognitive status at baseline when using the models for between-group comparisons. Nevertheless, patients with identical cognitive status can express large variations in pathological burden and clinical phenotype [28]. Severity of the disease has been described as an important predictor of the rate of cognitive decline in AD patients [20].

There are no studies published previously that predict the cognitive long-term effects of ChEI in a routine clinical setting. For verification of the regression models, exact comparisons between our models and the previous long-term extension trials are not possible to perform, as this requires access to the original data sets. Nevertheless, rough approximate scores of cognitive change can be estimated based on the reported mean cognitive scores at baseline. One study [10] reported an MMSE decline of 4.92 points after continuous treatment with donepezil during 3 years, which is consistent with the predictions from our model. In 2 extension trials with continuous galantamine treatment [23, 29], the patients' ADAS-cog changes after 3 years had deteriorated by 10.2 and 12.4 points, respectively. An approximation from our regression model will estimate an outcome of around 10 points, indicating that it can also be applied to treatment with galantamine.

One extension trial of rivastigmine [24] describes a faster MMSE decline than in our predicted models. However, in this study a substantial number of patients had extensive interruptions of their treatment before entering the extension study and consequently had less than 2 full years of exposure to rivastigmine at the 2-year assessment [26]. Persistent therapy seems to be required to maintain maximum drug benefits [8].

In a combined study from 3 large randomized placebo-controlled trials of rivastigmine [30], cohorts with more advanced cognitive dysfunction at baseline tended to show better treatment versus placebo response on the ADAS-cog scale than those with milder baseline cognitive dysfunction. This is consistent with our regression models that predict a more pronounced improvement in cognition after 6 months of treatment for the more severely affected patients.

In conclusion, this study shows that the SATS longitudinal data set can be used to calculate models with a high degree of explanation for the prediction of cognitive change in cohorts of continuously donepezil-treated AD patients. Future long-term studies in clinical practice are needed for further evaluation of the presented models and verification if they can be applied to other types of ChEI treatment.

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## Paper 2



# Predictors of long-term cognitive outcome in Alzheimer's disease

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## Abstract

**Introduction:** The objective of this study was to describe the longitudinal cognitive outcome in Alzheimer's disease (AD) and analyze factors that affect the outcome, including the impact of different cholinesterase inhibitors (ChEI).

**Methods:** In an open, three-year, nonrandomized, prospective, multicenter study, 843 patients were treated with donepezil, rivastigmine, or galantamine in a routine clinical setting. At baseline and every 6 months, patients were assessed using several rating scales, including the Mini-Mental State Examination (MMSE) and the Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-cog) and the dose of ChEI was recorded. Sociodemographic and clinical characteristics were investigated. The relationships of these predictors with longitudinal cognitive ability were analyzed using mixed-effects models.

**Results:** Slower long-term cognitive decline was associated with a higher cognitive ability at baseline or a lower level of education. The improvement in cognitive response after 6 months of ChEI therapy and a more positive longitudinal outcome were related to a higher mean dose of ChEI, nonsteroidal anti-inflammatory drug (NSAID)/acetylsalicylic acid usage, male gender, older age, and absence of the apolipoprotein E (APOE)  $\epsilon 4$  allele. More severe cognitive impairment at baseline also predicted an improved response to ChEI treatment after 6 months. The type of ChEI agent did not influence the short-term response or the long-term outcome.

**Conclusions:** In this 3-year AD study performed in a routine clinical practice, the response to ChEI treatment and longitudinal cognitive outcome were better in males, older individuals, noncarriers of the APOE  $\epsilon 4$  allele, patients treated with NSAIDs/acetylsalicylic acid, and those receiving a higher dose of ChEI, regardless of drug agent.



# 1. Introduction

Alzheimer's disease (AD) is the most prevalent cause of dementia among the elderly, accounting for 50%–60% of cases [1]. This progressive neurodegenerative disease affects approximately 24 million individuals worldwide, with one new case detected every 7 seconds [2]. AD patients exhibit symptoms of decline in executive functions, memory impairment, visuospatial and language difficulties, and behavioral disturbances [3].

The loss of cholinergic transmission is assumed as one of the causes of the cognitive deterioration detected in patients with AD [4]. Based on this cholinergic hypothesis, several acetylcholinesterase inhibitors (ChEIs) have been introduced as treatments for AD. The ChEIs available currently (i.e., donepezil, rivastigmine, and galantamine) yielded modest improvements in cognition and global performance compared with placebo treatment in subjects with varying degrees of AD severity. The benefits of this treatment regarding activities of daily living (ADL) and behavior were also observed [5, 6].

However, not every patient benefits from ChEI treatment. The heterogeneity in cognitive outcome and response to treatment emphasize the importance of identifying patients who respond positively to the treatment, to enhance the drug efficacy and its cost benefits in AD [7].

No prospective head-to-head studies of ChEI therapy in AD longer than 2 years have been published. Two long-term randomized studies have been reported: a 2-year trial of donepezil vs rivastigmine [8] and a 1-year comparison of donepezil and galantamine [9]. The three drug agents were compared in several naturalistic 6–9-month studies from the Italian Chronos project [10–12] and in one study from Spain [13]. Regarding cognition, all but one study found no differences between the drugs. A 12-week open-label trial showed that donepezil was superior to galantamine [14]. Conflicting results concerning ADL have been described [8, 10, 14].

The longitudinal course of AD is complex and several sociodemographic and clinical factors, such as younger age or higher education [15, 16],

being a carrier of the apolipoprotein E (APOE)  $\epsilon 4$  allele [17], or moderate-to-severe level of dementia [15, 18] have been suggested to increase the rate of cognitive decline in untreated patients. Other studies showed that these variables had no effect on disease progression: age [16], education [19], presence of the APOE  $\epsilon 4$  allele [20], or level of dementia [21]. An improved response to ChEI treatment was observed in patients who were more cognitively impaired [7, 22]. Inconsistent results were found regarding gender [23, 24] and age [10, 25]. The divergent results of these studies imply that the influence of these factors needs further investigation. Advanced multivariate methods can provide a clearer pattern of the complex impact of predictors.

In this study, we used mixed-effects models (linear and nonlinear) to achieve a higher resolution in the analysis of the long-term association between potential predictive characteristics, including a comparison of the three ChEI agents, on the cognitive outcome of AD patients in a routine clinical setting.

The aims of this study were: 1) to identify the sociodemographic and clinical factors that influence the longitudinal cognitive outcome and response to ChEI treatment, and 2) to study the impact of different ChEI agents and dosages.

## 2. Methods

### 2.1. Study and subjects

The Swedish Alzheimer Treatment Study (SATS) was started to investigate the long-term efficacy of ChEI treatment in naturalistic AD patients in clinical practice. SATS is a 3-year, open-label, observational, nonrandomized, multicenter study that was described in detail previously [26]. Its purpose is the evaluation of cognition, global performance, and ADL every 6 months. The subjects were prospectively recruited from 14 memory clinics located in different areas of Sweden. Most participants are in the mild-to-moderate stages of the disease and the SATS is still ongoing. All subjects exhibiting a baseline Mini-Mental State Ex-

amination (MMSE) [27] score ranging from 10 to 26 and for whom at least three measurements were available per individual (to model nonlinearity in the trajectories better) [28, 29] were included in this study. Eight hundred forty-three patients (donepezil,  $n = 456$ ; rivastigmine,  $n = 183$ ; and galantamine,  $n = 204$ ) who were enrolled until the end of December 2005 fulfilled these criteria, thus having the opportunity to complete the full 3-year SATS program.

Outpatients aged 40 years and older who met the criteria for the clinical diagnosis of dementia, as defined by the Diagnostic and Statistical Manual of Mental Disorders, 4<sup>th</sup> ed (DSM-IV) [30], and for possible or probable AD, according to the criteria of the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer’s Disease and related Disorders Association (NINCDS-ADRDA) [31], were considered for inclusion. All patients were diagnosed by physicians specialized in dementia disorders. Moreover, the selected patients had to live at home at the time of diagnosis, have a responsible caregiver, and be assessable with the MMSE at the start of the ChEI treatment (baseline). After the baseline assessments, patients were prescribed a ChEI treatment according to the approved product labeling and paid for their own medication, as in a routine clinical practice. The choice of drug and dosage for the individual patient was left entirely up to the physician’s discretion and professional judgment. Medications other than antidementia drugs were allowed and documented during the study. Reasons for study withdrawal were recorded and presented for this cohort of patients. Nursing-home placement was not a reason for dropout if the patient was able to continue to visit the clinic. All patients and/or caregivers provided informed consent to participate in the study, which was conducted according to the provisions of the Helsinki Declaration and was approved by the Ethics Committee of Lund University, Sweden.

## 2.2. Outcome measures

Cognitive ability was assessed using the MMSE, with scores ranging from 0 to 30 (a lower score

indicating more impaired cognition), and the Alzheimer’s Disease Assessment Scale-cognitive subscale (ADAS-cog) [32], with a total range of 0 to 70 (a higher score indicating more impaired cognition).

The Instrumental Activity of Daily Living (IADL) scale [33] consists of eight different items: ability to use the telephone, shopping, food preparation, housekeeping, laundry, mode of transportation, responsibility for own medications, and handling of finances. Each item was scored from 1 (no impairment) to 3–5 (severe impairment), which yielded a total range of 8–31 points. A mathematical correction of the sum of the IADL scores was performed to avoid gender-dependent activities affecting the result [34]. The Physical Self-Maintenance Scale (PSMS) [33] consists of six different items: toilet, feeding, dressing, grooming, physical ambulation, and bathing. Each item was scored from 1 (no impairment) to 5 (severe impairment), which allowed a total range of 6–30 points. Trained dementia nurses obtained the ADL evaluation from an interview with the caregiver. To facilitate the comparison of rates in MMSE, ADAS-cog, IADL, and PSMS scores, changes in score were converted to positive values, which were indicative of improvement, and negative values, which were indicative of decline.

## 2.3. Statistical analyses

The IBM SPSS statistics software (version 18.0; SPSS Inc., Chicago, IL, USA) was used to perform the statistical analyses. The level of significance was defined as  $p < 0.05$  if not otherwise specified. Observed-case analyses were performed to avoid overestimation of the treatment effect by imputing higher, previous outcome scores in a long-term study of a progressively deteriorating disease.

One-way analysis of variance (ANOVA) with Bonferroni correction was used to compare the differences between the means obtained for the three independent groups, a  $t$  test was performed to analyze two independent groups, and a  $\chi^2$  test was computed to analyze categorical variables.

Estimates of effect sizes were computed using Cohen's  $d$  ( $d = \text{difference in group means/error SD}_{\text{within}}$ ). Cohen's  $d$  was calculated as the difference between predicted means from the final mixed-effects model for a given pair of groups divided by the estimated within-group error standard deviation in the model.

### 2.3.1. Mixed models

Mixed, linear and nonlinear, fixed and random coefficient regression models [35] using "subject" as a hierarchical variable (i.e., to allow correlation within subjects) were analyzed. The mixed models method also takes into account variations in the number of follow-up assessments available for the participants and unequal time intervals between the collected data points, which are common statistical limitations observed in longitudinal studies. The noncompleters contributed information during the time of participation; thus, we considered the trajectories of all patients. Collinearity analyses of the variables included in the models showed no sign of multicollinearity, i.e., the undesirable situation where one independent variable is a linear function of other independent variables. Model assumptions were checked using residual analyses.

Time was defined as the exact number of months between the baseline and each visit, thus using all data points at the correct time intervals. To adjust for baseline differences, the initial cognitive scores for each patient and their interaction with linear and quadratic terms for months in the study (to enable a nonlinear rate of decline in the models) were included as fixed effects, i.e., Time in months (or Time in months<sup>2</sup>)  $\times$  MMSE (or ADAS-cog) baseline score. Thus, the dependent variables were the cognitive scores assigned at the second and subsequent assessments for each patient, that is, the models do not intend to predict the scores at the start of ChEI treatment. The random terms in the models were an intercept and time in months, with an unstructured covariance matrix. Several sociodemographic and clinical background variables were also included as fixed effects. The predictors investigated were classi-

cal risk factors, such as age at first assessment (in years), the clinician's estimate of age at onset (in years), gender, years of education, carrier of the APOE  $\epsilon 4$  allele, solitary living, functional ability, and number of medications at baseline. In addition, concomitant medications (antihypertensive/cardiac therapy, antidiabetics, lipid-lowering agents, estrogens, nonsteroidal anti-inflammatory drugs (NSAIDs)/acetylsalicylic acid, antidepressants, antipsychotics, and anxiolytics/sedatives/hypnotics) were included. The impact of ChEI treatment was analyzed using the different drug agents and dosages. Finally, some biologically plausible interactions with cognitive severity at the start of treatment or with time in the study were included in the models, i.e., gender, education, age, and functional ability at baseline. The terms "gender with carrier of APOE  $\epsilon 4$  allele" and "type of ChEI with dose" were also included.

The ChEI agents were coded as a set of dummy variables. The dose could vary during the treatment period for an individual patient and between patients. Therefore, the mean dose used during the entire follow-up period was calculated for each patient. Furthermore, to obtain a similar metric of percent maximum dosage for the three ChEIs, the mean dose was divided by the maximum recommended dose for each drug, i.e., 10 mg for donepezil, 12 mg for rivastigmine, and 24 mg for galantamine. The change of dosage between the assessments was also calculated using the percentage of maximum dose. Nonsignificant variables ( $p > 0.05$ ) were removed in a backward stepwise elimination manner. The hierarchical principle was observed in these analyses; terms that appeared in interactions were not considered for elimination.

## 3. Results

### 3.1. Baseline characteristics

The demographic and clinical characteristics of the 843 patients, who were divided into groups corresponding to the three ChEI-agents, donepezil ( $n = 456$ , 54%), rivastigmine ( $n = 183$ , 22%),

and galantamine ( $n = 204$ , 24%), are displayed in Table 1. The rivastigmine cohort exhibited a significantly smaller proportion of individuals living alone (22%) compared with the donepezil (38%) and galantamine (35%) groups ( $p < 0.001$ ).

Lipid-lowering agents were only used by 6% of the donepezil-treated subjects, whereas 16% of the patients in the other two cohorts were treated with this type of medication ( $p < 0.001$ ). The usage of antidiabetics and antipsychotics differed between the donepezil and the galantamine cohort: 4% vs 8% ( $p = 0.048$ ) and 6% vs 2% ( $p = 0.015$ ), respectively.

The donepezil-treated subjects had a higher mean age of onset of AD ( $F(2, 836) = 3.80$ ,  $p = 0.023$ ), were older ( $F(2, 840) = 5.69$ ,  $p = 0.004$ ), and exhibited a more impaired basic ADL ability ( $F(2, 825) = 4.40$ ,  $p = 0.013$ ) at the start of the ChEI treatment compared with the galantamine cohort. A higher level of education was found among the individuals treated with galantamine ( $F(2, 838) = 8.00$ ,  $p < 0.001$ ), whereas lower cognitive ability, as assessed using ADAS-cog scores ( $F(2, 824) = 10.32$ ,  $p < 0.001$ ) (but not using the MMSE), and more impaired instrumental ADL ability at baseline ( $F(2, 825) = 14.18$ ,  $p < 0.001$ ) were detected for the donepezil cohort compared with the other patients.

The three ChEI groups did not differ in gender, carrier status of APOE  $\epsilon 4$  allele, completion rate after 3 years, medication use (antihypertensive/ cardiac therapy, estrogens, NSAIDs/acetylsalicylic acid, antidepressants, and anxiolytics/sedatives/ hypnotics), estimated duration of AD, MMSE baseline score, number of medications at baseline, or number of visits per subject.

No difference in MMSE or ADAS-cog scores at the start of ChEI treatment was detected regarding gender, presence of the APOE  $\epsilon 4$  allele (no/yes), or usage of NSAID/acetylsalicylic acid therapy (no/yes). Male patients had significantly more years of education compared with females (mean  $\pm$  SD,  $9.7 \pm 2.8$  vs  $9.2 \pm 2.3$  years;  $t(839) = 3.09$ ;  $p = 0.003$ ). A higher level of education was also observed for individuals carrying the APOE  $\epsilon 4$  allele compared with noncarriers ( $9.6 \pm 2.6$  vs  $9.1 \pm 2.2$  years;  $t(825) = -2.68$ ;  $p = 0.005$ ). No significant

difference regarding mean years of education was found between those who used NSAID/acetylsalicylic acid therapy and those who did not. Carriers of the APOE  $\epsilon 4$  allele were significantly younger at the start of ChEI treatment compared with noncarriers ( $74.2 \pm 7.2$  vs  $76.4 \pm 6.7$  years;  $t(827) = 4.08$ ;  $p < 0.001$ ). Patients receiving NSAID/acetylsalicylic acid therapy were older than those not using this medication ( $77.4 \pm 5.5$  vs  $73.9 \pm 7.5$  years;  $t(839) = -6.76$ ;  $p < 0.001$ ). No significant age difference was detected between genders.

To describe and compare the cognitive ability at baseline among patients with various ages and years of education, patients were divided into three subgroups according to age ( $\leq 70$ , 71–80, and  $> 80$  years) and education ( $\leq 9$ , 10–12, and  $> 12$  years). The oldest age group ( $> 80$  years) was significantly more impaired than the other groups regarding its ADAS cog score of  $22.4 \pm 9.0$  compared with  $19.9 \pm 9.5$  for the  $\leq 70$  years group and  $20.2 \pm 8.5$  for the 71–80 years group ( $F(2, 824) = 4.47$ ,  $p = 0.012$ ). Using the MMSE scale, there were no differences in baseline scores among the age groups. The group with the lowest level of education ( $\leq 9$  years) had a significantly lower cognitive ability at baseline (MMSE,  $21.1 \pm 3.8$ ; ADAS-cog,  $21.2 \pm 8.8$ ) compared with the highest educated group ( $> 12$  years) (MMSE,  $22.9 \pm 3.3$ ;  $F(2, 838) = 11.43$ ;  $p < 0.001$ ; and ADAS-cog,  $17.6 \pm 8.5$ ;  $F(2, 822) = 7.87$ ;  $p < 0.001$ ).

## 3.2. Long-term outcomes

The MMSE mean difference from the baseline score [95% confidence interval (CI)] was  $-0.6$  ( $-0.8$  to  $-0.3$ ) after 1 year of ChEI treatment,  $-2.3$  ( $-2.7$  to  $-1.9$ ) after 2 years, and  $-3.2$  ( $-3.7$  to  $-2.7$ ) after 3 years. The ADAS-cog mean difference from the baseline score (95% CI) was  $-1.8$  ( $-2.3$  to  $-1.3$ ),  $-4.8$  ( $-5.6$  to  $-4.0$ ), and  $-7.3$  ( $-8.5$  to  $-6.1$ ), at 1, 2, and 3 years after the start of treatment, respectively. No differences were detected among the three ChEI agents.

### 3.2.1. ChEI dose

During the study, an increasing number of patients received higher doses of ChEI. After 1 year,

the mean  $\pm$  SD doses of donepezil, rivastigmine, and galantamine were  $7.7 \pm 2.5$ ,  $7.7 \pm 2.9$ , and  $18.8 \pm 4.5$  mg, respectively. After 2 years, they were  $8.3 \pm 2.4$ ,  $8.2 \pm 2.9$ , and  $19.4 \pm 4.7$  mg, respectively. Finally, after 3 years, the doses were  $8.4 \pm 2.4$ ,  $8.3 \pm 2.7$ , and  $20.0 \pm 4.7$  mg, respectively.

### 3.2.2. Dropout analyses

Overall, 56% of the patients who had at least three assessments did not complete the 3-year study. The reasons for dropout from the study were: admission to nursing home (13%,  $n = 110$ ), initiation of concomitant memantine therapy (8%,  $n = 66$ ), poor effect/deterioration (6%,  $n = 48$ ), death (5%,  $n = 44$ ), withdrawal of informed consent (5%,  $n = 39$ ), compliance problems (4%,  $n = 37$ ), side effects (4%,  $n = 35$ ), switching to another study (3%,  $n = 24$ ), switching to another ChEI agent (2%,  $n = 18$ ), somatic disease unrelated to ChEI treatment (2%,  $n = 17$ ), and other reasons (4%,  $n = 35$ ).

Table 2 shows that the completers exhibited significantly better cognitive and functional abilities at the start of the ChEI treatment compared with the noncompleters ( $p < 0.001$ ) and received a higher mean dose of ChEI during the study ( $p < 0.001$ ). The other variables of interest in this study, such as gender, presence of the APOE  $\epsilon 4$  allele, age at baseline, years of education, and usage of NSAIDs/acetylsalicylic acid, did not differ between the completers and those who discontinued the study.

In the multivariate mixed models, a better 6-month response to ChEI therapy was observed for the completers using both MMSE and ADAS-cog scores as outcome variables ( $p = 0.001$ ). However, the subsequent long-term rate of cognitive decline was not different between the completers and the noncompleters. Adjustment for “dropout” (no/yes) as an additional independent variable in the models did not alter the outcome of the other significant predictor variables.

### 3.3. Factors that affected the outcome

Mixed-effects (fixed and random, linear and non-linear) models were performed (4,136 observa-

tion points) to identify the sociodemographic and clinical factors that affected the long-term MMSE and ADAS-cog outcomes. The models, significant predictors, and unstandardized  $\beta$  coefficients with 95% CI are presented in Table 3; the predicted mean scores with 95% CI are presented in Table 4. Estimates of effect sizes using Cohen's  $d$  for significant predictors in the final mixed models are presented in Table 5. Slower deterioration in cognitive ability was observed for patients with less cognitive impairment at baseline. Noncarriers of the APOE  $\epsilon 4$  allele (ADAS-cog only) and patients receiving NSAID/acetylsalicylic acid therapy or a higher dose of ChEI (regardless of drug agent) exhibited a greater response to ChEI therapy after 6 months, with Cohen's  $d$  values ranging from 0.22 to 0.50, indicating small to medium effect sizes. The interaction effects of cognitive severity and age at baseline, time in months from the start of treatment, gender, and years of education showed that these variables cannot be interpreted separately. Male patients exhibited a greater response to ChEI treatment after 6 months compared with females, as measured using the MMSE scale, although the effect size was small (0.19) (Fig. 1a). In addition, an interaction effect between gender and ADAS-cog score at baseline demonstrated that this difference and the magnitude of effects were more pronounced in subjects who were more cognitively impaired (Fig. 1b). As an example, male individuals with a baseline ADAS-cog score of 40 responded, on average, 3.1 points better than females, and males with a baseline ADAS-cog score of 20 responded an additional 0.9 points better compared with females.

Older individuals exhibited a better response to treatment compared with younger subjects, if they had MMSE scores  $< 22$  at baseline (Fig. 2a) and through all levels of ADAS-cog score (Fig. 2b). The interaction Cognitive ability  $\times$  Age at start of treatment exhibited a greater age difference and larger effect sizes (0.53–1.55) for patients with more cognitive severity. For example, 85-year-old individuals with a baseline MMSE score of 15 responded on average 2.2 points better than 65-year-old individuals, and 85-year-old individuals with a baseline ADAS-cog score of 40

responded an additional 6.2 points better compared with 65-year-old individuals after 6 months of ChEI treatment. Moreover, there was an interaction effect between years of education and time in the study. Differential dropout over time did not cause this effect, as no difference regarding mean years of education was detected for patients with different numbers of assessments ( $F(5, 835) = 1.56; p = 0.168$ ). A higher level of education implied increased cognitive impairment over time, with a magnitude of effects of 0.38–1.10 after 3 years. As an example, a subject with 15 years of education exhibited on average an additional 2.2 points of MMSE and 3.0 points of ADAS-cog deterioration after 3 years compared with an individual with 9 years of education.

If not otherwise specified, the arbitrary examples of patients presented in the figures were based on an average male that was aged 75 years, was a carrier of the APOE  $\epsilon 4$  allele, did not receive NSAID/acetylsalicylic acid therapy, had 9 years of education, exhibited an IADL score of 16, and received 65% of the maximum recommended dose of ChEI.

The background variables solitary living, concomitant medications (with the exception of NSAIDs), age at onset, basic ADL ability, type of ChEI agent, change of dosage and the interaction effects, Gender  $\times$  Carrier of APOE  $\epsilon 4$  allele, and Type of ChEI  $\times$  Dose were not significant when included in the mixed models. The percentages of variance accounted for in the dependent variable, regarding all fixed predictors, were 53.7% for MMSE and 57.8% for ADAS-cog, which implies a good fit of the models ( $p < 0.001$ ).

## 4. Discussion

Using mixed models, we found that a higher mean dose of ChEI, male gender, older age, NSAID/acetylsalicylic acid therapy, and absence of the APOE  $\epsilon 4$  allele were predictors of a better short-term ChEI-treatment response and long-term outcome. The type of ChEI did not influence the results. The patients that were more severely impaired cognitively exhibited a better response to

ChEI therapy, but declined faster subsequently. Individuals with a lower level of education showed a slower cognitive decline. These findings were similar for both the MMSE and ADAS-cog scales; however, ADAS-cog is more sensitive in detecting effects, which gives credibility to the results. For example, the graded effects of baseline cognitive ability with gender or with age were observed more clearly using the ADAS-cog scale and had larger effect sizes.

Our SATS cohort reflects the alteration of patient characteristics and treatment of AD over more than one decade. During the years that ChEI treatment has been available, the patient population has evolved to become younger, better educated, and exhibit less disease severity at baseline. The prescription of lipid-lowering agents has become more common, whereas antipsychotics have been less used, as more patients seek care and treatment at an earlier stage of AD. In this study, these differences were observed between the donepezil cohort enrolled earlier and the galantamine subjects included later. Similar changes were described in other long-term studies [36] and show the need for using advanced multivariate methods, such as mixed models, to compensate adequately for differences and effects of interactions or time between the treatment cohorts.

The rate of disease progression varies among AD patients; however, the knowledge on prognostic factors is limited [37]. In the present study, a faster deterioration in cognition was observed for the patients that were more severely impaired after their initial response to treatment. A more rapid decline in ADL performance in individuals with lower cognitive ability was also described in a recent study from our group [34]. Moreover, in this study, a better cognitive response to treatment was observed among males, which was in agreement with the multivariate results obtained in a 3-month study of tacrine and galantamine [23]. A lower percentage of males was also described among the rapid progressors in a longitudinal study of progression rate [38]. Inconsistently, a review of sex influences on ChEI treatment in AD found that a clear relation was not established between gender and response to therapy. The pos-

sible sex differences reported in that review were small and exhibited large individual variation; thus, this subject requires further investigation. The morphological brain differences between genders or sex hormones are theories that could explain this dissimilar response to treatment [39].

Older age was a predictor of a better treatment response in the current study, whereas the subsequent rate of cognitive deterioration was not related to age. However, an interaction effect between age and cognitive severity was identified. The oldest patients (> 80 years) in this study were more cognitively impaired at baseline and exhibited a marked positive response to ChEI therapy; however, severity, and not age, predicted a faster long-term progression. In contrast, the younger-age group (< 65 years) showed greater improvement in a 3-month donepezil study that used a univariate analysis [25]. However, the patients had a somewhat lower mean cognitive ability compared with that of our cohort, and the analysis did not adjust for that factor, which could influence the outcome (as discussed above). A recent meta-analysis model of AD progression reported the absence of a significant impact of age; however, the distribution of the mean age in the model was narrow [40]. Other studies found a faster rate of cognitive decline in younger individuals [15, 37]. It is reasonable to assume that AD progresses more rapidly when the disease is detected at younger ages, as hereditary and more aggressive variants of the disease may have a greater influence on the outcome [37].

In the present study, the individuals with the highest education (> 12 years) were less cognitively impaired at their baseline assessment, which is consistent with the patient characteristics described in a recent paper on progression rate [38]. A higher level of education was associated with faster cognitive deterioration in this study, as well as in several other reports [15, 16, 41], and with faster ADL decline, as reported in a previous study from our group [34]. Bennett et al. [42] suggested that the association between senile plaques and the level of cognitive function varies according to years of education, as it appeared that more education provides some form

of cognitive reserve. Furthermore, in accordance with this “brain-reserve hypothesis” [41], subjects with more years of education are expected to have higher cognitive ability during adulthood, thus requiring a relatively greater burden of pathology when dementia is clinically evident [42]. Nevertheless, some studies found inconsistent results or no association between the level of education and the rate of cognitive decline. Years of education or age had no significant effects in a multivariate comparison of ChEI- and memantine-treated patients, performed by Atri et al. [29]; however, the measures of dispersion in that cohort were small compared with those of our study. In contrast to the results of the current study, the group of slow preprogressors observed by Doody et al. [38] had a higher level of education, but this variable was not a significant predictor of longer-term ADAS-cog outcome. The high value of mean years of education (~13–14 years) reported in these American cohorts [29, 38] suggests a more narrow selection of patients compared with the sample included in the SATS (mean, 9.4 years of education). In Sweden, the health system is publicly funded and the income or insurance coverage of individuals is rarely an issue when seeking care [43].

In line with the results of this study regarding APOE genotype, Martins et al. [44] used a mixed model with nonlinear terms and observed that the presence of at least one APOE  $\epsilon 4$  allele may precipitate the rate of cognitive decline. Conflicting evidence regarding whether the  $\epsilon 4$  allele influences disease progression was found in other studies that used linear models [17, 20]. Nonlinear models proved to fit the data better compared with linear models in Martins’ study [44]; moreover, the mixed models method also takes the individual variability into account, which increases the variance explained to a larger extent. Unlike some studies of response to tacrine, which exhibited inconsistent associations between APOE genotype and gender, an open-label trial of donepezil demonstrated an absence of significant differences between the responses of  $\epsilon 4$ -carriers and noncarriers [24].

Interestingly, divergent results concerning the relationship between AD progression and NSAID

treatment have been discussed and this potential connection remains unresolved. In epidemiological studies, NSAIDs exhibited neuroprotective effects, suggesting a greater reduction in risk of AD with longer use of these drugs [45]. The Rotterdam study showed that a reduction in risk was only observed after the first 2 years of cumulative NSAID therapy [46] and the US Veterans study reported a marked decrease in the odds ratio for AD after 4 years of NSAID usage [47]. In contrast to our naturalistic study, the two randomized trials reported most recently, an 18-month [48] and a 12-month [49] study, found no beneficial effect of NSAID treatment vs placebo on cognitive response in AD populations. It is possible that these trials did not include a follow-up time that was sufficient for a protective effect to emerge compared with the longer perspective of the SATS. Longitudinal naturalistic studies with more detailed information regarding the specific NSAIDs used, dosing, etc. are needed to investigate further this potentially important finding. Knowledge of the factors that cause differences in outcome is essential for a better understanding of AD and its rate of progression.

Our study, as well as most previous publications comparing the three ChEI agents, showed no difference in effect on cognitive outcome among the drugs [11, 12]. However, higher doses of ChEIs were associated with a more positive long-term cognitive outcome in the present study, which is in agreement with the results of a meta-analysis of randomized trials, as the latter showed that larger ChEI doses were related to a larger effect [50]. Theoretically, if we assumed that the patients received 100% of the maximum recommended ChEI dose, instead of the average 65% observed in the SATS, our model would estimate a 6-month mean response to therapy of 4.0 ADAS-cog points, instead of 2.6 points. Treatment with a higher dose of ChEI was also related to significant delays in nursing-home placement [51, 52]. These results suggest the importance of using adequate ChEI doses in AD therapy.

The advantages of the SATS are the well-structured and prospective assessments of a large number of ChEI-treated AD patients in routine clinical

settings. Recognized scales are administered in a uniform manner across all centers. The scheduled 6-month visits and access to a responsible contact nurse for each subject represent security, continuity, and good quality of care. The 3-year completion rate of 44% obtained for the present cohort is high compared with other AD extension or naturalistic studies. Most prior publications report 20%–39% completers after 3 years [53–55]. The high dropout rate in long-term AD studies may contribute to greater mean cognitive scores for the patients remaining in the study, assuming that they benefit more from ChEI therapy. Our results showed that the completers received a higher mean dose of ChEI during the study, suggesting a better tolerance of the treatment. In the models, the outcomes of the noncompleters were also included during their time of participation. Other than the lower cognitive and functional abilities at baseline observed for the noncompleters, which the multivariate mixed models took into account, those patients were similar to the completers regarding the other characteristics. The reasons for dropout in long-term AD studies are complex and may vary considerably. For example, dropout caused by nursing-home placement might depend not only on the worsening of AD, but also on somatic diseases or changes in the health status of the caregiver.

The SATS is an open-label, nonrandomized study that might have variations between the treatment cohorts, which were not addressed by the model variables. The fact that placebo-controlled designs are not permitted (because of ethical concerns) is a limitation of AD therapy studies longer than 6 months; therefore, no control group was enrolled in the SATS. The presence of behavioral, psychotic, and extrapyramidal symptoms was not recorded in this study; these are factors that have been reported as affecting the rate of decline [28]. To compensate somewhat for this limitation, the use of psychiatric medications was included in the models; however, these variables exhibited no significant effect on outcome.

The ability to predict and distinguish overall outcomes would provide clinicians and social services with better tools to estimate the disease prognosis,



manage the patients, and plan for the future. It is important to recognize and treat patients with a better probability of response or a more aggressive course of AD as early as possible [56]. Knowledge and awareness of critical characteristics that may influence the response to, and outcome of, pharmaceutical trials are important. To improve the management of patients and enhance the efficacy of ChEI therapy and its cost benefits, it is essential to understand factors that influence response to treatment and longitudinal outcome in a routine clinical setting. For example, the patients that had more cognitive impairment in our study exhibited a better response to therapy, stressing the importance of not excluding this group from treatment opportunities.

## 5. Conclusions

In conclusion, this study showed that male gender, older age, absence of the APOE  $\epsilon 4$  allele, and NSAID/acetylsalicylic acid treatment or a higher mean dose of ChEI were predictors of better response to ChEI therapy and of a more favorable longitudinal outcome. Lower cognitive ability at baseline was a predictor of improved response to ChEI treatment. The long-term outcome was better for patients with a higher cognitive level at the start of therapy or for less-educated individuals. The demographic and clinical composition of the AD cohort under study may be one of the explanations for the heterogeneity of results observed in different studies. Future studies are warranted to investigate differences in response to treatment and longitudinal outcome based on various patient characteristics. Long-term protective effects, such as the possible impact of NSAIDs or other protective treatments, may take years to develop. The knowledge gained from naturalistic ChEI treatment studies will continue to be important.

## List of abbreviations

AD Alzheimer's disease

ADAS-cog	Alzheimer's Disease Assessment Scale – cognitive subscale
ADL	Activities of Daily Living
APOE	Apolipoprotein E
ChEI	Cholinesterase inhibitors
CI	Confidence interval
IADL	Instrumental Activities of Daily Living Scale
MMSE	Mini-Mental State Examination
NSAIDs	Non-Steroidal Anti-Inflammatory Drugs
PSMS	The Physical Self-Maintenance Scale
SATS	Swedish Alzheimer Treatment Study
SD	Standard deviation

## Competing interests

The authors declare that they have no competing interests.

## Authors' contributions

CW participated in the study, supervised the data collection, was responsible for the statistical design and for carrying out the statistical analyses, interpreted the results, and drafted the paper. AKW and EL participated in the study, assisted in the analysis and interpretation of the data, and revised the manuscript critically. LM designed the study and revised the manuscript critically. All authors read and approved the final manuscript.

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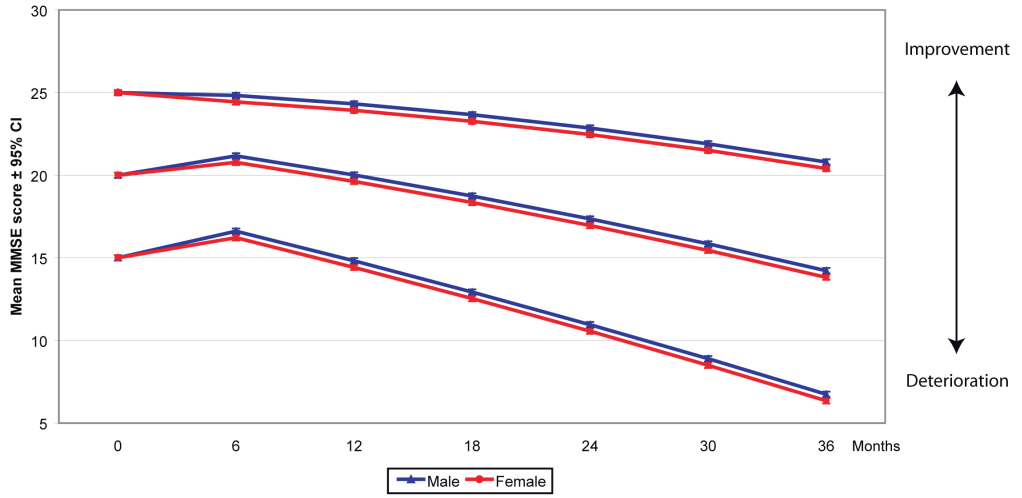
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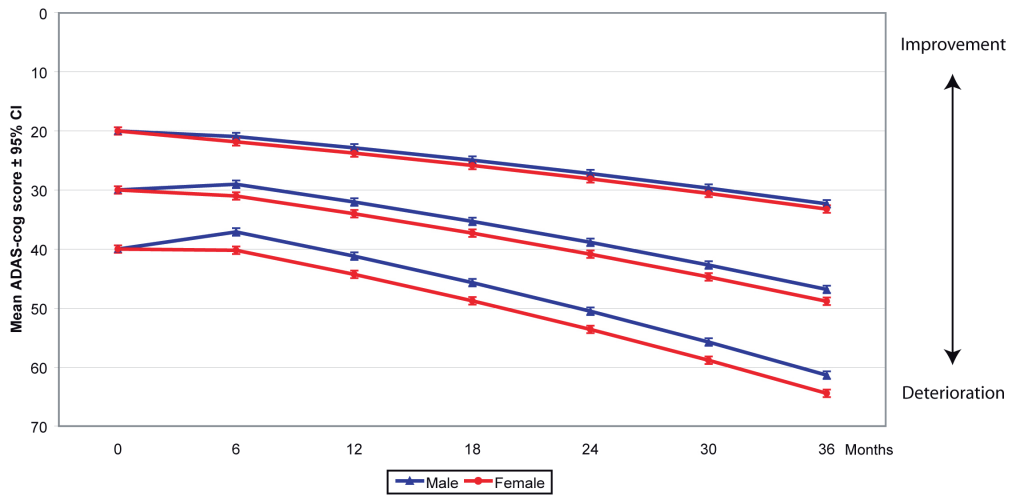
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**a** MMSE, prediction of outcome for different baseline scores divided by gender



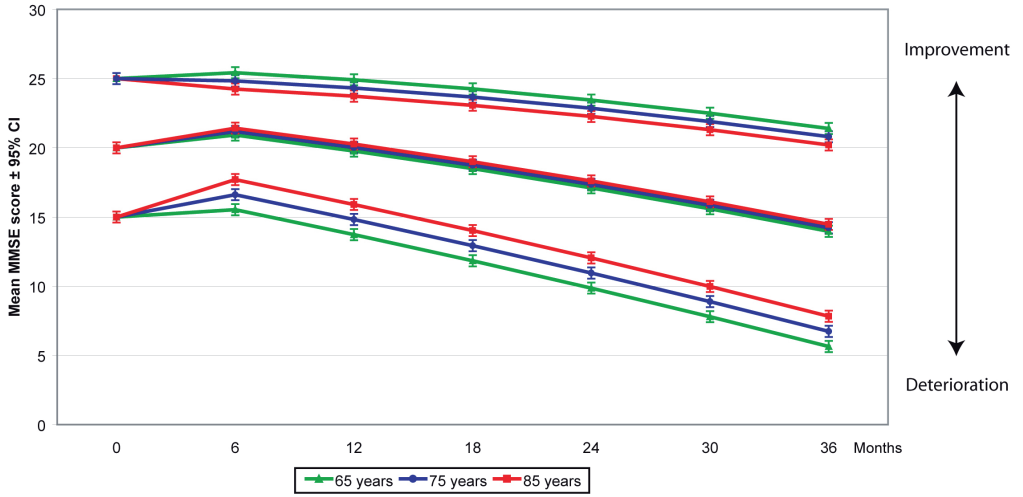
**b** ADAS-cog, prediction of outcome for different baseline scores divided by gender



Wattmo Figure 1

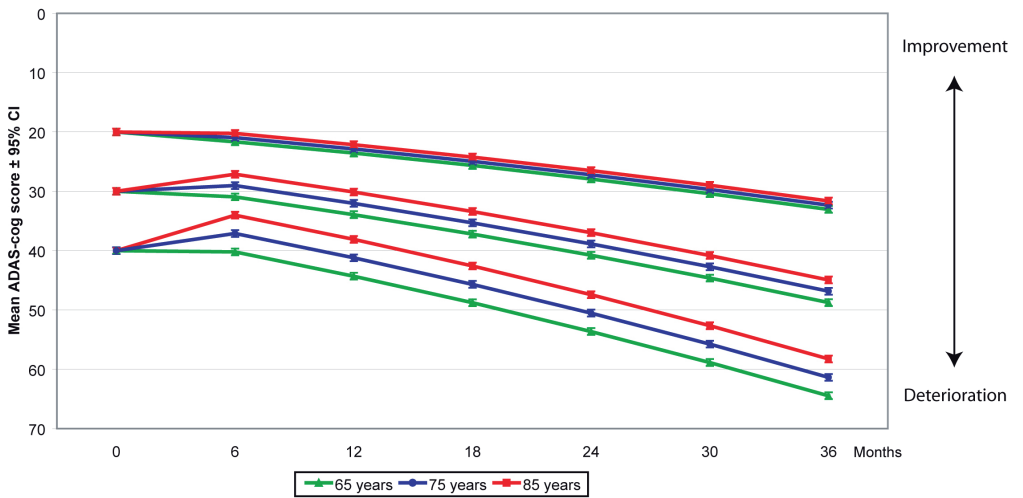
**a**

**MMSE, prediction of outcome for different baseline scores and ages**



**b**

**ADAS-cog, prediction of outcome for different baseline scores and ages**



Wattmo Figure 2

## Figure legends

### **Fig. 1a. MMSE, prediction of outcome for different baseline scores divided by gender**

Three-year mean outcomes with 95% confidence intervals predicted by the mixed models for patients with different Mini-Mental State Examination (MMSE) scores (15, 20, and 25 were used as arbitrary examples), at the start of ChEI treatment and according to gender. Males demonstrated a better 6-month treatment response compared with females ( $p = 0.010$ ). The calculated outcomes were based on a 75-year-old patient who did not receive NSAID/acetylsalicylic acid treatment, had 9 years of education, exhibited an IADL baseline score of 16, and received 65% of the maximum recommended dose of ChEI.

### **Fig. 1b. ADAS-cog, prediction of outcome for different baseline scores divided by gender**

Three-year mean outcomes with 95% confidence intervals predicted by the models for patients with different Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-cog) scores (20, 30, and 40 were used as arbitrary examples), at the start of treatment and according to gender. Male subjects showed a better response to treatment compared with females. An interaction effect of ADAS-cog baseline score  $\times$  Gender was detected ( $p = 0.015$ ), i.e., the difference between genders increased with lower baseline scores. The calculated outcomes were based on a 75-year-old patient who was an APOE  $\epsilon 4$  carrier, did not receive NSAID/acetylsalicylic acid treatment, had 9 years of education, exhibited an IADL baseline score of 16, and received 65% of the maximum recommended dose of ChEI.

### **Fig. 2a. MMSE, prediction of outcome for different baseline scores and ages**

Three-year mean outcomes with 95% confidence intervals predicted by the mixed models for patients with different Mini-Mental State Examination (MMSE) baseline scores (15, 20, and 25) and ages (65, 75, and 85 years), used as arbitrary examples. Older subjects with a baseline MMSE score  $< 22$  exhibited a better 6-month treatment response compared with younger patients ( $p < 0.001$ ). In addition, the interaction MMSE score  $\times$  Age at the start of ChEI treatment showed a more pronounced age difference at lower baseline scores ( $p < 0.001$ ). The calculated outcomes were based on a male

patient who did not receive NSAID/acetylsalicylic acid treatment, had 9 years of education, exhibited an IADL baseline score of 16, and received 65% of the maximum recommended dose of ChEI.

### **Fig. 2b. ADAS-cog, prediction of outcome for different baseline scores and ages**

Three-year mean outcomes with 95% confidence intervals predicted by the models for patients with different Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-cog) baseline scores (20, 30, and 40) and ages (65, 75, and 85 years), used as arbitrary examples. Older individuals exhibited a better response to treatment compared with younger subjects ( $p = 0.043$ ). The interaction ADAS-cog score  $\times$  Age at the start of treatment showed a greater age difference at lower baseline levels ( $p < 0.001$ ). The calculated outcomes were based on a male patient who was an APOE  $\epsilon 4$  carrier, did not receive NSAID/acetylsalicylic acid treatment, had 9 years of education, exhibited an IADL baseline score of 16, and received 65% of the maximum recommended dose of ChEI.

**Table 1. Demographic and clinical characteristics**

Variable	Donepezil n=456 / 54%	Rivastigmine n=183 / 22%	Galantamine n=204 / 24%	Total subjects n=843	p value
Female gender	295 / 65%	106 / 58%	133 / 65%	534 / 63%	0.229
APOE ε4 carrier, (n=829)	303 / 68%	119 / 66%	143 / 72%	565 / 68%	0.456
Solitary living at baseline	173 / 38% <sup>a</sup>	40 / 22% <sup>b</sup>	72 / 35% <sup>a</sup>	285 / 34%	<0.001
Completion rate after 3 years	190 / 42%	85 / 46%	93 / 46%	368 / 44%	0.447
Antihypertensives/Cardiac therapy	177 / 39%	83 / 45%	70 / 35%	330 / 39%	0.096
Antidiabetics	16 / 4% <sup>a</sup>	8 / 4% <sup>a,b</sup>	16 / 8% <sup>b</sup>	40 / 5%	0.048
Lipid-lowering agents	29 / 6% <sup>a</sup>	30 / 16% <sup>b</sup>	33 / 16% <sup>b</sup>	92 / 11%	<0.001
Estrogens	38 / 8%	13 / 7%	8 / 4%	59 / 7%	0.124
NSAIDs/Acetylsalicylic acid	127 / 28%	65 / 36%	61 / 30%	253 / 30%	0.160
Antidepressants	114 / 25%	42 / 23%	53 / 26%	209 / 25%	0.754
Antipsychotics	26 / 6% <sup>a</sup>	4 / 2% <sup>a,b</sup>	3 / 2% <sup>b</sup>	33 / 4%	0.015
Anxiolytics/Sedatives/Hypnotics	63 / 14%	26 / 14%	24 / 12%	113 / 13%	0.750

Variable	Mean ± standard deviation (SD)				p value
Estimated age at onset, years	72.6 ± 6.8 <sup>a</sup>	71.6 ± 7.9 <sup>a,b</sup>	70.9 ± 8.4 <sup>b</sup>	71.9 ± 7.4	0.023
Estimated AD duration, years	3.1 ± 2.2	3.1 ± 2.5	2.9 ± 1.6	3.0 ± 2.1	0.380
Age at first assessment, years	75.7 ± 6.4 <sup>a</sup>	74.6 ± 7.5 <sup>a,b</sup>	73.7 ± 8.1 <sup>b</sup>	75.0 ± 7.1	0.004
Education, years	9.3 ± 2.4 <sup>a</sup>	9.0 ± 2.3 <sup>a</sup>	10.0 ± 2.8 <sup>b</sup>	9.4 ± 2.5	<0.001
MMSE score at baseline	21.2 ± 3.8	21.6 ± 3.8	21.8 ± 3.6	21.4 ± 3.8	0.070
ADAS-cog score (0-70) at baseline	21.8 ± 8.8 <sup>a</sup>	19.6 ± 8.9 <sup>b</sup>	18.7 ± 8.7 <sup>b</sup>	20.6 ± 8.9	<0.001
IADL score at baseline	16.7 ± 5.5 <sup>a</sup>	15.3 ± 5.1 <sup>b</sup>	14.4 ± 5.3 <sup>b</sup>	15.9 ± 5.4	<0.001
PSMS score at baseline	7.6 ± 2.3 <sup>a</sup>	7.4 ± 1.8 <sup>a,b</sup>	7.1 ± 2.0 <sup>b</sup>	7.4 ± 2.1	0.013
Number of medications at baseline	2.8 ± 2.3	3.0 ± 2.6	2.8 ± 2.5	2.8 ± 2.4	0.448
Mean dose of ChEI during the entire follow-up period, mg/day	7.1 ± 1.8	6.5 ± 2.1	16.1 ± 3.4		
Follow up-visits per subject	5.9 ± 1.8	6.1 ± 1.7	6.1 ± 1.7	6.0 ± 1.8	0.380

<sup>a,b</sup>Results from post hoc tests (Bonferroni correction) are indicated by superscript letters (two groups with the same letter do not differ significantly within that variable).

Abbreviations: ADAS-cog – Alzheimer’s Disease Assessment Scale-cognitive subscale; APOE – Apolipoprotein E; ChEI – Cholinesterase inhibitors; IADL – Instrumental Activities of Daily Living scale; MMSE – Mini-Mental State Examination; NSAID – Nonsteroidal anti-inflammatory drugs; PSMS – Physical Self-Maintenance Scale.



**Table 2. A comparison of the completer and non-completer groups**

Variable	Completers n=368 / 44%	Non-completers n=475 / 56%	p value
Female gender	64%	62%	0.614
APOE ε4 carrier	67%	69%	0.652
Estimated age at onset, years <sup>a</sup>	71.8 ± 7.4	72.1 ± 7.5	0.513
Age at first assessment, years <sup>a</sup>	74.9 ± 7.1	75.0 ± 7.2	0.744
Education, years <sup>a</sup>	9.4 ± 2.5	9.4 ± 2.5	0.978
MMSE score at baseline <sup>a</sup>	22.3 ± 3.4	20.7 ± 3.9	<0.001
ADAS-cog score (0-70) at baseline <sup>a</sup>	18.2 ± 8.3	22.4 ± 8.9	<0.001
IADL score at baseline <sup>a</sup>	14.5 ± 5.3	16.9 ± 5.2	<0.001
PSMS score at baseline <sup>a</sup>	7.0 ± 1.7	7.8 ± 2.3	<0.001
Number of medications at baseline <sup>a</sup>	2.8 ± 2.5	2.8 ± 2.3	0.827
NSAIDs/acetylsalicylic acid	29%	31%	0.649
ChEI-dose <sup>b</sup>	70%	63%	<0.001

<sup>a</sup>Mean ± standard deviation

<sup>b</sup>Mean percentage of the maximum recommended dose i.e., 10 mg donepezil, 12 mg rivastigmine and 24 mg galantamine.

Abbreviations: ADAS-cog – Alzheimer’s Disease Assessment Scale-cognitive subscale; APOE – Apolipoprotein E; IADL – Instrumental Activities of Daily Living scale; MMSE – Mini-Mental State Examination; NSAID – Nonsteroidal anti-inflammatory drugs; PSMS – Physical Self-Maintenance Scale.

**Table 3. Factors affecting the long-term outcome with MMSE or ADAS-cog score as dependent variables**

Percentage of variance accounted for, all fixed terms	MMSE			ADAS-cog		
	53.7%, p<0.001			57.8%, p<0.001		
Significant predictors in final mixed models	$\beta$	95% CI ( $\beta$ )	p value	$\beta$	95% CI ( $\beta$ )	p value
<b>Fixed terms</b>						
Intercept	-25.766	-36.047, -15.484	<0.001	-8.756	-19.030, 1.518	0.095
Time in months from baseline	-0.507	-0.605, -0.409	<0.001	-0.211	-0.381, -0.040	0.016
MMSE (ADAS-cog) baseline score	2.666	2.074, 3.259	<0.001	1.604	1.157, 2.051	<0.001
MMSE (ADAS-cog) baseline score <sup>2</sup>	-0.018	-0.028, -0.008	<0.001			ns
Time in months $\times$ MMSE (ADAS-cog) baseline score	0.023	0.019, 0.027	<0.001	0.016	0.011, 0.021	<0.001
Time in months <sup>2</sup> $\times$ MMSE (ADAS-cog) baseline score	-0.0001	-0.0001, -0.0001	<0.001	0.0001	0.00004, 0.0002	0.004
<b>Background variables:</b>						
Gender (male=0, female=1)	-0.395	-0.718, -0.072	0.017	-1.290	-3.262, 0.681	0.199
MMSE (ADAS-cog) baseline score $\times$ Gender			ns	0.110	0.020, 0.199	0.016
APOE $\epsilon$ 4 carrier (no=0, yes=1)			ns	1.072	0.239, 1.906	0.012
NSAIDs/Acetylsalicylic acid (no=0, yes=1)	0.440	0.094, 0.785	0.013	-1.037	-1.890, -0.184	0.017
Education, years	0.085	0.017, 0.153	0.014	-0.147	-0.339, 0.044	0.131
Time in months $\times$ Education, years	-0.013	-0.019, -0.007	<0.001	0.018	0.003, 0.033	0.016
Age at first assessment, years	0.361	0.237, 0.485	<0.001	0.168	0.036, 0.300	0.013
MMSE (ADAS-cog) baseline score $\times$ Age	-0.017	-0.023, -0.011	<0.001	-0.012	-0.018, -0.006	<0.001
IADL score at baseline	-0.090	-0.124, -0.056	<0.001	0.256	0.170, 0.343	<0.001
ChEI-dose <sup>a</sup>	0.010	0.001, 0.018	0.024	-0.040	-0.062, -0.019	<0.001
<b>Random terms (variance)</b>						
Intercept	2.613	2.166, 3.153	<0.001	13.887	10.274, 18.770	<0.001
Time in months	0.027	0.023, 0.032	<0.001	0.131	0.108, 0.158	<0.001

Solitary living, concomitant medications with the exception of NSAIDs/Acetylsalicylic acid, age at onset, basic ADL ability, change of dosage and the variable comparing the ChEI agents were not significant.

$\beta$  values were unstandardized and are expressed per 1 unit increase for continuous variables and for the condition present in dichotomous variables.

<sup>a</sup>Mean percentage of the maximum recommended dose i.e., 10 mg donepezil, 12 mg rivastigmine and 24 mg galantamine.

Abbreviations: ADAS-cog – Alzheimer’s Disease Assessment Scale-cognitive subscale; APOE – Apolipoprotein E; ChEI – Cholinesterase inhibitors; CI – Confidence interval; IADL – Instrumental Activities of Daily Living scale; MMSE – Mini-Mental State Examination; NSAID – Nonsteroidal anti-inflammatory drugs; ns – not significant.

**Table 4. Predicted mean scores from the mixed models (95% confidence interval)**

Months in study	MMSE		ADAS-cog	
	Mean	95% CI	Mean	95% CI
6	21.6	(21.3, 21.8)	22.1	(21.4, 22.7)
12	20.6	(20.3, 20.8)	24.0	(23.3, 24.8)
18	19.4	(19.2, 19.7)	26.2	(25.4, 27.0)
24	18.2	(17.9, 18.5)	28.6	(27.8, 29.5)
30	16.8	(16.4, 17.2)	31.2	(30.2, 32.2)
36	15.3	(14.9, 15.7)	34.0	(32.9, 35.0)

Abbreviations: ADAS-cog – Alzheimer’s Disease Assessment Scale-cognitive subscale; MMSE – Mini-Mental State Examination.

**Table 5. Cohen’s *d* effect size estimates for significant predictors in final mixed models**

Time in months from start of ChEI treatment	MMSE			ADAS-cog <sup>a</sup>				
	6	12	36	6	12	36		
<b>Pairs of groups</b>								
Males vs females <sup>b</sup>	0.19	0.19	0.19	ADAS-cog score 40	0.77	0.77	0.77	
				30	0.50	0.50	0.50	
				20	0.23	0.23	0.23	
Age, 85 vs 65 years <sup>b</sup>	MMSE score 15	1.07	1.07	1.07	ADAS-cog score 40	1.55	1.55	1.55
	20	0.24	0.24	0.24	30	0.95	0.95	0.95
	25	-0.58	-0.58	-0.58	20	0.36	0.36	0.36
Age, 85 vs 75 years <sup>b</sup>	MMSE score 15	0.53	0.53	0.53	ADAS-cog score 40	0.78	0.78	0.78
	20	0.12	0.12	0.12	30	0.48	0.48	0.48
	25	-0.29	-0.29	-0.29	20	0.18	0.18	0.18
Age, 75 vs 65 years <sup>b</sup>	MMSE score 15	0.53	0.53	0.53	ADAS-cog score 40	0.78	0.78	0.78
	20	0.12	0.12	0.12	30	0.48	0.48	0.48
	25	-0.29	-0.29	-0.29	20	0.18	0.18	0.18
Education, 9 vs 15 years	-0.03	0.20	1.10		-0.06	0.10	0.75	
Education, 12 vs 15 years	-0.01	0.10	0.55		-0.03	0.05	0.38	
Education, 9 vs 12 years	-0.01	0.10	0.55		-0.03	0.05	0.38	
APOE ε4, noncarrier vs carrier	ns	ns	ns		0.27	0.27	0.27	
NSAIDs/Acetylsalicylic acid therapy, yes vs no	0.22	0.22	0.22		0.25	0.25	0.25	
ChEI-dose, 100% vs 50% <sup>c</sup>	0.24	0.24	0.24		0.50	0.50	0.50	

<sup>a</sup>To facilitate comparisons of effect sizes, the plus/minus sign is reversed for ADAS-cog.

<sup>b</sup>Due to the interaction effects ADAS-cog baseline score × Gender, MMSE baseline score × Age and ADAS-cog baseline score × Age, effect sizes are presented for MMSE scores of 15, 20 and 25 and for ADAS-cog scores of 20, 30 and 40, which are used as arbitrary examples.

<sup>c</sup>Mean percentage of the maximum recommended dose i.e., 10 mg donepezil, 12 mg rivastigmine and 24 mg galantamine.

Abbreviations: ADAS-cog – Alzheimer’s Disease Assessment Scale-cognitive subscale; APOE – Apolipoprotein E; ChEI - Cholinesterase inhibitors; MMSE – Mini-Mental State Examination; NSAID – Nonsteroidal anti-inflammatory drugs; ns – not significant.

# Paper 3



# Long-term Outcome and Prediction Models of Activities of Daily Living in Alzheimer Disease With Cholinesterase Inhibitor Treatment

Carina Wattmo, BSc, RN, Åsa K. Wallin, MD, PhD, Elisabet Londos, MD, PhD,  
and Lennart Minthon, MD, PhD

**Abstract:** In untreated patients with Alzheimer disease (AD) the functional ability is gradually lost. What happens to the patients after continuous long-term cholinesterase inhibitor (ChEI) treatment is less investigated. The objective of this study was to describe the longitudinal functional outcome and analyze factors affecting the outcome in ChEI-treated patients. In an open, 3-year, non-randomized, prospective, multicenter study in a routine clinical setting, 790 patients were treated with either donepezil, rivastigmine, or galantamine. At baseline and every 6 months, they were assessed with several rating scales including Instrumental Activities of Daily Living (IADL), Physical Self-Maintenance Scale (PSMS), and Mini-Mental State Examination (MMSE). A faster functional decline was associated with lower cognitive ability at baseline, older age, and the interaction of higher education and longer time in the study. The patients residing with a spouse or relative showed slower deterioration in IADL score. A higher mean dose of ChEI, regardless of drug agent, was also related to slower instrumental ADL decline. Prediction models for longitudinal functional outcome were provided. AD severity at baseline is a key factor in obtaining reliable clinical prognoses of the long-term ADL ability. The dosage of ChEI treatment could possibly lead to a different functional outcome.

**Key Words:** Alzheimer disease, activities of daily living, cholinesterase inhibitors, longitudinal study, statistical models, disease progression

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Alzheimer disease (AD) is the most common form of dementia in the elderly, and is considered today to be one of the principle causes of cost increments in the health care and social systems.<sup>1</sup> In addition to increasing cognitive impairment, patients with AD also experience a decline in

their ability to carry out activities of daily living (ADL). Deterioration in functional abilities is one of the most troubling aspects of dementia for patients and caregivers. The severity of disability is also considered to be the most critical factor behind nursing home placement.<sup>2</sup> Despite these facts, there has been appreciably less focus, on the investigation of ADL ability than that of cognitive severity in earlier long-term studies. An advantage ADL scales have over cognitive tests is that the information can be obtained from caregivers without having to test the patients. Furthermore, evaluations of functional abilities can extend the range of possible assessments in later, more severe stages of the disease when the usual cognitive evaluations become less sensitive.

Functional decline in AD is progressive and once lost, the ability to carry out daily activities is rarely recovered. The effect of cholinesterase inhibitor (ChEI) treatment on function is most likely to be observed as a delay in the time to decline rather than as an improvement over baseline.<sup>3</sup> Placebo-controlled clinical trials with a duration of up to 1 year have shown that ChEIs are effective in slowing functional deterioration.<sup>3–6</sup> Moreover, extension studies with ADL as a secondary efficacy measure have suggested that the effect of ChEI may last even longer,<sup>7,8</sup> and one cohort-matched study has shown functional benefits from ChEIs after 2 years of treatment.<sup>9</sup> Nevertheless, there are studies that have reported no significant effect on ADL ability compared with placebo<sup>10</sup> and studies with inconsistent results.<sup>11</sup>

Prior studies including untreated AD patients have reported on long-term functional outcome and expected functional decline has been analyzed earlier using mathematical models.<sup>12–15</sup> Studies on potential predictive factors that affect the longitudinal functional outcome in naturalistic ChEI-treated AD patients are scarce. One long-term randomized double-blind trial aimed to determine whether donepezil produced worthwhile improvements in disability,<sup>16</sup> and a naturalistic study examined the effects of ChEI and memantine on time to nursing home admission.<sup>17</sup> These studies, however, did not report the impact of the potential predictive characteristics on the longitudinal outcome. The long-term ADL trajectory, including possible affecting factors, was analyzed in a study that focused on the comparison of 3 naturalistic AD cohorts (untreated, ChEI-treated, and treated with ChEI + memantine).<sup>18</sup> Our group has earlier presented statistical models for prediction of the cognitive outcome in ChEI-treated cohorts,<sup>19</sup> and similar models regarding ADL ability have recently been requested by Feldman and Jacova.<sup>20</sup> Predictive models can be useful in clinical research and when assessing new disease-modifying therapies.

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The aims of this study were: (1) to describe the long-term functional ability in a cohort of AD patients treated with ChEI, (2) to analyze which sociodemographic and clinical factors have prognostic impact on the outcome, and (3) to build regression models for the prediction of the functional outcome based on data at the start of ChEI treatment.

## METHODS

### Study and Participants

The Swedish Alzheimer Treatment Study (SATS) was started to investigate the long-term efficacy of ChEI treatment (donepezil, rivastigmine, galantamine) in naturalistic AD patients in a routine clinical setting. SATS is a 3-year, open-label, observational, nonrandomized, multicenter study, described at length in an earlier publication.<sup>21</sup> The participants were prospectively recruited from 14 memory clinics in different parts of Sweden. Most patients are in the mild-to-moderate stages of the disease and the study is still ongoing. A total of 790 patients with baseline Mini-Mental State Examination (MMSE)<sup>22</sup> scores ranging from 10 to 26 and at least 1 postbaseline assessment, were included up until the end of October 2004 thereby having the opportunity to complete the full 3-year SATS program. This level of disease severity was considered suitable for the analysis, as the instrumental ADL ability should already have been impaired and the ability to carry out basic ADL functions essentially unaffected. In the regression analyses, only the patients with 3 or more assessments ( $n = 694$ , 88%) were included. At least 3 measurements per individual and an average follow-up period of at least 2 years, were preferable in estimating the regression slopes, as described in prior studies of untreated patients.<sup>13,23</sup>

Before inclusion, all patients underwent a thorough clinical investigation including medical history, physical and neurologic examinations, laboratory tests, and a cerebral computerized tomography (CT) to rule out other causes of dementia. Outpatients aged 40 years and older who received the clinical diagnosis of dementia as defined by the Diagnostic and Statistical Manual of Mental Disorders, 4th ed (DSM-IV)<sup>24</sup> and possible or probable AD according to the criteria of the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and related Disorders Association (NINCDS-ADR-DA)<sup>25</sup> were considered for inclusion. In addition, the selected patients had to be living at home at the time of diagnosis, had to have a caregiver and had to be assessable with the MMSE at the start of ChEI treatment (baseline). Medications other than anticholinergic drugs were allowed and documented during the study. Reasons for study withdrawal were also recorded and presented for this cohort of patients. Nursing home placement was not a reason for dropout if the patient was able to continue the visits to the clinic.

All patients and/or caregivers gave their informed consent to participate in the study, which was conducted according to the provisions of the Helsinki Declaration and approved by the Ethics Committee of Lund University, Sweden.

The SATS patients were assessed in a structured 3-year follow-up program, which evaluated cognition, global functioning, and ADL every 6 months. Trained dementia nurses obtained the ADL evaluation from an interview with the caregiver. Following inclusion and baseline assessments, the patients were prescribed ChEI according to the approved product labeling. The choice of drug and dosage for the

individual patient was left entirely up to the physician's discretion and professional judgment. The patients paid for their own medication according to routine clinical practice.

## Outcome Measures

### Instrumental Activities of Daily Living Scale (IADL)

The IADL<sup>26</sup> consists of 8 different items: ability to use telephone, shopping, food preparation, housekeeping, ability to do laundry, mode of transportation, responsibility for own medications, and ability to handle finances. Each item was scored from 1 (no impairment) to 3 to 5 (severe impairment), giving a total range of 8 to 31 points. A score of 5 (unable to participate in any housekeeping tasks) had been added to the item "housekeeping." If an item was not applicable to the individual, that is, not carried out in their premorbid state, the score of this item was 0. Some of these activities were gender-dependent, especially among the elderly; for example, women doing the laundry and men managing the finances. To provide a common scale of measurement for all patients, a linear mathematical transformation was conducted on the data from patients who were not rated on one or more of the IADL items. The transformation used the data from the rated items to estimate a total score within the range of the total IADL scale (8 to 31). The formula was adapted from Green et al.<sup>12</sup>

Estimated IADL score =  $8 + [23(IADL_0 - \min)] / (\max - \min)$

Where: IADL<sub>0</sub> = original IADL score i.e. the sum of the rated items, min = minimum possible score for IADL<sub>0</sub>, max = maximum possible score for IADL<sub>0</sub>

### Physical Self-Maintenance Scale (PSMS)

The PSMS<sup>26</sup> consists of 6 different items: toilet, feeding, dressing, grooming, physical ambulation, and bathing. Each item was scored from 1 (no impairment) to 5 (severe impairment), allowing a total range of 6 to 30 points.

## Statistical Analyses

The Statistical Package for Social Sciences (SPSS) software (version 17.0; SPSS Inc., Chicago, IL) was used to carry out the statistical analyses. The level of significance was defined as  $P < 0.05$  if not otherwise specified. Observed case analyses were done to avoid overestimating the treatment effect by imputing higher, earlier outcome scores over a long-term study of patients suffering from a progressively deteriorating disease.

One-way Analysis of Variance (ANOVA) with Bonferroni correction (post hoc test) was used to compare the differences between the means for the groups based on length in the study, and  $\chi^2$ -test was computed for analyses of categorical variables. Pearson correlation coefficient was calculated investigating any linear associations between changes during the course of the disease. Paired sample  $t$  test was conducted to assess the mean difference at the different time intervals, between the observed scores in this study and the predicted scores from the earlier IADL model of untreated patients. Friedman test was used to study possible differences in change between the individual items in the ADL scales. This test is nonparametric to compensate for ordinal scales with few levels (1 to 5) per item.

## Mixed Models

Mixed, linear and nonlinear, fixed and random coefficient regression models using “subject” as a hierarchical variable (ie, to allow correlation within subjects) were analyzed. The noncompleters contributed information during the time of participation, thus considering the trajectories for all patients. The 95% confidence interval (CI) was illustrated in the figures as a measure of dispersion in the regression models. This interval with 95% certainty contains the true mean functional score for a cohort of patients. Collinearity analyses of the variables included in the models showed no sign of multicollinearity, that is the undesirable situation in which one independent variable is a linear function of other independent variables. Models assumptions were checked by residual analyses.

Time was defined as the exact number of months between baseline and each visit, thus using all data points at the correct time intervals. The fixed-effect terms included in the analysis were: time in months from baseline, ADL (IADL or PSMS) score at baseline, and the interaction effect Time in months  $\times$  ADL baseline score. In addition, the squares of these terms were included to enable a nonlinear rate of decline in the models. The random terms in the models were an intercept and time in months, with an unstructured covariance matrix. Several sociodemographic and clinical background variables were also included in the models as fixed effects. The selection of these variables was based on evidence-based knowledge and well-known risk factors of AD. The selected background variables were: age at first assessment, clinician’s estimate of duration of illness, sex, years of education, APOE  $\epsilon 4$  carrier status, solitary living, cognitive severity at baseline measured by MMSE, medication use (antihypertensive/cardiac therapy, antidiabetic and lipid-lowering agents), type of ChEI agent, and drug dose. The ChEI agents were coded as a set of dummy variables. The ChEI dose could vary during the treatment period for an individual patient and between patients. Therefore, the mean dose used during the entire follow-up period was calculated for each patient. Furthermore, to obtain a similar metric of percent maximum dosage for the 3 ChEI agents, the mean dose was divided by the maximum recommended dose for each drug agent, that is, 10-mg donepezil, 12-mg rivastigmine, and 24-mg galantamine. The change of dosage between the assessments was also calculated using the percentage of maximum dose. Finally, the possible interaction effects of time in months with years of education, and time in months with ChEI dose were included in the models to determine whether these effects were consistent over time. The term type of ChEI with dose was also included. Nonsignificant variables ( $P > 0.05$ ) were removed in a backward stepwise elimination manner. The hierarchical principle was observed in these analyses; terms that appeared in interactions were not considered for elimination.

Green et al<sup>12</sup> developed a simple linear regression equation to predict the subsequent rate of functional change in untreated AD patients on the basis of IADL scores at study entry. Green’s model was based on 104 patients that were followed from 12 to 66 months [ $30.75 \pm 15.9$  mo, mean  $\pm$  standard deviation (SD)], with a reported baseline ADAS-cog score of  $37.4 \pm 18.6$  points (5 to 70, range), an IADL score of  $22.3 \pm 6.4$  points (9 to 30), and a PSMS score of  $12.8 \pm 7.2$  points (6 to 29). This baseline-dependent equation has been used to calculate historical controls in an earlier publication,<sup>14</sup> and was used

in the present study to compute the estimated IADL outcome if the patients had remained untreated.

The Green model:  $\Delta IADL = 10.124 - 0.332 * IADL_{Bas}$  where  $\Delta IADL$  is the annual rate of decline of IADL and  $IADL_{Bas}$  is the IADL score at baseline.

The PSMS outcome in Green’s study<sup>12</sup> was displayed as an example of the mean rate of decline with 95% CI for a nontreated AD cohort.

## RESULTS

### Long-term Outcome

Depending on the length of participation in the SATS study the 790 patients were divided into 4 groups: 3-year completers (group 3,  $n = 337$ ), 2-year completers (group 2,  $n = 179$ ), 1-year completers (group 1,  $n = 191$ ), and 6-month completers (group 0.5,  $n = 83$ ).

Figure 1A illustrates the longitudinal IADL mean  $\pm$  95% CI outcome for the 4 different groups based on length of time in the study. The actual mean IADL outcome in the ChEI-treated patients showed a favorable effect compared with the computed scores from the baseline-dependent (comparable initial level of function) Green equation,<sup>12</sup> assuming that the patients in this study had remained untreated. This estimation indicated significant differences between the IADL mean scores from 6 months and onward ( $P < 0.001$ ).

The mean PSMS outcomes for the four different groups of completers are displayed in Figure 1B. As an illustration of the mean rate of PSMS decline with 95% CI for a cohort of nontreated AD patients, the longitudinal study by Green et al<sup>12</sup> was used.

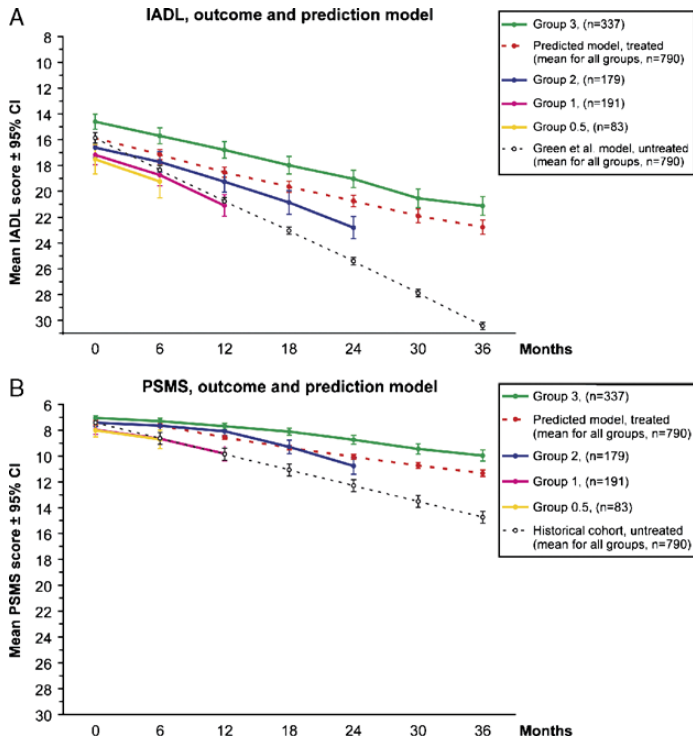
Performance on the IADL and PSMS scales was stable (no change or improvement) in 32% and 56% of the patients respectively after 1 year, 18% and 38% after 2 years and 14% and 32% after 3 years.

### Group Characteristics

The sociodemographic and clinical characteristics of the groups and the total cohort are displayed in Table 1. Group 3 was significantly better preserved than the other groups with respect to the mean MMSE and IADL scores at the start of ChEI treatment ( $P < 0.001$ ). The mean PSMS baseline score for groups 2 and 3 was similar, but was significantly different from groups 0.5 and 1, which had poorer basic ADL ability ( $P < 0.001$ ). The 4 groups did not differ in sex, carrier of the APOE  $\epsilon 4$  allele, solitary living at baseline, medication use (antihypertensive/cardiac therapy, antidiabetic, and lipid-lowering agents), duration of illness, age at onset or at baseline, years of education, or distribution of drug type or dosage.

After 6 months of ChEI treatment, the IADL mean (95% CI) decline from baseline was 1.2 (1.0 to 1.4) points. No difference was detected between the 4 groups. The PSMS mean decline, however, showed significance between group 3: 0.2 (0.0 to 0.3) points, versus groups 1: 0.6 (0.3 to 1.0) and 0.5: 0.8 (0.3 to 1.2) ( $P = 0.004$ ). Moreover, we studied whether the initial change of ADL ability during the first 6 months of treatment had any linear association with functional change in later stages of the disease in the individual patient. When IADL and PSMS changes during 0 to 6 months were compared to the changes during 18 to 24 months and 30 to 36 months, no significant correlations were found.





**FIGURE 1.** A, The longitudinal Instrumental Activities of Daily Living scale (IADL) mean  $\pm$  95% confidence interval (CI) outcome for the 4 different groups based on length of time in the study. The mean predicted scores with 95% CI from the Green equation<sup>12</sup> was used as estimations of the IADL outcome for the total cohort, based on calculations as if all the patients in this study had remained untreated. Predicted IADL mean scores with 95% CI for the entire cohort from our simple baseline-dependent regression model regarding cholinesterase inhibitor treated patients are also presented. B, The longitudinal Physical Self-Maintenance Scale (PSMS) mean  $\pm$  95% CI outcome for the four different groups based on years of participation in the study. Group 1's trajectory is identical with group 0.5. As an illustration of the mean rate of PSMS decline with 95% CI for a cohort of nontreated Alzheimer patients, the longitudinal study by Green et al<sup>12</sup> was used. Predicted PSMS mean scores with 95% CI for the total cohort from our simple regression model concerning cholinesterase inhibitor treated patients are also presented.

### Cholinesterase Inhibitor Dose

During the study, an increasing number of patients received higher doses of ChEI. After 1 year the mean  $\pm$  SD doses of donepezil, rivastigmine, and galantamine were  $7.7 \pm 2.5$ ,  $7.7 \pm 2.9$ , and  $19.1 \pm 4.5$  mg, respectively. After 2 years they were  $8.3 \pm 2.4$ ,  $8.3 \pm 3.0$ , and  $19.7 \pm 4.8$  mg, respectively and finally after 3 years  $8.4 \pm 2.4$ ,  $8.4 \pm 2.7$ , and  $20.2 \pm 4.7$  mg.

### Reasons for Dropout

In total, 57% of the patients did not complete the 3-year study. The main reasons for dropout from the study were: admission to nursing home (14%,  $n = 107$ ), concomitant memantine therapy initiated (7%,  $n = 58$ ), poor effect/deterioration (6%,  $n = 45$ ), death (5%,  $n = 43$ ), compliance problems (5%,  $n = 37$ ), withdrawal of informed consent (5%,  $n = 37$ ), side-effects (4%,  $n = 35$ ), switch to other ChEI (2%,  $n = 18$ ), and somatic disease unrelated to ChEI treatment (2%,  $n = 16$ ).

### Activities of Daily Living—Change in Individual Items

The mean differences from the baseline score for each item on the IADL scale for group 3 are illustrated in

Figure 2A. A linear transformation was computed so that all individual items obtained the same numerical range (1 to 5). There was a weak significant difference ( $P = 0.046$ ) between the items regarding the mean ranks after 36 months of ChEI treatment.

Figure 2B shows the mean differences from baseline scores for each item on the PSMS scale for group 3. There was a significant difference ( $P < 0.001$ ) between the items regarding the mean ranks after 36 months from baseline. The items “grooming” and “bathing” showed the largest decline from the start of treatment. The items that showed the least amount of decline were “feeding” and “toilet.” The order of restriction in the ADL scales was similar in the noncompleter groups, when analyzing the difference between the baseline score and the last assessment (figures not shown).

### Factors Affecting the Outcome

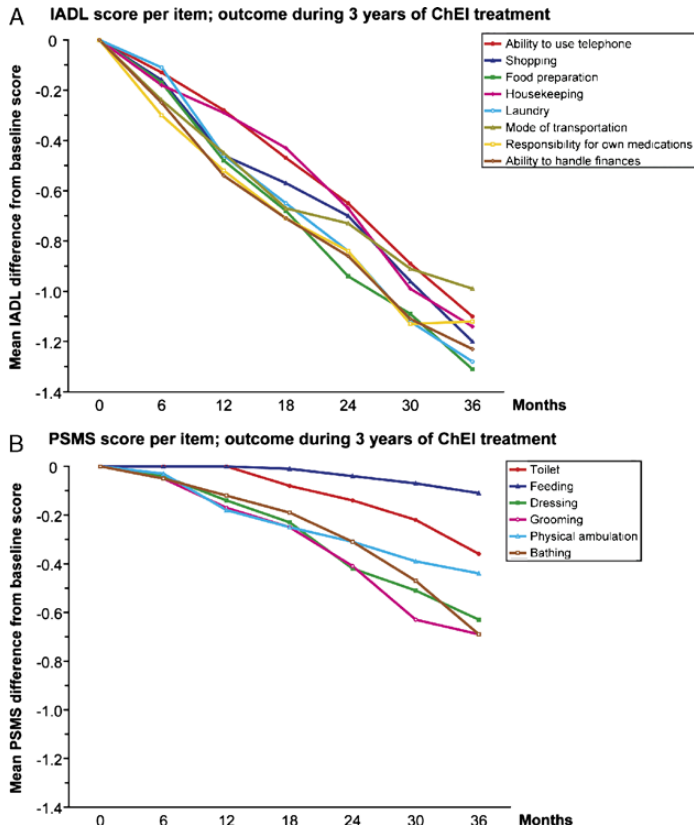
Mixed (fixed and random, linear and nonlinear) effects models were carried out (2818 observation points) to identify the sociodemographic and clinical factors that affected the long-term IADL and PSMS outcomes. The models and the significant predictors are presented in Table 2.

**TABLE 1. Demographic and Clinical Characteristics**

Variable	Group 0.5, 6mo Completers n = 83/10%	Group 1, 1y Completers n = 191/24%	Group 2, 2y Completers n = 179/23%	Group 3, 3y Completers n = 337/43%	Total Participants n = 790	P
Female sex	56/68%	125/65%	100/56%	215/64%	496/63%	0.160
APOE ε4 carrier, (n = 775)	54/69%	135/72%	117/66%	227/68%	533/69%	0.669
Solitary living at baseline	33/40%	63/33%	62/35%	107/32%	265/34%	0.563
Antihypertensives/cardiac therapy	29/35%	82/43%	61/34%	132/39%	304/38%	0.325
Antidiabetics	2/2%	8/4%	10/6%	13/4%	33/4%	0.661
Lipid-lowering agents	6/7%	21/11%	16/9%	34/10%	77/10%	0.786
Estimated age at onset, years	73.8 ± 7.2	72.0 ± 7.1	Mean ± standard deviation (SD) 71.3 ± 7.8	71.7 ± 7.4	71.9 ± 7.4	0.089
Estimated AD duration, years	2.8 ± 1.5	3.0 ± 1.9	3.3 ± 2.6	3.1 ± 2.2	3.1 ± 2.1	0.348
Age at first assessment, years	76.5 ± 6.7	75.0 ± 7.0	74.6 ± 7.3	74.8 ± 7.1	75.0 ± 7.1	0.200
Education, years	9.4 ± 2.4	9.3 ± 2.6	9.3 ± 2.4	9.4 ± 2.5	9.4 ± 2.5	0.959
MMSE score at baseline†	20.6 ± 4.0*	20.6 ± 4.1*	21.0 ± 3.7*	22.2 ± 3.4†	21.4 ± 3.8	<0.001
IADL score at baseline†	17.5 ± 5.2*	17.2 ± 5.3*	16.6 ± 5.2*	14.6 ± 5.4†	16.0 ± 5.5	<0.001
PSMS score at baseline†	8.0 ± 2.2*	8.0 ± 2.6*	7.4 ± 1.8†	7.1 ± 1.8†	7.5 ± 2.1	<0.001
Donepezil mg, (n %) <dd>‡</dd>	6.3 ± 1.6 (69%)	5.9 ± 1.5 (60%)	6.4 ± 1.7 (57%)	6.3 ± 1.7 (56%)	6.2 ± 1.7 (n = 463)	0.164
Rivastigmine mg, (n %) <dd>‡</dd>	4.1 ± 1.1 (12%)	4.8 ± 1.1 (25%)	4.9 ± 1.1 (19%)	5.0 ± 1.3 (23%)	4.9 ± 1.2 (n = 170)	0.141
Galantamine mg, (n %) <dd>‡</dd>	12.5 ± 3.3 (19%)	11.8 ± 3.0 (15%)	13.3 ± 3.1 (24%)	13.3 ± 2.5 (21%)	13.0 ± 2.9 (n = 157)	0.100

\*†Results from post hoc tests (Bonferroni correction) are indicated by superscript letters (2 groups with the same letter do not differ significantly within that variable).  
‡Percentage of subjects in each group receiving the specific ChEI-agent within brackets (χ<sup>2</sup>-test, P = 0.066).

IADL indicates Instrumental Activities of Daily Living scale; MMSE, Mini-Mental State Examination; PSMS, Physical Self-Maintenance Scale.



**FIGURE 2.** A, The mean difference scores from baseline for each individual item in the Instrumental Activities of Daily Living scale (IADL) for the completers (group 3). A weak significant difference ( $P=0.046$ ) was found between the items regarding the mean ranks after 36 months of cholinesterase inhibitor treatment. B, The mean difference scores from baseline for each individual item in the Physical Self-Maintenance Scale (PSMS) for the completers (group 3). There was a significant difference ( $P<0.001$ ) between the items concerning the mean ranks after 36 months from the start of cholinesterase inhibitor treatment.

Patients with more severe cognitive impairment at baseline and older individuals deteriorated faster, regarding both instrumental and basic ADL abilities. In addition, there was a significant interaction effect between time in months and years of education, that is, a higher level of education implied increased impairment over time. As an example, a participant with 15 years of education showed an additional 2.2 points IADL and 1.4 points PSMS deterioration after 3 years, on average, compared with an individual with 9 years of education.

The participants living alone showed a more rapid decline in IADL score. The interaction of baseline PSMS score with months in the study showed a quadratic association across time. Patients tended to exhibit improvement in basic ADL ability during the first 6 months after the start of ChEI treatment, and then slowly started to deteriorate. The individuals that received a higher mean dose of ChEI during the study showed a slower decline in instrumental ADL ability.

The background variables sex, carrier of the APOE  $\epsilon 4$  allele, medication use (antihypertensive/cardiac therapy,

antidiabetic and lipid-lowering agents), duration of illness, type of ChEI agent, change of dosage, and the interaction effects Time in months  $\times$  ChEI dose or Type of ChEI  $\times$  Dose were not significant when included in the mixed models. The percentages of variance accounted for in the dependent variable were 64.7% for IADL ( $P<0.001$ ) and 44.7% for PSMS ( $P<0.001$ ), which implies a good fit of the statistical models.

### Prediction Models

Simple nonlinear regression models for calculation of the predicted IADL and PSMS score for a cohort of ChEI-treated mild-to-moderate AD patients based on the baseline ADL scores are provided. These models explained a substantial degree of variance in the data set, that is, demonstrated a good fit, IADL: ( $R^2=0.643$ ,  $R=0.802$ ,  $P<0.001$ ), and PSMS: ( $R^2=0.388$ ,  $R=0.623$ ,  $P<0.001$ ), 3022 observation points. All coefficients were significant at the  $P<0.001$  level. The predicted IADL and PSMS mean outcomes with 95% CI for the total cohort are illustrated in Figures 1A and B.

**TABLE 2.** Factors Affecting the Long-term Outcome With IADL and PSMS Score as Dependent Variables (Terms Retained in Final Mixed Models)

Significant Predictors	Percentage of Variance Accounted for IADL 64.7%, <i>P</i> < 0.001			PSMS 44.7%, <i>P</i> < 0.001		
	$\beta$	95% CI ( $\beta$ )	<i>P</i>	$\beta$	95% CI ( $\beta$ )	<i>P</i>
<b>Fixed terms</b>						
Intercept	0.374	-3.007, 3.756	0.828	3.218	1.505, 4.932	< 0.001
Time in months from baseline	0.128	0.065, 0.190	< 0.001	0.009	-0.081, 0.100	0.839
ADL baseline score*	1.571	1.341, 1.800	< 0.001	0.797	0.703, 0.891	< 0.001
ADL baseline score <sup>2</sup> ,*	-0.023	-0.029, -0.016	< 0.001			ns
Time in months $\times$ ADL baseline score*			ns	-0.002	-0.011, 0.008	0.755
Time in months <sup>2</sup> $\times$ ADL baseline score*			ns	0.0003	0.0001, 0.0005	0.004
<b>Background variables:</b>						
Education, years	-0.009	-0.111, 0.092	0.857	-0.020	-0.094, 0.054	0.599
Time in months $\times$ Education, years	0.011	0.004, 0.017	0.002	0.007	0.0004, 0.014	0.038
Solitary living at baseline (no = 0, yes = 1)	0.465	0.019, 0.911	0.041			ns
Age at first assessment, years	0.032	0.0002, 0.063	0.048	0.020	0.003, 0.037	0.023
MMSE score at baseline	-0.208	-0.271, -0.145	< 0.001	-0.150	-0.182, -0.117	< 0.001
ChEI-dose†	-0.012	-0.024, -0.001	0.039			ns
<b>Random terms (variance)</b>						
Intercept	5.653	4.657, 6.863	< 0.001	1.677	1.137, 2.475	< 0.001
Time in months	0.025	0.021, 0.030	< 0.001	0.026	0.021, 0.032	< 0.001

Sex, APOE  $\epsilon$ 4 carrier status, duration of AD and the variable comparing the ChEI agents were not significant.

$\beta$  values are expressed per 1 unit increase for continuous variables and for the condition present in dichotomous variables.

\*ADL, Instrumental Activities of Daily Living scale (IADL) or Physical Self-Maintenance Scale (PSMS) respectively.

†Mean percentage of the maximum recommended dose that is, 10-mg donepezil, 12-mg rivastigmine and 24-mg galantamine.

CI indicates confidence interval; ns, not significant.

Predicted IADL score in ChEI-treated patients:

$$\hat{Y} = -5.0142 + (0.2291 * t) + (1.7749 * x_i) - (0.0263 * x_i^2)$$

Predicted PSMS score in ChEI-treated patients:

$$\hat{Y} = 1.2141 + (0.7344 * x_i) + (0.0223 * tx_i) - (0.00001 * (tx_i)^2)$$

Where  $t$  = time in months between the baseline score and the actual visit,  $x_i$  = baseline ADL (IADL or PSMS) score.

## DISCUSSION

In this study, we found that the patients that completed all 3 years had significantly better preserved cognitive and functional abilities at the start of treatment than the noncompleters. The sociodemographics and other clinical characteristics, however, did not differ. A faster decline in IADL and PSMS scores was associated with lower cognitive ability at baseline and older age. The interaction effect higher level of education by longer time in the study was also related to a faster functional deterioration. Baseline PSMS score by time indicated an improvement in basic ADL ability during the first 6 months after the start of ChEI treatment. Participants living alone showed faster decline in IADL score, whereas those that received a higher mean dose of ChEI during the study, irrespective of drug agent, exhibited a slower instrumental ADL deterioration. The individual items in the PSMS scale exhibited different long-term rates of decline, whereas the outcomes of the individual IADL items were more homogeneous. The long-term instrumental and basic ADL abilities for a group of ChEI-treated patients with mild-to-moderate AD were possible to predict with a substantial degree of explanation of the variance, which implies a good fit of the statistical models.

A study group, followed for a long period of time, is not necessarily clinically representative for the whole sample included at baseline. In this cohort the cognitive

and functional abilities at baseline significantly affected the length of participation. Correspondingly, the 4% of patients remaining after 5 years in the long-term extension of rivastigmine treatment by Small et al<sup>27</sup> were similar to those of the overall population in age, sex, and duration of dementia, whereas they tended to have less cognitive impairment at baseline (functional ability was not addressed). The mean rate of IADL decline after 6 months of ChEI treatment did not differ between the groups of completers, whereas the mean rate of PSMS differed. The instrumental ADL ability in this population of mild-to-moderate AD patients was already impaired at baseline, whereas the ability to carry out basic ADL functions was essentially unaffected. The dropout of the more severely functionally affected participants implies that the failure of the basic ADL ability leads to an increased difficulty to remain in the study. This may contribute to a higher functional ability for the long-term completers. The functional changes seen at baseline to 6 months, however, did not predict later changes for the individual patient.

Untreated patients with AD seem to show a pattern of relatively slow ADL decline at the level of mild dementia, acceleration during the moderate level, and slowing during severe dementia (when patients reach the floor of ADL measures).<sup>28</sup> The predictive IADL model of untreated patients<sup>12</sup> takes into consideration the patients' baseline IADL score when calculating the expected IADL outcome for a cohort over time. Therefore, identical functional severity at baseline was assumed between the treated SATS cohort and the calculated untreated cohort. Regarding the PSMS outcome, no similar baseline-dependent models were available. Thus, the display of PSMS score for the untreated cohort should only be regarded as an example. The baseline clinical characteristics reported in Green's study<sup>12</sup> showed that the untreated patients were, on average, more cognitively and functionally deteriorated

than the SATS patients. However, the measures of dispersion were large; therefore, the untreated participants exhibited a wide range of disease severity at study entry. If a larger number of those individuals had severe dementia, the mean PSMS rate of decline probably would be more similar to the mild-to-moderate outcome observed for the cohort in the SATS study. Nevertheless, if a majority of the untreated participants were in the moderate stage of AD, the trajectory may be steeper than that of the SATS patients. Younger individuals,<sup>29</sup> longer duration of dementia and younger age at onset<sup>30</sup> have been reported to be associated with faster cognitive deterioration in nontreated individuals. Other studies show that neither age, duration<sup>31</sup> nor age at onset<sup>23</sup> had any effect on cognitive decline. Atri et al<sup>18</sup> used a multivariate model to compare untreated, ChEI-treated, and ChEI + memantine-treated patients and found that age at baseline and duration of AD did not affect the long-term functional decline. The study presented here included only ChEI-treated patients that were, on average, somewhat older and exhibited greater age differences; the results showed that older participants deteriorated faster, whereas duration of illness did not influence the ADL progression rate. A more pronounced rate of functional decline compared with cognition might be expected in older individuals owing to the aging process.

The finding that the interaction between more years of education with longer time in the study was associated with faster functional decline, as shown in this study of ChEI-treated patients, can be interpreted in several ways. Better initial performance on cognitive tests in more educated participants might delay the diagnosis, and make progression seem more rapid once the disease is diagnosed. A higher education level might also provide a reserve that delays the onset of clinical manifestations. Years of education were not significant in the multivariate comparison of ChEI and memantine-treated patients<sup>18</sup>; the participants in that study had a higher education level, with small variations, compared with our patients. In studies of untreated AD patients, a higher level of education was related to faster cognitive deterioration,<sup>29,31</sup> yet did not influence the rate of MMSE decline.<sup>30</sup> This coincides with the earlier finding that participants with a low level of formal education show an early deficit in cognitive performances whereas their functional abilities are relatively spared.<sup>32</sup> The faster functional deterioration observed in this study for patients living alone may be explained by social isolation and symptoms of depression associated with increased dependence on social support to carry out daily activities. Wilson et al<sup>33</sup> showed that loneliness was associated with a faster cognitive decline and an increased risk of AD-like dementia in older individuals. Another study<sup>34</sup> of nondemented participants that lived alone showed that apathy seemed to have a marked effect on their ability to carry out routine ADL. Additional examination and understanding of the influence of AD on these background characteristics is clearly needed.

There are few published long-term studies comparing ChEI-agents. In this study, patients that received a higher mean dose of ChEI exhibited a slower decline in IADL score. No difference was detected among the 3 drug agents. Correspondingly, Bullock et al<sup>35</sup> showed, in a 2-year double-blind randomized study of donepezil and rivastigmine with a 57.9% completion rate (in our study 57.3% after 2y), no significant difference in ADL ability, when

comparing the observed cases (with no imputation of last observation carried forward). A 1-year rater-blinded randomized study of donepezil versus galantamine<sup>36</sup> reported significant advantages in the treatment response to galantamine on cognition. The annual mean change in functional ability from baseline, however, did not differ between the treatment groups. In line with our finding that a higher dose of ChEI was related to slower instrumental ADL decline, Geldmacher et al<sup>37</sup> suggested that the use of effective doses of donepezil (> 5 mg/d) and longer-term sustained donepezil use were associated with significant delays in nursing home placement. The multiple washout periods in the AD2000 study<sup>16</sup> may have reduced the effects of donepezil. The SATS is an open and nonrandomized study and there might be nonspecific differences between the treatment groups. The multivariate mixed model approach only adjusts for the independent variables included in the models. Our results need replication in other large-sample longitudinal studies.

A general deterioration was observed in all ADL items during the 3-year study with a more homogeneous decline in the instrumental abilities. The basic PSMS abilities, in contrast, showed a heterogeneous long-term outcome. The implication for clinical practice suggests that it is not necessary to evaluate all IADL items; a few key questions regarding the ability to carry out instrumental tasks might reveal information about all instrumental ADL abilities. In contrast, the different mean rates of decline for the individual PSMS items shows the clinical importance of a more thorough evaluation of basic ADL abilities. Information about the expected deterioration in different abilities might also make it easier for the caregiver and the community-based services to plan the appropriate assistance and compensate for the gradual loss of functions.

As an example of verification of the regression models, Imbimo et al<sup>14</sup> described, in an open-label extension of eptastigmine treatment in mild-to-moderate AD, an IADL mean decline of 6.0 points after 2 years. Predictions from our baseline-dependent model estimated a mean IADL decline of 6.1 points.

Changes in progression rate predicted from statistical models can be valuable in clinical research, and when measuring the efficacy of new therapies that might modify the course of the disease. Trials assessing the effects of new drugs are at present being carried out in patients already treated with ChEI.

The advantages of the 3-year SATS study are the regular, prospective, well-structured, follow-up investigations of large cohorts of naturalistic AD patients. The 3-year completion rate of 43% in the present cohort is high compared with other naturalistic or ChEI extension studies. Winblad et al<sup>7</sup> showed 39% completion rate in an extension study, whereas other studies<sup>27,38,39</sup> report 20% to 33% after 3 years. Long-term AD-studies suffer from high dropout rates and this may contribute to higher mean scores for the patients remaining in the study, assuming they benefit more from ChEI treatment. In our study, the outcomes for the groups of noncompleters were also displayed and considered when building the regression models. The reasons for dropout in this naturalistic study are diverse and sometimes multifaceted, and may not always be related to the patient and AD. For example, concomitant somatic disease or changes in the caregiver's situation can contribute to withdrawal of informed consent, compliance problems or nursing home placement.

A limitation of AD treatment studies longer than 6 months is that placebo-controlled designs are not allowed owing to ethical issues. Thus, we were confined to describe estimations of the long-term functional outcome for nontreated AD patients, using a baseline-dependent mathematical model and previously reported ADL data. These comparisons might have shortcomings, such as potential differences in clinical characteristics at baseline between the treated and historical group. Cohort effects such as life conditions, general health, or medications might also influence the outcome. To minimize possible deviations, our regression models and earlier models of untreated patients<sup>12,14,23</sup> use the actual functional ability at baseline, when calculating the estimated scores for cohorts of patients. As shown in this study and in the prior studies, the baseline scores and the time were of great importance for models with a high degree of explanation, when predicting the long-term outcome.

In conclusion, this study shows that the functional ability declined during the 3-year ChEI-treatment program but was, not surprisingly, best preserved among the 3-year completers. Lower cognitive ability at baseline, older age, higher education levels, and solitary living were identified as risk factors for faster decline in ADL ability, whereas a higher mean dose of ChEI during the study was associated with slower IADL decline. Regression models for treated naturalistic patients were built and could predict the long-term IADL and PSMS outcomes with the variance explained to a large extent. Furthermore, long-term ADL studies in clinical practice are needed, as ADL ability is a key domain in AD and functional evaluations should be regarded as important as cognitive. Recommendations and general acceptance for a common ADL scale that is non gender biased in future placebo-controlled trials and clinical studies would be desirable, to facilitate comparisons between studies.

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# Paper 4





# Risk Factors for Nursing Home Placement in Alzheimer's Disease: A Longitudinal Study of Cognition, ADL, Service Utilization, and Cholinesterase Inhibitor Treatment

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**Purpose of the Study:** To identify risk factors for early nursing home placement (NHP) in Alzheimer's disease (AD), focusing on the impact of longitudinal change in cognition, activities of daily living (ADL), service utilization, and cholinesterase inhibitor treatment (ChEI). **Design and Methods:** In an open, 3-year, prospective, multicenter study in a routine clinical setting, 880 AD patients were treated with either donepezil, rivastigmine, or galantamine. At baseline and every 6 months, they were assessed with several rating scales including Mini-Mental State Examination, Instrumental Activities of Daily Living scale (IADL), and Physical Self-Maintenance scale. Moreover, the dose of ChEI, the amount of weekly assistance (home help service and adult day care), and the date of NHP were recorded. Cox regression models were constructed to predict the risk of NHP. **Results:** During the study, 206 patients (23%) were admitted to nursing homes. Factors that precipitated institutionalization were lower cognitive and functional abilities at baseline, faster rate of decline in IADLs, female gender, solitary living, and a lower mean dose of ChEI. The men living alone and patients with a substantial increase in adult day care also demonstrated shorter time to NHP. **Implications:** The rate of functional but not cognitive decline was a strong risk factor for NHP. The results could be used to identify the care

recipients that might risk early NHP to ensure that these individuals receive a sufficient level of assistance. Furthermore, higher doses of ChEI might postpone institutionalization in AD.

**Key Words:** Adult day care, Home help service, Predictors

Cognitive impairment is one of the strongest predictors of nursing home placement (NHP) (Gaugler, Duval, Anderson, & Kane, 2007), and the cost of care in patients with Alzheimer's disease (AD) rises dramatically with increasing severity of dementia. In 2003, the described total annual cost of care in AD was an average of 172,000 SEK (~23,200 USD) per individual, ranging from 60,700 SEK (~8,200 USD) in mild dementia to 375,000 SEK (~50,500 USD) in severe dementia. About half of these costs referred to special accommodations and community-based care (Jonsson et al., 2006). In a survey from the National Board of Health and Welfare in Sweden (Engstrom, 2001), approximately half of the nursing home residents were found to suffer from severe cognitive impairment. Similarly, the prevalence of dementia in new admissions to nursing homes in the United States was estimated to be 48%–54% (Magaziner et al., 2000).

The institutionalization process is complex; individual studies have reported several sociodemographic variables that predict early NHP in subjects with dementia, such as older age (Hatoum, Thomas, Lin, Lane, & Bullock, 2009; Heyman, Peterson, Fillenbaum, & Pieper, 1997), a lower level of education (Smith, Kokmen, & O'Brien, 2000), and solitary living (Gaugler, Kane, Kane, Clay, & Newcomer, 2003; Yaffe et al., 2002). Conflicting results regarding gender have been shown (Gaugler et al., 2003; Hatoum et al.). Furthermore, clinical factors such as lower cognitive (Gaugler et al., 2003; Heyman et al.; Yaffe et al.) and functional abilities (Gaugler et al., 2003; Hebert, Dubois, Wolfson, Chambers, & Cohen, 2001; Heyman et al.), behavioral and psychological symptoms (Gaugler et al., 2003; Yaffe et al.), and caregivers' poor health and burden (Gaugler et al., 2003; Hebert et al.) were also described as predictors for reduction of time to NHP.

The majority of previous publications have investigated sole predictors; however, few authors have analyzed the potential interactive effects between the critical predictors (Fisher & Lieberman, 1999; Gaugler, Yu, Krichbaum, & Wyman, 2009). Moreover, most prior studies only consider baseline predictors, which offer little insight into the effect of possible longitudinal events that precipitate NHP. Gaugler et al. (2003) requested inclusion of predictors that measured long-term change, for example, functional status and service utilization, and sufficient follow-up to produce a more conclusive understanding of the institutionalization process.

A recent systematic review (Gaugler et al., 2009) reported that studies regarding cholinesterase inhibitor (ChEI) treatment in AD with NHP as an outcome measure were few and inconclusive. Some studies show that ChEI treatment delays admission to nursing homes (Gillette-Guyonnet et al., 2006; Lopez et al., 2002), others do not (Courtney et al., 2004). Furthermore, extension studies have suggested that effective dosages and sustained use might postpone institutionalization (Geldmacher, Provenzano, McRae, Mastey, & Ieni, 2003; Knopman et al., 1996).

There are no previously published naturalistic AD studies that consider the effect of the different ChEI agents and dosages on the time to institutionalization. Moreover, prognostic NHP models that include cognitive and functional rates of decline and long-term changes in service utilization are scarce.

Identifying factors that precipitate NHP in persons with dementia can be an important tool in clinical research as well as in planning for future care needs. Such information may also affect the targeting of clinical interventions and social strategies that allow those individuals to stay in their homes as long as possible (Gaugler et al., 2009; Luppá, Luck, Brahler, König, & Riedel-Heller, 2008).

The aim of this study was to investigate sociodemographic and clinical factors leading to early NHP in AD, focusing on the impact of longitudinal change in cognition, ADL, service utilization, and ChEI treatment.

## Methods

### *Study and Subjects*

The Swedish Alzheimer Treatment Study (SATS) was started in order to investigate the long-term efficacy of ChEI treatment (donepezil, rivastigmine, and galantamine) and to evaluate the longitudinal course of AD using ADL and service utilization measures such as assistance and NHP in naturalistic AD patients in a routine clinical setting. SATS is a 3-year, open-label, observational, nonrandomized, multicenter study, and the treatment and follow-up protocol have been thoroughly described earlier (Wallin et al., 2007). The subjects were prospectively recruited from 14 memory clinics in different parts of Sweden. Most patients are in the mild to moderate stages of the disease and the study is still ongoing. A total of 880 subjects with baseline Mini-Mental State Examination (MMSE) (Folstein, Folstein, & McHugh, 1975) scores ranging from 10 to 26 were included up until the end of October 2004, thus having the opportunity to complete the full 3-year SATS program. The MMSE score limits of 10–26 are often used when the intention is to include a population of mild to moderate AD patients (Gillette-Guyonnet et al., 2006). This level of disease severity was considered suitable for the analysis. Thus, the instrumental ADL (IADL) ability should already have been impaired and the ability to perform basic ADL functions essentially unaffected.

Before inclusion, all patients underwent a thorough clinical investigation including medical history, physical and neurological examinations, laboratory tests, and a cerebral computerized tomography in order to rule out other causes of dementia. Outpatients aged 40 years and older who received the clinical diagnosis of dementia as defined by the Diagnostic and Statistical Manual of

Mental Disorders, 4th edition (DSM-IV) (Frances & American Psychiatric Association, 1994) and possible or probable AD according to the criteria of the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) (McKhann et al., 1984) were considered for inclusion. In addition, the patients lived at home with or without community-based service at the time of diagnosis, had a responsible caregiver (in most cases the spouse or an adult child), and had to be assessable with the MMSE (i.e., had to have the capacity to communicate and sufficient visual and hearing abilities) at the start of ChEI treatment (baseline). Medications other than antedementia drugs were allowed and documented during the study, and the reason for study withdrawal was recorded.

All patients and/or caregivers gave their informed consent to participate in the study, which was conducted according to the provisions of the Helsinki Declaration and approved by the Ethics Committee of Lund University, Sweden.

The SATS patients were assessed in a structured 3-year follow-up program, which evaluated cognition, global functioning, ADL, and the amount of service utilization (home help service and adult day care) every 6 months. Trained dementia nurses obtained the ADL evaluation and the amount of service per week from an interview with the caregiver. Following inclusion and baseline assessments, the patients were prescribed ChEI as a part of the ordinary health care system in accordance with the approved product labeling. The patients paid for their own medication obtained from the pharmacy according to routine clinical practice. The SATS is an open and nonrandomized study and the choice of drug and dosage for the individual patient was left entirely up to the physician's discretion and professional judgment.

### Outcome Measures

Cognitive ability was assessed with the MMSE, ranging from 0 to 30, a lower score indicating a more impaired cognition. The Instrumental Activities of Daily Living scale (IADL) (Lawton & Brody, 1969) consists of eight different items: ability to use telephone, shopping, food preparation, housekeeping, ability to do laundry, mode of transportation, responsibility for own medications, and ability to handle finances. Severity was scored per item (1 = *no impairment* to 3–5 = *severe impairment*), giving a total range of 8–31 points. A score of 5 (*unable*

*to participate in any housekeeping tasks*) had been added to the item "housekeeping." If an item was not applicable to the individual, that is, not performed in their premorbid state, the score of this item was 0. Furthermore, a mathematical correction of the sum of the IADL scores was performed to prevent gender-dependent activities from having an affect on the results. The transformation used the data from the rated items to estimate a total score within the range of the total IADL scale (8–31). The formula was adapted from Green, Mohs, Schmeidler, Aryan, and Davis (1993).

Estimated IADL score

$$= 8 + (23(IADL_0 - \min)) / (\max - \min)$$

where  $IADL_0$  = original IADL score, that is,

the sum of the rated items;

min, minimum possible score

for  $IADL_0$ ; max, maximum

possible score for  $IADL_0$

The Physical Self-Maintenance scale (PSMS) (Lawton & Brody, 1969) consists of six different items: toilet, feeding, dressing, grooming, physical ambulation, and bathing. Each item was scored (1 = *no impairment* to 5 = *severe impairment*), allowing a total range of 6–30 points.

The widely used generic IADL scale and PSMS have the advantages of good reliability and validity, being easy to use, and not being as time-consuming as many of the more detailed dementia-specific ADL scales. Disease-specific scales might be more sensitive to functional losses that result from cognitive deficits; however, a scale that separated standard items of functioning into cognitive aspects of that function may be measuring cognition and not function (Desai, Grossberg, & Sheth, 2004; Spector, 1997).

### Nursing Home Placement

NHP was defined as admission to a licensed skilled nursing facility with 24-hr care. The date of placement was obtained from study records and was only applied for permanent care, that is, rehabilitative NHP and respite care were not included. If hospitalization occurred prior to NHP, the date of hospital admission was used. Time was defined as the actual number of months between the start of ChEI treatment and each assessment or NHP. The subjects lost to follow-up were censored,

which implies they contributed with information during the time they participated in the study.

**Predictors.**—The research is based on the World Health Organization's framework, "The International Classification of Functioning, Disability and Health," which is a classification of health and health-related domains. These domains are classified from the perspective of the body functions and structure, individual (activity and participation), and environment (e.g., societal). In the first Cox regression model, the investigated predictors were classical risk factors such as age at baseline, age at onset, gender, level of education, carrier of the apolipoprotein E (APOE)  $\epsilon 4$  allele, the number of medications at baseline, and living status (living alone or not). The impact of ChEI treatment was analyzed using the different drug agents and dosages. In addition, based on the findings of the clinical dementia investigation, cognitive and functional ability at baseline and the rate of change in cognition and function per month were included in the models to provide measures of the severity of AD and the progression rate. Finally, changes in the amount of community-based services per week during the past 6 months before NHP were included as measures of resource utilization given by the social services.

The rates of cognitive and functional change for the individuals who were admitted to nursing homes were calculated as the change in score from baseline to the last assessment before NHP, divided by the number of months between these assessments. For those not admitted, the rates of change were computed as the change in score from baseline to their last assessment, divided by the number of months. To facilitate comparisons of rates in MMSE, IADL and PSMS scores, change of score was converted to positive values indicating improvement and negative values showing decline.

The ChEI dose could vary during the treatment period for the individual patient and between the patients. Therefore, the mean dose used during the entire follow-up period was calculated for each patient. The impact of dose (high versus low) was analyzed using the median for each drug as the cutoff value; that is, donepezil 6.9 mg, rivastigmine 6.0 mg, and galantamine 16.0 mg.

The amount of home help service was defined as the number of hours per week, and adult day care as the number of days per week. The majority of subjects did not receive community-based service at baseline, 740 used no home help service, and 837 no adult day care. Thus, these potential predictors

were treated as categorical variables due to the skewed distributions. Home help service was categorized: up to 0.5 hr/day in average ( $\leq 3.5$  hr/week), 0.5–1 hr/day in average (3.75–7 hr/week), etc.

In the second Cox regression model, some biologically plausible interaction terms among the demographic variables (gender, age, and living status) and cognitive and ADL ability at baseline were included in the analysis, together with the variables from the first model. The interaction term Type of ChEI  $\times$  Dose was also included. Because most individuals used no service at baseline and thus the events analyzing changes in service utilization were few in this cohort of mild to moderate AD patients, the possible interactions between cognitive and functional abilities or its change versus service utilization were not analyzed in this study.

### *Statistical Analyses*

The Statistical Package for Social Sciences (SPSS) software (version 17.0; SPSS Inc., Chicago, IL) was used to perform the statistical analyses. The level of significance was defined as  $p < .05$  if not otherwise specified.

Independent sample  $t$  tests were used to compare the differences between the means for the patients admitted to NHP and the other subjects, as well as between the groups with different socio-demographic and clinical characteristics. One-way analysis of variance with Bonferroni correction was performed if more than two independent groups and chi-square test was computed for analyses of categorical variables.

Kaplan–Meier graphs were used to illustrate the differences in time to NHP regarding the categorical variables gender, living status, and dose of ChEI. The distribution of time for the categorical variables was compared using the log-rank test.

Cox proportional hazards models were used to separately estimate the effects of different risk factors on the relative risk of time to NHP. The analyses were done with adjustment for potential confounding of the baseline sociodemographic variables gender, age, and living status. The assumption of proportional hazards was tested with log minus log plots for the categorical covariates, and with time interaction test (the interaction term between the covariate and time was added to the model and generated a regression coefficient not significantly different from zero) for the time-dependent variables. No violation of the assumption of proportional hazards was detected.

**Table 1. Demographic and Clinical Characteristics (*n* = 880)**

Variable	NHP ( <i>n</i> = 206), <i>n</i> (%)	Not-NHP ( <i>n</i> = 674), <i>n</i> (%)	<i>p</i>
Female gender	149(72)	405(60)	.002
Higher level of education <sup>a</sup>	50(24)	204(30)	.124
Carrier of APOE ε4 allele	141(73)	448(67)	.180
Solitary living at baseline	104(50)	199(30)	<.001
Variable	Mean ± SD (range)	Mean ± SD (range)	<i>p</i>
Estimated age at onset, years	72.9 ± 7.2 (48–86)	71.8 ± 7.4 (45–87)	.055
Age at first assessment, years	76.4 ± 6.2 (53–87)	74.7 ± 7.2 (47–88)	.001
MMSE score at baseline	20.0 ± 4.1 (10–26)	21.7 ± 3.6 (10–26)	<.001
IADL score at baseline	18.3 ± 5.2 (8–29)	15.5 ± 5.5 (8–31)	<.001
PSMS score at baseline	8.1 ± 2.6 (6–21)	7.4 ± 2.0 (6–21)	<.001
Number of medications at baseline	2.8 ± 2.3 (0–10)	2.9 ± 2.4 (0–12)	.690
Mean dose of ChEI during the follow-up period			
Donepezil ( <i>n</i> = 518)	6.8 ± 1.8 (3.8–9.4)	6.9 ± 1.8 (2.8–9.4)	.464
Rivastigmine ( <i>n</i> = 198)	5.9 ± 1.8 (2.5–10.3)	6.2 ± 2.2 (2.2–10.5)	.465
Galantamine ( <i>n</i> = 164)	15.3 ± 3.6 (8.0–21.3)	16.4 ± 3.5 (8.0–22.0)	.129

Notes: IADL= Instrumental Activities of Daily Living scale; MMSE = Mini-Mental State Examination; NHP = subjects admitted to nursing homes during the study; PSMS = Physical Self-Maintenance scale.

<sup>a</sup>Education, compulsory = 9 years or less, higher = more than 9 years.

Backward stepwise elimination Cox regression models were used to (a) simultaneously estimate the effect of all the previously described candidate predictors (main effects model) on the time to NHP, and (b) explore the possibility of two-way interactions among the demographic variables (gender, age, and living status) and cognitive and ADL ability at baseline by adding all such terms to the first model. The hierarchical principle was observed in these analyses; variables were not considered for elimination if they appeared in interactions. Variables with *p* > .05 were removed from the stepwise models.

The backward elimination analysis begins with a full model, including all the candidate predictor variables. It then removes the least significant variable, that is, the one with the highest *p* value at each step. The fit of the model is tested after eliminating each variable to ensure that the model still fits the data adequately. When no more variables can be eliminated from the model, the analysis has been completed and should contain the most important predictors. In our Cox regression analyses, the models for selecting the predictor variables and their *p* values were stable.

## Results

### Baseline Characteristics

Of the 880 patients, 206 (23%) were admitted to nursing homes during the study, 53 of those

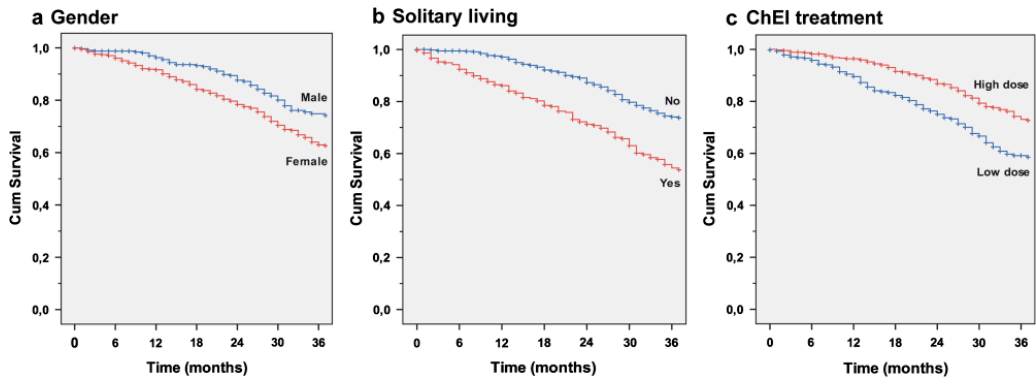
admitted were able to fulfill the entire study. The remaining 674 subjects completed the 3-year study (*n* = 286, 33%) or withdrew for reasons other than NHP (*n* = 388, 44%).

The demographic and clinical characteristics of the patients divided into two groups, admitted or not admitted to a nursing home, are given in Table 1. Gender and living status significantly influenced the event NHP. During the study, 18% of the men and 27% of the women were admitted to a nursing home (*p* = .002). Of the patients living alone, 34% were admitted compared with 18% of those living with their spouse or another family member (*p* < .001). This difference was not explained by variations in age, disease severity, or the number of medications at baseline between these groups.

At the start of ChEI treatment, the patients later admitted to nursing homes were older (*p* = .001) and more cognitively (*p* < .001) and functionally impaired (*p* < .001) compared with those not admitted (Table 1). No differences regarding level of education, carrier of the APOE ε4 allele, age at onset, number of medications at baseline or mean ChEI dose during the follow-up period were found between the two groups. The variable living status was not associated with high versus low drug dose (*p* = .125).

### Nursing Home Placement

Median time from the estimated onset of AD to NHP was 56 months (4.7 years), and median time



**Figure 1.** Kaplan-Meier graphs of the distribution of time from the start of ChEI treatment to NHP for the significant category variables gender, living status, and drug dose. Log-rank test showed differences between gender ( $p = .001$ ), solitary living ( $p < .001$ ), and dose of ChEI ( $p < .001$ ). Cutoff median values for ChEI dose were donepezil 6.9 mg, rivastigmine 6.0 mg, and galantamine 16.0 mg.

from the start of ChEI treatment to NHP was 20 months (1.7 years). Figure 1 demonstrates Kaplan-Meier graphs for the significant category variables gender, living status, and drug dose. Analyses of the distribution of time from the start of treatment to NHP showed differences between gender ( $p = .001$ ), solitary living ( $p < .001$ ), and dose of ChEI ( $p < .001$ ). The median time from baseline to NHP was 24 months for men versus 18 for women, and 17 months for subjects living alone versus 23.5 for those residing with a spouse or relative. The patients who received a high dose of ChEI exhibited longer median time to NHP, 23.5 months, compared with 16.5 for those who received a lower dose.

**Univariate Cox Regression Models.**—Univariate Cox proportional hazards modeling suggested several risk factors to be associated with time to NHP. Shorter time to NHP was associated with lower cognitive and functional ability at baseline or a faster rate of decline; younger age at onset or older age at baseline, solitary living; a lower (0.25–3.5 hr) or higher (>7 hr) increase in home help service per week; more adult day care at baseline or an increase in three or more days per week; and a lower dose of ChEI and treatment with donepezil or rivastigmine. The hazard ratios with 95% confidence interval (CI) and  $p$  values for these variables are listed in Table 2.

The association between living status and increase in service utilization was investigated; the individuals living alone receive a greater increase in home help service per week ( $p < .001$ ). No

significant difference was found regarding living status versus increase in adult day care per week. IADL ability at baseline differed between the treatment groups. Individuals treated with galantamine showed better function at baseline, IADL mean  $\pm$  standard deviation (SD) score:  $14.6 \pm 5.4$  versus donepezil  $16.8 \pm 5.6$  and rivastigmine  $15.5 \pm 5.3$ ,  $p < .001$ . After adjusting for baseline IADL ability in the Cox univariate type of ChEI model, no significant difference in the time to NHP between the specific drugs was found ( $p = .368$ ).

**Multivariate Cox Regression Models.**—When subjected to multivariate backward elimination modeling, only seven of the variables from the univariate analyses were retained in the model. These variables were living status, dose of ChEI, MMSE, and IADL score at baseline; rate of change in IADL score per month; weekly increase in more than 7 hr of home help service; and an increase in three or more days per week in adult day care. Basic ADL ability, the rate of change in cognition and basic ADLs, age at onset and age at baseline, weekly assistance at baseline, and the type of ChEI were not significant predictors for the time to NHP in the multivariate models. The coefficients, hazard ratios with 95% CI, and  $p$  values for the significant predictors are described in Table 3, Model 1.

In Model 2, including the interaction terms, the variable home help service, increase in hours per week was eliminated from the model. Instead, gender and the interaction effect, Gender  $\times$  Living status were retained (Table 3). The interaction terms incorporating the variables age, cognitive

**Table 2. Univariate Cox Proportional Hazards Modeling of Time to Nursing Home Placement**

	Hazard ratio (95% CI) <sup>a</sup>	<i>p</i>
Gender ( <i>male</i> = 0, <i>female</i> = 1)	1.31 (0.95–1.81)	.100
Level of education (≤9 years = 0, >9 years = 1)	0.92 (0.67–1.28)	.636
Carrier of APOE ε4 allele ( <i>no</i> = 0, <i>yes</i> = 1)	1.25 (0.90–1.72)	.178
Solitary living at baseline ( <i>no</i> = 0, <i>yes</i> = 1)	1.94 (1.45–2.60)	<.001
ChEI dose <sup>b</sup> ( <i>low</i> = 0, <i>high</i> = 1)	0.58 (0.44–0.76)	<.001
Type of ChEI <sup>c</sup>		
Rivastigmine	0.76 (0.53–1.10)	.143
Galantamine	0.59 (0.39–0.89)	.011
Estimated age at onset, years	0.95 (0.91–0.99)	.026
Age at first assessment, years	1.03 (1.01–1.05)	.010
MMSE score at baseline	0.88 (0.85–0.91)	<.001
IADL score at baseline	1.11 (1.08–1.14)	<.001
PSMS score at baseline	1.13 (1.07–1.19)	<.001
MMSE score, rate of change per month	0.53 (0.32–0.86)	.010
IADL score, rate of change per month	0.22 (0.13–0.38)	<.001
PSMS score, rate of change per month	0.11 (0.06–0.20)	<.001
Number of medications at baseline	0.98 (0.92–1.04)	.427
Home help service at baseline, hr/week <sup>d</sup>		
0.50–3.50 ( <i>n</i> = 61)	1.55 (0.94–2.57)	.088
3.75–7.00 ( <i>n</i> = 48)	1.68 (1.00–2.84)	.051
≥7.25 ( <i>n</i> = 30)	1.65 (0.91–3.00)	.099
Adult day care at baseline, days/week <sup>d</sup>		
1–2 ( <i>n</i> = 27)	1.94 (1.04–3.59)	.036
≥3 ( <i>n</i> = 15)	3.67 (1.93–6.97)	<.001
Home help service, increase in hr/week <sup>d</sup>		
0.25–3.50 ( <i>n</i> = 58)	1.67 (1.06–2.61)	.026
3.75–7.00 ( <i>n</i> = 44)	1.34 (0.78–2.31)	.285
≥7.25 ( <i>n</i> = 29)	2.28 (1.28–4.07)	.005
<–0.25, i.e., utilization decreased ( <i>n</i> = 35)	1.73 (1.01–2.96)	.045
Adult day care, increase in days/week <sup>d</sup>		
1 ( <i>n</i> = 26)	0.84 (0.39–1.78)	.640
2 ( <i>n</i> = 40)	0.84 (0.43–1.65)	.621
≥3 ( <i>n</i> = 15)	2.70 (1.32–5.53)	.007
<–1, i.e., utilization decreased ( <i>n</i> = 10)	0.34 (0.05–2.44)	.284

Notes: Hazard ratios are expressed per 1 unit increase for continuous variables and for the condition present in categorized variables. ChEI = cholinesterase inhibitor treatment; CI = confidence interval; IADL = Instrumental Activities of Daily Living scale; MMSE = Mini-Mental State Examination; PSMS = Physical Self-Maintenance scale.

<sup>a</sup>Adjusted (if applicable) for the baseline variables gender, age, and solitary living.

<sup>b</sup>Cutoff median values for ChEI dose were donepezil 6.9 mg, rivastigmine 6.0 mg, and galantamine 16.0 mg.

<sup>c</sup>Donepezil was the reference category.

<sup>d</sup>0 hr/day/week was the reference category.

and ADL ability at the start of ChEI treatment were not significant nor was the term Type of ChEI × Dose. Because of the interaction, the effects of gender and living status cannot be interpreted in isolation. For the men living alone, the hazard ratio for the time to NHP was 3.73 compared with 1.0 for those men not living alone, and for the women living alone, the hazard ratio was 2.94 versus 1.69 for women living with their spouse or another relative. The relative hazards for various combinations of risk factors can be computed based on the coefficients listed in Table 3. Figure 2 illustrates the cumulative survival function for the interaction term Gender × Living Status. Analyses of the distribution of time from the start of treatment to NHP showed a significant difference (*p* < .001) for all pairwise comparisons except for the combination men living alone–women living alone.

#### Differences in Clinical Characteristics at the Last Assessment Prior to Nursing Home Entry

At the last assessment prior to NHP, 114 (55%) of the 206 subjects were living alone, and their mean ± *SD* age was 78.0 ± 6.1 years. The last cognitive and functional mean ± *SD* outcomes before admission for these subjects were MMSE score 17.4 ± 6.0, IADL score 22.8 ± 4.7, and PSMS score 10.6 ± 3.8.

The individuals living alone prior to NHP had better cognitive (MMSE score: 18.4 ± 5.3 vs. 16.1 ± 6.6, *p* = .007) and IADL ability (IADL score: 21.7 ± 4.7 vs. 24.2 ± 4.3, *p* < .001) before admission compared with those living with a spouse or other relative. No significant differences in age or basic ADL ability were detected. The interaction term Gender × Living Status was also analyzed concerning the cognitive and functional outcomes at the last assessment prior to NHP. The patients living alone exhibited IADL scores of 21.8 ± 4.1 (men) and 21.5 ± 5.0 (women) compared with those not living alone, men: 24.6 ± 4.0 and women: 23.9 ± 4.4 (*p* = .001). There were no significant differences in age, MMSE, or PSMS scores before admission regarding these groups. The classical risk factors gender, level of education, carrier of the APOE ε4 allele, and the received dose of ChEI demonstrated no differences on the last cognitive and functional outcomes before NHP nor did the type of ChEI regarding the difference in cognition and function between the start of treatment and NHP.



**Table 3. Significant Predictors in Multivariate Cox Proportional Hazards Regression of Time to Nursing Home Placement**

	$\beta$ (SE)	Hazard ratio (95% CI)	<i>p</i>
Model 1, excluding interaction terms			
Solitary living at baseline ( <i>no</i> = 0, <i>yes</i> = 1)	0.686 (0.163)	1.99 (1.44–2.73)	<.001
ChEI dose <sup>a</sup> ( <i>low</i> = 0, <i>high</i> = 1)	-0.486 (0.151)	0.62 (0.46–0.83)	.001
MMSE score at baseline	-0.058 (0.022)	0.94 (0.90–0.98)	.008
IADL score at baseline	0.110 (0.017)	1.12 (1.08–1.16)	<.001
IADL score, rate of change per month	-2.117 (0.307)	0.12 (0.07–0.22)	<.001
Home help service, increase in hr/week <sup>b</sup>			
0.25–3.50	0.477 (0.243)	1.61 (1.00–2.60)	.049
3.75–7.00	-0.036 (0.307)	0.96 (0.53–1.76)	.907
≥7.25	0.773 (0.312)	2.17 (1.18–3.99)	.013
<-0.25, i.e., utilization decreased	0.512 (0.282)	1.67 (0.96–2.90)	.069
Adult day care, increase in days/week <sup>b</sup>			
1	-0.291 (0.393)	0.75 (0.35–1.62)	.458
2	-0.270 (0.349)	0.76 (0.38–1.51)	.439
≥3	0.949 (0.369)	2.58 (1.25–5.32)	.010
<-1, i.e., utilization decreased	-1.477 (1.008)	0.23 (0.03–1.65)	.143
Model 2, including interaction terms			
Gender ( <i>male</i> = 0, <i>female</i> = 1)	0.524 (0.215)	1.69 (1.11–2.58)	.015
Solitary living at baseline ( <i>no</i> = 0, <i>yes</i> = 1)	1.316 (0.303)	3.73 (2.06–6.75)	<.001
ChEI dose <sup>a</sup> ( <i>low</i> = 0, <i>high</i> = 1)	-0.458 (0.151)	0.63 (0.47–0.85)	.002
MMSE score at baseline	-0.057 (0.022)	0.94 (0.90–0.98)	.009
IADL score at baseline	0.112 (0.017)	1.12 (1.08–1.16)	<.001
IADL score, rate of change per month	-2.164 (0.286)	0.12 (0.07–0.20)	<.001
Adult day care, increase in days/week <sup>b</sup>			
1	-0.180 (0.398)	0.84 (0.38–1.82)	.650
2	-0.336 (0.344)	0.72 (0.36–1.40)	.329
≥3	0.983 (0.366)	2.67 (1.30–5.48)	.007
<-1, i.e., utilization decreased	-1.221 (1.007)	0.30 (0.04–2.12)	.225
Gender × Living Status	-0.760 (0.349)	0.47 (0.24–0.93)	.030

Notes:  $\beta$  values and hazard ratios are expressed per 1 unit increase for continuous variables and for the condition present in categorized variables. ChEI = cholinesterase inhibitor treatment; CI = confidence interval; IADL = Instrumental Activities of Daily Living scale; MMSE = Mini-Mental State Examination; PSMS = Physical Self-Maintenance scale; SE = standard error.

<sup>a</sup>Cutoff median values for ChEI dose were, donepezil 6.9 mg, rivastigmine 6.0 mg, and galantamine 16.0 mg.

<sup>b</sup>0 hr/day/week was the reference category.

## Discussion

In this longitudinal study, we found that the rate of change in IADL decline, but not in cognitive deterioration, was an important predictor of the time to NHP, after controlling for multiple factors previously shown to be of importance. Moreover, higher doses of ChEI, regardless of the specific drug agent, might postpone institutionalization in AD. Other factors that precipitated admission to nursing homes in the multivariate Cox regression model were lower cognitive and functional abilities at baseline; female gender; solitary living; and the interaction effect, men living alone. A substantial increase in adult day care predicted shorter time to NHP as well.

This study shows that a more rapid deterioration in IADL increases the risk for early NHP. One possible explanation could be that the subjects

who undergo change or decline in functional health status while living at home may cause greater strains to caregivers and support services than those who remain stable over time, even with low ADL ability. Considerable changes in function can make it difficult for the caregivers and the service providers to adapt to, and offer sufficient home-based care (Wolinsky, Callahan, Fitzgerald, & Johnson, 1993).

In the present study, which includes patients from routine clinical settings, the multivariate Cox regression models demonstrated that individuals with an average decline of -0.2 IADL points/month were 1.54 times more likely (hazard ratio) to be admitted to nursing homes as those with no decline. Consistent with our findings, results from a long-term clinical trial (Hatoum et al., 2009) suggested that deterioration in ADL provided a

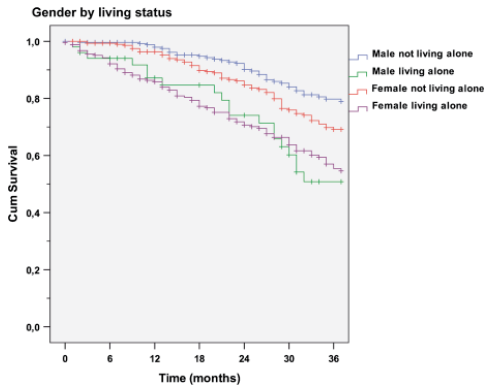


Figure 2. Kaplan–Meier graph of the distribution of time from the start of ChEI treatment to NHP for the interaction term gender by living status. Log-rank test showed a significant difference ( $p < .001$ ) for all pairwise comparisons except for the combination men living alone–women living alone.

better predictive measure for NHP than deterioration in cognition. A patient with mean ADL decline participating in that trial exhibited a hazard ratio of 1.65 for NHP. Similarly, a large-scale 3-year dementia evaluation (Gaugler et al., 2003), which controlled for a considerable number of discrete variables, showed that subjects who had an increase of one or more ADL limitations were 1.48 times more likely to be institutionalized earlier.

A faster decline in IADL ability leading to early NHP may also have an impact on the amount of service utilization. In the present study, a lower (0.25–3.5 hr) or higher (>7 hr) increase in home help service per week, and an increase in three or more days per week in adult day care predicted early admission. The individuals living with a spouse or other relative received a smaller increase in home help service per week than did those living alone. A low increase in home help service that preceded NHP indicated that the increased level of care was not sufficient to support the caregiver and prevent institutionalization. This is in agreement with the observations made by Gaugler et al. (2003), who described a similar relationship between community-based service and admission to nursing homes. By identifying the care recipients at risk of an inadequate level of service, and focusing on their actual needs, it might be possible to postpone NHP for these individuals.

The increase in adult day care of more than 2 days/week remained a predictor of early NHP in the multivariate models in this study. Consistent with our findings, Hope, Keene, Gedling, Fairburn, and Jacoby (1998) described in a dementia study

that one of the four best characteristics predicting NHP was, being away from the caregiver for more than 16 hours/week (the majority of time due to day care). When the care recipient gradually spends more time away from the home, the caregiver might become more accustomed to leaving the daily care to the social services, thus experiencing some relief in their burden, which perhaps facilitates the decision to resign care (Gaugler et al., 2003). Similarly, a previous AD study of adult day care services (McCann et al., 2005) suggested that those using more adult day care per week had an increased risk of NHP, even after adjusting for disease severity and caregiver burden. This indicates that adult day care served more as a transitional period to institutionalization than a form of respite, and thus precipitated NHP.

In this longitudinal naturalistic study, we found that a higher mean dose of ChEI, regardless of the specific drug agent, might postpone institutionalization in AD. Previously, few studies have investigated the impact of pharmacological interventions such as ChEI treatment on the outcome of NHP. In a recent review of predictors of NHP by Gaugler et al. (2009), the utilization of various types of medication yielded no consistent outcome. In an early open label extension of tacrine (Knopman et al., 1996), patients who remained on the drug and received effective doses of more than 80 mg/day were less likely to have entered a nursing home than those on lower doses. No similar dose–time to NHP effect was detected in a long-term naturalistic tacrine study from our group (Wallin, Gustafson, Sjogren, Wattmo, & Minthon, 2004); however, these patients received the higher effective doses during the 5 years. In a pooled study of AD patients previously enrolled in randomized placebo-controlled trials and subsequent extensions, Geldmacher et al. (2003) proposed that the use of effective doses of donepezil (>5 mg/day) and longer term sustained donepezil use was associated with significant delays in NHP. Lopez et al. (2002, 2005) showed in a comparison between treated and untreated matched AD cohorts that ChEI use was associated with a delay in institutionalization. In summary, these results suggest the clinical importance of prescribing sufficient doses of ChEI to the individual patient.

When investigating possible interaction effects between the risk factors in this study, the only significant interaction term was the association between gender and living status. The effect of these variables should therefore be interpreted

together. A substantial number of previous dementia studies have separately analyzed the effects of gender and marital status but hardly any considered the interaction (Luppa et al., 2008). In our study, the risk of NHP was almost fourfold for a man living alone compared with a man living with the spouse or relative. For a woman living alone, the risk was less than double compared with a woman living with a family member. A prior study of AD patients (Heyman et al., 1997), focusing on this interaction effect, found that the median time from enrollment in that study to NHP was at least a year less among the unmarried men compared with the married men and all the women.

The strengths of the 3-year SATS study are the prospective, regular, well-structured, semiannual follow-up investigations of large cohorts of ChEI-treated AD patients in routine clinical settings. This longitudinal study adds to the current knowledge, regarding NHP, measures of change in cognition, function, and service utilization. Moreover, it enables analyses of clinical characteristics before the event NHP, as well as of potential differences between the ChEI agents and doses. The scheduled 6-month visits at the memory clinic and the presence of an identified contact nurse for each individual represent security and continuity for the patients. This work procedure reduces the risk that it is mainly the patients with active informal caregivers whose clinical and functional problems are reported to the attending physician and therefore receive better management of treatment and service utilization. The SATS study design has evolved into a clinical follow-up program, within the context of offering individualized care, which is nowadays applied to all AD patients in our memory clinic. One implication of this study, which is directly applicable to clinical praxis in our clinic, was that the occupational therapists would observe and follow up, in particular, the male patients living alone.

In Sweden, the amount of community-based care or admission to a nursing home is based solely on the individual's need and is almost exclusively publicly funded (Holm, Liss, & Norheim, 1999). Decisions on the adequate level of care are made in a similar way within the social services system regardless of the care recipient's place of residence. The family's income or insurance coverage is rarely an issue when deciding the necessary amount of care given by the social services. Another advantage of the SATS is that only patients fulfilling the diagnostic criteria for AD are included. Prior studies regarding NHP mainly included the diagnosis

of dementia in general and different diagnostic criteria were used or not reported, complicating the possibility of comparisons (Luppa et al., 2008). Different dementia diagnoses may yield different outcomes and costs. Bostrom, Jonsson, Minthon, and Londos (2007) showed, in a comparison between AD and dementia with Lewy bodies (DLB) cohorts, matched for identical cognitive severity, that the DLB patients utilized more community services and care resources than the AD patients.

The limitations of this study are that other factors that may influence the time to NHP, such as concomitant somatic diseases, behavioral symptoms of dementia, and the caregivers' situation, were not evaluated in the SATS program. The inclusion of additional candidate predictors might influence the multivariate models. Yet, our results are consistent with other studies and there are no indications that the significant predictors would be less important even if mediated by other variables. For example, past research (Fisher & Lieberman, 1999; Severson et al., 1994) showed that when caregiver factors are predictive of NHP, they interact with the severity of the disease. Moreover, half of the individuals in this study later admitted to nursing homes were living alone at baseline. The influence of caregiver factors for those subjects, therefore, may be limited.

Future research should focus on how the service providers can best identify care recipients at risk of an inadequate level of service utilization. Moreover, identifying the interventions that would be most effective in helping the individuals at risk—for example, those with a faster rate of functional decline—remain at home longer. To provide a more conclusive understanding of the association between AD and resource utilization given by the social services, longitudinal analysis of the possible interactions between changes in disease severity, service utilization, and ChEI treatment are needed.

In conclusion, this study shows that a faster rate of IADL decline and a lower dose of ChEI were essential predictors for early NHP. Other risk factors were lower cognitive and functional abilities at baseline, female gender, solitary living, the interaction of men living alone, and a substantial increase in the use of adult day care. These critical characteristics could be used as a tool by the clinician in the multifaceted AD investigation and treatment process, involving both medication and support to patients and caregivers. Furthermore, the use of an effective dose of ChEI is important because this appears to prolong the

time to NHP in AD. Service providers might use the results to identify care recipients at considerable risk of NHP, thus ensuring that they receive a sufficient amount of home care intervention.

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