Early diagnosis of Alzheimer’s disease (AD) and an early onset of AD-targeted medication to promote and maintain the Quality of Life (QoL) are among the main aims in AD patient care. This five-year follow-up study compared self- and caregiver-rated AD patient QoL measures in relation to disease progression and examined the ability of patients to complete QoL questionnaires with or without assistance. Furthermore, the study examined the prevalence and significance of neuropsychiatric symptoms with an emphasis on their influence on the QoL of AD patients.
Quality of life and neuropsychiatric symptoms in patients with Alzheimer’s disease – The ALSOVA follow-up study
KRISSIINA HONGISTO

Quality of life and neuropsychiatric symptoms in patients with Alzheimer’s disease – The ALSOVA follow-up study

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ABSTRACT
Alzheimer’s disease (AD) is characterized by progressive cognitive impairment together with declining activities of daily living, neuropsychiatric symptoms (NPS), and behavioral changes. Early diagnosis of AD and an early onset of AD-targeted medication to promote and maintain the Quality of Life (QoL) are among the main aims in AD patient care.

The aims of this doctoral study were to compare self- and caregiver-rated patient QoL measures in relation to disease progression and examine the ability of patients to complete QoL questionnaires with or without assistance. Additional aims were to examine the prevalence and significance of NPS in patients with very mild and mild AD with an emphasis on their influence on the QoL of AD patients, and furthermore, to investigate the association of self- and caregiver-rated patient QoL with NPS of patients at baseline and during a five-year follow-up.

This study formed part of the ALSOVA project, conducted by the Department of Neurology, University of Eastern Finland. The participants were 236 patients with very mild (CDR 0.5) or mild (CDR 1) AD and their caregivers from three Finnish hospital districts. Participants were recruited during the first year after the AD diagnosis and then followed-up annually for three years after an initial baseline visit, with an additional fifth-year visit. At baseline, 5 of the 241 examined patients were excluded from the follow-up.

NPS were common, even in the early stages of AD. The most frequent symptoms were apathy, depression, irritability, and agitation. The strongest predictor of decreased self-reported QoL-AD scores was depressive symptoms, whereas functional decline and the presence of NPS predicted poor patient QoL rated by caregivers. The ability of patients to complete QoL questionnaires with or without assistance declined at early moderate stage of AD, and the self- and caregiver-rated QoL scores began to diverge in patients with very mild AD. Over the 5-year follow-up period, patient self-reported QoL did not change significantly, despite the progression of AD and increase in NPS. However, caregiver-rated patient QoL declined significantly during the follow-up as the disease progressed and total NPI scores increased.

In conclusion, the ability of AD patients to complete QoL questionnaires diminishes earlier than previously estimated. Moreover, the patients themselves are unable to notice the deterioration in their QoL, even with severe AD-related symptoms. However, caregiver-rated QoL-AD scores correlated well with disease progression and increased NPS.
National Library of Medicine Classification: WA 30, WT 120, WT 150, WT 155, WY 200
Medical Subject Headings: Activities of Daily Living; Alzheimer Disease; Apathy; Caregivers; Cognition Disorders; Cognitive Dysfunction; Depression; Disease Progression; Early Diagnosis; Follow-Up Studies; Irritable Mood; Prevalence; Quality of Life; Self Report
TIIVISTELMÄ

Alzheimerin taudille (AT) ovat tyypillisiä etenevät vaikeudet muistitoiminnoissa, päivittäisen toimintakyvyn heikkeneminen ja käytös- ja mielialaonireiden esiintyminen. Alzheimerin tautia sairastavien hyvän hoidon tavoitteena ovat sairauden mahdollisimman varhainen toteaminen, lääkehoidon varhainen aloittaminen ja elämänlaadun yllämpytäminen.

Tämän väitöskirjan tarkoituksena oli selvittää hyvin lievää (CDR 0.5) ja lievää (CDR 1) AT:ta sairastavien henkilöiden elämänlaatua ja neuropsykiatrisia oireita AT:n diagnossivaiheessa ja sairauden edetessä. Lisäksi verrattiin potilaan ja omaisen arvioimana potilaan elämänlaatua suhteessa sairauden vaikeustaseeseen ja selvitettiin potilaan kykyä vastata elämänlaatuun mittaaviin kysymyksiin itsenäisesti tai autettuna. Viiden vuoden seurantatutkimuksen tavoitteena oli myös selvittää neuropsykiatristen oireiden vaikutusta potilaan elämänlaatuun potilaan insensä ja omaisen arvioimana.


Potilaan kyky arvioida tilaansa heikkeni aiempaa arvioitua enemmän. Tämän vuoksi terveydenhoitohenkilöstön tulisikin nykyistä enemmän hyödyntää potilaan hyvin tuntevan omaishoitajan näkemystä potilaan terveydentilasta ja elämänlaadusta.

Luokitus: WA 30, WT 120, WT 150, WT 155, WY 200
Yleinen suomalainen asiasanasto: Alzheimerin tauti; apatia; arviointi; elämänlaatu; kyselytutkimus; käyttävyys; masennus; mieliala; muistihäiriöt; oireet; omaishoitajat; potilaat; seurantatutkimus; toimintakyky
To my Family
Acknowledgements

The ALSOVA study was conducted by the Neurology Unit of the University of Eastern Finland (UEF) and Neuro-Center of Kuopio University Hospital during the years 2001-2014 in collaboration with North Carelian Central Hospital, Jyväskylä Central Hospital, UEF Departments of Nursing Science, Psychology, Health and Social Management, and Pharmacoeconomics and the Outcomes Research Unit. I want to sincerely thank all the patients and their caregivers who participated in the ALSOVA study for their time and effort.

Combining research, teaching, working at the memory clinic, and having a baby during this dissertation project has been extremely interesting and challenging. This work would not have been possible without numerous people. I am very grateful to everyone who helped, guided, and encouraged me during these years.

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I would like to honor the memory of Professor Tuula Pirttilä (†2010), who originally led the ALSOVA study and kindly offered me a place in her research group. Here support and excellent guidance in the early stages of my studies was invaluable.

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I would like to warmly thank all the members of the ALSOVA Study Group. It has been such a pleasure to be a researcher in this group, to know that I am not alone. I especially want to thank my co-authors, Ilona Hallikainen, PhD, Adjunct Professor Janne Martikainen, PhD, Tuomas Selander, MSc, Soili Törmälehto, MSc, Tarja Välimäki, PhD, and Saku Väätäinen, MSc, for scientific insight, statistical assistance, contributions to the original publications, and all their help, support and nice company during these years.

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Kuopio, January 2017

Kristiina Hongisto
List of original publications

The dissertation is based on the following original publications, which are referred to in the text by their Roman numerals:


*) The authors contributed equally

The publications were adapted with the permission of the copyright owners.
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Abbreviations

AD                      Alzheimer’s Disease
ADCS-ADL       Alzheimer’s Disease Co-operative Study - Activities of Daily Living
ADL                    Activities of Daily Living
ALSOVA            Alzheimerin taudin sopeutumisvalmennustutkimus
                        (Psychosocial intervention study in Alzheimer’s disease)
CDR                    Clinical Dementia Rating
CDR-SOB           Clinical Dementia Rating- Sum of Boxes
CSF                     Cerebrospinal fluid
CT                       Computer Tomography
IADL                   Instrumental Activities of Daily Living
MCI                     Mild Cognitive Impairment
MMSE                 Mini-Mental State Examination
MRI                     Magnetic Resonance Imaging
NFT                     Neurofibrillary tangle
NPI                      Neuropsychiatric Inventory
NPS                     Neuropsychiatric symptoms
PET                     Positron Emission Tomography
QoL-AD                Quality of Life in Alzheimer’s Disease
VAS                    Visual Analogue Scale
1 Introduction

Alzheimer's disease (AD) is the most common etiology of dementing disorders, accounting for 60 to 80 percent of all cases. AD has become a major public health concern worldwide with the aging of population, because of its increasing prevalence, serious consequences for patients, and burden on caregivers (Conde-Sala et al., 2009). AD is characterized by cognitive impairment, functional limitations, and behavioral and psychological symptoms (Naglie et al., 2011).

In Finland, approximately 80,000 people have AD and 9000 people receive an AD diagnosis each year (National Dementia Action Plan 2012-2020, Finnish Ministry of Social Affairs and Health).

Early diagnosis of AD ensures that persons with AD can receive available drug and non-drug therapies that maintain their cognition and preserve daily functioning, prevent neuropsychiatric symptoms (NPS), reduce the caregiver burden, enhance the quality of life (QoL), and delay institutionalization (Alzheimer’s Disease International; World Alzheimer Report 2011). Nowadays, the early diagnosis of AD and the onset of AD-targeted medication to promote and maintain QoL are among the main aims in AD patient care. QoL is a multidimensional and complex concept including aspects of physical, psychological, and social functioning (Vogel et al., 2006; Sousa et al., 2013). QoL can be estimated subjectively or objectively, but it is primarily a subjective phenomenon, which encompasses “how good” a person’s life is overall. There have been hardly any Finnish and only a few international longitudinal follow-up studies on the QoL of AD patients in relation to disease severity and the factors related to the change in QoL.

NPS such as apathy, depression, agitation, and irritability are common manifestations of AD (Vogel et al., 2010; Steinberg et al., 2014). Almost all patients with AD develop NPS during their disease (Aalten et al., 2007; Lyketsos et al., 2011). Agitation, irritability, anxiety (Shin et al., 2005; Huang et al., 2012; Khoo et al., 2013), aggression (Shin et al., 2005), sleep disorders, delusion, and hallucinations (Allegrì et al., 2006; Huang et al., 2012), are among the most challenging and distressing symptoms from the caregivers’ perspective. NPS are associated with functional decline (D’Onofrio et al., 2012), increased mortality, hospital stays (Wancata et al., 2003), caregiver burden and depression, earlier institutionalization, and a significant increase in the cost of care (Gauthier et al., 2010; Vogel et al., 2010). NPS also significantly influence the QoL of AD patients according to both the patients and their caregivers (Shin et al., 2005; Hurt et al., 2008; Gomez-Gallego et al., 2012).

This study formed part of the multidisciplinary, five-year ALSOVA follow-up study, which was conducted by the Unit of Neurology, School of Clinical Medicine, University of Eastern Finland (UEF) and Neuro-Center of Kuopio University Hospital in collaboration with North Carelian Central Hospital, Jyväskylä Central Hospital, UEF Departments of Nursing Science, Psychology, Health and Social Management, and the Pharmacoeconomics and Outcomes Research Unit. The aim of this study was to examine
the QoL of patients with very mild or mild AD at the time of diagnosis and the change in QoL in relation to disease progression during a five-year follow-up period. Furthermore, the association of NPS with QoL in AD patients was evaluated, as well as the ability of patients to complete QoL questionnaires with or without assistance. This study focused on providing new information on the life of AD patients as the disease progress, and on improving patient QoL and preventing early institutionalization.
2 Review of the literature

In 1906, the German psychiatrist and neuropathologist Alois Alzheimer described the case of Auguste D., a patient who had suffered from progressive memory loss, sleep disturbance, hallucinations, and delusions. He was the first clinician who connected these symptoms to microscopic brain changes at autopsy, such as significant shrinkage and abnormal deposits in and around nerve cells (Alzheimer’s Association, http://www.alz.org). Alzheimer’s disease (AD) was first named in 1910 in the Handbook of Psychiatry by Emil Kraepelin, a German psychiatrist who worked with Dr. Alzheimer (Maurer et al., 1997; Hippus et al., 2003). In 1976, Alzheimer's disease was recognized as the most common cause of dementia and a major public health challenge by neurologist Robert Katzman (Alzheimer’s Association, http://www.alz.org).

2.1 EPIDEMIOLOGY OF ALZHEIMER’S DISEASE

2.1.1 Incidence and prevalence

A rising life expectancy is associated with an increased prevalence of chronic diseases such as dementia. The most common form of dementia is AD, accounting for 60% to 80% of all the dementia cases (Figure 1). Worldwide, 47 million people have dementia, and there are 9.9 million new dementia cases every year, implying one new case every 3 seconds. The number of people with dementia is projected to reach 75 million in 2030, and 135 million in 2050 (World Health Organization, 2015).

The incidence of dementia increases with age. It doubles with every 6-year increase in age, from 4 per 1000 person years at age 60-64 to 105 per 1000 person years at age 90 and over. In Asia, the peak number of new dementia cases is among people aged 75-84 years, while in Africa it is among people aged 65-74, and in Europe and the Americas among people aged 80-89. Almost 50% of the new dementia cases occur in Asia, 25% in Europe, 18% in the Americas and 8% in Africa. The incidence of new dementia cases has increased in Asia, Africa and the Americas, but is decreasing in Europe (Alzheimer’s Disease International, World Alzheimer Report 2016).

In Finland, there are approximately 9000 new AD diagnoses each year. It has been estimated that 80 000 people in Finland have AD (National Dementia Action Plan 2012-2020, Finnish Ministry of Social Affairs and Health).

AD can be divided into familial or sporadic and early-onset or late-onset form. Up to 5% of AD patients have the early-onset disease form (onset before at the age of 65 years). It is still unclear what exactly causes AD. In early-onset AD, genetic mutations are more common. Late-onset (onset at the age of 65 years or later) AD can be sporadic or familiar, and arises from a complex series of brain changes that occur over decades (National Institute of Aging, Alzheimer’s Disease Education and Referral Center).
2.1.2 Risk -and protective factors

The exposure to different factors over the life span determines the risk of AD. The effect of risk or protective factors largely depends on age. Therefore, a life-course perspective is appropriate for chronic disorders such as AD, which have a long latent period (Mangialasche et al., 2012). Several factors may increase or decrease a person’s risk of developing AD. These factors include age, genetics, and lifestyle, as well as vascular and metabolic factors (Table 1). The importance of these factors may differ between individuals. Some risk factors for AD are modifiable through pharmacological treatment and lifestyle alterations, while others are non-modifiable, such as age and genetics (Alzheimer’s Association, http://www.alz.org; Sindi et al., 2015).

The main risk factor for AD is advancing age (Kivipelto et al., 2006). Risk genes, such as apolipoprotein E-e4 (Corder et al., 1993; Saunders et al., 1993; Tang et al., 1998), increase the likelihood of developing AD. The effect of apolipoprotein E-e4 is partly determined by other risk factors. The mutations of deterministic genes, such as amyloid precursor protein (APP), presenilin-1 (PS-1), and presenilin-2 (PS-2) (Hardy, 1997; Selkoe, 2002) in most cases leads to AD. Cardiovascular, metabolic and lifestyle risk factors include elevated blood pressure, high cholesterol levels (Kivipelto et al., 2001, 2002, 2006; Solomon et al., 2009; Meng et al., 2014), diabetes (Ahtiluoto et al., 2010; Huang et al., 2014), obesity (Whitmer et al., 2007; Tolppanen et al., 2014,2015; ) and work-related stress (Sindi et al., 2016) in midlife, a low educational level (<10 years of education) (Kivipelto et al., 2006, Exalto et al.,

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Figure 1. The prevalence of the most common memory disorders according to National Current Care Guidelines.
Head trauma has also been identified as a risk factor for developing AD later in life (Plassman et al., 2000; Shively et al., 2012; Exalto et al., 2014).

Protective factors for AD appear to be a healthy diet (i.e. low amounts of saturated fatty acids, fish, vegetables, fruits, nuts) (Solfrizzi et al., 2011; Ngandu et al., 2015; Morris et al., 2015), physical exercise (Rovio et al., 2005; Lautenschlager et al., 2008; Sattler et al., 2011; Ngandu et al., 2015), cognitive training (Ngandu et al., 2015), increased educational and occupational attainment (Stern et al., 1994; Sattler et al., 2012) and social activity (Fratiglioni et al., 2004; James et al., 2011; Sattler et al., 2012).

During the past decades, several other factors have also been suggested to be protective for AD. However, thus far, none of the studies have convincingly demonstrated that, for example, a single-drug such as NSAIDs, hormone replacement treatment, statins, vitamins or the ginkgo biloba extract works in prevention if the outcome is AD incidence (Breitner et al., 2011; Vellas et al., 2012). The only exception from that is anti-hypertensive medication, while there is evidence for their protective effect against AD (Peters et al., 2008).

At the moment, there are three ongoing large multidomain randomized controlled trials in Europe; the Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER) (Kivipelto et al., 2013), the Multidomain Alzheimer Prevention Trial (MAPT) (Carrié et al., 2012), and the Prevention of Dementia by Intensive Vascular Care (PreDIVA) (Richard et al., 2009) study. These studies are specifically focused on identifying successful preventive strategies fitted to different groups of people (groups defined for instance, according to age, biological markers, cognitive status, lifestyle, vascular or metabolic profiles) at risk of dementia (Mangialasche et al., 2012; Solomon et al., 2014).
Table 1. The risk and protective factors for AD according to current publications.

<table>
<thead>
<tr>
<th>Risk factors</th>
<th>Protective factors</th>
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<tr>
<td><strong>Advanced age</strong></td>
<td></td>
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<tr>
<td><strong>Genetic factors:</strong></td>
<td><strong>Genetic factors:</strong></td>
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<tr>
<td>Apolipoprotein E-e4 allele</td>
<td>Apolipoprotein E-e2 allele</td>
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<tr>
<td>Family history of AD</td>
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<tr>
<td><strong>Vascular and metabolic:</strong></td>
<td><strong>Vascular and metabolic:</strong></td>
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<tr>
<td>High blood pressure in middle age</td>
<td>Adequate treatment of high blood pressure</td>
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<tr>
<td>High cholesterol levels in middle age</td>
<td></td>
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<tr>
<td>Diabetes in middle age</td>
<td><strong>Lifestyle:</strong></td>
</tr>
<tr>
<td>Metabolic syndrome</td>
<td>Healthy diet</td>
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<tr>
<td>Cerebrovascular diseases</td>
<td>Physical activity</td>
</tr>
<tr>
<td><strong>Lifestyle:</strong></td>
<td>High educational level</td>
</tr>
<tr>
<td>Smoking</td>
<td>Wide social network</td>
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<tr>
<td>High alcohol consumption</td>
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<td>Diet with high amounts of saturated fatty acids</td>
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<td>Obesity</td>
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<td>Low physical activity</td>
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<td>Low educational level</td>
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<td>Loneliness, lack of social networks</td>
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<tr>
<td><strong>Other:</strong></td>
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<td>Traumatic brain injury</td>
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</table>
2.2 PATHOGENESIS OF ALZHEIMER’S DISEASE

2.2.1 Pathogenesis in general
AD is a chronic progressive neurodegenerative disorder in which pathogenesis is multifactorial. Several mechanisms have thought to account for the connection between AD pathophysiology and genetic and environmental factors (Orsucci et al., 2013). AD causes significant disruption of normal brain structure and function (Alzheimer’s Association, 2015, http://www.alz.org). Macroscopically seen changes in the brain include cortical atrophy and ventricular dilatation. Neuropathological hallmarks of AD consist of amyloid plaques, formed of extracellular amyloid β peptide aggregates (Masters & Selkoe 2012), and intracellular neurofibrillary tangles (Hardy and Selkoe, 2002; Montine et al., 2012) (Figure 2). Neuronal and synapse loss also present as the disease progresses. The synapse loss related to cognitive decline occurs both in the hippocampal structure and neocortex (Scheff et al., 2016). It is assumed that the important early events which lead to disease progression and synaptic dysfunction are microtubule changes and oxidative damage (Scheff et al., 2016).

According to recent studies, in addition to amyloid β plaques and neurofibrillary tangles, microglial activation and neuroinflammation has a significant role in neuropathology of AD (Lyman et al., 2014; Calsolaro & Edison, 2016). In central nervous system, microglial cells and astrocytes are the main types of cells in charge of the inflammatory response. Patients with AD have increased levels of pro-inflammatory cytokines in brain tissue and serum compared to healthy people. In AD patient’s brain also occurs amyloid β deposits in T-cells and activated microglial cells and reactive astrocytes, as well as microglial cells enclosing amyloid plaques in cerebral cortex (Calsolaro & Edison, 2016). Neuroinflammatory response causes synaptic impairment and neuronal death (Lyman et al., 2014).

![Figure 2. Biomarkers and development of AD. Adapted from Jack et al. 2010](image-url)
2.2.2 The amyloid cascade
The earliest pathological event in AD is cerebral amyloid β aggregation (Jansen et al., 2015). The prevalence of cerebral amyloid pathology specified by positron emission tomography (PET) imaging or cerebrospinal fluid (CSF) analyses among healthy people have shown that there is a 20- to 30-year interval between the first signs of amyloid positivity and the onset of AD (Jack et al., 2010; Braak and Del Tredici, 2015; Jansen et al., 2015) (Figure 2). The neuropathological changes are characterized by extracellular deposition of the amyloid β peptide in senile plaques. Amyloid can appear in non-fibrillary diffuse plaques or a fibrillary form with dystrophic neurites causing neuritic plaques. Amyloid β deposition is related to microglial and astrocytic activation, oxidative stress, synaptic dysfunction and the development of intracellular neurofibrillary tangles (Hardy and Selkoe, 2002; Parihar and Brewer, 2010; Mosconi et al., 2010). This process leads finally to neurotransmitter deficits, synaptic dysfunction, loss of neurons, and the development of AD. However, the total amyloid β load correlates only weakly with the clinical manifestations and progression of AD (Ingelsson et al., 2004; Nelson et al., 2012). In the amyloid angiopathy, amyloid is deposited in the arteries, arterioles and capillaries walls in the central nervous system. This makes the vessels very fragile and easy to rupture, causing hemorrhages or clotting of the vessels and leading to ischemic lesions.

2.2.3 Tau-pathology
Neurofibrillary tangles are intracellular aggregates of hyperphosphorylated tau protein. Normal tau protein binds transiently to axonal microtubules and stabilizes them (Ballatore et al., 2007). However, abnormal hyperphosphorylated tau forms insoluble filaments that deposit in the cell body of the neuron as neurofibrillary tangles, making straight and paired helical filaments. Neurofibrillary tangles are common in normal aging subjects and are also found in several brain diseases. Thus, neurofibrillary tangles are not specific for AD. Important factors in AD neuropathology are the density and neuroanatomic localization of neurofibrillary tangles. Widespread neocortical neurofibrillary tangles are mostly connected with AD, instead, neurofibrillary degeneration, which is limited to subcortical areas is usually age related (Braak & Del Tredici, 2011). Amyloid β protein and tau, when presenting in aggregated form are highly resistant to degradation or removal and accumulate in the brain tissue (Shen et al., 2011; Braak and Del Tredici, 2015). These aggregates are first observed in the mesial temporal cortex, hippocampus, and amygdala. With AD progression, neurofibrillary tangles are also seen in neocortical structures (Schff et al., 2016). The progression of tau pathology has showed to correlate with severity and clinical symptoms of AD (Dolan et al., 2010; Robinson et al., 2011; Nelson et al., 2012).

Hippocampal pathology and atrophy have been found to be important in early disease pathogenesis (Reitz et al., 2009). However, neocortical neuritic amyloid plaques and neocortical neurofibrillary tangles are correlating Alzheimer’s disease pathology with dementia (Braak and Braak, 1991; Mirra et al., 1991; Dolan et al., 2010).
2.3 MILD COGNITIVE IMPAIRMENT

According to the new diagnostic guidelines, AD progresses on a continuum with three stages (McKhann et al., 2011; Jack et al., 2011; Dubois et al., 2014). The first is an early, preclinical stage with no symptoms, followed by a middle stage of mild cognitive impairment (MCI) and a final stage of AD dementia. During the past decades, MCI has been actively investigated. The term MCI was invented in the late 1980s by the New York University study group to recognize persons whose cognition was not normal for their age, but they did not have developed dementia. Flicker et al. in 1991 described their outcomes in an article which examined predictors of dementia. MCI is a heterogeneous syndrome with cognitive characteristics between normal aging and dementia. MCI is defined as greater cognitive decline than expected for a particular age and educational level, but that does not notably interfere with activities of daily living and thus, criteria of dementia are not fulfilled (Gauthier et al., 2006; Forrester et al., 2015).

Petersen et al. (1997, 1999) proposed the following clinical criteria for MCI: (1) memory problems, (2) objective memory impairment, (3) absence of other cognitive disorders or repercussions on daily life, (4) normal general cognitive function and (5) no evidence of dementia. Recently it has been noted that people with MCI may not have totally adequate functional abilities, especially in the performance of instrumental activities of daily living (IADL) (Giovannetti et al., 2008; Burton et al., 2009). The latest clinical criteria for MCI suggested by Petersen (2004) and Winblad et al. (2004) have pointed out that very mild problems in instrumental activities of daily living (IADL) are consistent with MCI. The National Institute on Aging (http://www.nia.nih.gov) and the Alzheimer’s Association (http://www.alz.org) have developed diagnostic criteria for the MCI due to AD, which include the following: (1) core clinical criteria that could be used by healthcare providers without access to advanced imaging techniques or cerebrospinal fluid analysis, and (2) research criteria that could be used in clinical research settings, including clinical trials. The second criteria contain the use of biomarkers based on imaging and cerebrospinal fluid measures. However, in the DSM-5, MCI is classified as a mild neurocognitive disorder (Dillon et al., 2013).

MCI is considered to be an independent risk factor of AD (Manly et al., 2008, Forrester et al., 2015), but in fact some MCI patients might suffer from an early AD (Sperling et al., 2011). The prevalence of MCI has ranged from 3 to 19% in adults older than 65 years in population-based epidemiological studies. MCI is classified into two types: amnestic and non-amnestic. Amnestic mild cognitive impairment does not meet the criteria for dementia, although it causes clinically significant memory impairment. Non-amnestic mild cognitive impairment is defined by a decline in functions which are not related to memory, such as addressing attention, use of language, or visuospatial skills. (Petersen et al., 2001; Winblad et al., 2004). There is a high risk of progression to AD among people suffering from an amnestic subtype of mild cognitive impairment. Following persons with MCI over time, some progress to AD or other types of dementia, but some remain stable or even recover (Petersen, 2011). The annual rate of AD diagnosis for patients with MCI is approximately 10 to 15%.
Neuropsychiatric symptoms are also common in MCI. At least one neuropsychiatric symptom is present in 35–75% of MCI patients. Apathy, anxiety, depression, irritability, and agitation seem to be the most common behavioral symptoms. Less common are aberrant motor behavior, euphoria, hallucinations, and disinhibition (Apostolova & Gummings, 2008).

2.4 CLINICAL FEATURES OF ALZHEIMER’S DISEASE

AD is characterized by advanced cognitive deterioration together with declining activities of daily living and neuropsychiatric symptoms or behavioral changes. The most common early symptom of AD is the loss of short-term memory, which shows up as difficulty in remembering recently learned things and an inability to attain new information (Alzheimer’s Association, http://www.alz.org). Significant impairment of motor (apraxia), speech (aphasia), and visual skills (agnosia) often accompanies memory loss (Helmes et al., 2002).

Symptoms usually develop slowly and worsen over time. Clinical symptoms of AD are presented in Table 2. According to the Clinical Dementia Rating Scale (CDR), the severity of AD can be divided into four stages: very mild, mild, moderate, and severe. In the mild stage of AD, patients may have problems in finding the right word or name, they have difficulties in learning and remembering new information, they might lose or misplace a valuable object, they have trouble in planning or organizing activities, and it takes longer than before to accomplish normal daily tasks. Family and friends also begin to notice difficulties (National Institute of Aging, Alzheimer’s Association; American Psychological Association, APA). In the moderate stage of AD, the symptoms appear to become more noticeable to others. Patients suffer from increasing memory loss, they may be confused about the place they are or what day it is, they need help in choosing the appropriate clothing for the season or the occasion, they have an increased risk of wandering and becoming lost, and they might be suspicious and have delusions, paranoia, and sleeping disturbances. In the severe stage of AD, patients need around-the-clock assistance with daily personal care. Patients have increasing problems in communicating with other people, they lose their ability to be aware of their environment, walk, sit, and finally swallow, and they also have an increased risk of infections, especially pneumonia, which is the main cause of death among patients with AD (National Institute of Aging, Alzheimer’s Association; American Psychological Association, APA).

The rate of progression of AD varies, being approximately eight years after the diagnosis, but survival can range from four to 12 years, depending on age and other diseases (Alzheimer’s Association, http://www.alz.org)
Table 2. Clinical symptoms in different stages of AD. Adapted from National Current Care Guidelines for Memory Disorders.

<table>
<thead>
<tr>
<th></th>
<th>Very mild and mild AD MMSE 18-26, CDR 0.5-1</th>
<th>Moderate AD MMSE 10-22, CDR 1-2</th>
<th>Severe AD MMSE 0-12, CDR 2-3</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cognitive symptoms</strong></td>
<td>Slight forgetfulness, problems with episodic memory</td>
<td>Increased memory loss and confusion</td>
<td>Severe memory loss</td>
</tr>
<tr>
<td></td>
<td>Difficulties in reading and learning new things</td>
<td>Problems in finding words and speaking</td>
<td>Major problems in speaking and understand speech</td>
</tr>
<tr>
<td></td>
<td>Deterioration in executive functions</td>
<td>Difficulties in understanding visual images and spatial relations</td>
<td>Inability to communicate</td>
</tr>
<tr>
<td></td>
<td>Challenges in planning and problem-solving</td>
<td>Disorientation to time and place</td>
<td>Severe apraxia</td>
</tr>
<tr>
<td></td>
<td>Ability to concentrate declines</td>
<td>Apraxia</td>
<td>Severe concentration problems</td>
</tr>
<tr>
<td></td>
<td>Difficulties in finding words</td>
<td>Loss of insight</td>
<td>Severe difficulties in orientation to time and place</td>
</tr>
<tr>
<td></td>
<td>Difficulties in calculation</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Changes in daily life</strong></td>
<td>Troubles following and joining a conversation</td>
<td>Decreased independence in IADL</td>
<td>Assistance needed in basic ADL</td>
</tr>
<tr>
<td></td>
<td>Withdrawal from hobbies or social activities</td>
<td>Difficulties in carrying out multistep tasks, e.g. dressing</td>
<td>Incontinence of bowel and bladder</td>
</tr>
<tr>
<td></td>
<td>Difficulties in completing familiar tasks at home or at work</td>
<td>Reminding is needed to carry out basic ADL, e.g. shaving, tooth brushing, taking a shower</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Difficulties in planning financial matters and using money</td>
<td>Problems in recognizing family and friends</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Difficulties in driving by car</td>
<td>Difficulties in finding places</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Losing things or misplacing them in odd places</td>
<td>Getting lost</td>
<td></td>
</tr>
</tbody>
</table>
Table 2. Continued. Clinical symptoms in different stages of AD. Adapted from National Current Care Guidelines for Memory Disorders.

<table>
<thead>
<tr>
<th></th>
<th>Very mild and mild AD MMSE 18-26, CDR 0.5-1</th>
<th>Moderate AD MMSE 10-22, CDR 1-2</th>
<th>Severe AD MMSE 0-12, CDR 2-3</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Common neuropsychiatric symptoms</strong></td>
<td>Apathy</td>
<td>Delusions</td>
<td>Agitation</td>
</tr>
<tr>
<td></td>
<td>Depression</td>
<td>Hallucinations</td>
<td>Apathy</td>
</tr>
<tr>
<td></td>
<td>Irritability</td>
<td>Apathy</td>
<td>Aberrant motor behavior</td>
</tr>
<tr>
<td></td>
<td>Anxiety</td>
<td>Aberrant motor behavior</td>
<td>Sleep disturbances</td>
</tr>
<tr>
<td></td>
<td>Delusions</td>
<td>Sleep disturbances</td>
<td></td>
</tr>
<tr>
<td><strong>Somatic symptoms</strong></td>
<td>Weight loss</td>
<td>Weight loss</td>
<td>Extrapyramidal symptoms</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Seizures</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Difficulties in walking</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Difficulties in swallowing</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Primitive reflex</td>
</tr>
<tr>
<td></td>
<td></td>
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<td>Secondary frailty</td>
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</tbody>
</table>
2.5 NEUROPSYCHIATRIC SYMPTOMS IN ALZHEIMER’S DISEASE

Neuropsychiatric symptoms (NPS) are the non-cognitive, behavioral, and psychiatric symptoms of AD. NPS are common even in the early stages of Alzheimer’s disease (AD) (Khoo et al., 2013), and almost all patients with AD develop NPS at some stage of their disease (Aalten et al., 2007; Lyketsos et al., 2011). The frequency of NPS alternate from 60 to 90% over the course of AD (Youn et al., 2011; Balthazar et al., 2014). NPS can appear at any stage of AD, but they generally become more prevalent with the progression of the disease (Conde-Sala et al., 2016).

2.5.1 The pathogenesis and development of neuropsychiatric symptoms

The pathogenesis of NPS has not been clearly defined, but recent studies have emphasized the significance of anatomic and structural changes related to pathological features (such as neurofibrillary tangles, neuritic plaques, and loss of synaptic density) in the paralimbic, limbic, and neocortical regions (García-Alberca et al., 2014). The pathogenesis of NPS may also be associated with dysfunction of several neurotransmitter systems, e.g. cholinergic, serotonergic, noradrenergic owing to neuronal death in specific origin of transmitter nucleus (Cummings, 2000; Balthazar et al., 2013). In addition, social, environmental and psychological factors have a role (Moore et al., 2013).

Different biological, environmental, psychosocial, and psychological factors in AD lead to the development and presence of NPS (Table 3). During the course of AD, the brain pathology is progressing, which is from a biological perspective, associated with the appearance of NPS (Gauthier et al., 2010). NPS may also be an expression of physical factors, unmet psychological needs, and environmental factors. People with AD are often unable to verbalizing their needs, and might react to specific situations with behaviors that may be distressing to other persons (Moore et al., 2013).
Table 3. Factors associated with the development and presence of NPS in AD.

1. Degenerative process in brain

2. Physical factors
   - other diseases (infections, coronary heart disease, heart failure, cerebral stroke, subdural hematoma, lung dysfunction, fractures, tumors, etc.)
   - pain
   - thirst, hunger
   - obstipation/urinary retention
   - inappropriate medication
   - alcohol and drug use
   - metabolic disturbances (hyponatremia, hypo/hyperglycemia, renal dysfunction, liver dysfunction, hypo/hyperthyroidism)

3. Individual factors
   - personality
   - life history

4. Interactional factors
   - behavior distressing to other persons
   - feelings of abandonment
   - excessive demands

5. Environmental factors
   - general atmosphere
   - confusing surroundings
   - excessive noise/stimulation
   - lack of daily routine
   - inadequate lighting
2.5.2 The assessment of neuropsychiatric symptoms

The early identification of neuropsychiatric symptoms is necessary in order to receive the appropriate treatment. NPS are also the main source of caregiver burden and are closely associated with the institutionalization of AD patients (McKhann et al., 2011; Dubois et al., 2014; Sousa et al., 2016).

There are several instruments that have been used to measure neuropsychiatric symptoms (NPS). The most commonly used tool to assess NPS in AD is the Neuropsychiatric Inventory (NPI). The instruments that can be used to measure NPS are described in Table 4. There are also scales that can be used to assess different specific types of challenging behavior in more depth. These scales are, for example the Cohen-Mansfield Agitation Inventory (CMAI) (Cohen-Mansfield, 1996), Beck Depression Inventory (BDI) (Beck et al., 1961), Cornell Scale for Depression in Dementia (CSDD) (Alexopoulos et al., 1988), Geriatric Depression Scale (Yesavage et al., 1983), Apathy Evaluation Scale (AES) (Marin et al., 1991) and Apathy Inventory (AI) (Robert et al., 2002).

The detection and recognition of NPS is often based on caregiver reports. However, this may lead to bias, because those caregivers who are more burdened might report a higher frequency and severity of NPS (Stella et al., 2015). Previous studies suggest that it is quite challenging for caregivers to accept the NPS in AD patients, because these symptoms implicate constant supervising and coping skills (Truzzi et al., 2013). The Neuropsychiatric Inventory-Clinician Rating Scale (NPI-C) is a new approach (De Medeiros et al., 2009), which permits a consistent assessment of NPS, even in the early stage of AD. NPI-C scale includes a the description of the patient's symptoms by the caregiver, direct patient observation by a clinician, patient records information, and the clinician’s interpretation for each symptom based on the overall data accessed. The clinician's judgment reduces emotional and cognitive interferences, which might cause under- or overestimations of the patient’s symptoms, if the caregiver suffers from the emotional stress, displaying symptoms such as depression, anxiety, or sleep disorders (David et al., 2010).
Table 4. Assessment tools for neuropsychiatric symptoms, modified from David et al. (2010) and Gitlin et al. (2014).

<table>
<thead>
<tr>
<th>Author</th>
<th>Assessment tool</th>
<th>Items</th>
<th>Domains</th>
<th>Rater</th>
<th>Collection</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cummings, 1997</td>
<td>NPI</td>
<td>12–91</td>
<td>12 domains: delusions, hallucination, agitation, anxiety, depression, euphoria, apathy, disinhibition, irritability, aberrant motor behavior, sleep disturbances, appetite disturbances</td>
<td>Caregiver</td>
<td>Interview</td>
<td>- assess also caregiver’s distress</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>- developed for dementia syndromes</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>- widely used in clinical trials and population based studies</td>
</tr>
<tr>
<td>De Medeiros et al., 2009</td>
<td>NPI-C</td>
<td>14–142</td>
<td>14 domains: delusions, hallucination, agitation, aggression anxiety, depression, euphoria, apathy, disinhibition, irritability, aberrant motor behavior, sleep disturbances, appetite disturbances, aberrant vocalizations</td>
<td>Caregiver and clinician</td>
<td>Interview, observation, information from patient records</td>
<td>- assess also caregiver’s distress</td>
</tr>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>- rated also by clinician</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>- expanded version of the NPI</td>
</tr>
<tr>
<td>Devanand et al., 1992</td>
<td>BSSD</td>
<td>24</td>
<td>5 domains: disinhibition, apathy catastrophic reactions, indifference, sun-downing, denial</td>
<td>Caregiver</td>
<td>Interview</td>
<td>- short</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>- not widely used</td>
</tr>
</tbody>
</table>
Table 4. Continued. Assessment tools for neuropsychiatric symptoms, modified from David et al. (2010) and Gitlin et al. (2014).

<table>
<thead>
<tr>
<th>Author</th>
<th>Assessment tool</th>
<th>Items</th>
<th>Domains</th>
<th>Rater</th>
<th>Collection</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kaufer et al., 2000</td>
<td>NPI-Q</td>
<td>12 screening questions from NPI, severity, and caregiver distress</td>
<td>12 domains: delusions, hallucination, agitation, anxiety, depression, euphoria, apathy, disinhibition, irritability, aberrant motor behavior, sleep disturbances, appetite disturbances.</td>
<td>Caregiver</td>
<td>Interview</td>
<td>-brief form of the NPI</td>
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<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>-suitable for clinical practice</td>
</tr>
<tr>
<td>Reisberg et al., 1996</td>
<td>BEHAVE-AD</td>
<td>26</td>
<td>7 domains: delusions, hallucinations, activity disturbances, aggressiveness, anxiety/phobia, diurnal rhythm disturbances, affective disturbance</td>
<td>Caregiver</td>
<td>Interview</td>
<td>-suitable for clinical practice</td>
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<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>-evaluate the efficacy of AD treatment</td>
</tr>
<tr>
<td>Levin et al., 1987; Sultzer et al., 1995</td>
<td>NRS</td>
<td>28</td>
<td>6 domains: cognition, agitation/disinhibition, behavioral retardation, anxiety/depression, verbal output disturbance, psychosis</td>
<td>Patient</td>
<td>Interview</td>
<td>-measures cognitive and non-cognitive behavioral symptoms</td>
</tr>
<tr>
<td>Weyer et al., 1997</td>
<td>ADAS-cog</td>
<td>11; 8 performance-based; 3 language impairment</td>
<td>11 domains: word recall, orientation, ideational practice, drawing, commands, naming, word recognition, recall of test instructions, expressive language, language comprehension, word finding difficulties</td>
<td>Patient and caregiver</td>
<td>Interview, observation</td>
<td>-cognitive section</td>
</tr>
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<td></td>
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<td></td>
<td></td>
<td></td>
<td>-widely used in clinical trials</td>
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<tr>
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<td></td>
<td></td>
<td></td>
<td>-evaluate the efficacy of AD treatment</td>
</tr>
<tr>
<td>Weyer et al., 1997</td>
<td>ADAS-non-cog</td>
<td>10</td>
<td>10 domains: tremors, pacing, motor restlessness, tearfulness, depression, delusions, hallucinations, appetite, concentration, uncooperativeness</td>
<td>Patient and caregiver</td>
<td>Interview, observation</td>
<td>-non-cognitive section</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>-widely used in clinical trials</td>
</tr>
</tbody>
</table>
NPI = Neuropsychiatric Inventory
NPI-C = Neuropsychiatric Inventory-Clinician Rating Scale
NPI-Q = Neuropsychiatric Inventory – Questionnaire Scale
BSSD = Behavioral Syndromes Scale for Dementia
BEHAVE-AD = Behavioral Pathology in AD Rating Scale

NRS = Neurobehavioral Rating Scale
ADAS-cog = Alzheimer's disease assessment scale cognitive
ADAS non-cog = Alzheimer's disease assessment scale non-cognitive
2.5.3 The prevalence and impact of neuropsychiatric symptoms

Apathy, depression, agitation and irritability are the most common NPS (Vogel et al., 2010, 2014; Steinberg et al., 2014). The prevalence of individual NPS varies in different stages of AD (Table 5). In MCI and early AD, depression and apathy are the most frequently observed symptoms. During all stages of AD, the incidence of agitation also stays high (Lopez et al., 2003; Aalten et al., 2007; Lyketsos, 2011; Bettney et al., 2012). Delusions, hallucinations and aggression become more frequently, as AD progresses, whereas apathy remains the most common NPS throughout all disease stages (Lyketsos, 2011). Patient age, educational level, and disease duration can influence the prevalence of NPS (Zhao et al., 2016). Peters et al. (2015) found that clinically significant NPS such as aggression, agitation, and psychosis predict earlier progression of AD to severe dementia and death. However, mild NPS were associated with earlier death, but not with earlier progression to severe dementia.

Previously, four sub-syndromes have been identified that link the 12 specific NPS assessed by the NPI (Aalten et al., 2008). These sub-syndromes classified by Aalten include “affective behaviors” (including depression, sleep disturbances, and changes in appetite), “hyperactive behaviors” (agitation, euphoria, irritability, disinhibition, and aberrant motor behavior), “apathy” and “psychosis” (hallucinations and delusions).

NPS have a large impact on the quality of life of patients with AD and their caregivers. NPS in AD are associated with poorer outcomes, including increased functional impairment, higher rates of institutionalization, poorer quality of life, accelerated progression to severe dementia or death, higher caregiver burden, and depression and a significant increase in care costs (Rocca et al., 2010; Mohamed et al., 2010; Lyketsos et al., 2011; Geda et al., 2013; Canevelli, Peters et al., 2015; Ismail et al., 2016). Hallucinations, aberrant motor behavior, sleeping disturbances, apathy, aggression, and anxiety are reported to be the most burdening NPS for the caregivers (Allegri et al., 2006; Matsumoto et al., 2007).
Table 5. The prevalence (%) of neuropsychiatric symptoms in different stages of Alzheimer’s disease in some previous studies.

<table>
<thead>
<tr>
<th></th>
<th>Garcia-Alberca et al., 2013</th>
<th>Gonfrier et al., 2012</th>
<th>Wadsworth et al., 2012</th>
<th>Garcia-Alberca et al., 2011</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number of patients (n)</strong></td>
<td>80</td>
<td>479</td>
<td>188</td>
<td>125</td>
</tr>
<tr>
<td><strong>Patient age (y), mean (SD)</strong></td>
<td>77.3 (5.7)</td>
<td>78.4 (6.8)</td>
<td>75.3 (7.5)</td>
<td>76.4 (6.1)</td>
</tr>
<tr>
<td><strong>MMSE mean (SD)</strong></td>
<td>15.0 (4.8)</td>
<td>19.5 (4.3)</td>
<td>23.3 (2.0)</td>
<td>14.5 (4.8)</td>
</tr>
<tr>
<td><strong>Delusions</strong></td>
<td>24 %</td>
<td>10 %</td>
<td>10 %</td>
<td>38 %</td>
</tr>
<tr>
<td><strong>Hallucinations</strong></td>
<td>18 %</td>
<td>4 %</td>
<td>5 %</td>
<td>20 %</td>
</tr>
<tr>
<td><strong>Agitation</strong></td>
<td>50 %</td>
<td>23 %</td>
<td>26 %</td>
<td>55 %</td>
</tr>
<tr>
<td><strong>Depression</strong></td>
<td>58 %</td>
<td>24 %</td>
<td>34 %</td>
<td>60 %</td>
</tr>
<tr>
<td><strong>Euphoria</strong></td>
<td>5 %</td>
<td>3 %</td>
<td>5 %</td>
<td>4 %</td>
</tr>
<tr>
<td><strong>Anxiety</strong></td>
<td>40 %</td>
<td>27 %</td>
<td>35 %</td>
<td>54 %</td>
</tr>
<tr>
<td><strong>Apathy</strong></td>
<td>92 %</td>
<td>44 %</td>
<td>34 %</td>
<td>74 %</td>
</tr>
<tr>
<td><strong>Disinhibition</strong></td>
<td>26 %</td>
<td>5 %</td>
<td>18 %</td>
<td>30 %</td>
</tr>
<tr>
<td><strong>Irritability</strong></td>
<td>63 %</td>
<td>21 %</td>
<td>37 %</td>
<td>66 %</td>
</tr>
<tr>
<td><strong>Aberrant motor behavior</strong></td>
<td>49 %</td>
<td>19 %</td>
<td>15 %</td>
<td>47 %</td>
</tr>
<tr>
<td><strong>Sleep disturbances</strong></td>
<td>46 %</td>
<td>12 %</td>
<td>26 %</td>
<td>36 %</td>
</tr>
<tr>
<td><strong>Appetite disturbances</strong></td>
<td>26 %</td>
<td>20 %</td>
<td>18 %</td>
<td>28 %</td>
</tr>
</tbody>
</table>

SD = Standard Deviation, MMSE = Mini-Mental State Examination
2.6 THE DIAGNOSIS OF ALZHEIMER’S DISEASE

2.6.1 Diagnostic criteria of Alzheimer’s disease

The clinical diagnosis of Alzheimer’s disease has been based on the National Institute of Neurological and Communicative Disorders and Stroke - Alzheimer’s Disease and Related Disorders Association (NINCDS-ADRDA) criteria (McKhann et al., 1984), the fourth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) criteria (American Psychiatric Association, 1994) and the 10th revision of the International Classification of Diseases (ICD-10) criteria (World Health Organization, 1994) (Cummings, 2012).

The NINCDS-ADRDA criteria were based on the clinico-pathological entity. According to these criteria, the diagnosis of AD is classified as probable, possible, and definite. The diagnosis of probable and possible AD can be established clinically, but a definite diagnosis requires histopathological confirmation (Jack et al., 2011). The NINCDS-ADRDA criteria were revised in 2011 because of increasing knowledge of the clinical manifestations and biology of AD over previous decades (Morris et al., 2016). Current evidence has showed that the clinico-pathological relation is not always consistent. Neuropathological hallmarks of AD, especially diffuse amyloid \( \beta \) plaques, can exist in the absence of any clinical symptoms (Polvikoski et al., 1995; Jack et al., 2011).

In the revised NINCDS-ARDA criteria, the diagnosis of AD is categorized into three disease stages: preclinical AD, MCI due to AD, and dementia due to AD (McKhann et al., 2011). The new criteria for AD dementia and MCI due to AD are intended to guide diagnosis in the clinical setting, while the criteria for preclinical AD are for research purposes only, and at the moment do not have any clinical utility (Jack et al., 2011). In preclinical AD, there are measurable changes in biomarkers that indicate the earliest signs of disease, before the clinical symptoms are noticeable. Nowadays, it is well known that AD related changes in the brain occurs years, and perhaps decades, before the clinical onset (Dubois et al., 2010; Albert et al., 2011). However, before biomarkers are validated for use in the preclinical diagnosis of AD, much additional research needs to be done (Jack et al., 2011; Sperling et al., 2011). In MCI due to AD, mild measurable changes occur in memory, especially in episodic memory, but these do not affect a person’s ability to independently carry out everyday activities. In dementia due to AD, memory loss and other cognitive and behavioral symptoms are evident, interfering with a person’s ability in daily life (Jack et al., 2011).

DSM-V was published in 2013, more than a decade after the previous edition, DSM-IV. DSM-V prefers to use the terms major neurocognitive disorder and mild neurocognitive disorder instead of the term dementia. The purpose of the addition criteria for mild neurocognitive disorder is to promote the early detection and treatment of cognitive decline. According to the DSM-V’s criteria, a person with major neurocognitive disorder have cognitive deficits that disturb their ability to independently carry out everyday activities, and persons with mild neurocognitive disorder may retain their ability to be independent (American Psychiatric Association, 2013). The DSM-V criteria corresponds
with the current dementia (major neurocognitive disorder) and MCI (mild neurocognitive disorder) definition.

### 2.6.2 Diagnostic procedure in Finland

In Finland, the National Current Care Guidelines for Memory Disorders also help in the clinical diagnosis of AD. These national guidelines are evidence-based and independent clinical practice guidelines done by physicians and researchers. The Current Care Guidelines include important issues related to health and medical treatment, as well as the prevention of diseases. AD is usually diagnosed by geriatricians or neurologists and the diagnose is based on an interview with patients and close informants that includes the past medical history, co-morbidities, family and educational history, cognitive symptoms, and the course of the illness. Physical and neurological examinations should be performed carefully in all patients, as well as assessment of cognitive function (CERAD; Consortium to Establish a Registry for Alzheimer’s Disease Neuropsychological Battery /neuropsychological testing, Morris et al., 1989), ADL, and behavioral and psychological symptoms. CT or preferably MRI is used to exclude other, potentially surgically treatable diseases and indicate specific findings for AD. Hippocampal atrophy is best seen in MRI, but may also be visualized using the modern type CT scanner. Hippocampal atrophy is classified by using Scheltens’ atrophy rating scale from 0 (no atrophy, normal) to 4 (severe atrophy). The imaging procedure should be carried out at least once for every patient. For differential diagnostic reasons blood levels of a complete blood cell count, glucose and thyroid stimulating hormone, calcium, vitamin B12, folate and renal and liver function tests should be evaluated at the time of diagnosis. Serological tests for syphilis, HIV, and Borrelia are also used in some cases (Waldemar et al., 2007; Hort et al., 2010).

Further specific examinations might also be needed. [(123)I]beta-CIT (2beta-carbomethoxy-3beta-(4-iodophenyl)tropane) SPECT is useful for the differential diagnosis between AD and Lewy body dementia (Errola et al., 2005). Most AD patients exhibit a decrease in cerebrospinal fluid (CSF) beta-amyloid 42 peptide (Aβ42) and an increase in CSF total tau protein (T-tau) and phosphorylated tau protein (P-tau) when compared with healthy controls. Thus, the combination of low Aβ42 and high levels of T-tau and P-Tau can help to diagnose AD in the early stages of the disease (Tapiola et al., 2009; Blennow et al., 2010).

Positron emission tomography (PET) with 2-[fluorine-18]fluoro-2-deoxy-D-glucose (FDG), i.e. FDG-PET can demonstrate a glucose metabolic reduction in the early stage of AD in the posterior cingulate, parietotemporal association cortices, and precuneus regions (Mosconi et al., 2010; Smailagic et al., 2015).

### 2.6.3 Future diagnostic possibilities

There is an obvious need for earlier AD diagnosis, since neuropathological changes, such as the accumulation of Aβ, tangle formation, synaptic dysfunction, and brain atrophy, take place years before to the appearance of clinical symptoms (Hardy and Selkoe, 2002; Jack et al., 2010; Weiner et al., 2010, 2013; Ewers et al., 2011; Sperling et al., 2011). Based on this
knowledge, in the future, it will be important to identify persons in the early stages of amyloid β deposition, when clinical symptoms of AD do not yet occur.

Investigators are seeking new neuroimaging techniques and biomarkers. Brain imaging might be a promising tool for the early detection of AD. Pittsburgh compound B (PiB) and the 18F-florbetapir positron emission tomography (PET) technique have been used to detect β-amyloid in vivo and it could therefore be rather useful for detecting AD in its early phases. PiB and 18F-florbetapir are tracers that allow the marking of β-amyloid plaques in the brain of a living person (Mathis et al., 2012; Edison et al., 2013). However, the early diagnosis of AD cannot only rely on a positive scan, since persons with AD co-existent with other pathologies may also have intermediate Aβ deposits in their brains. Amyloid deposits are not unique to AD, because they can occur in brain tissue in healthy elderly people and also in other neurodegenerative diseases as well (Polvikoski et al., 1995; Silverman et al., 2002; Jagust et al., 2007).

The recently identified PET tracer 18F-AV1451 (18F-T807), shows high affinity and selectivity for paired helical filament tau pathology in vitro (Chien et al., 2013; Xia et al., 2013; Marquie et al., 2015), and allows in vivo assessment of the regional tau load.

Nowadays, the wider use of molecular and functional neuroimaging is limited. Measurement of cerebral metabolism and perfusion can be useful in the differential diagnosis of AD and other degenerative brain disorders, and also in the assessment of suspected AD in the context of MCI.

The genetics of AD is complex and associated with many ethical concerns. Genetic testing of AD is generally not used in clinical settings. ApoE-e4 allele is the only genetic factor sometimes used, but so far there is no clinical evidence suggesting that ApoE-e4 allele testing is useful (Padovani et al., 2011; Van Cauwenberghe et al., 2015).

2.6.4 Importance of early diagnosis
It is important to diagnose AD as early as possible. When receiving a diagnosis at an early stage of the disease, people with AD can have access to drug and non-drug therapies that maintain their cognition and preserve daily functioning for some time, prevent NPS, reduce the caregiver burden, enhance the quality of life, and delay institutionalization. An earlier diagnosis also allows people to plan their future, while they still are capable of making important decisions (i.e. last will) (Alzheimer’s Disease International; World Alzheimer Report 2011).
2.7 QUALITY OF LIFE IN ALZHEIMER’S DISEASE

Quality of life (QoL) is a wide construct, including multiple domains such as physical health, psychological well-being, functioning, social activity, and environmental factors. QoL has both subjective and objective components. The World Health Organization (WHO) defines QoL as “individual’s perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns. It is a broad ranging concept affected in a complex way by the person’s physical health, psychological state, level of independence, social relationships, personal beliefs and their relationship to salient features of their environment”.

During recent years, the QoL in AD has been the subject of several studies, because of the increasing prevalence of AD in aging societies. Along with the early diagnosis of AD and early start of AD-targeted medication, the enhancement and maintenance of QoL is one of the main aims in AD patient care.

2.7.1 Assessment of quality of life

QoL measure instruments can be divided in two basic types: disease-specific instruments (Table 6) and generic instruments (health profile and utility measures) (Table 7). Disease specific instruments are considered to be more sensitive in evaluating change over time, because they concentrate on aspects of QoL that are particularly significant to the disease of interest, while generic instruments can be used in a wide range of populations and in economic analyses. Generic measures can also be used for comparisons between different states of disease (Naglie et al., 2011). Instruments have different dimensions that are observed (Jönsson et al., 2006).

Several approaches have been used to assess QoL in AD: self-rating, which is generally preferred if possible, depending on the disease severity; caregiver rating, which can be related to caregiver mind per se or to the rating the caregiver believes the patient would give of his/hers own situation (Bosboom et al., 2012) and direct observation of patient behavior (Lawton et al., 1991).

However, assessing QoL in AD is challenging. In an ideal situation, QoL should be assessed from the patients’ own perspective, because it is a subjective phenomenon. Nevertheless, declining cognition, difficulties in communication, and the probable lack of insight make this somewhat unreliable (Vogel et al., 2006). The main question is how to assess the subjective perceptions and experiences of the patients with AD in a reliable and valid way. Thus, information from the perspective of both patients and caregivers is necessary for optimal assessment of the QoL (Tatsumi et al., 2009). The use of AD-specific instruments, rather than generic measure of QoL, has consequently been preferred (Ettema et al., 2005). The QoL-AD scale is the most widely used instrument to determine QoL in AD. In the QoL-AD scale both patient and caregiver rate the same domains of patient QoL (Andrieu et al., 2016). These two perspectives can be considered as equally valid and yielding different aspects of QoL (Ready et al., 2004; Schiffczyk et al., 2010; Trigg et al., 2011).
Table 6. Dementia-specific instruments validated for QoL assessment in AD (modified from Schölzel-Dorenbos et al., 2007 and Mossello & Ballini, 2012).

<table>
<thead>
<tr>
<th>Author</th>
<th>Instrument, rater</th>
<th>Items/domains</th>
<th>Collection, disease state</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Logsdon et al., 2002</td>
<td>QoL-AD, patient and caregiver</td>
<td>13-items; physical health, energy, mood, memory, family, marriage, friends, living situation, chores, fun, money, self, and life as a whole</td>
<td>Interview, mild to moderate AD</td>
<td>-most widely used dementia-specific measure</td>
</tr>
<tr>
<td>Brod et al., 1999</td>
<td>DQoL, patient</td>
<td>29-items; five domains: positive affect/humor (frequency felt happy, hopeful), negative affect (frequency felt lonely, sad, angry, depressed, worried), feelings of belonging, self-esteem, and sense of aesthetics</td>
<td>Interview, mild to moderate AD</td>
<td>-easy to use -can be used in clinical practice, drug trials, service settings</td>
</tr>
<tr>
<td>Smith et al., 2005</td>
<td>DEMQOL, patient and caregiver</td>
<td>Patient 28-items, caregiver 31-items. Domains: feelings, memory, everyday life, overall QoL</td>
<td>Interview, mild to moderate AD</td>
<td>-both patient and caregiver developed instrument</td>
</tr>
<tr>
<td>Rabins et al., 1999</td>
<td>ADRQL, caregiver</td>
<td>47-items; only rated by caregiver. Five domains: social interaction, awareness of self, feelings and mood, enjoyment of activities, response to surroundings</td>
<td>Interview, all AD stages</td>
<td>-does not include items of cognition, ADL and physical status</td>
</tr>
<tr>
<td>Ready et al., 2002</td>
<td>CBS, clinician</td>
<td>19-items; clinical rating of bipolar items after brief interview with both patient and caregiver. Domains: mood, ideational disturbance, physical signs, behavioral disturbance, cyclic functions</td>
<td>Interview, mild to moderate AD</td>
<td>-does not include items of cognition and functional abilities</td>
</tr>
<tr>
<td>Hurley et al., 1992</td>
<td>DS-DAT, professional caregivers</td>
<td>9 behavioral indicators of discomfort in patients with severe AD and language disorders</td>
<td>Observation, severe AD</td>
<td>-can be used both in clinical trials and practice</td>
</tr>
<tr>
<td>Ettema et al., 2007</td>
<td>Qualidem, professional caregivers</td>
<td>49-items scale, 9 subscales of patients behavior</td>
<td>Observation, severe AD</td>
<td>-mostly used in clinical settings</td>
</tr>
</tbody>
</table>

QoL-AD = Quality of Life in Alzheimer’s disease scale  
DQoL = Dementia Quality of Life scale  
DEMQOL = Health-related Quality of Life for people with Dementia  
ADRQL = Alzheimer’s Disease Health-Related Quality of Life  
CBS = Cornell–Brown Scale for QoL in dementia  
DS-DAT = Discomfort Scale – Dementia of Alzheimer Type  
Qualidem = Quality of life in dementia
Table 7. Generic QOL instruments used in AD (modified from Ettema et al., 2005 and Mossello & Ballini, 2012).

<table>
<thead>
<tr>
<th>Author</th>
<th>Instrument, rater</th>
<th>Items/domains</th>
<th>Collection, disease state</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>The EuroQoL Group; 1990</td>
<td>EQ-5D, patient and/or caregiver</td>
<td>Consist of two parts: a self-administered health index and a VAS. 5 domains: mobility, self-care, pain/discomfort, usual activities, and anxiety/depression</td>
<td>Interview or self-administered questionnaire, mild to moderate AD</td>
<td>-short -easy to use</td>
</tr>
<tr>
<td>Selai et al., 2001</td>
<td>QOLAS, patient</td>
<td>10 items. Questions (two of each domain) are personally modified for each patient by asking what is important to his/her QoL. Domains: physical, psychological, social/family, work, and cognitive</td>
<td>Interview, mild to moderate AD</td>
<td>-patient own opinion -most AD patients need help to answer the questions</td>
</tr>
<tr>
<td>Sintonen et al., 1995, 2001</td>
<td>15D, patient</td>
<td>15 domains: mobility, vision, eating, hearing, breathing, sleeping, speech, excretion, usual activities, mental function, discomfort, depression, distress, vitality, and sexual activity</td>
<td>Self-administered questionnaire, mild to moderate AD</td>
<td>-short -easy to use -caregiver could also rate</td>
</tr>
<tr>
<td>WHOQOL Group, 1995</td>
<td>WHOQOL 100, patient</td>
<td>100 items. 6 domains: physical health, psychological, levels of independence, social relations, environment and spirituality/religion/personal beliefs</td>
<td>Self-administered questionnaire mild to moderate AD</td>
<td>-cross-cultural -available in different languages -wide</td>
</tr>
<tr>
<td>Kaplan et al., 1988</td>
<td>QWB, patient</td>
<td>Domains: self-care, usual/social activities, mobility and physical activities. Two to eight items per domains. Incorporate 21 symptom complexes pertaining to physical and emotional health, cognitive and sensory function, speech, general weakness, limbic function, and pain</td>
<td>Self-administered questionnaire, mild to moderate AD</td>
<td>-can be used to quantify the health effects of medical, preventive, and health policy interventions</td>
</tr>
<tr>
<td>Neumann et al., 1999, 2000</td>
<td>HUI 2, caregiver</td>
<td>7 domains: sensation, mobility, emotion, cognition, self-care, pain, and fertility</td>
<td>Interview, all AD stages</td>
<td>-widely used in clinical studies</td>
</tr>
<tr>
<td>Neumann et al., 2000</td>
<td>HUI 3, caregiver</td>
<td>8 domains; vision, hearing, speech, ambulation, dexterity, emotion, cognition, and pain</td>
<td>Interview, all AD stages</td>
<td>-widely used in clinical studies</td>
</tr>
</tbody>
</table>

EQ-5D = European Quality of Life Instrument, VAS = Visual Analogue Scale, QOLAS = Quality of Life Assessment Schedule, 15D = 15 Dimension Instrument, WHOQOL = The World Health Organization Quality of Life Instrument, QWB = Quality of Well Being Scale, HUI = Health Utilities Index, AD = Alzheimer’s Disease
2.7.2 Discrepancies between patient self-rated and caregiver-rated quality of life

Several previous studies have found that patients with AD rate their QoL higher when compared to caregivers or other informants (Ready et al., 2004; Vogel et al., 2006, 2012; Missotten et al., 2007; Conde-Sala et al., 2009, 2014, 2016; Buckley et al., 2012, Black et al., 2012; Gomez-Gallego et al., 2012; Andrieu et al., 2016). A few published longitudinal-studies have also indicated that patients’ self-rated QoL remains quite stable over time, while caregiver-rated patient QoL shows a clear decline as AD progress during the follow-up period (Tatsumi et al., 2009; Coned-Sala et al., 2014). The lack of change in patients' self-rated QoL over time could also be caused by lack of insight in patients due to increased cognitive impairment (Conde-Sala et al., 2015; Andrieu et al., 2016). It has been proposed that only patients with MMSE score 10 or over can reliably evaluate their own QoL (Logsdon et al., 2002; Andrieu et al., 2016). AD patients might also adapt by coping mechanisms to their new situation and may not perceive any QoL decline. Caregiver ratings of AD patients’ QoL may be influenced by their own expectations, the personality characteristics of the caregiver, caregiver mood and their relationship with the patient (Schiffczyk et al., 2010). In general, sons or daughters as caregivers have been found to score AD patient QoL lower than spousal caregivers. This might be associated with generational factors, but it also has been suggested that spouse caregivers might view the caring as a part of their marital commitment and also feel that caring gives a meaning and purpose to their lives in old age (Conde-Sala et al., 2009, 2010; Orgeta et al., 2015; Andrieu et al., 2016). Adult child caregivers usually have to combine the care tasks with own family and work which increases the burden (Conde-Sala et al., 2010). Caregiver stress and burden can also influence their ratings for patient QoL (Karlawish et al., 2001; Black et al., 2011).

2.7.3. Factors associated with quality of life in AD patients

In previous studies, the factors associated with a better patient self-rated QoL have been less frequent depressive symptoms (Conde-Sala et al., 2009, 2014; Bosboom et al., 2012; Naglie et al., 2011; Zucchella et al., 2015), lower dependence in activities of daily living (ADL) (Conde-Sala et al., 2009, 2013; Zucchella et al., 2015), a higher educational level (Buckley et al., 2012; Conde-Sala et al., 2010, 2014), a lower presence of neuropsychiatric symptoms (depression and apathy) (Matsui et al., 2006; Conde-Sala et al., 2009; Gomez-Gallego et al., 2012), better cognitive function (Matsui et al., 2006; Conde-Sala et al., 2013), the use of acetylcholine esterase inhibitors (Hoe et al., 2007), and male gender (Conde-Sala et al., 2009, 2014; Gomez-Gallego et al., 2012).

Instead, the factors associated with a lower patient self-rated QoL have been awareness of deficits (Bosboom et al., 2012; Conde-Sala et al., 2013, 2015; Sousa et al., 2013), high comorbidity (Buckley et al., 2012), the burden on family caregivers (Logsdon et al., 2002; Conde-Sala et al., 2009), and depressive symptoms in caregivers (Logsdon et al., 1999; Snow et al., 2005).

Caregiver-rated patient QoL is higher among patients who are more independent in ADL (Hoe et al., 2007; Tatsumi et al., 2009; Gomez-Gallego et al., 2012; Vogel et al., 2012; Conde-Sala et al., 2014; Orgeta et al., 2015; Andrieu et al., 2016), have better cognition
(Bosboom et al., 2012; Vogel et al., 2012), and a younger age (Orgeta et al., 2015). On the other hand, caregivers rate patients QoL lower if the patients are depressed (Hoe et al., 2007; Conde-Sala et al., 2014; Orgeta et al., 2015; Zucchella et al., 2015), have frequent NPS (Hoe et al., 2007; Tatsumi et al., 2009; Buckley et al., 2012; Zucchella et al., 2015; Conde-Sala et al., 2014, 2015; Andrieu et al., 2016), or more severe AD (Conde-Sala et al., 2015). Furthermore, the caregivers’ burden (Conde-Sala et al., 2009, 2014; Black et al., 2012; Zucchella et al., 2015; Andrieu et al., 2016), increasing age (Orgeta et al., 2015), and depression (Logsdon et al., 2002; Snow et al., 2005; Zucchella et al., 2015) are related to lower caregiver-rated patient QoL.

Table 8 summarizes the previously reported longitudinal QoL studies carried out in the community-dwelling AD patient study population. Table 9 presents the previously reported cross-sectional QoL studies carried out in the community-dwelling AD patient study population. Table 10 presents the factors that are associated with QoL in patients with AD according to current publications.
Table 8. Quality of life in community-dwelling Alzheimer’s disease patients: previous longitudinal studies.

<table>
<thead>
<tr>
<th>Author</th>
<th>Aims of the study</th>
<th>Follow-up time</th>
<th>Sample size (n) dyads</th>
<th>Drop-out rate (n)</th>
<th>MMSE (mean)</th>
<th>QoL instrument</th>
<th>Main findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Andrieu et al., 2016</td>
<td>To examine discrepancies between self and caregiver ratings of patient QOL during follow-up</td>
<td>2 years</td>
<td>501</td>
<td>170</td>
<td>19.5</td>
<td>QoL-AD; patient and caregiver rated</td>
<td>- Patient self-rated QOL did not change during follow-up</td>
</tr>
<tr>
<td></td>
<td>To assess factors explaining a low level of self- or caregiver-reported patient QoL at baseline</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>- Caregiver-rated patient QOL declined during follow-up</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>- Lower self-rated QOL associated with patient depression, decreasing ADL and caregiver burden</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>- Lower caregiver-rated QoL associated with increasing NPS, caregiver burden, and older patient age</td>
</tr>
<tr>
<td>Conde-Sala et al., 2016</td>
<td>To investigate the relationship between anosognosia, NPS, and QoL</td>
<td>2 years</td>
<td>221</td>
<td>94</td>
<td>18.3</td>
<td>QoL-AD; patient and caregiver rated</td>
<td>- Patients with anosognosia had more NPS and higher self-rated QoL</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>- lower caregiver-rated QoL associated with anosognosia and severe NPS</td>
</tr>
</tbody>
</table>
Table 8. Continued. Quality of life in community-dwelling Alzheimer’s disease patients: previous longitudinal studies

<table>
<thead>
<tr>
<th>Author</th>
<th>Aims of the study</th>
<th>Follow-up time</th>
<th>Sample size (n) dyads</th>
<th>Drop-out rate (n)</th>
<th>MMSE (mean)</th>
<th>QoL instrument</th>
<th>Main findings</th>
</tr>
</thead>
</table>
| **Trigg et al., 2015**  | To examine the relationship between AD severity and changes in QoL               | 18 months      | 145                  | -                  | 15.0        | 28-item DEMQOL, 31-item DEMQOL-proxy, EQ-5D; patient and caregiver rated | - Natural progression of AD over 18 months did not lead to significant decline in QoL.  
- EQ-5D proxy suggested a mean decline in QoL, whereas the DEMQOL-proxy indicated overall improvement |
| **Conde-Sala et al., 2014** | To identify the factors associated with changes in patient QoL                  | 3 years        | 337                  | 218                | 18.9        | QoL-AD; patient and caregiver rated   | - Patient self-rated QoL remained stable over time  
- Caregiver rated QoL declined over time  
- Patient self-rated QOL was higher in anosognosia  
- Caregiver-rated QoL was lower with caregiver’s burden and patient’s agitation, apathy, and disabilities |
Table 8. Continued. Quality of life in community-dwelling Alzheimer’s disease patients: previous longitudinal studies

<table>
<thead>
<tr>
<th>Author</th>
<th>Aims of the study</th>
<th>Follow-up time</th>
<th>Sample size (n) dyads</th>
<th>Drop-out rate (n)</th>
<th>MMSE (mean)</th>
<th>QoL instrument</th>
<th>Main findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vogel et al., 2012</td>
<td>To examine the change in caregiver-rated patient QoL over the follow-up period</td>
<td>3 years</td>
<td>102</td>
<td>-</td>
<td>24.2</td>
<td>QoL-AD and EQ-VAS; caregiver rated</td>
<td>Mean QoL declined both in QoL-AD and EQ-VAS.</td>
</tr>
<tr>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>QoL declined with decreasing ADCS-ADL and MMSE and increasing points in CSDD</td>
</tr>
<tr>
<td>Tatsumi et al., 2009</td>
<td>To examine the effect of NPS in QoL in AD over follow period</td>
<td>2 years</td>
<td>140</td>
<td>44</td>
<td>20.3</td>
<td>QoL-AD; patient and caregiver rated</td>
<td>Patient-rated QoL did not change significantly over time.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Caregiver-rated QoL declined over time</td>
</tr>
<tr>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>Lower caregiver-rated QoL associated with decrease in ADCS-ADL and increase in NPS</td>
</tr>
</tbody>
</table>

QoL= Quality of Life, NPS= Neuropsychiatric symptoms, ADL= Activities of Daily Living, AD = Alzheimer’s Disease, MMSE = Mini-Mental State Examination, QoL-AD = Quality of Life in Alzheimer’s Disease scale, DEMQOL = Health-related Quality of Life for people with Dementia, EQ-5D = European Quality of Life Instrument, VAS = Visual Analogue Scale, CSDD = Cornell Scale for Depression in Dementia, ADCS-ADL = The Alzheimer’s Disease Cooperative Study - Activities of Daily Living Inventory

<table>
<thead>
<tr>
<th>Author</th>
<th>Aims of the study</th>
<th>Sample size (n)</th>
<th>MMSE (mean)</th>
<th>QoL instrument</th>
<th>Rater</th>
<th>Main findings</th>
</tr>
</thead>
</table>
| Tay et al., 2014   | To identify predictors for discrepancies between patient- and caregiver-rated patient QoL | 165 dyads      | 18.4 (Chinese MMSE; score 0-28)  | QoL-AD         | Patient and caregiver         | - Patient-rated QoL was significantly higher than caregiver-rated QoL  
- Patient's educational level, depressive symptoms and severity of NPS predicted discrepancy.  
- Lower patient-rated QoL associated with depression and being cared for by other relative (non-spouse/adult child) |
| Orgeta et al., 2015| To compare patient- and caregiver-rated QoL and identify the most important factors influencing their ratings | 488 dyads      | Not measured. CDR=1; 74.6% of the patients, remaining had CDR=2 | QoL-AD and VAS | Patient and caregiver         | - Higher self-rated QoL associated with better ADL, treatment of depression and caregiver’s lower stress.  
- Higher caregiver-rated QoL associated with patient’s younger age, lower levels of depression, and better ADL, and caregiver’s lower stress and better health |

<table>
<thead>
<tr>
<th>Author</th>
<th>Aims of the study</th>
<th>Sample size (n)</th>
<th>MMSE (mean)</th>
<th>QoL instrument</th>
<th>Rater</th>
<th>Main findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sousa et al., 2013</td>
<td>To determine the non-cognitive factors associated with patient- and caregiver-rated QoL</td>
<td>41 dyads</td>
<td>21.0</td>
<td>QoL-AD</td>
<td>Patient and caregiver</td>
<td>Higher patient-rated QoL associated with patient’s impaired awareness</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Higher caregiver-rated QoL associated with caregiver’s higher education</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Lower caregiver-rated QoL associated with patient depressive symptoms</td>
</tr>
<tr>
<td>Black et al., 2012</td>
<td>To identify correlates of patient- and caregiver-rated QOL</td>
<td>254 dyads</td>
<td>17.8</td>
<td>QoL-AD (patient, caregiver), ADRQL (caregiver)</td>
<td>Patient and caregiver</td>
<td>Higher patient-rated QoL was related to race (white) and higher education, and lower QoL to depression, more medication, health problems, and NPS</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Higher caregiver-rated QoL related to race (white) and lower QoL to depression, more health problems, lower IADL, and MMSE</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Author</th>
<th>Aims of the study</th>
<th>Sample size (n)</th>
<th>MMSE (mean)</th>
<th>QoL instrument</th>
<th>Rater</th>
<th>Main findings</th>
</tr>
</thead>
</table>
| Gómez-Gallego et al., 2012    | To explore the QoL predictors considering three different sources of information: patients, caregivers and healthcare staff | 102 dyads       | 38 patients; MMSE > 20, 56 patients; MMSE 11-20; 8 patients; MMSE<11 | QoL-AD         | Patient and caregiver | - Patient-rated QoL mainly affected by their mood  
- Lower caregiver-rated QoL associated with patients' irritability and caregiver burden.  
- Lower staff-rated QoL associated with patient's psychotic symptoms and neuroleptic use |
| León-Salas et al., 2011       | To assess AD patient QoL according to family caregivers  
To analyze the correlates of QoL.                                                                                     | 92 dyads        | 14.1        | ADRQL           | Caregiver           | - Behavioral problems and deterioration in ADL indicated lower caregiver-rated QoL  
- Household income, ADL, mood, caregiver caring for another dependent person and caregiver burden associated with ADRQL |
| Naglie et al., 2011           | To assess whether the symptoms of AD predict patient self-rated QoL                                                                    | 370 dyads       | 22.3        | QoL-AD EQ-5D QWB VAS | Patient             | - Depression was the only significant predictor of patient self-ratings for all four QoL measures |

<table>
<thead>
<tr>
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<th>MMSE (mean)</th>
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<th>Rater</th>
<th>Main findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Naglie et al., 2011</td>
<td>To assess whether the symptoms of AD and caregiver factors predict family caregiver ratings of patient QOL</td>
<td>412 dyads</td>
<td>20.8</td>
<td>EQ-5D, QWB, HUI3, QoL-AD and SF-36</td>
<td>Caregiver</td>
<td>Patient function and depressive symptoms were the only independent predictors of caregiver-rated patient QoL across the QoL measures.</td>
</tr>
</tbody>
</table>
| Conde-Sala et al., 2010 | To identify the different variables in perceived patient QoL between patients and caregivers | 251 dyads       | MMSE >24; 26 patients, MMSE 15-23; 173 patients, MMSE 10-14; 52 patients | QoL-AD            | Patient and caregiver | Higher caregiver-rated QoL associated with caregiver higher educational level and patient’s greater functional independence  
- Lower caregiver-rated QoL associated with caregiver burden  
- Patient depression associated with lower ratings of patient QoL by adult child caregivers  
- Spouse caregivers rate patient QoL higher than adult child caregivers |

<table>
<thead>
<tr>
<th>Author</th>
<th>Aims of the study</th>
<th>Sample size (n)</th>
<th>MMSE (mean)</th>
<th>QoL instrument</th>
<th>Rater</th>
<th>Main findings</th>
</tr>
</thead>
</table>
| Conde-Sala et al., 2009 | To compare patient- and caregiver-rated QoL and identify associated factors       | 236 dyads       | MMSE > 20; 76 patients, MMSE 11-20; 154 patients, MMSE <11; 6 patients | QoL-AD             | Patient and caregiver  | - Patient’s rated their QoL higher than caregivers.  
- Caregiver’s rated patients QoL lower with more NPS and higher with greater functional autonomy of the patient |
| Vogel et al., 2006      | To investigate, whether patient- and caregiver-reported QoL differ in early AD    | 48 dyads        | 24.9        | EQ-5D          | QoL-AD                 | - Patients with early AD reported their QoL higher than caregivers.  
- This was associated with lack of insight.  
- Patient self-reported QoL did not correlate with the MMSE score.  
- Behavioral changes and depressive symptoms associated with low QoL. |

QoL = Quality of Life, NPS= Neuropsychiatric symptoms, ADL= Activities of Daily Living, AD = Alzheimer’s Disease, MMSE = Mini-Mental State Examination, QoL-AD = Quality of Life in Alzheimer’s Disease scale, CDR = Clinical Dementia Rating Scale, VAS = Visual Analogue Scale, ADRQL = Alzheimer’s Disease Health-Related Quality of Life, EQ-5D = European Quality of Life Instrument, QWB = Quality of Well Being Scale, HUI = Health Utilities Index, SF-36 = Short Form-36
Table 10. Factors associated with quality of life (QoL) in patients with Alzheimer’s disease according to current publications.

<table>
<thead>
<tr>
<th>Patient self-rated</th>
<th>Caregiver-rated</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Higher QoL</strong></td>
<td><strong>Higher QoL</strong></td>
</tr>
<tr>
<td>Fewer depressive symptoms</td>
<td>Independence in ADL</td>
</tr>
<tr>
<td>Independence in ADL</td>
<td>Better cognition</td>
</tr>
<tr>
<td>Higher educational level</td>
<td>Younger patient age</td>
</tr>
<tr>
<td>Fewer NPS</td>
<td></td>
</tr>
<tr>
<td>Better cognitive function</td>
<td></td>
</tr>
<tr>
<td>Use of acetylcholine esterase inhibitors</td>
<td></td>
</tr>
<tr>
<td>Male gender</td>
<td></td>
</tr>
<tr>
<td>Impaired awareness of deficits</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Lower QoL</strong></th>
<th><strong>Lower QoL</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Awareness of deficits</td>
<td>Patient depression</td>
</tr>
<tr>
<td>Caregiver burden</td>
<td>Frequent NPS</td>
</tr>
<tr>
<td>Caregiver depression</td>
<td>More severe AD</td>
</tr>
<tr>
<td></td>
<td>Caregiver burden</td>
</tr>
<tr>
<td></td>
<td>Caregiver depression</td>
</tr>
<tr>
<td></td>
<td>Higher caregiver age</td>
</tr>
</tbody>
</table>

QoL = Quality of Life, ADL = Activities of Daily Living, NPS = Neuropsychiatric symptoms, AD = Alzheimer’s Disease.
3 Aims of the study

The purpose of this study was to evaluate the QoL and factors that may be related to QoL in patients with AD at the time of diagnosis and during a five-year follow-up while the disease progressed. Furthermore, the purpose was to evaluate the association of neuropsychiatric symptoms with the quality of life in patients with AD.

The specific aims of the study were to examine

1. The prevalence and nature of different neuropsychiatric symptoms (NPS) in relation to disease severity and quality of life in patients with very mild and mild AD at baseline (Study I)

2. Patient’s ability to complete quality of life (QoL) questionnaires with or without assistance (Study II)

3. Differences in self-and caregiver-rated measures of QoL in relation to disease progression in very mild or mild AD (Study II)

4. The association of self- and caregiver-rated QoL with NPS in patients at baseline and during the five-year follow-up (Study III)

5. Which other factors than NPS and disease progression are associated with the changes in QoL (Study III)
4 Methods

4.1 ALSOVA FOLLOW-UP STUDY

4.1.1 Study design
This study was based on the data of the ALSOVA project, which was conducted by the Neurology Unit of the University of Eastern Finland (UEF) and Neuro-Center of Kuopio University Hospital in collaboration with North Carelian Central Hospital, Jyväskylä Central Hospital, UEF Departments of Nursing Science, Psychology, Health and Social Management and Pharmacoconomics and the Outcomes Research Unit. The ALSOVA-follow-up was a prospective, randomized and controlled rehabilitation study, evaluating the effectiveness of an early psychosocial intervention on the risk of institutionalization in very mild or mild AD at baseline. Other aims of the ALSOVA study were to examine the quality of life of AD patients and their caregivers, the sense of coherence of caregivers and adaptation to caregiving (Välimäki, 2012), cognitive performance and the progression of AD (Hallikainen, 2015), drug and health and service use by the AD patients and the impact of AD care on health economics.

Inclusion criteria for the patients were an age of over 65-years, very mild (CDR 0.5) or mild AD (CDR 1), community-dwelling and the presence of a family caregiver. The definition of caregiver was an individual preferably in daily contact with the patients. A family caregiver could be a spouse, sibling, child or some other relative. The endpoint of the study was permanent institutionalization or death.

The participants were recruited during the first year after the AD diagnosis (on average within five months), and were randomized into an intervention group or control group (1:2) at the baseline visit. A study nurse who was not participating ALSOVA project, carried out the randomization process. After the AD diagnosis, both groups were followed up regularly in a similar way and the intervention group also participated in the early rehabilitation planned especially for them. The control group did not take part in rehabilitation arranged by the ALSOVA study. At the time of AD diagnosis, all the participants received general information about AD and social services from the memory nurses. The ALSOVA study was not a clinical trial, and all the patients were provided with standard care, which reduced the bias.
Figure 3. Flow chart of this study

Baseline

5 patient did not meet the inclusion criteria

1-year follow-up

198 patient caregiver dyads

38 dyads dropped out

2-year follow-up

168 patient caregiver dyads

30 dyads dropped out

3-year follow-up

131 patient caregiver dyads

37 dyads dropped out

5-year follow-up

73 patient caregiver dyads

58 dyads dropped out

Notes:
- 241 patient and caregiver dyads at baseline
- 3 patient had moderate AD
- 1 patient did not have AD
- 1 patient had impaired vision
- 198 patient caregiver dyads at 1-year follow-up
- 3 patient had moderate AD
- 1 patient did not have AD
- 1 patient had impaired vision
- 168 patient caregiver dyads at 2-year follow-up
- 131 patient caregiver dyads at 3-year follow-up
- 73 patient caregiver dyads at 5-year follow-up
- 58 dyads dropped out at 5-year follow-up
Table 11. Drop-out rates and reasons of this study. Please, notice that the institutionalization or death of the patient were also regarded as the end-point of this follow-up study.

<table>
<thead>
<tr>
<th>Drop-out rates and reasons at each time point</th>
<th>Year 1 (n=198)</th>
<th>Year 2 (n=168)</th>
<th>Year 3 (n=131)</th>
<th>Year 5 (n=73)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death of the patient (n)</td>
<td>10</td>
<td>7</td>
<td>2</td>
<td>7</td>
</tr>
<tr>
<td>Institutionalization of the patient (n)</td>
<td>3</td>
<td>4</td>
<td>24</td>
<td>33</td>
</tr>
<tr>
<td>Deterioration of the patient health (n)</td>
<td>5</td>
<td>8</td>
<td>8</td>
<td>12</td>
</tr>
<tr>
<td>Caregiver related reasons (i.e. deterioration of health, burden, death) (n)</td>
<td>11</td>
<td>5</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Others (i.e. refusal of the patient) (n)</td>
<td>9</td>
<td>6</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Total drop-out rates at each time point (n)</td>
<td>38</td>
<td>30</td>
<td>37</td>
<td>58</td>
</tr>
</tbody>
</table>

4.1.2 Study population

Five of the 241 patients screened and evaluated at baseline were excluded from the follow-up study (Figure 3). One patient did not have confirmed AD, three patient had moderate AD at the baseline visit, and one patient was unable to complete the tests because of impaired vision. The final participants of the ALSOVA follow-up study were 236 patients with very mild (CDR 0.5) or mild (CDR 1) AD and their caregivers from three Finnish hospital districts. The participants were recruited during the first year after the AD diagnosis from April 2002 to September 2006. The final follow-up visits were arranged during 2011, and the final questionnaires to the caregivers were administered in 2012. During the five-year follow-up period 163 patient-caregiver dyads dropped out of the study. The drop-out rates and reasons at each time point are presented in Table 11.

AD was diagnosed by geriatricians or neurologists at the memory clinics of Kuopio University Hospital, the Central Hospital in Jyväskylä, and North-Carelia Central Hospital in Joensuu. All patients underwent diagnostic clinical evaluation, including laboratory tests, brain imaging (CT or MRI), and neuropsychological tests (CERAD, Consortium to Establish a Registry for Alzheimer’s Disease Neuropsychological Battery) (Chandler et al., 2005). AD was diagnosed according to the criteria devised by the National Institute of Neurological and Communicative Disorders and Stroke and Alzheimer’s Disease and Related Disorders Association (NINCDS-ADRDA) (McKhann et al., 1984) and the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) (American Psychiatric Association, APA., 1994). AD diagnoses were confirmed by a study neurologist. All the patients who participated in follow-up visits used the AD-targeted medication, i.e. acetylcholine esterase inhibitors or memantine. However, there were a few breaks in AD medication in some of the patients, due for example, to suspected side effects and a change in drugs at the time of the follow-up visits (Törmälehto et al., 2015).
4.1.3 Data collection and follow-up
Patient-caregiver dyads were invited to a baseline study visit that included a patient and caregiver interview by the study nurse and a CERAD examination conducted by the psychologist. The baseline visit lasted 3-4 hours. Data collected during the interview included socio-demographic details (age, gender, education measured as total years of schooling, living arrangements, income, activities) and general health (other diseases and use of drugs). During the visit, data were also collected with several scales that are described in more detail below (please, see Measurements section).

Patient-caregiver dyads were followed-up once a year for three years after the baseline visit, and at an additional five-year visit. The follow-up visits lasted 2-3 hours and included a patient and caregiver interview performed by the study nurse and a CERAD examination of the patient conducted by a psychologist. During each follow-up visit, the same data were also collected as at baseline. The ALSOVA study was not a clinical trial, so it did not include a regular doctor’s appointment, AD treatment, and follow-up, instead, all the patients were provided with the same standard care. The primary reason for discontinuation of the follow-up was asked for the participants. The dates of institutionalization and death were obtained from medical records.

4.2 MEASUREMENTS
Several instruments and scales were used in the ALSOVA study to collect the data from patients and caregivers (Table 12). Among other things study nurse interviewed the patients and together with them completed the patient self-rated QoL-AD, 15D, VAS, and Beck Depression Inventory. During the follow-up visits, a study nurse recorded whether the patients needed any assistance in responding to the QoL-AD, 15D or VAS–questionnaires. The assistance was given orally by explaining the questionnaires and made them more understandable for the patients. Some of the patient’s also needed help to choose the answer. The MMSE of the patients was examined as a part of the Consortium to Establish a Registry for Alzheimer’s Disease Neuropsychological Battery (CERAD-NB) by a psychologist. The study nurse also interviewed the caregivers and together with them assessed the patient’s NPI, CDR, and ADCS-ADL. The caregivers also rated the QoL-AD of the patients.
Table 12. Efficacy parameters of the ALSOVA baseline and follow-up data.

### Baseline assessment and annual assessments (1, 2, 3, 5 years)

**Carried out with the patient him/herself**
- **cognition** – MMSE, CERAD (psychologist)
- **depression** – BDI (psychologist)
- **quality of life** – 15D, AD-QoL, VAS (psychologist)

**Assessed by the family caregiver**
- **patient’s severity of dementia** – CDR (assessed on the basis of the patient and caregiver interview)
- **patient’s functional ability** – ADCS, IADL (study nurse)
- **patient’s quality of life** – AD-QoL (study nurse)
- **caregiver’s stress and quality of life** – GHQ, 15D, VAS (study nurse)
- **caregiver’s depression** – BDI (study nurse)

### 4.2.1 Quality of Life

In this study, three patient-reported instruments were used to assess quality of life (QoL): the generic 15D (Sintonen et al., 1995, 2001), the Quality of Life in Alzheimer’s Disease (QoL-AD) (Logsdon et al., 1999), and the Visual Analogue Scale (VAS) (Kertzman et al., 2004), as well as one caregiver-rated assessment of patient QoL (QoL-AD).

The 15D is a generic, multidimensional, standardized, self-administered measure that has both profile and single index score properties. The 15D assesses 15 dimensions: mobility, vision, hearing, breathing, sleeping, eating, speech, excretion, usual activities, mental function, discomfort and symptoms, depression, distress, vitality, and sexual activity. Each dimension has five grades of severity that are weighted using population-based preferences to obtain a single index score. The values of the 15D index range from 0.1062 (worst) to 1 (full health), on a scale where 0 represents being dead.

The QoL-AD is an AD-specific self- and caregiver-rated measure of wellbeing, which has been specifically developed for use with AD patients and their caregivers. The QoL-AD contains 13 items (physical health, energy, mood, living situation, memory, family, marriage, friends, self as a whole, ability to do chores, ability to do things for fun, money, and life as a whole). The 13-items are rated as poor, fair, good, or excellent. The items have response options from 1 (poor) to 4 (excellent) that are summed together to produce a summary score ranging between 13 (worst) and 52 (best).

In study I (baseline study), patient self-rated and caregiver-rated QoL assessments included only 168 patient and spouse caregiver dyads, since spouse caregivers and other
caregivers may differ in their ratings on the patient’s QoL-AD scale. In studies II and III, all the 236 patient and caregiver dyads were included.

The VAS was used to assess each patient’s satisfaction with life. The 10-cm VAS is a one-item assessment of QoL including a single question on general well-being with a rating from 0 (worst possible) to 100 best possible) ("We ask you to rate your satisfaction with your life today on the scale below. 100 describes the best possible situation, and 0 is the worst possible alternative. Please draw a horizontal line on the point that describes your own quality of life at this moment").

4.2.2 Neuropsychiatric Inventory
The 12-item Neuropsychiatric Inventory (NPI) was used to assess behavioral and psychological problems (neuropsychiatric symptoms) during the month prior to the examination (Cummings et al., 1994). The NPI is an interview-based tool that evaluates the frequency and severity of delusions, hallucinations, agitation, depression, anxiety, euphoria, apathy, nighttime behavior disturbances, appetite disorders, disinhibition, irritability, and aberrant motor behavior. Each item is rated on both frequency (scores from 1 to 4, with 1 being “occasionally” and 4 being “very frequently”) and severity (scores from 1 to 3, with 1 being “mild” and 3 being “severe”). If the symptom is absent, the score is zero (0). The NPI total score ranges from 0 to 144, with higher scores indicating worse symptoms.

4.2.3 Beck Depression Inventory
Depression was assessed by using the 21-item Beck Depression Inventory (BDI), which is a multiple-choice, self-reported instrument (Beck et al., 1961). The BDI is composed of 21 items assessing mood, pessimism, sense of failure, self-dissatisfaction, guilt, punishment, self-dislike, self-accusation, suicidal ideas, crying, irritability, social withdrawal, body image, work difficulties, insomnia, fatigue, appetite, weight loss, bodily preoccupation, and loss of libido. Each question contains a four-point scale, which ranges from 0 (symptom not present) to 3 (symptom very intense). The sum of all BDI item scores ranges from 0 to 78 (1-10 = normal, 11-16 = mild mood disturbance, 17-20 = borderline clinical depression, 21-30 = moderate depression, 31-40 = severe depression, over 40 = extreme depression).
4.2.4 Clinical Dementia Rating
The severity of AD was assessed by using the Clinical Dementia Rating Scale (CDR), which is a reliable and valid tool containing six domains: memory, orientation, judgment and problem solving, community affairs, home and hobbies, and personal care (Hughes et al., 1982; Morris et al., 1993). The rating is obtained through semi-structured interviews of patients and their caregivers, in which the six domains are rated on a 5-point scale: 0=no impairment; 0.5=questionable impairment; 1=mild impairment; 2=moderate impairment; and 3=severe impairment. The six domains are then either formulated into a global rating (0, 0.5, 1, 2, 3) through a complex scoring algorithm or to a CDR-SOB score, which is obtained by simply summing the domain ratings, ending with a continuous score ranging from 0 to 18. CDR-SOB scores have been demonstrated to correspond reliably to global scores: CDR-SOB scores of 0.5 to 4.0 correspond to a global score of 0.5; 4.5 to 9.0 to a global score of 1.0; 9.5 to 15.5 to a global score of 2.0; and 16.0 to 18.0 to a global score of 3.0 (O’Bryant et al., 2010; Coley et al., 2011).

4.2.5 Mini-Mental State Examination
Cognition was evaluated by using the Mini-Mental State Examination (MMSE) (Folstein et al., 1975), which is a widely used, brief, 30-point instrument to measure cognitive ability, assessing attention, memory, orientation, language, and visuospatial ability. The overall score ranges from 0 to 30, with higher scores indicating better cognitive function.

4.2.6 Activities of daily living
The Alzheimer’s Disease Cooperative Study - Activities of Daily Living Inventory (ADCS-ADL) was used to evaluate activities of daily living (Galasko et al., 1997). This is an informant/caregiver administered 23-item scale in which scores range from 0 to 78, with higher scores indicating better functioning. The informant/caregivers are asked in an interview format to rate the patient’s level of performance for each activity in the past four weeks.

4.3 STATISTICAL METHODS
4.3.1 Study I
In study I statistical analyses were carried out with SPSS software for Windows release 11.5.1. Means and proportions were calculated for continuous and categorical variables. Group differences were compared with paired t-tests and chi-square test. Pearson’s correlation test or Spearman’s correlation test was used to analyze the correlations between different variables. Factor analysis of NPI was carried out with principal component axis factoring with promax rotation. A cut-off point of eigenvalues over 1.0 was used. Sum variables were formed based on compounded factors and were later used
as continuous variables. The item content of the four compounded factors was labeled as Psychotic/agitation (factor 1), Affective (factor 2), Frontal-type behavior (factor 3), and other (factor 4). An age- and gender-adjusted linear regression model was used to analyze the predictors of the caregiver’s assessment of patient QoL. Missing data for 15D items (10 cases) were replaced by the median value. The variables showing a possible effect (p<0.2) on the caregiver assessment of patient QoL in the univariate linear analysis were also added to the linear regression model. A p-value of <0.05 was considered to indicate statistical significance.

4.3.2 Study II
In study II, statistical analyses were performed with IBM’s SPSS statistics software (version 20.0, SPSS Inc., Chicago, IL, USA) and STATA (version 9.0, StataCorp, Texas, USA). Descriptive statistical methods (i.e., means, percentages) were used to summarize the data. To evaluate disease progression (CDR-SOB) rates and QoL change, we first averaged the annual changes over the observed follow-up period for each participant. The statistical significance level was set at p<0.05, and 95%-confidence intervals (CIs) were used to report the results. We used generalized estimating equations (GEE) to adjust data for confounders in multivariate analyses. The advantage of a GEE model is the possibility to also use the data on dropouts. Model goodness-of-fit was examined using the Akaike information criterion (AIC) and residual plots (for goodness-of-fit of the mean models), as well as quasi-AIC (for correlation structures in GEE models).

To compare the sensitivity of different QoL measures, we examined the change in QoL scores as the percentage change from the mildest stages of AD (CDR-SOB 2 or less) to severe AD (up to a maximum CDR-SOB of 18). To compare the four QoL measures, we rescaled the unadjusted 15D and QoL-AD scores to the same range as the VAS (0 to 100) using the following equation: Rescaled 15D= (15D Score – 0.1062) * 100 / (1-0.1062) and Rescaled QoL-AD=(QoL-AD Score – 12) * 100 / (48-12). We then estimated the relative differences (% change) in QoL scores in relation to the mildest stages of AD (CDR-SOB 2 or less). Repeated-measures logistic regression (i.e., GEE) with the logit-link function and a binomial distribution was used to estimate odds ratios (ORs) for a patient requiring assistance in completing the questionnaires and for the patient completing the self-rated QoL questionnaires without assistance. The ORs were adjusted for age, gender, and years of education. The QoL data were adjusted for characteristics of the patients (age, gender, years of education, co-morbidities) and caregivers (age, gender, employment status, years of education, caregiver-patient relationship) to examine the relationship between QoL and AD severity. Adjusted estimates were stratified by the need for assistance in completing the QoL questionnaires to examine how assistance from the study nurse or psychologist may have affected patient self-rated QoL ratings. The adjustments were conducted using GEE models with a Gaussian distribution and the identity link function. The unstructured correlation matrix was most suitable for the VAS and 15D in the GEE models, and the first-order autoregressive correlation matrix for self- and caregiver-rated QoL-AD. The relationship between QoL measures and CDR-SOB appeared to be nonlinear, so we used
the CDR-SOB as a discrete category variable in adjustment of the models to avoid forcing the data into any specific function form. The adjusted estimates were plotted and smoothed using the Loess procedure with an Intercooled Stata v.9.0 default smoothing bandwidth of 0.8.

4.3.3 Study III
In study III statistical analyses were performed with R statistical software version 3.0.2. We used the R package nlme in model fitting. Descriptive statistical methods (i.e., means, percentages) were used to characterize the data. Univariate and multivariate statistical analysis was performed with a linear mixed effects model (LMM). The advantage of LMM models is the possibility to use all of the available longitudinal data, including the data on dropouts. The optimal residual correlation structure was chosen by comparing the Akaike information criterion. The AR(1) correlation structure gave the best value for the information criterion. The parameters that were statistically significant in univariate analysis were chosen for inclusion in multivariate analysis. The MMSE and ADCS-ADL measures the same features of AD as the CDR Global Rating, so we carried out two different multivariate analyses: one without the MMSE and ADCS-ADL and the other without the CDR Global Rating. We carried out backward variable selection for multivariate model. The least significant parameter was dropped out from the model until all the coefficients reached statistical significance. P-values < 0.05 were considered to indicate statistically significant results.

4.4 ETHICAL ASPECTS
The ALSOVA study was approved by the Ethical Committee of Kuopio University Hospital (original decision N0. 64/00, latest update 2015), the Finnish Supervisory Authority for Welfare and Health and the Finnish Ministry of Social Affairs and Health. All potential participants were informed about the study both orally and in written form, with an emphasis on the voluntary nature of participation and the confidentiality of collected data. Refusal to participate in the study did not affect patient care. Participants also had the opportunity to interrupt the study whenever they might want. The informed consent form was signed by both the patient and the caregiver. The caregivers also provided proxy consent on behalf of the patient.

The ALSOVA study was supported by grants from the Yrjö Jahnsson Foundation, the Finnish Brain Research and Rehabilitation Foundation Center Neuron and the Social Insurance Institute of Finland (Kela). Both the ALSOVA follow-up study and this study were supported by a Kuopio University Hospital VTR grant (5220/5772728).
5 Results

5.1 CHARACTERISTICS OF THE ALSOVA STUDY PARTICIPANTS

The demographics and characteristics of study participants at baseline and during the follow-up are presented in Table 13. At baseline, the mean age of the 240 patients was 75.1 years and 51.3% were female. Most of the patients were married and living with a spouse (70%) and the rest lived alone in their own home. The mean duration of the symptoms was 39.1 months before AD diagnosis. The mean MMSE was 21.5 and 34% had very mild AD (CDR 0.5). On average, patients used 4 different types of drugs (mean=3.7); 4.2% of the patients used antipsychotics and 10.9% used anti-depressives. The mean number of years of full-time education among the patients was 7.5. The reason for the fairly limited length of education is that the most of these patients were born in the 1920s to 1930s, and in their childhood and adolescence the compulsory education in Finland was only four to six years.

The mean length of full-time education was 9.1 years for spouses (they were somewhat younger than the patients) and 12.1 years for the other caregivers (mean age 52 years). The educational level of the patients and caregivers in our study is in line with the average population born at the same time in Finland. At baseline, the mean age of caregivers was 66.2 years and most of them (66.5%) were female. Nearly one-fourth (21.6 %) worked outside of the home.
<table>
<thead>
<tr>
<th>Table 13. Demographics and characteristics of study participants at baseline and during the follow-up.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline</strong> (n=236)*</td>
</tr>
<tr>
<td><strong>PATIENT</strong></td>
</tr>
<tr>
<td>Male, n (%)</td>
</tr>
<tr>
<td>Age, mean (SD)</td>
</tr>
<tr>
<td>Education years, mean (SD)</td>
</tr>
<tr>
<td>Co-morbidities</td>
</tr>
<tr>
<td>Diabetes, n (%)</td>
</tr>
<tr>
<td>CHF, CHD, or stroke, n (%)</td>
</tr>
<tr>
<td>Asthma or other lung disease, n (%)</td>
</tr>
<tr>
<td>Urinary incontinence, n (%)</td>
</tr>
<tr>
<td>Number of other co-morbidities, mean (SD)</td>
</tr>
<tr>
<td>Use of anti-dementia medication, n (%)</td>
</tr>
<tr>
<td>anticholinesterases</td>
</tr>
<tr>
<td>memantine</td>
</tr>
<tr>
<td>anticholinesterase and memantine</td>
</tr>
<tr>
<td>Use of psychothropic medication, n (%)</td>
</tr>
<tr>
<td><strong>CAREGIVER</strong></td>
</tr>
<tr>
<td>Male, n (%)</td>
</tr>
<tr>
<td>Age, mean (SD)</td>
</tr>
<tr>
<td>Education years, mean (SD)</td>
</tr>
<tr>
<td>Has been employed in past 3 months, n (%)</td>
</tr>
<tr>
<td>Relationship with patient, n (%)</td>
</tr>
<tr>
<td>Spouse</td>
</tr>
<tr>
<td>Child</td>
</tr>
<tr>
<td>Other</td>
</tr>
</tbody>
</table>
n = number of patients or caregivers, SD = standard deviation, CDR = Clinical Dementia Rating Scale, SOB = Sum of Boxes, CHF = chronic heart failure, CHD = coronary heart disease.
*) In study I, a total of 240 patients were evaluated. There were no significant differences in the presented values at baseline between study I and the baseline values of study II and study III populations.
5.2 NEUROPSYCHIATRIC SYMPTOMS AND QUALITY OF LIFE AT BASELIN E (STUDY I)

5.2.1 The prevalence and nature of different neuropsychiatric symptoms at baseline in relation to disease severity

At least one NPS was present in 76.5% of the patients with very mild AD (CDR 0.5) and in 84.9% of patients with mild (CDR 1) AD. Almost half of the patients in both the CDR 0.5 group (49.3%) and CDR 1.0 group (47.3%) had three or more neuropsychiatric symptoms. The most common symptoms were apathy, depression, irritability and agitation (Table 14). Spouse caregivers reported patients to have sleep disturbances significantly more often than other caregivers (16.9% vs 6.9, p<0.05). Delusions were more common in women (28.5% vs 16.2%, p=0.017) and aberrant motor behavior in men (25.6% vs 12.2%, p=0.008) with AD.

In factor analysis, apathy loaded in all four factors, but most prominently in the psychotic/agitation factor. Sleep disturbances and hallucinations loaded together in the fourth factor. Aberrant motor behavior and eating behavior did not load prominently onto any of the factors.

<table>
<thead>
<tr>
<th>Symptom</th>
<th>All patients n = 240 (%)</th>
<th>CDR 0.5 n = 81 (%)</th>
<th>CDR 1 or CDR 2 n = 159 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Delusions</td>
<td>54 (22.5)</td>
<td>14 (17.3)</td>
<td>40 (25.2)</td>
</tr>
<tr>
<td>Hallucinations</td>
<td>37 (15.4)</td>
<td>13 (16.0)</td>
<td>24 (15.1)</td>
</tr>
<tr>
<td>Agitation</td>
<td>71 (29.6)</td>
<td>19 (23.5)</td>
<td>52 (32.7)</td>
</tr>
<tr>
<td>Depression</td>
<td>89 (37.1)</td>
<td>26 (32.1)</td>
<td>63 (39.6)</td>
</tr>
<tr>
<td>Anxiety</td>
<td>62 (25.8)</td>
<td>23 (28.4)</td>
<td>39 (24.5)</td>
</tr>
<tr>
<td>Euphoria</td>
<td>14 (5.8)</td>
<td>4 (4.9)</td>
<td>10 (6.3)</td>
</tr>
<tr>
<td>Apathy</td>
<td>115 (47.9)</td>
<td>40 (49.4)</td>
<td>75 (47.2)</td>
</tr>
<tr>
<td>Disinhibition</td>
<td>35 (14.6)</td>
<td>15 (18.5)</td>
<td>20 (12.6)</td>
</tr>
<tr>
<td>Irritability</td>
<td>82 (34.2)</td>
<td>27 (33.3)</td>
<td>55 (34.6)</td>
</tr>
<tr>
<td>Aberrant motor behavior</td>
<td>45 (18.8)</td>
<td>13 (16.0)</td>
<td>32 (20.1)</td>
</tr>
<tr>
<td>Sleep disturbances</td>
<td>33 (13.9)</td>
<td>9 (11.1)</td>
<td>24 (15.3)</td>
</tr>
<tr>
<td>Eating disturbances</td>
<td>62 (25.8)</td>
<td>18 (22.2)</td>
<td>44 (27.7)</td>
</tr>
</tbody>
</table>

n = number of patients, CDR = Clinical Dementia Rating Scale. Results are expressed as number of patients (n) and percentages (%).

Depressive symptoms were common, with 32.5% of the patients scoring more than 12 points in the BDI. Women more frequently had depressive symptoms than men (10.9±6.9 vs 9.0±6.4, p=0.031). The correlation between patient self-rated BDI scores and the caregiver-assessed NPI depression score was significant (p=0.029).
5.2.2 Quality of life in patients with very mild and mild AD at baseline

Patient self-rated QoL did not differ significantly between patients with very mild and mild AD. Patient-rated 15D scores were higher in patients with a younger age (p=0.016) and those with better general health (lower number of drugs) (p< 0.05), but their ratings did not differ with gender, education, incomes, marital status, MMSE, ADCS-ADL, NPI, or BDI scores.

Patient self-rated QoL-AD was lower as a function of higher BDI scores (p < 0.001). There was also a significant positive association between self-rated QoL-AD and higher education and incomes. Conversely, there was no association between self-rated QoL-AD scores and age, MMSE, ADCS-ADL, or NPI scores.

Spouse caregivers rated all dimensions of patient QoL lower than the patients themselves. A lower functional capacity, more severe NPS, and higher total number of drugs in patients and depression in spouse caregivers were significant predictors of a lower assessment of patient QoL by spouse caregivers. Among patients with at least one NPS (82.1%), spouse caregivers rated patients QoL significantly lower if the patients had a lower ADCS-ADL (p=0.000), higher CDR (p=0.023), higher total number of drugs (p=0.038) and the spouse caregivers themselves had a higher BDI (p=0.002). However, in patients without NPS (17.9%), spouse caregiver-rated patient QoL was lower with a higher patient age (p=0.005) and lower ADCS-ADL (p=0.033).

5.3 PATIENT’S ABILITY TO COMPLETE QUALITY OF LIFE QUESTIONNAIRES (STUDY II)

The probability of patients needing assistance in completing questionnaires began to increase in the very early stages of AD, approximately after the CDR-SOB had reached 4-6 (Figure 4). The probability of a patient receiving assistance was 1.41 (95% CI 1.31-1.52) per one-point increase in the CDR-SOB (p<0.001). Moreover, the ability of patients to complete the QoL- questionnaires at all, with or without assistance, declined after the CDR-SOB reached 11 points, a value that correlated with an early moderate stage of AD and MMSE 11- 20.

None of the patients with severe AD (CDR-SOB of 16 to 18) were able to complete the VAS or QoL-AD without assistance. The probability of a patient being able to complete the 15D, VAS, or QoL-AD was 0.84 (95% CI 0.78 –0.90), 0.53 (95% CI 0.45–0.65), and 0.53 (95% CI 0.44–0.63), respectively, per one-point increase in CDR-SOB. All values were statistically significant (p<0.001) (Figure 5).

Both self-and caregiver-rated QoL-AD scores were lower than the self-rated 15D and VAS (Figure 6). The patients who received assistance in completing the VAS reported lower scores than the patients who did not require assistance. Caregiver-rated patient QoL-AD was lower if the patient had needed help in completing the QoL-AD questionnaire.
Figure 4. Probability of a patient needing help in completing the quality of life questionnaires as a function of Alzheimer's disease severity. CDR-SOB = Clinical Dementia Rating, Sum of Boxes. The data are adjusted for patient age, gender, and education. Probability estimated using generalized estimating equations with a binomial distribution, logit-link function, and unstructured correlation structure (repeated measures logistic regression).
Figure 5. Proportion of patients completing the self-rated quality of life questionnaires as a function of the severity of Alzheimer’s disease. CDR-SOB = Clinical Dementia Rating, Sum of Boxes. Curves are smoothed using the Loess procedure (smoothing bandwidth 0.8).
Figure 6. The mean relative differences in unadjusted quality of life scores across the Alzheimer's disease severity continuum. CDR-SOB = Clinical Dementia Rating, Sum of Boxes. Scores are rescaled to the same scale (0-100) using the equation: (Score – Minimum Score) * 100 / (Maximum score – Minimum Score). The starting point represents the mean quality of life in individuals with a CDR-SOB of 2 or less. CDR-SOB scores of 0.5- 4.0 correspond to a CDR global score of 0.5, i.e. very mild AD, CDR-SOB scores 4.5- 9.0 to a CDR global score of 1.0, i.e. mild AD, CDR-SOB scores 9.5- 15.5 to a CDR global score of 2.0, i.e. moderate AD, and CDR-SOB scores 16.0- 18.0 to a CDR global score of 3.0, i.e. severe AD.
5.4 SELF-AND CAREGIVER-RATED PATIENT QOL IN RELATION TO AD PROGRESSION (STUDY II)

During the five-year follow-up, AD had progressed to the mild (CDR 1) stage in 41.1% of the patients, the moderate (CDR 2) stage in 38.4% of the patients, and to the severe (CDR 3) stage in 17.8% of the patients. Changes in different patient variables measured during the follow-up are presented in Table 15. Between study visits, the mean annual increase in CDR-SOB was 1.75 (95% CI 1.55 – 1.94) points per year over the duration of follow-up (p<0.001). The mean individual annual increases in CDR-SOB were slightly smaller at 1.28 (95% CI 1.11 – 1.45) points per year (p<0.001) in patients who remained in the study for the full five-years.

None of the patient self-rated QoL scores changed significantly over the 5-year follow-up. However, the average annual change in the caregiver-rated QoL-AD during the follow-up was statistically significant, [mean change (95% CI): -1.88 (-2.15 to -1.60)] (p <0.001). The caregiver-rated QoL-AD showed the most marked change in patient QoL in relation to AD severity. The self- and caregiver-rated QoL scores began to diverge even in very mild cognitive impairment after CDR-SOB reached 4, a value that corresponds with an MMSE score of 25-30 and a CDR global rating of 0.5. The mean rescaled unadjusted 15D, VAS, self-rated QoL-AD, and caregiver-rated QoL-AD scores were 85.0 (95 % CI 84.3–85.7), 81.0 (79.8-82.1), 51.7 (50.6-52.8), and 37.9 (36.9-38.9).
Table 15. MMSE, ADCS-ADL, CDR, CDR-SOB, and QoL- measures during the follow-up of patients with very mild (CDR 0.5) and mild (CDR 1) AD at baseline and during the follow-up.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Baseline (n=236)</th>
<th>1-year follow-up (n=198)</th>
<th>2-year follow-up (n=168)</th>
<th>3-year follow-up (n=131)</th>
<th>5-year follow-up (n=73)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MMSE</td>
<td>21.5 (3.4)</td>
<td>19.3 (4.3)</td>
<td>17.8 (5.0)</td>
<td>16.8 (4.7)</td>
<td>13.8 (6.9)</td>
</tr>
<tr>
<td>ADCS-ADL</td>
<td>64.6 (8.9)</td>
<td>58.1 (12.7)</td>
<td>51.3 (15.9)</td>
<td>46.1 (18.4)</td>
<td>38.0 (19.7)</td>
</tr>
<tr>
<td>CDR Global Rating, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.5 - very mild</td>
<td>128 (54.2)</td>
<td>64 (32.3)</td>
<td>27 (16.1)</td>
<td>8 (6.2)</td>
<td>2 (2.7)</td>
</tr>
<tr>
<td>1 - mild</td>
<td>108 (45.8)</td>
<td>112 (56.6)</td>
<td>97 (57.7)</td>
<td>75 (58.1)</td>
<td>30 (41.1)</td>
</tr>
<tr>
<td>2 - moderate</td>
<td>0</td>
<td>22 (11.1)</td>
<td>42 (25.0)</td>
<td>40 (31.0)</td>
<td>28 (38.4)</td>
</tr>
<tr>
<td>3 - severe</td>
<td>0</td>
<td>0</td>
<td>2 (1.2)</td>
<td>6 (4.7)</td>
<td>13 (17.8)</td>
</tr>
<tr>
<td>CDR-SOB</td>
<td>4.1 (1.5)</td>
<td>5.6 (2.3)</td>
<td>7.1 (3.0)</td>
<td>8.3 (3.4)</td>
<td>10.8 (4.2)</td>
</tr>
<tr>
<td>QoL-AD, patient self-rated</td>
<td>30.3 (5.5)</td>
<td>30.6 (5.6)</td>
<td>30.9 (5.9)</td>
<td>30.3 (6.2)</td>
<td>31.1 (6.6)</td>
</tr>
<tr>
<td>15D, patient self-rated</td>
<td>0.860 (0.081)</td>
<td>0.864 (0.084)</td>
<td>0.867 (0.092)</td>
<td>0.875 (0.093)</td>
<td>0.883 (0.088)</td>
</tr>
<tr>
<td>VAS, patient self-rated</td>
<td>81.9 (16.1)</td>
<td>81.1 (17.1)</td>
<td>80.5 (16.1)</td>
<td>79.8 (17.3)</td>
<td>80.8 (15.0)</td>
</tr>
<tr>
<td>QoL-AD, caregiver-rated</td>
<td>27.4 (4.8)</td>
<td>25.9 (5.0)</td>
<td>24.8 (4.9)</td>
<td>23.6 (4.6)</td>
<td>22.1 (4.8)</td>
</tr>
</tbody>
</table>

Results are expressed as the mean (SD), unless otherwise specified. n = number of patients, SD = standard deviation, MMSE=Mini-Mental State Examination, scale 0-30; ADCS-ADL=The Alzheimer’s Disease Cooperative Study - Activities of Daily Living Inventory, scale 0-78; CDR=Clinical Dementia Rating, scale 0-3; CDR-SOB= Clinical Dementia Rating Scale-Sum of Boxes, scale 0-18; QoL-AD=Quality of Life in Alzheimer’s Disease, scale ranges between 13 (worst) and 52 (best); 15D=Generic quality of life instrument, index ranges from 0.1062 (worst) to 1 (full health); VAS=Visual Analogue Scale, rating from 0 (worst possible) to 100 (best possible).
5.5 THE ASSOCIATION OF NEUROPSYCHIATRIC SYMPTOMS WITH SELF- AND CAREGIVER-RATED QUALITY OF LIFE DURING THE FIVE-YEAR FOLLOW-UP (STUDY III)

Patient self-rated QoL-AD did not change significantly (p=0.245) over the five-year follow-up period, as the NPI total score increased (Figure 7). However, caregiver-rated patient QoL-AD declined significantly (p≤0.001), in relation to the increase in the NPI total score over the follow-up period (Figure 8).

Figure 7. The impact of neuropsychiatric symptoms on quality of life (QoL) scores as reported by the patient at each time point during the five-year follow-up. The figure also expresses the correlation between the measures which can be seen more narrow confidence intervals. Curves were smoothed using the Spline procedure. The grey area represents the confidence interval of mean value. NPI=Neuropsychiatric Inventory. NPI total score (0-144), range 0-73.
None of the NPS was associated with patient self-rated QoL-AD at baseline (Table 16). During the five-year follow-up, only apathy (p=0.007) had an effect on patient self-rated QoL-AD. However, at baseline, caregiver-rated patient QoL-AD associated significantly with the existence of all the NPS, especially (p≤0.001) with apathy, agitation, anxiety, irritability, and depression. During the 5-year follow-up, caregiver-rated patient QoL-AD correlated significantly (p<0.001) with delusions, hallucinations, apathy and appetite disturbances.

NPS increased with the progression of Alzheimer’s disease during the five-year follow-up period (Table 17).
Table 16. The impact of specific neuropsychiatric symptoms on quality of life

<table>
<thead>
<tr>
<th>NPS</th>
<th>Baseline</th>
<th>During 5-year follow up</th>
<th>Baseline</th>
<th>During 5-year follow up</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>p-value</td>
<td>p-value</td>
<td>p-value</td>
<td>p-value</td>
</tr>
<tr>
<td>Delusions</td>
<td>0.970</td>
<td>0.613</td>
<td><strong>0.000</strong></td>
<td><strong>0.000</strong></td>
</tr>
<tr>
<td>Hallucinations</td>
<td>0.609</td>
<td>0.240</td>
<td><strong>0.032</strong></td>
<td><strong>0.000</strong></td>
</tr>
<tr>
<td>Agitation</td>
<td>0.055</td>
<td>0.138</td>
<td><strong>0.000</strong></td>
<td>0.110</td>
</tr>
<tr>
<td>Depression</td>
<td>0.815</td>
<td>0.232</td>
<td><strong>0.000</strong></td>
<td>0.475</td>
</tr>
<tr>
<td>Anxiety</td>
<td>0.368</td>
<td>0.104</td>
<td><strong>0.000</strong></td>
<td><strong>0.002</strong></td>
</tr>
<tr>
<td>Euphoria</td>
<td>0.968</td>
<td>0.654</td>
<td>0.026</td>
<td>0.414</td>
</tr>
<tr>
<td>Apathy</td>
<td>0.998</td>
<td><strong>0.007</strong></td>
<td><strong>0.000</strong></td>
<td><strong>0.000</strong></td>
</tr>
<tr>
<td>Disinhibition</td>
<td>0.164</td>
<td>0.270</td>
<td>0.080</td>
<td>0.175</td>
</tr>
<tr>
<td>Irritability</td>
<td>0.381</td>
<td>0.904</td>
<td><strong>0.000</strong></td>
<td>0.202</td>
</tr>
<tr>
<td>Aberrant motor behavior</td>
<td>0.685</td>
<td>0.250</td>
<td><strong>0.002</strong></td>
<td><strong>0.017</strong></td>
</tr>
<tr>
<td>Sleep disturbances</td>
<td>0.124</td>
<td>0.211</td>
<td>0.637</td>
<td>0.064</td>
</tr>
<tr>
<td>Appetite disturbances</td>
<td>0.957</td>
<td>0.141</td>
<td><strong>0.002</strong></td>
<td><strong>0.000</strong></td>
</tr>
</tbody>
</table>

NPS = Neuropsychiatric symptoms
QoL-AD = Quality of Life in Alzheimer’s disease
p < 0.05 Statistically significant
p < 0.001 Statistically highly significant
Table 17. Neuropsychiatric symptoms at baseline and during the follow-up

<table>
<thead>
<tr>
<th></th>
<th>Baseline (n=236)</th>
<th>1-year follow-up (n=198)</th>
<th>2-year follow-up (n=168)</th>
<th>3-year follow-up (n=131)</th>
<th>5-year follow-up (n=73)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number (percentage) of patients with or without NPS, classified by NPI total score</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>no symptoms</td>
<td>41 (17.4)</td>
<td>26 (13.2)</td>
<td>14 (8.3)</td>
<td>11 (8.5)</td>
<td>8 (11.0)</td>
</tr>
<tr>
<td>mild symptoms &lt; 20</td>
<td>164 (69.5)</td>
<td>136 (69.0)</td>
<td>107 (63.7)</td>
<td>81 (62.3)</td>
<td>40 (54.8)</td>
</tr>
<tr>
<td>moderate symptoms 20-50</td>
<td>31 (13.1)</td>
<td>32 (16.2)</td>
<td>42 (25.0)</td>
<td>36 (27.7)</td>
<td>22 (30.1)</td>
</tr>
<tr>
<td>severe symptoms &gt; 50</td>
<td>0 (0.0)</td>
<td>3 (1.6)</td>
<td>5 (3.0)</td>
<td>2 (1.5)</td>
<td>3 (4.1)</td>
</tr>
<tr>
<td>NPI total score, mean (SD)</td>
<td>8.8 (9.6)</td>
<td>11.4 (11.8)</td>
<td>13.9 (13.0)</td>
<td>14.9 (13.5)</td>
<td>14.4 (14.4)</td>
</tr>
<tr>
<td>NPI total score, mean (SD) classified by the severity of AD</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CDR 0.5 - very mild</td>
<td>7.6 (8.3)</td>
<td>7.0 (9.0)</td>
<td>6.6 (7.7)</td>
<td>9.7 (9.8)</td>
<td>10.0 (8.4)</td>
</tr>
<tr>
<td>CDR 1 - mild</td>
<td>10.3 (10.9)</td>
<td>12.6 (12.2)</td>
<td>12.4 (11.5)</td>
<td>10.5 (9.8)</td>
<td>8.4 (6.1)</td>
</tr>
<tr>
<td>CDR 2 - moderate</td>
<td>0 (0.0)</td>
<td>19.1 (13.7)</td>
<td>20.8 (14.8)</td>
<td>20.9 (14.7)</td>
<td>21.2 (14.1)</td>
</tr>
<tr>
<td>CDR 3 - severe</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>30.0 (32.5)</td>
<td>33.8 (11.6)</td>
<td>27.6 (18.6)</td>
</tr>
</tbody>
</table>

n = number of patients, NPI = Neuropsychiatric Inventory, range 0 (minimum) to 144 (maximum), SD = standard deviation
AD = Alzheimer’s disease, CDR = Clinical Dementia Rating Scale classification, range 0-3
5.6 ASSOCIATION OF OTHER FACTORS WITH THE CHANGES IN QUALITY OF LIFE (STUDY III)

Patient self-reported QoL scores declined as a function of higher age ($p=0.021$), a lower level of education ($p=0.020$), and a diminished ADCS-ADL ($p=0.004$). In comparison, caregiver ratings for patient QoL appeared to decline with reduced patient MMSE ($p=0.001$), increased CDR global score ($p=0.000$), and among the more elderly caregivers ($p=0.004$).
6 Discussion

6.1 NEUROPSYCHIATRIC SYMPTOMS AT BASELINE

It has been estimated that the prevalence of NPS varies from 60 to 90% during the course of AD (Youn et al., 2011; Balthazar et al., 2014). In this study, NPS were common, even in the early stages of the disease, in line with previous studies (Lyketsos et al., 2011; Dillon et al., 2013; Khoo et al., 2013). At baseline, over 80% of the patients had at least one symptom and almost half of the patients displayed three or more symptoms. The most common NPS were apathy, anxiety, agitation, irritability, and depression, as in some previous studies (Vogel et al., 2010; Steinberg et al., 2014). Apathy appears to be the most common and persistent NPS in AD patients. Apathy is defined as loss of or diminished motivation for at least 4 weeks, accompanied with two of the following: diminished goal-directed behavior and cognitive activity, and diminished emotions (Lyketsos et al., 2011). Agitation, irritability, anxiety (Shin et al., 2005; Huang et al., 2012; Khoo et al., 2013), aggression (Shin et al., 2005), sleep disorders, delusion, and hallucinations (Allegri et al., 2006; Huang et al., 2012) are among the most challenging and distressing symptoms from the perspective of caregivers. In this study, NPS increased with the progression of AD. This finding is supported by Khoo et al. (2013) and Conde-Sala et al. (2015).

At baseline, NPS contributed to the functional capacity and well-being of patients, as well as depression in caregivers. NPS correlated with functional capacity, but not with cognitive ability. This finding is similar to some previous studies, which have reported that NPS are more closely associated with functional capacity than cognitive decline (Tractenberg et al., 2002; D’Onofrio et al., 2012).

6.2 ABILITY OF PATIENTS TO ASSESS THEIR QUALITY OF LIFE

Several previous studies have estimated that mildly to moderately impaired AD patients can provide reliable self-reported information about their well-being and health (Logsdon et al., 2002; Ready et al., 2004; Sands et al., 2004; Novella et al., 2006; Schulz et al., 2014). The cause for discrepancies between self- and caregiver-rated patient QoL has been attributed to caregivers generally underestimating the well-being and health of AD patients when compared to patient self-assessments (Sands et al., 2004; Novella et al., 2006; Schulz et al., 2014; Andrieu et al., 2016).

However, this study revealed that the ability of AD patient to complete QoL questionnaires unassisted or even assisted began to decline earlier than previously estimated, even in the mild stage of the disease. In the evaluation of AD severity, we used a global and continuous measure, the CDR-SOB. This measure does not appear to have the pitfalls of MMSE, which has been previously claimed to be inaccurate in reflecting the
total impact of AD and, its progression and consequences, and to produce volatile estimates (McLaughlin et al., 2010; O’Bryant et al., 2008, 2010; Coley et al., 2011).

The probability of a patient having received assistance in completing QoL questionnaires began to increase after the CDR-SOB reached approximately 4-6, a value that represents very mild AD. Moreover, the patients themselves were unable to perceive the deterioration in their QoL, even if they had impaired daily functions or other severe AD-related symptoms. Instead, caregiver-rated QoL-AD correlates well with AD progression and increased NPS. Researchers and clinicians should be aware that a patient’s ability to rate QoL may be compromised, and practitioners should take care to ascertain the well-being of patients and caregivers in collaboration with both the patient and the caregiver.

6.3 DISCREPANCIES IN SELF-AND CAREGIVER-RATED QUALITY OF LIFE IN RELATION TO ALZHEIMER’S DISEASE PROGRESSION

This study demonstrated that all three self-rated QoL measures (15D, QoL-AD, VAS) are relatively insensitive to disease progression, while caregiver-rated QoL-AD appears to be substantially more sensitive. Over the five-year follow-up period, none of the three self-rated QoL scores changed significantly. However, caregiver-rated QoL-AD had declined statistically significantly by the third follow-up visit. The self- and caregiver-rated QoL scores began to diverge with very mild AD after CDR-SOB reached 4, a value that corresponds with an MMSE score of 25-30 and a CDR global rating of 0.5. The finding of a divergence between self- and caregiver-rated QoL is supported by previous cross-sectional studies (Conde-Sala et al., 2009; Black et al., 2012; Sousa et al., 2013), as well as by a three-year longitudinal study by Vogel et al. (2012).

QoL is a subjective issue, unique to each individual. Loss of insight and the decline in cognitive functions may influence the patient’s awareness of his or her own situation and functional deficits. In previous studies (Naglie et al., 2006; Karlawish et al., 2008), approximately 50 % of AD patients have rated themselves as having perfect health. In this study, caregivers reported a lower QoL than the patients themselves, and the correlation between self-reported and caregiver-reported QoL of the patient was only weak. Similar findings have been reported in many previous studies (Snow et al., 2005; James et al., 2005; Shin et al., 2005; Ready et al., 2006; Naglie et al., 2006; Jönsson et al., 2006, Vogel et al., 2006, Conde-Sala et al., 2009, 2014; Sousa et al., 2013).

However, caregiver-rated QoL values for AD patients should also be interpreted with caution, because caregivers might project a part of their own QoL onto patients when assessing patient QoL (Arons et al., 2013; Välimäki et al., 2016). For instance, caregiver burden and depression seemed to influence caregiver ratings of patient QoL (Pfeifer et al., 2013).

Patient and caregiver reports on patient QoL may represent two unique but different perspectives, both of which are valid. AD patients' opinions of their own QoL are affected
by different components from those that affect caregiver assessment of patient QoL, even when both measurements are based on the same items. Differences in measurements are probably due to multiple factors, including caregiver distress and own QoL and patient cognitive deficits and impaired insight. Patient and caregiver relationship might also influence their ratings, as well as differences in aspects of what compose QoL (Black et al., 2012; Trigg et al., 2011, 2015).

6.4 THE ASSOCIATION OF NEUROPSYCHIATRIC SYMPTOMS AND SELF- AND CAREGIVER-RATED QUALITY OF LIFE AT BASELINE AND DURING THE 5-YEAR FOLLOW-UP

Based on previous studies, NPS affect the QoL of patients with AD (Shin et al., 2005; Matsui et al., 2006; Hurt et al., 2008; Gomez-Gallego et al., 2012). In this study, NPS at baseline were significantly associated with the caregiver assessment of patient QoL-AD, but not with the patient self-assessed QoL. NPS increased with progression of AD, a finding that is supported by Khoo et al. (2013) and Conde-Sala et al. (2016). Over the 5-year follow-up period, caregiver-rated patient QoL-AD declined significantly, when the NPI total score increased. Furthermore, almost all of the NPS at baseline, especially apathy, agitation, anxiety, irritability, depression, and delusions, as well as delusions, hallucinations, apathy, and appetite disturbances during the 5-year follow-up period, correlated significantly with caregiver-rated patient QoL-AD. However, patient self-rated QoL-AD remained quite stable during the follow-up, despite the increasing NPS. None of the NPS had an effect on patient self-rated QoL-AD at baseline, and only apathy had an effect on self-rated QoL-AD during the five-year follow-up.

Discrepancies between patient and caregiver ratings also increased over the follow-up. These findings are similar to the results cross-sectional studies by Shin et al. (2005), Buckley et al. (2012), and Gomez-Gallego et al. (2012) and longitudinal studies by Tatsumi et al. (2009) and Conde-Sala et al. (2016). Most patients with AD have loss of insight (Vogel et al., 2004, 2006; Conde-Sala et al., 2014, 2016), which might explain why the patients themselves failed to recognize the NPS. Recent studies by Vogel et al. (2010) and Conde-Sala et al. (2016) have reported that AD patients who lack self-awareness, suffers a higher level of NPS than patients who are aware of their condition and deficits.

Caregivers identify NPS in their care recipient and reported a decrease in patients QoL. However, caregivers may also reflect their own burden of care when evaluating NPS severity or QoL for patients as Black et al. (2012), Gomez-Gallego et al. (2012), and Andrieu et al. (2016) have recently indicated. This study showed that caregiver depression was associated with the presence of NPS and also significantly influenced their rating of patient QoL. Many studies have shown that NPS leads to an increasing burden on caregivers (Aquera-Ortiz et al., 2010; Mohamed et al., 2010; Vogel et al., 2010; Dillon et al., 2013; Khoo et al., 2013; Turro-Garriga et al., 2013; Välimäki et al., 2015) and increase the risk of premature institutionalization (Banerjee et al., 2003; Gauthier et al., 2010; Gaugler et
al., 2011; Dillon et al., 2013). On the other hand, caregivers may also have difficulties in identifying NPS in patients, especially in mild AD (Stella et al., 2015). This study demonstrated that it is important for clinicians to become aware of NPS in patients with AD and improve the early detection of NPS by asking about patient behavior in more detail using structured and validated questionnaires. Careful and immediate recognition and appropriate treatment of NPS may confer substantial benefits for the patient and alleviate the burden on the caregiver. Based on recent studies, there is evidence that early diagnosis and therapy with AD-targeted medication will maintain daily functions and NPS will not emerge as rapidly as in patients with more advanced disease at the time of diagnosis and start of medication (Wynn et al., 2004; Rodda et al., 2009; Hallikainen et al., 2013).

Based on the findings of this study, patient self-rated QoL-AD cannot be recommended as the only source for evaluating the effect of NPS on patient QoL, or as a measure of successful treatment of NPS. Instead, caregivers are usually more aware of patient QoL and NPS, and this knowledge should be actively used by health care professionals in clinical practice.

6.5 FACTORS ASSOCIATED WITH CHANGES IN THE QUALITY OF LIFE DURING THE 5-YEAR FOLLOW-UP

This study showed at baseline, that self-rated QoL as assessed by the 15D was as good in very mild and mild AD as QoL of the age-matched general population in a previous study by Saarni (2007). AD patients in the ALSOVA- study had other comorbidities, but they were in a stable phase at baseline, i.e. the presence of other severe diseases was an exclusion criterion. At baseline, the significant predictors of QoL were age and general health, as in the general population (Saarni 2007). These results suggest that patients with very mild and mild AD assess their QoL in a similar way to non-demented subjects. However, generic measures evaluate different aspects of QoL compared to disease-specific instruments (i.e. QoL-AD), which contain items that are specific for the problems associated with a particular disease, and may therefore be more sensitive at detecting changes.

At baseline, the correlation between patient rated 15D and QoL-AD scores was weak. Self-reported QoL did not show any correlation with the MMSE or functional capacity. Depressive symptoms in patients correlated inversely with the QoL-AD scores, but not with 15D scores, whereas age and general health correlated with 15D but not with the QoL-AD.

Depression is a common symptom and present in all stages of AD (Zubenko et al., 2003; Starkstein et al., 2005). Several studies have shown, that depressive symptoms are strongly associated with self-reported QoL (Hoe et al., 2007; Karlawish et al., 2008; Naglie et al., 2011; Vogel et al., 2006; Gomez-Gallego et al., 2012; Sousa et al., 2013; Conde-Sala et al.,
2014). However, the consequences of depression in AD are not well known. Many studies have suggested that depression increases the degree of functional impairment (Starkstein et al., 2005; Lam et al., 2007; Benoit et al., 2008). However, this study did not show a correlation between depression and functional capacity. The discrepancies between the findings of this study and previous studies may be accounted for by differences in the study cohorts and the measures used to assess depression and functional capacity. The patients of this study had early AD, with mild functional impairment, whereas the patients examined in previous studies have been more heterogeneous, including patients with advanced AD.

It has been assumed that patients define their QoL in terms of emotional well-being and general health whereas caregivers emphasize physical and functional aspects and the baseline results of this study support this hypothesis. The strongest predictor of self-reported QoL-AD at baseline was depressive symptoms whereas the presence of functional decline and NPS predicted a poor caregiver rating of patient QoL. The strong association between the caregiver rating of patient QoL and ADL functioning has been found in many previous studies (Vogel et al., 2012; Conde-Sala et al., 2014).

During the five-year follow-up period, patient self-reported QoL declined as a function of a higher age, a lower level of education, and functional loss in activities of daily living. However, caregiver rating of patient QoL appeared to decline with a lower level of cognitive function, the severity of AD, and a higher caregiver age.

6.6 STRENGTHS AND LIMITATIONS OF THE STUDY

The main strengths of this study are the well-designed study protocol, clinical setting, and careful diagnostic evaluation of the participants, as well as the regular follow-ups using validated methods. This study was not a clinical trial; rather, all the patients were living at home and treated according to standard care, which reduced the bias. This study also had the longest QoL follow-up data so far collected (five-years), and a homogeneous patient group with very mild or mild AD at baseline. The QoL assessment included both self- and caregiver opinion.

The study also has some limitations. Quite a large number of patients dropped-out during the five-year follow-up period, as expected in this age group. However, the drop-out rate in this study was in line with those observed in previous comparable studies (Conde-Sala et al., 2014; Missotten et al., 2007; Phung et al., 2014). Dropouts may lead to bias in statistical analyses and may influence the results. To avoid the bias as much as possible, we used LMM and GEE models in the statistical analyses. LMM and GEE models have an advantage compared to more conventional methods, because all available longitudinal data, including the data on dropouts, can be used in the analyses.

The study population was recruited from memory clinics, and subjects with other severe illnesses that could have impacted on survival were excluded. This may partially explain the good health-related QoL values. Another source of selection bias relates to both
patients and caregivers participating in this study voluntarily. The Beck Depression Inventory, which was used in this study, is not a specific test to examine the depressive symptoms in Alzheimer’s patients. Moreover, this study did not directly evaluate the functioning and behavior of the participants, but relied on the caregiver interview. However, this is the method used in both the academic studies and clinical trials to examine home-dwelling AD patients’ daily abilities or behavioral problems. The caregiver burden is closely related to their rating of patient symptoms. It cannot be excluded that burdened caregivers are more prone to report NPS and overestimate the extent of the functional decline in the patient. This bias is unavoidable in all studies that rely on interviews instead of objective observations.

6.7 IMPLICATIONS FOR CLINICAL WORK AND HEALTH CARE

This study indicates that NPS are common, even in the early stages of AD. Since NPS are associated with functional decline, mortality, hospital stays, a decrease in QoL, caregiver burden and depression, earlier institutionalization, and a significant rise in the cost of care, more attention should be paid to recognizing these symptoms. The early detection of NPS by asking about patient behavior in more detail using structured and validated questionnaires is important in clinical work and health care. Careful and immediate recognition and appropriate treatment of NPS may confer substantial benefits for the patient and alleviate the burden on the caregiver. It is also important that we increase the awareness of healthcare professionals about NPS in AD.

This study also demonstrated that depressive symptoms are common in AD, and they are related to a lower QoL in both patients and their caregivers. However, depression may remain unrecognized, emphasizing the need for careful and structured assessment of NPS before deciding on the appropriate treatment.

It is quite challenging to evaluate QoL in AD patients. These patients define their QoL in terms of emotional well-being and general health, whereas caregivers emphasize physical and functional aspects. In this study, caregivers reported a lower patient QoL than the patients themselves. This study also indicated that all three self-rated QoL measures (15D, QoL-AD, VAS) are relatively insensitive to disease progression, while caregiver-rated QoL-AD appears to be substantially more sensitive. The self-reporting of QoL by AD patients has been criticized and caregiver reporting has been used in many studies. The ability of patients to evaluate their QoL may be compromised because of the lack of insight into their own condition. However, caregiver-rated AD patient QoL should also be interpreted with caution, because caregivers might project a part of their own QoL onto the patients in their assessment.
This study confirmed that information from both patient and caregiver perspectives is necessary for an optimal assessment of QOL in AD in randomized clinical trials or in clinics. On the basis of the study results, disease-specific QoL instruments are recommended for use in studying QoL in AD patients. As long as the patient-and caregiver-rated QoL-AD measures do not diverge and they both remain stable, we can say that intervention has been successful. However, this study indicated that, the efficacy of any given intervention (e.g. medication or rehabilitation) cannot be evaluated only by using QoL measurements in progressive neurodegenerative diseases such as AD. Other validated measures, such as NPI, CDR/CDR-SOB and ADCS-ADL, are recommended for use at the time of diagnosis and in clinical follow-ups. Clinicians should take care to ascertain patient and caregiver well-being in collaboration with the patient and the caregiver.
7 Conclusions

1. Neuropsychiatric symptoms (NPS) were common even in the early stages of the disease, as over 80% of the patients had at least one symptom and almost half of the patients displayed three or more symptoms. The most common NPS were apathy, anxiety, agitation, irritability, and depression (Study I).

2. The ability of patients to complete QoL questionnaires unassisted or even assisted begins to diminish quite early on. The self-rated QoL of AD patients is much more insensitive to disease progression than caregiver ratings (Study II).

3. Over the five-year follow-up period, none of the three self-rated QoL scores (VAS, 15D, QoL-AD) changed significantly. On the other hand, caregiver-rated QoL-AD declined significantly by the third follow-up visit. The self- and caregiver-rated QoL scores began to diverge with very mild AD (Study II).

4. Patient’s self-rated QoL-AD remained quite stable during the 5-year follow-up, despite the increasing frequency of NPS. However, caregiver-rated patient QoL-AD declined significantly as the NPI total score increased over the follow-up. Discrepancies between patient and caregiver ratings increased over the follow-up (Study III).

5. Almost all of the NPS correlated significantly with caregiver-rated patient QoL-AD. None of the specific neuropsychiatric symptoms had an effect on the patient self-rated QoL-AD at baseline, and only apathy had an effect on the self-rated QoL-AD during the five-year follow-up (Study III).
8 Suggestions for future research

The emphasis of AD care in recent years has been on the early detection of AD, early onset of AD-targeted medication, and the maintenance or improvement of AD patient QoL. The concept of QoL in AD will become even more important in the future, as the next generation ages, because they have lived a very different life in the welfare society compared to their parents and grandparents, and they have different expectations regarding QoL. However, it is quite challenging to assess QoL in AD patients, as this study demonstrated, so there is a need to develop new better instruments to assess QoL in AD, that also take into account the severity of the disease at the time of assessment. The new assessment tools could be computer assisted and patient could evaluate their QoL daily via a home computer, for example over a two-week period. In the advanced stages of AD, patients reflect their inner feelings in the circumstances they are at the time of the measurement. They lose the sense of time and live in the moment. Measurements carried out at home might better describe their own feelings concerning QoL than measurements carried out at outpatient clinics.

NPS are common manifestations of AD, even in the early stages of the disease. NPS are known to have many severe side effects on the lives of AD patients and their caregivers. It would therefore be important to examine which NPS are the most burdening for caregivers, and whether these symptoms are also associated with the earlier institutionalization of AD patients. Moreover, further studies focusing on the effects of psychotropic use on AD patients QoL are warranted.
9 References


Alzheimer’s Disease International, World Alzheimer Report 2016. [www.alz.co.uk.research/world](http://www.alz.co.uk.research/world)


Finnish Ministry of Social Affairs and Health, National Dementia Action Plan 2012-2020


neuropsychiatric symptoms in Alzheimer's disease (AD)? Findings from a cross-sectional study. *Archives of Gerontology and Geriatrics*, 52(3): 264–269


World Health Organization. (2015), 10 facts on dementia, [www.who.int/dementia](http://www.who.int/dementia)

World Health Organization. (2016). The ICD-10 Classification of Mental and Behavioural Disorders


Early diagnosis of Alzheimer’s disease (AD) and an early onset of AD-targeted medication to promote and maintain the Quality of Life (QoL) are among the main aims in AD patient care. This five-year follow-up study compared self- and caregiver-rated AD patient QoL measures in relation to disease progression and examined the ability of patients to complete QoL questionnaires with or without assistance. Furthermore, the study examined the prevalence and significance of neuropsychiatric symptoms with an emphasis on their influence on the QoL of AD patients.