Polypharmacy in prodromal Alzheimer's disease

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Dementia and polypharmacy have been shown to be prevalent in elderly people. Polypharmacy has been previously associated with cognitive impairment and dementia in older populations. Prodromal Alzheimer's disease (AD), an early predementia phase of AD, is characterized by cognitive symptoms not severe enough to hinder activities of daily living. Prodromal AD was first described in the International Working Group (IWG-1) criteria, referring to early episodic memory impairment plus biomarker evidence from CSF and/or imaging for AD pathology confirmation. The objective of this study was to investigate the prevalence of polypharmacy in prodromal AD and the association of polypharmacy with cognitive and functional outcomes.

The Multimodal Preventive Trial for Alzheimer's disease (MIND-ADmini) is a randomized control trial that recruited participants with prodromal AD, which was defined according to IWG-1 criteria (episodic memory impairment and biomarker evidence for underlying AD pathology). Episodic memory disorder was defined as performance below one standard deviation (SD) on two out of eight cognitive tests (at least one memory). Evidence for underlying AD pathology was defined by either CSF biomarkers (beta amyloid 1-42/1-40 ratio less than 1 and /or elevated total tau and /or elevated phsopho-tau and /or low beta amyloid 1-42 based on local lab cutoffs) or medial temporal lobe atrophy on brain MRI or abnormal FDG-PET and /or Pittsburgh compound B (PiB) PET compatible with AD type change. Data from the screening/baseline visit (before the start of the intervention) were used from the first 62 recruited participants in Finland and Sweden. Polypharmacy was defined based on numerical definition (≥5 medications). Medication data were collected and verified by the study nurse, and were ATC coded as part of the present study. Statistical analysis was performed using IBM-SPSS software version 25. T-test, chi-square and Mann Whitney test were used to investigate differences between the groups with and without polypharmacy. Linear regression and binary logistic regression were used to investigate associations between polypharmacy and cognitive and functional outcomes.

The prevalence of polypharmacy was 43.5% in this MIND-ADmini prodromal AD population, a percentage that seems to be in between prevalence values previously reported for older general populations and populations with dementia. The most common medications were cardiovascular (e.g. antihypertensive and lipid-lowering drugs), and nervous system-related (e.g. hypnotics and sedatives, antidepressants, and also antidementia drugs). No statistically significant association between polypharmacy and cognitive and functional outcomes was found in the present study.

In conclusion, polypharmacy was prevalent in prodromal AD. The potential impact of polypharmacy on cognitive and functional outcomes in prodromal AD needs to be further studied in larger populations including follow-up data.

CONTENTS

ABBREVIATIONS

AD	Alzheimer's disease
ADL	Activities of daily living
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders-fourth edition
NINCSD-ADRDA	National Institute of Neurological Disorders and Stroke-Alzheimer Disease and Related Disorders
IWG	International Working Group
NIA-AA	The National Institute on Aging and Alzheimer's Association
CSF	Cerebrospinal fluid
PET	Positron Emission Tomography
MTL	Medial temporal lobe
MRI	Magnetic Resonance Imaging
FDG	Fluorodeoxyglucose
Aβ	Amyloid beta
MCI	Mild Cognitive Impairment
CERAD	Consortium to Establish a Registry for Alzheimer's disease
MMSE	Mini-Mental State Examination
YLD	Years Lived with Disability
APOE	Apolipoprotein
APP	Amyloid precursor protein
EOAD	Early onset Alzheimer's disease
LOAD	Late onset Alzheimer's disease
PSEN	Presenilin
PIMs	Potential Inappropriate medications
MAI	Medication Appropriateness Index
HEDIS	Healthcare Effectiveness Data and Information Set
STOPP	Screening Tool of Older Person's Prescriptions
START	Screening Tool to Alert to Right Treatment
ADR	Adverse Drug Reactions
ADE	Adverse Drug Effect
OTC	Over the Counter

FINGER	Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability
FCSRT	The Free and Cued Selective Reminding Test
WMS-R	Wechsler Memory Scale-Revised
TMT	Trail Making Test
NTB	Neuropsychological Test Battery
CDR	Clinical Dementia Rating
ADCS-ADL	Alzheimer's Disease Cooperative Study- Activities of Daily Living
LDD	LipiDiDiet
BMI	Body Mass Index
ATC	Anatomical Therapeutic Chemical
CDR-SB	Clinical Dementia Rating-sum of boxes

1 INTRODUCTION

Alzheimer's disease (AD) is a progressive neurodegenerative disorder, characterized by memory decline and deterioration of other cognitive functions, such as language and reasoning, changes in mood and behavior, and impairment in activities of daily living (ADL). AD is the most common cause of dementia, accounting for an estimated 60-80 percent of cases. Dementia is one of the leading causes of physical disabilities among older people (Alzheimer's Association 2019). The population is aging rapidly and around 50 million people are living with dementia worldwide now, with almost 60 percent living in low- and middle-income countries. Every year, around 10 million new cases are reported. Approximately, 5 to 8 out of 100 people aged 60 or over are living with dementia. The projected number of people with dementia is estimated to 82 million in 2030 and 152 million in 2050. Currently, there is no cure for AD and available treatments are primarily symptomatic (WHO 2019).

The clinical diagnosis of AD has been traditionally based on Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV) and National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer Disease and Related Disorders Association (NINCDS-ADRDA) criteria which require presence of dementia that is cognitive impairment severe enough to interfere with the ability to carry out daily activities (McKhann et al. 1984). Such a diagnosis is considered probable, as a definite diagnosis would require autopsy confirmation of the presence of beta amyloid plaques and neurofibrillary tau protein tangles, which are the hallmarks of AD pathology (Dubois et al. 2007). To enable an earlier diagnosis of AD before onset of dementia several research criteria have been proposed. All criteria incorporate AD biomarkers. The main idea for revised diagnostic criteria proposed by the International Working Group 1 (IWG-1) (Dubois et al. 2007), International Working Group 2 (IWG-2) (Dubois et al. 2014), The National Institute on Aging and Alzheimer's Association (NIA-AA 2011) (Albert et al. 2011) and NIA-AA 2018 (Jack et al. 2018), is to diagnose earliest stages of AD even years before onset of dementia. These biomarkers include beta amyloid accumulation (decreased cerebrospinal fluid, CSF levels of beta amyloid; increased uptake of amyloid specific tracers in Positron Emission Tomography, PET), and other markers e.g. increased CSF level of total tau and phosphorylated tau; medial temporal lobe (MTL) atrophy on structural magnetic resonance imaging (MRI); hypometabolism of fluorodeoxyglucose (FDG) PET (Dubois et al. 2007). The different research criteria use different terminologies and biomarkers in different combinations to classify individuals based on their probability of having AD and its severity as well. Criteria are still evolving, and these are research criteria which are still not used in routine clinical practice.

The earliest symptomatic predementia phase of AD which usually includes mild cognitive impairment is prodromal AD. Prodromal AD was first described in the IWG-1 criteria and is characterized by symptoms not severe enough to hinder activities of daily living (Dubois et al. 2007) Prodromal AD refers to early episodic memory impairments plus biomarker evidence from CSF and/or imaging for pathologic confirmation (Dubois et al. 20017, Dubois et al. 2014).

It has been estimated that up to half of cognitively normal individuals older than 60 years may have some degree of beta amyloid deposition in the brain. The prevalence of amyloid positivity seems to be even higher in people with mild cognitive symptoms (Jansen et al. 2015). However, this is still a new area of research, and the prevalence and clinical characteristics of prodromal AD have not yet been fully investigated.

Polypharmacy is commonly reported in older people who are more likely to have multimorbidity, which is a chronic state of two or more diseases (Corcorn 1997). Aging related changes can impact pharmacokinetics and pharmacodynamics. Comorbidity and medication use may contribute to increased risk of adverse events (Le Couteur et al. 2012). Clinically, significant adverse outcomes of medication use in older people are e.g. adverse drug reactions, fractures, and hospitalization, physical and cognitive impairments (Hilmer et al. 2012). While there is evidence on the association of polypharmacy and adverse outcomes in older people, there is no general agreement about the actual number of medications that would be defined as polypharmacy (Gnjidic et al. 2012). In the literature, the most commonly reported definition of polypharmacy is five or more medications used daily by a patient (Masnoon et al. 2017). Although polypharmacy is defined mainly by number of medications used daily, sometimes it has been associated with other descriptive characteristics, e.g. appropriateness of medication prescription (Masnoon et al. 2017), duration of therapy, and type of healthcare setting (e.g. in-patient or out-patient settings) (Sganga et al. 2014).

Older people are at higher risk of both AD and polypharmacy. Present literature illustrates that polypharmacy has been mostly studied in relation to dementia, e.g. associations between polypharmacy and cognitive impairments in patients with incident dementia (Soysal et al. 2019), impact of polypharmacy on progression of dementia (Zgheib et al. 2018), and prevalence of polypharmacy in people with dementia versus without dementia (Kristensen et al. 2014). Polypharmacy with respect to appropriateness and inappropriateness of prescription has also been investigated in few studies in people with dementia to find out prevalence and impact (Disalvo et al. 2018). The main conclusion found in most studies was that polypharmacy is highly prevalent in people with dementia and has potential to negatively influence disease progression (Leelakanok &

D'Cunha 2018). Mostly cohort study design (Soysal et al. 2019), cross sectional design (Zgheib et al. 2018), and/or case control design (Park et al. 2017) have been used in the literature.

Given that polypharmacy has not been investigated before among individuals with prodromal AD, this thesis focuses on characterizing this recently defined population in terms of medication use.

2. LITERATURE REVIEW

2.1 Alzheimer's disease (AD)

2.1.1 Definition

Alzheimer's disease (AD) is a neurodegenerative disorder, characterized by memory decline and deterioration of other cognitive functions, such as language and reasoning, changes in mood and behavior, and impairment in activities of daily living (ADL). It is estimated that 60 to 80 percent cases of dementia are caused by AD (Alzheimer's Association 2019).

AD is progressive disorder. It is assumed that early clinical symptoms may include apathy, forgetting recently visited places, persons and conversations. Disorientation, confusion, poor decision-making, fluctuations in mood, uncomfortable walking, swallowing, speaking and communication might be later stage symptoms of AD (Alzheimer's Association 2019). However, brain pathology may start long before the onset of the first clinical symptoms.

The US Alzheimer's Association and the National Institute of Aging of the National Institute of Health has proposed three stages of the AD disease continuum (Alzheimer's Association 2019). The first stage is preclinical and might last for ten years or more. This preclinical stage has been described as an asymptomatic period that starts with brain pathology until the appearance of initial symptoms. The second stage of mild cognitive impairment (MCI) has been described as a phase with both brain pathology and symptoms, during which individuals can still perform daily activities without assistance. The third stage of Alzheimer's disease is dementia, a phase with brain pathology and symptoms severe enough to hinder ADL (Dubois et al. 2007).

The earliest symptomatic predementia phase of AD which usually includes mild cognitive impairment has also been defined as prodromal AD. Prodromal AD was first described in the IWG-1 criteria and is characterized by symptoms not severe enough to hinder activities of daily living (Dubois et al. 2007). Prodromal AD refers to early episodic memory impairments plus biomarker evidence from CSF and/or neuroimaging for pathologic confirmation (Dubois et al. 2007, Dubois et al. 2014).

It has been estimated that up to half of cognitively normal individuals older than 60 years may have some degree of beta amyloid deposition in the brain. The prevalence of amyloid positivity seems to be even higher in people with mild cognitive symptoms (Jansen et al. 2015). However, this is still a new area of research, and the prevalence and clinical characteristics of prodromal AD have not yet been fully investigated.

2.2.2 Diagnosis

AD dementia is diagnosed clinically by evaluating cognitive symptoms along with brain changes by neuroimaging techniques. Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV) has been used to diagnose AD dementia. DSM-IV criteria include memory impairment and cognitive disturbances; aphasia (language disturbance), apraxia (disturbed motor activities although intact motor action), agnosia (impairment of identifying things although intact sensory function), disturbance in executive functions (that is planning, organizing, sequencing and abstracting). Progressive cognitive impairment leads to impaired social and professional activities. DSM-IV criteria for diagnosis of AD ruled out cognitive impairment caused by other central nervous system disorders (e.g., cerebrovascular disease, Parkinson's disease etc.), systemic conditions (e.g., hypothyroidism, vitamin B_{12} or folic acid deficiency, HIV infection), substance-induced conditions, and major depressive disorder (American Psychiatric Association 2013).

The National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria proposed three terms for dementia caused by AD, i.e. probable AD dementia, possible AD dementia (for clinical settings), and probable or possible AD dementia with evidence of AD pathophysiology (for research). Histopathological certification was required for definite diagnosis of AD. Assessment of cognitive impairment was proposed to cover different cognitive domains that are memory, language, skills, attention, orientation, constructive abilities, functional abilities and problem solving (McKhann et al. 2011).

There are currently a variety of test batteries and assessment scales for impairment in cognition and daily life functioning, and assessment batteries in routine clinical use can vary between clinics and countries. For example, the Mini-Mental State Examination (MMSE) is one of the most used tests. CERAD (Consortium to Establish a Registry for Alzheimer's Disease) has developed standard recommendations for cognitive evaluation (Fillenbaun et al. 2008). In Finland, national guidelines mention e.g. CERAD and MMSE testing (Finnish Medical Association Duodecim 2017).

Diagnosis of AD requires neuropsychological tests for cognitive function, assessment of ADL, and can also be based on laboratory testing of cerebrospinal fluid (CSF) biomarkers, magnetic resonance imaging (MRI), positron emission tomography (PET) and genetic testing as appropriate. In addition, other laboratory evaluations may be performed as needed, e.g. blood counts, electrolytes, blood glucose, liver function test, renal function test, calcium phosphate, thyroid function test, vitamin B_{12}, folate and C-reactive protein (Li et al. 2008).

DSM-IV and NINCDS-ADRDA criteria have been traditionally used which require presence of dementia and such a diagnosis is considered probable as a definite diagnosis would require autopsy confirmation of presence of biomarkers (Dubois et al. 2007). To enable an early diagnosis of AD before onset of dementia several newer criteria have been proposed. The main idea for revised diagnostic criteria proposed in International Working Group (IWG-1) (Dubois et al. 2007), International Working Group (IWG-2) (Dubois et al.2014), The National Institute on Aging and Alzheimer's Association (NIA-AA 2011) (Albert et al. 2011), and NIA-AA 2018 (Jack et al. 2018), is to diagnose earlier stages of AD (including prodromal AD) even years before onset of dementia.

2.2.3 Neuropathological Findings

The exact causes of AD are not yet fully clear. The main pathological hallmarks associated with AD are beta amyloid plaques (extracellular) and tau tangles (intracellular).

Amyloid beta plaques have been initially proposed as causative of AD, and hypothesized to lead to neurofibrillary tangles, neuronal loss, and dementia (Hardy and Higgins 1992). The amyloid hypothesis was later revised, and focus was shifted towards soluble amyloid beta oligomers which form fibril deposits. Amyloid beta along with tau accumulation have synergistic toxic impact on synaptic function. Tau tangles have been linked to synaptic dysfunction (Li et al. 2018), and there is also a tau hypothesis of AD where it is assumed that tau pathology has a central role in the disease process (Cotman et al. 2005). In addition to amyloid and tau pathology, other pathological processes such as inflammation, oxidative stress, vascular dysfunction, or dysfunction of lipid metabolism have been associated with AD (Butterfield & Halliwell 2019).

The presence of AD-related pathology can be currently assessed in vivo using e.g. CSF or neuroimaging biomarkers. Atrophy of medial temporal lobe (MTL) can be visualized on MRI and is often used in clinical practice to aid with AD diagnosis. Although MTL atrophy on MRI was part of the IWG-1 criteria, it was not included in the IWG-2 criteria for AD due to concerns related to specificity, since MTL and hippocampal atrophy may have other causes than AD (Dubois et al. 2014). AD specific biomarkers in CSF are low amyloid beta concentration and increased concentration of

total and phosphorylated tau proteins. Reduction in glucose metabolism on PET in bilateral temporal parietal and posterior cingulate regions has been considered as distinguishing feature of AD (Dubois et al. 2007). In addition, amyloid and tau accumulation in the brain can be visualized using specific PET tracers. While amyloid-PET is already available for clinical use, tau-PET is still under development.

2.2.4 Epidemiology

Prevalence and incidence of dementia are estimated as higher in low- and middle-income countries than high income countries. Proportionate increase in number of people with dementia aged 60 years or more have been estimated from 2015 to 2050 in Asia 194 percent, Asia Pacific high-income 115 percent, Central Asia 184%, East Asia 193%, South Asia 225%, Europe 78%, and Africa 291%. Approximately every 3 seconds a new case of dementia is reported (World Alzheimer Report 2015).

The population is aging rapidly and around 50 million people are estimated to be living with dementia worldwide now, with almost 60% living in low and middle-income countries. Every year, around 10 million new cases are reported. Approximately 5 to 8 out of 100 people aged 60 years or over have dementia. The projected number of people with dementia has been proposed to 82 million in 2030 and 152 million in 2050 (Alzheimer's Association 2019). It is predicted by using system dynamics model based on data from Eurostat that population suffering with AD in EU may be almost 8.8 million in 2020, 10.8 million in 2030, 13.1 million in 2040, 14.9 million in 2050, and 15.4 million in 2060 (Tomaskova et al. 2016).

2.2.5 Impact

Alzheimer's disease is predicted as the fifth leading cause of death in people aged 65 years or older worldwide.AD is a leading cause of disability and morbidity worldwide. As the disease progresses, individuals experience decreased ADL and significantly increased risk of acute conditions that make it hard to distinguish between death with AD dementia and death from AD dementia. Death certificates usually mentioned the main cause of death as e.g. pneumonia rather than death caused by AD, although AD might have played a role to cause that acute disease. It has been estimated that deaths from AD have increased 145 % between 2000 to 2017worldwide (Alzheimer's Association 2019). International guidelines and changes in the definition of causes of death have during the past years led to more accurate estimates. For example, among older individuals in Finland, dementia was the third leading cause of death after cardiovascular diseases and cancer in 2017 (Statistic Finland 2017).

AD causes functional disabilities, which result in years of life loss. Dementia is the second leading cause of disabilities and approximately contributes to 13.1% to Years Lived with Disability (YLD) (World Alzheimer Report 2015). The increase in incidence and prevalence of AD increases disease burden and in turn increases cost of care and financial burden on society as well (Alzheimer's Association 2019).

It was estimated that 604 billion US dollars was the cost for dementia in 2010 worldwide. This increased to 817.9 billion US dollars in 2015 and it is forecasted to increase up to 2000 US dollars in 2030 (World Alzheimer Report 2015). Cost contributing factors are caregiving, long term hospital stays due to impaired ADL along with treatment. It was approximated that more than 18.5 billion hours of caregiving have been utilized for patients with AD and dementia, which contribute to 234 billion US dollars. Forecast of 290 billion US dollars for AD and dementia in 2019 was estimated (Alzheimer's Association 2019).

2.2.6 Risk Factors

AD, like other complex chronic diseases, may result from multiple factors rather than a single cause. Some factors are modifiable while others are non-modifiable risk factors for AD.

2.2.6.1 Non-modifiable risk factors

In consideration with age, AD is categorized into early onset, EOAD before 65 years, and late onset of AD, LOAD after 65 years. EOAD accounts for 1-5% of cases while LOAD is estimated more than 95%. EOAD follows Mendelian pattern of inheritance while the risk of LOAD is enhanced in a non-Mendelian way (Reitz & Mayeux 2014).

Amyloid precursor protein (APP) breakdown and amyloid beta protein formation is controlled by three genes (APP, PSEN1 and PSEN2) that have been strongly associated in pathophysiology of EOAD. People with inherited mutations in amyloid precursor protein and presenilin 1 are assured to develop the disease, while for presenilin 2 they have 95% probability of AD (Reitz & Mayeux 2014).

LOAD risk factors include age, APOE e4 and family history (Rahman et al. 2019). Age is the strongest risk factor for AD dementia among non-modifiable risk factors. However, AD dementia is not normal aging and older age is not enough to cause AD. AD risk is also influenced by the e2, e3, and e4 polymorphic alleles of the apolipoprotein E (APOE)gene. Among alleles, e4 carrier individuals are at higher risk (Liu et al. 2013).

Prevalence of AD and other dementias is higher in women than men especially in elderly population (Winblad et al. 2016). Women are at higher risk of AD dementia than men. It has been hypothesized that this may be at least partly due to higher life expectancy in women, although there may be other causes as well (Liu et al. 2013).

2.2.6.2 Modifiable risk factors

Several modifiable risk factors for AD have been described in the literature (Winblad et al. 2016). Some of the most investigated factors are summarized in Table 1.

Active smoking and previous smoking are significantly associated with increased risk of AD (Durazzo et al. 2014). It has been estimated that lifetime smoking may lead to 70% higher risk for AD. Smoking has been associated with LOAD by reducing the period of preclinical phase to younger age by enhancing smoking-induced oxidative stress, which ultimately promotes AD pathophysiology (Durazzo et al. 2014).

Risk factors for cardiovascular diseases, e.g. hypertension, have also been associated with higher risk of dementia (Alzheimer's association 2019). It has been hypothesized that midlife high blood pressure may interfere with cerebrovascular function by damage to vessels and may thus influence cognitive function and amyloid regulation. The mechanisms by which hypertension increases AD risk are still not fully clarified (Iadecola 2014). There is evidence that treatment of hypertension might decrease the risk of AD and dementia (Williamson et al. 2019) although conflicting findings exist as well (Middelaar et al. 2018).

An association between hypercholesterolemia and increased risk of AD has been reported, especially for midlife high serum cholesterol levels. Findings are however more mixed for cholesterol at older ages. Some studies have reported that associations between serum total cholesterol and dementia might be bidirectional (Solomon et al. 2007). Statins, lipid-lowering drugs, were found associated to decreased amyloid plaque burden (Serrano-Pozo & Growdon 2019). However, a Cochrane review on statins had concluded no significant relation between use of statins and dementia (McGuinness et al. 2009).

Diabetes may be associated with AD and high risk of dementia through impaired glucose metabolism in the brain, as well as through increased risk of vascular pathology (Alzheimer's association 2019). Some longitudinal studies have shown positive association between midlife diabetes mellitus and risk of LOAD. In interventional studies, metformin (antidiabetic medicine) was suggested to have a protective effect in mild MCI and early stage AD (Serrano-Pozo & Growdon 2019).

Physical inactivity and obesity have been indicated as risk factors for AD and dementia (Alzheimer's association 2019). Several studies have reported that low level of physical activity and high body mass index and or waist-to-hip-ratio increased the risk for AD and dementia. Since these factors are modifiable, an increase in physical activity and decrease in obesity may result in a beneficial impact on the onset of AD and dementia (Serrano-Pozo & Growdon 2019).

Healthy dietary habits, including e.g. consumption of fruits, vegetables, fish and whole grain cereals, have been associated with protective effect on MCI, AD and dementia. In contrast, high consumption of sugar and saturated fats has been associated to higher risk of AD and dementia (Scarmeas et al. 2018).

Association between alcohol drinking and dementia is not simple to understand as many confounding factors like education and financial status, physical activity and diet, may play role as well (Serrano-Pozo & Growdon 2019). According to available literature, moderate alcohol drinking might have a protective effect while heavy drinking has been associated with elevated risk of AD and dementia (Scarmeas et al. 2018).

People with low level of education have been shown to have higher risk of AD and dementia (Serrano-Pozo & Growdon 2019), while higher education has been associated with reduced risk of AD (Larsson et al. 2017). Education helps the brain function more efficiently by developing cognitive reserve which plays a protective role. Chronic traumatic encephalopathy and traumatic brain injury have been indicated as risk factors for Alzheimer's dementia. Brain health has been reported to improve with social and cognitive activities which may support to reduce risk to Alzheimer's dementia (Alzheimer's association 2019). These modifiable factors are associated with lifestyle, and AD and dementia risk may be reduced by developing healthier lifestyle patterns through e.g. education, involvement in social activities and with healthy dietary intake.

Glucocorticoid secretion level with stress has been associated with neuronal dysfunction, cognitive disorders and mood disorders like depression. Chronic stress and depression have been reported to increase the risk of AD. Glucocorticoid secretion might be involved in the pathology of AD (Sotiropoulos 2015). Findings regarding the role of activated microglia in AD pathology and reported effects of regular long-term use of anti-inflammatory medicines have provided evidence that inflammation may have an important role as a risk factor for AD in late life (McGeer et al. 2016).

Table.1 Risk factors of AD

Risk factors of AD

Modifiable	Non-Modifiable
Smoking	Age
Hypertension	Gender
Hypercholesterolemia	Genetics
Diabetes	
Physical inactivity	
Obesity	
Diet	
Alcohol drinking	
Level of education	
Stress	
Social activities	

Physical activity, tobacco cessation, dietary and nutritional interventions, social activities and management of hypertension, diabetes, and high cholesterol have been included in the recent World Health Organization guidelines to decrease risk of dementia (WHO 2019).

2.2 Polypharmacy

2.2.1 Introduction

Multimorbidity, co-existence of two or more chronic health conditions, has been observed to be more prevalent in older populations (Salive 2013). The number of older people living with multimorbidity is significantly increasing as life expectancy has increased with the development of health care, resulting in an increased burden of multimorbidity. Multiple chronic conditions make therapeutic management more complex and decrease quality of life. Multimorbidity treated with multiple medicines is commonly referred to as polypharmacy (Masnoon et al. 2017). The cut off of 5 medications has been found to be associated with adverse drug reactions such as functional disability, falls, weakness and death (StatPearls 2019).

There is no unanimous definition for polypharmacy. The most reported definition is use of five or more medications in existing literature.

2.2.2 Types

Many terms have been used to define polypharmacy.

Polypharmacy and associated terms have been categorized based on:

1. Number of medicines used daily (Numerical only)

Based on number of medicines used, polypharmacy and associated terms were classified in available literature as shown in Table 2:

Table.2 Types of polypharmacy based on number of medicines. (Masnoon et al. 2017).

Type of polypharmacy	Number of medicines
Polypharmacy	2 to 11 or more
Minor	2-4
Moderate	4-5
Major	≥ 5-9, ≥ 6-9
Hyper, excessive, or severe	≥ 10

Wide variability in defining polypharmacy and associated terms exists in literature, ranging from two to eleven medications used daily by a patient. Most commonly polypharmacy is defined as five or more medications used daily, and second most common definition is six or more medications used daily. Number of medications remains the main focus, while most studies do not consider whether medications belong to the same class or different classes (Masnoon et al. 2017).

2 Based on number of medicines used in given duration of therapy or health care setting, polypharmacy has been categorized as shown in Table 3:

Table.3 Types of polypharmacy based on duration of medicines used. (Masnoon et al. 2017).

Type of polypharmacy	Number of medicines and duration
Polypharmacy	≥ 2 for > 240 days, > 5 for ≥ 90 days, ≥5 at hospital discharge
Major	≥ 10 medications in a year
Hyper	≥ 10 for ≥ 90 days
Excessive	≥ 10 in same quarter of a year
Persistent	≥ 5 for 181 days
Chronic	≥ 5 in 1month for 6 months in a year

Numerical definitions of polypharmacy incorporating duration of therapy or healthcare setting are less used as compared to numerical only definitions of polypharmacy. This type of definitions ranges from two or more medications for more than 240 days to five to nine medications used for 90 days or more (Nishtala & Salahudeen 2015). Polypharmacy incorporating healthcare setting include e.g. five or more medications at hospital discharge or use of ten or more medications during hospital stay (Sganaga et al. 2014).

Descriptive definitions of polypharmacy are least used. Different wordings to convey similar meanings of polypharmacy have been used, for example co-prescribing multiple medications and simultaneous and long-term use of different drugs by the same patient, while some studies have

referred to medications being appropriate or inappropriate clinically for the patient (Masnoon et al. 2017).

3 Descriptive definitions of polypharmacy are shown in Table 4:

Table.4 Types of polypharmacy based on descriptive definitions. (Masnoon et al. 2017).

Type of polypharmacy	Description
Polypharmacy	Use of many medicines, potential inappropriate medications, medication duplication.
Appropriate	Use of medications agrees with best evidence
Rational	Legitimate prescribing, indiscriminate prescribing refers to inappropriate prescribing.
Pseudo	Recording more medications than actual

Most of the studies in present literature focused on prevalence of polypharmacy and prevalence of inappropriate prescribing or inappropriate polypharmacy. There are many tools available to evaluate inappropriate medications or polypharmacy, e.g. 46 tools were described in a systematic review (Parsons 2017). Among these few have been used commonly which are briefly described below:

- Beers Criteria have been used most to evaluate potentially inappropriate medications (PIMs). It includes lists of PIMs which need to be avoided in elderly population, and also drugs which need dose adjustments based on kidney function in older adults and drug-drug interactions (American Geriatric Society 2015).
- Another criterion to evaluate inappropriate medications or prescribing is STOPP&START. Screening tool of older person's prescriptions (STOPP) and screening tool to alert to right treatment (START) have been designed to determine potential errors in prescribing and adverse drug reactions. 65 STOPP and 22 START criteria were published (Mahony et al. 2010).

Other criteria include Medication Appropriateness Index (MAI), Healthcare Effectiveness Data and Information Set (HEDIS) etc. (Masnoon et al. 2017).

2.2.3 Causes

Some commonly observed reasons for polypharmacy are (Kaur 2013):

- Multimorbidity in general and specifically in older age groups requires multiple medications to treat different health conditions.
- Patients in low socioeconomic status areas have been found to be following different prescriptions at the same time due to switching physicians frequently.
- Self-medication with OTC drugs and herbal products usage without concern for contraindications and side effects.
- Few physicians do prescribe medicines with monopoly with local companies to make revenue or malpractice.

2.2.4 Concerns of polypharmacy

Polypharmacy raises important concerns in older population groups due to the below mentioned reasons.

Multimorbidity is associated with physiological and pathological changes which increase the risks of polypharmacy. Adverse drug reaction (ADR) is harmful or unwanted reaction of drug at normal dose while adverse drug effect (ADE) is harmful reaction of drug not at normal dose (WHO 1972). Preventable ADEs are due to inappropriate medication use in elderly patients. Elderly people have changed metabolic and drug clearance rates. Drug classes commonly associated with preventable ADEs are e.g. cardiovascular, anticoagulant, hypoglycemic, diuretics, and NSAIDs. (StatPearls 2019).

Change in response to a drug due to the presence of another drug is drug-drug interaction. Its probability is increased in the case of polypharmacy. The most reported drug-drug interaction outcomes are neuropsychological dysfunctions, acute renal dysfunction and hypotension. (Mere & Paauw 2017).

An ADE can be mistaken for a new health condition to be treated, which increases the prescribing cascade. Common examples of such symptoms are fatigue, sleepiness, low mood, decreased activeness, constipation, diarrhea, loss of ADL etc. (StatPearls 2019).

Some drugs and polypharmacy have been associated with falls and hip fractures in elderly people. Over the counter (OTC) drugs like analgesics, laxatives, minerals and vitamins, have been found to

be prevalent at older ages. Safety of OTC medications has not been regulated to the same standards as for prescription medications. Herbal medicine is also another risk factor in elderly people as herb-drug interactions are not monitored (StatPearls 2019).

Transition in care regarding settings like home, hospital, nursing home or frequent change of family physicians puts patients at higher risk of inappropriate polypharmacy. Change in pharmacokinetics and pharmacodynamics at older ages also put people at increased risk of negative outcomes of polypharmacy (StatPearls 2019).

2.2.4 Polypharmacy and dementia

For an overview of the extensive available literature on polypharmacy and dementia, a PubMed search was conducted. The search criteria were ((("polypharmacy"[MeSH Terms] OR "polypharmacy"[All Fields]) OR multimedications[All Fields]) AND ("dementia"[MeSH Terms] OR "dementia"[All Fields]) AND (systematic[sb] OR Review[ptyp]). The search result was 157 publications. On screening based on polypharmacy in people with or without dementia and relevance to polypharmacy resulted in 4 articles (3 systematic reviews and 1 review) (Table 5). On removing filters and sorting by repetition of studies, the resulted studies (11) including reviews focusing on prevalence, association or correlation of polypharmacy and dementia were added. Mostly, polypharmacy was studied with the aim to identify prevalence, and potential inappropriate medications in patients with or without dementia. Most of the studies concluded that polypharmacy was more prevalent in people with dementia than people without dementia, that polypharmacy was associated with dementia, and that it was also a risk factor for dementia.

Among 11 selected studies few being unique being unique in respect of geographical and socioeconomic bases relating to polypharmacy and dementia are described. A retrospective study of 218 nursing home residents with advanced dementia in Australia (IDEAL study) concluded that longer nursing home stay for residents with dementia was related to higher prevalence of inappropriate polypharmacy (Disalvo et al. 2018).

A cohort study in South London of 12148 participants with dementia concluded that polypharmacy was present in 39% individuals at time of dementia diagnosis (Soysal et al. 2019). A cross-sectional study of Danish people, aged 65 or older from 2000-2014, reported that prevalence of polypharmacy was higher in people with dementia than people without dementia (Kristensen et al. 2019).

A retrospective observational study of people with dementia in Taiwan's national health insurance research database found that about 10% of all patients were prescribed never appropriate medications at the end of their life (Chuang et al. 2017). A cross sectional study in UK of 10258 people with

dementia concluded that polypharmacy was highly prevalent (Claque et al. 2016). A case control study of a South Korean cohort from 2002-2013 reported that prolonged polypharmacy was linked to dementia (Park et al. 2017).

Table.5 Polypharmacy and dementia

Study	Type	Number of included studies	Population	Polypharmacy assessment	Results
Hukins et al. 2019	Systematic review	26	26534 people participated in 26 studies. 80% had dementia or cognitive impairment, 4% had MCI, 16% were controls without cognitive impairment.	Review followed recommendations of PRISMA, with aim to investigate prevalence of Potential inappropriate prescribing (PIP) and prevalence of polypharmacy.	Prevalence of polypharmacy ranged from 25% to 98% for people with dementia or cognitive impairment. Prevalence of PIP for one potential inappropriate medication (PIM) in people with dementia ranged from 14% to 74% and 11% to 44% for non-cognitively impaired controls.
Leelakanok and Cunha 2018	Systematic review and meta-analysis	7	Older population aged>65 years with dementia as outcome	Association between polypharmacy and dementia	Polypharmacy was strongly associated with dementia (pooled adjusted risk ratio (aRR)= 1.30 (96%CI:1.16-1.46), I^2 = 68%). Excessive polypharmacy was also strongly associated with

					dementia (pooled aRR =1.52 (95%CI:1.39-1.67), I^2 = 24%).
Redston et al. 2018	Systematic review	47 studies (European 42.6%, Asian 23.4%, Australian 12.8%, North Americans 8.5%).	Participants aged 65 years or older with and without cognitive impairment.	Review followed the recommendations of PRISMA, to study prevalence of PIMs defined by polypharmacy in older inpatients with and without cognitive impairment.	In studies investigating polypharmacy, prevalence of PIMs ranged from 53.2% to 89.8% and 30.4% to 97.1% for inpatients with and without cognitive impairment respectively.
Parsons 2017	Narrative review	11 studies	People with dementia	Review investigated prevalence of PIP and tools to assess the appropriateness of medication regimen, several medications and medication classes.	People with dementia were at higher risk of suboptimal prescribing and PIP. Review focused on anticholinergic, psychotropic, antibiotic, and analgesic medications, drug-drug and drug-disease interactions.

2.2.5 Polypharmacy and Mild cognitive imapirment

A PubMed search was conducted to identify studies on polypharmacy and MCI. The search strategy was (("polypharmacy"[MeSH Terms] OR "polypharmacy"[All Fields]) OR multimedications[All Fields]) AND ("cognitive dysfunction"[MeSH Terms] OR ("cognitive"[All Fields] AND "dysfunction"[All Fields]) OR "cognitive dysfunction"[All Fields] OR ("mild"[All Fields] AND "cognitive"[All Fields] AND "impairment"[All Fields]) OR "mild cognitive impairment"[All Fields]). The search resulted in 107 publications. On removing repetitions and based on relevance to polypharmacy and MCI, 4 studies were included (Table 6). All studies reported results showing that polypharmacy was associated with an increased risk of MCI / cognitive impairment.

Table.6 Polypharmacy and MCI

Study	Design and setting	Study population	Follow up	Polypharmacy assessment	Cognitive impairment assessment	Results
Khezrian et al. 2019	The Aberdeen 1936 Birth Cohort	498 dementia free individuals, Scotland	1999-2004	5 Or more medications	At age 64, cognitive ability was measured by AVLT, DS, BLK, RPM.	Prevalence of Polypharmacy was 12.3%. Polypharmacy was associated with impairment in cognition in older population (β=3.6, p=0.003)
Silay et al. 2017	Cross sectional	105 participants of age 65-74,75-84 and 85 or older years	Not applicable	Not applicable	Mini-Mental State Examination	Polypharmacy had significant correlation with MMSE score and a risk factor for cognitive impairment.
Niikawa et al. 2017	Mailed survey and home visit to collect	1270 people participated in interview and questionnaire in Tokyo, Japan	Not applicable	6 or more medications	MMSE measured by cognitive status and tests of memory, orientation, attention and language	Prevalence of polypharmacy was 28%, polypharmacy was associated with cognitive impairment (OR 1.83, 95% CI 1.10-3.02).
Cheng et al. 2018	Cross sectional	7422 participants of age 65 years or older of Taiwan	Not applicable	5 or more medications	MMSE, CDR	Polypharmacy was associated with 1.75-fold increased odds of MCI and 2.33- fold increased odds of dementia.

2.2.6 Polypharmacy and prodromal AD

No study was found in present literature using PubMed. The search terms used were ((("polypharmacy"[MeSH Terms] OR "polypharmacy"[All Fields]) OR multimedications[All Fields]) AND (prodromal[All Fields] AND Alzheime's[All Fields] AND ("disease"[MeSH Terms] OR "disease"[All Fields])).

3 AIMS

The first aim of this study was to investigate the use of medications and prevalence of polypharmacy in patients with prodromal AD. The second aim was to investigate the association between polypharmacy and cognitive and functional performance.

4 METHODS

4.1The MIND-ADmini trial

This study was conducted using the baseline data of participants included in the Multimodal Preventive Trial for Alzheimer's Disease (MIND-ADmini, clinicaltrials.gov identifier NCT03249688) a 6-month randomized controlled pilot trial ongoing in Sweden, Finland, Germany and France. Only screening/baseline data (before the start of the intervention) from the first Finnish and Swedish participants were available for the present study (N=62). The main aim of the trial is to evaluate the feasibility of a multidomain lifestyle intervention among patients with prodromal AD. In MIND-AD mini, participants were randomly divided into 3 groups. First group (control group) receives regular health advice (healthy lifestyle counseling). Second group receives a multidomain lifestyle intervention which includes nutritional guidance, exercise, cognitive training and monitoring and management of vascular and metabolic risk factors. The multidomain lifestyle intervention has been adapted from the Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER) trial (NCT01041989) (Ngandu et al. 2015). Third group receives multidomain lifestyle intervention plus medical food (Fortasyn Connect). Fortasyn Connect is a specific combination of nutrients containing omega-3 fatty acids docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA), uridine monophosphate, choline, vitamins B12, B6, C, E, and folic acid, phospholipids, and selenium (Soininen et al. 2017). AD has multifactorial etiology which is why a multidomain approach may be required for prevention of dementia. Multidomain lifestyle interventions have not been tested previously in prodromal AD. Fortasyn Connect was shown to have some beneficial effects on cognition and function in the LipiDiDiet study targeting prodromal AD (Soininen et al. 2017).

4.2 Study population

The study population in MIND-AD mini consists of patients with prodromal AD aged 60-85 years. Prodromal AD was defined according to the IWG-1 criteria (Dubois et al. 2007): mild episodic memory impairment and evidence for underlying AD-type pathology. Cognitive impairment was defined as -1 SD on 2 out of 8 neuropsychological tests of which at least 1 was a memory test. Memory tests were the Free and Cued Selective Reminding Test (FCSRT) delayed free recall (≤ 8 points), FCSRT free recall learning (≤ 22 points) , Wechsler Memory Scale-Revised (WMS-R), story delayed recall (≤ 75%), and WMS-R delayed recall of figures (≤ 75%). Non-memory tests were The Trail

Making Test (TMT) part A (≥ 60 seconds), TMT part B (≥ 150 seconds), Symbol Digit Substitution Test (≤ 35 points in 120 seconds), and Category Fluency ≤ 16 (points in 60 seconds).

Underlying AD pathology was defined as having at least one of the following AD-type biomarkers: cerebrospinal fluid (CSF) beta amyloid 1-42/1-40× 10 ratio < 1 and/or low beta amyloid 1-42 and/or elevated total tau and/or elevated phosphorylated tau ; MTA on magnetic, MRI, (MTA score 1 or higher); Fluorodeoxyglucose (FDG)-positron emission tomography (PET) or Pittsburgh Compound B (PIB)PET scan typical for AD.

Secondly, participants were required to have vascular and/or lifestyle-related risk factors, and thus, potential for lifestyle improvement. This was assessed with the lifestyle index (a score of 2 or more required for eligibility). The lifestyle index score was based on the following items (score was calculated by adding 1 point for each factor):

- Less than 2.5 hours a week of physical activity which leads to sweating and some breathlessness.
- Less than 5 portions of fruits and vegetables per day.
- Less than 2 portions of fish per week.
- Diagnosis of hypertension or current use of antihypertensive medications or systolic blood pressure > 140 mmHg or diastolic blood pressure > 90 mmHg.
- Diagnosis of diabetes or current use of antidiabetic treatment or elevated fasting blood glucose or Hb1Ac within the last 6 months.
- Sleep disturbances, depressive symptoms or stress symptoms for at least one month.

Participants were also required to have a MMSE score of at least 24 and a responsible study partner. People with dementia diagnosed according to DSM-IV, alcohol or drug abuse, a serious disease, major depression, severe loss of vision or communication inability, as well as those with a MRI scan showing signs of stroke, intracranial bleeding, mass lesion or NPH, were excluded from the trial. Other exclusion criteria were use of omega-3-products > 500mg EPA+DHA per day, regular intake of vitamin B6, B12, C, E, and/or folic acid > 200% RDI (recommended daily intake) without prescription, and simultaneous participation in other trials / recent participation within the last 30 days.

4.3 Assessment of cognitive and functional performance

Cognition was assessed at screening with Mini-Mental State Examination (MMSE) (range 0-30, higher scores reflecting better performance) (Folstein et al. 1975), and at baseline with the extensive Neuropsychological Test Battery (NTB) conducted by the psychologist (test scores converted to z-scores, higher scores reflecting better performance). Clinical Dementia Rating (CDR), based on interviews with the participants and their study partners, was performed at screening, and the sum of boxes (CDR-SB) was calculated (range 0-18, higher scores reflecting worse cognitive/functional performance) (O'Bryant et al. 2008). Functional ability was assessed using the Alzheimer's Disease Cooperative Study- Activities of Daily Living (ADCS-ADL) scale (structured interview with the study partner). ADCS-ADL scores range from 0 to 78, with higher scores reflecting better performance (Grill et al. 2015).

The NTB composite and domain-specific scores for memory, executive functioning, and processing speed were calculated as in previous studies (Ngandu et al. 2015, Soininen et al. 2017). Individual test scores were first converted to z scores standardized to baseline mean and SD and averaged to obtain the composite and domain-specific scores. NTB composite score (FINGER version) was based on 14 tests: 6 memory tests (WMS-Visual paired associates test immediate and delayed recall, WMS-Verbal memory immediate and delayed recall, CERAD 10-word list learning and delayed recall); 5 executive functioning tests (category fluency test, WMS-digit span, concept shifting test subtest C, Trail Making Test B-A, Stroop test 3-2), and 3 processing speed tests (letter digit substitution test, concept shifting test subtest A, Stroop test condition 2). NTB total score (LipiDiDiet version) was based on 16 tests; composite LipiDiDiet score included 5 of these tests (CERAD 10-word list learning, delayed recall and recognition, category fluency test, letter digit substitution test). Memory score was based on 3 tests (CERAD 10-word list learning, delayed recall and recognition) and executive functioning score on 4 tests (category fluency test, digit span, concept shifting test subtest C, letter digit substitution test).

4.4 Assessment of medication use and polypharmacy

Medication data (name, dosage) were self-reported data collected and verified at the screening/baseline visit by the study nurse or physician. Both prescription and non-prescription medications were recorded, as well as use of any dietary supplements and vitamin / mineral products. All the medications and supplements which were used by the study participants at baseline were coded according to ATC (Anatomical Therapeutic Chemical) classification system. Only one ATC code was assigned to each product; when necessary, information about dosage and indication was used to identify the correct code. Total number of medications (excluding vitamins, minerals, dietary

supplements) was calculated for each participant. Based on median number of drugs, as well as previous literature, participants were categorized into two groups: no polypharmacy (<5 medications) and polypharmacy (≥5 medications) (Masnoon et. al 2017).

4.5 Statistical Analysis

IBM SPSS software version 25 was used to analyze the data. The distribution of the variables was checked by normality test and by exploring histograms. To investigate differences in baseline characteristics between two groups, Independent sample T-test was performed for normally distributed scale variables (e.g. age, years of education); For continuous variables which were not normally distributed nonparametric Mann Whitney U-test was performed. chi-square test was used for categorical variables (e.g. gender, country). As MMSE, CDR-SB, and ADCS-ADL scores were not normally distributed, they were dichotomized based on median values (MMSE ≤ 27 and ≥28; CDR-SB ≤ 1 and ≥ 1.5; ADCS-ADL-total <76) and ≥ 76).

Linear regression was performed to analyze association between number of drugs / polypharmacy and cognition (NTB scores). Binary logistic regression was performed when analyzing MMSE, CDR-SB, and ADCS-ADL-total as outcomes. Three models were analyzed: model 1 was unadjusted, model 2 was adjusted for age, education, gender, and model 3 was adjusted for age, education, gender and country. Statistical significance was set at $p < 0.05$.

4.6 Ethical aspects

The MIND-ADmini trial received ethical approval from the local ethics committees in Finland, Sweden, France, and Germany. All participants and their study partners gave written informed consent before enrollment, and the trial is conducted in accordance with the Declaration of Helsinki and principles of Good Clinical Practice.

5. RESULTS

5.1 Baseline characteristics and use of medications

Table 7 illustrates the baseline characteristics of the study population. A sample of 62 participants from Kuopio (n=30), Finland, and Stockholm (n=32), Sweden was included. The mean number of drugs used by all participants was 4.7 (SD 3.6) and median was 4 (Range 0-14). The mean was 2.1 (SD 1.4) and median was 2 (range 0-4) in no polypharmacy group. The mean was 8.2 (SD 2.5) and median was 7 (range 5-14) in polypharmacy group. A significant difference was observed between no polypharmacy and polypharmacy groups (P-value <0.001). Mean age was 72.2 years (SD 6.2) in the whole study population, and participants in polypharmacy group were older than those in no

polypharmacy group (p=0.039). Study participants had on average 12.5 years of education and 50% were male; no differences were observed between the two groups.

Regarding cardiovascular and metabolic factors, a statistically significant between-group difference was observed in total cholesterol (p=0.047). The mean total cholesterol was 5.3 mmol/l (SD 1.4) in no polypharmacy group and 4.6 mmol/l (SD 1.1) in polypharmacy group. Similarly, the low-density lipoprotein (LDL) cholesterol was lower in the polypharmacy group (p=0.008).

Pulse, systolic blood pressure, diastolic blood pressure, body mass index, waist to hip ratio, high density lipoproteins, triglycerides, and fasting glucose were not significantly different in no polypharmacy and polypharmacy groups.

The median MMSE score in the whole study population was 27.00 (range 24-30), median CDR-SB score was 1.00 (range 0.00-4.50), and median ADCS-ADL-total score was 75.50 (range 61-78). Participants in the polypharmacy group tended to have slightly higher MMSE scores than those in the no polypharmacy group (p=0.05); no other between-group differences were observed in cognitive and functional performance.

Table 7. Baseline characteristics of the study population

Characteristics	Total n=62	No Polypharmacy n=35	Polypharmacy n=27	P-value
Number of drugs	4.7 (3.6) 4 (0-14)	2.1 (1.4) 2 (0-4)	8.2 (2.5) 7 (5-14)	**<0.001**
Demographics				
Age, years	72.2 (6.2)	70.8 (6.1)	74.1 (5.9)	**0.039**
Education, years	12.5 (3.6)	12.3 (3.3)	12.9 (4.0)	0.497
Male	31 (50.0%)	17 (48.6%)	14 (51.9%)	0.789
Study center: Sweden Finland	 32 (51.6%) 30 (48.4%)	 16 (45.7%) 19 (54.3%)	 16 (59.3%) 11(40.7%)	0.290
Cardiovascular and metabolic factors				
Pulse, bpm	63.3 (10.3)	61.7 (8.7)	65.3 (11.9)	0.174
Systolic blood pressure, mmHg	144.6 (16.9)	143.7 (16.9)	145.9 (17.2)	0.625
Diastolic blood pressure, mmHg	81.9 (9.5)	82.5 (9.2)	81.0 (10.0)	0.548
Body Mass Index, kg/m^2	25.8 (3.4)	25.3 (2.7)	26.4 (4.0)	0.231
Waist to hip ratio	0.9 (0.1)	0.9 (0.1)	0.9 (0.1)	0.102
Cholesterol-total, mmol/l	4.9 (1.3)	5.3 (1.4)	4.6 (1.1)	**0.037**
High density lipoproteins, mmol/l	1.6 (0.4)	1.6 (0.5)	1.6 (0.3)	0.561
Low density lipoproteins, mmol/l	3.0 (1.1)	3.3 (1.2)	2.6 (0.8)	**0.008**
Triglycerides, mmol/l	1.2 (0.6) 1 (0.5-3.9)	1.1 (0.6) 1 (0.5-3.9)	1.3 (0.6) 1 (0.5-2.7)	0.154
Fasting: glucose, mmol/l	5.9 (0.6) 5 (4.7-8.5)	5.8 (0.5) 5 (4.7-6.8)	6.1 (0.8) 5 (5.1-8.5)	0.393
HbA1c, mmol/mol	38.4 (4.0) 38 (33-55)	37.6 (2.4) 38 (33-42)	40.5 (5.1) 39 (34-55)	**0.027**
Cognitive and functional performance				
MMSE MMSE ≤27 MMSE ≥28	27(24-30) 34 (54.8%) 28 (45.2%)	27(24-30) 23 (65.7%) 12 (34.3%)	28(24-30) 11 (40.7%) 16 (59.3%)	**0.050**
CDR-SB CDR-SB ≤1 CDR-SB ≥1.5	1(0.0-4.5) 37 (59.7%) 25 (40.3%)	1(0.0-4.5) 22 (62.9%) 13 (37.1%)	1(0.0-3.0) 15 (55.6%) 12 (44.4%)	0.561
ADCS-ADL ADCS-ADL-total <76 ADCS-ADL-total ≥76	75.5(61-78) 29 (50.0%) 29 (50.0%)	76(65-78) 14 (42.4%) 19 (57.6%)	74(61-78) 15 (60.0%) 10 (40.0%)	0.185
NTB compositeLDD	-0.001 (0.627)	-0.001 (0.650)	-0.005 (0.609)	0.981
NTB composite FINGER	-0.024 (0.538)	-0.065 (0.586)	0.028 (0.490)	0.505
NTB Memory LDD	0.006 (0.782)	-0.008 (0.852)	0.025 (0.718)	0.874
NTB Memory FINGER	-0.008 (0.766)	-0.039 (0.860)	0.031 (0.664)	0.718
NTB Executive functioning LDD	-0.009 (0.630)	-0.001 (0.609)	-0.020 (0.687)	0.906

NTB Executive functioning FINGER	-0.018 (0.620)	-0.042 (0.612)	0.013 (0.623)	0.732
NTB total LDD	0.006 (0.462)	-0.008 (0.488)	0.023 (0.490)	0.811
NTB processing speed FINGER	0.020 (0.798)	-0.069 (0.712)	0.133 (0.896)	0.338

Data are mean (SD), median (range), or N (%).

MMSE (Mini Mental State Examination Score), CDR-SB (Clinical Dementia Rating- Sum of the Boxes scale), ADCS-ADL (Alzheimer's Disease Cooperative Study-Activities of Daily Living), NTB (Neuropsychological Test Battery), LDD (LipiDiDiet), FINGER (Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability).

Table 8 illustrates the use of medications in the study population. Drugs acting on cardiovascular system (C) were used by 43 participants (69.4%). Participants in the polypharmacy group used cardiovascular drugs significantly more often than those in the no polypharmacy group (88.9% vs. 54.3%, p=0.003).

Antihypertensive drugs were used by 36 (58.1%) in study population. Participants in the polypharmacy group used antihypertensive drugs significantly more often than those in the no polypharmacy group (81.5% vs. 40.0%, p=0.001).

Lipid lowering drugs were used by 22 (35.5%) in study population. Participants in the polypharmacy group used lipid lowering drugs significantly more often than those in the no polypharmacy group (51.9% vs. 22.9%, p=0.018).

Drugs acting on nervous system (N) were used by 37 (59.7%) in study population. Participants in the polypharmacy group used N drugs significantly more often than those in the no polypharmacy group (81.5% vs. 42.9%, p=0.002).

Psycholeptic drugs (N05) were used by 16 (25.8%) in study population. Participants in the polypharmacy group used N05 drugs significantly more often than those in the no polypharmacy group (48.1% vs. 8.6%, p=0.000). Psycholeptic drugs were mainly hypnotics and sedatives.

Antidiabetic drugs (A10) were used by 5 (8.1%) in study population. Participants in the polypharmacy group used A10 drugs significantly more often than those in the no polypharmacy group (18.5% vs. 0.0%, p=0.012).

Antithrombotic drugs (B01) were used by 19 (30.6%) in study population. Participants in the polypharmacy group used B01 drugs significantly more often than those in the no polypharmacy group (51.9% vs. 14.3%, p=0.001). Antianemic preparation of iron, B12, folic acid) (B03) were used by 27 (43.5%) in study population. Participants in the polypharmacy group used antianemic preparations significantly more often than those in the no polypharmacy group (63.0% vs. 28.6%, p=0.007).

Use of antidepressants (ATC code N06A), antidementia drugs (N06D), vitamins (A11), minerals (A12), musculoskeletal drugs (M), and anti-inflammatory/antirheumatic drugs (M1) was similar in no polypharmacy and polypharmacy groups. In the whole study population, Thyroid therapy (H03) and drugs for obstructive airway diseases (R03) were used only by 4 and 5 participants, respectively.

Table 8 Use of medications in the study population

Drug class	ATC codes	Total n=62	No polypharmacy n=35	Polypharmacy n=27	P-value
Cardiovascular	C	43 (69.4%)	19 (54.3%)	24 (88.9%)	**0.003**
Antihypertensive	C02-03, C07-09	36 (58.1%)	14 (40.0%)	22 (81.5%)	**0.001**
Lipid lowering	C10	22 (35.5%)	8 (22.9%)	14 (51.9%)	**0.018**
Nervous system	N	37 (59.7%)	15 (42.9%)	22 (81.5%)	**0.002**
Psycholeptic	N05	16 (25.8%)	3 (8.6%)	13 (48.1%)	**<0.001**
Antidepressant	N06A	9 (14.5%)	3 (8.6%)	6 (22.2%)	0.160
Antidementia	N06D	19 (30.6%)	10 (28.6%)	9 (33.3%)	0.687
Antidiabetic	A10	5 (8.1%)	0 (0.0%)	5 (18.5%)	**0.012**
Vitamins	A11	6 (9.7%)	3 (8.6%)	3 (11.1%)	1.000
Minerals	A12	10 (16.1%)	5 (14.3%)	5 (18.5%)	0.735
Antithrombotic	B01	19 (30.6%)	5 (14.3%)	14 (51.9%)	**0.001**
Antianemic preparation (iron, B12, folic acid)	B03	27 (43.5%)	10 (28.6%)	17 (63.0%)	**0.007**
Musculo-skeletal	M	11 (17.7%)	4 (11.4%)	7 (25.9%)	0.185
Anti-inflammatory &antirheumatic	M1	8 (12.9%)	3 (8.6%)	5 (18.5%)	0.218

Data are N (%).

5.2 Association of number of drugs and polypharmacy with cognitive and functional performance

Associations of the total number of drugs and polypharmacy with MMSE, CDR-SB and ADCS-ADL scores are shown in Tables 9 and 10. Number of drugs was not associated with MMSE, CDR-SB or ADCS-ADL scores (p-values > 0.05, Table 9). No association was observed between polypharmacy and CDR-SB or ADCS-ADL scores (Table 10), but there was a trend towards a significant association

between polypharmacy and MMSE: polypharmacy seemed to be associated with higher MMSE scores (OR 2.78, 95% CI 0.99-7.87, p=0.05). This trend was observed also in the fully adjusted model (OR 2.73, 95% CI 0.88-8.50, p=0.08).

Table 9. Binary logistic regression to study association between number of drugs and cognitive and functional outcomes

	Model 1			**Model 2**			**Model 3**		
Outcome	**OR**	**95% CI**	**P-value**	**OR**	**95% CI**	**P-value**	**OR**	**95% CI**	**P-value**
MMSE	1.13	0.97-1.30	0.10	1.10	0.95-1.28	0.19	1.13	0.96-1.32	0.12
CDR-SB	1.09	0.94-1.26	0.24	1.12	0.95-1.30	0.17	1.08	0.91-1.28	0.40
ADCS-ADL-total	0.90	0.77-1.05	0.17	0.90	0.77-1.05	0.18	0.90	0.77-1.05	0.20

MMSE (Mini Mental State Examination Score), CDR-SB (Clinical Dementia Rating- Sum of Boxes scale), ADCS-ADL (Alzheimer's Disease Cooperative Study-Activities of Daily Living), C.I (Confidence interval). OR=odds ratio. (MMSE ≤ 27 and ≥28; CDR-SB ≤ 1 and ≥ 1.5; ADCS-ADL-total <76) and ≥ 76).

Model 1 Unadjusted.

Model 2 Adjusted for Age, Education and Gender.

Model 3 Adjusted for Age, Education, Gender and Country.

Table 10. Binary logistic regression to analyze association between polypharmacy and cognitive and functional outcomes.

	Model 1			Model 2			Model 3		
Outcome	**OR**	**95% CI**	**P-value**	**OR**	**95% CI**	**P-value**	**OR**	**95% CI**	**P-value**
MMSE	2.78	0.99-7.87	0.05	2.38	0.80-7.12	0.12	2.73	0.88-8.50	0.08
CDR-SB	1.35	0.50-3.80	0.56	1.45	0.48-4.36	0.50	1.18	0.35-4.02	0.79
ADCS-ADL-total	0.50	0.17-1.41	0.18	0.50	0.17-1.51	0.22	0.51	0.17-1.54	0.24

MMSE (Mini Mental State Examination Score), CDR-SB (Clinical Dementia Rating- Sum of Boxes scale), ADCS-ADL (Alzheimer's Disease Cooperative Study-Activities of Daily Living), C.I (Confidence interval). OR=odds ratio

Model 1 Unadjusted.

Model 2 Adjusted for Age, Education and Gender.

Model 3 Adjusted for Age, Education, Gender and Country (Finland & Sweden).

Association of the number of drugs and polypharmacy with cognition/NTB scores are shown in tables 11 and 12. Number of drugs and polypharmacy were not associated with any of the NTB cognitive outcomes (P-value >0.05).

Table 11. Linear regression analysis to study association between number of drugs and cognition.

	Model 1		Model 2		Model 3	
Outcomes	**β**	**P-value**	**β**	**P-value**	**β**	**P-value**
NTB Composite LDD	-0.011	0.930	0.008	0.952	0.079	0.524
NTB Composite FINGER	0.056	0.666	0.071	0.587	0.128	0.326
NTB Memory LDD	0.010	0.940	0.004	0.976	0.126	0.325
NTB Memory FINGER	-0.016	0.901	-0.025	0.851	0.083	0.479
NTB Executive functioning LDD	0.001	0.996	0.035	0.792	0.020	0.884
NTB Executive functioning FINGER	0.076	0.562	0.092	0.486	0.093	0.495
NTB Total LDD	0.003	0.980	0.006	0.964	0.043	0.755
NTB processing Speed FINGER	0.132	0.320	0.162	0.224	0.118	0.380

β is standardized regression coefficient

Model 1 Unadjusted.

Model 2 Adjusted for Age, Education and Gender.

Model 3 Adjusted for Age, Education, Gender and Country.

Table 12. Linear regression to analyze association between polypharmacy and cognitive and functional outcome

	Model 1		Model 2		Model 3	
Outcome	**β**	**P- value**	**β**	**P- value**	**β**	**P- value**
NTB Composite LDD	-0.003	0.981	0.042	0.750	0.089	0.478
NTB Composite FINGER	0.086	0.505	0.129	0.332	0.166	0.203
NTB Memory LDD	0.021	0.874	0.035	0.800	0.112	0.378
NTB Memory FINGER	0.045	0.727	0.051	0.707	0.123	0.295
NTB Executive functioning LDD	-0.015	0.906	0.044	0.743	0.034	0.803
NTB Executive functioning FINGER	0.045	0.732	0.089	0.507	0.089	0.517
NTB total LDD	0.032	0.811	0.050	0.720	0.077	0.584
NTB processing speed FINGER	0.127	0.338	0.178	0.189	0.146	0.280

β is standardized regression coefficient

Model 1 Unadjusted.
Model 2 Adjusted for Age, Education and Gender.
Model 3 Adjusted for Age, Education, Gender and Country (Finland & Sweden).

As a borderline significant association was observed between polypharmacy and MMSE, we investigated further the association between specific types of medications and MMSE scores. Results showed that the use of antidementia drugs tended to be associated with lower MMSE scores, with OR (95% CI) of 0.22 (0.05-1.06) (p=0.06). No significant associations between other drug classes and MMSE score were found (Table 13).

Table 13. Binary logistic regression to analyze associations between use of medications and MMSE.

Drug class	MMSE	
	OR (95%CI)	P
Antihypertensive	2.09 (0.62-7.06)	0.235
Lipid lowering	1.24 (0.41-3.72)	0.708
Psycholeptic	2.37 (0.67-8.34)	0.179
Antidementia	0.22 (0.05-1.06)	0.06
Antithrombotic	1.75 (0.51-5.99)	0.371
Antianemic	0.98 (0.33-2.94)	0.977

Table 14 shows cognitive/functional outcomes in people with and without antidementia drugs. Use of antidementia drugs was statistically different in MMSE low (less than or equal to 27 score) and MMSE high (equal to 28 or higher scores) groups (P-value 0.011). 19 (44.2%) and 24 (55.8%) participants were not on antidementia drugs in MMSE low and MMSE high categories respectively. Most of the dementia drugs users, 15 (78.9%), had low MMSE scores compared with 4 (21.1%) in the MMSE high score category.

Antidementia drugs were statistically different in CDR-SB low (less than or equal to 1 score) and CDR-SB high (equal to 1.5 or higher scores) groups (P-value 0.015). 30 (69.8%) and 13 (30.2%) participants were not on antidementia drugs in CDR-SB low and CDR-SB high categories respectively. Most of the dementia drugs users, 12 (63.2%), had high CDR-SB scores compared with 7 (36.8%) in the CDR-SB low score category.

The mean for NTB composite FINGER was significantly different in no dementia drugs group 0.066 (SD 0.5) and dementia drugs group -0.231 (SD 0.5) with P-value 0.046. The mean for NTB memory LDD was significantly different in no dementia drugs group 0.14 (SD 0.7) and dementia drugs group

-0.322 (SD 0.8) with P-value 0.035. The mean for NTB memory FINGER was significantly different in no dementia drugs group 0.206 (SD 0.7) and dementia drugs group -0.494 (SD 0.6) with P-value 0.001. The mean for NTB total LDD was significantly different in no dementia drugs group 0.107 (SD 0.4) and dementia drugs group -0.232 (SD 0.5) with P-value 0.012.

There was no significant difference between dementia drugs users and non-users for ADCS-ADL-total, NTB composite LDD, NTB executive LDD, NTB executive FINGER and NTB speed FINGER.

Table 14. Baseline differences in cognitive and functional performance between participants with and without antidementia drugs

Cognitive and functional performance	**No antidementia drugs n=43**	**Antidementia drugs n=19**	**P-value**
MMSE ≤27	19 (44.2%)	15 (78.9%)	**0.011**
MMSE ≥28	24 (55.8%)	4 (21.1%)	
CDR-SB ≤1	30 (69.8%)	7 (36.8%)	**0.015**
CDR-SB ≥1.5	13 (30.2%)	12 (63.2%)	
ADCS-ADL-total <76	19 (55.6%)	10 (55.6%)	0.570
ADCS-ADL-total ≥76	21 (52.5%)	8 (44.4%)	
NTB composite LDD	0.093 (0.604)	-0.219 (0.641)	0.070
NTB composite FINGER	0.066 (0.536)	-0.231 (0.516)	**0.046**
NTB memory LDD	0.14 (0.749)	-0.322 (0.814)	**0.035**
NTB memory FINGER	0.206 (0.748)	-0.494 (0.609)	**0.001**
NTB executive functioning LDD	0.005 (0.654)	-0.042 (0.618)	0.792
NTB executive functioning FINGER	0.021 (0.615)	-0.103 (0.615)	0.467
NTB total LDD	0.107 (0.448)	-0.232 (0.495)	**0.012**
NTB processing speed FINGER	-0.024 (0.831)	0.128 (0.722)	0.513

MMSE (Mini Mental State Examination Score), CDR-SB (Clinical Dementia Rating- Sum of the Boxes scale), ADCS-ADL (Alzheimer's Disease Cooperative Study-Activities of Daily Living), NTB

(Neuropsychological Test Battery), LDD (LipiDiDiet), FINGER (Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability)

6 DISCUSSION

6.1 Prevalence of polypharmacy and types of medications

The present study investigated polypharmacy in a population of 62 individuals with prodromal AD participating in a clinical trial. 43.5% of participants were exposed to polypharmacy (5 or more drugs) at the baseline visit, before the start of the intervention. A systematic review by Elmstahl and Linder in 2013 reported that the prevalence of polypharmacy in older people ranged from 19% to 83%. A prospective cohort study from Sweden found 44% prevalence of polypharmacy in older adults (Morin et al. 2018), while a cross sectional study of Danish people reported a prevalence of polypharmacy of 62.6% in people with dementia (Kristensen et al. 2018). Prevalence of polypharmacy in prodromal AD in the present study thus seemed to be in between values previously reported in older general populations, and in populations with dementia.

Drugs to treat CVDs (antihypertensive and lipid lowering) were found to be most commonly used in this prodromal AD population. 69.4% of the participants were taking medications to treat CVDs; 58.1% were on antihypertensive treatment and 35.5% were on lipid lowering therapy respectively. This is not entirely surprising given that CVDs are among the most common chronic non-communicable conditions in older age groups (WHO 2020). Also, one of the inclusion criteria was presence of hypertension, which can be another reason for the high percentage of antihypertensive users in this study. The polypharmacy group had significantly more users of antihypertensive medications, as well as more people on lipid lowering therapy, which may explain why participants in the polypharmacy group had significantly lower total cholesterol and low-density lipoproteins compared with the group without polypharmacy.

Hypertension increases the risk of brain diseases (WHO 2019). Hypertension has been shown to be associated with elevated risk for dementia and use of antihypertensive medications has been hypothesized to be beneficial in preventing cognitive decline and dementia (Duron & Hanon 2008). A systematic review by Rouch and colleagues (Rouch et al. 2015) concluded that antihypertensive drugs may reduce risk and progression of cognitive decline and dementia, but lowering blood pressure has not been found associated to decreased risk of dementia in a more recent meta-analysis (Middelaar et al. 2018). Hypertension management was recently shown to reduce the risk of incident dementia and MCI in a randomized controlled trial (Williamson et al. 2019), suggesting that in hypertensive patients, control of systolic blood pressure may help prevent cognitive impairment (Yaffe 2019).

Hypercholesterolemia has been associated with increased risk for cardiovascular disease and has been linked to dementia risk as well (Justin et al. 2013). Statins or lipid lowering drugs have been assumed to be beneficial in reducing incidence of MCI, AD and dementia (Che-sheng et al. 2018). However, randomized controlled trials have so far not found statins to be associated with better cognition, and use of statins has not shown significant benefits in patients with dementia due to AD (Mejias-Trueba et al. 2018).

Drugs used for treating conditions related to the nervous system were the second most common drug class in this study. That might be because inclusion criteria were prodromal AD, current symptoms of sleep disturbances or symptoms of psychological stress and depressive moods. Among drugs acting on the nervous system, psycholeptic, antidepressants and antidementia medications were found in this study. In the psycholeptic class, mainly hypnotics and sedatives were used, probably to treat sleep disturbances. Sleep disturbances have been reported to be common in elderly patients with MCI or dementia (Kim et al. 2017). Although exposure to hypnotics and sedatives has been reported to increase the risk of AD dementia (Lee et al. 2018), it is not fully clear whether this may be at least partly due to reverse causality, given that sleep disturbances can be among the early symptoms of AD. Psycholeptic drugs were used significantly more often in the polypharmacy group compared with the no polypharmacy group. However, antidepressants were not significantly different between the no polypharmacy and polypharmacy group, which may be since in this study people with diagnosed major depression were excluded. If antidepressants were prescribed before 65 years of age, prevalence of antidepressants would be increased in worse cognitive impairment or people with dementia (Moraros et al. 2017).

Although people diagnosed with dementia were excluded from this study, antidementia drugs were used by 30.6% of the participants with prodromal AD. Since biomarker-based evidence of early stage of disease was required to identify prodromal AD, this may explain why some of the patients were receiving antidementia drugs even before the onset of dementia. Chi square analysis showed that among antidementia drug users compared with non-users there was a significantly higher percentage of individuals with lower MMSE scores (78.9% versus 44.2%), and higher CDR-SB scores (63.2% versus 30.2%). Global cognition (NTB composite total score) and memory (NTB memory score) were also significantly lower in patients treated with antidementia drugs. Antidementia drugs thus seemed to have been prescribed primarily in patients with poorer cognition and poorer daily life functioning, who may be closer to dementia onset. Although diabetes was a part of inclusion criteria in this study, few people (8.1%) were on antidiabetic medication. All participants on antidiabetic therapy were in the polypharmacy group. Diabetes has been associated with increased risk of

cognitive impairment and dementia (Xue et al. 2019). Antidiabetic drugs (metformin and glitazones) had been negatively associated with dementia while insulin was positively associated with dementia (Bohlken et al. 2018). This could be illustrated as antidiabetic drugs have been suggested to have potential benefits on cognition and dementia prevention, more randomized controlled trials are needed to test this hypothesis.

Antithrombotic medications were used by 30.6% people in this study. Antianemic preparations were used by 43.5% of the participants, and anti-inflammatory and antirheumatic drugs were used by 12.9% of the study participants. While observational studies have suggested that use of anti-inflammatory medications may have benefits in preventing dementia, randomized control trials have not shown an association between anti-inflammatory treatment and AD (Wang et al. 2015).

6.2 Association of polypharmacy with cognitive and functional outcomes

In the present study, the number of drugs or polypharmacy (yes/no) was not significantly associated with cognitive and functional outcomes.

Surprisingly, there was a trend for polypharmacy to be associated with higher MMSE score. This is in contrast with existing literature reporting associations between polypharmacy and MCI or dementia, and associations to poorer cognition (Rawle et al. 2018). The reasons for this finding are not fully clear. Although about one third of the study participants were already using antidementia drugs, which may have led to some benefit on cognition, no significant difference was found between the no polypharmacy and polypharmacy groups regarding use of antidementia drugs. It is possible that selection of the study population may be a key reason for the observed trend regarding polypharmacy and MMSE scores. The individuals with prodromal AD were part of an ongoing randomized clinical trial, where eligibility criteria excluded patients with poorer health status for safety reasons. Eligible patients may have also had better controlled medication. Polypharmacy would need to be studied with respect to appropriateness or inappropriateness, with appropriate polypharmacy referring to correct diagnosis and choice of specific drug class, dose and duration of treatment. In addition, participants included in this study had MMSE scores $\geq$ 24 points. Polypharmacy has not been associated with cognitive decline measured with MMSE in a previous study (Soysal et al. 2019).

6.3 Strengths of the study

This study investigated participants with prodromal AD, a population group that was relatively recently defined, and has not yet been fully characterized. No other studies were found on polypharmacy and prodromal AD in the literature. Although some previous studies have investigated polypharmacy and MCI, prodromal AD and MCI are not identical concepts. While MCI has been defined primarily using clinical criteria based on cognitive testing, and covers populations with a variety of possible causes of cognitive impairment, prodromal AD is more specific because it also requires biomarker-based evidence of AD. In addition, the present study used a comprehensive cognitive test battery (NTB), and a sensitive measure of functional impairment (CDR-SB).

6.4 Limitations of the study

This study has several important limitations. Firstly, the small sample size (N=62) most likely limited statistical power and the possibility of detecting significant associations of polypharmacy, with cognition and daily life functioning level. Secondly, polypharmacy was mainly studied with respect to numerical definition (≥ 5 drugs). More detailed data were not available regarding dose and duration of drug treatments, and appropriateness and inappropriateness. Thirdly, the study population was highly selected, i.e. participants in a prodromal AD randomized controlled trial who were otherwise relatively healthy; and demographically not diverse as this study only included trial sites in Nordic countries (Sweden and Finland). This limits the representativeness of the population. Fourthly, since the trial was still ongoing, only baseline data for a subsample of trial participants were available for the present study, and longitudinal analyses on the potential impact of polypharmacy on change in cognitive and functional level over time could not be conducted.

The MIND-AD trial used the IWG-1 definition of prodromal AD (Dubois et al. 2007), which includes MTL atrophy on MRI in addition to other biomarkers. This criterion was removed from the more recent IWG-2 criteria due to concerns regarding specificity for AD of MTL atrophy (Dubois et al. 2014). However, it has been shown that IWG-1 criteria work well for identifying prodromal AD, e.g. 88% of patients fulfilling IWG-1 criteria have amyloid CSF levels indicative of AD (Soininen et al. 2017).

7 CONCLUSIONS

Polypharmacy seems to be prevalent among individuals with prodromal AD. 43.5% participants of this study were exposed to 5 or more number of medications. No significant association was found between number of drugs or polypharmacy (yes/no) and cognitive and functional outcomes in the prodromal AD population in this study.

Prodromal AD is a relatively newly defined group, and more studies are needed to fully characterize this population with respect to polypharmacy and other characteristics. Studies with larger sample size, longer-term follow-up, and more detailed data on polypharmacy (e.g. especially with respect to appropriateness) are needed to fully characterize the impact of polypharmacy on cognitive and functional decline, including rate of progression to dementia.

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