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Ilona Hallikainen

Cognitive Performance and Progression of Alzheimer's Disease: measurement and intervention

The ALSOVA Follow-up Study

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ABSTRACT

In developed countries, the change in the age distribution of the population brings on an increasing prevalence of disorders that cause memory deficits and dementia. The most common of them is Alzheimer's disease (AD). It is characterised by progressive deficits in memory and other cognitive domains, deterioration of daily functions, neuropsychiatric symptoms (NPS), and an increasing need of assistance. In order to plan and evaluate the necessary treatment and care, one needs knowledge about the progression of AD-related symptoms and functional assessment methods. Furthermore, support programmes for persons with AD and their caregivers are needed.

The aim of this series of studies was to investigate the progression of cognitive deficits and other symptoms in persons with very mild or mild AD over a three-year follow-up period and to assess the usability of the CERAD Neuropsychological Battery as a follow-up method. A further aim was to analyse the effects of early psychosocial intervention on institutionalisation and AD-related symptoms.

This doctoral dissertation is based on a psychosocial intervention study in Alzheimer's disease, referred to as the ALSOVA Study. It was a prospective, randomised and controlled follow-up and intervention study of persons with AD and their caregivers. A total of 241 participants with recently diagnosed AD were recruited from three hospital districts in Finland. Out of those recruited, 236 persons with very mild or mild AD at baseline were included and followed up for three years. A total of 129 participated in all four annual visits, which included interviews and cognitive assessments by a study nurse and a psychologist. Cognition was assessed with the CERAD Neuropsychological Battery and the Mini-Mental State Examination (MMSE).

The study revealed an association of cognitive performance with the severity of dementia and the managing of daily functions. However, cognitive impairment did not correlate with NPS. Both cognitive deficits and NPS were associated with the person's ability to manage everyday life activities. Progressive deterioration in cognitive functions and in the activities of daily living (ADL) plus increases in NPS were detected during the three years. The decline of ADL functions was slower in persons with very mild AD at baseline. The CERAD Neuropsychological Battery total score was found to be a suitable tool for AD follow-up trials, and a short version of the battery was constructed. The study showed no long-term effects of early psychosocial intervention on nursing-home placement or AD-related symptoms.

In conclusion, the study added to our knowledge of the progression of AD during the first few years after diagnosis. It showed up the CERAD Neuropsychological Battery as a more sensitive follow-up tool than the MMSE and highlighted the importance of early diagnosis and assessment of daily functions and neuropsychiatric symptoms. However, the results do not support the recommendation to offer intensive psychosocial intervention to all persons with very mild or mild AD.

National Library of Medicine Classification: WM 220; WT 155; WL141.5.N46
Medical Subject Headings: Alzheimer disease; Activities of Daily Living; Cognition; Early Diagnosis; Disease Progression; Neuropsychological tests; Rehabilitation; Follow-Up Studies; Intervention studies; Prospective studies

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TIIVISTELMÄ

Väestön ikärakenteen muutos kehittyneissä maissa lisää muistivaikeuksien ja muistisairauksien määrää. Yleisin muistisairaus on Alzheimerin tauti (AT). Sille on tyypillistä etenevät vaikeudet muistamisessa ja muissa tiedonkäsittelytoiminnoissa, päivittäisen toimintakyvyn heikentyminen, käytös- ja mielialaoireiden esiintyminen sekä lisääntyvä avuntarve. Tietoa taudinkulusta sekä toimivista arviointimenetelmistä tarvitaan hoidon suunnittelua ja arviointia varten.

Tämän väitöskirjan tarkoituksena oli selvittää kognitiivisten toimintojen sekä muiden oireiden etenemistä hyvin lievää tai lievää Alzheimerin tautia sairastavilla kolmen vuoden seurannassa, sekä tutkia CERAD kognitiivisen tehtäväsarjan käytettävyyttä taudin etenemisen arviointimenetelmänä. Lisäksi tavoitteena oli selvittää varhaisen psykososiaalisen kuntoutuksen vaikuttavuutta laitoshoitoon siirtymiseen ja Alzheimerin taudin oireisiin.

Väitöskirja pohjautui ALSOVA (Alzheimerin taudin sopeutumisvalmennustutkimus) -hankkeeseen, joka on prospektiivinen, satunnaistettu ja kontrolloitu seuranta- ja interventiotutkimus. Tutkimukseen osallistui 241 AT:a sairastavaa ja heidän omaishoitajaansa kolmen sairaanhoitopiirin alueelta Suomesta. Yhteensä 236 hyvin lievää tai lievää AT:a sairastavaa täytti sisäänottokriteerit, ja seuranta kesti kolmen vuoden ajan. Yhteensä 129 tutkittavaa osallistui kaikille neljälle tutkimuskäynnille. Vuosittaiset käynnit sisälsivät tutkimushoitajan ja psykologin tekemiä haastatteluja ja kognitiivisen arvioinnin. Kognitiivisia tomintoja arvioitiin CERAD tehtäväsarjalla sekä MMSE-testillä.

Väitöskirjaan sisältyvien tutkimusten mukaan kognitiivinen suoriutuminen oli yhteydessä taudin vaikeusasteeseen ja päivittäiseen toimintakykyyn. Sen sijaan yhteyttä kognition ja neuropsykiatristen oireiden välillä ei todettu. Sekä kognitio että neuropsykiatriset oireet olivat yhteydessä AT:a sairastavan kykyyn suoriutua päivittäisistä toimista. Kolmen vuoden aikana kognitiiviset toiminnot ja päivittäinen toimintakyky heikkenivät etenevästi ja neuropsykiatriset oireet lisääntyivät. Päivittäisen toimintakyvyn lasku oli hitaampaa henkilöillä, joilla oli hyvin lievä AT tutkimuksen alussa. CERAD kognitiivisen tehtäväsarjan kokonaispistemäärä osoittautui toimivaksi mittariksi seurantatutkimuskäytössä, ja lisäksi kehitettiin tehtäväsarjan lyhyt versio. Varhaisella psykososiaalisella kuntoutuksella ei todettu olevan pitkäkestoisia vaikutuksia laitoshoitoon siirtymiseen tai AT:n oireisiin.

Tutkimus tuotti lisää tietoa AT:n etenemisestä ensimmäisinä vuosina taudin toteamisen jälkeen. CERAD tehtäväsarjaa voidaan suositella MMSE-testiä herkempänä menetelmänä taudin seurannassa. Tulokset korostavat varhaisen taudin toteamisen sekä päivittäisen toimintakyvyn ja neuropsykiatristen oireiden arvioimisen merkitystä. Sen sijaan tulokset eivät tue psykososiaalisen kuntoutuksen tarjoamista kaikille lievää AT:a sairastaville.

Yleinen Suomalainen asiasanasto: Alzeimerin tauti; dementia; kognitio; kognitiiviset taidot; psykososiaalinen kuntoutus; toimintakyky; CERAD; arviointimenetelmät; testit; seurantatutkimus

To my Family

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II Hallikainen I, Hänninen T, Fraunberg M, Hongisto K, Välimäki T, Hiltunen A, Karppi P, Sivenius J, Soininen H, Koivisto AM; Alsova Study group. Progression of Alzheimer's disease during a three-year follow-up using the CERAD-NB total score: Kuopio ALSOVA Study. *International psychogeriatrics 25: 1335-44, 2013.* Cambridge University Press.

III Hallikainen I, Martikainen J, Lin PJ, Cohen JT, Lahoz R, Välimäki T, Hongisto K, Väätäinen S, Vanhanen M, Neumann PJ, Hänninen T, Koivisto AM. The progression of Alzheimer's disease can be assessed with a short version of the CERAD Neuropsychological Battery: The Kuopio Alsova Study. *Dementia and geriatric cognitive disorders Extra 4: 494-508, 2014.* S. Karger, Basel.

IV Koivisto AM, Hallikainen I, Välimäki T, Hongisto K, Hiltunen A, Karppi P, Sivenius J, Soininen H, Martikainen J. Early psychosocial intervention does not delay institutionalization in persons with mild Alzheimer disease neither have impact on disease progression or caregivers' wellbeing: ALSOVA 3-year follow-up. *Submitted.*

Contents

Abbreviations

AD	Alzheimer's Disease
ADL	Activities of Daily Living
ADCS-ADL	Alzheimer's Disease Cooperative Study – Activities of Daily Living
ALSOVA	Alzheimerin taudin sopeutumisvalmennus-tutkimus (Psychosocial intervention study in Alzheimer's disease)
APA	American Psychiatric Association
CDR	Clinical Dementia Rating
CDR-sb	Clinical Dementia Rating Sum of Boxes
CERAD-NB	Consortium to Establish a Registry for Alzheimer's Disease Neuropsychological Battery
CSF	Cerebrospinal fluid
DSM-IV	Diagnostic and statistical manual of mental disoders, 4th edition
DSM-5	Diagnostic and statistical manual of mental disorders, 5th edition
IADL	Instrumental Activities of Daily Living
ISTAART	International Society to Advance Alzheimer's Research and Treatment
MMSE	Mini-Mental State Examination
MCI	Mild Cognitive Impairment
MRI	Magnetic Resonance Imaging
NIA	National Institute of Aging
NINCS-ADRDA	National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association
NPI	Neuropsychiatric Inventory
PET	Positron Emission Tomography
Qol-AD	Quality of Life in Alzheimer's Disease
VAS	Visual Analog Scale

1 Introduction

Alzheimer's disease (AD) is a progressive neurodegenerative disease and the most common cause of dementia. The prevalence of disorders that cause memory deficits and dementia increases as the population ages. The present number of persons with dementia in Finland has been estimated to be approximately 120 000 (Memory disorders: Current Care Guidelines, 2010), and by 2050 the number has been estimated to double (Alzheimer's Association, 2014). AD is characterised by progressive memory deficits, problems in other cognitive domains, decline in daily functions, and behavioural and psychological problems (Cummings, 2007). Researchers have identified the brain pathology and many protective and risk factors involved in AD (e.g., Seppälä et al., 2013; di Marco et al., 2014), but the ultimate cause of AD onset is still unknown, and no inhibitory or interceptive medication is available.

Recent research and clinical practice have focused on early detection of AD, and less attention has been paid to following up the progression of the disease. The course of the disease has been documented, and predictors of rapid progression of AD have been sought. Unfortunately, the measures used have been variable and the follow-up periods often limited. Oftentimes, only the MMSE test (Folstein et al., 1975) has been used as a measure of global cognition and the severity of the disease; this practice has also been criticised (e.g., Atchinson et al., 2004; Clark et al., 1999). At the same time, scientific knowledge and diagnostic criteria have advanced substantially in recent decades. Persons can now be diagnosed at an earlier stage of the disease (Dubois et al., 2010; Jack et al., 2011; American Psychiatric Association, 2013), and AD-targeted medication is available to slow down the progression of the disease (Memory disorders: Current Care Guidelines, 2010). There is thus a clear need of further studies to track the course of the disease in medicated persons with very mild or mild AD.

The Consortium to Establish a Registry for Alzheimer's Disease (CERAD) was founded as early as the 1980s to develop standardised measures for the assessment of AD. The CERAD Neuropsychological Battery (CERAD-NB), developed to measure early cognitive impairments in AD (Welsh et al., 1994), was translated into Finnish in the 1990s (Hänninen et al., 1999). Nowadays the CERAD-NB is used as a screening tool for AD-related cognitive deficits (Sotaniemi et al., 2012). The CERAD-NB total score (Chandler et al., 2005), developed later, has also proved to be a reliable measure to distinguish early AD from normal aging (Paajanen et al., 2013). But as to the use of the CERAD-NB as a follow-up tool to measure the progression of AD-related symptoms, much less is known. Because the CERAD-NB is widely used at the stage of diagnosis, it would make sense to extend its use to follow-up as well. In research settings in particular, the CERAD-NB total score might be a more accurate measure of global cognition than the MMSE, besides being easier to use in analyses than the single cognitive tests that measure different cognitive domains.

Due to the increasing costs of dementia care and the sharpened awareness of the effects of the disease on the lives of people with AD and their caregivers, different kinds of interventions have been developed to ease AD-related symptoms, to reduce caregiver burden, and to delay nursing-home placement (Pinqart & Sörensen, 2006; Olazar et al., 2010; van Mierlo et al., 2010; Vernooij-Dassen et al., 2011). However, the results have been contradictory. Previous literature indicates that different clinical characteristics of the participants affect the efficacy of the interventions and that the outcomes attained may also vary according to the particular interventions used. Only multicomponent interventions have succeeded in delaying nursing-home placement, but some recent studies have failed to show any long-term effects of psychosocial intervention on institutionalisation.

In this study, persons with recently diagnosed very mild or mild AD at baseline and their caregivers were followed up for three years. On annual study visits, a wide range of evaluations was carried out. The participants were randomised into control groups and intervention groups, and the members of both groups participated in the study visits and visits to their regular health-care system. The psychosocial intervention courses were arranged during the first two years of the study. The aim of the study was to evaluate the course of the disease during the three years after diagnosis, focusing on cognition, daily functions, and neuropsychiatric symptoms. Furthermore, the effects of early psychosocial interventions on AD-related symptoms and nursing-home placement were evaluated and the usability of the CERAD-NB as a follow-up tool was assessed. The assessment focused on the use of the CERAD-NB total score and the subtests of the CERAD-NB over the three-year follow-up period. To advance the follow-up of the progression of AD-related symptoms, a short version of the CERAD-NB was constructed.

2 Review of the Literature

2.1 ALZHEIMER'S DISEASE

In 1906, Dr. Alois Alzheimer described the case of Auguste D, a patient who suffered from a form of dementia; later on, the condition became known as Alzheimer's disease (AD) (Maurer et al., 1997). Nowadays AD is known to be a progressive neurodegenerative disease. The term dementia is used to describe a condition in which the deterioration of cognition affects the person's ability to perform everyday activities (Alzheimer Association, 2014; American Psychiatric Association, 1994; 2013), and AD is the most common cause of it, accounting for 50 - 80 % of the cases (Plassman et al., 2007; Alzheimer's Association, 2014). AD is a condition typically characterised by progressive deterioration of memory, accompanied by other cognitive, behavioural, and psychological changes, which eventually affect the person's everyday life and social functions and causes an increasing need for assistance (Small et al., 2009; World Health Organization, 2012; Alzheimer's Association, 2014). During the last few decades, scientific knowledge and clinical practice pertaining to AD have advanced substantially and continue to do so. In describing the large scientific field of AD-related symptoms and AD pathology, it is therefore more appropriate to refer to handbooks, reviews, consensus and position papers, and reports rather than single scholarly articles.

The pathological process of AD begins years or decades before any clinical symptoms emerge. The hallmarks of AD pathology are progressive accumulation of the protein beta-amyloid outside neurons, seen as senile plaques, accompanied by abnormalities in the synaptic function and eventually leading to the death of neurons, which is seen as an abnormal form of the protein tau (neurofibrillary tangles) accumulation inside neurons (Small et al., 2009; Alzheimer's Association, 2014; Seppälä et al., 2013). According to present knowledge, AD develops as a result of diverse risk and protective factors. The most important risk factor for dementia is age. Approximately 3.0 % of women and 2.3 % of men aged 65 - 69, and 24.7 % and 17.4 %, respectively, aged 85 - 89 have dementia (Prince et al., 2013). The prevalence doubles with every five-year increment in age after 65 (World Health Organization, 2012). Other known risk factors include a family history of AD (Donix et al., 2012), and the apolipoprotein E ε4 allele (Farrer, 1997; Weiner et al., 2013). Disease-modifying factors may increase or decrease the risk of AD. Cardiac and cardiovascular disease risk factors such as high blood pressure, obesity (Kivipelto et al., 2005; Meng et al., 2014), diabetes (Meng et al., 2014), smoking (Rusanen et al., 2010; di Marco et al., 2014), high cholesterol (Solomon et al., 2009; Meng et al., 2014) at mid-life, and traumatic brain injury (Shively et al., 2012) have also been found to increase the risk of AD. Some studies have shown an association between a healthy diet and decreased risk of AD (Eskelinen et al., 2011). A recent review, however, reported conflicting results concerning the protective role of healthy dietary habits (di Marco et al., 2014). Social and cognitive activity has been found to protect against dementia (di Marco et al., 2014), and there have been promising results concerning the effects of physical exercise on cognitive functions in old age (Kirk-Sanchez & McGough, 2014).

The change in the age distribution of the population and the consequent increase of memory disorders pose a challenge to the society and its health-care system. In the United States, approximately 11 % of people who are 65 or older, and about one third of people aged 85 or older, have AD (Alzheimer's Association, 2014). Worldwide, 35.6 million people were estimated to have dementia in 2010, and there are 7.7 million new dementia cases each year (World Health Organization, 2012). In Finland, approximately 35 000 people have been estimated to have mild dementia and 85 000 people to have at least moderate dementia,

and approximately 13 000 people are found to contract a memory disorder every year (Memory disorders: Current Care Guidelines, 2010The numbers are expected to almost double every 20 years (Prince et al., 2013). However, some recent studies (Schrijvers et al., 2012) indicate that the incidence of dementia may be descending. Yet Solomon et al. (2014) point out that it is difficult to know whether the real incidence of dementia-related diseases has changed during the last few decades, for the diagnosing of memory diseases has been influenced by factors such as revised diagnostic criteria, increasing awareness, and several new drugs developed after the year 2000. The average life expectancy of people with AD is four to ten years after the diagnosis (Ganguli, 2005; Waring, 2005; Helzner, 2008; Xie, 2008; American Psychiatric Association, 2013), partly because persons with AD are at an advanced age. Some of them live even 20 years with the disease (American Psychiatric Association, 2013). AD affects not only the wellbeing of the persons with the disease (Karttunen et al., 2011) but the whole family and the family caregivers as well (World Health Organization, 2012; Välimäki et al., 2014). In Finland, the direct costs of AD therapy and care were estimated to be about one billion dollars in 2009, and the total costs of AD amounted to about 1.3 – 1.7 billion dollars when the costs of family caregiving were taken into account. The annual costs of care per each person with AD was approximately 17 000 – 25 000 dollars (Wimo et al., 2010).

2.2 THE CONTINUUM OF ALZHEIMER'S DISEASE

Cognitive functions include different skills, such as memory, language, psychomotor speed, visuospatial functions, and executive functions. These skills are needed in processing information and thus in everyday life. Memory can be divided into different components according to time (short-term and long-term memory) or content (Squire, 2004; Salmon & Bondi, 2009). Long-term memory can be divided into declarative and non-declarative, where the former includes conscious remembering and the latter, unconscious effects of previous experiences (e.g., skills and habituation). Declarative memory can be further divided into episodic memory (remembering events and experiences) and semantic memory (knowledge) (Squire, 2004). The most typical cognitive domains affected by normal aging are the learning phase and the recall phase of memory and the speed of performance, but no remarkable forgetting from long-term memory should normally happen (Salmon & Bondi, 2009).

2.2.1 Mild Cognitive Impairment (MCI), prodromal Alzheimer's disease, and dementia

AD pathology begins to develop in the brain many years before any symptoms arise. The continuum of AD proceeds from the pre-symptomatic phase to the phase where mild memory problems or problems in other cognitive domains are manifested, and finally to the phase where the symptoms interfere with the person's ability to work or to carry out daily activities or affect the person's social skills (Albert et al., 2011; Jack et al., 2011; Sperling et al., 2011; Seppälä et al., 2013).

There is a transitional phase between normal ageing and the phase where a disease that causes dementia can be diagnosed. The term mild cognitive impairment (MCI) has been used to describe this grey area between intact cognitive functioning and clinical dementia (Petersen, 2014). In MCI, at least one cognitive domain deteriorates more than would be expected for the person's age and educational background. Even so, persons with MCI carry out their daily tasks independently or with minimal assistance. Cognitive deficits may cause mild problems in complex tasks but do not result in any significant impairment of social or occupational functioning (Albert et al., 2011). This heterogeneous condition may be associated with various underlying etiologies (Dubois et al., 2010).

MCI constitutes a risk of AD and other dementias. Specific diagnostic criteria for MCI due to AD were proposed in 2011 (Albert et al.). Dubois et al. (2010) point out that

traditionally the term MCI has included persons who could be diagnosed to have symptomatic prodromal AD according to the new criteria. They suggest that MCI or amnestic MCI should be kept as a classification that includes individuals who do not meet these criteria. They propose the term prodromal AD or predementia stage of AD to be used to characterise the early symptomatic phase in which clinical symptoms, including episodic memory loss, are present but not sufficiently severe to affect the person's daily life and thus do not warrant a diagnosis of dementia and in which the biomarker evidence is supportive. In their Diagnostic and statistical manual of mental disoders, 5th edition (DSM-5) (2013), the American Psychiatric Association defined the concept of mild neurocognitive disorder due to AD, which is equivalent to the concept of MCI due to AD. However, not all individuals with MCI become demented. The term dementia is used to describe a condition where the deterioration of memory or another cognitive domain affects the person's ability to perform everyday activities and causes an increased need of assistance (Alzheimer Association, 2014; American Psychiatric Association, 1994; 2013).

2.2.2 Diagnostic criteria of Alzheimer's disease

The criteria that have been most commonly used for diagnosing AD include the DSM-IV (American Psychiatric Association, 1994) and the criteria of the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimers Disease and Related Disorders Association (NINCDS-ADRDA; McKhann et al., 1984). These criteria have been recently updated (DSM-5; American Psychiatric Association, 2013; McKhann et al, 2011).

Dubois et al. (2010) and Jack et al. (2011) have reviewed the history and development of the diagnostic criteria for AD. AD has been conceptualised as a clinico-pathological condition that requires a clinical phenotype typically centred on the presence of progressive dementia, which includes episodic memory impairment, deterioration of other cognitive domains, and specific neuropathological changes (Cummings et al 2007; Dubois et al. 2010; Jack et al., 2011). As neuropathological investigations cannot be performed on live patients, AD has been a predominantly clinical entity diagnosed as probable AD (McKhann 1984; Dubois et al., 2010). It has been assumed that in most cases the subjects who met the clinical criteria had AD pathology as the underlying etiology (Jack et al., 2011). A diagnosis can be made only at the dementia stage by excluding other possible causes (Dubois et al., 2010).

However, scientific knowledge about AD pathology has somewhat increased over the last few decades. Laboratory cerebrospinal fluid (CSF) and neuroimaging biomarkers correlate with the neuropathological lesions of AD (Dubois et al., 2010). In 2007, the International Work Group proposed a new diagnostic framework for research settings with the intention to move beyond the NINCS-ADRDA criteria, and this framework has been recently specified (Dubois et al., 2007; Dubois et al., 2010). The diagnosis should be made with both clinical and in-vivo biological evidence of AD pathology present (Dubois et al., 2010). In 2009 the National Institute of Aging (NIA) and the Alzheimer's Association's work group also started to revise the diagnostic criteria so as to incorporate the new scientific advances. They formulated new diagnostic criteria separately for the dementia phase, the symptomatic non-dementia phase (MCI due to AD), and the asymptomatic preclinical phase of AD (Jack et al., 2011). The main two differences from the NINCS-ARDRA criteria (1984) concern the incorporation of biomarkers of the underlying disease state and the formalisation of the different stages. However, as Jack et al. (2011) emphasise, a great deal of additional work is needed to validate the application of biomarkers for diagnostic purposes. For clinical practice, they recommend clinical criteria for diagnosing AD dementia and MCI due to AD, but preclinical criteria they recommend for research purposes only. The clinical phase of AD-related dementia can be considered to have been reached when there are cognitive symptoms severe enough to interfere with the person's social functioning and activities of daily life and there are changes in episodic memory and at least in one other cognitive domain. Typical AD is characterised by progressive

impairment of episodic memory, followed by other cognitive impairments and neuropsychiatric changes and supported by in-vivo biomarkers (Dubois et al., 2010). One can also distinguish atypical AD, which has a less common but well characterised clinical phenotype occurring with AD pathology (Dubois et al., 2010).

In the diagnosis of dementia due to Alzheimer's disease according to the DSM-IV (American Psychiatric Association, 1994), the person is presumed to have a progressive deficit in memory and at least in one other cognitive domain with a gradual onset that causes significant impairment in social or occupational functioning and cannot be accounted for by reference to other reasons. The revised diagnostic criteria presented in DSM-5 are still based on cognitive, functional, and clinical features of AD, and the significance of standardised neuropsychological testing is emphasised. In addition, it is suggested that diagnostic markers (Positron Emission Tomography, PET; Magnetic Resonance Imaging, MRI; Cerebrospinal fluid, CSF) may have diagnostic value. A major cognitive disorder is distinguished from a mild one on the basis of their effects on everyday activities, and physicians are required to specify whether the condition is due to AD or other conditions.

2.2.3 Cognition and the phases of dementia in relation to brain pathology

According to Braak's hypothesis, progressive neurofibrillary changes begin from the entorhinal cortex and the hippocampus-related medial temporal structures and subsequently spread to the neocortical association areas (Braak et al., 1991; Dubois et al., 2010). This pathway of regional neuropathology correlates with the typical pattern of cognitive changes in AD (Dubois et al., 2010). The clinical dementia rating reflects the gradual development of the clinical severity of the disease, corresponding to stage IV and higher in Braak's model (Jack et al., 2011). In regard to severity, the phases of AD have been divided into the mild, the moderate, and the severe one (Hughes et al., 1982; Morris et al., 1993).

Patophysiological biomarkers (SCF) correspond to some extent to the etiological degenerative processes that characterise AD pathology, the amyloidosis path to neuronal plaques, and the extent of the regional distribution of neurofibrillary tangles (the tauopathy path) mainly in early stages of the disease. Topographical biomarkers (MRI, PET scans) are used to assess the brain changes that typically correlate with the regional distribution of AD pathology, including medial temporal lobe atrophy (MRI) and reduced glucose metabolism in tempo-parietal regions (PET) (Dubois et al., 2010; Jack et al., 2011; Seppälä et al., 2013). The pathophysiological changes precede the topographical changes associated with neurodegeneration, starting during the long preclinical phase, whereas the development of neurofibrillary pathology accelerates slightly before the onset of the symptomatic phase of AD. The structural brain changes map onto the Braak stages of neurofibrillary tangle deposition, and neurodegeneration, particularly synapse loss, is most closely coupled with cognition (Dubois et al., 2010; Jack et al., 2009; 2011). The progression of clinical symptoms is a close parallel of the progressive worsening of neurodegenerative biomarkers (Jack et al., 2011). In the past decade, however, a better understanding of the distinctions and overlaps between non-AD and AD has been reached (Jack et al., 2011). There is also a clinical variant of AD that does not follow the typical AD phenotype (Dubois et al., 2010).

Table 1 presents typical cognitive symptoms of very mild, mild, moderate, and severe AD and their consequences for the person's everyday life. In the very mild phase there are notable problems with episodic memory and learning, mild problems in executive functions or other cognitive domains may show up, and the person has problems in complex everyday tasks, such as financial issues. Persons in the very mild phase typically ask the same questions over and over or recall events partially. The mild phase of the disease is characterised by moderate problems in memory and in time relationships. The person has difficulty in learning new things and forgets them quickly. Problems in

executive functions and language skills, e.g., naming, start to emerge. Perception deficits may also occur. These changes affect the person's instrumental activities of daily living (IADL), such as shopping, cooking, driving, or finding a route from one place to another. Apathy, depression, irritability, and paranoid beliefs are typical neuropsychiatric symptoms, and the person's awareness of his or her deficits may be lacking. In the moderate phase, the memory loss and the orientation problems are severe. The person forgets new things quickly and finds it difficult to recall even old things. There are also remarkable problems in other cognitive domains, such as speaking and understanding, the visuospatial domains, and attention. The person needs assistance in the basic activities of daily living, such as dressing and personal hygiene. In the severe phase of the disease, the person needs constant assistance (Hughes et al., 1982; Kuikka et al., 2002; Pirttilä et al., 2010). Although AD causes significant functional deficits, social cognition and procedural memory (e.g., dancing) may be preserved relatively well for extended periods (American Psychiatric Association, 2013).

Table 1. Symptoms of very mild, mild, moderate, and severe AD. Based on Hughes et al. (1982), Kuikka et al. (2002) and Pirttilä et al. (2006).

	Very mild AD		**Mild AD**		**Moderate AD**		**Severe AD**	
Cognitive domain	Typical symptoms	Impact on everyday life	Typical symptoms	Impact on everyday life	Typical symptoms	Impact on everyday life	Typical symptoms	Impact on everyday life
Memory	Problems in episodic memory and learning, forgetting, consistent slight forgetfulness	Partial recollection of recent events, asking the same questions again and again	Moderate, more wide memory loss	More marked forgetting of recent events, interference with everyday activities, forgetting meetings, difficulty in learning new methods, asking about the same things	Severe memory loss	Only thoroughly learned material retained, new material is forgotten rapidly, memory aids do not help	Severe memory loss	Only fragments remain
Orientation	Slight difficulty with time relationships		Moderate difficulty with time relationships	Moderate difficulty with time and place orientation, may have geographic disorientation, getting lost	Severe difficulty with time relationships	Usually disoriented to time, often to place	Severe difficulty with time and place orientation	Oriented only to person
Executive functions, problem solving, judgement	Executive functions may deteriorate, perseveration, problems in planning, slight impairment in problem-solving	Problems in complex tasks (e.g., financial)	Executive functions deteriorate, ability to concentrate declines, initiative and planning problems, moderate impairment in problem-solving	Problems in IADL (e.g., spending, shopping, cooking, driving); possibly problems in following conversation, isolation, social judgement often preserved	Clearly attenuated executive functions, severely impaired handling of problems	Decreased independent initiative, does not manage IADL, needs reminding about basic ADL (e.g., washing), social judgement often impaired, can be left alone only for short period	Unable to make judgements or solve problems, unable to concentrate	Needs assistance even in basic ADL

Table 1 to be continued

Table 1. (Continued) Symptoms of very mild, mild, moderate and severe AD. Based on Hughes et al. (1982), Kuikka et al. (2002) and Pirttilä et al. (2006).

	Very mild AD		**Mild AD**		**Moderate AD**		**Severe AD**	
Visuospatial and constructional skills	Normal or mild problems	No problems or mild ones	Normal or mild difficulty in visuospatial and constructional tasks	Getting lost in unfamiliar environments, may be losing things	Clear visuospatial problems, misperceptions may cause neuropsychiatric symptoms	Getting lost even in familiar environments, losing things, problems in dressing	Severe visuospatial problems	
Language	No problems or mild ones	Complex verbal ability may start to decline, may get word-finding problems	Word-finding difficulty, may find problems with complex sentences	Mild or moderate problems in naming, problems in following conversation	Problems in expressive language, word-finding difficulty, problems in understanding complex speech	Problems in everyday conversation	Major problems in expressive language and understanding speech	Little conversation
Typical somatic symptoms			Loss of weight		Loss of weight, apraxia, extrapyramidal symptoms	Problems in dressing, shaving, etc.	Severe apraxia, extrapyramidal symptoms, primitive reflex	Incontinence, instability in walking, solidity
Typical NPS	Apathy, irritability, depression, anxiety		Apathy, depression, irritability, paranoid beliefs	e.g., thinking that people are stealing from them, jealousy	Hallucinations, delusions, restlessness, sleep disturbances	e.g., wandering, wants to leave home, seeing unreal people, entanglement	Apathy, restlessness, sleep disturbances, aberrant motor behavior, agitation, anxiety	

IADL = Instrumental activities of daily living; ADL = Activities of daily living; NPS=Neuropsychiatric symptoms

2.2.4 Neuropsychiatric symptoms

Terms neuropsychiatric symptoms (NPS), non-cognitive symptoms, and behavioural and psychological symptoms have been used to describe a wide range of non-cognitive manifestations of AD. An international group of experts (The Neuropsychiatric Syndromes of AD Professional Interest Area (NPS-PIA) of the International Society to Advance Alzheimer's Research and Treatment (ISTAART)), have divided the NPS in AD into five syndromic areas: depression, apathy, sleep, agitation, and psychosis (Geda et al., 2013). Earlier, NPS were thought to emerge primarily in more severe stages of AD, but currently they are known to appear frequently in very early and even prodromal phases of the disease (Lyketsos et al., 2011; Dillon et al., 2013). From the perspective of the caregiver, friends, family, clinicians, and persons with AD, NPS are often the most difficult problems to deal with (Dillon et al., 2013; Kales et al., 2013), and they often get worse as AD progresses. The manifestation of NPS may fluctuate during the course of the disease (Dillon et al., 2013), but eventually they affect almost all patients with serious consequences (Geda et al., 2013) and commonly lead to early nursing home placement, hospitalisation, and caregiver stress (Kales et al., 2013).

Imaging has implicated some underlying neurobiological causes for the occurrence of NPS in AD, but the relationship between primary AD pathology and NPS remains to be elucidated (Geda et al., 2013). Dillon et al. (2013) sum up that NPS probably arise through interaction among psychological, social, and biological causes, including neurochemical, neuropathological, and genetic factors. Geda et al. (2013) have proposed four possible mechanisms for the relationship between AD and NPS. The etiological pathway model proposes that NPS reflect an underlying pathology, which is causally linked to the development of AD pathology. Another explanation proposes that there are shared risk or confounding factors that lead to both AD and NPS. Neuropsychiatric symptoms may also be a direct cause of AD. A person may have depression or anxiety, for example, as a psychological reaction to cognitive problems. Furthermore, AD may affect key brain areas underlying one's behaviour and emotions. The fourth mechanism proposed assumes that it is interaction between NPS and biological factors that leads to AD (Geda et al., 2013).

2.2.5 Clinical features of Alzheimer's disease

Knowledge about the natural course of the disease is needed for planning and evaluating suitable care and treatment and providing persons with AD and their families with information about the first years in the course of the disease. Table 2 summarises some relevant follow-up studies of AD conducted over the past ten years. Interpreting the results is rather challenging, however, because of variation in the use of terms and measures and differences in the populations studied and the follow-up periods employed. Generally, cognition and daily functioning deteriorated and NPS tended to increase during the follow-up period. Cognitive deterioration seemed to be slower during the mild phase of the disease (Feldman et al., 2005), and in some studies the rate of decline was non-linear (Bozoki et al., 2009; Vellas et al., 2012). Also, the rate of cognitive decline varied among individuals (Bozoki et al., 2009; Cotes et al., 2008; Gillette-Guyonnet et al., 2011), and some persons with AD were found to be stable even years after the onset of dementia (Cortes et al., 2008; Tschanz et al., 2011). Recently, it has been proposed that deterioration may occur at a slower rate than previously thought (Gillette-Guyonnet et al., 2011; Vellas et al., 2012); such observations may be due to improved diagnostic procedures and treatments.

Measures of daily functioning seem to be more sensitive than cognitive measures to discern changes in the characteristics of persons with AD. According to a French follow-up study (Cortes et al., 2005; Cortes et al., 2006; Cortes et al., 2008; Nourhashemi et al., 2008; Nourhashemi et al., 2009; Gillette-Guyonnet et al., 2011), activities of daily living deteriorated faster in the oldest age group (<85 years). Furthermore, ADL functions deteriorated more slowly in persons at the very mild phase of the disease (CDR=0.5) than

persons with more advanced dementia. No corresponding group differences were observed in regard to the rate of cognitive decline.

Apathy and depression are the most prevalent neuropsychiatric symptoms in AD (Serra et al., 2010; Karttunen et al., 2011; Dillon et al., 2013). Other common symptoms include psychotic symptoms (hallucinations, delusions, paranoia), agitation and irritability (Dillon et al., 2013). In particular, apathy (Dillon et al., 2013), delusions and irritability (Serra et al., 2010) increase with the progression of the illness. Features typical for AD also include euphoria, sleep and appetite disturbances, and motor restlessness (Cummings et al., 2007; Dillon et al., 2013). Most studies indicate that neuropsychiatric symptoms (NPS) and cognition are not substantially related (Dillon et al., 2013) but are rather individual manifestations of AD; however, opposite results have also been reported (Serra et al., 2010).

Table 2. Progression of Alzheimer's disease: follow-up reports.

	Follow-up time, population	**Measurements used**	**Annual changes**	**Main findings**
Cortes et al. 2005 Cortes et al. 2006 Cortes et al. 2008 Nourhashemi et al. 2008 Nourhashemi et al. 2009 Gillette-Guyonnet et al. 2011 **REAL.FR Study**	1 – 4 years n = 233 – 686 very mild, mild and moderate AD at baseline More than 85 % AD medicated	MMSE, Adas-Cog, NPI, ADL (Katz index)	MMSE: -2.4 CDR-sb: +4.17 / 2 years Adas-Cog: +4.5 Annual incidence of incapacities for ADL 52.5 % Annual incidence of worsening in NPI 51.1 % Annual rate of mortality 7.4 % Annual rate of institutionalisation 13.4 % 10.8 % evolved twice as rapidly as the whole cohort on MMSE (first two years) 23.3 % stable (first two years)	No group differences: family history / no family history (2 years) ADL declined faster in the oldest old group (<85), not in MMSE CDR 0.5 / CDR 1 or more at baseline: CDR 0.5 group younger, shorter duration of symptoms, rate of cognitive decline was similar, decline of ADL was more significant in CDR 1 group
Feldman et al. 2005	1 year placebo data pooled from two trials mild to moderate AD	Adas-Cog, DAD (ADL)	Adas-Cog: +5.6 DAD: -12.4	Greater decline in moderate patients (MMSE<18) MMSE 16 a key point in which most instrumental ADL were lost and major losses of basic IADL began to occur over the next year Caregivers spent more time assisting with ADL at the end of the one year follow-up
Lam et al. 2006	mean follow-up time 22.5 months 104 late-onset AD at psychogeriatric clinics	CDR, NPI, List learning, Verbal fluency	Mean NPI at baseline 16.3 13 % had no NPS at baseline	Three NPS classes at baseline: low (44 %), affective (32%), psychosis (24 %) Association between cognition and NPS was not significant

Table 2 to be continued

Table 2. (Continued) Progression of Alzheimer's disease: follow-up reports.

	Follow-up time, population	**Measurements used**	**Annual changes**	**Main findings**
Scarmeas et al. 2006	Mean follow-up time 5.6 years 312 AD	Standardised composite score from 12 tests GEE models	Cognition: 9 % of a standard deviation	Rates of decline before and after AD onset were similar Association between higher education and faster cognitive decline
Agüera-Ortiz et al. 2009	1 year 857 moderate to severe AD	MMSE, CDR-sb, CGIC, Zarit burden, BDS	MMSE: -0.90 CDR-sb: +0.28	Significant progressive functional and cognitive impairment was found Patients' behaviour and caregiver burden improved slightly
Coin et al. 2009	1 year 53 probable AD	MMSE		AD patients treated with ACHEI at the moment of diagnosis showed improvement in MMSE after six months and maintained it after 1 year. Subjects beginning ACHEI at the six-month visit showed worsened MMSE even after six months.
Serra et al. 2010	1 year 54 AD	MBD, Adas-Cog, NPI-10		baseline: depression, apathy, and anxiety were the most frequent and severe NPS Delusions and irritability increased significantly during the follow-up Significant correlations between cognition and NPS at baseline and the progression rate of these symptoms
Tschanz et al. 2011 **Cache County Study**	Mean follow-up time 3.8 years 328 possible/probable AD	MMSE, CDR-sb, NPI	MMSE: -1.53 CDR-sb: +1.44 NPI: +2.55	Among surviving participants, 30-58% progressed less than one point per year on these measures even 5-7 years after dementia onset MMSE, CDR-sb, and MMSE changes correlated
Handels et al. 2013 **Kungsholmen project**	Up to 6 years 323 AD	MMSE, ADL (Katz Index)	MMSE: -1.8 / year MMSE: -1.2 / 6 months after diagnosis	The decline of physical functioning was associated with age, education, and cognition, not with gender 49 % died within 6 years after diagnosis

Table 2 to be continued

Table 2. (Continued) Progression of Alzheimer's disease: follow-up reports.

	Follow-up time, population	**Measurements used**	**Annual changes**	**Main findings**
Vellas et al. 2012 **European ICTUS Study**	2 years 1306 AD from 11 countries All ACHEI treated	MMSE, Adas-Cog, NPI, ADL, IADL, Zarit burden	MMSE: -1.5 / first year MMSE: -2.5 / second year	Cognition declined non-linearly Progression of NPI was linear No regional differences (MMSE, NPI) Functional decline more rapid in Southern Europe Progression of burden most rapid in Northern Europe Incidence of hospitalisation lowest in the South Cognition and functional decline was slower than in former cohorts

The PubMed database was searched with the keywords Alzheimer disease, cognition, progression and follow-up, and only articles from the previous ten years were included. Of the 598 hits, 121 were more carefully evaluated on the basis of the headings. Articles focusing on MCI, other dementia types, genes, lumbar puncture, brain scans, or methodology were excluded, and so were the ones that had a study population <40, were not written in English, had insufficient information available, or had not applied a follow-up period of at least one year. In addition, 31 articles were excluded because they dealt with prediction, intervention, or institutionalisation. Finally, 15 articles were included that focused on cognitive performance of persons with Alzheimer's disease and had applied a follow-up period of at least one year.

NPS = Neuropsychiatric symptoms; ADL=Activities of daily living; IADL=Instrumental activities of daily living; MMSE=Mini-Mental State Examination; CDR(-sb)=Clinical Dementia Rating (Sum of boxes); NP(-10)=Neuropsychiatric Inventory (10-item version); Adas-Cog=Alzheimer's Disease Assessment Scale – Cognitive subscale; DAD=Disability Assessment for Dementia; MDB=Mental Deterioration Battery; CGIC=Clinical Global Impression of Change

2.2.6 Predicting the progression of symptoms in Alzheimer's disease

Many studies have have sought to find out how the personal characteristics and the cognitive profile of the person with AD at the time of the diagnosis could be used to predict the course of the disease. This information would be helpful for planning the treatment, the care, and the follow-up needed. Traditionally, a rapid cognitive decline is often defined in terms of a reduction in the score of the Mini-Mental State Examination (MMSE, Folstein et al., 1975) (Marra et al., 2000; Atchison et al., 2004; Buccione et al., 2007; Musicco et al., 2009, 2010; Palmer et al., 2011; Sona et al., 2013). But this method has also been criticised for being insensitive to the progression of AD (Atchinson et al., 2004; Clark et al., 1999), and its limitations, e.g., with aphasia patients, have been acknowledged (Schmidt et al., 2011). Table 3 presents studies in which a rapid progression of AD symptoms was predicted with baseline assessments.

Neuropsychological tests have been used to predict the progression of AD-related symptoms. However, many of the studies were conducted in the 1990s, and the variability in their use of measures complicates their interpretation. Previous studies have found the predictors of rapid symptom progression to include impairment in executive function and attention (Musicco et al., 2010; Marra et al., 2000), in verbal memory and language skills (Marra et al., 2000; Cosentino et al., 2006), in visuospatial and visuoconstructional skills (Sarazin et al., 2005; Atchinson et al., 2007), in the processing speed (Atchinson et al., 2007), and in short-term memory (Sarazin et al., 2005). Accordingly, other cognitive skills than performance in delayed-memory tasks may be better predictors of the progression of AD-related symptoms. The global severity of cognitive impairment at the time of the diagnosis (Atchinson et al., 2004; Sarazin et al., 2005; Buccione et al., 2007; Ousset et al., 2008; Lopez et al., 2010) has also been found to predict a rapid progression of AD-related symptoms.

Of other AD-related and demographic characteristics, younger age (van der Vlies et al., 2009; Lopez et al., 2010; Musicco et al., 2010; Sakurai et al., 2011; Ito et al., 2011; Sona et al., 2013), higher education (Musicco et al., 2010; Sakurai et al., 2011), and more severe dementia at baseline (Lopez et al. 2010; Zhou et al., 2010; Sona et al., 2013) have been associated with a rapid cognitive decline. As indicated in the review of Sona et al., 2013, these characteristics were consistently associated with a rapid progression of the disease, even though opposite results have been obtained as well (Rabins et al., 2013; Grønning et al., 2012; Cosentino et al., 2006; Rountree et al., 2012). Accordingly, younger and highly educated persons with more severe AD at baseline seem to have a worse prognosis. The impact of education on the progression rate of the symptoms may be different before and after a certain phase. According to Hall et al. (2007), formal education delayed the time when the memory decline accelerated, but after the acceleration had started, the rate of decline increased with additional years of education. The findings concerning the impact of gender on rapid symptom progression have been contradictory; both male (Zhou et al. 2010; Ito et al., 2011; Rountree et al., 2012; Sona et al., 2013) and female gender (Rabins et al., 2013) have been found to predict a rapid symptom progression. Furthermore, the number or severity of neuropsychiatric symptoms at baseline (Wilson et al., 2006; Buccione et al., 2007; Lopez et al., 2010; Palmer et al., 2011; Rabins et al., 2013), especially psychotic ones (Buccione et al., 2007; Wilkosz et al., 2010) has been associated with a rapid symptom progression.

On the basis of their consensus papers and reviews, Soto et al. (2008) and Schmidt et al. (2011) argue that there is a need to define rapid decliners more clearly. Though they acknowledge the limitations of the MMSE, they both suggest that the loss of three or more points in the MMSE within six months or six points within a year should be used in clinical practice as an indicator of a rapid decline.

Table 3. Published reports: prediction of the progression of Alzheimer's disease.

	Follow-up time, Population	**Measure of rapid cognitive decline or other endpoint, statistical methods**	**Predictive factors of rapid decline**
Atchison et al. 2004	1 year 211 AD	MMSE	A single factor from cognitive tests
Sarazin et al. 2005	mean follow-up time 4.5 years 252 AD	Dependency scale Equivalent institutional care rating Cox proportional hazard models	Global cognition (mMMSE) Temporospatial orientation Short-term memory Visuoconstructive score Long-term memory and language were not predictive
Cosentino et al. 2006	15 years 161 AD	Mortality Cox proportional hazard models	52 % reached the mortality end point with a median survival time of 5.5 years Older age Lower verbal fluency
Pavlik et al. 2006	mean follow-up time 3.2 years 478 AD	MMSE, Adas-Cog, CDR-sb Random-effects linear regression analysis Cox proportional hazard	Lower intelligence quotient No association with survival

Table 3 to be continued

Table 3. (Continued) Published reports: prediction of the progression of Alzheimer's disease.

	Follow-up time, Population	**Measure of rapid cognitive decline or other endpoint, statistical methods**	**Predictive factors of rapid decline**
Wilson et al. 2006	mean follow-up time 2.2 years 478 AD	MMSE, other neuropsychological tests Mortality Linear mixed-effects models	Hallucinations Delusions and misperceptions had no association
Atchison et al. 2007	150 AD	Lawton physical self-maintenance (PSM)	Neuropsychological measures (visual spatial skills, processing speed, concept formation) at the time of diagnosis
Buccione et al. 2007	2 years 58 AD	decline based on sample median in MMSE Neuropsychological battery CDR	Cognitive decline was predicted by diffuse cognitive impairment Functional progression was predicted by visuospatial deficits Psychotic symptoms (NPI) predicted faster progression in both cognitive and functional dimensions
Hall et al. 2007	117 dementia	Buschke memory test	Formal education delayed the time of accelerated decline; post-acceleration, the rate of memory decline increased with additional years of education
Helzner et al. 2007	283 AD		Greater participation in pre-leisure activities
Ousset et al. 2008	1 year 160 very mild AD	CDR change	Baseline lower nutrition status Baseline lower cognition (Adas-Cog)

Table 3 to be continued

Table 3. (Continued) Published reports: prediction of the progression of Alzheimer's disease.

	Follow-up time, Population	**Measure of rapid cognitive decline or other endpoint, statistical methods**	**Predictive factors of rapid decline**
Soto et al. 2008 REAL.FR	2 years 565 AD	Mortality Institutionalisation	Moderate disease Rapid cognitive decline
Fong et al. 2009	408 AD	Subtest from Blessed Dementia Rating Scale Linear mixed-regression models	Delirium
Musicco et al. 2009	Mean follow-up time 26 months 154 mild to moderate AD	5-point decrease in MMSE within two years Survival analysis	Younger age More education Vascular factors no association Diabetes reduced the risk
Norton et al. 2009	mean follow-up time 20 months 167 AD	MMSE Linear mixed models	Dyads with higher levels of closeness and with spouse caregivers had a slower decline
van der Vlies et al. 2009	291 AD	MMSE	Early onset (<65 years) ApoE ε4 non-carriers with early onset showed faster decline than old non-carriers

Table 3 to be continued

Table 3. (Continued) Published reports: prediction of the progression of Alzheimer's disease.

	Follow-up time, Population	**Measure of rapid cognitive decline or other endpoint, statistical methods**	**Predictive factors of rapid decline**
Lopez et al. 2010	2 years 3748 AD Pooled data from 14 trials (placebo groups)	Change in MMSE Change in Adas-Cog Multivariate logistic regression	Younger age, more severe baseline cognitive, global (CDR) and behavioural (NPI) status Donepezil treatment reduced the risk
Musicco et al. 2010	154 AD	5-point decrease in MMSE within 2 years	More educated More severe deterioration in executive functions
Zhou et al. 2010	5 years 467 AD	Mortality Survival analysis (proportional hazard model)	Male gender Disease severity at baseline Higher cognitive total score, verbal fluency and executive function test (Stroop) predicted longer survival
Wilkosz et al. 2010	up to 13.5 years 210 AD	MMSE Mixture models of quadratic trajectories	Psychotic symptoms

Table 3 to be continued

Table 3. (Continued) Published reports: prediction of the progression of Alzheimer's disease.

	Follow-up time, Population	**Measure of rapid cognitive decline or other endpoint, statistical methods**	**Predictive factors of rapid decline**
Ito et al. 2011 ADNI	5 years 817; control, MCI and mild to moderate AD	Adas-Cog a mathematical model	Baseline Adas-Cog Younger age ApoE ε4 Male gender
Palmer et al. 2011	177 AD	a loss of >=1 points in ADL (Katz's Index) or >= MMSE Hazard ratios	Affective syndrome had an increased risk of functional decline Manic syndrome and euphoria were associated with cognitive decline
Sakurai et al. 2011	24-60 months 150 AD	MMSE	Younger age More education Hypertension Other vascular factors, gender, initial MMSE, and diabetes had no association
Scarmeas et al. 2011	357 AD	Mortality Cox proportional hazard models	Lower physical activity

Table 3 to be continued

Table 3. (Continued) Published reports: prediction of the progression of Alzheimer's disease.

	Follow-up time, Population	**Measure of rapid cognitive decline or other endpoint, statistical methods**	**Predictive factors of rapid decline**
Grønning et al. 2012	42 AD	MMSE, Addenbrooke's cognitive examination	No difference between early- and late-onset AD
Rountree et al. 2012	641 AD	Mortality Cox proportional hazard models	Older age Male gender Functional ability worsening Antidementia drugs do not prolong survival
Rabins et al. 2013 Cache County	335 AD	Severe dementia, defined as MMSE <10 or CDR=3	Median survival time till severe AD was 8.4 years Female gender Less than high school education At least one clinically significant NPS (NPI) at baseline Youngest, oldest Worse health
Sona et al. 2013	82 papers	Review	Younger age More education More impaired at baseline ApoE ε4 no or small effect

Table 3 to be continued

Table 3. (Continued) Published reports: prediction of the progression of Alzheimer's disease.

The PubMed database was searched with the keywords Alzheimer disease and rapid progression or Alzheimer disease and predict progression, and only articles from the previous ten years were included. Of the 437 hits, 82 were more carefully evaluated on the basis of the headings. Articles focusing on MCI, other dementia types, genetic factors, or physical conditions were excluded, and so were the ones that had a study population of <40, were not written in English, had insufficient information available, or had not applied a follow-up period of at least one year. In addition, 7 articles were excluded because they dealt with progression, intervention, or institutionalisation. Some previously found papers were included. Finally, 28 articles were included that focused on the prediction of the decline rate of persons with Alzheimer's disease.

AChEI=Acetylcholinesterase inhibitors; NPS = Neuropsychiatric symptoms; ADL=Activities of daily living; MMSE=Mini-Mental State Examination; CDR(-sb)=Clinical Dementia Rating (Sum of boxes); NPI=Neuropsychiatric Inventory; Adas-Cog=Alzheimer's Disease Assessment Scale – Cognitive subscale

2.3 MEASURING THE PROGRESSION OF SYMPTOMS IN ALZHEIMER'S DISEASE

2.3.1 Progression of cognitive decline, measured with the CERAD Neuropsychological Battery and the Mini-Mental State Examination

The Consortium to Establish a Registry for Alzheimer's Disease (CERAD) was founded in the 1980s to develop standardised measures for the assessment of AD. The CERAD Neuropsychological Battery (CERAD-NB) was developed to measure early cognitive impairment in AD (Welsh et al., 1994), and later studies have supported the use of the CERAD-NB as a reliable measure for screening AD-related cognitive deficits (Fillenbaum et al., 2008; Sotaniemi et al., 2012; Wolfsgruber et al., 2013). In Finland, the CERAD-NB was introduced in 1999, and as in some other countries, it has been established as a screening tool for memory disorders in primary health care for persons of 55 and older (Hänninen et al., 1999; Sotaniemi et al., 2012).

The CERAD-NB has been compiled from previously published tests measuring cognitive domains known to become impaired in the course of AD. The original test battery includes subtests that measure naming skills, verbal fluency, verbal learning, delayed recall, delayed recognition, and visuospatial skills (constructional praxis) (Welsh et al., 1994). As additions to the Finnish version (Hänninen et al., 1999), there is a test of delayed recall of visual items (constructional praxis delayed recall) and a clock-drawing test (Freedman et al., 1994). The measures of episodic memory in particular have been efficient in distinguishing normal aging from early AD (Welsh et al., 1991, 1992; Sotaniemi et al., 2012). Individual CERAD-NB subtests have also been used to distinguish the stages of AD dementia in cross-sectional studies, but there is a lack of follow-up data on the CERAD-NB subtests for persons with AD. While memory tasks have not been found effective (Welsh et al., 1991; Barth, et al. 2005) in distinguishing the stages of dementia, the best individual subtests have been verbal fluency (Welsh et al., 1992; Bertolucci et al., 2001; Barth et al., 2005) and praxis (Welsh et al., 1992; Barth et al., 2005). Recognition memory (Welsh et al., 1992) and the Boston naming test (Bertolucci et al., 2001) have also effectively classified the severity of dementia in cross-sectional studies.

Recent studies have also shown that the CERAD-NB total score, which was developed later (Chandler et al., 2005), is a valid and useful tool both for screening (Paajanen et al., 2013) and for monitoring the progression of symptoms in AD-related dementia (Rossetti et al., 2010). Significant differences have been observed in the CERAD-NB total scores across different stages of dementia (Seo et al., 2010), and also significantly greater annual changes in the CERAD-NB total scores for AD patients than for the controls (Rossetti et al., 2010). Annual changes in the CERAD-NB total score correlate significantly with the severity of dementia and the person's functional ability (Rossetti et al., 2010).

The whole CERAD-NB is often too time-consuming to be used in clinical settings as a follow-up tool for the progression of AD. On the other hand, the commonly used MMSE (Folstein et al., 1975) has been claimed to be of limited value as an instrument for screening (Mitchell, 2009) and measuring the progression of AD-related symptoms (Atchinson et al., 2004; Clark et al., 1999). In a meta-analysis Mitchell et al. (2009) noted that the MMSE had restricted value for diagnosing MCI against healthy controls and a limited capability of helping to identify cases of Alzheimer's disease against MCI. They suggest that the MMSE offers modest accuracy for ruling out a diagnosis of dementia in primary care but that for all other purposes it should be combined or replaced with other methods. The MMSE has been claimed to have a large measurement error and substantial variation in the annual scores measuring the progression of AD symptoms (Clark et al., 1999). As the early detection of AD has been the main focus of research, more information and more reliable measures for assessing cognitive deficits during the course of AD are needed.

2.3.2 Clinical rating of dementia, activities of daily living, and the Neuropsychiatric Inventory

Staging the severity of AD with global measures is a common and useful practice in both clinical and research settings for many reasons (O'Bryant et al., 2008). The Clinical Dementia Rating Scale (CDR), a scale based on a semi-structured interview, was developed for this purpose in the 1980s (Hughes, 1982; Morris et al., 1993). It is a commonly used instrument that provides a global score (questionable, mild, moderate, or severe dementia) and a more detailed quantitative index, the CDR sum of boxes score (CDR-sb). It combines information obtained from the caregiver or other informant with that obtained from the person with AD, and the scale tracks the change from the person's previous level as a cause of cognitive problems.

Alzheimer Disease Cooperative Study Activities of Daily Living (ADCS-ADL) (Galasko et al., 1997) is a commonly used measure of daily functions in clinical trials (Ard et al., 2013), but functional ability has also been assessed with a variety of other measures in AD studies (Table 2). In Finland, the ADCS-ADL measure is commonly a part of the diagnostic procedures (Memory disorders: Current Care Guidelines, 2014). It includes questions about the basic and instrumental activities of daily living, and the real functioning of the person with AD in different tasks of everyday life is rated by a caregiver or other informant.

The neuropsyciatric inventory (NPI) (Cummings et al., 1994) is the most widely used scale for assessing behavioural and psychological problems (neuropsychiatric symptoms, NPS) in cognitive disorders, allowing the assessment of a broad spectrum of neuropsychiatric symptoms (Dillon et al., 2013). It is a structured interview designed to obtain data from the caregiver or other informant. The NPI includes twelve behavioural and psychological domains that are typically related to AD: delusions, hallucinations, agitation, anxiety, depression, apathy, irritability, euphoria, motor behavior, sleep disturbances, and appetite disturbances.

2.4 INTERVENTIONS FOR DELAYING NURSING-HOME PLACEMENT

Due to increasing costs of dementia care and treatment and a lack of disease-modifying medication for AD, different kinds of interventions have been developed to delay nursing-home placement or affect the wellbeing of persons with AD and their caregivers (Table 4). The results of these studies, however, have been contradictory. Meta-analyses and reviews of various interventions and several outcome measures suggest that specific interventions work on specific targets and that only multicomponent interventions have succeeded in delaying institutionalisation. Studies on multicomponent interventions are limited in number, but they have been analysed in several meta-analyses (Pinquart & Sörensen, 2006; Olarazan et al., 2010; and de Vugt & Verhey, 2013).

2.4.1 Multicomponent interventions to delay nursing-home placement

In the review by Olazaran et al. (2010), different kinds of non-pharmacological interventions were evaluated. By pooling three high-quality randomised and controlled trials (Lawton et al., 1989; Mittelmann et al., 1993, and Belle et al., 2006) that had tested multicomponent interventions for the caregivers, the reviewers showed that by means of such interventions a delay had been attained in the institutionalisation of persons with mild to moderate AD. The essential components of these interventions were individual assessment, information, counselling, and support. Also, the role of skill training, respite services, support groups, and continuous availability of a therapist was emphasised. Similarly, the review by Pinqart & Sörensen (2006) also evaluated a range of interventions targeted to caregivers of persons with AD or dementia in general. A delaying effect on institutionalisation emerged only for the structured multicomponent interventions, but the long-term effects were impossible to assess. The multicomponent interventions combined different forms of intense intervention such as education, support, and respite. Pinqart &

Sörensen (2006) remark that the reasons why other interventions lacked effect may have been that some interventions prepared the caregivers for institutionalisation, that the dosage of many interventions may have been too low, and that even the best interventions have only a limited effect on some stressors, such as the progression of AD.

The review by van Mierlo et al. (2010) indicated that personal characteristics such as the type and severity of dementia, gender, and the presence of behavioural or mental health problems were connected with intervention outcomes. Of caregiver characteristics, being female and a spouse was associated with a longer delay in institutionalisation (Pinquart & Sörensen, 2006). Four of the studies examined showed delayed nursing-home placement of persons with mild to moderate AD or other dementia (van Mierlo et al., 2010); these studies were partly the same as cited above: a training programme for dementia caregivers (Brodaty et al., 1997), individual and family counselling (Mittelman et al., 1996), meeting-centre support programme (Dröes et al., 2004), and reality orientation therapy (Metitieri et al., 2001). In the studies reported by Dröes et al. (2004) and Metitieri et al. (2001), however, the samples were small and not randomised.

2.4.2 Interventions focused on specific targets

In a review focusing on cognitive reframing for family carers (Vernooij-Dassen et al., 2011) no effects were found on institutionalisation or caregiver-related measures, even if the intervention seemed to reduce the subjective stress of the caregiver. This is in line with the results of Pinqart & Sörensen (2006). The authors conclude that cognitive reframing may be an effective component of individualised multicomponent interventions (Vernooij-Dassen et al., 2011). Caregiver interventions also showed positive immediate effects of small-to-medium sizes on factors such as dementia caregivers' burden, depression, and ability/knowledge, and the results were considered to have practical significance, too (Pinquart & Sörensen, 2006). The long-term effects could not be evaluated, however, and many intervention effects were specific to particular outcomes.

Occupational interventions have been found to delay functional disability (McLaren et al., 2013), and some results encourage the use of cognitive stimulation for general cognitive enhancement (Spector et al., 2012). Interventions for behavioural symptoms have also yielded promising results (Spira & Edelstein, 2006).

2.4.3 Recent intervention studies with no positive effects found

Although some multicomponent interventions have been reported to delay institutionalisation, recent studies by Brodaty et al. (2009) and Phung et al. (2013) found no long-term effects of psychosocial intervention on nursing-home placement or on other outcome measures. In the study by Brodaty et al. (2009), caregivers in the treatment group received individual and family counselling sessions. Ad hoc counselling by telephone was available on demand for up to two years. The authors point out that there were several important differences between this study (Brodaty et al., 2009) and the previous one, in which they found positive intervention effects (Mittelman et al., 1999). The participants in the later study were less impaired, ad hoc counselling was available for a shorter period, the participants were treated with AD-targeted medication (donepezil), and general awareness, expectations, and mainstream treatments were somewhat different in the later decade. The authors suggest that for better outcomes, the interventions should meet the needs of the participants better. They also remark that issues of the availability and affordability of community care may keep patients at home a longer time and that differences in community care between countries may cause differences in intervention results. In the study by Phung et al. (2013), a multifaceted semi-tailored psychosocial intervention programme targeted to persons with recently diagnosed mild AD or Lewy Body dementia had no long-term effects (in a three-year follow-up) on any patient-related or caregiver-related outcome measure or on institutionalisation. The intervention included counselling, information, and support for persons with dementia and their caregivers.

Individual counselling sessions, group courses, and telephone contacts were arranged for 8-12 months. Even though there were no quantitative results, almost all persons with AD and their caregivers in the intervention group found the programme beneficial. The authors remark that in planning the support, the needs of persons with AD and their caregivers should be assessed and that regular follow-up is important for identifying the emerging needs that require intervention. The type, dosage, intensity, and duration of early intervention should probably be better tailored to match the needs of the persons with AD and their caregivers. Contradictory results in different studies may be caused by differences in population selection or in intervention procedures. Furthermore, the time the study was carried out is probably significant, for diagnostic procedures, treatment and care, knowledge, and attitudes change.

Table 4. Intervention studies for persons with Alzheimer's disease.

	Intervention procedure	**Main results**
Pinquart & Sörensen, 2006	Meta-analysis 127 intervention studies	Only multicomponent interventions reduced the risk for institutionalization
Spira & Edelstein, 2006	Evaluative review 23 articles	Interventions for behavioural symptoms had considerable promise, although there were some methodological issues
Brodaty et al., 2009	Psychosocial intervention for caregivers	Over a mean of 5.4 years, there were no differences in nursing-home placement or mortality between the intervention and the control group. There were differences by country: Australians were institutionalised earlier than patients in the US or the UK.
van Mierlo et al., 2010	Review	Type and severity of dementia, gender, and the presence of NPS are related to intervention outcomes Four studies were found to delay institutionalisation
Olazaran et al., 2010	Review	Grade A recommendation was achieved for institutionalisation: multicomponent interventions for caregiver Grade B for persons with dementia For improvement in cognition: cognitive training or simulation or multicomponent intervention For improvement in ADL: ADL training, multicomponent intervention For behaviour: cognitive simulation, behavioural interventions, professional cognitive training, multicomponent interventions
Vernooij-Dassen et al., 2011	Systematic review Cognitive reframing interventions for family carers	Good results on some caregiver-related measures No effects on institutionalisation

Table 4 to be continued

Table 4. (Continued) Intervention studies for persons with Alzheimer's disease.

	Intervention procedure	**Main results**
Spector et al., 2012	Review Cognition-based psychological interventions	For cognitive stimulation, there was good evidence for general cognitive enhancement For cognitive training, it was not possible to conclude which, if any, domains are most amenable to change
McLaren et al., 2013	Systematic review 18 trials: occupational therapy, exercise, or multifaceted interventions	Non-pharmacological interventions can delay progression of functional disability
Phung et al., 2013 Daisy	Psychosocial intervention for three years	Did not show any positive long-term effects
de Vugt & Verhey, 2013	Review	The most promising caregiver interventions focus on mild to moderate stages and combine multiple elements
Dröes et al., 2014	Meeting-centre Support Program	Delayed nursing-home placement in comparison with regular daycare

The PubMed database was searched with the keywords Alzheimer, institutionalization and intervention or Alzheimer, psychosocial intervention, and cognitive, and only articles from the previous ten years were included. Of the 78 hits, 41 were more carefully evaluated on the basis of the headings. Only those studies were included that had patient-related outcomes. Articles focusing on MCI or drug treatment were excluded. Finally, 13 studies were included.

3 Aims of the Study

This doctoral dissertation aimed at assessing the clinical features of persons with very mild or mild AD in a three-year follow-up started after diagnosis and at evaluating the suitability of the Consortium to Registry for Alzheimer's Disease Neuropsychological Test battery (CERAD-NB) (Welsh et al., 1994; Hänninen et al., 1999) for use in measuring the progression of cognitive deterioration in AD. More specifically, the aims of the studies forming the basis of this dissertation were as follows:

1. To find out whether global cognitive performance assessed with the CERAD-NB total score is associated with the severity of dementia, activities of daily living, and neuropsychiatric symptoms in persons very mild or mild AD. (Study I)

2. To examine the changes in cognition, activities of daily living, neuropsychiatric symptoms, and the severity of AD over a three-year follow-up of persons with very mild or mild AD at baseline. An additional aim was to examine whether the CERAD-NB total score is a suitable instrument for monitoring cognition in following up persons with very mild and mild AD. (Study II)

3. To find out which CERAD-NB subtests and which combination of subtests are the best indicators of changes in the severity of AD during the three-year follow-up. A further aim was to investigate the possibility of predicting the progression of AD symptoms by means of baseline demographic and CERAD-NB subtest information. (Study III)

4. To examine the efficacy of an extended psychosocial intervention programme administered to persons with very mild or mild AD and their family caregivers during the first two years after diagnosis. (Study IV)

4 Subjects and Methods

4.1 STUDY DESIGN

All the four studies were part of the ALSOVA Project, which was a prospective, randomised and controlled follow-up study of persons with AD and their caregivers. The main aim of ALSOVA was to evaluate the effectiveness of early psychosocial intervention on the institutionalisation of persons very with mild or mild AD at baseline, the progression of AD in normal care, the wellbeing of the caregivers, and the impact of AD care on health economics. A total of 241 volunteering patient-caregiver dyads from three municipalities in Finland were recruited after they had received an AD diagnosis in 2002-2006, and the dyads were monitored annually for up to five years. Due to issues in the availability of the data and the drop-out rates, the present studies are based on three-year follow-up data.

The first annual study visit was arranged soon after the AD diagnosis (five months later on average). The caregiver was interviewed by a study nurse and the person with AD was evaluated and interviewed by a psychologist. The extended data collected included age, gender, education, physical health, medication, household composition, living arrangements, wellbeing, caregiver burden, and the utilisation of society resources (for details, see Välimäki, 2012). The dates of institutionalisation and death were verified from the medical records, also for those participants who dropped out during the three-year follow-up period.

The subjects were randomised into a psychosocial intervention group and a control group (1:2) at the time of the baseline visit (for Study IV). The lots were drawn by a study nurse who otherwise took no part in the study. The psychosocial intervention, totalling 16 days, was carried out at the Brain Research and Rehabilitation Center Neuron during the first two years after the diagnosis (Appendix, Study IV, Figure 1). It included programmes for both the persons with AD and their caregivers. They had opportunities to discuss their life situation. To provide them with information about AD and the social services available, lectures were given by neurologists and a social worker. Group discussions were organised for the persons with AD and their caregivers separately. The domain of stress reduction was addressed by means of a variety of creative activities. During the intervention, both the persons with AD and their caregivers were encouraged to engage in physical exercise. The final meeting included a social activity, which was intended to encourage the persons with AD and their caregivers to engage in social activities such as concerts. The patient-caregiver dyads remained the same for the two-year intervention period. The goal was to support networking among them. Altogether, 11 course groups were arranged. A maximum of 10 families were invited to each course. The control group was followed up annually in a way similar to that for the intervention group except that it did not receive the psychosocial intervention.

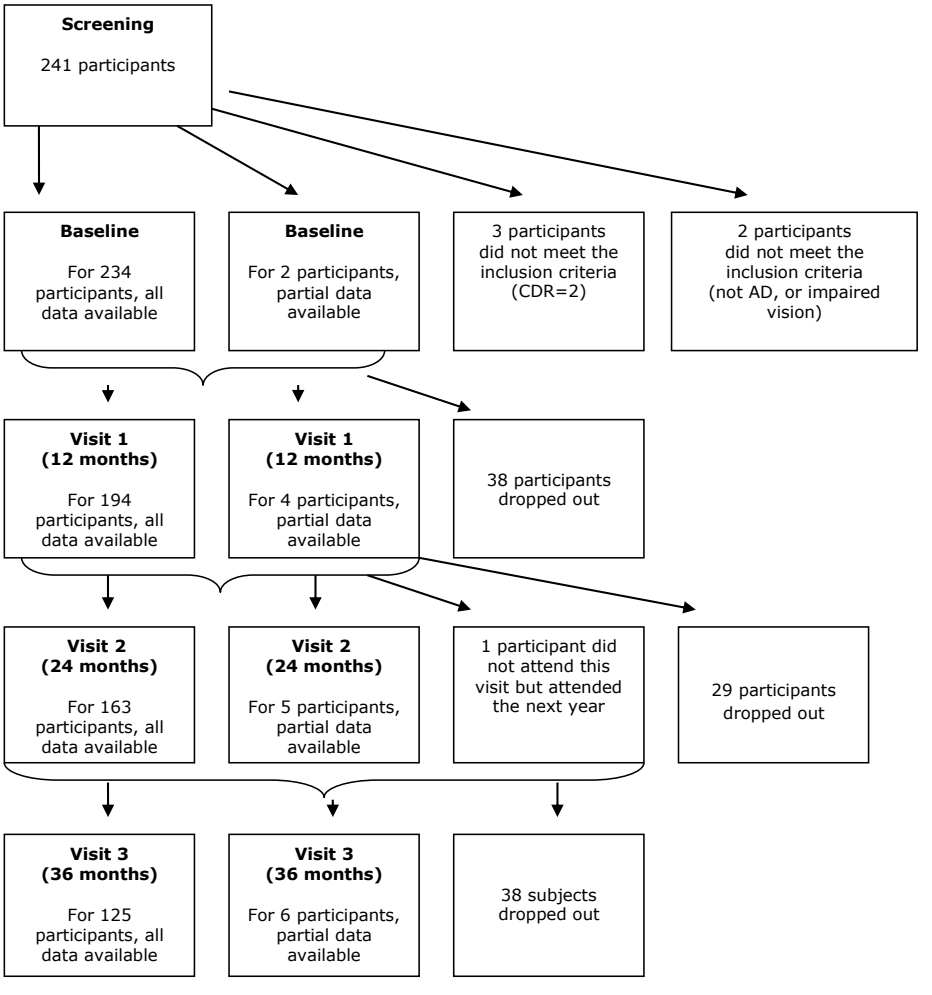


Figure 1. The study design

4.2 PARTICIPANTS

The participants were diagnosed by a geriatrician or a neurologist at their local clinics in accordance with the NINCDS-ADRDA (McKhann et al., 1984) and DSM-IV (American Psychiatric Association, 1994) guidelines. The diagnostic procedure included brain imaging (CT or MRI), different diagnostic laboratory tests, and a neuropsychological examination.

The criteria of inclusion in the ALSOVA follow-up study were that the participants had been diagnosed with very mild or mild AD at baseline, were fluent in Finnish, community-dwelling, were free of co-morbid conditions that could have affected their cognition at baseline, and were able to do the CERAD-NB at baseline. In the Alsova Study, the endpoints were institutionalisation and/or death. Out of the 241 participants screened, one was excluded at the baseline visit on account of unconfirmed AD. Three participants were excluded on account of having moderate AD (Clinical Dementia Rating, CDR=2) at baseline and one on account of impaired vision. The final study population comprised 236 voluntary participants. The ALSOVA research design is presented in Figure 1. To be included in the Alsova Study, the participants had to have a family caregiver who was in daily contact with them. The caregiver could be the spouse (n=166), a child, a sibling, a son- or daughter-in-law, or another close relative. In addition to the annual study visits, the participants received treatment in their regular health care system. The use of AD-targeted medication was recommended, and the participants might have been using other medication as well.

In Study II, only those participants were included for whom the CERAD-NB results and caregiver interview data were available from the baseline visit and all the three follow-up visits. Besides, only those participants were included who had an MMSE score of $\leq$ 18, which had been set as the cut-off point for mild AD. Thus a total of 115 subjects were included in Study II. The numbers of participating subjects and the data collected in Studies I-IV are presented in Table 5.

Table 5. Measures used and numbers of observations made in studies I-IV.

Measures	**Study I**	**Study II**				**Study III**				**Study IV**			
	Baseline	**Baseline**	**Year 1**	**Year 2**	**Year 3**	**Baseline**	**Year 1**	**Year 2**	**Year 3**	**Baseline**	**Year 1**	**Year 2**	**Year 3**
CERAD-NB subtests (Consortium to Establish a Registry for Alzheimer's Disease) Welsh et al. 1994; Hänninen et al. 1999	-	-	-	-	-	235-236	195-198	163-167	125-126	-	-	-	-
CERAD-NB total score Chandler et al. 2005	234	115	115	114	113	234	194	163	125	234	194	163	125
MMSE (Mini-Mental State Examination) Folstein et al. 1975	236	115	115	114	113	236	198	166	125	236	198	166	125
CDR (Clinical Dementia Rating) Hughes et al. 1982; Morris et al. 1993	236	115	115	114	115	236	198	168	128	236	198	168	128
ADCS-ADL (Alzheimer's Disease Cooperative Study – Activities of Daily Living) Galasko et al. 1997	236	115	115	114	115	-	-	-	-	236	198	168	131

Table 5. Measures used and numbers of observations made in studies I-IV.

NPI (Neuropsychiatric Inventory) Cummings et al. 1994	236	115	115	114	115	-	-	-	-	236	197	168	130
QoL-AD (Quality of Life in Alzheimer's Disease) Logsdon et al. 1999	-	-	-	-	-	-	-	-	-	236	198	162	122
VAS (Visual Analog Scale)	-	-	-	-	-	-	-	-	-	236	196	161	124

- = the measure was not used in the study

4.3 MEASUREMENTS

4.3.1 Assessment of cognition

Cognition was evaluated with the CERAD-NB (Welsh et al., 1994) and the Mini-Mental State Examination (Folstein et al., 1975). The CERAD-NB is a test battery compiled from previously published tests measuring cognitive domains known to be impaired in AD. For each subject, the CERAD-NB total score was calculated with the subtest addition method (range 0-100) (Chandler et al., 2005). The Finnish version of the CERAD-NB included all subtests from the original English test battery: the Boston naming test (15-item version; range 0-15), verbal (category) fluency (animals; range from 0 to no limit), word list learning (range 0-30), word list recall (range 0-10), word list recognition (range 0-20), and constructional praxis (range 0-11). In addition, the Finnish version included the clock-drawing test (range 0-6) and the constructional-praxis delayed recall test (range 0-11) (Hänninen et al., 1999).

Verbal fluency is a measure of verbal production, semantic memory, and language skills, and it also requires executive function skills. The Boston naming test is a test of visual naming, revealing word-finding difficulties. The word list learning task measures the ability to learn new verbal information and to recall it later, both freely and with cues: The score of the word list recall test measures the amount of verbal information retained over the delay interval, and the word list recognition test measures the recognition and discrimination of the words presented earlier. The constructional-praxis task measures visuospatial and constructional abilities, and constructional praxis recall is a measure of delayed visual memory. The clock-drawing test measures visuospatial and constructional skills, and planning and executive function skills are also covered. (Welsh et al., 1994; Pulliainen et al., 1999)

4.3.2 Assessment of the severity of dementia

The severity of AD was measured with the Clinical Dementia Rating (Hughes et al., 1982; Morris, 1993). The CDR is a semi-structured interview, which includes six areas: memory, orientation, judgement and problem-solving, community affairs, home and hobbies, and personal care. Each area is scored from zero to three, and the scores are added up to produce the CDR Sum of Boxes (CDR-sb) score (range 0-18) and a global score indicating the stage of dementia (0=no dementia, 0.5=very mild, 1=mild, 2=moderate, 3=severe). The stages of dementia can also be assessed in terms of the CDR-sb score as follows: 0=normal, 0.5-4.0=questionable cognitive impairment, 3.0-4.0=very mild dementia, 4.5-9.0=mild dementia, 9.5-15.5=moderate dementia, and 16.0-18.0=severe dementia (O'Bryant et al., 2008). In Study III, the CDR-sb score was used as an outcome measure.

At the time of the baseline visits, the subjects were classified into those with very mild AD (CDR=0.5) and those with mild AD (CDR=1) on the basis of the CDR interview in accordance with clinical practice. Later on, the Washington University CDR-assignment algorithm was used (www.alz.washington.edu/cdrnacc.html). Thus, before analysing the data for Study III, all the CDR global scores were re-calculated, and the classification of 48 borderline cases was changed. This did not affect the CDR-sb scores.

4.3.3 Other measures

Functional ability was assessed with the Alzheimer's Disease Cooperative Study – Activities of Daily Living Inventory (ADCS-ADL, range 0-78) (Galasko et al., 1997), which is a set of informant-based items describing the performance of ADL by persons with AD. A caregiver is asked to evaluate 23 basic (e.g., eating, walking) and instrumental (e.g., finances, household chores) activities of the daily living of the person with AD during the past four weeks. For each domain, the informant is to indicate the level of functioning, e.g., whether the person with AD functions independently, with supervision, or with assistance.

Behavioural and psychological symptoms were evaluated with the Neuropsychiatric Inventory (NPI) (Cummings et al., 1994). It is an informant-based interview, which assesses twelve behavioural disturbances occurring in persons with dementia: delusions, hallucinations, agitation/aggression, depression/dysphoria, anxiety, elation/euphoria, apathy/indifference, disinhibition, aberrant motor behaviour, sleep and night-time behaviour, and appetite and eating disorders. The NPI is designed to assess the changes that have appeared in the person's behaviour since the onset of AD. Each domain includes subquestions, which provide examples of the disturbance in question. If a behaviour is present, its frequency (occasionally, often, frequently, very frequently) and severity (mild, moderate, severe) are indicated. The total NPI score is the sum of the subscale scores (frequency x severity, range 0-144). Higher scores indicate more severe behavioural disturbance.

The effect of early psychosocial intervention on the quality of life of persons with AD was assessed with the disease-specific QoL-AD (Quality of life in Alzheimer's Disease Scale) and the VAS (Visual Analog Scale) wellbeing and life satisfaction instrument. The QoL-AD is a 13-item measure specifically developed for use with persons with AD and their caregivers (Logsdon et al., 1999). The maximum score (indicating high QoL) is 52 and the minimum 13. The 10-cm VAS scale is a one-item indicator of QoL, including a single question of the general wellbeing of the person on a scale of 0 (worst possible) to 100 (best possible).

4.4 STATISTICAL ANALYSES

Statistical analyses were performed by using SPSS (SPSS Inc., Chicago, Ill., USA). In Studies III and IV, use was also made of STATA (StataCorp, Texas, USA). The level of statistical significance was set at $p<0.05$. To summarise the data, descriptive statistics (means, standard deviations, medians, percentages, etc.) were used. To analyse the differences between groups (genders, CDR 0.5 or 1 at baseline, different intervention groups, and participants with three-year follow-up data vs. dropouts), either independent-samples t-tests or Mann-Whitney U-tests were used, depending on the normality of the distribution of the variable. To analyse the group differences in dichotomic variables, the chi-square test was used. To analyse the relations among the variables, either Pearson's product-moment correlation or Spearman's rank-order correlation was used, depending on the normality of the distribution.

In Study II, linear regression models adjusted for age, gender, and education were created to evaluate the association between the CERAD-NB total score and the other efficacy parameters and the severity of AD at the baseline visit and at the three-year follow-up visit, and also to study the effect of education on the CERAD-NB total score. For the regression models, covariates with significance less than 0.2 in univariate analyses were selected. To estimate the significance of change in each efficacy parameter between the follow-up visits, a paired-samples t-test was used.

In Study III, to determine which CERAD-NB subtests and demographic variables and which subtest combination were the most associated with the severity of AD (CDR-sb), Generalised Estimating Equation (GEE) models were made use of, together with repeated measures of CERAD-NB subtests and CDR-sb. Also, baseline subtest data was used to predict the severity of AD (repeated measures of CDR-sb). All GEE models were specified with a Gaussian distribution, identity link function, and an unstructured correlation matrix. To compare the power of the models and determine how much of the variation in the outcome was explained by the models, goodness-of-fit diagnostics and pseudo-R2 statistics (Twisk, 2013) were used. A detailed explanation of the creation and selection of the models is to be found in the original research article (Appendix, Study III).

For Study IV, an appropriate sample size was determined on the basis of the primary outcome measure (i.e., nursing-home placement). A target size of about 240 (with a 1:2 randomisation) was estimated to ensure 80-% power and a significance level of 0.05 to detect an approximate 20-% difference between the study groups after the three-year follow-up. The differences in the rates of nursing-home placement between the control group and the intervention group were evaluated with the proportional subhazard (sHR) regression model to adjust the impact of a competing risk (i.e., death) on the cumulative risk of institutionalisation over the 36-month follow-up. The regression estimates were adjusted for age, gender, and education. The differences in the mortality rates between the control group and the intervention group were analysed with the Cox hazard ratios. The differences in secondary outcomes between the control group and the intervention group were analysed as adjusted annual mean changes from the baseline. Use was made of the Linear Mixed Model (LMM) with a repeated-measures structure, Gaussian distribution, identity link function, and an unstructured correlation matrix.

4.5 ETHICAL CONSIDERATIONS

The protocol of the ALSOVA Study was approved by the ethical committee of Kuopio University Hospital (No. 64/00). All potential participants were informed about the procedures of the study orally and in in writing. The voluntariness of participation and the confidentiality of the data to be collected were emphasised. An Informed Consent Form was signed by each participating person with AD and each caregiver. The caregiver also provided a proxy consent on behalf of the person with AD.

All the four studies (I-IV) were conducted as part of the ALSOVA Study. I participated in the data collection as a psychologist in the years 2006 to 2011 and was involved in the recording and processing of the data. As to Studies I, II, and III, I planned the research designs and was in charge of the statistical analyses and the interpretation of the data under the guidance of my supervisors. In these three studies I was the first author while the co-authors participated in the collection and processing of the data and furnished critical comments on the manuscripts. In addition, professional statistical consultation was made use of with the more complex analyses. In Study IV, I contributed to the interpretation of the data and the drafting of the manuscript.

5 Results

5.1 GENERAL CHARACTERISTICS OF THE PARTICIPANTS IN THE ALSOVA STUDY

Demographic characteristics of the participants in the four studies are presented in Table 6. Study I focused on the baseline data of the participants (n=236), who were then followed up for three years in Study III and Study IV. The CDR classification of some subjects was changed after re-calculations (see Methods, page 32). Study II includes the three-year data for the subgroup (n=115). The mean age of both the whole population and the subgroup (Study II) was 75.1, and the mean years of education were 7.6 for the whole population and 7.8 for the subgroup. The age at baseline ranged between 53 and 90 years, but most of the participants (94.5 %) were 65 or older at the time of the baseline visit. In 70.3 % of the cases the caregiver was the spouse and in 23.7 % of the cases, a child of the person. The remaining 6 % of the caregivers were siblings or children's spouses.

A small majority of the participants were women in both the whole population (51.3 %) and the subgroup of Study II (56.5 %). There was no difference at baseline in the CERAD-NB total score, the MMSE, the CDR-sb, or the NPI score between the genders. Women performed better in the baseline ADCS-ADL than men (p<.001) (Study I, data not shown). In an adjusted regression model, gender was not associated with cognition (CERAD-NB total score) at baseline or at visit 3 (Table 4, Study II). There were some differences between men and women in CERAD-NB subtests during the three-year follow-up (Study III, data not shown). Men outperformed women in the Boston naming test at baseline (p<.001), at visit 1 (p=.022), and at visit 3 (p=.015). Men also outperformed women in the word list recognition test at visit 3 (p=.031). In contrast, women outperformed men in the word list learning test at baseline (p=.022) and in constructional praxis at visit 3 (p=.044). Women also had lower (i.e., better) CDR-sb scores than men at visit 1 (p=.026) and at visit 2 (p=.028).

On the basis of their CDR scores at baseline, the participants were classified into cases of very mild (the CDR 0.5 group) and mild dementia (the CDR 1.0 group). During the three-year follow-up, both groups showed a notable prevalence of mild dementia (CDR=1). Figure 2 presents the annual proportions of CDR classes. In 20 cases out of the whole population, the CDR stage improved temporarily from the previous visit; however, all of these participants showed deterioration later in the follow-up. Eight participants in the CDR 0.5 group and 26 in the CDR 1 group were stable throughout the three-year follow-up. Forty-nine participants in the CDR 0.5 group and 26 in the CDR 1 group advanced to the next, more severe CDR stage during the three-year follow-up. Fourteen participants in the CDR 0.5 group and three in the CDR 1 group advanced by two CDR stages. Finally, three participants advanced by three CDR stages (from very mild to severe dementia). In the Study II subgroup (n=115), too, more than a half of the subjects still had very mild or mild AD after the three years.

In all the studies, the CDR 0.5 group and the CDR 1 group did not differ significantly in age. The CDR 0.5 group was slightly more educated in Study III (p=.004) and Study II (p=.012). However, this difference was not found in Study I, in which a different kind of CDR classification was used. Differences in the proportion of female subjects came close to reaching significance in the corrected data (p=.054) and in the subgroup of Study II (p=.088) but not in Study I (with a different CDR classification) (p=0.583).

Table 6. Age, gender, and education of the participants in studies I-IV.

	Study I			**Study II**			**Study III**			**Study IV**		
	All	**CDR=0.5**	**CDR=1**	**All**	**CDR=0.5**	**CDR=1**	**All**	**CDR=0.5**	**CDR=1**	**All**	**Control**	**Intervention**
	n=236	n=80	n=156	n=115	n=61	n=54	n=236	n=128	n=108	n=236	n=152	n=84
Gender, men %	48.7	46.2	50.0	43.5	36.1	51.9	48.7	43.0	55.6	48.7	48.0	50.0
						p=.088			p=.054			p=.477
Mean age, years (SD)	75.1 (6.6)	73.9 (7.0)	75.8 (6.3)	75.1 (6.6)	75.1 (6.3)	75.1 (6.9)	75.1 (6.5)	74.5 (6.3)	75.9 (6.8)	75.1 (6.5)	75.1 (6.2)	75.3 (7.1)
			p=.245			p=.962			p=.097			p=.729
Mean education, years (SD)	7.6 (3.3)	8.1 (3.3)	7.3 (3.3)	7.8 (3.3)	8.5 (3.5)	6.9 (3.0)	7.6 (3.3)	8.1 (3.5)	6.9 (2.9)	7.6 (3.3)	7.4 (3.1)	7.9 (3.6)
			p=.350			p=.012			p=.004			p=.352

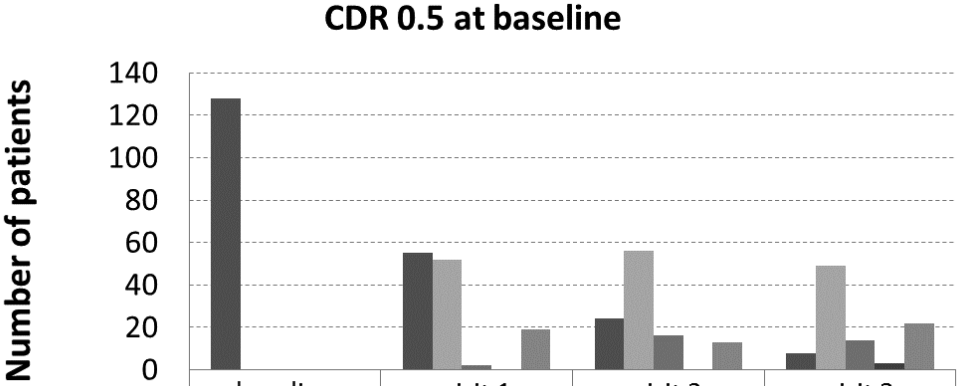
CDR=Clinical Dementia Rating, CDR=0.5 = Clinical Dementia Rating 0.5 at baseline (very mild Alzheimer's disease), CDR=1 = Clinical Dementia Rating 1 at baseline (mild Alzheimer's disease), SD=Standard Deviation

Pairwise comparisons of the differences between very mild (CDR 0.5) and mild (CDR 1) AD at baseline and between the control and the intervention group were analysed by means of the t-test, the Mann-Whitney U –test, or the χ^2 test, depending on the characteristics of the variable.

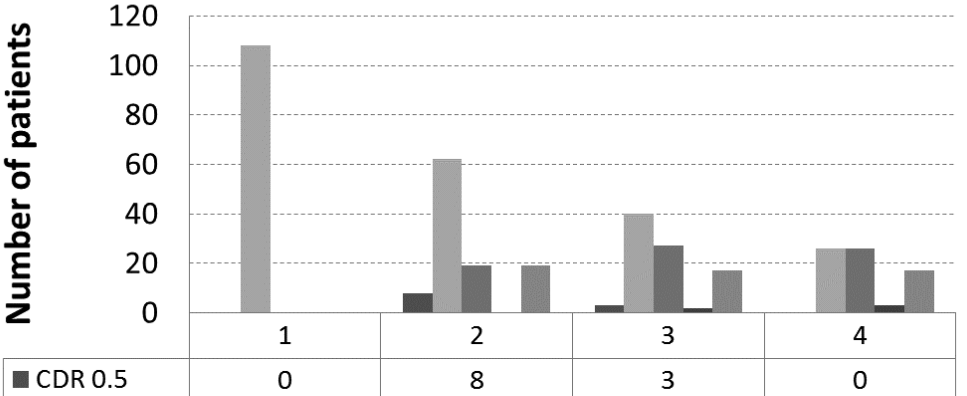
Correlations among age, education, and clinical characteristics at baseline (n=236) (Table 2, Study I) and at the third follow-up visit (n=115) were analysed (Table 3, Study II). The length of education correlated with cognition at baseline (CERAD-NB total r=.334, p<.001; MMSE 0.278, p<.001) and at the third follow-up visit (CERAD-NB total r=0.257, p=.006; MMSE r=.0232, p=0.013), but no significant correlation was found between age and baseline cognition (table 2, study I). Also, in the subgroup of Study II (n=115), analysed with the adjusted regression model, education affected cognitive performance (CERAD-NB total score) both at baseline (p<.001) and at the third follow-up visit (p=.001), while age (baseline p=.135, visit 3 p=.350) and gender did not (baseline p=.785, visit 3 p=.870) (Table 4, Study II).

The verbal fluency and the clock-drawing test were the only subtests that did not correlate with education at any visit. Age correlated only with the naming-test scores (Study III, data not shown).

Age and education correlated with the ADCS-ADL (age r=-.201, p<.05, education r=.357, p<.001) and education with the CDR-sb scores (age r=.159, p=ns; education r=-.204, p<.05 at baseline, i.e., younger age and more years of education were related with better ADL, and more years of education with milder AD. The NPI did not correlate with age or education at baseline (Table 2, Study I).



	baseline	visit 1	visit 2	visit 3
CDR 0.5	128	55	24	8
CDR 1	0	52	56	49
CDR 2	0	2	16	14
CDR 3	0	0	0	3
dropped out	0	19	13	22



	1	2	3	4
CDR 0.5	0	8	3	0
CDR 1	108	62	40	26
CDR 2	0	19	27	26
CDR 3	0	0	2	3
dropped out	0	19	17	17

Figure 2. Clinical Dementia Rating (CDR) classes of persons with very mild (CDR=0.5) or mild (CDR=1) AD at baseline during the three-year follow-up

5.2 DROP-OUT ANALYSIS

During the three-year follow-up, a total of 106 participants dropped out of the study (Figure 1). The most common reasons for dropping out were institutionalisation (34/236), death (20/236), and deterioration of health (15/236) of the persons with AD. Other reasons included caregiver-related reasons (health, burden, death, or refusal, 20/236), refusal of the person with AD (8/236), and some other causes (9/236). The disease severity of the drop-outs (CDR-sb) at baseline had been similar to that of the participants who continued through the follow-up (p=.155). However, those who dropped out had more severe cognitive impairments (CERAD-NB total p=.047, MMSE p=.033, the clock-drawing test p=.003) at baseline. The two groups did not differ in education (p=.667), age (p=.407), or other CERAD-NB subtest scores at baseline.

For Study IV, the participants were randomised into an intervention and a control group, with the intervention group receiving psychosocial intervention (see Methods, page 27). The drop-out rate in the control group was significantly higher (76 out of 152 as opposed to 30 out of 84 in the intervention group, p=0.035). Nine participants (11 %) deceased from the intervention group and 18 (12 %) from the control group (age- and gender-adjusted HR=0.755 (95 % CI 0.323 to 1.766); p=0.517). The average time from dropping out to dying was 20.4 months (95 % CI 11.3-29.5 months). The participants who died at nursing homes died in 8.5 months on average (95 % CI 3.8-12.9 months) after nursing-home placement (Study IV).

5.3 CORRELATIONS OF THE CERAD NEUROPSYCHOLOGICAL BATTERY WITH OTHER MEASURES (STUDY I)

The year-to-year development of the participants' clinical characteristics is presented in table 7. A minority of the participants (18.2 %) had no neuropsychiatric symptoms at the beginning of the study. Out of all subjects, 21.5 % had one symptom, 13.1 % had two, and 47.0 % displayed symptoms in at least three different NPI domains. The most common neuropsychiatric symptoms were apathy (48.3 %), depression (36.4 %), and irritability (33.9 %). The mean ADCS-ADL score was 64.53 at baseline (Table 6). The subjects with very mild AD (CDR 0.5) had better cognition (CERAD-NB total, p<.001; MMSE, p<.001), better activities of daily living (ADCS-ADL, p<.001), and fewer neuropsychiatric symptoms (NPI, p=0.028) than the subjects with mild AD (CDR 1).

Table 8 presents the correlations of the values of the main variables at baseline and in year 3. Cognition (CERAD-NB total, MMSE) correlated with the severity of AD (CDR-sb) and activities of daily living (ADCS-ADL). However, no correlation was found between cognition and neuropsychiatric symptoms (NPI). Instead, the NPI total score correlated with the severity of AD (CDR-sb) and activities of daily living (ADL).

Table 7. Test results over the three-year follow-up of persons with very mild or mild AD at baseline.

	Baseline			**Visit 1**			**Visit 2**			**Visit 3**		
	CDR 0.5	CDR 1	All	CDR 0.5	CDR 1	All	CDR 0.5	CDR 1	All	CDR 0.5	CDR 1	All
CERAD-NB total		n=234			n = 194			n = 163			n = 125	
mean (SD)	54.6 (11.7)	48.0 (11.0)	51.9 (11.9)	49.6 (13.2)	43.7 (12.9)	46.9 (13.0)	45.0 (15.0)	38.1 (13.6)	42.1 (14.8)	42.3 (16.0)	35.7 (14.7)	39.5 (15.7)
MMSE		n = 236			n = 198			n = 165			n = 125	
mean (SD)	22.7 (3.1)	20.2 (3.4)	21.5 (3.4)	20.5 (3.9)	17.9 (4.4)	19.3 (4.3)	18.5 (4.9)	16.9 (5.0)	17.8 (5.0)	17.4 (5.0)	15.9 (4.1)	16.8 (4.7)
CDR-sb		n = 236			n = 197			n = 168			n = 129	
mean (SD)	3.1 (0.8)	5.4 (1.0)	4.1 (1.5)	4.7 (1.8)	6.8 (2.4)	5.6 (2.3)	6.1 (2.7)	8.4 (2.9)	7.1 (3.0)	7.3 (3.3)	9.6 (3.1)	8.3 (3.4)
ADCS-ADL		n = 236			n = 198			n = 168			n = 131	
mean (SD)	68.8 (6.3)	59.6 (9.0)	64.6 (8.9)	63.8 (9.8)	51.2 (12.6)	58.1 (12.7)	56.4 (13.4)	44.4 (16.6)	51.3 (15.9)	53.3 (14.6)	36.3 (18.6)	46.1 (18.4)
NPI		n = 236			n = 197			n = 168			n = 130	
mean (SD)	7.7 (8.3)	10.2 (11.0)	8.9 (9.7)	9.4 (9.9)	13.8 (13.6)	11.4 (11.9)	11.4 (11.4)	17.2 (14.6)	13.9 (13.1)	12.1 (13.2)	18.7 (13.2)	14.9 (13.5)

CDR 0.5 = Clinical Dementia Rating 0.5 at baseline; CDR 1 = Clinical Dementia Rating 1 at baseline; CERAD-NB total = Consortium to Establish a Registry for Alzheimer's Disease Neuropsychological test battery total score; MMSE = Mini-Mental State Examination; CDR-sb = Clinical Dementia Rating sum of boxes; ADCS-ADL = Activities of Daily Living – Alzheimer Disease Cooperative Study; NPI = Neuropsychiatric Inventory

SD = standard deviation

Table 8. Correlations among test results at baseline and at the third follow-up visit.

	CERAD-NB total		**MMSE**		**CDR-sb**		**ADCS-ADL**	
	Baseline	**Year 3**	**Baseline**	**Year 3**	**Baseline**	**Year 3**	**Baseline**	**Year 3**
MMSE								
Baseline	**.618**							
Year 3		**.762**						
CDR-sb								
Baseline	**.319**		**-.443**					
Year 3		**-.627**		**-.643**				
ADCS-ADL								
Baseline	**.250**		**.314**		**-.580**			
Year 3		**.484**		**.394**		**-.817**		
NPI								
Baseline	.087		.049		**.231**		**.339**	
Year 3		-.061		-.074		**.453**		**.521**

Baseline values: n = 236, baseline CERAD-NB total n = 234, baseline CERAD-NB subtests n = 235-236

Year 3 values: n = 115, year 3 CERAD-NB total n = 113, year 3 CERAD-NB subtests n = 125-126

The coefficient used was either Pearson's product-moment correlation or Spearman's rank-order correlation, depending on the characteristics of the variable.

Bold = $p<.05$

5.4 DECLINE IN COGNITION AND OTHER CLINICAL FEATURES DURING THE THREE-YEAR FOLLOW-UP (STUDY II)

Cognition (i.e., the changes in the CERAD-NB total and the MMSE) and the activities of daily living (i.e., the changes in the ADCS-ADL) deteriorated and the severity of AD (i.e., the change in the CDR-sb) increased significantly ($p<.02$) every year (Table 2, Figure 1, Study II). The annual means and the means of annual changes in the whole data of the ALSOVA Study participants are presented in Tables 7 and 9.

Persons with very mild AD (CDR 0.5) at baseline had better cognition during the three-year follow-up than those with mild AD (CDR 1) did, as shown in the CERAD-NB ($p<.05$ at all visits), but the MMSE did not distinguish between the two groups ($p>.02$) (Study II). In Study III, however, the larger sample brought out a difference in the MMSE that was statistically significant for the first and the second follow-up visit as well. Also, the CDR 0.5 group had better activities of daily living (ADCS-ADL, $p <.001$ at all visits) and fewer neuropsychiatric symptoms during the follow-up than the CDR 1 group did (NPI, $p<.05$ at baseline and the second and third follow-up visit, $p=.057$ at the first follow-up visit) (Study II). The CDR 0.5 group had smaller changes in ADCS-ADL during the three-year follow-up ($p=.027$), but no differences in the progression rate of other measures were found (data not shown). Because the NPI scores were not normally distributed, the median values were also analysed. In Study II, the CDR 0.5 group exhibited a lower median value even at the third follow-up visit than the CDR 1 group did at baseline (data not shown). The same was noted for the whole population (data not shown).

All clinical characteristics, i.e., cognition (CERAD-NB total and MMSE), activities of daily living (ADCS-ADL), and neuropsychiatric symptoms (NPI), still correlated significantly ($p<.001$) with the severity of AD (CDR-sb) at the third follow-up visit (Table 8). Similarly to the results of the baseline visit, cognition correlated with the activities of daily living but not with neuropsychiatric symptoms at the third follow-up visit. However, the changes in cognition and in the NPI did correlate with each other (data not shown). The activities of daily living correlated with neuropsychiatric symptoms at the third visit also.

Table 9. Annual mean changes in the MMSE, the CERAD-NB total, the ADCS-ADL, and the NPI of persons with Alzheimer's disease during the three-year follow-up.

	Baseline – Year 1	**Year 1 – Year 2**	**Year 2 – Year 3**
CERAD-NB	n = 193	n = 162	n = 124
range	-28 – 17	-32 – 9	-31 – 11
mean (SD)	-5.32 (7.75)	-5.91 (7.75)	-5.52 (7.94)
MMSE	n = 198	n = 165	n = 124
range	-11 – 5	-13 – 6	-11 – 5
mean (SD)	-2.28 (3.22)	-1.96 (3.23)	-2.39 (2.83)
CDR-sb	n = 198	n = 168	n = 127
range	-3.5 – 8	-3 – 6	-3 – 10
mean (SD)	1.49 (1.92)	1.59 (2.02)	1.91 (2.18)
ADCS-ADL	n = 198	n = 168	n = 130
range	-40 – 14	-44 – 20	-31 – 7
mean (SD)	-6.94 (8.37)	-8.08 (10.30)	-8.03 (9.24)
NPI	n = 197	n = 167	n = 129
range	-16 – 32	-19 – 28	-21 – 33
mean (SD)	2.44 (8.65)	3.54 (8.83)	2.88 (9.83)

CERAD-NB total = Consortium to Establish a Registry for Alzheimer's Disease Neuropsychological test battery total score; MMSE = Mini-Mental State Examination; CDR-sb = Clinical Dementia Rating sum of boxes; ADCS-ADL = Activities of Daily Living – Alzheimer Disease Cooperative Study; NPI = Neuropsychiatric Inventory

Mean = mean of annual change from previous visit; SD = standard deviation

Table 10. Correlations of the CERAD-NB subtest results with the CERAD-NB total score, the MMSE, and the CDR-sb at baseline and at the third follow-up visit.

	CERAD-NB total		**MMSE**		**CDR-sb**	
	Baseline	**Follow-up**	**Baseline**	**Follow-up**	**Baseline**	**Follow-up**
Verbal fluency						
Baseline	**.717**		**.334**		**-.210**	
Follow-up		**.633**		**.665**		**-.641**
Naming						
Baseline	**.638**		**.400**		**-.147**	
Follow-up		**.733**		**.523**		**-.345**
Word List Learning						
Baseline	**.713**		**.435**		**-.311**	
Follow-up		**.847**		**.674**		**-.534**
Word List Recall						
Baseline	**.532**		**.388**		**-.234**	
Follow-up		**.578**		**.374**		**-.346**
Word List Recognition						
Baseline	**.533**		**.378**		**-.223**	
Follow-up		**.611**		**.409**		**-.404**
Constructional Praxis						
Baseline	**.442**		**.351**		**-.174**	
Follow-up		**.478**		**.458**		**-.485**
Praxis recall						
Baseline	**.448**		**.417**		**-.280**	
Follow-up		**.453**		**.420**		**-.260**
The clock-drawing test						
Baseline	**.439**		**.462**		**-.339**	
Follow-up		**.620**		**.604**		**-.488**

Table 10 to be continued

Table 10. (Continued) Correlations of the CERAD-NB subtest results with the CERAD-NB total score, the MMSE, and the CDR-sb at baseline and at the third follow-up visit.

Baseline values: n = 236, CERAD-NB total n = 234, CERAD-NB subtests n = 235-236

Follow-up values: n = 115, CERAD-NB total n = 113, CERAD-NB subtests n = 125-126

The coefficient used was either Pearson's product-moment correlation or Spearman's rank-order correlation, depending on the characteristics of the variable.

In Study I, Bonferroni corrections were used.

All correlations were statistically significant at $p<.05$.

5.5 THE CERAD NEUROPSYCHOLOGICAL BATTERY SUBTESTS AS INSTRUMENTS IN A FOLLOW-UP STUDY OF ALZHEIMER'S DISEASE (STUDY III)

Performance in all the CERAD-NB subtests declined during the three-year follow-up period (Figure 1, Study III). At baseline, the CDR 0.5 group outperformed the CDR 1 group in the MMSE, the CERAD-NB total, the CDR-sb and most of the CERAD-NB subtests. Throughout the visits, the two groups were distinguished by differences in verbal fluency, the CERAD-NB total, and the CDR-sb scores. In the CDR 1 group, the word list recall, constructional praxis, and the clock-drawing test mean scores were higher at visit 3 than at visit 2. Verbal fluency and the clock-drawing test were the only subtests that did not correlate with education at any visit (Study III, data not shown.) The global cognitive measures (the CERAD-NB total and the MMSE) correlated with all subtests at baseline and at all follow-up visits (Table 10).

5.5.1 The short version of the CERAD Neuropsychological Battery as a follow-up tool

To discover the best subtest combination for AD follow-up, GEE-models were used. Table 3, Study III, presents the GEE-models used, which incorporated the MMSE (Model 1), the CERAD-NB total score (Model 2), both the MMSE and the CERAD-NB total score (Model 3), and the best CERAD-NB subtest combination (Model 4) for the purposes of modelling the severity of AD. The best explorative model comprised gender, time, verbal fluency, word list learning, word list recall, constructional praxis, and the clock-drawing test (Study III, data not shown); that model explained the CDR-sb better than the model that included all the subtests. The model including only gender, time, verbal fluency, constructional praxis, and the clock-drawing test produced nearly the same pseudo-R^2 estimate (i.e., explanatory power). The addition of the MMSE boosted the pseudo-R^2 of the model, and education and age were included because they are commonly used covariants. With this method, the model including age, gender, education, the MMSE, verbal fluency, constructional praxis, and the clock-drawing test (Model 4, Table 3, Study III) was determined to provide the best results. Although Model 3, which combined the MMSE and the CERAD-NB total score, provided a better explanation of the variance in the CDR-sb than either Model 1 or Model 2, Model 4 produced an even higher pseudo-R^2 estimate (i.e., better explanatory power). This combination of the MMSE, three CERAD-NB subtests, and the covariates explained 62.1 % of the variance in the severity of dementia (measured in terms of the CDR-sb) during the three-year follow-up period.

5.5.2 Predicting the progression of Alzheimer's disease with the baseline CERAD Neuropsychological Battery subtests

The baseline variables of the same models as were used to explain the severity of AD during the follow-up were used to predict the progression of AD symptoms. The model that included the baseline values of the MMSE, verbal fluency, constructional praxis, the clock-drawing test scores, and the covariates predicted the progression of CDR-sb during the three year follow-up period better than the MMSE alone, the CERAD-NB total score alone, or the combination of the MMSE and the CERAD-NB did (Table 4, Study III). The model that included only the baseline measurements had a pseudo-R^2 value of 36.6 %. In addition to these subtests, naming ability was found to be a significant predictor in a univariate analysis (data not shown).

5.6 THE EFFECT OF EARLY PSYCHOSOCIAL INTERVENTION ON ALZHEIMER'S DISEASE (STUDY IV)

5.6.1 The delaying effect of the intervention on institutionalisation

No differences in the rate of institutionalisation were found between the intervention and the control group after the three-year follow-up. By the third follow-up visit, 18 of 84 subjects (21 %) from the intervention group and 24 of 152 (16 %) from the control group had been placed in nursing homes. The adjusted sHR estimate for the difference in the rate of nursing-home placement between the intervention and the control group was 1.30 (95 % CI 0.69 to 2.45).

5.6.2 Effects of the intervention on symptoms related to Alzheimer's disease

At the follow-up visits, the intervention group performed worse than the control group in the CERAD-NB; their proxy-rated ADCS-ADL scores were also lower and their CDR-sb scores higher (Figure 3, Study IV, Appendix). No differences in the NPI were observed between the groups during the 36-month follow-up, nor were there any differences in the subjects' quality-of-life measures (15D, QoL-AD, and VAS) (Figure 3, Study IV, Appendix).

6 Discussion

6.1 PROGRESSION OF ALZHEIMER'S DISEASE SYMPTOMS DURING THE THREE-YEAR FOLLOW-UP

6.1.1 Cognitive deterioration

In Study II, the annual decline in the CERAD-NB total scores, varying between -5.3 and -5.9 points in the different years, was slightly less than found previously (-7.2 points, Rossetti et al., 2010). It should be noted that according to Rossetti et al. (2010), the change in the CERAD-NB total scores should be over 10 points to represent a clinically meaningful change. However, Rossetti et al. (2010) also point out that decreases that fail to exceed a specific limit may not necessarily be insignificant.

There was no difference in the mean annual change of the CERAD-NB total score between the CDR 0.5 group and the CDR 1 group (CDR 0.5 and 1 at baseline), which is in line with a previous study by Rossetti et al. (2010). However, Rossetti et al. (2010) included persons with moderate AD at baseline, thus comparing groups of mild and moderate AD (CDR≥2 or <2).

In Study II, the annual deterioration of the MMSE test scores (with the loss varying between -2.0 and -2.4 points in the different years) was in line with those found in recent studies (Gillette-Guyonnet et al., 2011; Tschanz et al., 2011; Vellas et al., 2012; Handels et al., 2013; Phung et al., 2013), and no acceleration of the cognitive decline was found during the three-year follow-up. Vellas et al. (2012) found that the decline was faster in the second follow-up year than in the first. They had collected a large body of data from several countries. However, as their data also included persons with moderate AD (MMSE 10-26), their results may not be representative of the first years of Alzheimer's disease diagnosed at the mild stage, as is expected nowadays. In Gillette-Gyuonnet et al.'s study (2011), too, though other characteristics of the participants were quite similar to those in the present study in that AD patients on antidementia drugs were enrolled in memory clinics and followed up over four years, there was the difference that the cohort included persons with very mild to moderate AD.

The rate of cognitive decline varied widely from person to person. In this study, 26.0 % of those participants who went through the three-year follow-up were relatively stable (i.e., staying at the same CDR stage), and 63.4 % were still in the mild phase of the disease at the end of the study (CDR 0.5 or 1). One third of the participants had reached the moderate stage at the end of the study, and only six participants were at the severe stage of the disease. These results are in line with those reported previously (Cortes et al., 2008). The most common reasons for dropping out of this study was institutionalisation, death, and comorbidities; thus it was probably the persons with more advanced dementia that dropped out, as has been reported in the previous studies, too.

In this study, the CERAD-NB total score distinguished between the groups with very mild and with mild AD at baseline all through the follow-up period, while the MMSE did not (Study II). When the different cognitive domains were examined in more detail (Study III), it was found that at baseline all the CERAD-NB subtests distinguished the CDR 0.5 group from the CDR 1 group but that at the last (third) follow-up visit the only differences found were in verbal fluency and the CERAD-NB total score. These results concur with those of previous cross-sectional studies (Welsh et al., 1992; Bertolucci et al., 2001; Barth et al., 2005). Although the typical first sign of AD is memory problems, other aspects of cognition, such as the executive function and visual perception, may provide better information for staging AD, as suggested by Welsh et al. (1992).

In conclusion, the progression rate of cognitive symptoms was found to be similar to those found in recent reports. This progression seems to be similar regardless of the stage of dementia, at least in the first few years of the disease, yet variable from person to person.

6.1.2 Increase in neuropsychiatric symptoms

The Neuropsychiatric Inventory (NPI) mean score (8.9 points) obtained for the participants at baseline in Study I can represent several occasional mild symptoms, two moderate symptoms that occur weekly or one severe symptom, for example. A minority (18 %) of the persons with very mild or mild AD at baseline had no NPS. Lam et al. (2006) reported almost twice as many NPS (NPI score 16.3). The difference may be explained by the fact that they included persons with mild to moderate AD in their study. In Study I, almost a half of the participants (47.0 %) displayed at least three different symptoms. The most common symptoms were apathy and depression, as had been found in previous studies (Serra et al., 2010; Dillon et al., 2013). In the present study, the annual change in the NPI score (between +2.4 and +3.5 points) represents one new symptom that occurs weekly or the worsening of one previously displayed symptom, for example. These findings are in line with those reported previously (Tschanz et al., 2011).

It has been emphasised recently that unlike previously thought, NPS are common at the early stage of the disease already (Lyketsos et al., 2011; Dillon et al., 2013). As NPS are emotional and behavioural manifestations, they are often more difficult for persons with AD, caregivers, and professionals to deal with than memory loss is. A person with AD may feel depressed and distressed and be irritable or abusive towards caregivers, for example (Dillon et al., 2013; Kales et al., 2013; Välimäki et al., 2014).

6.1.3 Decline in activities of daily living in relation to the progression of AD

For the whole population of this study, an annual decrease of 7-8 points was found in the measure of the activities of daily living (ADCS-ADL). A decline of this magnitude can be seen to represent a need of increased supervision or a one-level functional decline in 7-8 domains of daily functions, or the total loss of two activities, for example. The result corresponds to the findings of Phung et al. (2013), who found a loss of 22.3 points (control group) and 26.7 points (psychosocial intervention group) over a three-year follow-up. Also, an annual loss of one activity by one half of the sample of persons with AD has been reported in previous work (Gillette-Gyuonnet et al., 2011).

Persons with late-onset AD in particular have comorbidities that affect their functional abilities (American Psychiatric Association, 2013), and the ADCS-ADL measure (Galasko et al., 1997) does not specify whether the decline of functional abilities is caused by cognition or physical problems. Instead, the CDR-sb may be seen as a global score to describe a person's deficits in carrying out daily functions due to cognitive deterioration and the change in cognition and daily functioning from the person's previous level. In this study, the annual changes in the CDR-sb scores varied between +1.5 and +1.9 points. Previous studies have reported annual increases of +1.44 points in the CDR-sb scores (Tschanz et al., 2011) and increases of +4.17 points over 2 years (Cortes et al., 2008).

In conclusion, the progression of the three essential domains of AD, i.e., cognition, neuropsychiatric symptoms, and the activities of daily living, found in this study was quite similar to that reported in recent literature.

6.1.4 Differences in the progression of symptoms between the group with very mild and the one with mild Alzheimer's disease at baseline

As expected, the CDR 0.5 group (= very mild AD at baseline) showed better global cognition (as measured with the CERAD-NB) and daily activities (ADCS-ADL) and fewer neuropsychiatric symptoms (= lower NPI) than the CDR 1 group (= mild AD at baseline) throughout Study II. A slower decline in the daily activities was observed in the CDR 0.5 group, which was also found to be somewhat more highly educated. There are very few

reports in the literature that compare the long-term progression of AD-related symptoms in groups with very mild and ones with mild AD, but Nourashemi et al. (2008) report findings similar to those found in this study. The CDR 0.5 group also displayed fewer NPS throughout the three-year follow-up than the CDR 1 group had displayed at baseline.

There might have been some basic differences between the groups, or else, the early start of treatment and care might have affected the progression of AD-related symptoms. In addition to the possible benefit of AD-targeted medication, the persons with AD in the CDR 0.5 group and their caregivers started getting information and support earlier. It is also possible that the progression rate accelerates at some point in the disease and that the CDR 0.5 group were to reach this point only after the three-year follow-up was over.

6.1.5 Association of the CERAD Neuropsychological Battery with other measures of the progression of Alzheimer's disease

In Study I the cognition of persons with AD was significantly associated with ADL, which was consistent with previous findings obtained with the CERAD-NB total score (Seo et al., 2010) or other cognitive measures (e.g., Tractenberg et al., 2005; Bowens et al., 2009). An association was also found between ADL and neuropsychiatric symptoms, which was in line with the results of many other studies (e.g., Peters et al., 2006; Okura et al., 2010). These correlations tended to exist throughout the three-year follow-up (Study II). In the literature, most reports have indicated that behavioural symptoms and cognition are not directly related (Dillon et al., 2013). Changes in behavioural symptoms have been found to be independent from changes in cognitive measures (Tractenberg et al., 2005), but opposite results have also been reported (Serra et al., 2010). In this study, NPS did not correlate with cognition (as measured with the MMSE and the CERAD-NB total score) at baseline, nor did they correlate at the third follow-up visit, but the rates of the decline of both did correlate. Although the correlations between cognition and other clinical characteristics were modest at best, they were clearly significant. In contrast, the correlations between cognition and NPS did not even come close to significance. One may thus conclude that cognition and neuropsychiatric symptoms are independent manifestations of AD, even if they progress in parallel with the progression of the disease. Still, both cognitive deficits and neuropsychiatric symptoms affect the person's ability to manage the activities of everyday life and cause an increased need of caregiving. In future work it would be valuable to examine in more detail whether some specific cognitive and neuropsyciatric domains are related to each other or to activities of daily living.

6.1.6 Association of age, gender, and education with the progression of Alzheimer's disease

The association of the number of years of formal education with cognition has been widely noted previously (e.g., Karrasch et al., 2003), and in this study, too, cognition was associated with education. It was also noted that persons with very mild AD at baseline (CDR 0.5) were more highly educated than persons with mild AD. Gender was found to affect functional ability, with women receiving higher scores in the ADCS-ADL, which probably reflects the tradition of this particular generation to share housework, and this needs to be taken into account in the interpretation of the measures of ADL.

In a more detailed analysis of the CERAD-NB subtests carried out in Study III, it was noticed that education did not correlate with verbal fluency and the clock-drawing test, which both are measures of executive functions. Fluency did not correlate with education in Welsh et al.'s study (1994), either. However, in contrast to the findings obtained in the present study, a previous review suggests a link between education and the clock-drawing test (Pinto et al., 2009). In the past, educational opportunities were limited in Finland; therefore the educational level of members of the oldest age group is typically low, so that educational background is not necessarily a good indicator of cognitive capacity in this study. In Finnish normative data, both verbal fluency and the clock-drawing task correlated

with education (Karracsh et al., 2003). The influence of education in normal aging may be different from that in AD. Interestingly, educational level did not predict the progression of AD in this study as it has done in the many other studies (Sona et al., 2013).

6.1.7 Predicting the progression of symptoms in Alzheimer's disease

Although the ADCS-ADL was the only measure that correlated with gender, the male gender was associated with a faster progression rate of AD-related symptoms in Study III, which was in line with most previous reports (Zhou et al., 2010; Ito et al., 2011; Rountree et al., 2012; Sona et al., 2013). In contrast to most previous studies, however, the findings of this study suggested that age was not a significant predictor of the progression of AD symptoms (Sona et al., 2013). This discrepancy may be explained by the fact that most of the participants in this study were old at the onset of the disease (mean age 75.2 years).

In Study III, a new short version of the CERAD-NB was drawn up in order to follow up the progression of AD symptoms. It comprised the MMSE and tests of verbal fluency, constructional praxis, and clock-drawing, plus covariates (age, gender, and education). In addition to these subtests, naming ability was found to be a significant predictor in a univariate analysis. Previously, too, visuoconstructive and visuospatial skills, verbal fluency, and the executive function (Sarazin et al., 2005; Cosentino et al., 2006; Atchinson et al., 2007; Zhou et al., 2010; Musicco et al., 2010), and also global cognition (Sarazin et al., 2005; Atchinson et al., 2004; Buccione et al., 2007) have been found to predict the progression rate of AD symptoms. Although the short version of the CERAD-NB explained the progression of AD symptoms better than the MMSE or the CERAD-NB did, its predictive accuracy was moderate (less than 40 %). Therefore, to predict the progression of AD symptoms soon after diagnosis, information about cognitive performance should be supplemented with information about different AD symptoms and comorbidities.

6.2 THE EFFECT OF A PSYCHOSOCIAL INTERVENTION PROGRAMME ON ALZHEIMER'S DISEASE

6.2.1 Intervention to delay institutionalisation

Previous results of interventions to delay nursing-home placement have been contradictory. The meta-analyses and reviews conducted on various interventions and outcome measures suggest that specific interventions are effective on specific targets and that only multicomponent interventions have had an effect on institutionalisation. However, it is to be noted that meta-analyses such as Pinquart & Sörensen (2006), Olarazan et al. (2010), and Vugt et al. (2013) have evaluated only a limited number of studies. Study IV brought out no effect of early psychosocial rehabilitation on delaying nursing-home placement. The result concurs with those of recent studies by Brodaty et al. (2009) and Phung et al. (2013), in which no long-term effects of psychosocial intervention on nursing-home placement or on other outcome measures were found. The intervention procedures, the follow-up times, and the participant selection in Phung et al. (2013) were similar to those in this study. Thus the inconsistent results obtained in other studies may be a consequence of different participant selection and different intervention procedures. Also, the decade in which the studies were conducted is probably of importance, for diagnostic procedures, treatment and care, and knowledge and attitudes have changed since the days of the older studies mentioned. Pinquart & Sörensen (2006) point out that some interventions may prepare the caregivers for the institutionalisation of the person with AD. In this study it was also noticed that the persons with AD lived at home with a family caregiver rather a long time. Indeed, one might ask whether it is a realistic idea at all to prolong the period of home care by means of intervention. Many authors emphasise that an intervention or a follow-up intended to assess the support needed should last long enough, be continuous, and be individually tailored. On the basis of previous studies and reviews,

the results of this study, and the findings of Välimäki et al. (2014), one may propose a combination of regular follow-up and individually tailored support, which takes account of the needs of the person with AD and the family caregiver.

6.2.2 The effect of intervention on Alzheimer's disease-related symptoms

In Study IV, no effect of the psychosocial intervention on the progression of AD-related symptoms was found, which was in line with recent studies by Phung et al. (2013) and Brodaty et al., (2009). There is evidence that intervention can have an effect on neuropsychiatric symptoms (Spira et al., 2006), cognition (Spector et al., 2012), and ADL (Olazaran et al., 2010), but in these studies the interventions focused specifically on these particular outcomes. Even though the intervention group and the control group were equal at the baseline visit, members of the intervention group appeared in Study IV to have a faster progression of AD symptoms on average than those of the control group. The caregivers of the intervention group rated the activities of daily living and the severity of AD of their family members as worse than those of the control group. Possibly, the caregivers who received more information became more sensitive to AD-related symptoms. Then again, the same difference in the progression of AD-related symptoms was also noted in the objective measures (the MMSE and the CERAD-NB). In spite of these negative intervention effects, it was noticed that the patient-caregiver dyads in the intervention group dropped out of the study less frequently. It is a moot point, though, whether this was due to good experiences acquired from the intervention. In Phung et al.'s study (2013), too, the participants felt that they had benefited from the intervention even though no quantitative effects were found.

6.3 THE CERAD NEUROPSYCHOLOGICAL BATTERY AS A FOLLOW-UP TOOL

In the present study, the CERAD-NB total score was used as a follow-up measure of global cognitive deterioration in persons with very mild or mild AD. Originally, the CERAD-NB (Welsh et al., 1994) was developed to distinguish AD-related cognitive disturbances from changes in cognitive performance occurring in normal aging. In Finland, as in some other countries, the CERAD-NB has been established as a screening tool to detect cognitive difficulties earlier than can be done with the MMSE, and it has been used widely as a screening method in primary health care (Hänninen et al., 1999; Sotaniemi et al., 2012). The use of the total score, developed later (Chandler et al., 2005), has simplified the use of the CERAD-NB, especially in research settings, relative to the use of the individual subtests, but only a few studies (Rossetti et al., 2010; Seo et al. 2010) have analysed the usability of the CERAD-NB total score in follow-up studies of AD. However, especially in clinical practice the whole CERAD-NB total score is time-consuming and may distress persons with AD. There was therefore a need to develop a short version of the CERAD-NB for use alongside the commonly used but also criticised (Atchinson et al., 2004; Clark et al., 1999; Galasko et al., 2000) MMSE test.

6.3.1 The use of the CERAD Neuropsychological Battery total score

Both at baseline and during the follow-up, the CERAD-NB total score correlated strongly with other cognitive and global measures but not with the measure of neuropsychiatric symptoms; this was as expected. The CERAD-NB total score was more sensitive than the MMSE in distinguishing the CDR stages, and it did not show floor or ceiling effects. At every follow-up visit in Study II, the CERAD-NB indicated that the differences in cognition between the two groups with different severity of dementia at baseline (CDR 0.5 and CDR 1) remained but that the rates of decline were identical. These results are in line with previously reported ones (Rossetti et al., 2010; Seo et al., 2010) and support the use of the

CERAD-NB total score not only as a screening tool but also as a suitable and sensitive follow-up tool for measuring global cognition during the progression of AD.

6.3.2 The use of the subtests of the CERAD Neuropsychological Battery

Generally, performance in all the subtests declined during the three years in Study III. An explorative short version of the CERAD-NB was drawn up, including the MMSE, verbal fluency, constructional praxis, and the clock-drawing test, and this subtest combination was found to get support from previous cross-sectional studies (Barth et al., 2005; Bertolucci et al., 2001; Welsh et al., 1992; Pinto et al., 1999). These subtests measure executive functions and visuospatial skills, and in a recent meta-analysis an association was found between executive functions and activities of daily living in dementia (Martyr & Clare, 2012), and visuospatial skills have also been found to be associated with the progression of functional decline (Atchinson et al., 2007). These findings support the interpretation that the test results from the new short version of the CERAD-NB may reflect the person's ability to carry out daily functions. Although memory problems are the first signs of the disease, test results derived from other cognitive domains may be more useful for monitoring the progress of the disease, as pointed out by Welsh et al. (1992). The test of verbal fluency and the clock-drawing test were the only subtests that were not associated with education, which makes the interpretation of their results easier.

6.3.3 The new short version of the CERAD Neuropsychological Battery

In Study III, a new short version of the CERAD-NB was developed and found to be more comprehensive than the MMSE alone while yet relatively brief and easy to administer. It may facilitate the following up of the progression of AD by providing a tool for assessing the progression of cognitive deficits. Thus it may be applied to the planning of treatment and care, for instance. However, this explorative model must be tested with other samples to establish its usability. It should also be kept in mind that these results concerning cognitive assessment do not reduce the need of multifaceted evaluation, including information about the functional ability, psychological and behavioural symptoms, and the life situation of the person with AD, as well as the family caregiver's situation, in the monitoring of the progression of AD in clinical and research settings.

6.4 STRENGTS AND LIMITATIONS OF THE STUDY

The ALSOVA Study, a prospective, randomised, and controlled trial of early psychosocial intervention for persons with very mild or mild AD and their caregivers with a relatively long follow-up, was one of the largest published. The participants were recruited soon after their diagnosis and were treated within the regular health care system, including treatment with AD-targeted medication. The study population was homogeneous, representing persons with AD living at home with their caregivers and normal heath-care support. Persons with other neurodegenerative diseases or more severe AD at baseline, as well as persons with comorbidities that could affect cognition, were excluded.

This study set out to add to our knowledge of the progression of cognitive deficits and clinical symptoms in persons with very mild or mild Alzheimer's disease. Several different measures were used simultaneously, including a more extensive evaluation of cognition than is often used, in a fairly large study population with a longitudinal design. The measures used were validated and well known, and they have been used with other populations and cultures and in clinical practice.

There are certain limitations in this study. The course of AD is usually longer than three years (American Psychiatric Association, 2013), so that most participants still had mild AD at the end of the study. A longer follow-up would provide more information about the

severe phase and the last years of the course of AD, but then, matters such as the drop-out rate and the ability of persons with moderate and severe AD to perform cognitive tests might become problems. All the participants and their caregivers participated in this longitudinal intervention study voluntarily, which may have produced a selection bias. The participants were required to have a family caregiver and not to have severe problems with vision or hearing or other conditions that could have affected their cognition. Because of that and the homogeneity of the population in terms of all having a recently diagnosed very mild or mild AD, the results may not be generalisable to persons with more advanced AD, persons with comorbid conditions, or persons living alone or in nursing homes. The educational level of older persons in Finland is often lower than that in other Western countries, which needs to be considered in the interpretation of education-related results. The participants of the intervention group dropped out more seldom than those of the control group. This may have caused a higher proportion of persons with more severe symptoms in the intervention group at the end of the study, which may have affected the group comparisons in Study IV.

Before the data for Study III was analysed, all CDR stages were re-calculated, which resulted in changing the classification of some borderline cases. In Study III, the CDR 0.5 group was more highly educated than the CDR 1 group, which had not been the case in Study I. It is possible that some highly educated persons were classified to have mild AD because of a notable decline in their memory from the baseline level even though their functional ability was still fairly good because of a cognitive reserve. However, this did not affect the continuous CDR-sb variable.

It should also be acknowledged that in the measuring of variables that were not directly observable, the measures themselves posed some possible limitations. The group differences, or lack of them, obtained in the CERAD-NB subtests may reflect not only the nature and progression of AD but also the properties of the measures. The decline of scores found in some subtests came close to showing a floor effect during the three-year follow-up, which was in line with the results reported by Welsh et al. (1991). In contrast, the decline in some other subtests was slow, especially in the CDR 0.5 group.

During the three-year follow-up, almost a half of the participants dropped out, as might have been expected of this age group (e.g., Phung et al., 2013), which could have led to a bias in the results. Even though the drop-out rate was so high, the GEE modelling method was used in Study III. The advantage of this method is its capability to use all available longitudinal data. Other statistical methods often require complete data on every subject, or else the subject must be excluded from the analysis.

In the ALSOVA Study, the persons with AD were required to have a family caregiver who had regular contacts with the person, and the end-point of the study was institutionalisation, which may limit the generalisability of the results. On the other hand, these specifications enabled us to collect interview data on the subjects' actual functional ability at home. Furthermore, one aim of the study was to evaluate the progression of AD-related symptoms in persons with mild AD who lived at home by means of help from their family caregivers. Thus the results may not be generalisable to persons living alone or in nursing homes.

6.5 SUGGESTIONS FOR FUTURE RESEARCH

The emphasis of research in recent years has been on early detection of AD. Less attention has been paid to assessing the progression of the disease, which is, after all, essential for the planning of functional treatment and care. The measurements used are rather variable, and the follow-up periods are often quite short. In this study, a new short version of the CERAD-NB was put forward, but its usability needs to be tested on another

population. So does its accuracy of assessment and prediction at the level of the individual patient.

The associations of global cognition and neuropsychiatric symptoms with the activities of daily living raise the interesting question of whether these associations can be accounted for by some specific domains. A further interest is whether there are correlations to be found between some specific cognitive and neuropsychiatric domains.

The participants of this study had been advised to use AD-targeted medication. It would also be of interest and value to investigate how the use of other medications, especially psychopharmacon, relates with cognition.

For modelling and predicting the progression of AD-related symptoms after diagnosis, it would be interesting to improve the existing models by applying multiple domains. For example, information on cognition, the activities of daily living, neuropsychiatric symptoms, comorbidities, use of medication, the social and health-care resources available, and caregiver-related factors could be analysed all at the same time.

On the basis of the results of this study, it may be concluded that the multifaceted psychosocial intervention did not delay the nursing-home placement or affect the AD-related symptoms of the subjects. Even so, the fact that the drop-out rate was lower in the intervention group, the experiences gained from clinical practice, and the qualitative analyses carried out on the ALSOVA data (Välimäki 2012) suggest that help and support is needed for persons with AD and their families. It is necessary to develop and evaluate an individually tailored support programme, which takes into account the needs of both the person with AD and the caregiver. Besides, the utililisation rates of social and health-care services could be analysed so as to assess the cost-effectiveness of the intervention provided.

6.6 IMPLICATIONS FOR HEALTH CARE

In clinical practice, as in research, a great deal of attention has been paid to early detection of AD. But that is not enough. After the diagnosis, the person must not be left alone but needs to be followed up regularly. Appropriate support, treatment, and care should be provided for persons with AD and their families alike. This study provides new insights into the progression of symptoms in AD during three years after the diagnosis in persons treated in the Finnish health-care system. These results may help clinicians to inform persons with AD and their caregivers on the progression of the disease during the first few years after the diagnosis. The results may also enable clinicians and decision-makers to plan better treatment and care and evaluate their effectiveness from the point of view of both the individual and the society. Especially when these results are combined with other results from the ALSOVA Study, such as those concerning the use of medication, quality-of-life aspects, neuropsychiatric symptoms, the use of resources, and caregiver-related factors, a versatile and unique model of the progression of AD can be provided for research, clinical, and societal use.

In this study, persons with very mild AD at baseline showed a slower decline of daily functions and fewer neuropsychiatric symptoms than persons with mild AD at baseline did. These findings emphasise the significance of early diagnosis. They also point at the importance of using sensitive methods to measure cognition and assess the neuropsychiatric symptoms and the activities of daily living both at the diagnostic visit and during the follow-up. The new short version of the CERAD-NB (including the MMSE) could improve the follow-up assessments of the progression of AD-related symptoms in clinical settings as well.

The results of this study do not support the recommendation to automatically offer early intensive psychosocial intervention to all persons with very mild or mild AD and their

caregivers. The life situation and needs of both the person with AD and the caregiver need to be evaluated and individually tailored help and support be offered.

7 Conclusions

1. Cognitive performance, as assessed with the CERAD-NB total score and the MMSE, was associated with the severity of dementia and the activities of daily living in persons with very mild or mild AD. It did not correlate, however, with neuropsychiatric symptoms. Both cognitive deficits and NPS were associated with the person's ability to manage everyday life activities (Study I).
2. During the three-year follow-up, progressive deterioration was observed in cognitive functions and the activities of daily living, and increases were noted in neuropsychiatric symptoms. The decline of ADL functions was slower in persons with very mild AD at baseline. The CERAD-NB total score correlated with other cognitive and functional measures, lacked ceiling or floor effects, and outperformed the MMSE in distinguishing the severity stages of dementia; it was thus considered to be a suitable tool for longitudinal AD trials (Study II).
3. The combination of the MMSE and the CERAD-NB subtests of verbal fluency, constructional praxis, and clock-drawing had the highest correlation with the severity of dementia during the three-year follow-up. The baseline values of this shortened version of the CERAD-NB, with demographical characteristics, accounted for approximately 40 % of the progression of the disease (Study III).
4. The study did not show any long-term effect of early psychosocial intervention on nursing-home placement, the progression of AD-related symptoms, behavioural symptoms, or the quality of life in persons with very mild or mild AD (Study IV).

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Ilona Hallikainen

Cognitive Performance and Progression of Alzheimer's Disease: measurement and intervention

The ALSOVA Follow-up Study

In recent years, the emphasis in research and clinical practice concerning Alzheimer's disease (AD) has been on early detection of the disease. Besides that, ways of measuring the progression of AD-related symptoms and providing support after the diagnosis are also needed. In this study, cognition, activities of daily living, neuropsychiatric symptoms, and the severity of the disease in persons with very mild or mild AD at baseline were followed up for three years, and the usability of the CERAD Neuropsychological Battery as a follow-up method was evaluated. Furthermore, the study analysed the effects of early psychosocial intervention on institutionalisation and AD-related symptoms.

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