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Effect of exercise on cognition, physical functioning, fall rate, and neuropsychiatric symptoms in people with dementia

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Academic Dissertation

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“Walking is man’s best medicine”

(Hippocrates)

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Original publications

List of original publications

This dissertation is based on the following original publications:

1. Öhman H, Savikko N, Strandberg TE, Pitkälä KH. Effect of physical exercise on cognitive performance in older adults with mild cognitive impairment or dementia: a systematic review. Dement Geriatr Cogn Disord 2014; 38, 5-6: 347-365.

2. Öhman H, Savikko N, Strandberg TE, Kautiainen H, Raivio MM, Laakkonen ML, Tilvis R, Pitkälä KH. Effects of Exercise on Cognition: The Finnish Alzheimer Disease Exercise Trial: A Randomized, Controlled Trial. J Am Geriatr Soc 2016; 64, 4: 731-738.

3. Öhman H, Savikko N, Strandberg T, Kautiainen H, Raivio M, Laakkonen ML, Tilvis R, Pitkälä KH. Effects of Exercise on Functional Performance and Fall Rate in Subjects with Mild or Advanced Alzheimer's Disease: Secondary Analyses of a Randomized Controlled Study. Dement Geriatr Cogn Disord 2016; 41, 3-4: 233-241.

4. Öhman H, Savikko N, Strandberg TE, Kautiainen H, Raivio MM, Laakkonen ML, Tilvis R, Pitkälä KH. Effects of frequent and long-term exercise on neuropsychiatric symptoms in patients with Alzheimer's disease – Secondary analyses of a randomized, controlled trial (FINALEX). EGM 017; 8, 2: 153–157.

Abbreviations

AD	Alzheimer's disease
ADAS-cog	Alzheimer's Disease Assessment Scale Cognitive Subscale
ADL	Activities of daily living
APO E	Apolipoprotein E
APP	Amyloid-ß precursor protein
BDNF	Brain-derived neurotrophic factor
CBT	Cognitive behavioural therapy
CCI	Charlson comorbidity index
CDR	Clinical Dementia Rating
CDT	Clock Drawing Test
CG	Control group
ChEIs	Acetylcholinesterase inhibitors
CSDD	Cornell Scale for Depression in Dementia
CT	Computed tomography
CVD	Cerebrovascular disease
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, fourth edition
DSM-V	Diagnostic and Statistical Manual of Mental Disorders, fifth edition
FIM	Functional Independence Measure
GDS-15	Geriatric Depression Scale, 15-item version
GE	Group exercise
HE	Home-based exercise
HPA	Hypothalamic-pituitary-adrenal axis
ICD-10	International Classification of Diseases, 10th revision
IGF-1	Insulin-like growth factor-1
IRR	Incidence Rate Ratio
MC	Multicomponent intervention
MCI	Mild cognitive impairment
MMSE	Mini-Mental State Examination

MRI	Magnetic Resonance Imaging
NINCDS-ADRDA	National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association
NMDA	*N*-methyl-D-aspartate
NPI	Neuropsychiatric Inventory
NPS	Neuropsychiatric symptom(s)
PET	Positron emission tomography
PWD	Patient(s) with dementia
PSEN1	Presenilin 1
PSEN2	Presenilin 2
RCT	Randomized controlled trial
SD	Standard deviation
SPECT	Single-photon emission computed tomography
SPPB	Short Physical Performance Battery
TMT	Trail Making Test
TAU	Treatment as usual
VD	Vascular dementia
VF	Verbal Fluency
WHO	World Health Organization

Abstract

Alzheimer's disease (AD) is a progressive degenerative disorder that leads to cognitive and functional decline, various neuropsychological symptoms (NPS), and often early placement in institutional care. The current options of prevention or pharmacological treatment of AD are very limited, and thus, interest in non-pharmacological approaches is growing. One of the most keenly studied subjects is physical exercise as a therapeutic strategy for persons with AD. Numerous studies have shown that physical exercise has a positive effect on cognition in healthy adults. However, findings in subjects with cognitive impairments are scarce and conflicting.

This study, comprising four sub-studies, explores the effects of exercise on persons with cognitive impairment or dementia. Study 1, a systematic review, aims to explore the evidence from randomized controlled trials (RCTs) of cognitive benefits of exercise in people with mild cognitive impairment (MCI) or dementia. In Studies 2 and 4, an RCT investigates the effects of an exercise intervention on cognition, NPS, and rate of institutionalization in participants with AD compared with controls receiving treatment as usual. In addition, in Study 3 the effects of exercise on physical function and fall rate in persons with mild AD and persons with advanced AD are studied separately to determine whether the treatment effects differ at different stages of AD.

In Study 1, a systematic search of databases (PubMed, Cochrane, Dare, Ovid Nursing) was performed to identify RCTs reporting the effects of exercise interventions on cognition in MCI or dementia patients. Three independent investigators rated the relevant studies according to methodological quality and summarized the extracted data descriptively.

FINALEX (Finnish Alzheimer Disease Exercise Trial) is an RCT (n=210) examining the effects of a 12-month exercise programme (60 minutes twice a week) in community-dwelling AD patients randomized into three study arms: home-based exercise (HE) (n=70), group-based exercise (GE) (n=70), and control group (CG) (n=70) without active intervention. The HE group exercised at their own homes supervised by a physiotherapist. The GE group trained in adult day-care centres in groups of ten supervised by two physiotherapists.

Study 2 reports the effects on cognition. Cognitive function was measured using the Clock Drawing Test (CDT), Verbal Fluency (VF), Clinical Dementia Rating (CDR), and Mini-Mental State Examination (MMSE) at baseline and at 3, 6, and 12 months of follow-up.

In Study 3, the intervention groups were merged, and participants were re-grouped according to their CDR scores into mild dementia and advanced dementia groups. Effects of exercise on physical

functioning (measured with the Functional Independence Measure, FIM) and fall rate were then explored separately in these groups. The incidence of falls was collected from fall diaries kept by each participant's spousal caregiver.

Changes in NPS were examined after exercise intervention between the three original groups in Study 4. NPS were assessed with the Neuropsychiatric Inventory (NPI) at baseline and at 6 months, and with the Cornell Scale for Depression in Dementia (CSDD) at baseline and at 12 months. Data on institutionalizations were retrieved from central registers.

For the systematic review, 22 trials meeting the inclusion criteria were found. The studies among older subjects with MCI reported some positive effects of physical exercise on cognition, mainly on global cognition, executive function, attention, and delayed recall. However, studies performed among older subjects with dementia showed inconsistent results. The studies had also various methodological problems.

In Study 2, home-based exercise was associated with a modest gain in executive function measured with the CDT compared with controls at 12 months (adjusted for age, sex, and CDR, $p=0.03$). No clear effects of the intervention on other measures of cognition (VF, MMSE) were found. Among participants with mild dementia (CDR ≤ 1), the deterioration in physical functioning was slower in the intervention group than in the controls. Changes in FIM at 12 months were -2.7 (95% CI -0.5 to -4.9) in the intervention group and -10.1 (95% CI -7.0 to -13.3) in the control group ($p < 0.001$). A reduction in fall rate in participants with advanced dementia (CDR 2-3) was observed in the exercise group compared with controls during the 12-month follow-up, with an incidence rate ratio of 0.47 (95% CI 0.37-0.60; $p < 0.001$) (Study 3). No difference between the exercise and control groups was found in NPI score at 6 months or in CSDD score at 12 months when analyses were adjusted for age, sex, baseline CDR, and FIM. Furthermore, the exercise intervention did not reduce the rate of institutionalization among AD patients (Study 4).

Compliance with the exercise intervention in both groups was very good, and attrition rate was low. The exercise intervention was safe; no falls or major injuries occurred during the sessions.

The current literature provides evidence that exercise interventions may have beneficial effects on cognition in persons with cognitive impairments. A 12-month regular, multicomponent, home-based intervention improved executive function in AD patients. In addition, the exercise intervention showed a positive effect in slowing the rate of functional decline in mild AD and reducing falls in participants with advanced AD. However, the intervention did not decrease NPS or change the rate of permanent placement in institutional care.

Tiivistelmä

Alzheimerin tauti on etenevä degeneratiivinen tila, joka aiheuttaa kognitiivisen ja fyysisen toimintakyvyn heikentymistä sekä neuropsykiatrisia oireita. Alzheimerin tauti lisää myös riskiä joutua pitkäaikaiseen laitoshoitoon. Alzheimerin tautiin ei ole tällä hetkellä ehkäisevää tai parantavaa lääkkeellistä hoitoa ja tästä syystä kiinnostus lääkkeettömiä hoitoja kohtaan onkin kasvanut. Liikunnan mahdollisuuksia Alzheimerin taudin ehkäisyssä ja hoidossa tutkitaan innokkaasti. Tutkimukset ovat osoittaneet, että liikunnalla on myönteisiä vaikutuksia terveiden ikääntyneiden kognitiivisiin toimintoihin. On mahdollista, että liikunnan avulla voidaan ylläpitää kognitiota ja toimintakykyä sekä vähentää neuropsykiatrisia oireita Alzheimerin tautia sairastavilla henkilöillä, mutta tutkimusnäyttö tästä on vielä varsin vähäistä ja ristiriitaista.

Tutkimus sisältää neljä osatyötä, joiden tarkoituksena on selvittää liikunnan vaikutuksia muistisairailla henkilöillä. Ensimmäisen osatyön (1) tavoitteena on selvittää tutkimusten tuottamaa näyttöä liikunnan vaikutuksista kognitioon henkilöillä, joilla oli todettu lievä kognitiivinen heikentymä sekä henkilöillä, joilla on muistisairaus. Toisen ja neljännen osatyön tavoitteena on tutkia pitkäaikaisen liikuntaintervention vaikutuksia Alzheimerin tautia sairastavien henkilöiden kognitioon ja neuropsykiatrisiin oireisiin sekä laitoshoitoon joutumiseen. Kolmannen osatyön tavoite on selvittää liikuntaintervention vaikutuksia toimintakykyyn ja kaatumisten määrään lievää ja edennyttä Alzheimerin tautia sairastavilla.

Ensimmäinen osatyö on systemaattinen katsaus, jota varten tehtiin kirjallisuushaku käyttäen PubMed, Cochrane, Dare ja Ovid Nursing -tietokantoja. Katsaukseen hyväksyttyjen tutkimusten tuli olla satunnaistettuja, kontrolloituja tutkimuksia, jotka raportoivat liikuntaintervention vaikutuksia kognitioon lievästä kognitiivisesta heikentymisestä tai muistisairaudesta kärsivillä henkilöillä. Kolme tutkijaa arvioi tutkimusten metodologisen laadun ja tuloksia tarkasteltiin systemaattisesti.

FINALEX (Finnish Alzheimer Disease Exercise Trial) on satunnaistettu, kontrolloitu tutkimus (n=210), jossa selvitettiin 12 kuukauden liikuntaintervention (60 minuuttia kahdesti viikossa) vaikutuksia kotona asuvilla Alzheimerin tautia sairastavilla. Tutkittavat jaettiin kolmeen ryhmään: kotiharjoittelijat (n=70), ryhmäharjoittelijat (n=70) sekä verrokkiryhmä (n=70), joka jatkoi tavanomaisessa hoidossa. Kotiharjoittelijat kuntoilivat omassa kodissaan fysioterapeutin ohjaamina, kun taas 10 hengen ryhmät harjoittelivat päivätoimintakeskuksissa kahden fysioterapeutin johdolla.

Toinen osatyö kuvaa FINALEX-tutkimuksen liikuntaintervention vaikutuksia Alzheimerin tautia sairastavien kognitioon. Kognitiota mitattiin kellotestillä, kielellisen sujuvuuden testillä, MMSE-

testillä (Mini-Mental State Examination) ja CDR -luokituksella (Clinical Dementia Rating) alkuvaiheessa, 3, 6 ja 12 kuukauden kohdalla.

Kolmatta osatutkimusta varten kotiharjoittelijat ja ryhmäharjoittelijat yhdistettiin yhdeksi liikuntaryhmäksi ja osallistujat ryhmiteltiin uudelleen Alzheimerin taudin vaikeusasteen mukaan lievää ja edennyttä tautia sairastaviin. Tutkittavien fyysistä toimintakykyä arvioitiin FIM-mittarilla (Functional Independence Measure) ja kaatumisten määrää tarkasteltiin omaishoitajien pitämillä kaatumispäiväkirjoilla.

Neljännessä osatyössä verrattiin liikuntaintervention vaikutuksia neuropsykiatrisiin oireisiin ja laitoshoitoon joutumiseen kolmen alkuperäisen ryhmän välillä. Neuropsykiatrisia oireita arvioitiin alkuvaiheessa ja 6 kuukauden kohdalla käyttäen NPI-mittaria (Neuropsychiatric Inventory) ja alkuvaiheessa sekä 12 kuukauden kodalla käyttäen CSDD-mittaria (Cornell Scale for Depression in Dementia).

Tiedonkeruu tuotti 22 tutkimuskriteerit täyttävää tutkimusta, jotka sisällytettiin systemaattiseen katsaukseen. Tutkimuksissa, joiden kohderyhmänä olivat lievää kognitiivista heikentymistä sairastavat iäkkäät henkilöt, todettiin positiivinen yhteys liikuntaharjoittelun ja kognition välillä. Tavallisimmin positiivisia vaikutuksia nähtiin kokonaisvaltaisesti kognitiota mittaavissa testeissä, toiminnanohjauksessa, tarkkaavaisuudessa ja viivästetyssä mieleen palautuksessa. Muistisairailla tutkimustulokset olivat ristiriitaisia ja tutkimuksissa todettiin metodologisia puutteita (Osatutkimus 1).

Pitkäaikainen kotiharjoittelu vaikutti positiivisesti tukittavien toiminnanohjaukseen (kellotesti) 12 kuukauden kohdalla (vakioituna ikä, sukupuoli ja CDR-luokka, $p=0.03$). Muihin kognitiotesteihin (kielellinen sujuvuus, MMSE) harjoittelulla ei ollut tilastollisesti merkitsevää vaikutusta (Osatutkimus 2). Lievää Alzheimerin tautia (CDR ≤ 1) sairastavilla fyysisen toimintakyvyn heikentyminen oli merkitsevästi hitaampaa liikuntainterventioryhmässä kuin verrokkiryhmässä. FIM-pisteiden muutos 12 kuukauden kohdalla oli -2.7 (95% CI -0.5 to -4.9) liikuntaryhmässä ja -10.1 (95% CI -7.0 to -13.3) verrokkiryhmässä ($p < 0.001$). Edennyttä Alzheimerin tautia (CDR 2-3) sairastavien ryhmässä liikuntaharjoittelu vähensi merkittävästi kaatumisia verrokkeihin nähden 12 kuukauden seurannassa. Ilmaantuvuustiheyksien suhde (IRR) oli 0.47 (95% CI 0.37-0.60; $p < 0.001$) (Osatutkimus 3). Liikunta – ja verrokkiryhmien välillä ei ollut merkitsevää eroa neuropsykiatrisissa oireissa mitattuna NPI-mittarilla 6 kuukauden kohdalla ja CSDD-mittarilla 12 kuukauden kohdalla, kun tulokset vakioitiin iän, sukupuolen, lähtötilanteen CDR-luokan ja FIM-

pisteiden suhteen. Liikuntainterventiolla ei myöskään ollut vaikutusta pitkäaikaiseen laitoshoitoon joutumiseen.

Sitoutuneisuus liikuntaharjoitteluun oli erittäin hyvää molemmissa liikuntaryhmissä ja poisjättäytyneiden määrä oli pieni. Liikuntaharjoittelu oli turvallista eikä harjoitusten aikana tapahtunut kaatumisia tai muita vakavia onnettomuuksia.

Tutkimusten mukaan liikunta vaikuttaa positiivisesti muistitoimintojen heikentymisestä kärsivien henkilöiden kognitioon. 12-kuukauden säännöllinen, monialainen, kotona tapahtuva liikuntaharjoittelu paransi Alzheimerin tautia sairastavien toiminnanohjausta. Lisäksi liikuntainterventio hidasti fyysisen toimintakyvyn heikentymistä lievää Alzheimerin tautia sairastavilla ja vähensi kaatumisia edennyttä tautia sairastavilla. Harjoittelu ei kuitenkaan vaikuttanut neuropsykiatrisiin oireisiin tai vähentänyt pysyvään laitoshoitoon joutumista.

1. Introduction

The age-specific risk of Alzheimer's disease (AD) and other dementias in higher income countries has declined in the past 25 years. This decline is thought to be caused by increasing levels of education and improved control of cardiovascular risk factors (Matthews et al. 2013). However, the total number of persons with AD and other dementias is expected to increase because of the population's shift to older ages (Alzheimer's Association 2015).

Today, dementia is among the leading causes of disability and death in the elderly, AD being the most common type of dementia in late life, and accounting for 50-70% of all dementia cases (Fratiglioni et al. 2000). AD is a neurodegenerative syndrome characterized by cognitive, functional, and psychiatric symptoms and leading to a decreased ability to perform activities of daily living and an increased need for support and care (Green et al. 2016). Since there is no cure for AD (Canter et al. 2016), the increase in the number of people with dementia will have a great impact on health and social care services.

Despite the lack of disease-modifying therapies for AD, research shows that active management of AD and other dementias can improve functional abilities, independence, and quality of life through all stages of the disease for affected persons, decreasing the burden of caregivers and society (Alzheimer's Association 2015).

Physical activity promotes "active ageing". Physical activity may reduce disability, improve quality of life, and preserve independence in older age (Crimmins et al. 2015). Epidemiological research has also found a significantly reduced risk of developing dementia among physically active older adults (Ahlskog et al. 2011). Physical inactivity is the most important preventable risk factor for AD (Matthews et al. 2013).

Exercise has been shown to have direct positive effects on the brain. It improves vascular health, thereby enhancing cerebral perfusion and maintenance (Haskell et al. 2007). Exercise may also be influential in preserving neuronal structures and promoting neurogenesis and angiogenesis (Colcombe et al. 2003).

A growing body of scientific evidence indicates that exercise may be a potential non-pharmacological treatment to alleviate symptoms of dementia or delay its progression (Lautenschlager et al. 2010).

Systematic reviews and meta-analyses evaluating the impact of exercise programmes on functional abilities in activities of daily living (ADL) in patients with dementia (PWD) consistently show

beneficial effects (Blankevoort et al. 2010, Littbrandt et al. 2011, Potter et al. 2011, Pitkälä et al. 2013, Rao et al. 2014, Forbes et al. 2015). The evidence of the effects of exercise on cognitive functioning, neuropsychiatric symptoms (NPS), and fall rate is less clear (Forbes et al. 2015). There is also a need to clarify whether persons in various stages of dementia benefit from exercise interventions similarly and the optimal quality and quantity of exercise.

This study aims to systematically evaluate the evidence from RCTs of the effects of exercise on cognition in persons with MCI or dementia. In addition, it explores the effects of long-term exercise intervention on AD patients regarding cognition, NPS, and rate of institutionalization. Effects on physical functioning and fall rate are explored in study groups of mild and advanced AD separately.

2. Review of the literature

2.1 AD

2.1.1 Epidemiology and pathophysiology of AD and other dementias

Dementia is a clinical syndrome characterized by cognitive impairment, such as memory loss, and impairment in executive function, skilled movements, language abilities, and neuropsychiatric features, causing significant decline from previous levels of functioning and reducing the capacity to perform usual activities (McKhann et al. 2011).

The World Alzheimer Report (2016) estimates that 46.8 million people worldwide were living with dementia in 2015, the annual incidence of new dementia cases being almost 10 million. The prevalence of dementia in people aged ≥ 60 years is 5-7% in most world regions (Prince et al. 2013). In Finland, approximately 120 000 people are suffering from clinical memory disease and another 120 000 are living with MCI. The annual incidence of clinical memory disease is 13 000 (National Institute for Health and Welfare, Finland 2017).

Dementia is often preceded by MCI, which describes the cognitive state between normal cognitive ageing and dementia. The person is experiencing cognitive decline, but does not yet fulfil the clinical criteria for dementia (Petersen et al. 1999). Some persons with MCI will progress to dementia, while others will remain stable or even show improvement. The presumed aetiology and the type of symptoms can be used to predict the type of dementia that the patient with MCI would most likely develop (Petersen et al. 2004).

Various neuropathologies may underlie dementia syndromes. AD is the most common type of dementia in late life, accounting for 60-70% of all dementia cases (Alzheimer's Association 2015). Other types of dementia include vascular dementia, dementia with Lewy bodies (dementia in Parkinson's disease and Lewy body dementia), frontotemporal dementia, and alcohol-related brain damage (Dubois et al. 2007). In many cases, multiple brain pathologies are encountered, the most common combination being AD and vascular dementia (Schneider et al. 2007).

Disorders like thyroid disease, pernicious anaemia, hypercalcaemia, chronic infections of the nervous system, hydrocephalus, Huntington's disease, Creutzfeldt-Jakob disease, brain injuries, and tumours may also cause dementia, but are more rarely encountered (Dubois et al. 2007).

AD is a progressive neurodegenerative disorder causing dementia. The exact mechanisms and order of neuropathological changes in AD are still uncertain. Accumulation of amyloid-beta peptide

is thought to start the cascade in which amyloid plaques and neurofibrillary tangles are formed, eventually leading to neuron death and brain atrophy (Aisen et al. 2017). Recent evidence indicates that amyloid-beta accumulation may not be the sole culprit, but additional factors, such as tau pathology and synaptic, mitochondrial, metabolic, inflammatory, neuronal, cytoskeletal, myelin, and other age-related alterations, may also be involved in the pathogenesis of AD (De Strooper et al. 2016).

The first neuropathological changes in the brain can be seen years before the first clinical symptoms of AD are detected (De Strooper et al. 2016). The state where only the molecular or imaging biomarkers are evident in cognitively healthy persons is called preclinical AD. Patients with preclinical AD may or may not have some subjective cognitive decline (Scheltens et al. 2016). Prodromal AD or amnestic MCI is often a precursor to Alzheimer's dementia. The annual rate of development of AD for patients with amnestic MCI is 10-15% (Tierney et al. 1996). AD can be categorized into mild, moderate, and severe stages of illness where cognitive, functional, and neuropsychiatric difficulties and dependence on others progressively increase (Forstl et al. 1999).

2.1.2 Symptoms of AD

Cognitive symptoms of Alzheimer's disease include progressive memory loss over years, with simultaneous or later occurring impairments in other cognitive domains such as executive functioning (e.g. planning and problem-solving), attention, communication (word-finding), or visuospatial abilities (agnosia, face recognition, and alexia) (Pena-Casanova et al. 2012). The cognitive symptoms are generally the earliest signs of AD, the most typical early complaints being problems with episodic memory and the ability to learn and retain new information (Dubois et al. 2007). However, several non-cognitive symptoms may accompany all stages of the disease. These symptoms can be equally or even more devastating and burdensome for the patient and the caregiver than the cognitive symptoms (Raudino et al. 2013).

Neuropsychiatric symptoms (NPS) are very common in AD patients, especially in the more advanced stages, but may also be present years before clinical diagnosis. These symptoms include depression, apathy, wandering, aggression, agitation, disinhibition, delusions, hallucinations, and sleep and eating disturbances, among others. NPS are often difficult to manage, they cause an excessive burden on caregivers, and may lead to early nursing home placement (Kales et al. 2015).

AD is strongly related to frailty, sarcopenia, gait impairments, and weight loss, all of which increase the risk of falls and decrease physical performance and ADL abilities (Buchman et al. 2008, Burns et al. 2010, Sugimoto et al. 2017). Studies show that gait disturbances may already be measurable

years before cognitive impairment is clinically manifest (Bridenbaugh et al. 2014). In the advanced stage of AD, incontinence is frequent and basic motor skills, such as chewing and swallowing, may be impaired. Other motor disturbances, such as rigidity and primitive reflexes as well as extrapyramidal symptoms, myoclonus, and epileptic seizures, may occur at the very late stage of AD (Förstl et al. 1999).

After the clinical diagnosis of AD, life expectancy is significantly reduced. In a large longitudinal study in the US, the median survival from initial diagnosis was 4.2 years for men and 5.7 years for women (Larson et al. 2004). Lengthy duration of symptoms, severity of AD, old age, male sex, and physical disease are major risk factors for mortality in AD (Bowen et al. 1996). In addition, decreased functional level, history of falls, findings of primitive reflexes, and abnormal gait are related to shorter life expectancy (Larson et al. 2004).

2.1.3 Risk factors and prevention of AD

The greatest risk factors for sporadic AD are age and family history with susceptible genes like the apolipoprotein E (*APOE*) ε4 gene. Those with the APOE ε4 form are more likely to develop AD at a younger age than those with the ε2 or ε3 forms of the gene (Corder et al. 1993). Researchers estimate that up to 65% of people diagnosed with AD carry one or two copies of the *APOE* ε4 gene (Mayeux et al. 1998). Cases of familial AD make up 1-5% of patients with AD, and they are the result of disease-causing, autosomal dominant mutations in APP (amyloid-ß precursor protein) or mutations in PSEN1 (Presenilin-1), PSEN2 (Presenilin-2), and Trisomy-21(Canter et al. 2016).

In addition to the non-modifiable risk factors, several modifiable risk factors for AD have been identified. Poorly managed cardiovascular risk factors, such as diabetes, hypertension, hyperlipidaemia, smoking, sedentary behaviour, and obesity, especially in mid-life, are connected to cognitive decline and AD in later life (Baumgart et al. 2015).

Regular physical activity, particularly leisure-time activity, may reduce the risk of Alzheimer's disease (Middleton et al. 2015, Iso-Markku et al. 2016, Santos-Lozano et al. 2016, Stephen et al. 2017). Adherence to a Mediterranean-style diet is associated with slower rates of cognitive decline and reduced conversion to AD in MCI patients (Hardman et al. 2016). A healthy diet in mid-life seems to be protective of AD in later life (Eskelinen et al. 2011). People with more years of formal education have a lower risk for AD than those with fewer years (Baumgart et al. 2015). Some studies have also found cognitive training (Ball et al. 2002) and engagement in mental activities and social activities to be beneficial for cognitive health and to reduce the risk of dementia (Baumgart et

al. 2015). Moderate and severe traumatic brain injuries may double or even quadruple the risk of developing Alzheimer's disease and other dementias (Plassman et al. 2000).

Alzheimer's disease is a complex disorder with numerous risk factors, and it is likely that multifactorial interventions are needed for prevention (Deckers et al. 2015). The Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER) was a two-year multidomain intervention of diet, exercise, cognitive training, and vascular risk monitoring that targeted older adults at risk for cognitive decline. The participants in the intervention group were able to improve or at least maintain their cognitive functioning (Ngandu et al. 2015).

2.1.4 Diagnosis of AD

The National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) and The Alzheimer's Disease and Related Disorders Association (ADRDA) criteria to diagnose AD are used in both clinical practice and research. These criteria were first devised in 1984 and then revised in 2011. First, according to NINCDS-ADRDA criteria the patient must meet the criteria of dementia (as described above), and second, have progressive cognitive deficits typical to AD detected by history-taking from the patient and informant and objective cognitive assessments. Other causes of dementia must be excluded (Mc Khann et al. 2011). Perhaps the most widely used diagnostic criteria for AD in clinical work is the International Classification of Diseases, 10th edition (ICD-10) (World Health Organization; 1990). The criteria of the Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-V) is commonly employed in mental health research (American Psychiatric Association 2013).

For diagnosis of AD, brain imaging and laboratory testing are required. Structural brain changes related to Alzheimer's disease are visible on MRI and computed tomography (CT). The first changes are in the medial temporal lobe (including entorhinal cortex and hippocampus), and later also more general cortical atrophy is seen. With laboratory tests, the secondary causes of dementia, such as hypothyroidism, hypercalcaemia, and B12 hypovitaminosis, can be excluded (Current Care Guidelines, Finland 2017).

When diagnosing AD in preclinical stages or when the clinical presentation is atypical, additional diagnostic measures are warranted. Cerebrospinal fluid shows changes in amyloid and tau levels. Low amyloid β_{1-42} concentrations, increased total tau concentrations, or increased phospho-tau concentrations, or combinations of the three suggest AD pathology (Olsson et al. 2016). Positron emission tomography (PET) or single photon emission computed tomography (SPECT) can be used to visualize molecular changes, such as hypometabolism or hypoperfusion, in temporoparietal areas

(Frisoni et al. 2017). Definite diagnosis of AD can be made only when neuropathological examination demonstrates the presence of AD pathology in a patient with previously diagnosed clinical AD (McKhann et al. 2011).

2.1.5 Treatment of AD

Today, no disease-modifying treatment for AD is available (Canter et al. 2016). The pharmacological and non-pharmacological options are symptom-relieving at best. Donepezil, rivastigmine, and galantamine, together known as the cholinesterase inhibitors (ChEIs), act by increasing the amount of acetylcholine in the extracellular space, which is thought to promote neuronal activity and cholinergic signalling in the brain. The ChEIs have been found to be efficacious in improving cognitive functioning for patients with mild to moderate AD (Birks et al. 2006). Another drug approved for the treatment of AD is memantine, an NMDA (*N*-methyl-D-aspartate) receptor antagonist affecting the glutamate metabolism and blocking the toxic effects of overactive glutamatergic activity. It is the only medical treatment approved in late-stage AD (Areosa et al. 2005). Research in development of new therapeutic interventions for AD has been active in the last decades. However, the inability to find a definitive connection between clinical symptoms and changes in biomarkers complicates this task. While many large clinical drug and vaccine trials have reached phase 3, all have thus far failed to show positive results in clinical outcomes (Canter et al. 2016).

Until a pharmacological breakthrough occurs, the non-pharmacological treatment options have engaged the attention of researchers. The most consistent evidence is from multicomponent interventions based on caregiver education and support to delay institutionalization, improve quality of life (both patient and caregiver), and reduce the costs of care (Eloniemi-Sulkava et al. 2009, Groot et al. 2016). Relative to these, the effects on cognition, mood, and daily performance are smaller, but of the same magnitude as those of AD drugs (Groot et al. 2016). Similar but smaller effects have been obtained for cognitive stimulation (Woods et al. 2012), multicomponent interventions targeted at the patient, cognitive and ADL training, and behavioural interventions (Olazaran et al. 2010). Regular, long-term exercise seems to improve physical functioning in participants with AD (Pitkala et al. 2013). Tailored nutritional guidance has also been found to enhance nutrition and quality of life and to prevent falls among community-dwelling individuals with AD (Suominen et al. 2015).

2.1.6 Cost and burden of AD to caregivers and society

AD is a life-changing issue for the patient and his/her family. Of persons with AD, 60-70% live in the community with most of the care provided by unpaid family carers (Lacey et al. 2013). In addition to the physical and emotional consequences to the patient, AD causes a burden on family carers, impairing their quality of life and health (Sörensen et al. 2011, Vernooij-Dassen et al. 2011). Family carers of dementia patients tend to have more health problems, visit health care professionals more often, suffer from isolation, and have an increased risk of depression and other illness than carers of people with other chronic illnesses (Vernooij-Dassen et al. 2011).

AD is also a major public health challenge, with a significant economic impact on health and social care services. The total estimated worldwide costs of dementia were US$ 604 billion in 2010. About 70% of the costs were incurred in western Europe and North America (Wimo et al. 2013). The economic burden of AD may even be underestimated since many indirect costs, such as adverse effects on care-givers' health and productivity, are not invariably included in cost estimates (Deb et al. 2017). Most of the costs come from institutional care and services, and only 1% come from disease diagnostics and medication (Current Care Guidelines, Finland 2017). AD costs increase with disease progression. The most significant association has been found between dependence of others (loss of functional abilities) and total care costs (Lacey et al. 2013).

2.2. Exercise and physical activity in dementia

To reduce the risk of cognitive decline in cognitively normal persons over 65 years of age, the World Health Organization (WHO) recommends a weekly minimum of 150 minutes of moderate-intensity aerobic activity or 75 minutes of vigorous-intensity aerobic activity with additional muscle-strengthening exercises. According to the WHO, this would also apply to patients with neurodegenerative disease (WHO 2010).

Physical activity and exercise are terms that are often used interchangeably. However, physical activity is, by definition, any bodily movement produced by skeletal muscles and resulting in energy expenditure, whereas exercise is a subset of physical activity that is planned, structured, and repetitive (Caspersen et al. 1985).
Declining cognition brings changes to physical activity and abilities to exercise. Dementia patients' physical activity levels are low compared with their healthy peers (Burns et al. 2008, Van Alphen et al. 2016). Several health-related factors, such as chronic health conditions, polypharmacy, a history

of falls, impaired physical performance (e.g. low gait speed), and day-time tiredness, have been found to be negatively associated with physical activity and participation in exercise (Stubbs et al. 2014)**.** Lower physical activity may also be the result of increasing problems with cognitive functions, especially with memory and executive functions (Van Alphen et al. 2016), and loss of motivation and initiation, which are symptoms of apathy, a very common NPS across all stages of AD (David et al. 2012). Violations of autonomy, i.e. feelings of "being forced", may also lower the motivation to physical activity (Stubbs et al. 2014). Similar to their healthy peers, some PWD may simply not like exercise and therefore need stronger motivators, support, and more tailored solutions than those who have a positive attitude towards exercise (Malthouse et al. 2014). Difficulties in finding the way, fear of unknown places, and lack of support or transportation are reported as barriers to dementia patients' exercise participation (Van Alphen et al. 2016). Caregivers' health, commitment, and attitude towards physical activity and exercise are important factors that also affect the physical activity level of PWD (Van Alphen et al. 2016).
An exercise companion is important to facilitate participation and PWD benefit from specially designed exercise programmes that are carried out in small groups, offering peer support and guidance by professionals (Malthouse et al. 2014).
Although the overall benefits of exercise and physical activity are widely recognized also in PWD, current recommendations by government guidelines, health authorities, and the World Health Organization are not specially directed to this patient group. According to studies, more specific recommendations from health care professionals and authorities would facilitate dementia patients' participation in exercise and improve their level of physical activity (Van Alphen et al. 2016).

2.3 Exercise and the brain

Regular physical activity throughout the lifespan has a strong association with better brain health (Rovio et al. 2005, Middleton et al. 2010, Sofi et al. 2011, Iso-Markku et al. 2016).

The mechanisms by which physical exercise can affect the ageing brain are various at systemic, molecular, and cellular levels. Exercise has positive effects on brain structure and function, thus creating resilience against the deteriorating effects of ageing and neurodegenerative diseases (Colcombe et al. 2003). Physical exercise lowers blood pressure and lipids and prevents metabolic syndrome (Haskell et al. 2007). It also improves cerebral circulation by increasing blood flow to the brain, thus improving oxygen supply and removing waste, and it has a restoring effect on endothelial function (Cotman et al. 2007). Regular exercise diminishes chronic inflammation, which has been linked to increased risk of cardiovascular diseases (Hillman et al. 2008). Lowering the risk

of cerebrovascular disease (CVD) with regular exercise might be particularly important and effective for certain subgroups of people such as carriers of the APOE 4 allele (Schuit et al. 2001).

The brain remains plastic throughout the lifetime. People with greater cardiovascular fitness tend to have larger cortical volume in the frontal, temporal, and parietal lobes as well as in the hippocampus (Colcombe et al. 2003). Hippocampal atrophy is associated with memory impairment and dementia (Jack et al. 2004). Animal studies have revealed that exercise stimulates neuron proliferation in hippocampal areas, and exercise may even increase the volume of the hippocampus in humans (Erickson et al. 2011). This increase is thought to be mediated by exercise-induced elevated levels of brain-derived neurotrophic factor (BDNF) (Erickson et al. 2011 Coelho et al. 2013). Other growth factors, such as insulin-like growth factor-1 (IGF-1) and vascular endothelial growth factor, are also linked to exercise-induced neurogenesis and angiogenesis (Ratey et al. 2011).

Many neurodegenerative diseases, such as AD, have been linked to ageing-related defects in mitochondria. It is hypothesized that disturbances in mitochondrial maintenance and quality control may result in insufficient energy production or accumulation of misfolded proteins, e.g. β-amyloid (Marzetti et al. 2013). This harmful development can be slowed down with lifestyle changes such as regular exercise (Lopez-Lluch et al. 2015).

Chronic stress can lead to dysfunction of the hypothalamic-pituitary-adrenal axis (HPA). This has been shown to decrease levels of BDNF and increase inflammation, oxidative damage, and amyloid-β peptides, which may lead to more rapid progression of cognitive decline (Csernansky et al. 2006). According to a longitudinal study of 200 older adults, women with the highest cortisol levels had the lowest cognitive test scores, and risk of cognitive decline increased when levels continued to rise during a 2.5-year follow-up (Seeman et al. 1997). In early stages of AD, patients' cortisol levels are markedly elevated relative to those of their non-demented counterparts, and higher levels predict more rapid disease progression (Davis et al. 1986). Physically inactive persons tend to have more stress and higher cortisol responses to stress than persons who are physically active. It is well established that exercise can significantly relieve stress and related symptoms (Scherder et al. 2010).

2.4 Effects of exercise in older adults with dementia

Scientific evidence of the effects of exercise on cognition, functional abilities, fall rate, and NPS in PWD is discussed in the following sections. Results from epidemiological and intervention studies are reviewed. RCTs included in this literature review are put into a tabular form, and their main characteristics and findings are reported. The methodological quality of the RCTs is assessed with the criteria disclosed below. A summary of the quality assessment is shown in Table 5.

2.4.1 Methodological quality of randomized controlled studies discussed in the literature review and the review article (Study 1)

Methodological quality of the studies included in the literature review and in the systematic review (Study 1) was assessed by using a modified rating system applying the criteria for randomized intervention trials used by Cochrane and collaborators (Higgins et al. 2011), the PEDro scale, a tool for measuring the methodological quality of clinical trials related to physiotherapy interventions (Maher et al. 2003), and criteria developed by the Evidence-Based Medicine Working group (Guyatt et al.1993, Guyatt et al. 1994). An additional criterion involving compliance was incorporated since compliance is often low in exercise studies. The 13 criteria are described in detail below. Each criterion is equivalent to 1 point. The quality of the research study is considered high with a score of 11-13 points, moderate with a score of 7-10 points, and poor with a score of <7 points.

1. The diagnosis of dementia is based on the DSM-IV (American Psychiatric Association 2013) or NINCDS-ADRDA criteria (McKhann et al. 2011) or is made by a geriatrician, a neurologist, or an old age psychiatrist.

2. Inclusion and exclusion criteria are satisfactorily described.

3. The intervention is described in sufficient detail.

4. The measurements and outcome measures are valid and adequately defined.

5. The study has sufficient statistical power to detect an effect ($n \geq 25$/group).

6. The randomization method is adequately described, and the method is valid (a computerized randomization programme or a separate randomization centre).

7. The group assignment is blinded when assessing the outcomes.

8. Intention-to-treat analysis is applied.

9. Groups are comparable at baseline regarding the most important indicators.

10. The drop-outs are described, and the analyses take them into account.

11. The compliance of participants is described.

12. Complications are reported.

13. A comparison is made in relation to outcome variables between the groups.

2.4.2 Effects of exercise on cognition in older adults with dementia

Physical activity has biological effects on brain functions and vascular risk factors, and thus, there is a direct link between cognition and exercise (Colcombe et al. 2003). Epidemiological studies have shown that increased engagement in lifetime physical activities reduces the risk of cognitive decline and dementia in older age (Hamer et al. 2009, Geda et al. 2010, Middleton et al. 2010, Buchman et al. 2012, Lee et al. 2015, Llamas-Velasco et al. 2015, Iso-Markku et al. 2016). However, systematic reviews and meta-analyses of RCTs examining the effects of exercise interventions on cognition among cognitively healthy older adults have found the evidence to be somewhat insufficient and conflicting (Colcombe et al. 2003, Angevaren et al. 2008, Smith et al. 2010, Snowden et al. 2011, Kelly et al. 2014, Young et al. 2015). Some meta-analyses suggest beneficial effects especially in executive function (Colcombe et al. 2003, Angevaren et al. 2008, Smith et al. 2010), yet, the more recent meta-analyses with larger data contradict these findings (Snowden et al. 2011, Kelly et al. 2014, Young et al. 2015). Differences have been described in participant profiles, study design, exercise programmes, adherence rates, and outcome measures across studies.

Interestingly, meta-analyses of RCTs performed among participants with MCI are rather consistent, revealing positive intervention effects (van Uffelen et al. 2008, Wang et al. 2014, Zheng et al. 2016). Nevertheless, the authors have suggested cautious interpretation of their results because of the methodological limitations of the incorporated RCTs and the small effect sizes diminishing the clinical value of the results (van Uffelen et al. 2008, Wang et al. 2014, Zheng et al. 2016).

The Cochrane review from 2015 found 17 RCTs examining the effects of exercise in dementia patients; of these, 9 RCTs (n=499) had outcomes related to cognition. The studies were relatively small, from 18 to 97 participants, and most were conducted in nursing homes. The review revealed no clear evidence of benefits of exercise intervention on cognition in PWD. However, the authors state that heterogeneity of the study population, diagnosis of dementia, type and frequency of the

exercise intervention, and methodological shortcomings may attenuate the overall results (Forbes et al. 2015). Groot and co-workers conducted meta-analyses of RCTs examining the effects of physical activity on cognitive function in dementia patients. They incorporated 18 relevant studies, with altogether 802 participants with dementia, into the meta-analyses. They found a positive effect of exercise on cognitive functions in dementia patients. The effect was driven by interventions including aerobic exercise, and was independent of the type of dementia. Yet, the authors emphasize that methodological limitations exist and larger studies of better methodological quality to examine the effects of exercise on cognition in PWD are warranted (Groot et al. 2016).

Since the forementioned meta-analyses, many new studies have been published. A database search (Medline, Ovid, PsycINFO, Cochrane Database) in September 2017 produced 25 RCTs (n=1781) examining the cognitive effects of exercise in PWD. The studies are shown in Table 1. Eleven studies were conducted in community settings (Burgener et al. 2008, Kwak et al. 2008, Miu et al. 2008, Steinberg et al. 2009, Vreugdenhil et al. 2011, Yaguez et al. 2011, Arcoverde et al. 2014, Holthoff et al. 2015, Hoffman et al. 2016, Dawson et al. 2017, Morris et al. 2017) and 14 in nursing homes (Friedman et al. 1991, Cott et al. 2002, van de Winckel et al. 2004, Stevens et al. 2006, Christofoletti et al. 2008, Hokkanen et al. 2008, Eggermont et al. 2009, Kemoun et al. 2010, Venturelli et al. 2011, Cheng et al. 2014, Bossers et al. 2015, Telenius et al. 2015, Cancela et al. 2016, Toots et al. 2017). In addition to the setting, the studies varied considerably in number of participants (range 20 to 200), severity of participants' cognitive impairment, type, intensity, and duration of exercise programmes, and whether or not an active control group was employed. Of the 25 studies, nine included only patients with Alzheimer's dementia (Friedman et al. 1991, Cott et al. 2002, Steinberg et al. 2009, Kemoun et al. 2010, Venturelli et al. 2011, Vreugdenhil et al. 2011, Yaguez et al. 2011, Holthoff et al. 2015, Hoffman et al. 2016), while the other study populations comprised patients with various types of dementia such as vascular dementia, Parkinson's dementia, frontotemporal dementia, mixed dementia, and dementia of unknown cause. This may further weaken the comparability of the studies, as cognitive functions may not be equally affected in different subtypes of dementia, and there is a substantial variation also in the trajectories of the cognitive symptoms (Oosterman et al. 2006, Ingles et al. 2007, Kandiah et al. 2009, Smits et al. 2015).

Three small studies among community-dwelling AD patients found positive effects after an exercise intervention: one study in global cognition measured with MMSE and ADAS-Cog (Vreugdenhill et al. 2011) and the others in executive function (Yaguez et al. 2011, Holthoff et al. 2015,) and in working and visual memory (Yaguez et al. 2011). A good-quality study with 200 participants with

mild AD in a community setting failed to show positive effects after 16 weeks of moderate to high intensity exercise. However, among those who adhered to the protocol there was a significant change in the Symbol Digit test in favour of exercise (Hoffmann et al. 2016).

Two studies conducted in communal settings that included patients with various types of dementia were able to show improvement in MMSE after fairly long exercise interventions of 40 weeks (Burgener et al. 2008) and 52 weeks (Kwak et al. 2008). In two studies with shorter interventions, no effects were detected (Miu et al. 2008, Steinberg et al. 2009).

Studies conducted in nursing home settings included higher numbers of participants, were on average more intensive and longer in duration, and involved patients in more advanced stages of dementia than those conducted among community-dwellers. The results were mixed.

MMSE and memory improved relative to the control group (recreational activities) after daily indoor cycling for 15 months in a large Spanish study with 189 moderately demented participants in nursing homes (Cancela et al. 2016). In an Italian study, global cognition (measured with MMSE) remained stable during a 16-week walking intervention, while participants receiving usual care deteriorated (Venturelli et al. 2011). Walking and balance exercises three times a week for 15 weeks improved participants' performance in a multidomain cognitive test battery consisting of tests for executive function and memory (Kemoun et al. 2010). Improvements in communication skills were found after 10 weeks of walking and conversation sessions in severely demented participants (Friedman et al. 1991). Cheng and co-workers randomized 110 participants to an exercise intervention of Tai Chi three times a week for three months or to two control activity groups (Mahjong card game or handicrafts). Those practising either Tai Chi or Mahjong improved in MMSE and Digit Span forward. The intervention effect was preserved as time progressed, and by nine months the Tai Chi group differed from the handicrafts group by a mean improvement of 3.7 points in MMSE (Cheng et al. 2014).

Twelve weeks of strength and balance exercises did not change MMSE scores in nursing home patients with moderate dementia. However, the primary outcomes of the study were balance and functional mobility, and the exercise programme was not designed to improve cognition (Telenius et al. 2015). Another fairly large and good-quality study showed no improvement in memory or executive function test after six weeks of a walking programme. The researchers discuss that the lack of beneficial effects could be due to the high number of co-morbidities in the study population and perhaps also the short intervention period (Eggermont et al. 2009). A Swedish study of good

methodological quality with 186 participants failed to show positive results in cognitive outcomes after 16 weeks of high-intensity exercise twice or thrice a week (Toots et al. 2017).

Morris and co-workers found evidence that improvements in cardiorespiratory fitness after 26 weeks of aerobic exercise intervention were related to brain volume change visible in MRI, yet they were unable to show positive changes in cognitive tests (Morris et al. 2017). As known from the previous research, an observation of structural changes in the brain may not necessarily equal corresponding effects on cognitive function (Erickson et al. 2011).

Whether exercise improves cognition in PWD remains unknown. The results from the RCTs are mixed, and the clinical significance of the positive results is unclear.

The neurocognitive tests used across studies are numerous and heterogeneous. This finding is consistent with the results of a recent article on neuropsychological tests used in studies investigating treatment effects on cognition in dementia patients (Bossers et al. 2012, Concalves et al. 2018). Tests measuring global cognition were more frequently used than tests covering a single cognitive domain. Global cognition was generally measured with MMSE, which has good reliability but may be insensitive to change (Tombaugh et al. 1992, Mulligan et al. 1996,). It may also be questioned whether any changes in global cognitive measures can be seen in a period as short as three or four months.

On the basis of the studies in Table 1, the key elements in an exercise intervention to improve cognition in dementia patients appear to be long duration (Burgener et al 2008, Christofoletti et al. 2008, Kwak et al. 2008, Vreugdenhil et al. 2011, Cancela et al. 2016), high intensity (van de Winckel et al. 2004, Burgener et al. 2008, Christofoletti et al. 2008, Kemoun et al. 2010, Venturelli et al. 2011, Vreugdenhil et al. 2011, Cheng et al. 2014, Bossers et al. 2015, Holthoff et al. 2015, Cancela et al. 2016) and aerobic exercise (Friedman et al. 1991, Arcoverde et al. 2014, Bossers et al. 2015, Holthoff et al. 2015, Cancela et al. 2016,). Conducting such studies can be difficult because of the high co-morbidity and vulnerability of this patient group (Table 1).

Table 1. Randomized controlled trials examining the effects of exercise on cognition in patients with dementia (positive findings highlighted).

Study	Participants	Intervention	Outcomes related to cognition	Methodological quality (see Table 5)/ Comments
Community-dwellers				
Arcoverde et al. 2014 Brazil n=20	PWD (AD, mixed) Mean age 79 y Mean MMSE 20	IG, n=10: Treadmill walking; 30 min x 2/week, 12 weeks CG, n=10: TAU	CAMCOG: Improvement in IG MMSE, VF, CDT, Trail making test A+B, verbal learning, Digit Span: No differences between groups	Moderate, 9/13 Low statistical power.
Burgener et al. 2008 USA n=43	PWD (AD, VD, FTD, LBD, mixed) Mean age 77 y Mean MMSE 24	IG, n=24: Tai Chi (adapted to PWD); 60min x 3/week, 40 weeks + CBT 90min, bi-weekly, 40 weeks + Support group 90min, bi-weekly, 40 weeks CG, n=19: TAU	MMSE: Improvement in IG by 0.4 points at 20 weeks, at 40 weeks remained stable. MMSE: CG decreased by 0.5 points at 20 weeks.	Poor, 4/13 Multicomponent intervention.
Dawson et al. 2017 USA n=23	PWD Mean age 74 y Mean MMSE 21	IG, n=13: Functional strength and balance program; x min x 2/week, 12 weeks CG, n=10: TAU	Trail making test B: No differences between groups	Moderate, 7/13 Small statistical power
Hoffman et al. 2016. Denmark n=200	AD patients Mean age 70.5 y Mean MMSE 24	IG, n=107: Moderate-high intensity aerobic exercise; 60 min x 3/week, 16 weeks CG, n=93: TAU	MMSE, ADAS-Cog, Verbal memory test, Symbol Digit, VF No difference between groups	Good, 13/13 Multicentre study. Primary outcome cognition
Holthoff et al. 2015 Germany n=30	AD patients Mean age 72 y Mean MMSE 21	IG, n=15: Training with movement trainer (MOTOmed); 30 min x 3/week, 12 weeks CG, n=15: TAU	VF, attention: Improvement in IG compared with CG MMSE: No difference between groups	Moderate, 9/13 Low statistical power
Kwak et al. 2008 Korea n=30	PWE Mean age 80 y Mean MMSE 14	IG, n=15: Strength and endurance exercise program; 30-40 min x 1/week, 52 weeks CG, n=15: TAU	MMSE: Improvement of 20% and 30% at 24 and 52 weeks, respectively, within IG	Poor, 2/13 Low statistical power
Miu et al. 2008 Hong Kong n=85	PWD (AD, VD, PD, mixed) Mean age 76 y Median MMSE 20	IG, n=36: Aerobic exercise (treadmill, bicycle); 45-60 min x 2/ week, 12 weeks CG, n=49: TAU	MMSE: No differences between groups ADAS-Cog: No differences between groups	Moderate, 9/13
Morris et al. 2017 USA n=76	PWD Mean age 74 y (IG), 71 y (CG) Mean MMSE 25	IG, n=37: Aerobic exercises 150 min/week, 26 weeks CG, n=39: Stretching and toning exercises Frequency?	Memory, executive function: No differences between groups	Moderate, 9/13 Improvement in cardiorespiratory fitness was related to benefits in hippocampal volume in IG.
Steinberg et al. 2009; USA n=27	AD patients. Mean age 75 y Mean MMSE 21 (IG), 16 (CG)	IG, n=14: Exercise programme (aerobic, strength, balance, and flexibility); 7 x week, 12 weeks CG, n=13: Home safety assessment	MMSE, verbal learning; No differences between groups.	Moderate, 10/13 Low statistical power

Table 1 continues

Vreugdenhil et al. 2011 Australia n=40	AD patients Mean age 82 y Mean MMSE 21	IG, n=19: Tailored exercise program (walking, strength training, balance) supported by PT (6 visits+5 calls); 7 x week, 26 weeks CG, n=21: Home-based education programme supported by OT (6 visits+5 calls)	MMSE: Improvement by 2.6 points in IG ADAS-Cog: Improvement by 7.1 points in IG	Moderate, 7/13 Intensive training in IG. Active CG
Yaguez et al. 2011 UK n=27	AD patients Mean age 70 y (IG), 75 y (CG) Mean MMSE 24	IG, n=15: Brain Gym®-training; 120min x 1/week, 6 weeks CG, n=12: Psychological support	Visual memory, sustained attention and working memory (measured with CANTAB): Improvement in IG compared with CG	Moderate, 7/13 Active CG Low statistical power.
Nursing-home residents				
Bossers et al. 2015 Netherlands n=123	PWD in NH Mean age 86 y Mean MMSE 16	IG1, n=41: Aerobic and strength training IG2, n=41: Walking CG, n=41: Social visits All groups: 30 min x 4/week, 9 weeks	MMSE, Executive function (VF, Digit Span, Picture completion test), Memory function (8-word test, picture recognition): IG 1 improved compared with CG Executive function: IG 2 improved compared with CG	Moderate, 9/13 Primary outcome cognition
Cancela et al. 2016 Spain n=189	PWD in NH Mean age 82 y Mean MMSE 15	IG, n=73: Indoor cycling CG, n=116: Recreational activities; Both groups: 15 min x 7/week, 64 weeks	MMSE: Stable in IG, decrease in CG Memory domain: Improvement in IG, decrease in CG	Good, 12/13 Active CG.
Cheng et al. 2014 Hong Kong n=110	PWD in NH Mean age 81 y Mean MMSE 19	IG 1, n=39; Tai Chi CG 1, n=36; Mahjong CG 2, n=35; handicrafts All groups: 60 min, 3x/week, 12 weeks	MMSE, Digit Span forward: Improvement in IG and CG 1 (Mahjong) compared with CG 2 Delayed recall: Improvement in CG 1 Immediate recall, Digit Span backwards: No differences between groups	Moderate, 8/13 Active CG
Christofoletti et al. 2008 Brazil n=54	PWD in NH Mean age 74 y Mean MMSE 19 (IG1), 13 (IG2), 15 (CG)	IG1, n=: Strength and balance exercises supervised by PT + arts and crafts supervised by OT + physical education; 120min x 5/week, 26 weeks IG2, n=: Strength and balance exercises supervised by PT; 60 min x 3/week, 26 weeks CG, n=: TAU	VF, CDT: Improvement in IG 1 compared with CG	Poor, 5/13 Multicomponent intervention
Cott et al. 2002 Canada n=86	AD patients Mean age 86 y Mean MMSE 6	IG1, n=30: Walking and talking in pairs CG1, n=30: Talk only Both groups: 30 min x 5/week, 16 weeks CG2, n=26: TAU	Communication skills: No differences between groups	Poor, 6/13 Active CG
Eggermont et al. 2009 Netherlands n=97	PWD Mean age 85 y Mean MMSE 18	IG, n= 51: Walking CG, n= 46: Social visits Both groups: 30 min x 5/week, 6 weeks	Memory domain (face recognition, picture recognition, eight words test): No difference between groups Executive functions domain (digit span, category and letter fluency): No difference between groups	Moderate, 8/13 Active CG
Friedman et al. 1991 USA n=30	AD patients Mean age 73 y Mean MMSE 7	IG, n=15: Walking and conversation CG, n=15: Conversation Both groups: 30 min x 3/week, 10 weeks	Communication skills: Improvement in IG compared with CG	Poor, 6/13

Table 1 continues

Hokkanen et al. 2008 Finland n=29	PWD (AD, VD, mixed) Mean age 80 y (IG), 75 y (CG) Mean MMSE 12	IG, n=19: Dance/Movement therapy CG, n=10: Social activities Both groups 30 min x 1/week, 9 weeks	CDT: Improvement in IG compared with CG MMSE, Word list savings: No differences between groups	Poor, 4/13
Kemoun et al. 2010 France n=31	AD patients Mean age 82 y Mean MMSE 12	IG, n= 16: Walking, endurance, and balance exercises; 60 minx 3/week, 15 weeks CG, n=15: TAU	Rapid cognitive evaluation: Improvement in IG compared with CG	Poor, 6/13
Stevens et al. 2006 Australia n=75	PWD Mean age 81 y MMSE 10-22	IG, n=24: Muscle strength training CG1, n=21: Social visits Both groups: 30min x 3/week, 12 weeks CG2, n=30: TAU	CDT: Improvement within IG	Poor, 3/13 Active CG.
Telenius et al. 2015 Norway n=170	PWD Mean age 87 y Mean MMSE 16	IG, n=87: Strength and balance exercises supervised by PT CG, n=83: Social meetings Both groups: 60 min x2/week, 12 weeks	MMSE: No difference between groups	Good, 13/13 Active CG.
Toots et al. 2017 Sweden n=186	PWD Mean age 85 y Mean MMSE 15	IG, n=93: High-intensity exercise (walking, strength, and balance training) CG, n=93: Social activity group (games, conversation); Both groups: 45 min x 5/2 weeks, 16 weeks	MMSE: No difference between groups ADAS-Cog: No difference between groups VF: No difference between groups	Good, 13/13 Active CG
Van de Winckel et al. 2004 Belgium n=25	AD or VD patients in psychiatric hospital Mean age 81 y Mean MMSE 11	IG, n= 15: Music-based dance therapy CG, n=10: Conversations Both groups: 30 min x 7/week, 12 weeks	MMSE, VF: Improvement in IG compared with CG Picture recognition, orientation, draw alternating sequences, copying figures, free recall: No differences between groups	Poor, 5/13 Active CG
Venturelli et al. 2011 Italy n=24	AD patents Mean age 85 y Mean MMSE 13	IG, n=12: Assisted walking; 30 min x 4/week, 16 weeks CG, n=12: TAU	MMSE: Stable in IG, slight decrease in CG	Moderate, 7/13 Low statistical power.

y=years, PWD= Patients with dementia, AD= Alzheimer's disease, VD= Vascular dementia, FTD= Frontotemporal dementia, LBD= Lewy Body Dementia, PD= Parkinson's disease dementia, IG= Intervention Group, CG= Control Group, VF= Verbal Fluency (Morris et al. 1989), CDT= Clock Drawing Test (Morris et al 1993), ADAS-Cog= Alzheimer's Disease Assessment Scale-Cognitive Subscale (Rosen et al. 1984), CANTAB=Cambridge Neuropsychological Test Automated Battery, CAMCOG= Cambridge Cognitive Examination, CDR= Clinical Dementia Rating (Hughes et al. 1982), TAU=Treatment as usual.

2.4.3 Effects of exercise on mobility and functional abilities in older adults with dementia

Deterioration of day-to-day functional abilities is a major feature of AD and other dementias, eventually leading to disability and loss of independence. This process begins already in the early stages of dementia and proceeds with the decline in cognition (Tschanz et al. 2011). Impaired muscle strength, mobility, and balance are known symptoms of dementia and are associated with difficulty in performing the basic activities of daily living (Roach et al. 2011). Co-morbidities and environmental factors are also important elements defining the course of functional decline (Haaksma et al. 2017).

In longitudinal studies, the rate of decline in daily performance has been found to be an even more predictive factor of early nursing home placement than cognitive deterioration (Wattmo et al. 2011). ADL abilities are also considered a key factor in the quality of life of people with dementia (Rolland et al. 2007). According to the European Task Force Group, assessment of the functional abilities in PWD is highly relevant in research as well as in a clinical context (Vellas et al. 2008).

Non-pharmacological therapies, such as caregiver education, occupational therapy, and exercise, can improve functioning in daily activities among dementia patients and postpone institutionalization (Olazaran et al.2010, Littbrand et al. 2011, McLaren et al. 2013). Benefits of active interventions can be achieved even in nursing home patients with advanced dementia (Luttenberger et al. 2012). Effects of exercise to improve mobility and functional abilities in PWD have been investigated in numerous studies. Systematic reviews and meta-analyses evaluating results of these studies appear to have reached similar conclusions regarding the beneficial effects of exercise. There seems to be no difference whether all kinds of studies (Blankevoort et al. 2010, Potter et al. 2011, Rao et al. 2014) or solely RCTs (Littbrand et al. 2011, Pitkälä et al. 2013) are included in the analyses.

A database search (Medline, Ovid, PsycINFO, Cochrane Database) in September 2017 produced 28 RCTs exploring exercise as a single intervention to improve or stabilize functional abilities and mobility in dementia. Descriptions and main outcomes of the studies are shown in Table 2. Nursing home residents with dementia have been assessed in 12 (Tappen et al. 2000, Cott et al. 2002, Toulotte et al. 2003, Stevens et al. 2006, Rolland et al. 2007, Christofoletti et al. 2008, Kemoun et al. 2010, Roach et al. 2011, Venturelli et al. 2011, Telenius et al. 2015, Cancela et al. 2016, Toots et al. 2016,) and community-dwellers in 16 of the studies (Pomeroy et al. 1999, Teri et al. 2003, Burgener et al. 2008, Kwak et al. 2008, Miu et al. 2008, Steinberg et al. 2009, Vreugdenhil et al. 2011, Hauer et al. 2012, Pitkälä et al. 2013, Suttanon et al. 2013, Arcoverde et al. 2014, Schwenk

et al. 2014, Holthof et al. 2015, Hoffman et al. 2016, Dawson et al. 2017, Morris et al. 2017). Despite large heterogeneity of the study populations, stage of dementia, study settings, exercise interventions, and methodologies, 23 (n=1804) out of the 28 studies examining the effects of exercise on functional abilities, mobility, and physical functioning found positive effects (Tappen et al. 2000, Teri et al. 2003, Toulotte et al. 2003, Stevens et al. 2006, Rolland et al. 2007, Christofoletti et al. 2008, Kwak et al. 2008, Miu et al. 2008, Steinberg et al. 2009, Kemoun et al. 2010, Roach et al. 2011, Venturelli et al. 2011, Vreugdenhil et al. 2011, Pitkälä et al. 2013, Suttanon et al. 2013, Arcoverde et al. 2014, Hauer et al. 2014, Schwenk et al. 2014, Holthof et al. 2015, Telenius et al. 2015, Cancela et al. 2016, Toots et al. 2016, Morris et al. 2017).

Positive results were associated with intensive multicomponent exercise and interventions lasting at least 12 weeks (Table 2). Studies without positive results were conducted either among severely demented nursing home patients (Cott et al. 2002) or the duration of the exercise intervention was very short (Pomeroy et al. 1999).

In 13 of the studies with positive results, the primary outcomes were physical measurements such as walking abilities, muscle strength, balance, and flexibility. The most frequently utilized measures were 2/4/6-minute walking distance, 4/10-m walking speed, Timed up and go (Mathias et al. 1986), leg press repetitions, Berg Balance Score (Berg et al. 1992), and Functional Reach (Duncan et al. 1992).

Although decreased balance and gait improvements have been associated with lower ADL function in dementia (Mazoteras-Munoz et al. 2010), these may be regarded as surrogate variables, and a direct extrapolation to improvements of actual functional abilities cannot be justified. Surprisingly, even in studies examining the effects of exercise on balance, only one study reported positive changes in fall risk related to improvement of balance after the intervention (Suttanon et al. 2013).

Assessments of functional abilities measured with multifaceted instruments (Katz-ADL (Katz et al. 1963), Barthel-ADL (Mahoney et al. 1965), Lawton-IADL (Lawton et al. 1969), FIM (Pollak et al. 1996), SF-36 (Hayes et al. 1995)) were performed in 12 studies. Eleven of these studies achieved positive results (Table 2). Long duration of the exercise intervention (12-52 weeks) and progressive increase in exercise intensity appeared to be decisive factors for success. Music was used in some successful studies during the exercise sessions to create a positive atmosphere and enhance adherence (Rolland et al. 2007).

Participants with non-Alzheimer's dementia benefitted from exercise intervention more than those with AD according to a high-quality Swedish study among nursing home residents. The differences

were thought to result from lower baseline cognition in AD patients, but also differences in motor skill learning abilities, as memory impairment is often more pronounced in AD patients than their non-AD counterparts (Toots et al. 2016). One large, good-quality study did not find improvements in ADL performance after 16 weeks of moderately intensive training. The authors discussed that the negative finding may have resulted from a ceiling effect, as the participants had mild AD with rather high baseline functioning (Hoffmann et al. 2016). This is supported by the finding that low baseline motor functioning predicted the most positive training response in participants with mild dementia after 12 weeks of resistance and functional training (Schwenk et al. 2010). Roach and co-workers also observed that participants with the lowest mobility at baseline showed the largest improvement in mobility scores after 16 weeks of multicomponent exercise training (Roach et al. 2011).

Exercise adherence was found to be a significant predictor of positive results in many studies (Rolland et al. 2007, Hauer et al. 2012, Telenius et al. 2015, Cancela et al. 2016). Especially concerning the effects of exercise on muscle strength, there appears to be a dose-response relationship, and it seems to require more effort to improve muscle strength than balance (Telenius et al. 2015).

Active control was employed in 13 of the 28 studies. Often the controls were offered social activities (Pomeroy et al. 1999, Tappen et al. 2000, Stevens et al. 2006, Roach et al. 2011, Telenius et al. 2015, Cancela et al. 2016, Toots et al. 2016), but low-intensity exercise such as stretching was also used (Hauer et al. 2012, Morris et al. 2017, Schwenk et al. 2014). The results appeared not to be dependent on whether the control group was active or continued normal care.

Sustainability of the effects of the exercise interventions on functional abilities has only been explored in a few studies (Teri et al. 2003, Miu et al. 2008, Hauer et al. 2012, Telenius et al. 2015, Hoffmann et al. 2016, Toots et al. 2016). In a German study among community-dwelling participants with mild dementia, the positive effects of 12 weeks of resistance and functional training were still detectable in walking abilities, balance and muscle strength at a three-month follow-up (Hauer et al. 2012). Similar results were obtained in nursing home residents with more advanced dementia (Telenius et al. 2015, Toots et al. 2016), although the Swedish study found sustainability in balance predominantly in those participants with better cognition at baseline (Toots et al. 2016). The effects of an exercise and behavioural management intervention were sustained in functional abilities measured with the SF-36 instrument at a 24-month follow-up in a community setting among participants with moderate AD (Teri et al. 2003). In a small study among patients with mild AD, the patients in the exercise intervention group remained stable in their ADL

performance during the 12-week study period and the 12-week follow-up, whereas the controls experienced a considerable decrease in performance (Holthoff et al. 2014).

The evidence supporting positive effects of exercise on functional abilities and mobility in PWD appears to be rather convincing. However, physical performance as represented in activities of daily living is multifactorial, with numerous factors and causes that may not be equally susceptible to changes. Therefore, better balance after exercise intervention may improve overall scores of ADL performance, but the effects on, for instance, urinary incontinence may be less pronounced. ADL abilities are associated strongly also with the level of cognition, especially executive functions, and it is safe to assume that interventions benefitting both physical functions and cognition would be the most effective (Table 2).

Table 2. Randomized controlled trials examining the effects of exercise on physical functioning in dementia patients (positive findings highlighted).

Study	Participants	Intervention	Functional outcomes	Methodological quality (see Table 5) /Comments
Community-dwellers				
Arcoverde et al. 2014 Brazil n=20	PWD Mean age 79 y Mean MMSE 20	IG, n=10: Treadmill walking 30 min x 2/week, 12 weeks CG, n=10: TAU	Balance, mobility: Improvement in IG compared with CG.	Moderate, 9/13 Low statistical power.
Burgener et al. 2008. USA n=43	PWD (various subtypes), Mean age 77 y Mean MMSE 24	IG, n=24: Tai Chi (adapted to PWD) 60 min x 3/week, 40 weeks + CBT 90 min, bi-weekly, 40 weeks + Support group 90 min, bi-weekly, 40 weeks CG, n=19: TAU	Balance: No difference between groups at 20 or 40 weeks	Poor, 4/13 Multicomponent intervention.
Dawson et al. 2017 USA n=23	PWD Mean age 74 y Mean MMSE 21	IG, n=13: Functional strength and balance programme x min x 2/week, 12 weeks CG, n=10: TAU	Lower extremity strength: IG improved compared with CG ADL/IADL: No differences between groups Balance: IG improved compared with CG Gait speed: No differences between groups	Moderate, 7/13 Low statistical power
Hauer et al. 2012. Germany n=122	PWD (various subtypes) mean age 83 y mean MMSE 22	IG, n=62: Resistance training, functional training (walking, climbing stairs) 120 min x 2/week, 12 weeks CG, n=60: Placebo motor training (upper body exercise, stretching); 60 min x 2/week, 12 weeks	Muscle strength and mobility: Improvement in IG compared with CG	Good 13/13 Active CG.
Hoffman et al. 2016. Denmark n=200	AD patients mean age 70.5 y mean MMSE 24	IG, n=107: Moderate- to high-intensity aerobic exercise 60 min x 3/week, 16 weeks CG, n=93: TAU	ADL: No difference between groups	Good, 13/13 Multicentre study. Primary outcome cognition
Holthoff et al. 2015 Germany n=30	AD patients Mean age 72 y Mean MMSE 21	IG, n=15: Training with movement trainer (MOTOmed); 30 min x 3/week, 12 weeks CG, n=15: TAU	ADL: Stable in IG, deteriorated in CG	Moderate, 9/13 Low statistical power
Kwak et al. 2008 Korea n=30	PWE mean age 80 y mean MMSE 14	IG, n=15: Strength and endurance exercise programme 30-40 min x 1/week, 52 weeks CG, n=15: TAU	Muscle strength, endurance, balance: Improvement in IG compared with CG ADL: Improvement in IG compared with CG	Poor, 2/13
Miu et al. 2008 Hong Kong n=85	PWD (various subtypes) mean age 76 y median MMSE 20	IG, n=36: Aerobic exercise (treadmill, bicycle) 45-60 min x 2/ week, 12 weeks CG, n=49: TAU	Walking, balance: Improvement in IG compared with CG	Moderate, 9/13

Table 2 continues

Morris et al. 2017 USA n=76	PWD Mean age 74y (IG), 71y (CG) Mean MMSE 25	IG, n=37: Aerobic exercises 150min/week, 26 weeks CG, n=39: Stretching and toning exercises Frequency?	Functional abilities (Disability Assessment of Dementia): Improvement in IG compared with CG	Moderate, 9/13 Improvement in cardiorespiratory fitness was related to benefits in hippocampal volume in IG.
Pitkälä et al. 2013 Finland n=210	AD patients mean age 78 y mean MMSE 18	IG 1, n=70: Individually tailored exercise (strength, endurance, dual-tasking) IG 2, n=70: Group exercise (strength, endurance, dual-tasking) Both groups: 60 min x 2/week, 52 weeks CG, n=70: TAU	Functional abilities: slower rate of deterioration in IG 1 and 2 than in CG Falls: Fewer falls in IG 1 and 2 than in CG	Good, 13/13
Pomeroy et al. 1999 UK n=81	PWD Mean age 82 y Mean MMSE	IG, n=43: Individual endurance and balance exercises CG, n=38: Individual social activities. Both groups: 30 min, 10 times in 2 weeks	Mobility, walking: No difference between groups	Moderate, 9/13 Very short intervention during respite care.
Schwenk et al. 2014 Germany n=61	PWD Mean age 82 y Mean MMSE 21	IG, n=26: Resistance training, functional training (walking, climbing stairs) 120 min x 2/week, 12 weeks CG, n=35: Placebo motor training (upper body exercise, stretching); 60min x 2/week, 12 weeks	Gait parameters: Improvement in IG compared with baseline. No improvement in CG.	Moderate, 10/13 Active CG. Dual-task-based exercise.
Steinberg et al. 2009 USA n=27	AD patients Mean age 75 y Mean MMSE 21 (IG), 16 (CG)	IG, n=14: Exercise programme (aerobic, strength, balance and flexibility) 7 x week, 12 weeks CG, n=13: Home safety assessment	Hand functions required in ADL: Improvement in IG within group Muscle strength, walking: No difference between groups	Moderate, 10/13 Low statistical power
Suttanon et al. 2013 Australia n=40	AD patients Mean age 82 y Mean MMSE 21	IG, n=19: Tailored exercise programme (walking, strength training balance) supported by PT (6 visits+calls) 7 x week, 26 weeks CG, n=21: Home-based education programme supported by OT (6 visits+calls)	Balance: Improvement in IG compared with CG Falls risk: Improvement in IG compared with CG	Good, 12/13 Low statistical power. Active CG.
Teri et al. 2003 USA n=153	AD patients Mean age 78 y Mean MMSE 17	IG, n=76: Exercise programme (endurance, strength, balance and flexibility training) 30 min x 2-4/week, 12 weeks + care-giver training CG, n=77: TAU	Physical activity: Improvement in IG compared with CG Physical functioning (SF-36): Improvement in IG compared with CG	Good, 13/13 Multicomponent intervention.
Vreugdenhil et al. 2011 Australia n=40	AD patients Mean age 82 y Mean MMSE 21	IG, n=19: Tailored exercise programme (walking, strength training balance) supported by PT (6 visits+5 calls) 7 x week, 26 weeks CG, n=21: Home-based education programme supported by OT (6 visits+5 calls)	Mobility: Improvement in IG compared with CG ADL: Improvement in IG compared with CG	Moderate, 7/13 Intensive training in IG. Active CG

Table 2 continues

Nursing-home residents				
Cancela et al. 2016 Spain n=189	PWD in NH Mean age 82 y Mean MMSE 15	IG, n=73: Indoor cycling CG, n=116: Recreational activities; Both groups: 15 min x 7/week, 64 weeks	ADL (Katz): Improvement in IG compared with CG.	Good, 12/13 Active CG.
Christofoletti et al. 2008 Brazil n=54	PWD Mean age 74 y Mean MMSE 19 (IG1), 13 (IG2), 15 (CG)	IG1, n=: Strength and balance exercises supervised by PT + arts and crafts supervised by OT + physical education 120 min x 5/week, 26 weeks IG2, n=: Strength and balance exercises supervised by PT 60 min x 3/week, 26 weeks CG, n=: TAU	Balance: Improvement in IG 1 and IG 2 compared with CG	Poor, 5/13 Multicomponent intervention.
Cott et al. 2002 Canada n=86	AD patients Mean age 86 y Mean MMSE 6	IG1, n=30: Walking and talking in pairs CG1, n=30: Talk only Both groups: 30 min x 5/week, 16 weeks CG2, n=26: TAU	Walking: No differences between groups	Poor, 6/13 Active CG.
Kemoun et al. 2010 France n=31	AD patients Mean age 82 y Mean MMSE 12	IG, n= 16: Walking, endurance, and balance exercises 60 minx 3/week, 15 weeks CG, n=15: TAU	Walking, gait parameters: Improvement in IG compared with CG	Poor, 6/13
Roach et al. 2011 USA n=82	AD patients Mean age 88 y Mean MMSE 9 IG1, CG,12 IG2	IG1, n=: Exercise programme (strength, endurance, balance, flexibility) IG2, n=: Supervised walking CG, n=: Social conversation All groups: 30 min x 5 /week, 16 weeks	Mobility and walking: Improvement in IG1compared with IG 2 and CG	Moderate, 8/13 Comparisons made also between two IGs.
Rolland et al. 2007 France n=134	AD patients Mean age 83 y Mean MMSE 9	IG, n=67: Walking, strength, balance, and flexibility training 60 min x 2/week, 52 weeks CG, n=67: TAU	ADL(Katz): IG declined 1/3 less than CG Walking: Improvement in IG compared with CG	Good, 13/13
Stevens et al. 2006 Australia n=75	PWD Mean age 81 y MMSE 10-22	IG, n=24: Muscle strength training CG1, n=21: Social visits Both groups: 30 min x 3/week, 12 weeks CG2, n=30: TAU	ADL: Improvement within IG	Poor, 3/13 Active CG.
Tappen et al. 2000 USA n=65	AD patients Mean age 87 y Mean MMSE 11	IG1, n=26: Assisted walking IG2, n=21: Walk and conversation CG, n=24: Conversation only All groups: 30 min x 3/week, 16 weeks	Walking abilities: IGI 1 and CG declined, IG2 (dual-task) remained stable	Moderate 8/13 Active CG.

Table 2 continues

Telenius et al. 2015 Norway n=170	PWD Mean age 87y Mean MMSE 16	IG, n=87: Strength and balance exercises supervised by PT CG, n=83: Social meetings; Both groups: 60 min x2/week, 12 weeks	Balance: Improvement in IG compared with CG ADL (Barthel): Improvement in IG compared with CG	Good, 13/13 Active CG.
Toots et al. 2016 Sweden n=186	PWD Mean age 85 y Mean MMSE 15	IG, n=93: High-intensity exercise (walking, strength, and balance training) CG, n=93: Social activity group (games, conversation); Both groups: 45 min x 5/2 weeks, 16 weeks	Balance: Improvement in IG in non-AD patients compared with CG ADL (Barthel, FIMmotor): Improvement in IG in non-AD patients compared with CG	Good, 13/13 Active CG
Toulotte et al. 2003 France n=20	PWD Mean age 81 y Mean MMSE 16	IG, n=10: Exercise programme (strength, balance, and flexibility training) 45 min, 2x/week, 16 weeks CG, n=10: TAU	Walking, mobility, balance, flexibility: Improvement in IG compared with CG	Moderate, 7/13 Low statistical power
Venturelli et al. 2011 Italy n=24	AD patents Mean age 85 y Mean MMSE 13	IG, n=12: Assisted walking 30 min x 4/week, 16 weeks CG, n=12: TAU	Walking: Improvement in IG compared with CG ADL (Barthel): Improvement in IG compared with CG	Moderate, 7/13 Low statistical power

y=years, MMSE= Mini-Mental State Examination Folstein et al. 1975), IG= Intervention group, CG= Control Group, TAU= Treatment as usual, AD= Alzheimer's disease, ADL= Activities of Daily Living, IADL= Instrumental Activities of Daily Living, PT= physiotherapist, OT= occupational therapist, ERFC = Rapid Evaluation of Cognitive Function, FIMmotor= Functional Independence Measure motor domain (Pollak et al. 1996), SF-36= 36-item Short-Form Health Survey of physical functioning (Hayes et al. 1995)

2.4.4 Effects of exercise on fall rate in older adults with dementia

A fall is an unexpected event whereby a person involuntarily comes to lie on the ground or another lower level with or without loss of consciousness (Lamb et al. 2005).

Falls are a common cause of morbidity, permanent functional decline, and mortality in people with dementia. The annual incidence of falls in this patient group is estimated to be as high as 70-80% (Shaw et al. 2007). These patients are also at higher risk of fall-associated major injuries such as fractures or head trauma (Meuleners et al. 2017). Furthermore, PWD are at greater risk of a hospital admission for an injury (Meuleners et al. 2017), and after an injurious fall at risk of early nursing home placement (Tinetti et al. 1997). PWD fall more often than their cognitively healthy peers (Allan et al. 2009, Taylor et al. 2013). This is seen in all subtypes of dementia, the patients with Parkinson dementia and dementia with Lewy bodies being at the highest risk (Allan et al. 2009).

The higher fall risk in PWD may result from various factors. Most of the common risk factors, such as increasing age, decline in balance and muscle strength, impaired vision, history of falls, multimorbidity, and polypharmacy, are shared with cognitively intact older people, but have a higher prevalence and greater severity in PWD (Shaw et al. 2007). Malnutrition or undernutrition is common in PWD (White et al. 1998, Volkert et al. 2015) and can lead to involuntary weight loss, sarcopenia, and frailty, resulting in increased fall risk (Evans et al. 1993).

Decline in cognition has a strong association with deterioration in gait parameters (Allali et al. 2016). Walking is to some extent an automatic task, but it also requires higher cortical functions, especially executive functions, and attention (LaJoie et al.1993). In older age, part of the automaticity of walking is lost due to physical changes in the body, e.g. sensory deficits and decline in muscle strength (Skelton et al. 1994). To overcome these physical handicaps, an older person needs to rely more on executive functions for safe walking than his younger peers. In persons with dementia, the cognitive resources may not be high enough to ensure safe walking, especially while dual-tasking, and the risk of falling increases (Bridenbaugh et al. 2015). Decline in MMSE score in PWD (Gleason et al. 2009) or poor executive function in older adults (Kearney et al. 2013) seem to indicate an increased risk for falling, supporting the forementioned theory.

In prospective studies, depression, orthostatic hypotension, use of cardioactive or psychotropic medication, low physical activity, and previous falls have been found to predict increased fall rate in PWD (Allan et al. 2009, McDonald et al. 2016). Central autonomic dysfunction seen frequently in PWD may contribute to the increased risk of orthostatic hypotension in addition to medication (Jensen-Dahm et al. 2015). NPS, such as wandering, can increase risk of falling (Kallin et al. 2005).

Recurrent falls may lead to fear of falling, causing reduced activity and ultimately loss of muscle strength, balance, and mobility. Injurious falls often lead to hospitalization and may eventually increase the risk of permanent nursing home placement (Shaw et al. 2007).

Preventive interventions that target falls are more likely to be effective in participants with normal cognition or with only minor cognitive problems (Montero-Odasso et al. 2012). Assessing environmental hazards, using assistive and protective (technological) aids, staff education, and vision assessment/correction seem to reduce the falls in older adults living in communal settings (American Geriatric Society guideline 2011, Rimland et al. 2016). Vitamin D and calcium supplementation may also be beneficial (American Geriatric Society guideline 2011).

According to the meta-analyses, the single-component non-pharmacological intervention with the most positive impact on fall prevention has been exercise. Exercise reduces the number of falls in older adults without cognitive decline (Gillespie et al. 2012), especially in those living in the community (Rimland et al. 2016). Exercise programmes seem to be effective also in preventing injurious falls in older adults (El-Khoury et al. 2013). Effective exercise programmes frequently comprise a combination of low-extremity strength training and balance exercises that are progressive in intensity (Rimland et al. 2016).

The most consistently effective intervention among various settings appears to be multifactorial and tailored to tackle individually assessed risk factors. Exercise has frequently been part of the multifactorial interventions (Rimland et al. 2016).

While it might be tempting to extrapolate earlier evidence to PWD, it is not an appropriate approach, as the underlying mechanisms for risk factors for falls may be various (Jensen et al. 2003, Guo et al. 2013, Meuleners et al. 2017). PWD are generally frailer and clinically more unstable than cognitively healthy older adults (Oliver et al. 2007). Results from fall prevention studies among PWD are conflicting or inconclusive generally due to methodological problems and/or small number of participants (Shaw et al. 2007, Am Ger Soc 2011) According to the American Geriatric Society Clinical Practice Guideline, there is insufficient evidence supporting any recommendations to reduce fall risk in older persons with cognitive impairment (Am Ger Soc 2011). A systematic review exploring the results of 43 studies among PWD reporting rate of falls in hospital or care home settings found that multifactorial interventions (including e.g. risk factor assessment, care planning, medical/diagnostic approaches, changes in physical environment, education programmes, medication review, hip protectors, removal of physical restraints, and exercise) seem to prevent falls in PWD. However, multifactorial interventions in care homes or single interventions (removal of

physical restraints, fall alarm devices, calcium/vitamin D, exercise, changes in physical environment, or medication review) in care homes or hospital settings showed no significant effect on falls (Oliver et al. 2007).

Studies addressing the effects of exercise as a single intervention on fall rate in dementia patients are scarce, albeit some good-quality RCTs (Pitkälä et al. 2013, Suttanon et al. 2013, Zieschang et al. 2017) and even systematic reviews exist (Chan et al. 2014, Burton et al. 2015).

In a recent systematic review investigating the effectiveness of exercise interventions in reducing falls in PWD, the authors were able to incorporate data from only seven relevant RCTs involving 781 participants (Chan et al. 2014). Four of the seven studies showed a significant effect in reducing the fall rate. The studies were heterogeneous in their setting (nursing home residents or community-dwellers) and the duration and intensity of the intervention, diminishing the generalizability of the results. According to the authors, the core elements of a successful intervention were multicomponent exercise (combination of strength, endurance, and balance training), supervision of the training by a professional trainer, and an individually tailored exercise programme adapted to the cognitive level of the participant (Chan et al. 2014). Another systematic review including four exercise intervention studies (n=243) conducted among community-dwelling PWD achieved similar results. The studies included in the review were of good methodological quality with sufficient statistical power (Burton et al. 2015). Authors of both reviews state that further research with studies using standardized outcomes, larger sample sizes, and longer follow-up periods is needed (Chan et al. 2014, Burton et al. 2015).

The number of dementia patients is growing fast, meaning more falls and increasing health care and economic burden (Davis et al. 2010). Cost-effective prevention programmes and novel models of intervention are warranted. Despite the small body of research so far, exercise has reasonably solid evidence of efficacy in reducing fall risk in PWD. Falls in PWD are likely of multifactorial origin, requiring multifactorial preventive measures, and exercise should be part of these programmes. Technology and digitalization are starting to be essential also in the lives of PWD, and new solutions for fall prevention, e.g. virtual exercise and balance training, or monitoring changes in patient's movements or vital signs, are already available. Sensor-derived physical activity parameters are independent predictors of fall risk and may have higher diagnostic accuracy in persons with dementia compared with conventional fall risk measures (Schwenk et al. 2014). However, only a few studies of these technology-assisted methods have been published to date (van der Cammen et al. 2016) (Table 3).

Table 3. Randomized controlled trials examining the effects of exercise on falls in dementia patients (positive findings highlighted).

Study	Participants	Intervention	Functional outcomes	Methodological quality (see Table 5)/ Comments
Pitkälä et al. 2013 Finland n=210	AD patients mean age 78 y mean MMSE 18	IG 1, n=70: Individually tailored exercise (strength, endurance, dual-tasking) IG 2, n=70: Group exercise (strength, endurance, dual-tasking) Both groups: 60 min x 2/week, 52 weeks CG, n=70: TAU	Number of falls: Fewer falls in IG 1 and 2 compared with CG	Good, 13/13
Shaw et al. 2003 UK n=274	PWD Mean age 84 y Mean MMSE 13	IG, n=130: Supervised home-based exercise (walking, balance, strength training, flexibility exercises) Frequency? 12 weeks + Multifactorial assessment (medical, occupational) CG, n=144: TAU	Number of falls: No difference between groups	Good, 13/13 High-risk patients with at least one previous fall. Multicomponent intervention.
Suttanon et al. 2013 Australia n=40	AD patients Mean age 82 y Mean MMSE 21	IG, n=19: Tailored exercise programme (walking, strength training, balance) supported by PT (6 visits+calls) 7 x week, 26 weeks CG, n=21: Home-based education programme supported by OT (6 visits+calls)	Falls risk: Improvement in IG compared with CG	Good, 12/13 Low statistical power. Active CG.
Zieschang et al. 2017 Germany n=110	PWD Mean age 82 y Mean MMSE 22	IG, n=55: Progressive resistance training, functional and balance training 120 min x 2/week, 12 weeks CG, n=55: Placebo motor training (flexibility exercises, calisthenics) 60 minx2/week, 12 weeks	Multiple fallers (n=33) showed a reduction in fall rate compared with CG during 12-month follow-up	Good 13/13 Active CG

y=years, AD= Alzheimer's disease, PWD= Patients with dementia, MMSE= Mini-Mental State Examination (Folstein et al. 1975), IG= Intervention group, CG= Control group, TAU= Treatment as usual.

2.4.5 Effects of exercise on neuropsychiatric symptoms in older adults with dementia

Neuropsychiatric symptoms in dementia is an umbrella term that covers several behavioural and psychological symptoms, such as agitation, depression, apathy, delusions, hallucinations, aberrant motor behaviour, disinhibition, irritability, euphoria, eating problems, and sleep impairment, occurring alone or in clusters of symptoms (Lyketsos et al. 2002, Aalten et al. 2007). These clusters of symptoms or subsyndromes may differ in prevalence, course over time, or pathophysiology (Robert et al. 2005, Aalten et al. 2007). Although minor differences in the studies exist, definitions of the subsyndromes of hyperactivity, mood, and psychosis are in general agreement and supported by clinical evidence (Levy et al. 1996, Robert et al. 2005, Aalten et al. 2007). Treatment interventions are considered to be more beneficial when targeting subsyndromes rather than individual symptoms (Aalten et al. 2007, Dechamps et al. 2008).
Multiple factors may contribute to NPS; they can be related to the patient, to the caregiver, or to the environment (Kales et al. 2015). Neuroscientific studies have revealed direct links between disrupted neuronal circuits, changes in neurotransmitter and synaptic function in brain areas associated with behaviour or emotion, and certain neuropsychiatric symptoms of dementia (Geda et al. 2013) Acute illness or discomfort, inability to express or satisfy needs, and patients' pre-existing psychiatric or personality problems may be factors leading to NPS (Kales et al. 2015). Providing care for a person with dementia is a risk for the caregiver's psychological well-being, especially when the care recipient is suffering from NPS (Pinquart et al. 2003). Moreover, caregiver stress and burden may elicit or aggravate NPS in the dementia patient and impede treatment strategies. Ability to cope with external or internal stressors is often decreased in PWD; change in daily routines, too much or a lack of stimuli, or tasks exceeding functional capacity may induce stress, leading to NPS (Kales et al. 2015).

The majority of PWD suffer from NPS over the course of the disease (Lyketsos et al. 2002, Aalten et al. 2005, Gonfrier et al. 2012). In the longitudinal Cache County Study, 75% of PWD exhibited one or several NPS over an 18-month period (Lyketsos et al. 2002), whereas in the Maasbed study the prevalence of NPS was as high as 95% in the two-year follow-up (Aalten et al. 2005). Separate NPS have their own specific prevalence and course over time, but overall, neuropsychiatric symptoms tend to be present chronically (Aalten et al. 2005). The course of the NPS can be persistent or intermittent, the frequency of the symptoms increasing with disease severity (Brodaty et al. 2015). The most persistent and frequent NPS seem to be apathy and aberrant motor behaviours; the latter term is often used interchangeably with agitation (Aalten et al. 2005). Single

symptoms best predicting early placement in permanent nursing home care seem to be aggression, hallucinations, and depression (Gilley et al. 2004).

NPS are associated with faster decline in daily performance and cognition, lower quality of life for the patient and the caregiver, and early institutionalization and higher public health costs (Lyketsos et al. 2002, Gilley et al. 2004).

Traditionally, pharmacological treatment has been used to relieve the NPS. Cholinesterase inhibitors (donepezil, galantamine, and rivastigmine) may improve neuropsychiatric symptoms in AD patients and are recommended as a first-line pharmacological therapeutic option (Rodda et al. 2009, Wang et al. 2015). The various cholinesterase inhibitors appear equal in efficacy (Trinh et al. 2003). For memantine, the results are conflicting, although some RCTs have found beneficial treatment effects, especially on agitation and irritability (Gauthier et al. 2010, Kales et al. 2015).

Atypical antipsychotics have the strongest evidence base when treating NPS in PWD. However, the treatment effects are modest, the effect size being 0.13-0.16, and mainly seen in reducing aggressive behaviour (Kales et al. 2015). Moreover, serious adverse effects, such as parkinsonism and cerebrovascular events, that are frequently seen in AD patients treated with antipsychotics, may outweigh the minor benefits (Schneider et al. 2005). The increased risk of cerebrovascular event is considered a class effect for all antipsychotics (Kales 2015). The only antipsychotic medicine approved by the European Medicine Agency for NPS is risperidone, but off-label use of other antipsychotics is frequent (EMA 2008).

Antidepressants may have positive effects on depressive symptoms and agitation in dementia, although results of recent meta-analyses have been somewhat conflicting (Kales et al. 2015). Antidepressants may, however, increase the risk of falls (Hartikainen et al. 2007). Mood stabilizers, such as lamotrigine or carbamazepine, have also shown some efficacy in NPS (e.g. in anxiety and irritability) in AD patients, but good-quality studies on these medications are scarce (Kales et al. 2015, Suzuki et al. 2015). Benzodiazepines are not recommended for treatment of NPS, as their profile of adverse effects (gait abnormalities, falls, worsening cognition, confusion) is poor, and they are to be left as emergency medicines, when the patient needs prompt sedation or relief of anxiety (Koenig et al. 2016).

Recent guidelines suggest non-pharmacological treatments as the first-line treatment choice for NPS (Current care guidelines, Finland 2017). The non-pharmacological treatments comprise various behavioural, environmental, and caregiver supportive interventions. A number of meta-

analyses and systematic reviews have explored these treatments (Olazaran et al. 2010, Brodaty et al. 2012, Thune-Boyle et al. 2012, Kales et al. 2015) Some positive effects have been found for music therapy (Preuss et al. 2016), physical exercise (Thune-Boyle et al. 2012, Kales et al. 2015, Preuss et al. 2016), cognitive stimulation (Olazaran et al. 2010), and multicomponent interventions (combining cognitive stimulation with, for example, physical exercise or ADL training) for PWD (Olazaran et al. 2010). The meta-analysis of 23 RCTs concluded that interventions aimed at family caregivers can significantly alleviate NPS, with effects that are at least comparable to those of antipsychotic drugs (Brodaty et al. 2012). Thus, the strongest evidence base seems to be for behavioural interventions (analysis and modification of unwanted behaviour; family caregiver education) (Olazaran et al. 2010, Kales et al. 2015) and professional caregiver education (Olazaran et al. 2010).

One of the most keenly studied non-pharmacological approaches to NPS in dementia is exercise. Directs effects of exercise on the brain and vascular health are discussed in detail elsewhere in this dissertation. It is possible that also such mechanisms as improved well-being and self-esteem and increased social contacts may generate symptomatic relief as a result of exercise in dementia patients (Thom et al. 2011).

A large body of evidence demonstrates that physical exercise among healthy older adults reduces depressive symptoms and anxiety and improves sleep and quality of life (Fox et al. 2007, Windle et al. 2010, Brindle et al. 2012, Bauman et al. 2016, Catalan-Matamoros et al. 2016) without major adverse effects (Catalan-Matamoros et al. 2016). The effects of exercise on depression seem to be fairly sustainable over time (Singh et al. 2001), and patients who are physically active are less likely to relapse (Babyak et al. 2000).

A physically active lifestyle can lower the risk of NPS in PWD. A Brazilian cross-sectional study categorized participants according to their type of dementia and level of physical activity (lower or higher). The AD patients with higher physical activity presented with fewer neuropsychiatric disturbances measured with the NPI. Among the other subgroups, the effects were smaller. However, the baseline dementia severity was not assessed, and thus, it is not possible to control the influence of dementia severity on NPI scores (Christofolletti et al. 2011). Another cross-sectional study performed among AD patients concluded that patients who exercised regularly were less likely to be depressed (Regan et al. 2005).

The results of RCTs examining the effects of exercise on NPS in dementia are more conflicting. Table 4 presents 19 RCTs with a study population composed of PWD, with exercise as the main intervention, and with NPS as the primary or secondary outcome. Of the studies, 11 were conducted

in nursing home settings (Alessi et al. 1999, van de Winckel et al. 2004, Rolland et al. 2007, Williams et al. 2008, Conradsson et al. 2010, Dechamps et al. 2010, Eggermont et al. 2010, Cheng et al. 2014, Telenius et al. 2015, Cancela et al. 2016, Fleiner et al. 2017) and eight among community-dwelling patients (Miu et al. 2008, Steinberg et al. 2009, McCurry et al. 2011, Vreugdenhil et al. 2012, Lower et al. 2014, Holthoff et al. 2015, Hoffman et al. 2016, Morris et al. 2017). The number of participants varied from 25 to 200, half of the studies being relatively large, with more than 100 participants (Rolland et al. 2007, Conradsson et al. 2010, Dechamps et al. 2010, Eggermont et al. 2010, McCurry et al. 2011, Lowery et al. 2014, Telenius et al. 2015, Cancela et al. 2016, Hoffman et al. 2016). The type of exercise in the interventions varied from yoga to indoor cycling. The most common type was multicomponent exercise, i.e. two or more exercise types together in one session. In all studies, participants exercised at least twice a week, in most of the studies three times a week or even daily. Ten studies had an active control group with social or recreational activities or light exercise (Alessi et al. 1999, van de Winckel et al. 2004, Williams et al. 2008, Conradsson et al. 2010, Eggermont et al. 2010, Cheng et al. 2014, Telenius et al. 2015, Cancela et al. 2016, Fleiner et al. 2017, Morris et al. 2017).

Ten of the 19 studies found a positive effect of the exercise intervention on one or several NPS.

Depression was studied in 12 studies (Rolland et al. 2007, Dechamps et al. 2008, Miu et al. 2008, Williams et al. 2008, Steinberg et al. 2009, Conradsson et al. 2010, Vreugdenhil et al. 2012, Chen et al. 2014, Telenius et al. 2015, Cancela et al. 2016, Hoffman et al. 2016, Morris et al. 2017). Only one study showed beneficial effects of exercise on depression (Williams et al. 2008). The study included participants with depressive symptoms at baseline. Cornell Scale for Depression in Dementia (CSDD) scores improved in both the exercise group and the control group with regular conversation sessions. Thus, no difference between the study groups was detected (Williams et al. 2008). Six larger studies (number of participants 160 to 200) observed no significant improvement in depressive symptoms after the exercise intervention (Rolland et al. 2007, Dechamps et al. 2008, Conradsson et al. 2010, Telenius et al. 2015, Cancela et al. 2016, Hoffman et al. 2016).

Neuropsychiatric symptoms were explored in ten RCTs using global assessment methods (van de Winckel et al. 2004, Rolland et al. 2007, Dechamps et al. 2008, Steinberg et al. 2009, Lowery et al. 2014, Holthoff et al. 2015, Telenius et al. 2015, Cancela et al. 2016, Hoffman et al. 2016, Fleiner et al. 2017). NPI was used in majority of the studies presented in Table 4.

Six out of ten studies found a positive effect of exercise on one or several NPS (Dechamps et al. 2008, Holthoffet al. 2015, Telenius et al. 2015, Cancela et al. 2016, Hoffman et al. 2016, Fleiner et

al. 2017). The single NPS showing the strongest positive association with exercise appeared to be apathy, agitation (or aberrant motor behaviour), irritability, and appetite (Dechamps et al. 2008, Telenius et al. 2015, Hoffman et al. 2016, Fleiner et al. 2017). The type of exercise intervention producing the most beneficial effects seemed to be a combination of aerobic, strength, and balance training (Williams et al. 2008, Telenius et al. 2015) or exercise demanding mind-body interaction such as Tai Chi or yoga (Dechamps et al. 2008). Intensive training from three to seven times a week was related to beneficial effects (Dechamps et al. 2008, Williams et al. 2008, Holthoff et al. 2015, Hoffman et al 2016). A large French study among AD patients residing in nursing homes found no improvement in NPI after a 12-month intervention with multicomponent training twice a week. However, participants in this study were extremely frail and the mean MMSE was 8.8, indicating severe dementia (Rolland et al. 2007). Another good-quality study failed to show improvement in NPI after intervention comprising 30-minute walking sessions five times a week for 12 weeks. However, the trend for lower NPI after exercise intervention was positive, although the changes did not attain significance. The researchers speculated that the unfavourable results may be related to poor adherence to the exercise and short duration of the intervention (Lowery et al. 2014).

Sleep as a primary outcome was explored in three studies (Alessi et al. 1999, Eggermont et al. 2010, McCurry et al. 2011). Sleep was measured with wrist actigraphies. McCarry and co-workers randomized community-dwelling AD patients to walking group, light exposure group, and a combination group (walking + light exposure). All groups improved in total wake time, especially those with better adherence to walking and light exposure recommendations (McCurry et al. 2011). A smaller study among nursing home patients showed similar results after 14 weeks' functional training performed five times a week. However, a short exercise study of six weeks found no effect on night-time restlessness among PWD living in nursing homes (Eggermont et al. 2010).

Only one study examined the impact of exercise on anxiety in AD patients. Patients enrolled in the study had mild or moderate depression at baseline. After a 16-week intervention of walking 30 minutes five times a week, the anxiety scores measured with the Observed Affect Scale (Lawton et al. 1996) showed improvement (Williams et al. 2008).

Psychotropic medication is widely used to alleviate the NPS in PWD. Many of the studies included in the review presented the baseline psychotropic medication, however, only one study analysed the effects of the intervention regarding the changes in psychotropic medication. In this study, no changes were detected in these medications after 16-week exercise intervention (Williams et al. 2008).

The summary data of RCTs are somewhat disappointing, with fairly weak and inconsistent evidence for beneficial effects of exercise on NPS. However, the lack of evidence is not necessarily indicative of a lack of efficacy. The trajectories of NPS are not easy to predict, as the symptoms may fluctuate over time and the controls may also experience spontaneous recovery (Brodaty et al. 2015). The NPS also differ in various dementia types and stages, and these baseline characteristics play an important part in predicting the subsequent course of symptoms (Brodaty et al. 2015, Caputo et al. 2008, Kim et al. 2003). Patients with severe behavioural disturbances may be less keen to participate in non-pharmacological intervention studies, and may even be excluded due to their challenging symptoms such as psychosis (Brodaty et al. 2012). In many studies, the baseline scores in neuropsychiatric assessments were relatively low, thus, there may have been a floor effect in reducing the NPS. However, stabilization of participants' NPS in a progressive disease may indicate that the exercise intervention is beneficial even without evidence of improvement.

According to longitudinal studies, depressive symptoms tend to decrease over time, whereas apathy, agitation, and aberrant motor behaviour increase as dementia progresses (Aalten et al. 2005, Brodaty et al. 2015). Different NPS, e.g. motor hyperactivity and apathy, can occur simultaneously in dementia, perhaps needing different clinical approaches (Gonfrier et al. 2012).

Regular exercise seems to benefit PWD regarding the NPS. However, the most positive results so far are from studies where individually tailored multi-component interventions combining cognitive stimulation and exercise and caregiver support or education are applied (Olazaran et al. 2010, Brodaty et al. 2012, Kales et al. 2015).

Table 4. Randomized controlled trials examining the effects of exercise on neuropsychiatric symptoms in dementia patients (Positive findings highlighted)

Study	Participants	Intervention	NPS explored	NPS outcomes	Methodological Quality (see Table 5)/ Comments
Community-dwellers					
Hoffman et al. 2016 Denmark n=200	AD patients Mean age 76 y Mean MMSE 24	IG, n=107; moderate- to high-intensity aerobic exercise 60 min, 3x/week, 16weeks CG, n=93; TAU	Depression Global neuropsychiatric assessment	HAMD-17: no change NPI: IG improved compared with CG (total, agitation, delusions, sleep, appetite)	Good, 13/13
Holthoff et al. 2015 Germany n=30	AD patients Mean age 72 y Mean MMSE 21	IG, n=15: Training with movement trainer (MOTOmed); 30 min x 3/week, 12 weeks CG, n=15: TAU	Global neuropsychiatric assessment	NPI: Improvement in IG compared with CG	Moderate, 9/13 Low statistical power
Lowery et al. 2014 UK n=131	PWD 65% AD Mean age 79 y Mean MMSE 15	IG, n= 67; walking 20-30 min, 5/x week, 12weeks CG, n=64; TAU	Global neuropsychiatric assessment	NPI: no differences between groups	Good, 13/13 Participants with some NPS
McCurry et al. 2011 USA n=132	AD patients Mean age 81 y Mean MMSE 19	IG 1, n=32; walking 30 min, 7x/week, 26 weeks IG 2, n=34; light 60 min, 7x/week, 26 weeks IG 3, n=33; combination (walk+light) CG, n=33; TAU	Sleep	Wrist actigraphy: improvement in total wake time in all three IGs compared with CG	Good, 13/13 Participants with sleeping problems.
Miu et al. 2008 Hong Kong n=85	PWD, 60% AD Mean age 77 y Median MMSE 20	IG, n=36: Aerobic exercise 60 min, 2x/ week, 12 weeks CG, n=49: TAU	Depression	CSDD: no differences between groups	Moderate, 7/13
Morris et al. 2017 USA n=76	PWD Mean age 74 y (IG), 71y (CG) Mean MMSE 25	IG, n=37: Aerobic exercises 150 min/week, 26 weeks CG, n=39: Stretching and toning exercises Frequency?	Depression	CSDD: No differences between groups.	Moderate, 9/13
Steinberg et al. 2009 USA n=27	AD patients Mean age 75 y Mean MMSE intervention 20 control 15	IG, n=14: Exercise programme (walking, strength, balance, and flexibility training 7 x/week, 12 weeks CG, n=13: Home safety assessment	Depression Global neuropsychiatric assessment	CSDD: no differences between groups NPI: no differences between groups	Moderate, 10/13 Low statistical power. Active CG.
Vreugdenhill et al. 2012 Australia n=40	AD patients Mean age 74 y Mean MMSE 22	IG, n=20: Exercise programme (walking, strength, and balance training) 7 x/week, 16 weeks CG, n=20: TAU	Depression	GDS-15: no significant differences between groups	Moderate, 7/13 Intensive training in IG. Active CG

Table 4 continues

Nursing home residents					
Alessi et al. 1999 USA n=29	PWD Mean age 88 y Mean MMSE 13	IG, n=15: Functional training + Night-time programme (reducing lights and noise, toileting only when needed) 5x/week, 14 weeks CG, n=14: Night-time programme	Sleep	Wrist actigraphy: night-time percent sleep improved in IG compared with CG	Moderate, 7/13 Small statistical power. Active CG.
Cancela et al. 2016 Spain n=189	PWD Mean age 81 y Mean MMSE 15	IG, n=73; indoor cycling 15 min, 7x/week, 64 weeks CG, n=116; recreational activities	Depression Global neuropsychiatric assessment	CSDD: CG (recreational activity) improved compared with IG NPI (total): IG improved compared with CG	Good, 12/13 Active CG.
Cheng et al. 2014 Hong Kong n=110	PWD Mean age 81 y Mean MMSE 19	IG, n=39; Tai Chi CG 1, n=36; Mahjong CG 2, n=35; Handicrafts all groups 60 min, 3x/week, 12 weeks	Depression	GDS: CG 1(Mahjong game) improved compared with CG2, no differences between IG (Tai Chi) and CG 1 or 2	Moderate, 8/13 Active CG
Conradsson et al. 2010 Sweden n=191	Older people living in residential care, 52% with dementia Mean age 85 y Mean MMSE 18	IG, n=91: Functional strength and balance training (HIFE) CG, n=100: leisure activities while sitting Both groups: 5x/2weeks, totally 29 sessions.	Depression Subjective psychological well-being	GDS-15: no differences between groups PGCMS: no differences between groups	Good, 11/13 Some participants without definite dementia diagnosis Active CG.
Dechamps et al. 2008 France n=160	PWD Mean age 83 y Mean MMSE 17 (IG 1) Mean MMSE 14 (IG 2, CG)	IG 1, n=51; Tai Chi 30 min, 4x/week, 26 weeks IG 2, n=49; cognition action 30 min, 2x/week, 26 weeks CG, n=60; TAU	Depression Global neuropsychiatric assessment	GDS-15: IG 2 improved compared with CG NPI: IG 1 and 2 improved compared with CG (total NPI, apathy, delusions, irritability, agitation)	Moderate, 9/13 IG 1 had higher MMSE at baseline.
Eggermont et al. 2010 Netherlands n=112	PWD, 32% AD Mean age 84 y Mean MMSE 19	IG, n=60; Walking CG, n=52: Social visits Both groups: 30 min, 5x/week, 6 weeks	Sleep	Actigraphy: no differences between groups in night-time restlessness	Moderate, 8/13 Active CG

Table 4 continues

Fleiner et al. 2017 Germany n=85	PWD in psychogeriatric hospital Mean age 80 y Mean MMSE 18	IG, n=46; Endurance and strengthening exercises 20 min x 3/d x 3/week, 2 weeks CG, n=39; Social stimulation 120 min/week, 2 weeks	Global neuropsychiatric assessment Agitation	ADCS-CGIC: IG improved compared with CG (emotional and psychomotor agitation, lability, verbal aggression) NPI: IG improved compared with CG (total NPI) CMAI: IG improved compared with CG (verbal agitation)	Good, 13/13 Very short intervention No intervention effect on antipsychotic or sedative medication.
Rolland et al. 2007 France n=134	AD patients Mean age 83 y Mean MMSE 8.8	IG, n=67; walking + strength, balance, and flexibility training 60 min, 2x/week, 52 weeks CG, n=67; TAU	Depression Global neuropsychiatric assessment	MADRS: no differences between groups NPI: no differences between groups	Good 13/13
Telenius et al. 2015 Norway n=170	PWD Mean age 87 y Mean MMSE 16	IG, n=87; high-intensity functional exercises (HIFE), strength, balance, endurance CG, n=83; light leisure activities Both groups: 60 min, 2x/week, 12 weeks	Depression Global neuropsychiatric assessment	CSDD: no differences between groups NPI: IG improved in apathy compared with CG	Good, 13/13 Active CG
Van de Winckel et al. 2004 Belgium n=25	PWD, AD 90%, 100% women Mean age 81 y Mean MMSE 12	IG, n=15; dance therapy CG, n=10; conversation sessions Both groups 30 min, 7x/week, 12 weeks	Global neuropsychiatric assessment	SGRS (Dutch version): no differences between groups	Poor, 5/13 Active CG.
Williams et al. 2008 USA n=45	AD patients with CSDD score≥7 Mean age 88 y Mean MMSE 7	IG 1, n=16; walking, strength, and balance training IG 2, n=17; walking CG n=12; conversation All groups: 30 min, 5x/week, 16weeks	Depression Anxiety	CSDD: All groups improved AMS: IG 1 and 2 improved compared with CG OAS: IG 1 improved compared with CG	Moderate, 8/13

y=years, PWD= patient(s) with dementia, AD= Alzheimer's disease, IG= Intervention group, CG= Control group, TAU= Treatment as Usual, CSDD= Cornell Scale of Depression in Dementia (Alexopoulos et al. 1988), GDS= Geriatric Depression Scale (Hughes et al. 1982), NPI= Neuropsychiatric Inventory (Cummings et al. 1997), PGCMS= Philadelphia Geriatric Center Morale Scale, CAPE-BRS= Clifton Assessment Procedures for the Elderly Behavior Rating Scale, HAMD-17= Hamilton Depression Rating Scale 17 items, MADRS= Montgomery-Asberg Depression Rating Scale, SGRS= Stockton Geriatric Rating Scale, AMS= Alzheimer's Mood Scale, OAS= Observed Affect Scale, ADCS-CGIC= Alzheimer's Disease Cooperative Study-Clinical Global Impression of Change, CMAI= Cohen-Mansfield Agitation Inventory

Table 5. Evaluation of quality criteria fulfilment in RCTs examining the effects of exercise interventions on Alzheimer's disease.

Study	Valid diagnosis of dementia or MCI	Inclusion and exclusion criteria described	Description of intervention	Valid measurements and outcome measures	Sufficient statistical power	Randomisation method valid	Blinded outcome assessor	Intention to treat-analysis	Groups comparable at baseline	Drop-outs described and included in analysis	Compliance described	Complications reported	Comparison of differences in changes between the groups in outcome variables	Quality
Alessi et al. 1999	?	+	+	+	-	?	-	-	+	+/-	+	+	+	7/13
Arcoverde et al. 2014	+	+	+	+	-	?	?	?	+	+	+	+	+	9/13
Bossers et al. 2015	+	+	+	+	+	-	+	-	+	-	+	-	+	9/13
Burgener et al. 2008	+/-	-	+	+	-	-	-	-	+	-	+/-	-	+	4/13
Cancela et al. 2016	+	+	+	+	+	?	+	+	+	+	+	+	+	12/13
Cheng et al. 2012	-	+	+	+	-	?	-	-	+	-	-	-	+	5/13
Cheng et al. 2014	-	+	+	+	+	?	-	+	+	+	-	-	+	8/13
Christofoletti et al. 2008	+/-	+	+	+	-	+	-	-	-	-	-	-	+	5/13
Conradsson et al. 2010	+	+	+	+	+	+	+	+	+	+	-	-	+	11/13
Cott et al. 2002	-	+	+	+	-	+	+	-	+	+/-	-	-	-	6/13
Dawson et al. 2017	-	+	+	+	-	+	?	-	+	-	+	+	+	7/13
Dechamps et al. 2010	-	+	+	+	+	+/-	?	+	-	+	+	+	+	9/13
Eggermont et al. 2009	-	+	+	+	+	+/-	+	+	+	+/-	-	-	+	8/13
Fleiner et al. 2017	+	+	+	+	+	+	+	+	+	+	+	+	+	13/13
Friedman and Tappen1991	+	+	+	+	-	+/-	-	-	+	?	-	-	+	6/13
Hauer et al. 2012	+	+	+	+	+	+	+	+	+	+	+	+	+	13/13
Hoffman et al. 2016	+	+	+	+	+	+	+	+	+	+	+	+	+	13/13
Hokkanen et al. 2008	-	-	+	+	-	?	?	-	+	-	-	-	+	4/13
Holthoff et al. 2015	+	+	+	+	+	?	-	-	+	-	+	+	+	9/13
Kemoun et al.2010	+	+	+	+	-	-	-	-	-	-	+	-	+	6/13
Kwak et al.2008	+/-	+	+	-	-	-	-	?	-	?	?	-	-	2/13

Table 5 continues

Lowery et al. 2013	+	+	+	+	+	+	+	+	+	+	+	+	+	13/13
McCurry et al. 2011	+	+	+	+	+	+	+	+	+	+	+	+	+	13/13
Miu et al. 2008	+	+	+	+	+	-	+	-	+/-	+/-	-	-	+	7/13
Morris et al. 2017	-	+	+/-	+	+	+	+	-	+	-	+	+	+	9/13
Pitkala et al. 2013	+	+	+	+	+	+	+	+	+	+	+	+	+	13/13
Pomeroy et al. 1999	+	+	+	+	+	-	+	-	+/-	+	+	-	+	9/13
Roach et al. 2011	+	+	+	+	+	?	+	-	+	-	+/-	-	+	8/13
Rolland et al. 2007	+	+	+	+	+	+	+	+	+	+	+	+	+	13/13
Schwenk et al. 2014	+	+	+	+	+	+	+	-	+	+	-	+	-	10/13
Shaw et al. 2003	+	+	+	+	+	+	+	+	+	+	+	+	+	13/13
Steinberg et al. 2009	+	+	+	+	-	-	+	+	+	-	+	+	+	10/13
Stevens and Killeen 2006	?	?	+	+	+	-	?	-	-	-	-	-	-	3/13
Suttanon et al. 2013	+	+	+	+	+	+	+	+	+/-	+	+	+	+	12/13
Tappen et al. 2000	+	+	+	+	-	-	+	-	+	-	+	-	+	8/13
Telenius et al. 2015	+	+	+	+	+	+	+	+	+	+	+	+	+	13/13
Teri et al. 2003	+	+	+	+	+	+	+	+	+	+	+	+	+	13/13
Toots et al.	+	+	+	+	+	+	+	+	+	+	+	+	+	13/13
Toulotte et al. 2003	?	+	+	+	-	-	+	?	-	+/-	+	+	+	7/13
Van de Winckel et al. 2004	+	+	+	+	-	-	-	-	+/-	+/-	-	-	+	5/13
Vreugdenhil et al. 2012	+	+	+	+	-	-	+	-	+	-	-	-	+	7/13
Venturelli et al. 2011	+	+	+/-	+	-	-	+	+	+/-	+/-	+	-	+	7/13
Williams et al. 2008	+	+	+	+	-	+/-	+	+	-	-	+	-	+	8/13
Yaguez et al. 2011	+	+	+	+	-	-	-	-	+	-	+	-	+	7/13
Zieschang et al. 2017	+	+	+	+	+	+	+	+	+	+	+	+	+	13/13

+ Criterion fulfilled; - Criterion not fulfilled; +/- Criterion partly fulfilled; ? Unclear

2.5 Summary of the literature

A growing body of evidence indicates that exercise may be a promising non-pharmacological intervention in the prevention and management of dementia (Ahlskog et al. 2011). Exercise improves brain health and decreases the risk of pathological symptoms associated with AD (Erickson et al. 2012). The effects of exercise can be symptom-relieving or even disease-modifying, as the exercise has direct neurobiological effects on the central nervous system and vascular health (Cassilhas et al. 2016).

The majority of epidemiological studies, systematic reviews, and randomized controlled trials referred to in this literature review have found a positive association between exercise and one or several symptoms of dementia. Beneficial effects of exercise are shown in cognition, mobility, functional abilities, risk of falls, and neuropsychiatric symptoms of dementia. However, conflicting results and insufficient evidence are also disclosed in the studies.

Heterogeneity in study design, selection of participants, data analyses, and methodological shortcomings can partly explain the inconsistency of the results in randomized controlled studies. Many studies include patients with different types of dementia and with different levels of cognitive impairment. There is still a lack of evidence regarding whether patients in various types and stages of dementia benefit from exercise in a similar way. In many of the studies, the participants have at least moderate or even severe stage of dementia. In advanced dementia, the complex network of low cognition, poor physical functioning, frailty, and behavioural problems may not be overcome with a single-component intervention. Based on this literature review, the optimal dose and intensity of the exercise remain unclear.

3. Aims of the study and research questions

The aim of this study is to examine the effects of a long-term, regular exercise intervention on persons with Alzheimer's disease.

Specific research questions in the individual studies are as follows:

1. What is the evidence from randomized controlled studies of the effects of exercise on cognition in persons with mild cognitive impairment or dementia when reviewed systematically? (Study 1)
2. What are the effects of a long-term, regular exercise intervention on cognition in persons with Alzheimer's disease compared with controls in usual treatment examined in a randomized controlled trial? (Study 2)
3. How do patients with a mild or advanced stage of Alzheimer's disease benefit from a long-term exercise intervention in terms of physical performance and risk of falling? (Study 3)
4. Does regular exercise alleviate neuropsychiatric symptoms and postpone institutionalization in patients with Alzheimer's disease examined in a randomized controlled trial? (Study 4)

4. Materials and methods

4.1 Study 1

Study 1 is a systematic review of randomized controlled trials examining the effects of exercise on cognition in participants with mild cognitive impairment (MCI) or memory disorder (dementia). Relevant studies were systematically searched in the electronic databases (PubMed, Cochrane, DARE, and Ovid Nursing) using a mix of keywords related to cognition and exercise (cogniti* OR demen* OR Alzheimer* OR memory decline OR memory disorder OR mild cognitive impairment) AND (physical activity OR physical exercise OR exercise OR fitness OR training OR aerobic OR strength OR functional training OR walk*). The original search was performed in January 2013 and repeated in May 2014. Some additional studies were found by hand-searching the reference lists of articles and the authors' own literature databases. The search strategy yielded 1599 articles. Duplicate articles and studies not relevant on the basis of the title or abstract were removed, leaving 118 articles. These articles were examined in detail and 98 did not meet the inclusion criteria. Study protocols, studies that were not RCTs, studies that did not evaluate effects of physical exercise on cognition, or studies that were not conducted among persons with MCI or dementia were excluded. Only studies written in English were included. The first database search produced 20 relevant studies and the second search in 2014 produced an additional two studies (Figure 1).

Each study included in this review was evaluated, and the following data were extracted: age of participants, dementia diagnosis (if mentioned), MMSE or other dementia rating score, whether the participant was a nursing home resident or community-dweller, inclusion and exclusion criteria, description of the intervention, duration and intensity of the intervention, sample size, outcome measures related to cognition, and intervention effect. To assess accuracy of extracted data, two reviewers independently extracted data from the same papers. No differences between the raters were detected.

Methodological quality of the studies was evaluated by three independent researchers using a modified rating system described in detail earlier in this dissertation. If differences of opinion emerged, the study was re-evaluated and discussed until consensus was reached.

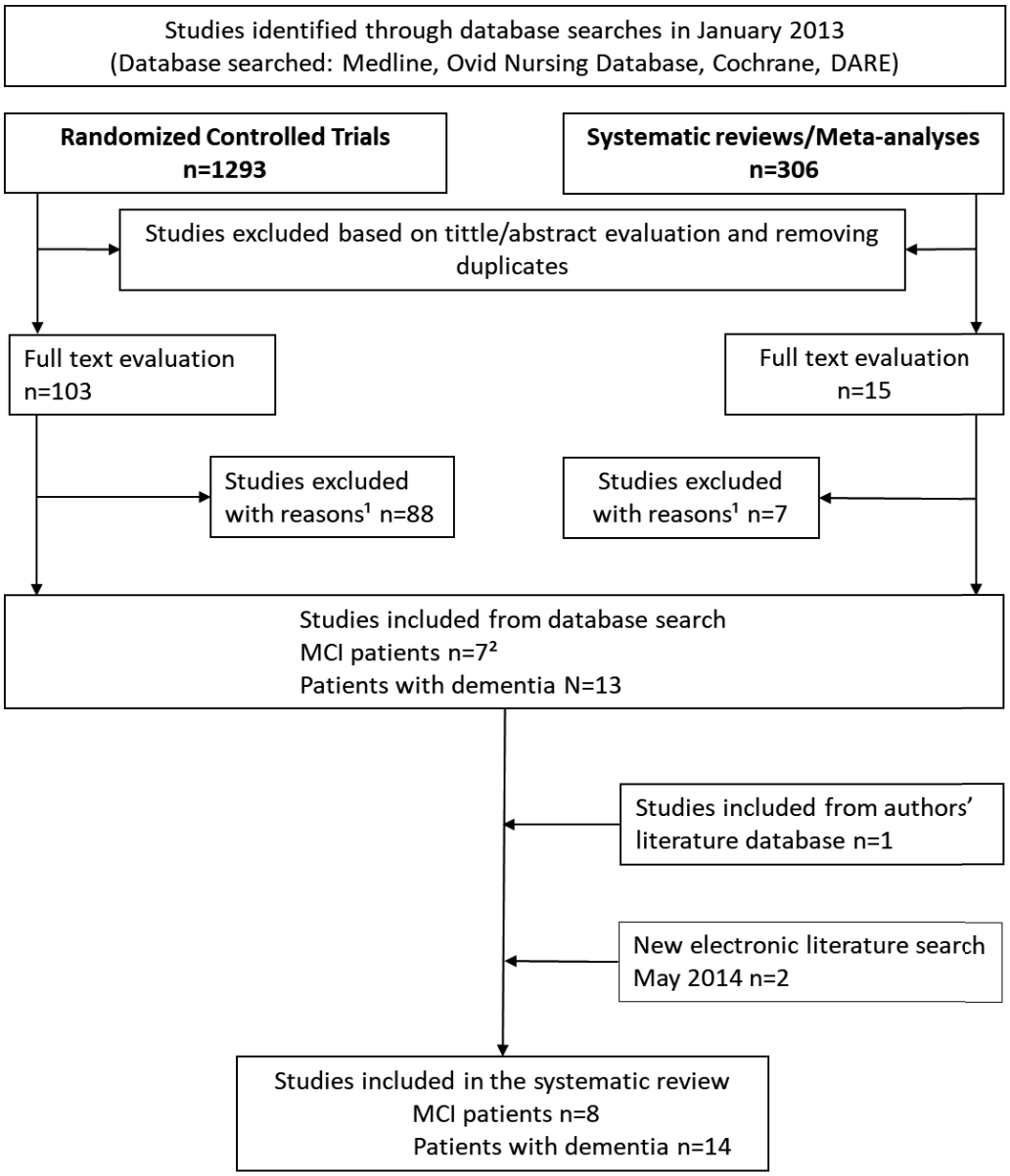

Figure 1 Flow Chart of Study 1.

[1] Study protocols, not RCTs, did not evaluate effects of physical exercise on cognition, were not conducted among older adults or persons with MCI or dementia, not written in English
[2] One study was reported in two publicatios

4.2. Studies 2, 3, and 4

4.2.1 Study samples and procedures

Studies 2, 3, and 4 report the results of the Finnish Alzheimer Disease Exercise Trial (FINALEX), which is a randomized controlled trial examining the effects of an exercise intervention conducted among home-dwelling participants with Alzheimer's disease compared with controls (Pitkälä et al. 2013).

AD patients (n=1264) living in the cities of Helsinki, Espoo, and Vantaa and derived from the AD drug reimbursement register of the Social Insurance Institution of Finland were contacted by mail to inquire about their interest in participating in the study. To be included in the above register, a person must be diagnosed with AD by a geriatrician or a neurologist based on the NINCDS-ADRDA Alzheimer's criteria (McKhann et al. 2011). The study nurses contacted those patients who returned the invitation letter and showed an interest in participating (n=497). Of these individuals, 12 had died before being contacted and 95 had moved to another city or their contact information was lacking or deficient. Altogether, 390 persons completed the telephone screen of inclusion criteria. Eighty-four persons refused to participate after receiving more information about the study and 96 failed to meet all inclusion criteria. Two hundred and ten participants fulfilled the inclusion criteria and were enrolled in the study.

Inclusion criteria of the study were as follows: an established diagnosis of AD, a spouse living at the same address, age ≥ 65 years, no diagnosed terminal disease, and the ability to walk independently with or without a mobility aid. The participants were also required to meet at least one of the following criteria for frailty: ≥1 fall in the past year, reduced walking speed, or unintentional weight loss.

After the baseline assessments, the participants were randomized into three study groups: home-based exercise group (HE), group-based exercise group (GE), and control group (CG) using computer-generated numbers received by telephone from a randomization centre. The participants were reassessed at 3, 6, and 12 months. The flow of participants and attrition rate are shown in Figure 2.

The study was designed to fulfil the 13 criteria of methodological quality described in detail earlier in this dissertation.

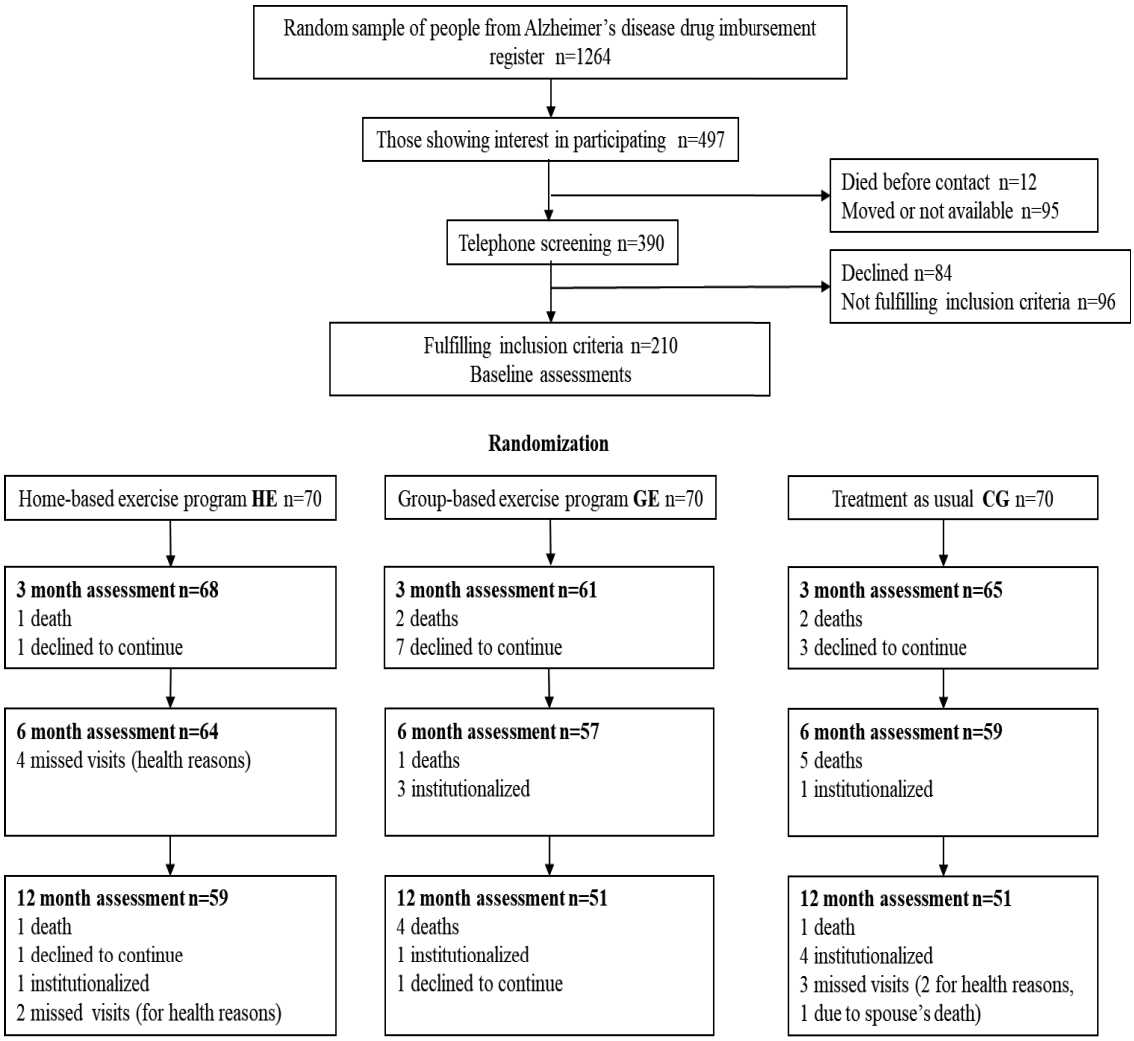

Figure 2. Flowchart of Studies 2 and 4.

4.2.2 Ethical considerations

The Ethics Committee of Helsinki University Central Hospital approved the study protocol for the RCT. All participants and their spousal caregivers provided written, informed consent before participation. In cases in which the participant's judgement capacity was impaired (CDR>1), the spouse gave consent for both.

4.2.3 Data collection

A registered nurse and a physiotherapist assessed participants and their spousal caregivers four times (baseline, 3, 6, and 12 months). The assessors were blinded to the group allocation.

At baseline, the demographic data and medical history were collected. The diagnoses and medications were confirmed from medical records. Based on the diagnosis, the Charlson co-morbidity index score (Charlson et al. 1987) was calculated to evaluate the overall disease burden. Functional Independence Measure (FIM) (Pollak et al. 1996) was used to assess physical functioning. Walking abilities and physical fitness were assessed with a 10-metre walk test. Cognition was tested with the Mini-Mental State Examination (MMSE) (Fostein et al. 1975), Clock Drawing Test (CDT) (Morris et al. 1993), and Verbal Fluency (animal category fluency, VF) (Morris et al. 1989). Clinical Dementia Rating (CDR) (Hughes et al.1982) was used to assess the stage of dementia and global cognitive abilities. Neuropsychiatric Inventory (Cummings et al. 1997) and Cornell Scale for Depression in Dementia (CSDD) (Alexopoulos et al.1988) were used to evaluate the neuropsychiatric symptoms. Blood pressure and weight were measured at every study visit.

In addition to the baseline visit, FIM, VF, and CDT were assessed at 3, 6, and 12 months, MMSE and CSDD at 12 months, and NPI at 6 months. The 10-metre walk test was performed at baseline and at 12 months. Data regarding falls (collected with a fall diary), utilization of social and health service, and nursing home placement were collected at 3, 6, and 12 months.

To ensure safety, a thorough medical examination by a geriatrician was performed on all participants randomized into exercise intervention groups before starting the intervention.

4.2.4 Measures

Outcome measures used in this study are all validated in the target population of older adults with AD (Bossers et al. 2012).

4.2.4.1 Cognitive measures

Global cognition was measured with the MMSE. It is an instrument widely used in clinical practice as well as in research (Tombaugh et al. 1992). The test examines cognitive functions, including orientation, attention, recall, language, ability to follow instructions, ability to produce a meaningful written sentence, and visual construction. The MMSE score is the total number of correct answers, with the maximum score being 30 points (Folstein et al. 1975). A meta-analysis of studies examining the annual rate of cognitive decline in AD found an average rate of change of 3.3 points per year on the MMSE (Han et al. 2000). Another review found considerable variations between studies, ranging from 0.8 to 4.0 points per year (Behl et al. 2005). MMSE scores correlate with those obtained from other types of cognitive screening tests such as Alzheimer's disease assessment scale - cognitive subscale (ADAS-Cog) (Webster et al. 2017). Age, education, and cultural background, but not gender, affect the test results (Tombaugh et al. 1992). Longitudinal studies have shown that cognitive change in dementia patients can be examined using the MMSE (Tombaugh et al. 1992). The minimum clinically important difference (MCID) of the MMSE is estimated to be 1.4 points (Howard et al. 2011).

Clinical Dementia Rating (CDR) is a 5-point scale used to characterize six domains of cognitive and functional performance in patients with Alzheimer's disease and related dementias: memory, orientation, judgement and problem solving, community affairs, home and hobbies, and personal care. The information is obtained by interviewing the patient and the informant. Each domain is rated, and the overall score is calculated through an algorithm: 0 = normal, 0.5 = very mild dementia, 1 = mild dementia, 2 = moderate dementia, 3 = severe dementia. The rating provides a clinically valid measure of the stage of cognitive impairment (Hughes et al. 1992).

Verbal Fluency (VF) was measured by asking the participant to name as many animals as possible in one minute. VF is part of the CERAD (Consortium to Establish a Registry for Alzheimer's Disease), which is a neuropsychological test battery for assessment of patients with the clinical diagnosis of Alzheimer's disease (Morris et al. 1989). VF measures executive function as well as semantic memory (Henry et al. 2004). The average score in the age group of 70-79 years in healthy persons is around 15 (Acevedo et. al 2000).

In the Clock Drawing Test, the participant was asked to draw a clock from memory and draw the clock arms at a fixed time. The maximum score in the CDT is six points. The CDT is used to measure executive function. However, the test also requires verbal understanding, memory, and visuoconstructive abilities (Agrell et al. 1998).

4.2.4.2 Functional measures

The primary outcome of this study was physical functioning measured with the Functional Independence Measure (FIM) (Pitkälä et al. 2013). FIM involves 18 specific tasks, grouped into two subscales, motor and cognitive. The tasks include activities such as mobility, walking, self-care, and communication. Each task is scored on a 7-point ordinal scale, ranging from a score of 1 to a score of 7. A higher score represents a higher level of independence. The total score for the FIM (the sum of the motor and cognition subscale scores) is a value between 18 and 126 (Pollak et al. 1996). In this study, the FIM assessments were based on a caregiver's evaluation of the patient's performance at home and an assessor's evaluation during study visits.

The 10-metre walk test was performed at baseline and at 12 months to assess the participant's physical fitness and walking speed. The 10-metre walk test has shown good reliability and is therefore recommended for use in clinical assessment of walking speed in older adults (Peters et al. 2013).

The caregivers were asked to keep a continuous fall diary for the participants. The number of falls was collected at each study visit. A fall diary has been found to be the most valid method to record the number of falls (Hannan et al. 2010).

4.2.4.3 Neuropsychiatric measures

The Neuropsychiatric Inventory (NPI) was used to examine the neuropsychiatric symptoms of participants. The NPI is the recommended measure in intervention studies among dementia patients (Cummings et al. 1997, Kales et al. 2015). The NPI evaluates 12 neuropsychiatric disturbances frequently seen in dementia: delusions, hallucinations, agitation, dysphoria, anxiety, apathy, irritability, euphoria, disinhibition, aberrant motor behaviour, night-time behaviour disturbances, and appetite and eating abnormalities. For each symptom, the frequency is multiplied by the severity, with the summed score providing the total NPI score. The score ranges from 0 (no NPS) to 144 (the highest number and most severe symptoms). The validity and reliability of NPI have been established, and the NPI has also been found to be sensitive to treatment (Cummings et al. 1997). There is no cut-off score in the NPI, as some neuropsychiatric symptoms, such as hallucinations, are

always abnormal. However, some researchers consider only a total NPI score greater than 11 points arising from at least three domains as evidence of marked neuropsychiatric symptoms (Rolland et al. 2007). Change of 8 or more indicates a clinically significant change (Howard et al. 2011). One of the weaknesses of the NPI is that it collects data only from the informant. To overcome this limitation, an international team of investigators has published a validated scale known as the Neuropsychiatric Inventory - Clinician rating scale (NPI-C), where the information is gathered not only from the proxy but also by clinically examining the patient (de Medeiros et al. 2010).

Depression was assessed using the Cornell Scale of Depression in Dementia (CSDD), which is the most widely used assessment method to measure depression in dementia. In CSDD, the information is obtained by interviewing the caregiver and by observing and interviewing the patient. The scale contains 19 items with a maximum score of 38 and a score >10 indicating depression (Alexipoulos et al. 1988). CSDD has a good sensitivity and specificity, and it has been validated in the dementia population (Alexopoulos et al. 1988, Körner et al. 2006).

4.2.4.4 Institutionalization

Data on admissions to permanent institutional care were retrieved from central registers. The definition of institutionalization in this study was placement in a nursing home or an intensified assisted living facility with 24-hour care for 3 months or longer.

4.2.5 Randomization

Patients fulfilling all inclusion criteria (n=210) were randomized after the baseline visit. The randomization was performed using computer-generated numbers received by telephone from a randomization centre. A total of 210 participants were randomized into three equal-sized (n=70) groups: 1) tailored home-based exercise (HE), 2) group-based exercise (GE), and 3) a control group (CG) continuing in community care.

4.2.6 Intervention

All participants and their spousal caregivers in both intervention groups and the control group received oral and written advice on nutrition and exercise by the study nurses.

Participants randomized into the home-based exercise group (HE) exercised twice a week for one hour over 12 months under the supervision of a physiotherapist specialized in dementia. The training sessions were organized at the participant's home or in the vicinity outdoors. The training was tailored to meet the participant's preferences and to address his/her needs and challenges in everyday life. Despite variations in details of the exercise programmes between participants, the

sessions consistently included elements of executive function training, dual-tasking, strength, balance, and endurance training as well as aerobic training. A more detailed description of the training is provided in Table 6. The exercise programme was goal-oriented. Intensity and degree of difficulty of the exercises were increased according to progress made. Co-operation with the spousal caregivers was intensive. During the home visits the physiotherapists were able to give support to the caregivers and strengthen their commitment to the study programme.

Physical exercise for the group-based exercise group (GE) was achieved in four-hour sessions in adult daycare centres twice a week over 12 months. Door-to-door taxi service and lunches were provided. Participants exercised in groups of 10 supervised by two physiotherapists specialized in dementia. The active exercise time/participant was approximately one hour/visit often divided into several shorter periods because of lunch and coffee breaks and waiting times for gym equipment.

Similar to in the HE group, the exercise programme consisted of aerobic training, endurance, balance, and strength training, as well as dual-tasking to improve executive functioning (Table 6). Individual programmes and goals were also set for participants in the GE group, and regular re-assessments (e.g. increasing the weights and repetitions in gym exercises) of the programme were conducted to ensure progress. However, whereas HE was tailored according to the participant's needs, the GE was based more on a fixed programme.

Because the primary outcome of the study was physical functioning, the focus of the exercise was on physical training. The dual-tasking exercises were rather simple and mainly performed alongside the physical training.

Participants in both intervention groups continued the regular exercise even in case of hospitalization or respite care. If more intensive rehabilitation was needed, e.g. after hospitalization, it was organized as inpatient care in a rehabilitation centre. The spousal caregivers received regular feedback from the physiotherapists and were also encouraged to share their questions or concerns.

Participants in the control group (CG) continued with the usual care provided by the Finnish health care system. They also had the right to physiotherapy provided by the community health system if needed (Table 6).

Table 6. Description of the exercise components used in the interventions.

	AEROBIC TRAINING	STRENGTH TRAINING	BALANCE TRAINING	EXECUTIVE FUNCTIONING TRAINING
HOME-BASED EXERCISE	Exercise/restorator bike, Nordic walking outdoors	Training with hand and ankle weights	Climbing the stairs, training with balance pillows, picking up items from the floor, practising getting up from the floor or the bath tub	Throwing a ball as accurately as possible Dual-tasking, e.g.: - talking while walking - singing while training - doing 2 different functions with the left and right hands while counting numbers forward or backward at the same time - walking across a room with a filled glass of water while turning head left and right and reciting months
GROUP-BASED EXERCISE	Rowing machine, restorator bike, Nordic walking outdoors, dancing	Training with various gym equipment	Walking on balance beam/line, trampoline jumping, picking up items from the floor, training with a bouncing ball, climbing a ladder, practising getting up from the floor, walking on a swamp mat	Throwing a ball as accurately as possible Dual-tasking, e.g.: - talking while walking - singing while dancing - doing 2 different functions with the left and right hands while counting numbers forward or backward at the same time - walking across a room with a filled glass of water while turning head left and right and reciting months

4.3 Data analyses

In the systematic review (Study 1), data were extracted and pooled where appropriate and possible (Lautenschlager et al. 2008, Lam et al. 2012), and the pooled treatment effects were estimated.

In the intervention study (Studies 2, 3, and 4), sample size was calculated based on the primary outcome measure FIM (Pitkala et al. 2013). A target sample size of about 210 (70 per group) was calculated to ensure 80% power to detect a 10-point difference in FIM measure between the treatment groups at two-sided α=0.05. The drop-out rate was estimated to be 10%.

The data appear as means with standard deviations or numbers with percentages. In Studies 2 and 4, statistical comparison between the groups at baseline was performed using analysis of variance (ANOVA), Kruskall-Wallis tests, and Chi-square test when appropriate. Difference in compliance between the HE and GE groups was tested with Mann-Whitney U-test. In all studies, 95% confidence intervals were calculated for main outcome measure estimates.

In Study 2, all patients assessed at baseline and at 3 months were included in the data analyses of changes in cognitive function (modified intention-to-treat). Repeated measures were analysed using generalized estimating equation (GEE) models with the unstructured correlation structure. GEEs were developed as an extension of the general linear model (e.g. OLS regression analysis) to analyse longitudinal and other correlated data. GEE models take into account the correlation between repeated measurements in the same subject; models do not require complete data and can be fitted even when individuals do not have observations at all time-points.

In Study 4, participants assessed at baseline and at 6 months for NPS with NPI (n=179) and participants assessed at baseline and at 12 months for depression with CSDD (n=149) were included in the analyses. When adjusting for confounding factors (age, sex, baseline CDR and FIM), analysis of covariance or logistic regression model was applied. In the case of violation of assumptions (e.g. non-normality), a bootstrap-type test was used.

In Study 3, the participants were re-grouped into mild dementia and advanced dementia. HE and GE intervention groups were combined and compared with the controls. The statistical comparisons at baseline between groups were performed with the t-test or the Mann-Whitney test and the Chi-square test when appropriate. Mixed-effect models were used with appropriate contrast to analyse the repeated measures. The incidence rate of falls was estimated and compared using Poisson regression models or negative binomial regression models when appropriate. Assumptions of over-dispersion were tested in the Poisson model using Lagrange multiplier test.

Effect size ("d") was calculated by using the method for paired samples: mean baseline scores minus mean follow-up scores, divided by the pooled baseline standard deviation. Effect size of 0.20 is considered small, 0.50 medium, and 0.80 large; 95 percent confidence intervals (95% CIs) were obtained by bias-corrected bootstrapping (5000 replications). In Study 2, the effect sizes of main outcomes for completed cases are also provided.

STATA 14.1, StataCorp LP (College Station, TX, USA) statistical package was used for the analyses.

5. Results

5.1 Characteristics and methodological quality of the RCTs examining the effects of exercise on cognition in MCI and AD patients

The 22 studies incorporated in the systematic review are described according to their characteristics, interventions utilized, study quality, and the effects of the interventions on various cognitive domains (Table 7).

Study participants were persons with MCI in eight studies and PWD in 14 studies (Table 7). The number of participants in the studies varied from 21 (Venturelli et al. 2011) to 389 (Lam et al. 2012). Study sizes of over 100 participants were found in five studies (Stevens et al. 2006, Lautenschlager et al. 2008, von Uffelen et al. 2008, Lam et al. 2012, Suzuki et al. 2013), only one of which (Stevens et al. 2006) was performed among PWD. The duration of the exercise intervention varied from six weeks (Scherder et al. 2005, Eggermont et al. 2009, Yaguez et al. 2011) to 52 weeks (Kwak et al. 2008, van Uffelen et al. 2008).

The exercise programmes predominantly concentrated on aerobic exercises such as walking, dancing, restorator or treadmill training combined with strength training, balance, and mobility exercises. Tai Chi was used in two of the studies as a sole exercise method (Lam et al. 2012) or part of a multicomponent intervention (Burgener et al. 2008). The exercise programmes were designed and supervised by physiotherapists, occupational therapists, or in some studies by the carers.

A wide range of cognitive measurements was used across the studies. The most frequently utilized tests were MMSE and ADAS-cog. These were used to measure global cognition in twelve studies. Executive functioning was examined predominantly with VF or CDT. Other tests measuring executive functions (such as Trail-making test, Task switching, Symbol-Digit, Stroop) were employed only in single studies. Attention and working memory were usually treated as separate domains, although they might also be considered as elements of executive functions (Diamond et al. 2013). In general, the cognitive measurements used in single studies were more numerous in the MCI studies than in the dementia studies, where only global cognition or one domain of cognition, such as executive function or communication, was examined.

Compliance was reported in six of the studies with MCI patients (Lautenschlager et al. 2008, van Uffelen et al. 2008, Baker et al. 2010, Nagamatsu et al. 2012, Suzuki et al. 2013) and in three of the studies with dementia patients (Steinberg 2009, Venturelli 2011, Yaguez 2011). In these, the

reported compliance (adherence to exercise intervention) was generally good, varying from 71% (van Uffelen 2008) to 94% (Baker et al. 2010).

Of the eight studies examining the effects of exercise on cognition in MCI patients, four were considered to be of good methodological quality, the remaining four of moderate quality. Of the studies among dementia patients, none was deemed of good quality, four of moderate quality, and eight of poor quality (Table 7).

The most common methodological problems were absent or poor definition of the diagnosis of dementia or MCI and low statistical power. Drop-outs were inadequately described, and intention-to-treat analysis was infrequently used.

5.2 Effects of exercise interventions on different domains of cognition

5.2.1 Global cognition

Three out of five studies among MCI participants and five out of eight studies among dementia patients found a positive effect of exercise intervention on global cognition (Table 7). These studies used combined exercise training (mostly combining aerobic and strength training) (Lautenchlager et al. 2008, Kwak et al. 2008, Kemoun et al. 2010, Suzuki et al. 2013), or Tai Chi (Burgener et al. 2008, Lam et al. 2012,), or the participants exercised daily (van de Winckel et al. 2004, Vreugdenhil et al. 2012). Pooled effect size for improvement in ADAS-cog was calculated for two of the largest studies (Lautenchlager et al. 2008, Lam et al. 2012). The effect size was small (0.29, 95% CI 0.09-0.48) (Table 7).

5.2.2 Executive function, attention, and working memory

Seven studies among the MCI patients examined the effects of exercise on executive function, attention, and/or working memory. Of these, six studies achieved results favouring the exercise intervention group (Table 7). High attendance in the exercise intervention (Van Uffelen et al 2008, Baker et al. 2010), female sex (van Uffelen et al. 2008, Baker et al. 2010), and higher level of cognition at baseline (Scherder et al. 2005, van Uffelen et al. 2008, Baker et al. 2010, Lam et al. 2012, Nagamatsu et al. 2013, Suzuki et al. 2013) seemed to be crucial for positive results. In the dementia population, the corresponding figure was four out of five studies. No single factor could be detected among the positive studies. Better baseline cognition (Yaguez et al. 2011), multicomponent intervention (Christofoletti et al. 2008), and using music-based dance therapy as an exercise intervention (van de Winckel et al. 2006) were factors distinguishing these studies from the others (Table 7).

5.2.3 Memory

Effects of exercise on memory domain were explored in seven MCI studies, three of which found beneficial effects, mostly on delayed recall (Table 7). These studies were of good methodological quality with a minimum training period of 24 weeks. However, in one study the positive effects were seen only in men with high attendance in the programme (Van Uffelen et al. 2008). None of the dementia studies showed positive results in the measures of memory (Table 7).

5.2.4 Communication

Communication as a sole outcome was examined in two studies, both conducted among dementia patients. The results were mixed. In the smaller study with only AD patients, walking and conversation sessions three times a week for 40 weeks improved participants' communication skills (Friedman et al. 1991). However, the larger study with a shorter intervention and patients with AD or VD failed to show any positive effects (Cott et al. 2002) (Table 7).

Table 7. Characteristics and methodological quality of RCTs examining the effects of exercise on cognition in MCI and AD patients (positive findings highlighted).

RCTs examining effects of exercise on cognition/ Domains of cognition examined	Global cognition	Executive function	Attention	Working memory	Delayed recall	Declarative memory	Communication
Study population with mild cognitive impairment (MCI)							
Baker et al. 2010 E: High intensity aerobic exercise, 45 – 60 min x 4/week, *24 weeks* **M: Moderate**		+	+		0	0	
Lam et al. 2012 E: Tai Chi, 30 min x 3/week, *12 weeks* **M: Moderate**	+	0	+		0		
Lautenschlager et al. 2008 E: Walking + strength training, 50 min x 3/ week, *24 weeks* **M: Good**	+	0		0	0		
Nagamatsu et al. 2012 E: Aerobic or resistance training, 60min x 2/week, *26 weeks* **M: Good**		+	+		+		
Scherder et al. 2005 E: Walking, 30 min x 3/week, *6 weeks* **M: Moderate**		+		0	0		
Suzuki et al. 2013 E: Aerobic exercise, strength training, balance, dual-tasking, 90 min x 2/week, *24 weeks* **M: Good**	+			+	+		
Van Uffelen et al. 2008/2009 E: Aerobic exercise (walking), 60 min x 2/week, *52 weeks* **M: Good**	0	0	+(f)		+(m)		
Varela et al. 2012 E: Aerobic exercise, two groups with different exercise intensities, 30 min x 3/week, *12 weeks* **M: Moderate**	0						
Study population with dementia							
Burgener et al. 2008 E: Tai Chi 60 min x 3/ week (+ CBT + support group), *40 weeks*. **M: Poor**	+						
Christofoletti et al. 2008 E: Physiotherapy (+occupation therapy + physical education), 120 min x 5/week, or Physiotherapy 60 minx 3/week, *24 weeks.* **M: Poor**	0	+ (MC)		0	0	0	
Cott et al. 2002 E: Walk and talk sessions, 30 min x 5/ week*, 16 weeks.* **M: Poor**							0
Eggermont et al. 2009 E: Walking, 30 min x 5/week, *6 weeks* **M: Moderate**		0		0	0	0	
Friedman and Tappen 1991 E: Walk and talk sessions, 30 min x 3/ week, *40 weeks* **M: Poor**							+
Kemoun et al 2010 E: Walking, ergocycling, dancing 60 min x 3/week, *15 weeks* **M: Poor**	+						
Kwak et al. 2008 E: Aerobic + strength training, 30-60 min x 2-3/ week, *52 weeks* **M: Poor**	+						

Table 7 continues

Miu et al. 2008 E: Aerobic + flexibility training, 60 min x 2/ week, *12 weeks* **M: Moderate**	0						
Steinberg et al. 2009 E: aerobic, strength, balance, and flexibility training, Daily, *12 weeks* **M: Moderate**						0	
Stevens and Killeen 2006 E: Strength training 30 min x 3/week, *12 weeks* **M: Poor**		+					
Van de Winckel et al. 2004 E: Dance therapy, 30 min daily, *12 weeks* **M: Poor**	+	+		0		+	
Venturelli et al. 2011 E: Walking, 30min x 4/week, *24 weeks* **M: Moderate**	0						
Vreugdenhil et al. 2012 E: Daily home-based exercises and walking, *16 weeks* **M: Moderate**	+						
Yaguez et al. 2011 E: Brain Gym®-training 120 min x 1/week, *6 weeks* **M: Moderate**			+	0			

E= Description of the exercise intervention, M= Methodological quality of the study, see page 50
0 = no difference between intervention and control groups, + = improvement, f = female, m=male, CBT= Cognitive behavioural therapy, MC= multicomponent intervention

5.3 Characteristics of participants in Studies 2, 3, and 4

The mean age of the participants in the FINALEX study was 78 years, and 61% were men. According to the CDR scores, almost two-thirds were suffering from advanced dementia (CDR 2 or 3), and the overall disease burden assessed with the Charlson comorbidity index was 2.7, indicating a relatively high number of chronic diseases. Of the participants, 96% were on Alzheimer's medication and 38% on psychotropic medication (comprising antipsychotic, antidepressive, anxiolytic, and sleep medications). At baseline, the mean MMSE in the study sample was 18 (range 0 to 29), mean score in Verbal fluency was 7.9 (range 0 to 21), and mean score in Clock Drawing Test was 2.3 (range 0 to 6). The baseline assessment of FIM showed already existing significant decline in functional abilities. The mean score in FIM was 89 (range 18 to 125), indicating that many of the participants needed assistance with several activities of daily living. The neuropsychiatric symptoms were rather minor at baseline. Mean score of CSDD was 4.9 (range 0 to 26), with scores ≥ 10 indicating probable depression. The baseline NPI scores were low, the mean total NPI points being 14 (range 0 to 71) (Table 8).

Table 8. Baseline characteristics of participants in Studies 2 and 4.

	Home-based exercise (n=70)	Group exercise (n=70)	Control group (n=70)	p-value[1]
Mean age, years (SD[2])	77.7 (5.4)	78.3 (5.1)	78.1 (5.3)	0.82
Women, n (%)	30 (42.9)	25 (35.7)	26 (37.1)	0.66
Education <8 years, n (%)	28 (40.6)	23 (32.9)	29 (41.4)	0.53
CDR[3], n (%)				
0.5 or 1	24 (34.3)	23 (32.9)	22 (31.4)	
2	30 (42.9)	37 (52.9)	37 (52.9)	
3	16 (22.9)	10 (14.3)	11 (15.7)	
MMSE[4], mean (SD)	17.8 (6.6)	18.5 (6.3)	17.7 (6.2)	0.64
CDT[5], mean (SD)	2.3 (2.0)	2.3 (2.0)	2.4 (2.1)	0.99
VF[6], mean (SD)	8.2 (4.7)	7.9 (4.2)	7.5 (4.4)	0.60
FIM[7] total, mean (SD)	88.9 (18.4)	90.1 (17.6)	89.1 (18)	0.92
CSDD[8], mean (SD)	4.8 (4.7)	3.9 (3.5)	5.9 (5.7)	0.23
NPI[9], mean (SD)	13.5 (12.6)	12.1 (9.8)	16.6(15.2)	0.33
On Alzheimer medication, n (%)	67 (95.7)	68 (97.1)	67 (95.7)	0.88
On psychotropic medication, n (%)	27(43)	20(35)	21(36)	0.61
CCI[10], mean (SD)	2.6 (1.8)	2.5 (1.8)	3.0 (1.7)	0.13
10-metre walking speed in m/s, mean (SD)	0.77 (0.26)	0.81 (0.27)	0.82 (0.23)	0.55

[1]Differences between the groups were tested by Chi-squared test for categorical variables and ANOVA or Kruskal-Wallis test for continuous, non-normally distributed variables. [2]SD: standard deviation; [3]CDR: Clinical Dementia Rating (Hughes et al. 1992); [4]MMSE: Mini-Mental State Examination (range 0-30) (Folstein et al. 1975); [5]Clock Drawing Test (range 0-6) (Morris et al. 1993); [6]Verbal Fluency (0->) (Morris et al. 1989); [7]FIM: Functional Independence Measure (0-126) (Pollak et al.1996); [8]CSDD: Cornell Scale of Depression in Dementia (0-38) (Alexipoulos et al. 1988); [9]NPI: Neuropsychiatric Inventory (0-144) (Cummings et al. 1997); [10]CCI: Charlson Comorbidity Index (Charlson et al. 1987)

The three study groups were comparable in demographic factors, functional and cognitive abilities, and neuropsychiatric symptoms at baseline. No significant differences in baseline assessments were detected between groups (Table 8).

In Study 3, the participants were re-grouped according to their baseline CDR scores to determine whether the exercise intervention has different effects on patients with mild dementia and patients with advanced dementia. Both intervention groups were also merged to achieve more statistical power; the quality and quantity of the exercise interventions in the home-based exercise group and the group-based exercise group were considered similar enough to allow this. Participants who remained in the trial until the first assessments of the intervention period were included in this sub-analysis (n = 194). The characteristics of these new sub-groups are shown in Table 9.

Table 9. Baseline characteristics of participants in Study 3.

	CDR[3] 0.5-1			CDR [3]2-3		
	Intervention N=44	Control N=22	p-value[1]	Intervention N=85	Control N=43	p-value[1]
Men, n (%)	29 (66)	16 (73)	0.57	51 (60)	23 (53)	0.48
Home-exercise, n (%)	23 (52)			45 (53)		
Age, mean (SD[2])	77 (5)	77 (6)	0.73	78 (5)	79 (5)	0.89
MMSE[4], mean (SD)	22.9 (3.6)	22.5(4.1)	0.70	15.8 (6.5)	15.6(5.5)	0.91
FIM[5], mean (SD)	104 (9)	102 (8)	0.37	80 (17)	80 (17)	0.38

[1]Differences between the groups were tested using the t test or the Mann-Whitney test, and the Chi-square test when appropriate. [2]SD: standard deviation; [3]CDR: Clinical Dementia Rating (Hughes et al. 1992); [4]MMSE: Mini-Mental State Examination (range 0-30) (Folstein et al. 1975); [5]FIM: Functional Independence Measure (range 0-126) (Pollak et al. 1996)

Adherence was good in both intervention groups. The HE group attended 91% of the exercise sessions, while the GE group attended 84% of the sessions. Sixty-five HE participants (93%) and 55 GE participants (79%) attended at least half of the training sessions.

No significant change in participants' physical fitness, measured with 10-metre walk test, was detected. The mean change from baseline to 12 months in 10-metre walking speed was in the HE group -0.09 (95% CI: -0.14 to -0.03), effect size -0.28 (95% CI: -0.48 to -0.08), in the GE group -0.12 (95% CI: -0.17 to -0.06), effect size -0.38 (95% CI: -0.60 to -0.19), and in the CG -0.16 (95% CI: -0.22 to -0.11), effect size -0.68 (95% CI: -0.94 to -0.42) (df=2, x^2=3.65; p = 0.16, adjusted for age, gender, and baseline value).

5.4 Effects of exercise intervention on cognition

Study 2 examined the effects of home-based and group-based exercise interventions on cognition compared with the control group. Cognition was measured with the MMSE, Verbal Fluency test, and Clock Drawing test.

MMSE was assessed at baseline and at 12 months. The scores decreased in all groups during the 12 months; the mean change from baseline to 12 months was in the HE group -1.63 (95% CI: -2.64 to -0.61), effect size -0.24 (95% CI: -0.40 to -0.10), in the GE group -1.23 (95% CI: -2.33 to -0.14), effect size -0.19 (95% CI: -0.34 to -0.06), and in the CG -1.08 (95% CI: -2.17. to 0.02), effect size -0.60 (95% CI: -0.34 to 0.03). No difference was detected between the study groups (df=2, x^2=0.60; p = 0.74, adjusted for age, gender, and baseline MMSE).

In the Clock Drawing Test, the mean change in HE was 0.48 (95% CI 0.058 to 0.91), effect size 0.25 (95% CI: 0.06 to 0.48), in the GE 0.01 (95% CI: - 0.44 to 0.46), effect size 0.03 (95% CI: -0.20 to 0.25), and in the CG - 0.21 (95% CI: - 0.67 to 0.25), effect size -0.10 (95% CI: -0.27 to 0.16) at 12 months. No differences between the three groups were present at 12 months (df=2, x2=5.3; p = 0.069, adjusted for age, gender, and CDR baseline). The difference between the HE group and the CG was significant at 12 months (p = 0.029, adjusted for age, gender, and CDR baseline), while the difference between the GE group and the CG was not significant (Figure 3).
Effect sizes for completed cases were 0.31 for HE, 0.07 for GE, and -0.07 for CG.

All groups deteriorated in Verbal Fluency, and the changes between the groups were not statistically significant when adjusted for age, gender, and CDR (Figure 3).

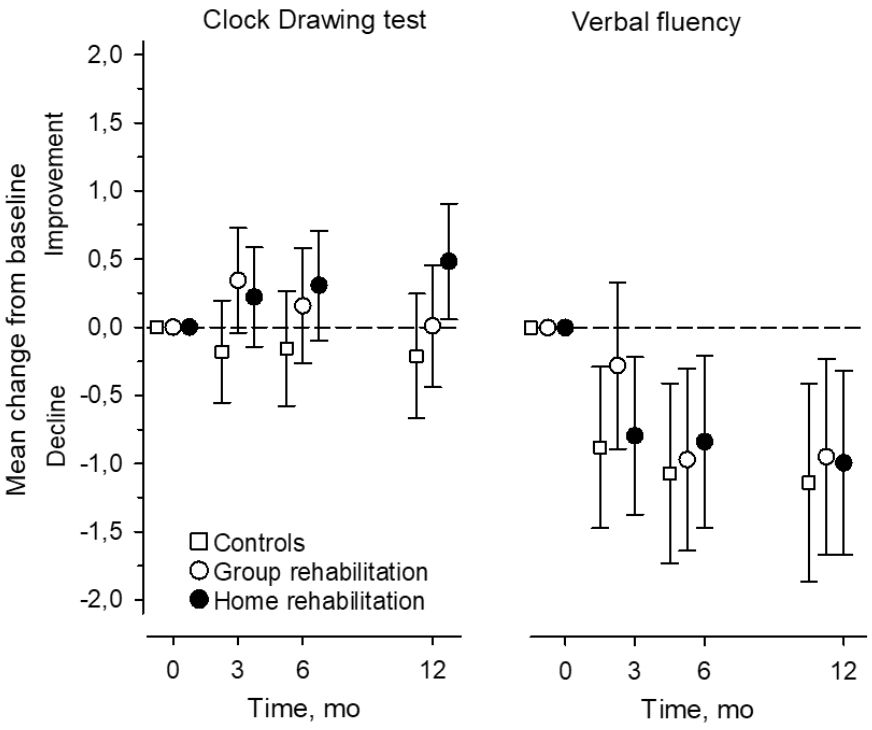

Figure 3. Mean changes in Clock Drawing Test and Verbal Fluency scores from baseline (adjusted for age, sex, and Clinical Dementia Rating) to 3, 6, and 12 months (mo).

5.5 Effects of exercise on functional abilities and falls in mild and advanced AD

Study 3 was a sub-analysis of a randomized controlled trial examining the effects of exercise in dementia patients. In the sub-analyses, the effects of exercise on functional abilities and falls rate in participants with mild or advanced AD were explored.

Among participants with mild AD (CDR 0.5-1), the FIM scores decreased in the intervention group as well as in the control group. However, scores in the intervention group declined significantly slower ($p < 0.001$) than those in the control group. The mean difference between the groups was significant at 6 months. FIM change was -3.3 (95% CI: -1.5 to -5.2) in the intervention group and -8.9 (95% CI: -5.2 to -12.7) in the control group ($p = 0.003$). The difference was even more pronounced at 12 months (FIM change, -2.7 [95% CI: -0.5 to -4.9] in the intervention group, -10.1 [95% CI: -7.0 to -13.3] in the control group; $p < 0.001$) (Figure 4).

Participants with moderate to severe AD (CDR 2-3) showed similar deterioration in both study groups. No significant difference was detected between the groups. At 6 months, the FIM change was -13.3 (95% CI: -7.8 to -19) in the intervention group and -12.7 (95% CI: -9.0 to -16.3) in the control group (p = 0.82). At 12 months, the respective figures were -9.9 (95% CI: -7.0 to -12.7) and -14.6 (95% CI: -8.6 to -20.6) (p = 0.18) (Figure 4).

The participants with mild AD fell on average 1.24 times/person/year (95% CI: 0.92 to 1.62) in the intervention group and 1.84 times/person/year (95% CI: 1.28 to 2.52) in the control group. The Incidence Rate Ratio (IRR) (adjusted for age, sex and CCI) was 0.65 (95% CI: 0.42 to 1.01; p = 0.055) (Figure 5).

The exercise intervention had a significant effect on the risk of falling among participants with moderate or severe AD (CDR 2-3). Among participants in the intervention group, the rate of falls was 1.78 falls/person per year (95% CI: 1.49 to 2.12), while among those in the control group it was 3.76 falls/person per year (95% CI: 3.15 to 4.45). The IRR (adjusted for age, sex, and CCI) was 0.47 (95% CI: 0.37 to 0.60; p < 0.001) (Figure 5).

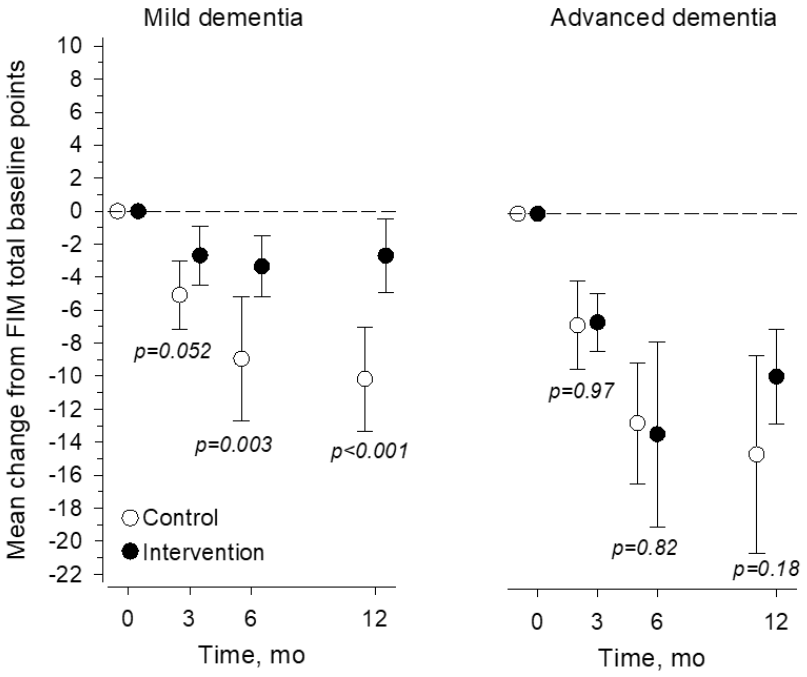

Figure 4. Changes in FIM relative to baseline in study groups divided according to the stage of dementia.

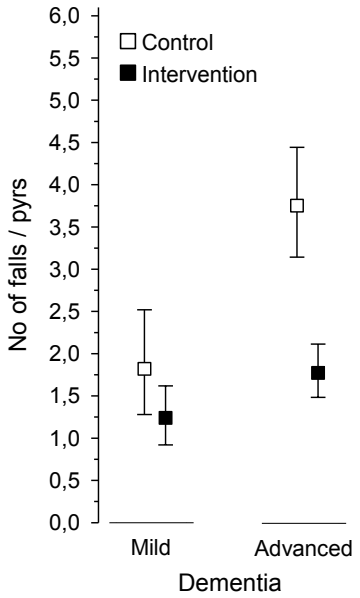

Figure 5. Number (No) of falls during 12-month follow-up in study groups with different stage of dementia.

5.6. Effects of exercise on neuropsychiatric symptoms in AD patients

Study 4 examined the effects of exercise intervention on NPS in AD patients in RCT. The NPS were measured with the CSDD and the NPI. In addition to these, the effects of intervention on neuropsychiatric subsyndromes such as "Hyperactivity" (agitation, aggressiveness, disinhibition, irritability, aberrant motor behaviour), "Mood and apathy" (depression, anxiety, euphoria, apathy, sleeping problems, eating problems), and "Psychosis" (hallucinations, delusions) were investigated. The NPI was administered at baseline and at 6 months. Complete NPI data for both time-points were obtained for 179 out of 210 participants. These participants were included in the analyses. Nearly 100% of the participants had one or several NPS throughout the study. The most frequently occurring single NPS was apathy, with 96% of participants suffering from at least some degree of this symptom during the study.

The mean scores in NPI were rather low at baseline: in HE 13.5, in GE 12.1, and in CG 16.6. At 6 months, no significant changes in total NPI or individual symptom scores were detected. In GE, a minor decrease in irritability scores was seen, -0.49 (95% CI: -0.99 to -0.54, $p = 0.03$). When examining the effects of exercise on symptom sub-groups, the effect sizes were below statistical significance (see Figure 1 in Study 4).

The CSDD was completed for 149 participants at baseline and 12 months. The changes over time were modest: in HE 0.50 (95% CI: -0.67 to 1.54), in GE 1.35 (95% CI: 0.14 to 2.66), and in CG 0.04 (95% CI: -1.56 to 1.40). The differences between the groups were not significant (p=0.81, adjusted for age, sex, baseline CDR and FIM).

5.7 Effects of exercise on institutionalization of AD patients

The exercise intervention did not have effects on the rate of permanent institutionalization in AD patients. Thirteen participants in each of the intervention groups, and 11 participants in the control group were institutionalized during the study period and at one-year follow-up (p=0.79, adjusted for age, sex, baseline CDR and FIM).

5.8 Adverse effects

Complications measured during the 12-month intervention period included falls, fractures, and number of hospitalizations per patient. In fractures and hospitalizations, the differences between the intervention and control groups were insignificant. All serious medical events and causes of death were related to pre-existing co-morbidity, and none were directly or indirectly attributable to the exercise intervention. No falls or major injuries befell the participants while attending the exercise sessions.

6. Discussion

The systematic review examining effectiveness of exercise on cognition in MCI and dementia patients suggested that exercise may have effects on global cognition, executive function, and attention. The eight studies performed among persons with MCI had in general more statistical power, better methodological quality, and larger variety of cognitive domains measured than the studies performed among dementia patients. Methodological quality of the latter studies was poorer than that of the MCI studies, with all of the dementia studies rated as moderate or poor quality. Thus, the grade of evidence is more conflicting among PWD.

Findings from the FINALEX study, a good-quality RCT examining the effects of exercise in AD patients, suggest that regular, long-term home-based exercise may have positive effects on executive function in community-dwelling older people with AD. The 12-month exercise intervention also slowed the deterioration of physical functioning in persons with mild Alzheimer's type dementia and reduced the rate of falls, especially among persons with advanced AD. However, it had no significant effect on NPS or the rate of institutionalizations.

6.1 Methodological considerations

In the studies included in the systematic review, the methodological shortcomings were mostly related to the small number of participants, inadequate description of the cognitive diagnosis, methods of randomization, insufficient reporting of methods of blinding, compliance, drop-outs, and violations of the intention-to-treat concept. These problems exposed the studies to high risk of bias. Since this systematic review, several new studies examining the effects of exercise on cognition in dementia patients have been published. These studies, discussed in more detail in the literature review section, are on average of better methodological quality, some of them using a checklist (such as CONSORT) to ensure a sound methodology (Cancela et al. 2016, Hoffman et al. 2016, Telenius et al. 2015, Toots et al. 2017).

Exercise programmes across the studies could often not be compared, even within the same exercise type, with large variations occurring in frequency, duration, and intensity. However, in both MCI and AD study populations, intensive, multicomponent exercise including an aerobic component and long duration of the intervention seemed to be the key elements leading to positive results. Nevertheless, a clear dose-response effect could not be detected. The participants in the negative studies may not have attained the minimum effective dose; the optimal intensity, frequency, and duration of the exercise needed to improve cognition remains uncertain.

An active control group was employed in 12 out of 22 studies. Low-intensity exercise, such as stretching, and social visits or conversation groups were frequently used as control activity. However, no significant differences in effects could be detected between the studies using an active or passive control group. In many studies with a control group continuing normal care, participants showed an improvement over the course of the studies. This may be due to the Hawthorne effect as a result of engagement of the study personnel with the participants, leading to a diluted intervention effect.

Large, high-quality studies are few as they are labour-intensive and expensive. While RCTs are considered "the gold standard", their results may be subject to selection bias and may not be generalizable to other patient groups (Brodaty et al. 2012). Persons interested in participating in exercise studies are often more physically active also in their normal life than PWD in general, which can diminish the effects of the intervention (Hoffman et al. 2016). It is also noteworthy that most of the RCTs examining the effects of non-pharmacological interventions, such as exercise, are conducted in nursing homes, although the largest impact on treatment might be gained in the community, where the majority of PWD live (Forbes et al. 2015).

The FINALEX study relied on rigorous methodology. The exclusion and inclusion criteria in the study were kept low to ensure a study population that represents well the general community-dwelling AD population. The participants of the study were AD patients living with a spousal carer in the metropolitan area of Helsinki. They were included in the AD drug reimbursement register of the Social Insurance Institution of Finland, indicating they had undergone a thorough diagnostic procedure for probable AD. This explains the high rate (95%) of the participants being on AD medication. The study included participants in all stages of AD with several co-morbidities and signs of frailty to strengthen the generalizability of the results. However, the participants were motivated volunteers living with a carer, thereby not representing the whole AD population. Since women are more often the primary caregivers to their spouses, the study population was male dominant, thus differing from most of the dementia studies (Heyn et al. 2004, van Uffelen et al. 2008).

The control group did not receive any active intervention, instead continuing treatment as usual. The CG continued with community care, and was, for example, entitled to physiotherapeutic

rehabilitation, if needed, during the study period. The community care of patients with memory disorders in Finland is in general of high quality, and this may have diluted the results of the study. The attrition rate of the participants was relatively low and comparable to other intervention studies conducted among community-dwelling AD patients (Teri et al. 2003 Suominen et al. 2015, Hoffmann et al. 2016, Kallio et al. 2018). Attendance to the training sessions was high, enabling real measurements of the intervention effects. Interestingly, the participants with better cognition attended less sessions than those with more advanced dementia.

The compliance was good in both intervention groups, but it was better in the HE group. Tailoring the exercises according to participant's needs and preferences, and training in familiar surroundings, as in the HE group, might be responsible for the difference in compliance. However, in group training, peer support was recognized to be a great asset to improving training motivation. Suttanon and co-workers have studied factors influencing adherence to exercise program in AD patients. The facilitating factors were, for instance, sense of commitment, perceived benefit, carer support, and skilled study personnel (Suttanon et al. 2012). In both groups, the physiotherapists performing the interventions were experienced in working with persons with cognitive impairments, the spousal carers were supported, and carers were asked to encourage the participants to participate in exercise sessions. Additional support was offered to those participants and/or carers who showed signs of dropping out. The intervention was continued, if possible, also during short terms of hospitalization or respite care. Barriers to participating were kept low e.g. by offering free transportation to the group exercise sessions.

The primary outcome of the study was physical functioning, and the training was planned accordingly. The major components of the exercises were aerobic and strength training, leaving less time for, for example, dual-tasking exercises. Training that combines motor and cognitive exercises, e.g. dual-task training, has been suggested to be the most beneficial in improving cognition (Law et al. 2014, Fritz et al. 2015). Moreover, to reduce neuropsychiatric symptoms in AD patients a tailored approach might be warranted. Different NPS may respond to different types of exercise, thus needing targeted interventions (Williams et al. 2008, Gonfrier et al, 2012).

Previous intervention studies have indicated that important components of a successful exercise programme for persons with memory disorders are concrete structure, familiarity with equipment, repetitive exercises, and permanent training personnel accustomed to working with persons with

cognitive impairments (Teri et al. 1998). The intervention in the present study was designed to meet these requirements.

The participants were not restricted in engaging in additional physical exercise during the study, and information regarding extra activities was not systematically collected. It is possible that the participants in the control group increased their physical activity during the study period. It may also have been the case that some participants in the intervention groups compensated for their extra activity over the rest of the day. This could explain why the exercise intervention failed to improve physical fitness (measured with 10-metre walk test) in the intervention groups. Some studies suggest that the total daily activity, including both structured and non-structured physical activity, may be decisive to the health and functioning of older persons (Warburton et al. 2006). Without utilizing e.g. wearable activity sensors that continuously monitor physical activity it was not possible in this study to measure the total amount of exercise performed by the participants.

6.2 Effects of exercise on cognition, physical functioning, fall rate, neuropsychiatric symptoms, and institutionalization in dementia

In the systematic review, of the studies conducted among participants with MCI, five found positive effects on executive function or attention. This finding is in line with other reviews of the subject (Heyn et al. 2004, Wang et al. 2014, Cai et al. 2016). Effects on global cognition were found only in two of the MCI studies. This is not surprising since global cognition was measured with the MMSE, ADAS-cog or CDR, measures that in this population may not be informative because of the ceiling effect.

In the dementia studies, 10 out of 14 were performed among populations with moderate or severe dementia, which leaves room for improvement. The most gains were achieved in global cognition and executive function measures. However, the small number of participants in the studies and lack of robust methodology weaken these results.

In line with the results of the systematic review, the cognitive effects of the long-term exercise intervention in the RCT were rather modest. The only statistically significant change in cognitive tests was seen in executive function, measured with the CDT, after 12 months of tailored home-based exercise. In MMSE and VF, the changes between groups were insignificant. Small studies among community-dwelling dementia patients have yielded similar results on executive function (Yaguez et al. 2011, Arcoverde et al. 2014, Holthoff et al. 2015). A large, good-quality study with 16 weeks of high- to moderate-intensity exercise three times a week found, however, no positive

effects on global cognition, executive function, or attention (Hoffman et al. 2016). Exercise trials with positive changes in several cognitive domains have mostly been conducted in nursing home settings and the exercise rate has been three to seven times a week. (Cheng et al. 2014, Bossers et al. 2015, Cancela et al. 2016) (Table 1). In the present study, the frequency of the exercise sessions or the intensity of the training may have been too low.

Cognitive functions are complex and difficult to quantify. Improvement was not seen in Verbal Fluency scores, although it is widely used as a measure of executive function. However, in addition to semantic fluency, which is considered a component of executive functioning, VF is also a measure of semantic memory (Henry et al. 2004). Therefore, deficits in VF may reflect problems with semantic memory, and not solely executive dysfunction. Previous studies have suggested that exercise may improve executive function more effectively than memory function (Colcombe et al. 2003, Smith et al. 2010). Although a strong association between the Clock drawing test and executive function has been established, the test results are also influenced by global cognition, visuospatial abilities, and semantic knowledge (Agrell et al. 1998).

Besides executive function, the intervention improved physical functioning (Pitkälä et al. 2013), especially in the HE group. It can be speculated that the improvement in HE participants' executive function was responsible for the improvement in physical function as well. In addition to better compliance, the reason for the HE group's improvements in executive function and physical functioning could be that the home-based, individually tailored intervention may have included more exercises meaningful for the participants that were performed in a familiar context, thus activating both motor and cognitive functioning.

It is well-established that exercise has direct positive effects on brain structure and functioning, as discussed more thoroughly elsewhere in this dissertation (Erickson et al 2012, Cassilhas et al. 2016). Nevertheless, the effects of exercise on cognition in patients with AD have been found to be relatively modest. The brain damage may be speculated to already be rather extensive at the stage of clinical AD, with the protective effects of exercise coming too late. This is supported by the finding that effects of exercise are more evident in MCI patients and in older persons without known cognitive impairment (Lautenschlager et al. 2008, Erickson et al. 2011).

In the present RCT, exercise intervention was found to have positive effects on physical functioning and fall rate in AD patients when following the original study design (Pitkälä et al. 2013). While the

study included participants in different stages of AD, the question emerged of whether all of the participants benefitted from the exercise intervention in a similar way. A literature search revealed that no previous studies had examined the effects of exercise in different stages of dementia. When regrouping the participants according to their stage of disease and studying these groups separately, a clear difference was seen. All groups deteriorated in their physical functioning over the study course, as is expected when examining persons with progressive disease. However, patients with better cognition and milder dementia seemed to benefit more from exercise intervention with respect to retaining their level of physical functioning than patients with more advanced disease. This finding is in line with some previous studies examining the effects of exercise in persons with mild dementia and fairly high mean MMSE score (Miu et al. 2008, Vreugdenhil et al. 2012). Positive effects of exercise on executive function in participants with milder cognitive decline could perhaps be the cause for the improvements in physical functioning. Those with mild dementia may still possess resources and capacity to restore their functioning, unlike those with advanced dementia.

To our knowledge, the present study is the first to show that a long-term exercise intervention may reduce the rate of falls in persons with advanced dementia. Thus far, only a few RCTs have focused on the effects of an exercise intervention for fall prevention specifically targeted to older people with dementia (Shaw et al. 2007, Suttanon et al. 2013, Zieschang et al. 2017). This is surprising since people with dementia have an increased risk for falls (Shaw et al. 2007) and for adverse outcomes when sustaining a fall (Montero-Odesso et al. 2012). Two studies have shown modest positive results in lowering the fall rate by employing a similar multicomponent exercise programme as the present study, however, their study populations comprised persons with mild or moderate dementia (Suttanon et al. 2013, Zieschang et al. 2017).

Improvements in muscle strength and function, balance, and mobility could be the primary causes of the positive effects of exercise on fall rate in dementia patients, as sarcopenia, frailty, and gait impairments are strongly related to AD, especially to its advanced stage (Burns et al. 2010, Sugimoto et al. 2017,). Since falls usually have a multifactorial cause and particularly people with dementia are prone to multiple risk factors, such as adverse drug effects and postural hypotension (Allan et al. 2009, McDonald et al. 2016), the best results in fall prevention could presumably be achieved using comprehensive assessments and tailored multifaceted interventions.
The results regarding fall rate in the milder dementia group may have been non-significant because of the lower likelihood of falls in this patient group and lower statistical power.

Exercise intervention did not have a significant effect on NPS or depression in AD patients in the present study. Neither was there any effect on the rate of institutionalization. These results are in line with some earlier studies where exercise intervention as a single intervention was unable to reduce NPS in dementia patients (Miu et al. 2008, Steinberg et al. 2009, Lowery et al. 2014). Nevertheless, contradictory findings also exist. A large Danish RCT (n=200) found an intervention of moderate- to high-intensity aerobic exercise (60 minutes, thrice a week for 16 weeks) to be effective in reducing the NPS measured with NPI in participants with mild AD. However, the mean change in NPI was only -3.5 points (Hoffmann et al. 2016). It is estimated that only changes of 8 points or more indicate a clinically meaningful change (Howard et al. 2010). The positive results seemed to be driven by some sub-items in NPI, mainly irritability (Hoffman et al. 2016). A significant change in the same sub-item was also found in the present study.

A good-quality study from Spain examined patients with moderate or severe dementia in nursing home settings. The intervention group engaged in indoor cycling for at least 15 minutes daily over 64 months (Cancela et al. 2016). The long duration and intensity of the intervention may explain the positive effects on NPS.

In the present study, the NPI was administered after only six months of exercise for practical reasons, allowing speculation of whether the results would have been more favourable after a longer intervention period. The NPI scores were relatively low at baseline, thus, there was a floor effect in reducing the change in NPS. Furthermore, 99% of the patients were on Alzheimer's medication, which may attenuate the NPS (Birks et al. 2006).

Physical activity has been reported to be effective in reducing depression in healthy older adults (Catalan-Matamoros et al. 2016), but this observation might not apply to older subjects with dementia. The negative results of the present study are supported by the finding that, among 12 RCTs examining the effects of exercise on depression in PWD, only one found a positive association (Williams et al. 2008). In their study, the participants were AD patients with depressive symptoms at baseline. However, the control group with conversation activities improved as well. Furthermore, in two other studies the control group with recreational activities (Cancela et al. 2016) or cognitive activation (Dechamps et al. 2008) showed more improvement in depressive symptoms than the exercise intervention group.

Since different NPS may respond to different interventions and since several NPS may occur simultaneously or in clusters, interventions may require individual tailoring. Thus far, the best results in non-pharmacological treatments for NPS in PWD have been achieved with

multicomponent interventions for patients combining exercise with, for example, support, and with educational programmes for carers (Borisovskaja et al. 2014, Kales et al. 2014).

The exercise intervention was unable to decrease the rate of permanent care placement in this study. Medical, social, and psychological factors leading to institutionalization of PWD may be too numerous and complex to be overcome with a single intervention such as exercise. Again, a more extensive and multifaceted approach may produce better results.

Abundant use of psychotropic medication in the study population may have affected the overall results. The data of psychotropic medication use were collected at baseline, but not at post-intervention, thus, it was not possible to determine whether the exercise intervention was effective in decreasing the use of these potentially harmful medications. This aspect has been only marginally explored previously (Barreto et al. 2015), and further studies are needed.

6.3 Strengths and limitations of the study

The systematic review was designed to answer a specific research question. It focused on the precise identification of participants, interventions, outcomes, and study design (PICOS). The flowchart of the study to demonstrate the identification and screening of the studies was presented according to PRISMA guidelines (Liberati et al. 2009). A meta-analysis of the incorporated data was not possible due to variations in study settings, interventions, and reporting of outcome measures. However, a descriptive analysis of individual results across the studies was performed and supplemented with a thorough methodological evaluation by three independent reviewers.
The rigorous methodology was the primary strength of this randomized controlled study examining the effects of an exercise intervention on AD patients. The sample size was large, compliance with the intervention was good, and attrition rate was low. The outcome measures were valid and widely used in dementia studies (Bossers et al. 2012).
In addition, all participants had a confirmed diagnosis of probable AD. Many intervention studies conducted among dementia patients include participants with various types of dementia or fail to report the definite dementia diagnosis of participants (Pitkälä et al. 2013), weakening the methodological quality and comparability with other studies. The exercise intervention in the present study was long-term, intensive, and included several domains of exercise (aerobic, strength, and balance). Both intervention types (group and home-based) were also simple enough to be easily implemented in community care.

For the systematic review, a great effort was made to ensure that all relevant studies would be identified through database and hand search. However, it is possible that some studies went unnoticed. In addition, a publication bias may exist. Lack of available homogeneous data also limited the possibility to combine studies for meta-analysis.

A limitation of the secondary analyses of the RCT reported in this dissertation is that the power calculations were based on the primary outcome (physical performance measured with FIM) of the study. Moreover, the primary focus was on physical performance, which restricted the number and timing of cognitive and neuropsychiatric measures. Because of the cognitive and physical frailty of the study participants, there was an intention to avoid exhaustive study visits with numerous assessments.

An additional limitation is that the study was not blinded, exposing the study to a risk of bias. In an exercise study it is not feasible to keep the participants and physiotherapists performing the intervention blinded. The outcome assessors were blinded to the group allocation, but the participants were often keen on sharing their experiences during the assessments, thus compromising the blinding. However, the outcome assessors were unaware of the precise study questions and they were not co-investigators.

In Study 3, the randomized study design was lost when the participants were regrouped according to their stage of dementia; interpretation of the results should therefore be done with caution. This violation of methodology was, however, the only way to measure the effects of exercise during various stages of dementia.

Some limitations in external validity exist because the participants were motivated volunteers living in their own homes with spouses in an urban area. Generalizing the results to other groups should be done cautiously.

7. Conclusions

A systematic review of RCTs examining the effects of exercise on cognition in MCI and dementia patients found a positive association between exercise intervention and improvements in cognition, especially global cognition, executive function, and attention, in participants with MCI. In studies among dementia populations, the results were more contradictory. Studies among MCI populations were in general more numerous and methodologically more rigorous than studies among dementia patients.

A large RCT was conducted among community-dwelling AD patients exploring the effects of a 12-month exercise intervention on cognition, physical functioning, NPS, institutionalization, and fall rate.

Participants in the home-based exercise group improved in executive function measured with the Clock Drawing Test compared with controls receiving no active intervention.

Participants with mild dementia had significant positive changes in their physical functioning, measured with the FIM, after 12 months of exercise. Participants with a moderate or severe stage of AD fell significantly less than their peers in the control group during the 12-month follow-up.

The exercise intervention had no effects on NPS or institutionalization of AD patients.

The exercise intervention was safe, with no adverse effects related to the study activities.

Combining the results of the present study and the primary results of the FINALEX study (Pitkälä et al. 2013), it can be concluded that exercise shows many benefits in AD patients at all stages of the disease. Exercise has no major adverse effects and is cost-effective. It could be recommended as a long-term treatment (add-on therapy) for all patients with AD.

8. Future implications

A growing body of evidence suggests that regular exercise may improve or slow the decline of functional abilities and cognition and reduce the rate of falls in PWD. However, large, rigorously conducted RCTs are still scarce, especially among community-dwelling PWD. Further research is needed to determine the optimal type, intensity, and duration of exercise as well as the optimal combination of various exercise domains. This kind of research could be implemented by using activity sensor technology or activity data from smart-phones, allowing the total amount of physical activity to be measured and everyday exercise routines to be monitored more accurately. Furthermore, the future generations of older adults as well as PWD are accustomed to using technological devices, and this could be utilized in exercise studies by, for instance, using virtual training.

The effectiveness of exercise on NPS has mostly been studied in trials in which NPS is a secondary endpoint, as in the present study, and the participants do not suffer from significant NPS. Future exercise studies should focus on participants who have significant NPS in order to avoid the floor effect. Use of psychotropic medicine to treat NPS in PWD is abundant. Studies exploring exercise as a potential treatment strategy to reduce the use of psychotropic medicine are almost non-existent. More studies in this area are warranted, as the adverse effects of psychotropics generally outweigh their benefits.

Caregiver training and coaching have been shown to be effective in PWD care. Future trials could integrate caregiver training and exercise to examine the benefits of these treatments.

Exercise is a symptom-relieving and perhaps even disease-modifying treatment of dementia that can be used together with pharmacological and other therapies. Physical exercise appeared to be safe even in this frail population. Tailoring the programmes to meet the needs and preferences of PWD and employing trainers experienced in working with PWD would likely provide the most beneficial results. Implementing regular exercise programmes into the normal care of PWD is strongly recommended.

Regular exercise at all stages of dementia should be part of normal, good-quality care. Its realization requires support from caregivers, health and social care providers, and society as a whole.

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Appendices

Appendix 1. Mini-Mental State Examination (MMSE)

Appendix 2. Clinical Dementia Rating (CDR)

Appendix 3. Clock Drawing Test and Verbal Fluency

Appendix 4. Neuropsychiatric Inventory (NPI)

Appendix 5. Cornell Scale for Depression in Dementia (CSDD)

Appendix 1.

MINI-MENTAL STATE EXAMINATION

POTILAS: _____ SYNTYMÄAIKA:_____

TUTKIJA: _____PVM:_____

Seuraavassa esitän Teille erilaisia pieniä muistiin ja älyllisiin toimintoihin liittyviä kysymyksiä ja tehtäviä:

		Väärin	Oikein
1.	**Mikä vuosi nyt on?**	0	1
2.	**Mikä vuodenaika nyt on?**	0	1
	(talvi = joulu, tammi, helmi kevät = maalis, huhti, touko kesä = kesä, heinä, elo syksy = syys, loka, marras; aina ± 1 vko)		
3.	**Monesko päivä tänään on? (± 1 pv)**	0	1
4.	**Mikä viikonpäivä tänään on?**	0	1
5.	**Mikä kuukausi nyt on?**	0	1
6.	**Missä maassa olemme?**	0	1
7.	**Missä maakunnassa olemme?** (Myös vanhan läänijaon mukaiset vastaukset hyväksytään)	0	1
8.	**Mikä on tämän paikkakunnan nimi?**	0	1
9.	**Mikä on tämä paikka jossa olemme?** (Sairaalan/terveyskeskuksen nimi, kotiosoite)	0	1
10.	**Monennessako kerroksessa olemme?**	0	1
11.	**Seuraavassa pyydän Teitä painamaan mieleen kolme sanaa. Kun olen sanonut ne, toistakaa perässäni.** (Kaksi vaihtoehtoista sarjaa) **PAITA – RUSKEA – VILKAS** **RUUSU – PALLO – AVAIN**		
	PAITA RUUSU	0	1
	RUSKEA tai PALLO	0	1
	VILKAS AVAIN	0	1
	(Merkitään ensimmäisellä kerralla muistetut sanat. Jos ensimmäisessä toistossa tulee virheitä, sanoja kerrataan, kunnes kaikki kolme sanaa on opittu.) Toistoja____(enintään 5 kertaa).		
12.	**Nyt pyydän Teitä vähentämään 100:sta 7 ja saamastanne jäännöksestä 7 ja edelleen vähentämään 7, kunnes pyydän lopettamaan.**		
	93.....	0	1
	86.....	0	1
	79.....	0	1
	72.....	0	1
	65.....	0	1
	(Kysymys voidaan toistaa kerran, jos sitä ei heti ymmärretä. Jos henkilö tekee välillä virheen, mutta jatkaa siitä oikein vähentäen 7 virheellisestä luvusta, tulee vääriä vastauksia 1. Kynää ja paperia ei saa käyttää.)		

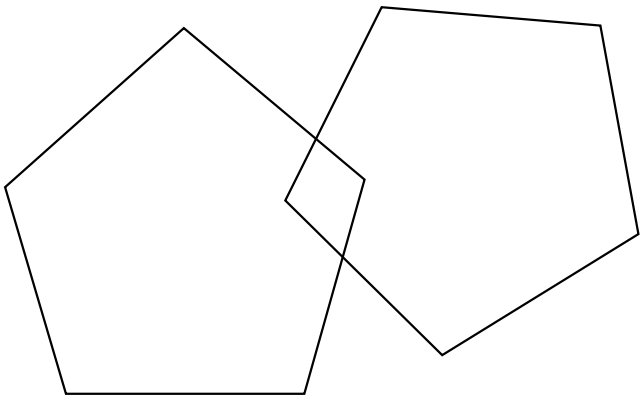
		Väärin	Oikein
13.	**Mitkä olivat ne kolme sanaa, jotka pyysin Teitä painamaan mieleenne?** (Sanojen järjestyksellä ei ole merkitystä.)		
	PAITA RUUSU	0	1
	RUSKEA tai PALLO	0	1
	VILKAS AVAIN	0	1
14.	**Nyt kysyn Teiltä kahden esineen nimeä.**		
	a) Mikä tämä on? – näytetään rannekelloa	0	1
	b) Mikä tämä on? – näytetään lyijykynää	0	1
15.	**Nyt luen Teille lauseen. Pyydän Teitä toistamaan sen perässäni:**		
	EI MITÄÄN MUTTIA EIKÄ JOSSITTELUA	0	1
	(Annetaan piste vain, jos lause on täysin oikein. Lausetta ei saa toistaa.)		
16.	**Seuraavaksi annan Teille paperin ja pyydän Teitä tekemään sille jotain.** (Paperi asetetaan pöydälle tutkittavan eteen.) **Ottakaa paperi vasempaan käteenne. Taittakaa se keskeltä kahtia ja asettakaa polvienne päälle.** (Ohjeita ja lausetta ei saa toistaa eikä henkilöä saa auttaa.)		
	Ottaa paperin vasempaan käteen	0	1
	Taittaa sen	0	1
	Asettaa paperin polville	0	1
17.	**Näytän Teille tekstin ”SULKEKAA SILMÄNNE”. Pyydän Teitä lukemaan sen ääneen ja noudattamaan sen ohjetta.** (Annetaan piste vain, jos sekä lukee tekstin että sulkee silmänsä.)	0	1
18.	**Kirjoittakaa kokonainen lyhyt lause mielenne mukaan.** (ks. seuraava sivu) (Yksi piste, jos lause on ymmärrettävä ja siinä on ainakin subjekti ja predikaatti. Kirjoitusvirheet eivät vaikuta.)	0	1
19.	**Voisitteko piirtää tämän kuvion alapuolelle samanlaisen kuvion.** (ks. seuraava sivu) (Annetaan piste, jos kaikki sivut ja kulmat ovat tallella ja leikkauspinta on nelikulmainen.)	0	1

MMSE-testin pistemäärä _____ /30

KÄÄNNÄ

Kirjoittaisitteko lauseen tähän.

Piirtäisittekö tämän kuvion alapuolelle samanlaisen kuvion.



Appendix 2.

CDR-luokitus

Pvm: _____ ***Tekijä:*** _____

Tutkittava: _____

CDR-LUOKKA

0 = normaali
0,5 = mahdollinen
1 = lievä
2 = keskivaikea
3 = vaikea

OSIO	CDR 0	CDR 0,5	CDR 1	CDR 2	CDR 3
MUISTI	Ei muistin huonontumista tai pientä muistamattomuutta toisinaan. ☐	Lievää jatkuvaa muistamattomuutta; tapahtumien osittaista muistamista; "hyvänlaatuista" muistamattomuutta. ☐	Kohtalaista muistin huonontumista, selvimmin koskien viimeaikaisia tapahtumia; vaikuttaa jokapäiväisiin toimintoihin. ☐	Vaikea muistihäiriö, vain hyvin opittu aines säilynyt; uusi aines unohtuu pian. ☐	Vaikea muistihäiriö; vain pirstaleita säilynyt. ☐
ORIENTAATIO	Täysin orientoitunut. ☐	Täysin orientoitunut lukuun ottamatta pieniä vaikeuksia aikasuhteissa. ☐	Jonkin verran vaikeuksia aikasuhteissa; tutkimustilanteessa orientoitunut paikkaan; muuten voi olla maantieteellistä desorientaatiota. ☐	Suuria vaikeuksia aikasuhteissa; yleensä desorientoitunut aikaan ja usein paikkaan. ☐	Orientoitunut vain henkilöön. ☐
ARVOSTELUKYKY	Ratkaisee jokapäiväiset ongelmat ja hoitaa taloudelliset asiansa hyvin; arvostelukyky hyvin säilynyt. ☐	Vain vähäistä huonontumista ratkaistaessa ongelmia, yhtäläisyyksiä ja eroja. ☐	Kohtalaisia vaikeuksia käsiteltäessä ongelmia, yhtäläisyyksiä ja eroja; sosiaalinen arvostelukyky yleensä säilynyt. ☐	Merkittäviä vaikeuksia käsiteltäessä ongelmia, yhtäläisyyksiä ja eroja; sosiaalinen arvostelukyky yleensä heikentynyt. ☐	Arvostelukyvytön ja kyvytön ratkaisemaan ongelmia. ☐
YHTEISÖLLISET TOIMINNOT	Toimii itsenäisesti tavanomaisella tasollaan työelämässä, ostosten teossa sekä vapaaehtoistyössä ja sosiaalisissa ryhmissä. ☐	Vain vähäistä huonontumista em. toiminnoissa. ☐	Kyvytön toimimaan itsenäisesti em. toiminnoissa joskin saattaa silti olla mukana joissakin; voi edelleen vaikuttaa normaalilta satunnaisesta tarkkailijasta. ☐	Ei itsenäistä toimintaa kodin ulkopuolella, joskin kykenee saatettuna osallistumaan kodin ulkopuoliseen toimintaan. ☐	Ei itsenäistä toimintaa kodin ulkopuolella; ei saatettunakaan kykene osallistumaan tällaiseen toimintaan. ☐
KOTI JA HARRASTUKSET	Eläminen kotona sujuu, älyllinen mielenkiinto ja harrastukset hyvin säilyneet. ☐	Eläminen kotona sujuu, älyllinen mielenkiinto ja harrastustoiminta korkeintaan lievästi heikentyneet. ☐	Lievää, mutta selkeää huonontumista toiminnoissa kotona; luopunut vaikeammista askareista; luopunut monimutkaisemmista harrastuksista ja toiminnoista. ☐	Vain yksinkertaisimmat askareet sujuvat; hyvin rajatut kiinnostuksen kohteet; keskittyy huonosti. ☐	Ei merkittävää toimintaa kotona. ☐
ITSESTÄ HUOLEHTIMINEN	Täysin kykenevä huolehtimaan itsestään. ☐		Tarvitsee kehotuksia ja muistutuksia. ☐	Tarvitsee apua pukeutumisessa, henkilökohtaisessa hygieniassa ja henkilökohtaisten tavaroidensa hoidossa. ☐	Tarvitsee paljon apua itsestään huolehtimisessa; usein inkontinentti. ☐

Appendix 3.

Tutkittavan nimi _____ Nro _____ Päiväys _____

Kellotestin tulos _____ pistettä

Verbal flow:

_____
_____
_____
_____
_____
_____
_____
_____

Yhteensä _____ kpl eläimiä/min

A *Harhaluulot*

☐ ***EA (Ei arvioitavissa)***

Seulontakysymys: Onko potilaalla uskomuksia, joiden tiedätte olevan todellisuudenvastaisia? Väittääkö hän esimerkiksi, että ihmiset yrittävät vahingoittaa häntä tai varastaa häneltä? Onko potilas sanonut, että perheenjäsenet eivät ole keitä sanovat olevansa tai että koti ei ole heidän kotinsa? En tarkoita pelkästään epäluuloisuutta, vaan sitä, että potilas on todella vakuuttunut siitä, että hänelle tapahtuu tällaista.

☐ Ei, siirry seuraavaan seulontakysymykseen seuraavalle sivulle.

☐ Kyllä, siirry lisäkysymyksiin.

Lisäkysymykset	**Ei**	**Kyllä**
1. Uskooko potilas olevansa vaarassa tai että muut aikovat vahingoittaa häntä?	☐	☐
2. Uskooko potilas, että muut varastavat häneltä?	☐	☐
3. Uskooko potilas, että hänen puolisonsa on uskoton?	☐	☐
4. Uskooko potilas, että hänen kodissaan asuu kutsumattomia vieraita?	☐	☐
5. Uskooko potilas, että hänen puolisonsa tai muut ihmiset eivät ole keitä sanovat olevansa?	☐	☐
6. Uskooko potilas, että hänen asuntonsa ei ole hänen kotinsa?	☐	☐
7. Uskooko potilas, että perheenjäsenet aikovat hylätä hänet?	☐	☐
8. Uskooko potilas, että televisiossa ja lehdissä esiintyvät ihmiset ovat todella hänen kotonaan? (Yrittääkö hön puhua heille tai olla muulla tavoin vuoro-vaikutuksessa heidän kanssaan?)	☐	☐
9. Onko potilaalla muita epätavallisia luuloja, joista en ole kysynyt?	☐	☐

Jos seulontakysymyksen vastaus on lisäkysymysten jälkeenkin KYLLÄ, arvioi harhaluulojen yleisyys ja vaikeusaste ja määritä niistä hoitajalle aiheutuva psyykkinen stressi.

Yleisyys:

1 Joskus – harvemmin kuin kerran viikossa.
2 Usein – noin kerran viikossa.
3 Hyvin usein – useita kertoja viikossa, muttei joka päivä.
4 Erittäin usein – vähintään kerran päivässä.

Vaikeusaste:

1. Lievä – potilaalla on harhaluuloja, mutta ne ovat harmittomia eivätkä näytä juuri vaivaavan potilasta.
2. Melko vaikea – harhaluulot ovat häiritseviä ja ahdistavia.
3. Vaikea – harhaluulot ovat hyvin häiritseviä ja merkittävä käyttäytymishäiriöitä aiheuttava tekijä.

Stressi: Kuinka häiritseviä harhaluulot ovat mielestänne?

0 Ei lainkaan
1 Hyvin vähän
2 Jonkin verran
3 Melko paljon
4 Paljon
5 Erittäin paljon

B *Aistiharhat*

☐ ***EA (Ei arvioitavissa)***

Seulontakysymys: Onko potilaalla aistiharhoja, esimerkiksi näkö- tai kuuloharhoja? Vaikuttaako siltä, että hän näkee, kuulee tai kokee olemattomia asioita? Tämä kysymys ei viittaa pelkästään vääriin uskomuksiin, kuten siihen, että joku, joka on kuollut, olisikin yhä elossa, vaan siihen, että potilaalla todella on poikkeavia kuulo- ja näköaistimuksia.

☐ Ei, siirry seuraavaan seulontakysymykseen seuraavalle sivulle.

☐ Kyllä, siirry lisäkysymyksiin.

Lisäkysymykset	**Ei**	**Kyllä**
1. Sanooko potilas kuulevansa ääniä tai käyttäytyykö hän ikään kuin kuulisi ääniä?	☐	☐
2. Puhuuko potilas olemattomille henkilöille?	☐	☐
3. Sanooko potilas näkevänsä asioita, joita muut eivät näe tai käyttäytyykö hän ikään kuin näkisi jotain, mitä muut eivät näe (ihmisiä, eläimiä, valoja jne.)?	☐	☐
4. Sanooko potilas haistavansa hajuja, joita muut eivät haista?	☐	☐
5. Sanooko potilas tuntevansa ihollaan jotain tai vaikuttaako hän muuten siltä kuin tuntisi jonkin ryömivän ihollaan tai koskettavan häntä?	☐	☐
6. Kuvaileeko potilas makuaistimuksia, joiden alkuperää ei tiedetä?	☐	☐
7. Kuvaileeko potilas muita epätavallisia aistikokemuksia?	☐	☐

Jos seulontakysymyksen vastaus on lisäkysymysten jälkeenkin KYLLÄ, arvioi aistiharhojen yleisyys ja vaikeusaste ja määritä niistä hoitajalle aiheutuva psyykkinen stressi.

Yleisyys:

1 Joskus – harvemmin kuin kerran viikossa.
2 Usein – noin kerran viikossa.
3 Hyvin usein – useita kertoja viikossa, muttei joka päivä.
4 Erittäin usein – vähintään kerran päivässä.

Vaikeusaste:

1. Lievä – potilaalla on aistiharhoja, mutta ne ovat harmittomia eivätkä näytä juuri vaivaavan potilasta.
2. Melko vaikea – aistiharhat ovat häiritseviä ja ahdistavia.
3. Vaikea – aistiharhat ovat hyvin häiritseviä ja merkittävä käyttäytymishäiriöitä aiheuttava tekijä.

Stressi: Kuinka häiritseviä aistiharhat ovat mielestänne?

0 Ei lainkaan
1 Hyvin vähän
2 Jonkin verran
3 Melko paljon
4 Paljon
5 Erittäin paljon

C *Levottomuus/aggressiivisuus* ☐ *EA (Ei arvioitavissa)*

Seulontakysymys: Onko potilaalla kausia, jolloin hän kieltäytyy yhteistyöstä tai ei ota vastaan apua? Onko häntä vaikea käsitellä?

☐ Ei, siirry seuraavaan seulontakysymykseen seuraavalle sivulle.

☐ Kyllä, siirry lisäkysymyksiin.

Lisäkysymykset	**Ei**	**Kyllä**
1. Hermostuuko potilas ihmisiin, jotka yrittävät huolehtia hänestä tai vastusteleeko hän esimerkiksi kylvettämistä tai vaatteiden vaihtamista?	☐	☐
2. Onko potilas itsepäinen ja vaatiiko hän, että asiat tehdään niin kuin hän haluaa?	☐	☐
3. Onko potilas yhteistyöhaluton, vastustaako hän tarjottua apua?	☐	☐
4. Käyttäytyykö potilas muulla tavoin siten, että häntä on vaikea käsitellä?	☐	☐
5. Huutaako tai kiroileeko potilas vihaisesti?	☐	☐
6. Paiskooko potilas ovia, potkiiko huonekaluja tai heitteleekö hän tavaroita?	☐	☐
7. Yrittääkö potilas lyödä tai vahingoittaa muita?	☐	☐
8. Käyttäytyykö potilas muuten aggressiivisesti tai kiihtyneesti?	☐	☐

Jos seulontakysymyksen vastaus on lisäkysymysten jälkeenkin KYLLÄ, arvioi levottomuuden/aggressiivisuuden yleisyys ja vaikeusaste ja määritä siitä hoitajalle aiheutuva psyykkinen stressi.

Yleisyys:
1 Joskus – harvemmin kuin kerran viikossa.
2 Usein – noin kerran viikossa.
3 Hyvin usein – useita kertoja viikossa, muttei joka päivä.
4 Erittäin usein – vähintään kerran päivässä.

Vaikeusaste:
1. Lievä – potilaan käyttäytyminen on häiritsevää, mutta hallittavissa rauhoittelulla ja ohjailulla.
2. Melko vaikea – käyttäytyminen on häiritsevää ja sitä on vaikea ohjailla ja hallita.
3. Vaikea – levottomuus/aggressiivisuus on hyvin häiritsevää ja aiheuttaa paljon vaikeuksia. Potilas saattaa vahingoittaa itseään.

Stressi: Kuinka häiritsevää levottomuus/aggressiivisuus on mielestänne?
0 Ei lainkaan
1 Hyvin vähän
2 Jonkin verran
3 Melko paljon
4 Paljon
5 Erittäin paljon

D *Masentuneisuus/alakuloisuus*

☐ *EA (Ei arvioitavissa)*

Seulontakysymys: Vaikuttaako potilas surulliselta tai masentuneelta? Sanooko hän olevansa surullinen tai masentunut?

☐ Ei, siirry seuraavaan seulontakysymykseen seuraavalle sivulle.

☐ Kyllä, siirry lisäkysymyksiin.

Lisäkysymykset	**Ei**	**Kyllä**
1. Esiintyykö potilaalla ajoittain itkuisuutta tai nyyhkimistä, joka viittaa surumielisyyteen?	☐	☐
2. Puhuuko tai käyttäytyykö potilas surullisen tai alakuloisen oloisesti?	☐	☐
3. Vähätteleekö potilas itseään tai sanooko hän olevansa epäonnistunut?	☐	☐
4. Sanooko potilas olevansa paha ihminen tai ansaitsevansa rangaistuksen?	☐	☐
5. Vaikuttaako potilas lannistuneelta tai sanooko hän ettei hänellä ole tulevaisuutta?	☐	☐
6. Sanooko potilas olevansa taakaksi perheelle tai että perheellä olisi parempi ilman häntä?	☐	☐
7. Ilmaiseeko potilas toivovansa kuolemaa tai puhuuko hän itsemurhasta?	☐	☐
8. Näkyykö potilaassa muita masennuksen tai surullisuuden merkkejä?	☐	☐

Jos seulontakysymyksen vastaus on lisäkysymysten jälkeenkin KYLLÄ, arvioi masentuneisuuden/alakuloisuuden yleisyys ja vaikeusaste ja määritä siitä hoitajalle aiheutuva psyykkinen stressi.

Yleisyys:

1 Joskus – harvemmin kuin kerran viikossa.
2 Usein – noin kerran viikossa.
3 Hyvin usein – useita kertoja viikossa, muttei joka päivä.
4 Erittäin usein – käytännöllisesti katsoen jatkuvasti.

Vaikeusaste:

1. Lievä – masennus ahdistaa potilasta, mutta lievittyy tavallisesti rauhoittelulla ja ohjailulla.
2. Melko vaikea – masennus ahdistaa potilasta, hän ilmaisee masennusoireet spontaanisti ja niitä on vaikea lievittää.
3. Vaikea – masennus on hyvin ahdistavaa ja aiheuttaa potilaalle paljon kärsimystä.

Stressi: Kuinka häiritsevää masentuneisuus/alakuloisuus on mielestänne?

0 Ei lainkaan
1 Hyvin vähän
2 Jonkin verran
3 Melko paljon
4 Paljon
5 Erittäin paljon

E *Ahdistuneisuus* ☐ *EA (Ei arvioitavissa)*

Seulontakysymys: Onko potilas hyvin hermostunut, huolestunut tai peloissaan ilman selvää syytä? Vaikuttaako hän hyvin jännittyneeltä tai rauhattomalta? Pelkääkö potilas jäädä yksin?

☐ Ei, siirry seuraavaan seulontakysymykseen seuraavalle sivulle.

☐ Kyllä, siirry lisäkysymyksiin.

Lisäkysymykset	**Ei**	**Kyllä**
1. Sanooko potilas, että tapahtumat, joita on suunniteltu, huolestuttavat häntä?	☐	☐
2. Onko potilaalla ajoittain hutera olo tai onko hän kykenemätön rentoutumaan ja ylijännittynyt?	☐	☐
3. Onko potilaalla ajoittain (tai valittaako hän) hengenahdistusta, hengenhaukkomista tai huokaileeko hän ilman muuta selvää syytä kuin hermostuneisuus?	☐	☐
4. Valittaako potilas, että ”hänellä on perhosia vatsassa” tai että hänen sydämensä hakkaa tai tykyttää hermostuksesta? (Potilaan sairauden tila ei selitä oireita.)	☐	☐
5. Välttääkö potilas paikkoja tai tilanteita, jotka lisäävät hermostuneisuutta, kuten autolla kulkemista, ystävien tapaamista tai väenpaljoutta?	☐	☐
6. Hermostuuko tai hätääntyykö potilas, jos hän joutuu eroon Teistä (hoitajastaan)? Takertuuko hän Teihin, jotta ei joutuisi Teistä eroon?	☐	☐
7. Osoittaako potilas muita ahdistuneisuuden merkkejä?	☐	☐

Jos seulontakysymyksen vastaus on lisäkysymysten jälkeenkin KYLLÄ, arvioi ahdistuneisuuden yleisyys ja vaikeusaste ja määritä siitä hoitajalle aiheutuva psyykkinen stressi.

Yleisyys:
1 Joskus – harvemmin kuin kerran viikossa.
2 Usein – noin kerran viikossa.
3 Hyvin usein – useita kertoja viikossa, muttei joka päivä.
4 Erittäin usein – vähintään kerran päivässä.

Vaikeusaste:
1. Lievä – ahdistuneisuus vaivaa potilasta, mutta lievittyy tavallisesti rauhoittelulla ja ohjailulla.
2. Melko vaikea – ahdistuneisuus vaivaa potilasta, hän ilmaisee ahdistusoireet spontaanisti ja niitä on vaikea lievittää.
3. Vaikea – ahdistuneisuus on hyvin voimakasta ja aiheuttaa potilaalle paljon kärsimystä.

Stressi: Kuinka häiritsevää ahdistuneisuus on mielestänne?
0 Ei lainkaan
1 Hyvin vähän
2 Jonkin verran
3 Melko paljon
4 Paljon
5 Erittäin paljon

F *Kohonnut mieliala/epäasianmukainen iloisuus* ☐ *EA (Ei arvioitavissa)*

Seulontakysymys: Vaikuttaako potilas liian iloiselta tai onnelliselta ilman syytä? En tarkoita normaalia iloisuutta, joka johtuu ystävien tapaamisesta, lahjojen saamisesta tai yhdessäolosta perheen kanssa. Kysyn sitä, onko potilas jatkuvasti poikkeavan hyväntuulinen tai onko hän huvittunut asioista, joita muut eivät pidä hauskoina?

☐ Ei, siirry seuraavaan seulontakysymykseen seuraavalle sivulle.

☐ Kyllä, siirry lisäkysymyksiin.

Lisäkysymykset	**Ei**	**Kyllä**
1. Vaikuttaako potilas liian tyytyväiseltä tai onnelliselta verrattuna siihen, millainen hän normaalisti on?	☐	☐
2. Nauraako potilas asioille tai onko hän huvittunut asioista, joita muut eivät pidä hauskoina?	☐	☐
3. Onko potilaalla lapsellinen huumorintaju ja taipumus kikattaa tai nauraa sopimattomissa tilanteissa (esim.toisen vahingolle)?	☐	☐
4. Kertooko potilas vitsejä tai esittääkö hän huomautuksia, jotka ovat hauskoja vain hänestä itsestään?	☐	☐
5. Tekeekö potilas lapsellisia kepposia, esim. nipistelee toisia tai leikkii hippaa huvin vuoksi?	☐	☐
6. Kerskaileeko potilas tai väittääkö hän omaavansa enemmän kykyjä tai varallisuutta kuin hänellä todellisuudessa on?	☐	☐
7. Vaikuttaako potilas muulla tavoin liian tyytyväiseltä tai onnelliselta?	☐	☐

Jos seulontakysymyksen vastaus on lisäkysymysten jälkeenkin KYLLÄ, arvioi kohonneen mielialan/epäasianmukaisen iloisuuden yleisyys ja vaikeusaste ja määritä siitä hoitajalle aiheutuva psyykkinen stressi.

Yleisyys:
1 Joskus – harvemmin kuin kerran viikossa.
2 Usein – noin kerran viikossa.
3 Hyvin usein – useita kertoja viikossa, muttei joka päivä.
4 Erittäin usein – käytännöllisesti katsoen jatkuvasti.

Vaikeusaste:
1. Lievä – ystävät ja perheenjäsenet huomaavat kohonneen mielialan, mutta se ei häiritse.
2. Melko vaikea – mielialan kohoaminen on selvästi epänormaalia.
3. Vaikea – mielialan kohoaminen on hyvin silmäänpistävää; potilas on euforinen ja pitää miltei kaikkia asioita hauskoina.

Stressi: Kuinka häiritsevää mielialan kohoaminen/epäasianmukainen iloisuus on mielestänne?
0 Ei lainkaan
1 Hyvin vähän
2 Jonkin verran
3 Melko paljon
4 Paljon
5 Erittäin paljon

G *Apatia/välinpitämättömyys* ☐ *EA (Ei arvioitavissa)*

Seulontakysymys: Onko potilas menettänyt kiinnostuksensa siihen, mitä hänen ympärillään tapahtuu? Onko hän menettänyt kiinnostuksensa asioiden tekemiseen tai puuttuuko häneltä motivaatio ryhtyä tekemään uusia asioita? Onko häntä aiempaa vaikeampi saada osallistumaan keskusteluun tai askareisiin? Onko potilas haluton tai välinpitämätön?

☐ Ei, siirry seuraavaan seulontakysymykseen seuraavalle sivulle.

☐ Kyllä, siirry lisäkysymyksiin.

Lisäkysymykset	**Ei**	**Kyllä**
1. Onko potilaan aloitekyky heikentynyt tai vaikuttaako hän passiivisemmalta?	☐	☐
2. Aloittaako potilas keskustelun entistä harvemmin?	☐	☐
3. Osoittaako potilas vähemmän hellyttä tai tunteitaan kuin tavallisesti?	☐	☐
4. Osallistuuko potilas aiempaa vähemmän kotitöihin?	☐	☐
5. Näyttääkö potilas olevan aiempaa vähemmän kiinnostunut toisten tekemisistä tai suunnitelmista?	☐	☐
6. Onko potilas menettänyt kiinnostuksensa ystäviä ja perheenjäseniä kohtaan?	☐	☐
7. Eikö potilas enää jaksa innostua häntä yleensä kiinnostavista asioista yhtä paljon kuin aiemmin?	☐	☐
8. Osoittaako potilas muulla tavoin ettei hän välitä ryhtyä mihinkään uuteen?	☐	☐

Jos seulontakysymyksen vastaus on lisäkysymysten jälkeenkin KYLLÄ, arvioi apatian/välinpitämättömyyden yleisyys ja vaikeusaste ja määritä siitä hoitajalle aiheutuva psyykkinen stressi.

Yleisyys:
1 Joskus – harvemmin kuin kerran viikossa.
2 Usein – noin kerran viikossa.
3 Hyvin usein – useita kertoja viikossa, muttei joka päivä.
4 Erittäin usein – käytännöllisesti katsoen jatkuvasti.

Vaikeusaste:
1. Lievä – apatia on havaittavaa, mutta ei juuri haittaa päivittäistä elämää; poikkeaa vain lievästi potilaan normaalista käyttäytymisestä; potilas suostuu, jos hänelle ehdotetaan toimintaa.
2. Melko vaikea – apatia on hyvin selvää; hoitaja saattaa onnistua voittamaan sen suostuttelemalla ja rohkaisemalla; potilas reagoi spontaanisti vain merkittäviin tapahtumiin, kuten sukulaisten tai perheenjäsenten vierailuun.
3. Vaikea – apatia on hyvin selvää, eikä potilas yleensä reagoi rohkaisuun tai siihen, mitä hänen ympärillään tapahtuu.

Stressi: Kuinka häiritsevää apatia/välinpitämättömyys on mielestänne?
0 Ei lainkaan
1 Hyvin vähän
2 Jonkin verran
3 Melko paljon
4 Paljon
5 Erittäin paljon

H *Estottomuus* ☐ *EA (Ei arvioitavissa)*

Seulontakysymys: Näyttääkö potilas toimivan hetken mielijohteesta ajattelematta ensin? Tekeekö tai sanooko hän asioita, joita ei yleensä tehdä tai sanota julkisesti? Tekeekö hän asioita, jotka ovat hämmentäviä Teille tai muille?

☐ Ei, siirry seuraavaan seulontakysymykseen seuraavalle sivulle.

☐ Kyllä, siirry lisäkysymyksiin.

Lisäkysymykset	**Ei**	**Kyllä**
1. Käyttäytyykö potilas hetken mielijohteesta ajattelematta seurauksia?	☐	☐
2. Puhuuko potilas ventovieraille ihmisille ikään kuin tuntisi heidät?	☐	☐
3. Sanooko potilas ihmisille tahdittomia tai loukkaavia asioita?	☐	☐
4. Puhuuko potilas karkeasti tai esittääkö hän seksuaalisia huomautuksia, mitä hän ei normaalisti tekisi?	☐	☐
5. Puhuuko potilas avoimesti hyvin henkilökohtaisista tai yksityisluontoisista asioista, joita ei yleensä kerrota muille?	☐	☐
6. Ottaako potilas vapauksia, kosketteleeko tai halaileeko hän ihmisiä tavalla, joka ei ole hänelle ominainen?	☐	☐
7. Osoittaako potilas muita merkkejä siitä, ettei hän hallitse mielijohteitaan?	☐	☐

Jos seulontakysymyksen vastaus on lisäkysymysten jälkeenkin KYLLÄ, arvioi estottomuuden yleisyys ja vaikeusaste ja määritä siitä hoitajalle aiheutuva psyykkinen stressi.

Yleisyys:
1 Joskus – harvemmin kuin kerran viikossa.
2 Usein – noin kerran viikossa.
3 Hyvin usein – useita kertoja viikossa, muttei joka päivä.
4 Erittäin usein – käytännöllisesti katsoen jatkuvasti.

Vaikeusaste:
1. Lievä – estottomuus on havaittavaa, mutta siihen voidaan yleensä vaikuttaa ohjailulla.
2. Melko vaikea – estottomuus on hyvin selvää ja hoitajan on vaikea vaikuttaa siihen.
3. Vaikea – hoitaja ei yleensä pysty mitenkään vaikuttamaan estottomuuteen ja se on kiusallista ja sosiaalisesti haittaavaa.

Stressi: Kuinka häiritsevää estottomuus on mielestänne?
0 Ei lainkaan
1 Hyvin vähän
2 Jonkin verran
3 Melko paljon
4 Paljon
5 Erittäin paljon

I *Ärtyisyys/mielialan vaihtelu* ☐ *EA (Ei arvioitavissa)*

Seulontakysymys: Ärtyykö tai häiriintyykö potilas helposti? Vaihteleeko hänen mielialansa herkästi? Onko hän poikkeavan kärsimätön? Tällä ei tarkoiteta muistin tai toimintakyvyn heikkenemisestä johtuvaa turhautumista, vaan sitä, onko potilas poikkeavan ärtyisä, kärsimätön tai tunteiltaan ailahteleva verrattuna siihen, millainen hän yleensä on?

☐ Ei, siirry seuraavaan seulontakysymykseen seuraavalle sivulle.

☐ Kyllä, siirry lisäkysymyksiin.

Lisäkysymykset	**Ei**	**Kyllä**
1. Onko potilas pahantuulinen, menettääkö hän helposti malttinsa pikkuasioista?	☐	☐
2. Vaihteleeko potilaan mieliala nopeasti niin, että hän on yhtenä hetkenä tyytyväinen ja seuraavassa hetkessä vihainen?	☐	☐
3. Onko potilaalla äkillisiä kiukunpurkauksia?	☐	☐
4. Onko potilas kärsimätön, onko hänen vaikea kestää viivytyksiä tai odottaa suunniteltujen asioiden tapahtumista?	☐	☐
5. Onko potilas kärttyisä ja ärtynyt?	☐	☐
6. Onko potilas riidanhaluinen ja onko hänen kanssaan vaikea tulla toimeen?	☐	☐
7. Osoittaako potilas muita ärtyisyyden merkkejä?	☐	☐

Jos seulontakysymyksen vastaus on lisäkysymysten jälkeenkin KYLLÄ, arvioi ärtyisyyden/mielialan vaihtelun yleisyys ja vaikeusaste ja määritä siitä hoitajalle aiheutuva psyykkinen stressi.

Yleisyys:
1 Joskus – harvemmin kuin kerran viikossa.
2 Usein – noin kerran viikossa.
3 Hyvin usein – useita kertoja viikossa, muttei joka päivä.
4 Erittäin usein – käytännöllisesti katsoen jatkuvasti.

Vaikeusaste:
1. Lievä – ärtyisyys/mielialan vaihtelu on havaittavaa, mutta niihin voidaan yleensä vaikuttaa rauhoittelulla ja ohjailulla.
2. Melko vaikea – ärtyisyys/mielialan vaihtelu on hyvin selvää ja hoitajan on vaikea vaikuttaa niihin.
3. Vaikea – ärtyisyys/mielialan vaihtelu on hyvin selvää eikä hoitaja yleensä pysty vaikuttamaan siihen. Potilaalle aiheutuu paljon kärsimystä.

Stressi: Kuinka häiritsevää ärtyisyys/mielialan vaihtelu on mielestänne?
0 Ei lainkaan
1 Hyvin vähän
2 Jonkin verran
3 Melko paljon
4 Paljon
5 Erittäin paljon

J *Poikkeava motorinen käyttäytyminen* ☐ *EA (Ei arvioitavissa)*

Seulontakysymys: Käveleekö potilas edestakaisin toistaen samoja asioita, esimerkiksi availlen kaappeja tai laatikoita, hypisteleekö hän esineitä tai kiertääkö esim. lankoja tai naruja kerälle?

☐ Ei, siirry seuraavaan seulontakysymykseen seuraavalle sivulle.

☐ Kyllä, siirry lisäkysymyksiin.

Lisäkysymykset	**Ei**	**Kyllä**
1. Käveleekö potilas ympäri asuntoa ilmaan selvää tarkoitusta?	☐	☐
2. Penkooko potilas paikkoja availlen ja tyhjentäen laatikoita tai kaappeja?	☐	☐
3. Pukeeko ja riisuuko potilas vaatteitaan toistuvasti?	☐	☐
4. Onko potilaalla tapoja tai toimintoja, joita hän toistaa toistamastaan päästyään?	☐	☐
5. Tekeekö potilas toistuvasti tiettyjä asioita, kuten sormeilee nappeja, hypistelee esineitä, kiertää naruja kerälle tms?	☐	☐
6. Liikehtiikö potilas hermostuneesti, onko hänen vaikea istua aloillaan, heilutteleeko hän jalkojaan tai rummuttaako hän sormillaan?	☐	☐
7. Toistaako potilas jotain muita toimintoja yhä uudestaan?	☐	☐

Jos seulontakysymyksen vastaus on lisäkysymysten jälkeenkin KYLLÄ, arvioi poikkeavan motorisen käyttäytymisen yleisyys ja vaikeusaste ja määritä siitä hoitajalle aiheutuva psyykkinen stressi.

Yleisyys:
1 Joskus – harvemmin kuin kerran viikossa.
2 Usein – noin kerran viikossa.
3 Hyvin usein – useita kertoja viikossa, muttei joka päivä.
4 Erittäin usein – käytännöllisesti katsoen jatkuvasti.

Vaikeusaste:
1. Lievä – poikkeava motorinen käyttäytyminen on havaittavaa, mutta ei juuri häiritse päivittäistä elämää.
2. Melko vaikea – poikkeava motorinen käyttäytyminen on hyvin selvää, mutta hoitaja pystyy lopettamaan sen.
3. Vaikea – poikkeava motorinen käyttäytyminen on hyvin selvää, hoitaja ei yleensä pysty vaikuttamaan siihen ja se aiheuttaa potilaalle suurta kärsimystä.

Stressi: Kuinka häiritsevää poikkeava motorinen käyttäytyminen on mielestänne?
0 Ei lainkaan
1 Hyvin vähän
2 Jonkin verran
3 Melko paljon
4 Paljon
5 Erittäin paljon

K *Unen häiriöt*

☐ ***EA (Ei arvioitavissa)***

Seulontakysymys: Onko potilaalla univaikeuksia? Onko hän hereillä öisin? Kuljeskeleeko hän yöllä, pukeutuuko tai häiritseekö hän muuten muiden unta? (Pelkkiä satunnaisia wc-käyntejä ei pidetä unen häiriöinä, jos potilas nukahtaa pian käynnin jälkeen uudelleen.)

☐ Ei, siirry seuraavaan seulontakysymykseen seuraavalle sivulle.

☐ Kyllä, siirry lisäkysymyksiin.

Lisäkysymykset	**Ei**	**Kyllä**
1. Onko potilaalla vaikeuksia nukahtaa?	☐	☐
2. Nouseeko potilas ylös yön aikana (pelkkiä satunnaisia wc-käyntejä ei lasketa, jos hän nukahtaa heti uudelleen)?	☐	☐
3. Kuljeskeleeko potilas, käveleekö hän edestakaisin tai ryhtyykö hän epäasiallisiin toimiin yöllä?	☐	☐
4. Herättääkö potilas Teidät yön aikana?	☐	☐
5. Heräkö potilas yöllä pukeutuen ja suunnitellen ulosmenoa ajatellen, että on aamu ja aika aloittaa päivä?	☐	☐
6. Heräkö potilas liian aikaisin aamulla (aikaisemmin kuin hänellä oli tapana)?	☐	☐
7. Nukkuuko potilas liikaa päivällä?	☐	☐
8. Onko potilaalla muita yöllisiä häiriintyneeseen uneen liittyviä toimintoja tai yönaikaista epäasiallista käyttäytymistä, jotka koette häiritseviksi ja joita ei ole kysytty edellä?	☐	☐

Jos seulontakysymyksen vastaus on lisäkysymysten jälkeenkin KYLLÄ, arvioi unen häiriöiden yleisyys ja vaikeusaste ja määritä siitä hoitajalle aiheutuva psyykkinen stressi.

Yleisyys:

1 Joskus – harvemmin kuin kerran viikossa.
2 Usein – noin kerran viikossa.
3 Hyvin usein – useita kertoja viikossa, muttei joka yö.
4 Erittäin usein –käytännöllisesti katsoen jatkuvasti.

Vaikeusaste:

1. Lievä – unen häiriöt ovat havaittavia, mutta eivät ole erityisen häiritseviä.
2. Melko vaikea – unen häiriöt ovat hyvin selviä ja ne häiritsevät hoitajan ja potilaan nukkumista; potilaalla voi olla useamman kuin yhdentyyppisiä unen häiriöitä.
3. Vaikea – potilaalla on useita erilaisia unen häiriöitä tai yöaikaisia käytösoireita; potilas on ahdistunut yöllä ja myös hoitajan uni häiriintyy merkittävästi.

Stressi: Kuinka häiritseviä unen häiriöt ovat mielestänne?

0 Ei lainkaan
1 Hyvin vähän
2 Jonkin verran
3 Melko paljon
4 Paljon
5 Erittäin paljon

L *Ruokahalun ja syömisen häiriöt* ☐ *EA (Ei arvioitavissa)*

Seulontakysymys: Onko potilaan ruokahalussa, painossa tai ruokailutottumuksissa tapahtunut muutoksia? Tätä kysymystä ei arvioida (merkitse EA), jos potilas on vuodepotilaana ja muiden syötettävänä. Onko mieltymyksissä eri ruokiin ilmennyt mitään muutoksia?

☐ Ei, siirry seuraavaan seulontakysymykseen seuraavalle sivulle.

☐ Kyllä, siirry lisäkysymyksiin.

Lisäkysymykset	**Ei**	**Kyllä**
1. Onko potilas menettänyt ruokahalunsa?	☐	☐
2. Onko potilaan ruokahalu lisääntynyt?	☐	☐
3. Onko potilaan paino pudonnut?	☐	☐
4. Onko potilaan paino noussut?	☐	☐
5. Onko potilaan ruokailutavat muuttuneet, ahtaako potilas liikaa ruokaa suuhunsa kerralla?	☐	☐
6. Onko potilaan ruokavaliossa tapahtunut muutosta, syökö hän liikaa makeisia tai joitain muita ruoka-aineita/ruokalajeja?	☐	☐
7. Syökö potilas aina samantyyppistä ruokaa tai aina tarkalleen samassa järjestyksessä?	☐	☐
8. Onko potilaalla ilmennyt mitään muita muutoksia ruokahalussa tai syömisessä?	☐	☐

Jos seulontakysymyksen vastaus on lisäkysymysten jälkeenkin KYLLÄ, arvioi ruokahalun ja syömisen häiriöiden yleisyys ja vaikeusaste ja määritä siitä hoitajalle aiheutuva psyykkinen stressi.

Yleisyys:

1 Joskus – harvemmin kuin kerran viikossa.
2 Usein – noin kerran viikossa.
3 Hyvin usein – useita kertoja viikossa, muttei joka päivä.
4 Erittäin usein – vähintään kerran päivässä.

Vaikeusaste:

1. Lievä – ruokahalussa ja syömisessä on muutoksia, mutta eivät ole johtaneet painon muutoksiin eivätkä ole häiritseviä.
2. Melko vaikea – muutokset ruokahalussa ja syömisessä ovat selviä ja ne aiheuttavat pieniä painon vaihteluja.
3. Vaikea – ruokahalussa ja syömisessä on suuria muutoksia, ne aiheuttavat painon vaihtelua ja ovat kiusallisia potilaalle tai häiritsevät häntä muuten.

Stressi: Kuinka häiritseviä unen häiriöt ovat mielestänne?

0 Ei lainkaan
1 Hyvin vähän
2 Jonkin verran
3 Melko paljon
4 Paljon
5 Erittäin paljon

Appendix 4.

Neuropsykiatrinen haastattelu (NPI) 13/15

Potilaan nimi: _____ ***Päivämäärä:*** _____

Henkilötunnus: _____ ***Haastateltu: puoliso/omainen/potilas/muu***

Osio	**EA**	**Ei esiinny**	**Yleisyys**	**Vaikeus**	**Y & V**	**Stressi**
Neuropsykiatriset oireet						
A. Harhaluulot	X	0	1 2 3 4	1 2 3	_____	1 2 3 4 5
B. Aistiharhat	X	0	1 2 3 4	1 2 3	_____	1 2 3 4 5
C. Levottomuus ja aggressiivisuus	X	0	1 2 3 4	1 2 3	_____	1 2 3 4 5
D. Masentuneisuus ja alakuloisuus	X	0	1 2 3 4	1 2 3	_____	1 2 3 4 5
E. Ahdistuneisuus	X	0	1 2 3 4	1 2 3	_____	1 2 3 4 5
F. Kohonnut mieliala/ epäasianmukainen iloisuus	X	0	1 2 3 4	1 2 3	_____	1 2 3 4 5
G. Apatia/välinpitämättömyys	X	0	1 2 3 4	1 2 3	_____	1 2 3 4 5
H. Estottomuus	X	0	1 2 3 4	1 2 3	_____	1 2 3 4 5
I. Ärtyisyys/mielialan vaihtelu	X	0	1 2 3 4	1 2 3	_____	1 2 3 4 5
J. Poikkeava motorinen käyttäytyminen	X	0	1 2 3 4	1 2 3	_____	1 2 3 4 5
Yhteensä					_____	_____
Neurovegetatiiviset muutokset						
K. Unen häiriöt	X	0	1 2 3 4	1 2 3	_____	1 2 3 4 5
L. Ruokahalun ja syömisen häiriöt	X	0	1 2 3 4	1 2 3	_____	1 2 3 4 5

Diagnoosi: _____

MMSE: _____

Ikä: _____ Sukupuoli: _____

Sairauden kesto: _____

Koulutus: _____

Lääkitys: _____

Neuropsykiatrinen haastattelu (NPI) 14/15

Pisteytysyhteenveto

Ohje: Lue haastattelua koskeva ohje ennen kysymysten esittämistä. Merkitse vastaukset tälle lomakkeelle ennen kuin arvioit oireiden yleisyyttä, vaikeusastetta tai niistä aiheutunutta stressiä.
K = oire esiintyy potilaalla, E = oiretta ei esiinny, EA = ei arvioitavissa.

A. Harhaluulot	**K**	**E**	**EA**
1. Uskoo olevansa vaarassa	☐	☐	☐
2. Uskoo häneltä varastettavan	☐	☐	☐
3. Uskoo puolison olevan uskoton	☐	☐	☐
4. Kutsumattomat vieraat	☐	☐	☐
5. Ihmiset ovat vaihtuneet	☐	☐	☐
6. Asunto ei ole koti	☐	☐	☐
7. Uskoo tulevansa hylätyksi	☐	☐	☐
8. Puhuu TV:n esiintyjille	☐	☐	☐
9. Muu harhaluulo	☐	☐	☐

Yleisyys _____
Vaikeusaste _____
Stressi _____

B. Aistiharhat	**K**	**E**	**EA**
1. Kuulee ääniä	☐	☐	☐
2. Puhuu olemattomille	☐	☐	☐
3. Näkee harhoja	☐	☐	☐
4. Haistaa harhoja	☐	☐	☐
5. Kosketustunnon harhoja	☐	☐	☐
6. Maistaa harhoja	☐	☐	☐
7. Muita aistiharhoja	☐	☐	☐

Yleisyys _____
Vaikeusaste _____
Stressi _____

C. Levottomuus/aggressiivisuus	**K**	**E**	**EA**
1. Hermostuu ihmisistä, vastustaa hoitoa	☐	☐	☐
2. Itsepäinen	☐	☐	☐
3. Yhteistyöhaluton	☐	☐	☐
4. Vaikea käsitellä	☐	☐	☐
5. Huutaa tai kiroilee	☐	☐	☐
6. Paiskoo ovia, potkii	☐	☐	☐
7. Lyö toisia	☐	☐	☐
8. Muita oireita	☐	☐	☐

Yleisyys _____
Vaikeusaste _____
Stressi _____

D. Masentuneisuus/alakuloisuus	**K**	**E**	**EA**
1. Itkuinen	☐	☐	☐
2. Alakuloisen oloinen	☐	☐	☐
3. Vähättelee itseään	☐	☐	☐
4. Sanoo olevansa paha ihminen	☐	☐	☐
5. Lannistunut, ei tulevaisuutta	☐	☐	☐
6. Taakka perheelle	☐	☐	☐
7. Kuoleman toiveita	☐	☐	☐
8. Muita masennusoireita	☐	☐	☐

Yleisyys _____
Vaikeusaste _____
Stressi _____

E. Ahdistuneisuus	**K**	**E**	**EA**
1. Huolissaan tulevasta	☐	☐	☐
2. Kyvytön rentoutumaan	☐	☐	☐
3. Huokaileva, haukkoo henkeään	☐	☐	☐
4. Perhosia vatsassa, rytmihäiriöitä	☐	☐	☐
5. Välttämiskäyttäytymistä	☐	☐	☐
6. Ahdistuu erosta	☐	☐	☐
7. Muita ahdistusoireita	☐	☐	☐

Yleisyys _____
Vaikeusaste _____
Stressi _____

F. Kohonnut mieliala	**K**	**E**	**EA**
1. Liian tyytyväinen, onnellinen	☐	☐	☐
2. Epätavallinen huumorintaju	☐	☐	☐
3. Nauraa sopimattomasti	☐	☐	☐
4. Kertoo tylsiä vitsejä	☐	☐	☐
5. Tekee lapsellisia kepposia	☐	☐	☐
6. Kerskaileva	☐	☐	☐
7. Muita euforisia oireita	☐	☐	☐

Yleisyys _____
Vaikeusaste _____
Stressi _____

Neuropsykiatrinen haastattelu (NPI) 15/15

Pisteytysyhteenveto

Ohje: Lue haastattelua koskeva ohje ennen kysymysten esittämistä. Merkitse vastaukset tälle lomakkeelle ennen kuin arvioit oireiden yleisyyttä, vaikeusastetta tai niistä aiheutunutta stressiä.
K = oire esiintyy potilaalla, E = oiretta ei esiinny, EA = ei arvioitavissa.

G. Apatia	**K**	**E**	**EA**
1. Passiivinen	☐	☐	☐
2. Ei aloita keskustelua	☐	☐	☐
3. Ei osoita tunteitaan	☐	☐	☐
4. Ei osallistu kotitöihin	☐	☐	☐
5. Toiset ihmiset eivät kiinnosta	☐	☐	☐
6. Perheenjäsenet ovat yhdentekeviä	☐	☐	☐
7. Ei kiinnostu asioista kuten aiemmin	☐	☐	☐
8. Muita apatian merkkejä	☐	☐	☐

Yleisyys _____
Vaikeusaste _____
Stressi _____

H. Estottomuus	**K**	**E**	**EA**
1. Impulsiivinen	☐	☐	☐
2. Tekeytyy tuttavalliseksi	☐	☐	☐
3. Käyttäytyy tahdittomasti	☐	☐	☐
4. Käyttäytyy karkeasti	☐	☐	☐
5. Liiallisen avoin	☐	☐	☐
6. Koskettelee ja halailee	☐	☐	☐
7. Muita oireita	☐	☐	☐

Yleisyys _____
Vaikeusaste _____
Stressi _____

I. Ärtyneisyys	**K**	**E**	**EA**
1. Menettää malttinsa	☐	☐	☐
2. Nopeita mielialan vaihteluja	☐	☐	☐
3. Kiukunpurkauksia	☐	☐	☐
4. Kärsimätön	☐	☐	☐
5. Kärttyisä	☐	☐	☐
6. Riidanhaluinen	☐	☐	☐
7. Muita oireita	☐	☐	☐

Yleisyys _____
Vaikeusaste _____
Stressi _____

J. Poikkeava motorinen käyttäytyminen	**K**	**E**	**EA**
1. Kävelee ympäriinsä	☐	☐	☐
2. Penkoo paikkoja	☐	☐	☐
3. Toistuvaa riisuuntumista ja pukeutumista	☐	☐	☐
4. Toistotapoja	☐	☐	☐
5. Hypistelyä, näpräilyä	☐	☐	☐
6. Hermostunutta liikehdintää	☐	☐	☐
7. Muita poikkeavia motorisia oireita	☐	☐	☐

Yleisyys _____
Vaikeusaste _____
Stressi _____

K. Unen häiriöt	**K**	**E**	**EA**
1. Nukahtamisvaikeuksia	☐	☐	☐
2. Nousee ylös yön aikana	☐	☐	☐
3. Kuljeskelee yöllä	☐	☐	☐
4. Herättelee yöllä	☐	☐	☐
5. Pukeutuu yöllä	☐	☐	☐
6. Herää liian aikaisin aamulla	☐	☐	☐
7. Nukkuu paljon päivällä	☐	☐	☐
8. Muita unen häiriöitä	☐	☐	☐

Yleisyys _____
Vaikeusaste _____
Stressi _____

L. Ruokahalun ja syömisen häiriöt	**K**	**E**	**EA**
1. Menettänyt ruokahalunsa	☐	☐	☐
2. Ruokahalu lisääntynyt	☐	☐	☐
3. Paino laskenut	☐	☐	☐
4. Paino noussut	☐	☐	☐
5. Ruokailutavat muuttuneet	☐	☐	☐
6. Lempiruoat muuttuneet	☐	☐	☐
7. Syömisessä rituaaleja	☐	☐	☐
8. Muita ruokailuun liittyviä oireita	☐	☐	☐

Yleisyys _____
Vaikeusaste _____
Stressi _____

Appendix 5.

Cornellin masennusasteikko – dementiaoireisten muistisairaiden depression mittari

Nimi:_____ ***Syntymäaika:***_____

Pvm:_____ ***Arvioitsija:***_____

Pisteet yhteensä:_____ ***Pisteytys:*** ***a*** ***ei voida arvioida*** ***0*** ***ei esiinny***
1 ***lievä tai satunnainen*** ***2*** ***vakava***

Pisteytyksen tulee pohjautua oireisiin ja löydöksiin, jotka ovat esiintyneet haastattelua edeltäneen viikon aikana. Pisteytystä ei tehdä niistä oireista, jotka johtuvat fyysisestä kyvyttömyydestä tai sairaudesta.

A	**Mielialaan liittyvät oireet**			
1. Ahdistuneisuus vaikuttaa ahdistuneelta, hautoo asioita, huolestunut	**a**	**0**	**1**	**2**
2. Surullisuus vaikuttaa surulliselta, surullinen ääni, itkuinen	**a**	**0**	**1**	**2**
3. Ei reagoi miellyttäviin tapahtumiin	**a**	**0**	**1**	**2**
4. Ärtyisyys	**a**	**0**	**1**	**2**
B	**Käyttäytymisen oireet**			
5. Levottomuus vaikuttaa kiihtyneeltä, väantelee käsiään, repii hiuksiaan	**a**	**0**	**1**	**2**
6. Hidastuminen hitaat liikkeet, hidas puhe, hitaat reaktiot	**a**	**0**	**1**	**2**
7. Moninaisten ruumiillisten oireiden valittaminen (pisteytys 0, jos vain vatsavaivoja)	**a**	**0**	**1**	**2**
8. Mielenkiinnon menetys osallistuu vähemmän tavanomaisiin toimintoihinsa (pisteytetään vain, jos muutos tapahtunut alle kuukauden aikana)	**a**	**0**	**1**	**2**
C	**Ruumiilliset oireet**			
9. Ruokahaluttomuus syö tavallista vähemmän	**a**	**0**	**1**	**2**
10. Laihtuminen (pisteytys 2, jos paino pudonnut yli 2 kg kuukauden aikana)	**a**	**0**	**1**	**2**
11. Energian puute uupuu helposti, ei jaksa ylläpitää aktiviteetteja (pisteytetään vain, jos muutos tapahtunut alle kuukauden aikana)	**a**	**0**	**1**	**2**
D	**Vuorokauden rytmiin liittyvät oireet**			
12. Mielialaoireet pahempia aamuisin	**a**	**0**	**1**	**2**
13. Nukahtaa myöhemmin kuin tavallisesti	**a**	**0**	**1**	**2**
14. Heräilee tavallista useammin yön aikana	**a**	**0**	**1**	**2**
15. Herää aikaisemmin kuin tavallisesti	**a**	**0**	**1**	**2**
E	**Vääristyneet mielikuvat**			
16. Itsetuhoisuus ei koe elämäänsä elämisen arvoiseksi, itsemurha-ajatuksia tai itsemurhayritys	**a**	**0**	**1**	**2**
17. Itsetunnon menetys moitiskelee itseään, huono omanarvontunne, epäonnistumisen tunteita	**a**	**0**	**1**	**2**
18. Pessimismi odottaa pahinta	**a**	**0**	**1**	**2**
19. Masentunutta mielialaa ilmaisevat harhaluulot	**a**	**0**	**1**	**2**