Alzheimers sykdom – betydningen av samtidig hjerte-karsykdom for sykdomsprogresjon og klinisk profil

Alzheimers sykdom (AS) er den vanligste årsaken til demens og medfører gradvis økende svekkelse i funksjon. Hjerte-karsykdom er risikofaktorer for AS og hyppig forekommende hos pasienter med AS. Det er lite kunnskap om prognostiske faktorer hos pasienter med AS og hvorvidt hjerte-karsykdom har betydning for prognose og symptomer.

Den overordnede målsetningen med avhandlingen var å studere sykdomsprogresjon ved AS generelt, samt hvorvidt samtidig hjerte-karsykdom påvirker sykdomsprogresjon og symptomprofil.

Det ble gjort en studie av 282 pasienter med AS, utredet ved tre norske hukommelses-poliklinikker, som ble fulgt opp etter gjennomsnittlig to år. Det ble tatt MR (magnetisk resonanstomografi) ved diagnosetidspunktet.

Det var en betydelig variasjon i sykdomsprogresjon og nesten halvparten av pasientene opplevde liten forverring over år. Dårlige skårer på kognitive tester ved diagnose-tidspunktet kunne knyttes til raskere progresjon, men forklarte lite av forskjellene.

Vi studerte hvorvidt risikofaktorer for hjerte-kar sykdom eller etablert hjerte-karsykdom var forbundet med sykdomsprogresjon, men fant ingen sammenheng.

AS fører til svinn av hjernevev i et område kalt mediale temporallapp (MT) som kan framstilles på MR. Vi fant imidlertid ingen sammenheng mellom svinn i MT og videre sykdomsutvikling hos pasienter som har AS.

En vil forvente at pasienter som har bare AS vil ha kommet lengre i sykdommen før de får kognitiv svikt sammenlignet med de som både har AS og karsykdom i hjernen og dermed at pasienter med bare AS har mindre uttalt svinn i MT. Vi fant imidlertid at de som både har AS og karsykdom i hjernen har mer svinn i MT enn de som bare har AS.

Pasienter som har kognitiv svikt på grunn av sykdom i hjernens blodårer skal ifølge diagnosekriterier ha andre symptomer og funn enn de som har AS. Vi sammenlignet derfor symptomer hos pasienter med bare AS og de som hadde både AS og sykdom i hjernens blodårer. Vi fant ikke forskjell i symptomer mellom disse to gruppene.

Studien viste at det var store forskjeller i hvor fort sykdommen utviklet seg, og verken hjerte-karsykdom eller atrofi i MT kunne forklare disse forskjellene. Nesten halvparten av pasientene opplevde liten eller ingen forverring i løpet av to år.

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List of papers

I. Eldholm, RS, Barca, ML, Persson, K, Knapskog, AB, Kersten, H, Engedal, K, Selbæk, G, Brækhus, A, Skovlund, E, Saltvedt, I. *Progression of Alzheimer's Disease: A Longitudinal Study in Norwegian Memory Clinics.* Journal of Alzheimer's Disease 61 (2018) 1221-1232.

II. Persson, K, Barca, ML, Eldholm, RS, Cavallin, L, Šaltytė Benth, J, Selbæk, G, Brækhus, A Saltvedt, I, Engedal, K. Visual Evaluation of Medial Temporal Lobe Atrophy as a Clinical Marker of Conversion from Mild Cognitive Impairment to Dementia and for Predicting Progression in Patients with Mild Cognitive Impairment and Mild Alzheimer's Disease. Dementia and Geriatric Cognitive Disorders 2017; 44:12-24.

III. Eldholm, RS; Persson, K; Barca, ML; Knapskog, AB; Cavallin, L; Engedal, K; Selbæk, G; Skovlund, E; Saltvedt, I. (2018). *Association between vascular comorbidity and progression of Alzheimer's disease: a two-year observational study in Norwegian memory clinics.* BMC Geriatrics. vol. 18 (120).

IV. Eldholm, RS; Barca, ML; Persson, K; Knapskog, AB; Cavallin, L; Engedal, K; Selbæk, G; Skovlund, E; Saltvedt, I. *Symptom Profiles in Patients With Alzheimer's Disease With and Without Concomitant Cerebrovascular Disease* (submitted for publication).

Summary

Background

Alzheimer's disease (AD) is the most common cause of dementia, responsible for 50 to 70% of all cases. AD is a progressive disease, but the course varies considerably among individuals. There is limited evidence for which factors are important for disease progression in general. Vascular risk factors (VRFs) increase the risk of developing AD, but it is not clear whether VRFs or comorbid cerebrovascular or other vascular conditions exert an impact on further disease progression following diagnosis. Diagnostic criteria for AD and vascular cognitive impairment (VCI) describe different cognitive profiles. AD patients with concomitant cerebrovascular disease (CVD) could, therefore, be expected to display symptoms of both AD and VCI. Medial temporal atrophy (MTA) on magnetic resonance imaging (MRI) is a biomarker of neurodegeneration in AD. As AD patients with concomitant CVD exhibit symptoms with less-severe AD pathology than those without CVD, they could be expected to have less-pronounced MTA. MTA has been found to predict progression from mild cognitive impairment (MCI) to dementia, but the ability to predict progression in AD has been less explored.

Aims

The main aim of this thesis was to study predictors of disease progression in AD, with a particular focus on how comorbid vascular diseases and VRFs and MTA influence progression. In addition, we wanted to study whether symptom profiles in AD patients with CVD differed from those of patients without CVD. Our hypotheses were that disease progression in AD could be predicted by patient characteristics at the time of diagnosis, that vascular burden would be associated with a more rapid progression of AD, and that AD patients with concomitant CVD would display symptom profiles different from those of other AD patients. We hypothesised that AD patients with CVD would have less-pronounced MTA and that MTA would be a predictor of progression in AD.

More specifically, the aims were explored in four substudies and published in four papers:

I. To study the overall progression of AD, as measured by the primary outcome measure Clinical Dementia Rating Scale Sum of Boxes (CDR-SB); secondly, to investigate whether patient characteristics at the time of diagnosis are significant for differences in progression and to examine the correlation between progression assessed by a global score (CDR-SB) and progression in cognitive (MMSE) and functional (IADL) measures.

II. To explore whether visual assessment of MTA using Scheltens MTA scale can predict conversion from MCI to dementia and whether MTA can predict progression as defined by an increase in CDR-SB in patients with MCI and mild AD dementia.

III. To investigate whether single VRFs and vascular diseases and total vascular burden are predictors of progression in AD.

IV. First, to examine cognitive test results and measures of depression in AD patients with amnestic mild cognitive impairment (aMCI) and mild dementia with and without CVD and, secondly, to assess MTA on MRI among AD patients with and without CVD.

The first part of the work is focused on disease progression and the second part on the importance of vascular diseases and risk factors for patients with AD.

Methods

Four substudies were conducted, all based on the Progression of Alzheimer's Disease and Resource use (PADR) study, a longitudinal observational study including 357 patients in three Norwegian memory clinics, 282 of whom were diagnosed with AD. Patients included in the PADR study had dementia or MCI at baseline and were home dwelling. Physical examinations, structural brain imaging, and a comprehensive cognitive test battery were performed at baseline, and cognitive tests were repeated after a mean of 24 months. VRFs were assessed based on medical history, drug use, and measurements, and vascular burden was estimated by the Framingham Stroke Risk Profile (FSRP). MRI scans were assessed for MTA, white matter hyperintensities, lacunes, and cortical infarcts.

The primary outcome measure used for substudy I–III was disease progression as measured by annual change in CDR-SB. As secondary outcome measures, substudy I

examined annual change in MMSE and IADL. Substudy II additionally examined the conversion of MCI to dementia. Substudy IV assessed the effect of CVD on cognitive test scores, depression scores, and MTA. Substudies I and III included the 282 patients assumed to have AD, i.e. patients with amnestic MCI (aMCI) in addition to patients with AD dementia. Substudies II and IV included patients who had undergone MRIs within six months of the baseline assessment and excluded patients with moderate dementia (CDR 2), but substudy II included only patients with coronal sections on MRI scans. Substudy II additionally included non-amnestic MCI patients, resulting in 218 patients in substudy II and 192 in substudy IV.

Results

Substudy I. Almost half of the patients progressed slowly, with less than a 1-point yearly increase in the CDR-SB. For the mean annual progression of AD, we observed a considerable variation in all disease stages. The mean annual increase in the CDR-SB was 1.6 (SD 1.8); the mean decrease in the MMSE score was 1.9 (SD 2.6); and the mean decrease in the IADL score was 0.13 (SD 0.14). Cognitive test results at baseline predicted progression rate and, together with age, ApoE, history of hypertension, and drug use, could explain 17% of the variance in the progression rate. Changes in the CDR-SB, MMSE, and IADL scores correlated, with the strongest correlation of change found between CDR-SB and IADL scores and the weakest between MMSE and IADL scores.

Substudy II. In adjusted models of the association between visual assessment of MTA and MCI conversion, word-list delayed recall and ApoE ε4 were identified as significant predictors and MTA was not significant. For progression of MCI and dementia in AD, an interaction between MTA and diagnosis was identified in an unadjusted analysis, while in the adjusted model, word-list delayed recall and age were found to be significant predictors. For MTA below 2, the association between MTA and change in the CDR-SB differed between patients with MCI and patients with AD dementia.

Substudy III. Neither vascular diseases and their risk factors, the Framingham Stroke Risk Profile (FSRP) score, nor cerebrovascular disease were associated with disease progression in AD.

Substudy IV. AD patients with concomitant CVD scored significantly lower on tests of attention, executive function, and immediate recall compared to the group without CVD. In analyses controlled for age and gender, concomitant CVD was not associated with significant differences in any cognitive test or in depressive symptoms. A significant association between AD with concomitant CVD and more pronounced MTA was identified.

Conclusion

The study generally identified few predictors of progression in AD, and these predictors explained only a small proportion of the variation in progression rates. Progression rate varied considerably among AD patients, and about half of the patients progressed slowly. Based on our findings, severe cognitive impairment at the time of diagnosis may predict more rapid progression, but the effect is weak. VRFs or cerebrovascular disease diagnosed through MRI does not imply a different prognosis. The effect of cerebrovascular disease in AD patients was not recognisable by symptom profile. Contrary to our expectations, AD patients with concomitant CVD had more-pronounced MTA.

Abbreviations

Aβ	amyloid beta
Aβ-42	amyloid beta 1-42
AD	Alzheimer's disease
ADL	activities of daily living
AF	atrial fibrillation
aMCI	amnestic mild cognitive impairment
ApoE	apolipoprotein E gene
APP	amyloid precursor protein
CSDD	Cornell Scale for Depression in Dementia
CDR	Clinical Dementia Rating Scale
CDR-SB	Clinical Dementia Rating Scale Sum of Boxes
CERAD	Consortium to Establish a Registry for Alzheimer's Disease
CSF	cerebrospinal fluid
CT	computed tomography
CVD	cerebrovascular disease
DSM	Diagnostic and Statistical Manual of Mental Disorders
EEG	electroencephalography
FDG-PET	fluorodeoxyglucose positron emission tomography
FSRP	Framingham Stroke Risk Profile
IADL	Instrumental Activities of Daily Living
ICD-10	International Classification of Diseases and Related Health Problems 10^{th} revision

IWG	International Working Group
MCI	mild cognitive impairment
MMSE	Mini-Mental State Examination
MRI	magnetic resonance imaging
MTA	medial temporal lobe atrophy
NIA-AA	National Institute on Aging – Alzheimer's Association
NINCDS-ADRDA	National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association
NorCog	Norwegian register of persons assessed for cognitive symptoms
NPI-Q	Neuropsychiatric Inventory Questionnaire
p-tau	phosphorylated tau protein
PADR	Progression of Alzheimer's Disease and Resource use
PET	positron emission tomography
SD	standard deviation
SPECT	single-photon computed tomography
SVD	small vessel disease
t-tau	total tau protein
TMT	Trail Making Test
VaD	vascular dementia
VCI	vascular cognitive impairment
VRF	vascular risk factor
WMHs	white matter hyperintensities

1 Introduction

Alzheimer's disease (AD) is the most common cause of dementia. As a result of the ageing populations of many countries, a dramatic increase in the number of individuals affected by AD is expected in the years to come. Risk factors for the development of AD have been studied extensively and a substantial fraction of AD cases are attributed to modifiable risk factors (1). However, we know little about the predictors for disease progression after symptoms have become evident. Information about the prognosis is important for people living with AD and for their families, but it is also essential for societies in order to plan for health care services.

Despite numerous attempts, there is still no treatment available to reverse or slow the progression of AD. In order to impact the course of the disease, we need to know what factors influence progression. Vascular risk factors (VRFs) and vascular diseases, such as stroke, have been shown to increase the risk of developing AD. If these factors affect the progression of AD, they could represent a potential target for intervention in the disease course of AD.

This thesis will focus on the progression of Alzheimer's disease and factors that influence disease progression. Emphasis will be on the impact of vascular risk factors (VRFs) and vascular diseases on the progression of Alzheimer's disease and on how the symptom profile of Alzheimer's disease is influenced by concomitant cerebrovascular disease.

In clinical work, it is important to diagnose not only whether a patient has cognitive impairment but also the underlying aetiology. Diagnostic classification systems are used to differentiate AD from other disorders causing dementia. Among older AD patients, mixed pathology is very common, and we want to determine whether the symptom profile differs in AD patients with and without concomitant cerebrovascular disease (CVD).

2 Background

2.1 Alzheimer's disease

Alzheimer's disease (AD) is a progressive neurodegenerative disorder, causing irreversible cognitive and functional decline and behavioural changes. Biochemical and neuropathological changes in the brain develop and gradually worsen, resulting in the patient's increasing difficulties in managing independently.

According to the prevailing theory of AD development, the biochemical and neuropathological changes in the brain associated with AD start insidiously many years or even decades before the first symptoms occur (2). At this early stage, symptoms may be vague, but with disease progression, the cognitive impairment will be recognisable to others and verifiable as low scores on cognitive tests or as a decline from previous intellectual levels. This stage is called mild cognitive impairment (MCI) (3). Ultimately, AD causes dementia when the decline in cognition is pronounced and interferes with activities of daily living, and further on, the condition becomes increasingly disabling.

2.1.1 Prevalence and incidence

Dementia is an acquired brain syndrome caused by many different diseases, with AD accounting for 50–70% of all cases. In most of the world, the age-standardised prevalence of dementia is 5–7% for people 60 years or older (4). Globally approximately 44 million people were living with dementia in 2016, with around eight million new cases every year, and the annual cost of dementia is estimated to be 818 billion USD (5). In Norway, the exact prevalence of dementia and of AD is unknown, but dementia was estimated to affect 78,000 individuals in 2013 (6).

Age is the primary risk factor for AD and dementia in general, and with ageing populations worldwide, a dramatic increase in the number of individuals affected by AD and dementia is expected. Globally, the number of people living with dementia has increased by 38% between 2006 and 2016 and is expected to reach 66 million by 2030 and 131 million by 2050 (5, 7). Although much of the increase seen over the last ten years has been because of ageing populations, there has been a slight increase in age-standardised rates over this decade. In the coming years, the largest increase in dementia cases is expected in low-income and middle-income countries, influenced by a rise in

non-communicable diseases in addition to the ageing societies observed globally. Trends for age-adjusted incidences of AD and dementia differ across the world. Several studies of populations in high-income countries have reported declining age-adjusted incidences for AD and dementia, possibly due to societal changes such as improvement in education and the successful prevention of cardiovascular disease (8-10). However, this trend has not been observed in low-income and middle-income countries, where the largest increase in dementia cases is expected. Moreover, despite the reduced age-adjusted incidences for AD and dementia, even high-income countries are expected to see a large increase in dementia prevalence in the coming years, driven by rising numbers of older adults. In Norway, the number of inhabitants over the age of 80 years is expected to triple from 2018 to 2060, increasing from 223,000 to 671,000 individuals. In low- and middle-income countries, the numbers of people living with dementia are expected to surge in the coming decades. Everywhere, the needs for care resulting from AD and dementia will put a strain on societies, and thus dementia is a great global challenge for health and social care in this century (4). In Norway, the rise of AD and dementia will constitute a major challenge to our society, not only because of the high prevalence of the disease, but also because many of those living with AD will be widowed and living alone, remaining spouses will be elderly themselves, and even their children, in many cases, will be old.

2.1.2 Symptoms

The most common early symptom of AD is a deficit in episodic memory. This is a widespread and reliable neuropsychological marker of AD, and in the beginning, AD is typically a progressive amnestic syndrome (11). The first symptoms are related to neuropathology involving structures in the medial temporal lobes. As the disease evolves, neuronal pathology spreads to encompass neocortical areas, and cognitive symptoms from other domains typically evolve, such as impaired orientation, language deficits, executive dysfunction, impaired thinking, and changes in mood and behaviour. In the late stages, problems with speaking, walking, and swallowing follow.

AD is a heterogeneous disease, with considerable individual variation in disease presentation, progression, and underlying pathology. Although the typical disease presentation is initial problems of episodic memory that, with time progress to

widespread cognitive impairment and functional problems, several atypical presentations exist, with predominant problems related to language (frontal type) or visual perception (posterior type) in the early stages. Psychological symptoms and changes in behaviour, such as anxiety, depressive symptoms, and irritability, may also present early in the disease course, sometimes before memory problems. Regardless of initial symptoms, the disease eventually causes deterioration in multiple cognitive domains, leading to progressive disability that interferes with daily functioning.

The pathogenesis of AD is not completely understood, but according to the prevailing theory of AD aetiology, the disease presents after many years of insidious accumulation of brain pathology, with the deposition of β-amyloid as plaques and hyperphosphorylated tau as neurofibrillary tangles (2). The cognitive decline of AD that ultimately leads to dementia evolves gradually over a number of years and is associated with the accumulation of brain pathology, although there is no linear relationship between symptoms and AD-related pathology in the brain (12-14).

There are indications that age-related, protective, and disease-promoting factors all play a role in how the disease evolves and at which point cognitive impairment develops. Some persons appear more resilient and are able to maintain normal function despite harbouring amounts of brain pathology that, in other individuals are associated with dementia. This ability is ascribed to cognitive reserve, a concept used to describe the ability to compensate for brain pathology or age-related changes, developed as a result of greater intellectual stimulation earlier in life (15). By contrast, individuals with AD who have other comorbid brain pathologies experience cognitive symptoms with a lower burden of AD pathology (16). Thus, the symptomatic threshold for AD pathology may result from a multifactorial process to which other factors of vulnerability and resilience might contribute.

The patient with AD pathology in the brain is first asymptomatic but may later notice subtle cognitive changes that are still not apparent to others in his or her environment, a stage called subjective cognitive impairment. When the cognitive impairment becomes discernible to others and can be verified as a low score or a decline from previous levels on a cognitive test, the patient has reached the MCI stage. Typically, impaired memory

is the most common deficit for AD patients, but the impairment related to MCI may also be non-amnestic and present in single or multiple domains.

Although MCI may be a precursor of AD or other dementias, it can be the result of other diseases, such as injury from a stroke or the cognitive effect of depression or other longstanding psychiatric disorders, therefore MCI is a heterogeneous condition (17). Although many patients with MCI later progress to dementia, others remain stable, and some even regain normal cognition (18). The prevalence of MCI in population-based studies is reported mostly in the range of 5–20% for people older than 60 years of age, and the annual conversion rate to AD dementia is 5–10% (18, 19). In specialist settings, many studies report higher conversion rates to AD dementia between 10% and 30% per year. Cumulative progression to dementia in robust population cohort studies with an observation period of five years or more seldom exceed 50%. Most often the cumulative progression to dementia in population studies is between 20% and 40%, depending on the study sample, setting, and the definition of MCI applied (18). Distinguishing between those patients with MCI who will later develop AD dementia, those who will develop other specific dementias, such as vascular dementia or dementia with Lewy bodies, and those patients who will not experience deterioration has been an important focus for research (20). Newer diagnostic criteria for AD in MCI that makes use of biomarkers stratify the likelihood of MCI being caused by AD. The higher the likelihood of MCI being caused by AD, the higher the progression rates to AD dementia. In MCI patients with the highest probability of AD as the underlying aetiology progression rates reach almost 60% within three years (21). In population-based studies, 30–50% of those found to have MCI revert to normal after two to five years of follow-up, while clinic-based studies report reversion rates of 14% (22, 23). These patients are, however, at increased risk for later dementia compared to people who never had MCI (24).

2.1.3 Risk factors

AD is a multifactorial disorder for which both genetic susceptibility and environmental factors across the lifespan influence the chance of developing the condition.

2.1.3.1 Age

Increasing age is the most important risk factor for dementia and AD. Dementia prevalence increases exponentially with ageing, doubling with approximately every six-year increment in age, and the prevalence is around 40% after the age of 90 years (4). However, some AD cases occurring before age 65 demonstrate that advanced age is not a prerequisite. However, for dementia in general, 2–5% of cases are early-onset (before 65 years). In this group, dementias other than AD are equally common (25, 26). Little is known about the risk factors of early-onset AD, but VRFs might be less common among patients with early-onset AD than among those with late-onset AD (27, 28). Although some cases of early-onset AD are familial, this is more frequently seen in early frontotemporal dementia.

2.1.3.2 Gender

A majority of AD patients are women, which has led to the assumption that women have a higher risk of dementia. There may be gender differences in AD, as several studies have reported higher prevalence and incidence of the disease in women than in men, especially among the oldest old (8). However, a meta-analysis of AD studies did not find significant differences in men and women's risks for developing AD from age 55 to 85 years (29).

2.1.3.3 Genetic factors

Genetic variants are risk factors for AD. However, mutations with a strong influence are rare, with autosomal dominant mutations in the genes for amyloid precursor protein (APP), presenilin 1 (PSEN1) and presenilin 2 (PSEN2) being the cause of some early-onset, hereditary AD cases. Additionally, people with Down syndrome have excess amyloid production due to having three copies of the APP gene located on chromosome 21. Among the more common genetic variants, the ε4 allele of the apolipoprotein E (ApoE) gene is the strongest risk factor for AD (30). Although this allele is neither necessary nor sufficient for the development of AD, it increases amyloid accumulation and the risk for developing AD and decreases the age of onset. The ApoE gene has three common isoforms; compared to the most common ApoE ε3, ApoE ε4 conveys increased risk for AD, while ApoE ε2 is protective. A dose effect of ApoE ε4 alleles is evident, as the impact of having two alleles is stronger than the effect of one (31). Other

common genetic variants with low effects on the risk for sporadic AD have been identified in recent years through whole-genome genotyping, revealing genes connected with inflammation, endocytosis, and cholesterol and lipid metabolism. Although associated with the risk for developing AD, these genes account only for a small fraction of the increased risk (31).

2.1.3.4 Environmental factors

Environmental or lifestyle factors are thought to be important for the development of AD. Extensive research has shown that factors associated with the risk for developing AD are as diverse as educational attainment, VRFs, mid-life obesity, physical inactivity, depression, social isolation, hearing loss, and traumatic brain injury. For all-cause dementia, it is proposed that a third of cases may be theoretically preventable, and this potential effect is related to environmental factors (9).

Education is an important risk factor for AD. Having less education, often defined as not having attended secondary school, is associated with an increased risk for AD (9). Missed educational opportunities are thought to increase the risk of cognitive decline because the individual has developed less cognitive reserve, making the brain less resilient to the effects of brain pathology later in life (32). It is not known whether higher education beyond secondary school is additionally protective (9).

VRFs in mid-life have been identified as risk factors for later AD in longitudinal epidemiological studies (33). VRFs are conditions associated with an increased risk of cardiovascular disease. Mid-life is poorly defined in studies, the label being used for diverse age spans within the range from 35 to 68 years, but the term is most frequently used to indicate 45–65 years of age (34). On the contrary, the same VRFs in late-life, e.g. older than the age of 75 years, are not necessarily associated with increased risk of AD (8). Longitudinal studies have shown that blood pressure, total cholesterol, body mass index and levels of physical activity start to decline years or even decades before dementia onset (35-38). Therefore, it has been suggested that decreasing levels of these VRFs in later life might be part of the disease process in AD. However, other studies have found that levels of VRFs tend to decline in the last years or decades of life, and the cause is unclear (39, 40). VRFs in mid-life associated with risk for later AD include

hypertension, high cholesterol, diabetes mellitus, high plasma homocysteine levels, obesity, lack of exercise, and smoking (8, 9).

Hypertension is considered a risk factor for AD, but uncertainties remain regarding this association. Observational studies have identified hypertension in mid-life but not in late-life as associated with increased risk for AD, and in late-life, hypertension might even be protective (41-44). The effect of blood pressure in late-life on the brain may differ depending on whether the individual was hypertensive in mid-life (45). Genetic factors connected with higher levels of systolic blood pressure are associated with lower risk for AD (46). Some studies indicate that hypertension might have an impact on AD pathology, but the evidence is conflicting (47-52). Reduced risk for AD in patients on antihypertensive medication has been reported, but there is no conclusive evidence from clinical trials that antihypertensive treatment may improve cognition (53).

The relationship between **cholesterol** and AD risk is unclear. Similar to the observations for hypertension, several epidemiological studies have found that elevated cholesterol in mid-life but not in late-life is associated with increased risk for later developing AD (54-57). The evidence is conflicting, as one large study found no association either with mid-life or with late-life cholesterol, and studies adjusting for ApoE genotype and CVD have reported inverse associations (57, 58). Cholesterol levels decrease with increasing age but may decline more in persons who develop AD than in others (54). ApoE is associated with cholesterol transport; the ApoE ε4 allele is associated with dyslipidaemia; and cholesterol levels have been associated with amyloid accumulation (59). Mendelian randomisation studies do not show any link between genetically elevated cholesterol levels and increased risk for AD (46). Adding to this, statins do not seem to prevent AD or cognitive decline (60).

Diabetes mellitus is associated with an increased risk for clinically diagnosed AD (61, 62). However, the amount of AD neuropathology in the brain is not associated with diabetes, but brain autopsies reveal more cerebrovascular pathology in individuals with diabetes (63). Type 2 diabetes is not associated with increased amyloid deposition, as evaluated by cerebrospinal fluid (CSF) or positron emission tomography (PET) biomarkers, but it is associated with an increase in MRI and PET biomarkers of

neurodegeneration (64). This might indicate that type 2 diabetes influences neurodegeneration through mechanisms other than AD-related pathology. Cerebral insulin resistance may be of importance in AD, as disturbances in insulin signalling have been found in AD patients regardless of type 2 diabetes. Insulin resistance is associated with lower regional glucose metabolism, which is related to worse memory performance (65, 66). Genetic factors linked to type 2 diabetes and insulin resistance have not been found to be associated with AD risk (46).

Elevated **body mass index** (BMI) in mid-life has been associated with an increased risk for AD, while most studies find that being overweight in late-life is associated with reduced risk (67). Genetic factors do not support a causal association between BMI and AD, but elevated BMI in mid-life has been associated with increased amyloid deposition (46, 68).

The evidence for an association between **smoking** and AD has been conflicting and unclear. Most observational studies have found an association between current smoking and risk for AD, and one study found that the total tobacco exposure for those who smoked in mid-life was related in a dose-response manner to the chance of developing AD in late-life (69). Although the increase in risk related to smoking has been relatively small, the importance on the population level has been regarded as considerable because smoking has been, and in many countries still is, very common (1).

Epidemiological studies have indicated many positive effects of physical activity on brain health, and **lack of exercise** is associated with an increased risk for AD (1). However, the direction of a possible causal relationship between exercise and cognitive decline in late-life is debatable, as the preclinical phase of AD may be associated with reduced physical activity. A recent epidemiological study with a long follow-up found no effect of physical activity on dementia risk, and meta-analyses of intervention studies have not shown a protective effect of physical activity on cognition among healthy elderly individuals (38, 70).

Elevated levels of plasma **homocysteine** are associated with risk for developing AD in observational studies, but results from homocysteine-lowering randomised clinical trials have been inconsistent (71). Elevated homocysteine has been associated with AD

neuropathology (72). Genetic factors linked to increased homocysteine are not associated with increased susceptibility to AD (73-75).

In addition to VRFs, several other conditions are associated with an increased risk for AD. Evidence from longitudinal studies suggests that **depression** may be a risk factor for AD, as cohort studies with long follow-ups have shown an association between the number of depressive episodes and subsequent risk for AD (76). Moreover, late-life depression has been associated with an increased risk for AD (77). Contrary to this, a cohort study with all-cause dementia as the outcome found that depressive symptoms were more prevalent among people with dementia than those without only in the ten years leading up to a dementia diagnosis (78). The temporal relationship between depression and dementia remains unclear (77, 79). While some studies have reported an association between depression and dementia-related pathology, other findings do not support this (80).

Mild **traumatic brain injuries** have been associated with an increased risk of developing AD in epidemiological studies, but evidence from systematic reviews has been conflicting (81, 82). Autopsy studies have shown more AD pathology than expected in a third of traumatic brain injury survivors who died many years later of causes unrelated to the brain injury, indicating that brain injuries might trigger subsequent neurodegeneration (83).

Hearing loss has been associated with cognitive impairment and dementia in prospective cohort studies but not with AD (84).

The evidence for an association between **alcohol consumption** and the development of dementia has been conflicting. In epidemiological studies, light to moderate alcohol consumption has been associated with a 30–40% reduced risk of AD and dementia, while other studies have linked heavy drinking to an increased risk of developing dementia (85-87). A cohort study with repeated measurements over thirty years of follow-up found that even moderate drinking was associated with hippocampal atrophy on MRI and increased cognitive decline, and no protective effect of small amounts of alcohol compared to abstinence was identified (88).

2.1.4 Pathogenesis of Alzheimer's disease

Microscopically, AD is characterised by two features: β-amyloid deposited in the cerebral parenchyma as plaques and in blood vessels as cerebral amyloid angiopathy, and neurofibrillary tangles, which consist of hyperphosphorylated tau. The pathogenesis of AD is not completely understood, but the prevailing theory holds amyloid accumulation as central to the start of the process (89). Genetic causes leading to increased production of amyloid are associated with early development of AD, as seen with the rare autosomal dominant mutations in hereditary AD and in Down syndrome (90). For other cases, failure of β-amyloid clearance may be essential (91). This may be induced by the accumulation of amylin amyloid that occurs in blood vessels and grey matter with age and metabolic diseases (92). ApoE mediates β-amyloid clearance, and the ε4 allele is less effective in this process than the other alleles (93). Even age-related changes in blood vessels may impair the clearance of β-amyloid (94).

For the neuropathological diagnosis of AD, elevated numbers of amyloid plaques are considered necessary but not sufficient. In dominantly inherited AD, biomarkers of amyloid pathology are the first biomarkers to change. Other changes are observed "downstream", occurring after increased amyloid accumulation. This encompasses activation of glia, neuroinflammation, hyperphosphorylation of tau with the formation of neurofibrillary tangles, and synaptic dysfunction.

There is much controversy regarding the role of amyloid in AD pathogenesis, and it is not clear whether amyloid causes the accumulation of tau or if this takes place independently. Although it is possible that amyloid plaques and neurofibrillary tangles do not have a causal role in AD, these abnormal protein accumulations define AD neuropathologically. Although the neuropathology criteria for AD have changed over time, the presence of amyloid plaques, neurofibrillary tangles, and neuritic plaques have remained unchanged (95).

Macroscopically, AD is characterised by brain atrophy, both whole-brain and hippocampal atrophy, and ventricular expansion (96). Post-mortem studies show that typical AD, the multidomain amnestic type, first affects structures in the medial temporal lobe (entorhinal cortex, hippocampal formations, parahippocampal gyrus) with

neurofibrillary tangles and neurodegeneration, and that this phenomenon later spreads to all of the allocortex and to neocortical areas (97), in a temporal and spatial pattern that is quite consistent in AD. Structural brain changes, as observed on imaging and macroscopically post-mortem, are associated both with the number of neurofibrillary tangles in the respective brain areas and with particular cognitive deficits, with atypical AD displaying patterns different from those of typical AD (98, 99).

Traditionally, there has been a distinction between types of dementia based on established clinical criteria thought to represent clinicopathological entities, but data from population-based neuropathology studies indicate that many people with dementia have several different pathologies in their brains (100, 101). Autopsy studies suggest that combinations of different types of neuropathology are increasingly common with age, account for most dementia cases in the oldest group of patients, and can be found in up to 75% of older adults in autopsy materials from community-based studies (102). Furthermore, older adults frequently have amounts of AD neuropathology sufficient for a histopathological diagnosis of AD dementia. However, some resilient individuals show no cognitive impairment despite a high burden of AD neuropathology, and these often have minimal or no brain comorbidities (103). The most common mixed pathology is AD and cerebrovascular lesions. Other common neuropathological findings are AD mixed with Lewy bodies, hippocampal sclerosis, TAR DNA-binding protein 43 (TDP-43) inclusions, and tauopathies not related to AD (104, 105).

How these different pathologic processes interact is unclear, and whether the deposition of one brain pathology may also cause the accumulation of a different pathology is not known, although some experimental data suggest that this may happen (106). Moreover, it is unclear whether having two or more pathologies concomitantly leads to additive or synergistic effects on cognition (103, 107).

As cerebrovascular disease in AD is a subject of this thesis, vascular brain pathology will be described in greater detail, while other brain pathologies will not be covered.

2.1.5 Cerebrovascular disease

Vascular lesions in the brain are increasingly common with advancing age and very common among people who meet the diagnostic criteria for AD. Neuropathological

studies of community-dwelling elderly people (both with and without dementia) show that almost half have microinfarcts at the end of life, a third have macroinfarcts, and a similar proportion has lacunes, while almost 60% show small-vessel disease (105). Some of these lesions are clinically recognised as strokes, but many of the smaller lesions lead to insidious changes that go unnoticed.

Cerebrovascular pathology is heterogeneous, encompassing both changes in the brain parenchyma and in the blood vessels themselves. Most patients have multiple types of cerebrovascular pathology, and for the majority, the vascular abnormalities are accompanied by other pathologies, most often of the AD type (105). CVD may occur in arteries of any size and sometimes in the veins, and it can be divided into large-vessel and small-vessel domains. Large ischaemic parenchymal lesions can be caused by occlusions, as a result of emboli, plaque ruptures, thrombotic occlusions, or dissections, but they can also result from haemodynamic events, causing watershed lesions. Although atherosclerosis in the large arteries to the brain is common in old age, large parenchymal lesions occur in only a subset of individuals, and on a population level, these large lesions are not a major contributor to cognitive impairment (108).

In contrast, parenchymal lesions caused by abnormalities in small vessels (the small arteries, arterioles, capillaries, and venules) in the brain are much more common, and these lesions are strongly associated with cognitive impairment (108). Changes in the vessels include atherosclerosis, lipohyalinosis, fibrinoid necrosis, microatheromas, and cerebral amyloid angiopathy. Parenchymal lesions associated with these vessel abnormalities include recent small subcortical infarcts, white matter hyperintensities (WMHs), lacunes, prominent perivascular spaces, cerebral microbleeds, microinfarcts, and atrophy. Changes in white matter may be caused by demyelination, axonal loss, astrocytosis, oedema, and macrophage reaction (109). Microinfarcts are small ischaemic lesions, 0.5–5 mm wide, found on microscopic examination (110). Abnormalities in the small vessels and the parenchymal lesions they cause are collectively referred to as small vessel disease (SVD). SVD mainly causes subcortical lesions, and the resulting cognitive decline is typically insidious.

Among memory clinic patients, microbleeds and lacunar infarcts are common findings, and about one-third may have WMHs severe enough to affect cognition (99, 111). The threshold for how much CVD is "abnormal" at various ages is debatable. Some types of SVD are especially common with advanced age and are found in cognitively normal people as well as in those who are cognitively impaired. Although there is evidence that cerebrovascular lesions are important for cognition on a group level, many cerebrovascular lesions, especially with SVD, are not very strongly associated with cognitive function in individual patients.

The cognitive impairment typical of CVD include deficits in executive dysfunction, slow information processing, and disturbances in working memory (112, 113). In addition, problems with visuospatial skills, language, and memory are common. However, as CVD can affect any cognitive domain, it can mimic the cognitive profiles of neurodegenerative diseases (113, 114). Typical behavioural changes include apathy, personality changes and depressive symptoms. Gait disturbances and urinary incontinence frequently occur early in the course of cognitive impairment, as opposed to the case in AD (113).

The literature shows conflicting results regarding whether concomitant CVD in AD leads to distinct cognitive deficits (115-117). The cognitive effects of SVD may be heterogeneous and not particularly distinct, and neuropsychological profiles have only a modest ability to distinguish between AD and subcortical VaD (114, 118). Increasing vessel pathology has been associated with an increased likelihood of being diagnosed with AD dementia, independent of the effect of infarcts and AD pathology, and associated with low scores on almost all cognitive domains, including episodic memory (119). At a given level of dementia severity, AD patients with coexisting CVD show a lower burden of AD lesions at autopsy than AD patients without other pathologies (120). Longitudinal studies with repeated cognitive assessments followed by post-mortem examination of the brain indicate that cerebrovascular disease in late-life reduces the level of cognition but that the effects remain relatively stable over time (121). Gross infarcts but not microinfarcts were associated with a faster rate of decline (122).

To establish that cerebrovascular disease has contributed to the development of cognitive impairment or dementia, there must be evidence of cognitive impairment where cerebrovascular disease can be established as a plausible cause. Sometimes the causative link is established from the medical history, as when an individual suffers a major stroke with abrupt cognitive impairment that becomes chronic. Otherwise, neuroimaging plays an important role in establishing the presence and extent of cerebrovascular disease.

2.1.6 Biomarkers in Alzheimer's disease

A biomarker is an objective and quantifiable characteristic of a biological process. Biomarkers in AD are objective medical signs of the disease process that can be measured accurately and reproducibly. They are widely used in research and partly used in the clinic as proxies for disease state or change. Biomarkers of AD in current use are obtained from cerebrospinal fluid, and from structural and functional neuroimaging, and there are promising research results for the development of plasma biomarkers for AD (123). In addition, there are genetic biomarkers (mutations) for the inheritable forms of AD (124). Biomarkers of AD fall into different categories. Some show the underlying pathophysiology, demonstrating the presence of amyloid or tau, and are markers of diagnosis. Others are downstream markers, demonstrating brain changes that are thought to result from the molecular pathology of AD and manifesting as neurodegeneration, which causes atrophy. These topographic biomarkers are closely linked to cognitive symptoms of the disease; as such, they may be biomarkers of the disease stage and may predict decline in patients with AD (2, 91, 125). The grouping of biomarkers has changed over time, with a recent position paper for AD research from the National Institute on Aging – Alzheimer's Association (NIA-AA) dividing biomarkers of pathophysiology as biomarkers of amyloid-β (A) and aggregated tau biomarkers (T), resulting in three categories of AT(N), where (N) stands for neurodegeneration (126). Whereas A and T biomarkers are indicators of neuropathological changes specific to AD, the (N) biomarkers are not specific to AD.

2.1.6.1 Biomarkers of Alzheimer's disease pathophysiology

The biomarkers of AD pathophysiology come from CSF and PET imaging. **Amyloid-β biomarkers** are CSF Aβ-42, or Aβ-42/ Aβ-40 ratio, and amyloid PET. In carriers of

autosomal dominant mutations causing AD, amyloid biomarkers are the first to become abnormal, and a common perception is that amyloid-β biomarkers represent the first evidence of AD neuropathological change (126). The typical findings in AD are decreased Aβ-42 in CSF and amyloid that can be detected on PET scans. Whereas amyloid PET can be used to measure amyloid plaque load, CSF Aβ-42 is associated with the formation of amyloid plaques but is not a measure of plaque load. CSF Aβ-42 has good specificity for AD, is highly correlated with neuropathological examinations in AD post-mortem, and increases diagnostic accuracy (127, 128). Amyloid-PET imaging has a very good agreement with the post-mortem validation of amyloid pathology, is a good predictor of progression from MCI to AD dementia, and has good concordance with CSF Aβ-42 (129-131). However, it has low sensitivity to change in the dementia stages, and it may be that CSF Aβ-42 becomes abnormal before amyloid-PET (132, 133). So far, amyloid-PET is used mostly in research. CSF biomarkers are widely used in memory clinics in the diagnostic workup.

Increased levels of CSF p-tau and t-tau is shown in AD and most research criteria have used elevated CSF p-tau and t-tau as biomarkers of AD pathophysiology (134). CSF t-tau and p-tau are closely correlated both in AD patients and in controls (135). The classification of **tau biomarkers** varies in diagnostic criteria for AD. The recently proposed NIA-AA criteria for research suggest only CSF p-tau and not CSF t-tau as a tau biomarker. This is based on observations that CSF t-tau may increase temporarily in stroke patients and in victims of traumatic brain injury and may reach very high levels in Creutzfeldt-Jakob disease, and therefore, it may be an indicator of ongoing neurological damage (126). In contrast to this, AD is thought to be the only disease that consistently shows an increase in p-tau (126, 134). Tau-PET is a recent addition to AD biomarkers and has gained some use in research. It has been added to tau biomarkers, as uptake values are associated with the amount of tau accumulation (126).

The high occurrence of abnormal biomarkers in the elderly limits their usefulness with increasing age. By age 70 amyloid biomarkers are abnormal in approximately one-third of cognitively normal persons, increasing to around one of two persons at age 85 (136-138). CSF t-tau is abnormal in around one of six persons with normal cognition at age 70, increasing to almost half in this group by 85 years of age (136, 137).

2.1.6.2 Biomarkers of neurodegeneration

The neurodegenerative or topographical biomarkers in AD become abnormal at a later stage than amyloid biomarkers do and are not specific to AD (126, 139). They include medial temporal lobe atrophy (MTA) on cerebral MRI and CT and reduced glucose metabolism in temporal-parietal regions on fluorodeoxyglucose positron emission tomography (FDG-PET) (140, 141). In the recent NIA-AA research framework, CSF t-tau is classified as a neurodegeneration biomarker.

MTA or hippocampal atrophy can be determined either by visual rating scales or by quantification, by manual segmentation, or by automated or semi-automated software (142). MTA correlates well with neurofibrillary tangle deposition, the number of neurons in the area, and cognitive deficits (143-145). Visual rating scales of MTA discriminate reasonably well between AD and normal controls, with 80–85% sensitivity and specificity for the distinction between AD dementia compared to normal controls and only slightly lower levels of sensitivity and specificity for aMCI (99). However, as a biomarker of neurodegeneration, hippocampal atrophy is not specific for AD, and MTA may have less ability to discern between different underlying brain pathologies, which limits the usefulness of the marker. In addition to pathologically confirmed AD cases, considerable hippocampal atrophy is found in hippocampal sclerosis, frontotemporal dementia, and degeneration caused by neurofibrillary tangles only (146). Some AD cases occur with atypical atrophy patterns with sparing of the medial temporal lobe (147-149). Visually assessed MTA is the most commonly available AD biomarker in clinical practice.

FDG-PET demonstrates areas with brain dysfunction by showing reduced glucose uptake and has good sensitivity to detect early changes in AD and to track progression with time (141, 150). It may be used to distinguish between different neurodegenerative disorders as the cause of dementia. Generally, PET scans are used in dementia diagnostics in the clinic only for highly selected cases, although they have found more use in research.

2.1.6.3 Other biomarkers

Other less commonly used biomarkers may also be used to distinguish AD from other forms of dementia. Single-photon computed tomography (SPECT) is a method for assessing brain metabolism, where the pattern of hypometabolism may aid in distinguishing different types of dementia. The method may be used to separate AD from dementia with Lewy bodies and from healthy controls, but as FDG-PET is superior in this regard, it has become the method of choice when available. Dopamine transporter (DAT) scan, which is a SPECT scan that demonstrates dopamine uptake in vivo, is useful in distinguishing dementia with Lewy bodies from AD and has shown a sensitivity of 78% and a sensitivity of 90% for this (151). However, Lewy bodies and AD neuropathology often occur together (152).

Electroencephalography (EEG) measures brain activity and reflects functioning synapses and neuronal signalling, and thus may be altered in dementia. EEG may also demonstrate functional aberrations, and topographical changes may indicate regions of pathology. The method may distinguish between different types of dementia and discriminate between dementia and healthy controls. Whereas EEG has been found to perform well in differentiating moderate and severe forms of AD from healthy controls and may be useful in separating dementia with Lewy bodies and Parkinson's disease dementia from other forms of dementia, it is unclear whether the diagnostic accuracy is good enough to make distinctions in other situations (153, 154).

2.1.7 Structural imaging in Alzheimer's disease and cerebrovascular disease

Originally, the role of structural imaging in diagnosing AD was limited to the exclusion of non-dementia disorders, for which computed tomography (CT) is sufficient. With the development of imaging biomarkers, structural imaging has gained a more important role and is informative for aetiological differential diagnoses, for which the resolution of MRI is superior to CT. In addition to MTA, described above, structural imaging yields information about other regional atrophy patterns, global atrophy, and cerebrovascular changes. Visual scales exist to evaluate global cortical atrophy, atrophy of the frontal brain regions, and posterior atrophy, and also to quantify WMHs (155-158). The typical appearance of AD on structural imaging is of global brain atrophy

with early pronounced and symmetrical MTA. Symmetrical MTA has a specificity and sensitivity of 80–85% in separating AD from normal ageing (159).

Neuroimaging plays an important role in establishing the presence and extent of CVD. MRI is more sensitive than CT, detecting microbleeds and providing better visualisation of WMHs. Neuroimaging does not visualise the vessel lesions but rather shows only the associated parenchymatous lesions. Based on the types of findings on neuroimaging, assumptions about vascular causes are made. Infarcts larger than 15 mm are generally thought to derive from large vessel or cardioembolic disease. Smaller infarcts and lacunes are ascribed to SVD, and this is the most common cause of large spontaneous intracerebral haemorrhages. Notably, neuroimaging is not able to visualise microinfarcts, which have been found in neuropathological studies to have a strong association with cognitive impairment (160). For WMHs, the potential causes are many, but when observed in older people, they are presumed to be of vascular origin, representing SVD. What is visualised on MRI as WMHs may reflect a wide range of neuropathological abnormalities, from slight changes to varying degrees of myelin and axonal loss, and white matter areas appearing normal on MRI may have neuropathological changes (161). Enlarged perivascular spaces are fluid-filled spaces around vessels that, focally, are wider than normal and have been associated with SVD. Cerebral microbleeds are small (typically 2–5 mm, but up to 10 mm) lesions. Lobar microbleeds are common with cerebral amyloid angiopathy, while deep periventricular microbleeds are associated with hypertension (110).

2.1.8. Diagnostic criteria

2.1.8.1 Diagnostic criteria for MCI

The term MCI was introduced to describe a transitional state of cognitive impairment before the dementia stage is reached. Several different MCI criteria have been proposed, of which the most widely used have been the International Working Group or Winblad criteria and the Petersen/Mayo Clinic criteria (3, 17, 162). All MCI criteria require the absence of dementia, some report of cognitive decline, and maintenance of basic activities of daily living. The Winblad criteria require the patient to have impairment on objective cognitive tasks accompanied either by self- and/or informant-reported decline or evidence of decline over time on tests. In addition, there must be only minimal

impairment in complex instrumental functions (17). The Petersen/Mayo Clinic criteria for MCI require cognitive complaints but preserved general cognitive function. There is no formal cut-off score for the objective memory impairment for age, but it is meant to represent a change from a previous level of function for the individual. In the original Mayo Clinic study on an MCI cohort, the mean performance of persons with MCI was 1.5 SD below the age normal (3). If an objective memory impairment is found, the condition is called amnestic MCI (aMCI), which can be either single domain or multiple domain. MCI without memory impairment is termed non-amnestic MCI, which can be single or multiple domain.

The DSM-5 uses the term "mild neurocognitive disorder" for MCI and bases the diagnosis on reports of decline in one or more cognitive domains and mild deficits (e.g. 1–2 SD below mean) on objective testing or a significant decline on serial testing. Deficits are not sufficient to interfere with independence (163). The new ICD-11 criteria use the same term as DSM-5 and characterise this as a subjective experience of cognitive decline accompanied by objective evidence of impairment in performance on one or more cognitive domains, relative to what should be expected of the individual and not sufficiently severe to interfere with activities of daily living (164).

Wide MCI criteria may lead to the inclusion of many conditions that do not represent the prodromal phase of a dementia disorder. Depression is mentioned as a cause of MCI (17). The demarcation between MCI and dementia may be difficult to ascertain, especially in older people. Additionally, the criterion of preserved functional abilities in MCI may be difficult to apply consistently, as many people with MCI will sometimes have problems with daily functioning and may need some assistance, and greater effort or compensation is often required.

2.1.8.2 Diagnostic criteria for dementia

Dementia is a syndrome characterised by a loss of intellectual abilities of sufficient severity to interfere with functioning in daily life, and the diagnosis of dementia is based on the presence of defined symptoms and signs. All diagnostic criteria for dementia require evidence of cognitive decline and of its consequences for patients'

daily lives and changes in behaviour, but other criteria have not been consistent between classification systems.

This study was conducted using the International Classification of Diseases 10th Revision (ICD-10) diagnostic criteria for dementia, which has as a prerequisite impairment of memory and at least one additional cognitive domain, with intact consciousness, and deterioration in emotional control, social behaviour, or motivation, that has lasted at least six months (165). The other widely used coding system for dementia apart from the ICD-10 is the Diagnostic and Statistical Manual of Mental Disorders (DSM) criteria. Until recently, all criteria have required memory impairment to be present for diagnosing dementia. However, in the latest diagnostic criteria, this has been altered, as memory problems are not necessarily a predominant feature of all types of dementia. The recently published International Classification of Diseases 11th revision (ICD-11) (164) requires two impaired cognitive domains, but these do not have to include memory. A similar modification was made in the DSM-5 version; however, these criteria limited the minimum number of affected cognitive domains to one.

2.1.8.3 Diagnostic criteria for Alzheimer's disease

AD has traditionally been regarded as a clinicopathological entity that was diagnosed as probable or possible AD based on clinical symptoms while the patient was alive and confirmed only by a post-mortem examination (166). Since definite diagnosis requires the histological confirmation of brain tissue, this could be obtained only after the patient had died, except in rare cases where a brain biopsy was done or where an autosomal dominant mutation in the APP or presenilin genes had been identified. For all other AD patients, diagnoses given to living patients could only be "probable" or "possible", depending on how well the clinical symptom profile fit the disease criteria. AD neuropathology may also be found in post-mortem examinations in individuals who never displayed clinical symptoms of AD and does not qualify for a diagnosis of AD (167).

Based on the original National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria, a two-step procedure has been necessary to diagnose AD (166). First,

a diagnosis of dementia must be confirmed and, subsequently, other causes of dementia must be ruled out by blood investigations and neuroimaging, and in some cases, additional tests such as cerebrospinal fluid (CSF) examinations. Then, symptom profile and test results supporting AD as a cause of the dementia syndrome could lead to the diagnosis of AD. The NINCDS-ADRDA criteria for AD describe deficits in two or more areas of cognition, with progressive worsening of memory and other cognitive functions. Progressive deterioration of specific cognitive functions such as language, motor skills and perception, and impaired activities of daily living (ADL) and behavioural changes support the diagnosis while a history or neurologic findings suggestive of a stroke make the diagnosis of AD uncertain or unlikely.

The widely used International Classification of Diseases and Related Health Problems 10th revision (ICD-10) criteria for dementia in AD are similar, requiring the disease to be in the dementia stage and the dementia criteria fulfilled. Additionally, the disease progression in AD should be gradual and slow; there should be no evidence suggesting other causes of the dementia condition; and there should be no signs of a sudden onset, as with a stroke (165).

The recently published ICD-11 criteria describe two stages of AD; mild neurocognitive disorder, which corresponds to MCI, and dementia (164). The criteria for AD are not substantially changed from the ICD-10 version, but no longer emphasises the exclusion of other diseases or sudden onset and state that positive genetic testing, family history and gradual cognitive decline are highly suggestive of dementia due to AD (164).

The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, (DSM-5) also describes two stages, applying the terms mild and major neurocognitive disorders due to AD, where major neurocognitive disorder corresponds to dementia (163). These criteria contain a distinction is between probable and possible AD. The criteria for probable AD require clear evidence of decline in memory and one other cognitive domain, gradual decline and no evidence of mixed aetiology. Evidence of a causative AD genetic mutation also qualifies for probable AD. All other cases are classified as possible AD (163).

Newer diagnostic criteria for AD for use in research, as described below, have been developed to replace the NINCDS-ADRDA and other earlier AD criteria, making use of biomarkers. AD is still a clinical diagnosis, but biomarkers are extensively used for research diagnoses and increasingly applied in the clinic, as well, where MTA on MRI is the most widely available biomarker.

2.1.8.4 Newer diagnostic criteria for Alzheimer's disease for use in research

AD has a long preclinical period, followed by a prodromal phase with mild symptoms, the MCI stage, before the disease reaches the dementia stage. AD pathology is already widespread by the time patients develop the first cognitive symptoms and long before they meet the diagnostic criteria for dementia. Therefore, there is increasing focus on early diagnosis enabling drug trials before the dementia stage, when considerable and irreversible loss of neurons has occurred. Thus, much research in AD has centred on identifying disease biomarkers and characteristics that would enable earlier diagnosis. From the patients' perspective an early diagnosis may be important as an explanation of symptoms, and some patients can profit from information about their prognosis.

The original NINCDS-ADRDA diagnostic criteria for AD had low diagnostic accuracy, with shortcomings both in their ability to distinguish AD from other types of dementia and in the correlation between the clinical symptom profile and the neuropathological diagnosis (168). Between 10% and 30% of cases diagnosed clinically as AD dementia by experts do not show AD neuropathological changes at post-mortem examinations, and a similar fraction has normal CSF or PET amyloid (169). The multidomain amnestic dementia phenotype is, therefore, not specific for AD. However, 30–40% of elderly persons with normal cognition have AD neuropathological changes at autopsy, and abnormal amyloid biomarkers are found in a similar proportion (170, 171).

The precision of the diagnostic workup has improved through the identification and characterisation of other dementia disorders with specific criteria, such as dementia with Lewy bodies, frontotemporal dementia, and corticobasal degeneration, and through the development of biomarkers for AD. The inclusion of biomarkers in diagnostic criteria has improved the diagnostic accuracy of AD and has led to a major change in the conceptualisation of the disease. Two new conceptual frameworks for the diagnosis of

AD has been proposed in recent years by the International Working Group (IWG) and by the National Institutes of Aging – Alzheimer's Association (NIA-AA), based on the requirements for earlier and more-specific diagnoses of AD (91, 124, 125, 172-174). In these frameworks, AD is regarded as a continuum, starting before clinical symptoms appear and extending through the MCI stage in addition to the dementia stage. In these diagnostic systems, abnormal biomarkers can be used as surrogate markers of the underlying AD pathology, enabling a diagnosis of AD *in vivo*.

The IWG criteria, first published in 2007 and updated in 2010 and 2014, have emphasised AD as a clinical and biological entity that includes all phases of the disease (124, 125, 172). The diagnosis of AD is based on a specific clinical symptom profile, either with deficits in episodic memory or with one of the non-amnestic types of AD: the language variant (logopenic aphasia), the visuospatial variant (posterior cortical atrophy), or the variant with executive dysfunction (frontal variant). Biomarkers are supportive measures that serve to confirm AD as the underlying cause and can be considered surrogate markers for neuropathological changes; the diagnosis of AD can then be made *in vivo*. In these criteria, AD diagnosis is no longer limited to the dementia stage, and the MCI stage is classified as prodromal AD.

Similar to the IWG criteria, the NIA-AA criteria divide the clinical phase of AD into MCI and AD dementia. Biomarkers are applied to classify whether MCI is caused by AD. The NIA-AA criteria can be applied without supporting biomarkers but at the expense of diagnostic specificity. Recently, the NIA-AA proposed a new framework for research dividing the major AD biomarkers into three categories based on the type of pathological change each measures: β-amyloid (A), pathological tau (T), and neurodegeneration (N), with the aim of increasing the specificity of AD diagnoses (175).

2.1.9 Alzheimer's disease with cerebrovascular disease

Mixed pathologies of the brain are common in patients with dementia, and the most frequent combination is AD and vascular disease (102). Despite this, there are no clinically or neuropathologically established criteria for the type of symptoms or amount of pathology that must be present in order to diagnose mixed dementia or AD

with cerebrovascular disease. Several diagnostic criteria for dementia include separate categories for AD with cerebrovascular disease or have separate classifications of mixed dementia in general. There is discrepancy between the diagnostic criteria in what is regarded as mixed dementia. Some definitions require patients with mixed dementia to meet diagnostic criteria for both conditions while to other definitions it is enough to fulfil criteria for one of them, with evidence of the other aetiology (112, 163, 165, 173, 176). Thus, meaning of the term "mixed dementia" varies considerably, and some use the term "AD with cerebrovascular disease" (124, 163, 164, 177). Although cerebrovascular lesions are the most common neuropathology seen with AD, other pathologies are frequent, such as Lewy bodies, TDP-43, and hippocampal sclerosis, but these will not be addressed in this thesis.

To establish that cerebrovascular disease has contributed to the development of cognitive impairment or dementia, there needs to be evidence of cognitive impairment where cerebrovascular disease can be established as a plausible cause. Sometimes, the causative link is established by the patient's medical history, as when an individual suffers a major stroke with an abrupt cognitive impairment that becomes chronic. Otherwise, neuroimaging plays an important role in establishing the presence and extent of cerebrovascular disease. The typical symptom profile of vascular cognitive impairment is described as impaired frontal-executive functioning, complex attention and/or speed of information processing, in addition to gait disturbances, urinary symptoms not explained by urologic disease, and changes in personality and mood (113).

2.1.10 Treatment for Alzheimer's disease

Despite numerous drug trials in recent years, there is still no medication available for AD that can halt or reverse the disease process (178). The only treatment options at the present time are drugs that modulate the levels of neurotransmitters to provide temporary symptomatic improvement. Cholinesterase inhibitors, including donepezil, rivastigmine and galantamine, block the enzyme, thereby decreasing the breakdown of acetylcholine and increasing the available levels of the neurotransmitter in the neuronal synaptic cleft. The N-methyl-D-aspartate (NMDA) receptor antagonist memantine modulates glutamate activity at the postsynaptic membrane. These drugs offer only

modest symptomatic effects, and there is no evidence that treatment influences or prolongs survival. Several non-pharmacological interventions, including exercise programs, psychosocial interventions, music, aroma and light therapy, cognitive training, and alternative medicine have been researched but will not be addressed in this thesis (179).

2.2 Progression of Alzheimer's disease

There is considerable variation in disease-progression rates, for both AD and dementia in general. Although extensive research has focused on risk factors for developing AD, little is known about predictors for disease course after the onset of symptoms. Reliable predictors of disease course would be important for patients and their families, as well as for society in planning for care, but currently these are impossible to provide. Evidence about factors associated with progression would enhance the understanding of disease mechanisms and possibly enable interventions to slow the rate of decline. This is particularly interesting as there is still no effective drug available to repair or halt the damage caused by AD.

2.2.1 Prognosis of Alzheimer's disease

The clinical course in AD is a generally irreversible deterioration over time, but the rate of decline varies considerably. With the passage of time, cognitive decline leads to functional impairments, first apparent in complex and demanding tasks, such as handling financial issues. Gradually, problems evolve with different instrumental activities of daily living (IADL), such as shopping and cooking, and progress to difficulties with basic activities of daily living such as dressing and hygiene. Whereas cognitive and functional impairment typically deteriorates with disease duration, behavioural changes may occur in all phases of the disease course. Some changes in behaviour or mental status may be transient, while others, such as loss of initiative, are often constant. Functional decline is associated with increasing needs for both informal and formal care, often aggravated by neuropsychiatric symptoms, and reduced quality of life (180).

2.2.1.1 Survival

Longitudinal studies have established that decline in cognitive test scores starts more than a decade before dementia becomes apparent, followed by accelerated decline a few

years before dementia diagnosis (181-184). About 10–15% of patients with aMCI convert to AD dementia per year during the first years of follow-up, and ultimately, 20–40% of all MCI patients progress to dementia (18, 185). People with AD survive an average of 5–10 years after being diagnosed with dementia, but some individuals survive up to 20 years (186-188). Measured from the onset of symptoms, median survival vary from 3 to 12 years. According to WHO, in general, people with dementia typically spend the first couple of years in the mild or early stage of dementia, followed by the moderate stage from the second to the fourth or fifth year, and are ultimately in the severe stage from the fifth year onwards (4). Norwegian studies have previously found a median survival of 6.9 years from dementia diagnosis in AD patients. For all-cause dementia, a mean disease duration of 8.1 years has been shown, with 3.0 years from the start of symptoms to diagnosis, 3.0 years from diagnosis to the patient entering a nursing home, and 2.1 years in a nursing home before death (6, 189). Mortality is increased in all symptomatic stages of AD, including MCI, and greater risk of death has even been reported in asymptomatic individuals with positive biomarkers of AD, compared to normal controls (190, 191). In late-stage AD, the excess mortality is 8% compared to age- and gender-specific mortality rates (192). In population-based studies, people with MCI have approximately 1.5–2 times greater risk of death within five years than those with normal cognition. Predictors for increased mortality are older age and lower baseline cognitive and functional abilities (190). The potential years of life lost due to dementia have been estimated as three to five years for people with dementia who are older than 75 years (186, 193).

2.2.1.2 Predictors of survival

The large variation in reported survival time for AD patients likely reflects differences in study samples, settings, diagnostic criteria, doctors' competence regarding dementia, and at what point in the disease course patients receive a diagnosis. Older age, more-severe disease at the time of diagnosis and comorbidities are associated with shorter survival times (194). Comorbidities are more prevalent among AD patients compared to controls, and vascular diseases are frequent (195-197). For the oldest patients with dementia, comorbidities and disabilities may be stronger predictors of mortality than dementia. Male gender is associated with increased mortality in many but not all studies

(186, 187, 198). More-recent studies report longer survival times in dementia, but this may be explained by trends towards earlier dementia diagnosis and better general health and longer life expectancy in the elderly population (199).

2.2.1.3 Assessment of decline

Apart from measuring survival time, disease progression in AD can be assessed by the use of continuous or staging scales measuring changes over time. Continuous scales may measure cognitive, functional, or behavioural aspects of the disease or integrate several dimensions of dementia in a global score. Alternatively, scales may define disease stages. Measuring disease progression with continuous or staging scales enables the assessment of AD progression across all disease stages. The use of a global score may integrate cognitive and functional aspects of the disease.

Corresponding to the heterogeneity in reported survival rates in AD dementia, there are considerable differences in reported progression rates as measured by the various scales. There might be several explanations for these differences. Study samples vary, and AD research is often performed in memory clinics and other specialist settings where patients differ from the general dementia population. Memory clinic patients tend to be younger, in earlier stages of the disease, have fewer comorbidities and have higher levels of education attainment and fewer comorbidities.

To be useful for determining progression in AD, measurement scales should be sensitive to changes in the disease stages where the patient is currently and where he or she could be expected to be during the period of follow-up, while assessment scales often have different inherent properties and vary in their performance in the different stages of AD. A general problem is that many tests are insensitive to changes either in the early stages of dementia or in the late stages, phenomena described as ceiling and floor effects of the scales. This commonly applies to cognitive tests. They are frequently used to measure disease progression in AD and may be sensitive to change at an early stage where no functional changes are recognisable, but people with MCI or even mild dementia might still perform within the normal range. Among patients with severe dementia, cognitive tests often cannot be applied, as the patient becomes unable to perform them.

Loss of function is a key component of the dementia diagnosis. Functional impairment typically occurs at a later stage than cognitive problems in AD, and functional scales may detect changes even in severe stages when cognitive testing may be impossible. Functional scales measure the ability to perform ADL, which can be divided further as the more-complex instrumental activities of daily living (IADL), such as taking care of financial issues, medications, household chores and transportation, and basic or personal ADL functions, such as toileting, bathing, dressing, and eating. Thus, functional scales will have to include IADL functions to capture early losses but may still be insensitive to initial impairments in AD. In order to capture changes across the entire disease spectrum, both IADL and ADL should be assessed. Global scales that integrate both cognitive and functional aspects of the disease have the possibility of being sensitive in a wide range of disease stages.

2.2.1.4 Scales to measure decline

Numerous scales of cognition, function, neuropsychiatric symptoms, and global ratings are used both in clinical work and in AD research. Commonly used global rating scales include the Clinical Dementia Rating scale (CDR), the Global Deterioration Scale (GDS) and the Functional Assessment Staging (FAST) (200-202). The Mini-Mental State Examination (MMSE) is the most widely used cognitive test; other commonly used cognitive scales include the Alzheimer's Disease Assessment Scale – Cognitive Subscale (ADAS-Cog), the CERAD neuropsychological test battery, and the Montreal Cognitive Assessment (MoCA) (203-206). Many different functional scales are used, such as the IADL scale and the Physical Self-Maintenance Scale (for ADL) by Lawton and Brody, the Alzheimer's disease Cooperative Study – Activities of Daily Living Inventory (ADCS-ADL), the Disability Assessment for Dementia Scale (DAD), the Functional Activities Questionnaire, and the Barthel Index (207-211). Although behavioural changes in dementia may be transient, these symptoms may also persist and show increasing severity; therefore, compound measures may be relevant, such as the Neuropsychiatric Inventory Questionnaire (NPI-Q) (212-214).

There have been attempts to model disease progression in AD dementia in a multidomain framework, where the progression of cognitive, functional and behavioural changes has been assessed separately, and a worsening in at least one of these domains

has counted as AD progression (215). Each domain may be divided into mild, moderate, and severe states, and in a large study analysing data from 3000 patients seen at Alzheimer disease centres across the United States, almost three of four patients experienced a change of state in at least one domain over 12 months. The majority of them changed in just one domain, and for >70% of patients, the change was not in cognition (215). This contrasts with many studies of AD progression that merely or primarily considered cognitive function (216). Studies indicate that changes in cognition and function are related, but changes in neuropsychiatric symptoms may occur independently (214, 217).

Current methods available for measuring AD progression offer useful insights, but all have limitations. As each approach differs, both in use of scales or endpoints and mathematical methods used for analyses, the consequences are different estimates for survival times, hazard ratios, transition probabilities, or regression equations. Therefore, results cannot be compared directly.

2.2.1.5 Measures of progression rates

Progression is generally described as slower in the initial stages than in more-advanced stages of the disease, which is reflected both in global and cognitive scales (214, 218-220). Therefore, assessments of progression rates may differ according to disease stage, and predictions about progression may not be valid across stages. If disease progression accelerates with time, assuming linearity in progression rates may lead to erroneous assumptions. To avoid these effects, calculations of disease-progression rates should preferably be based on serial measurements (at least three), allowing for non-linear trajectories, or analysed separately by disease stages. Differences in study participants' disease stages and in analytic methods across studies may explain some of the observed variations in progression rates.

Considerable individual variation is observed in progression rates (221, 222). Notably, there may be differences between samples derived from specialised memory clinics and those from population-based studies, the latter having shown slower progression (214, 223). Slow progression, defined as a yearly change of less than one point on the MMSE and the global scale Clinical Dementia Rating Sum of Boxes (CDR-SB), has been

observed in 23–52% of AD cases (214, 222, 224). Rapid progression, defined as a decrease of three to five points per year on the MMSE, has been shown in 10–30% of AD cases, depending on the threshold set and the population studied (225, 226). The concept of rapid progression, as defined by a larger-than-normal loss of points on the MMSE over a relatively short period, has been criticised. A study following 324 AD patients, clustering them as "rapid", "intermediate", and "slow" progressors based on the number of points lost in the first 12 or 18 months, did not find persistent differences between the groups when examining disease progression for four years (227). Notably, this period of follow-up exceeds those of most other studies that have examined rapid progression.

For patients with MCI, the most commonly used progression measure is the percentage of patients who convert to dementia or the likelihood of progression within a given time. Estimates vary widely with study population, duration, and MCI criteria applied.

As newer diagnostic criteria for AD have regarded the disease as a continuum with MCI as the early symptomatic stage, many recent studies have measured disease progression with continuous measurement scales, such as the CDR-SB or the MMSE, starting from the MCI stage and continuing in dementia (228, 229).

2.2.2 Predictors of progression in Alzheimer's disease

Since there are large individual differences in progression rates for AD, several studies have examined factors of importance for the disease course. While a risk factor is connected with the chance of developing a condition, a predictor or prognostic factor can be used to estimate the future course of a disease. Predictors of disease course are much-less studied than risk factors for developing AD. Many of the identified AD risk factors have also been hypothesised to be predictors of disease course, and some studies have been conducted to explore these. Predictors that are potentially modifiable, such as depression and VRFs, have attracted interest as possible targets for intervention.

Most studies, but not all, find that young age at onset is associated with a more rapid progression in AD patients (221, 230). This variability regarding the effect of age may be explained by differences in study populations and whether the studies have controlled for comorbidities. There are conflicting results regarding gender differences

in the progression of AD, and at present, there is no consensus on these (221, 230, 231). Results are heterogeneous regarding the association between ApoE genotype and progression of AD dementia, but the ApoE ε4 genotype is associated with a moderately increased risk for progression from MCI to AD dementia (230, 232). Patients with dementia and a high level of education seem to have a more rapid progression in the majority of studies, although some studies have reported no effect of education on disease progression (221, 230). For patients with aMCI, the number of years of education does not predict disease progression to dementia (233, 234). More-severe cognitive and functional impairment at the time of diagnosis is associated with a more rapid progression in AD patients, and impairment in executive functions may predict progression (221, 226, 230, 235). There is inconsistent evidence as to whether neuropsychiatric symptoms predict disease progression from aMCI to AD dementia, and findings have been conflicting as to whether depression can impact AD progression (234, 236-238). In the PADR study, we found that a more rapid progression of AD was associated with increased depressive symptoms (236-238). Research on comorbidity burden as a predictor of progression in AD has rendered inconsistent results, but overall, studies suggest that comorbidities may contribute to a more rapid progression (194).

2.2.2.1 Vascular risk factors and progression of Alzheimer's disease

Although many studies identify one or several VRFs as associated with disease progression in AD, the evidence is conflicting, and a systematic review found inconsistent results for VRFs (239). Table 1 shows the result of studies on VRFs and their association with progression in AD. Generally, most studies identified one or several VRFs as predictors of progression, but in many cases, effect sizes were small, and not all studies reported having adjusted for performing multiple analyses.

2.2.2.2 Biomarkers and progression of AD

The CSF biomarkers Aβ-42, p-tau, and t-tau have been shown to predict MCI conversion with 83–95% sensitivity and 72–83% specificity (240, 241). In patients with AD dementia, high or very high levels of p-tau and t-tau in combination with low levels of Aβ-42 are associated with worse clinical outcomes over time (242, 243). FDG-PET has been found to have a sensitivity of 89% and a specificity of 85% for predicting conversion from MCI to AD dementia, while amyloid PET has a higher sensitivity at

95% but lower specificity at 57% (244). Tau PET is a new and less explored biomarker of AD but may be more closely associated with cognitive decline than other neuroimaging biomarkers (245).

2.2.2.3 Medial temporal lobe atrophy on MRI

MTA has been found to be a predictor of disease progression from MCI to dementia in AD, with an overall specificity of 75% (95%CI 67–82%) and a sensitivity of 60% (95%CI 51–68%) for visual ratings (246). The ability of MTA to predict disease progression later in the disease course of AD has been less studied, and one recent study of mild AD dementia found no difference in baseline hippocampal volume between patients with rapid progression and others (99, 231). In longitudinal measurements, more-pronounced hippocampal volume loss is associated with rapid progression in AD (247).

Table 1. Studies on the effect of vascular factors on disease progression in AD

Factor	Faster progression	No effect on progression	Slower progression
Vascular risk factors in general	Roselli et al. (248) 2009; Li et al. (249) 2010; Kume et al. (250) 2011	Bhargava et al. (251) 2006; Regan et al. (252) 2006; Abellan van Kan et al. (253) 2009; Blom et al. (254) 2014	
Vascular burden	Viticchi et al. (255) 2015; Viticchi et al. (256) 2017	Mielke et al. (257) 2007	
Hypertension	Bellew et al. (258) 2004; Mielke et al. (257) 2007; Razay et al. (259) 2009; Li et al. (249) 2010; Li et al. (260) 2011; Sakurai et al. (261) 2011; Blom et al. (254) 2014, Qiao et al. (262) 2014	Bhargava et al. (251) 2006; Ravaglia et al. (263) 2006; Abellan van Kan et al. (253) 2009; Musicco et al. (264) 2009; Helzner et al. (265) 2009; Prasad et al. (266) 2011; Sona et al. (267) 2012; Bergland et al. (268) 2017; Bos et al. (269) 2017	
Hypercholesterolaemia	Evans et al.. (270) 2004; Helzner et al. (265) 2009; Li et al. (260) 2011	Abellan van Kan et al. (253) 2009; Musicco et al.. (264) 2009; Li et al.. (249) 2010; Prasad et al. (266) 2011; Sakurai et al. (261) 2011; Sona et al. (267) 2012; Blom et al. (254) 2014; Qiao et al. (262) 2014; Bergland et al. (268) 2017; Bos et al. (269) 2017	

Diabetes mellitus	Helzner et al. (265) 2009; Roselli et al.. 2009; Li et al. (249) 2010; Li et al. (260) 2011	Regan et al. (252) 2006; Barghava et al. (251) 2006; Ravaglia et al. (263) 2006; Abellan van Kan et al. (253) 2009; Prasad et al. (266) 2011; Sakurai et al.. 2011; Sona et al. (267) 2012; Blom et al. (254) 2014; Qiao et al. (262) 2014; Bergland et al. (268) 2017; Bos et al. (269) 2017	Mielke et al. (257) 2007; Sanz et al. (271) 2009; Musicco et al. (264) 2009; Ravona-Springer et al. (272) 2010;
Smoking	Bergland et al. (268) 2017	Bhargava et al. (251) 2006; Regan et al. (252) 2006; Fellows et al. (273) 2008; Helzner et al. (265) 2009; Li et al. (249) 2010; Li et al. (260) 2011; Sona et al. (267) 2012; Blom et al. (254) 2014; Bos et al. (269) 2017	
Obesity	Dumont et al. (274) 2003	Abellan van Kan et al. (253) 2009; Li et al. (249) 2010; Blom et al. (254) 2014; Bos et al. (269) 2017	Cova et al. (275) 2016; Bergland et al. (268) 2017
Hyperhomocysteinaemia	Qiao et al. (262) 2014		
Atrial fibrillation	Mielke et al. (257) 2007	Regan et al. (252) 2006; Li et al. (249) 2010	
Heart disease	Helzner et al. (265) 2009; Bleckwenn et al. (276) 2017	Li et al. (249) 2010; Sona et al. (267) 2012; Blom et al. (254) 2014	
Cerebrovascular disease	Mungas et al. (277) 2001; Regan et al. (252) 2006; Sheng et al. (278) 2007; Helzner et al. (265) 2009; Ezzati et al. (279) 2017	Del Ser (280) 2005; Bruandet et al. (281) 2009; Li et al. (249) 2010; Sona et al. (267) 2012; Blom et al. (254) 2014; Bos et al. (269) 2017	

3 The present study

3.1 Aims and hypotheses

The main aim of this thesis was to study predictors of disease progression in AD, with a particular focus on how comorbid vascular diseases and VRFs and MTA influence progression. In addition, we wanted to study whether symptom profiles in AD patients with CVD differed from those of patients without CVD. Our hypotheses were that disease progression in AD could be predicted by patient characteristics at the time of diagnosis, that vascular burden would be associated with a more rapid progression of AD, and that AD patients with concomitant CVD would display symptom profiles different from those of other AD patients. We hypothesised that AD patients with CVD would have less-pronounced MTA and that MTA would be a predictor of progression in AD.

More specifically, the aims were explored in four substudies and published in four papers:

I. To study the overall progression of AD, as measured by the primary outcome measure CDR-SB; secondly, to investigate whether patient characteristics at the time of diagnosis are significant for differences in progression and to examine the correlation between progression assessed by a global score (CDR-SB) and progression in cognitive (MMSE) and functional (IADL) measures.

II. To explore whether visual assessment of MTA using Scheltens MTA scale can predict conversion from MCI to dementia and whether MTA can predict progression as defined by an increase in CDR-SB in patients with MCI and mild AD dementia.

III. To investigate whether single VRFs and vascular diseases and total vascular burden are predictors of progression in AD.

IV. First, to examine cognitive test results and measures of depression in AD patients with aMCI and mild dementia with and without CVD, and, secondly, to assess MTA on MRI among AD patients with and without CVD.

The first part of the work is focused on disease progression and the second part on the importance of vascular diseases and risk factors for patients with AD.

3.2 Methods

3.2.1 Study design

To address the aim, we conducted four substudies, all based on the same longitudinal observational study, the Progression of Alzheimer's Disease and Resource use (PADR) study. The study started with patients from Oslo University Hospital, Ullevål and Innlandet Hospital Trust who had been included in a clinical research register recruiting patients from memory clinics with standardised assessments, the Norwegian register for persons with cognitive symptoms (NorCog). Later he study was extended to St. Olavs hospital, Trondheim University Hospital.

The PADR study was originally designed with the goal of exploring predictors of progression in dementia and MCI. Patients with dementia or MCI were considered eligible for the study. In the current substudies on vascular disease, it was later decided to include only those patients with AD dementia and aMCI in analyses. The patients with aMCI were categorised as AD in analyses, as described in section 3.2.3. St. Olavs hospital, Trondheim University Hospital recruited patients with a clinical diagnosis of AD; and in addition, patients with cognitive impairment who had diagnostic CSF were included due to another study.

The baseline assessment was conducted at the time of diagnostic workup in the three participating memory clinics, and one follow-up assessment was done after a mean of two years. Assessments took place between 2009 and 2015. Substudies I, II, and III had a longitudinal design, whereas substudy IV had a cross-sectional design.

3.2.2 Study participants

Patients were recruited from three Norwegian memory clinics, one at Oslo University Hospital, Ullevål; one at Innlandet Hospital Trust in Hamar; and one at St. Olavs Hospital, Trondheim University Hospital. Patients were mostly referred to the memory clinics by general practitioners but in some cases by other specialists.

Patients eligible for the PADR study were those who met the following criteria: diagnosed with dementia or MCI; were home-dwelling; had a proxy who could serve as an informant; spoke Norwegian; did not have serious comorbid diseases with life

expectancy shorter than two years; lived close enough to the centres to be reassessed; and had the capacity to consent to the study.

The memory clinics at Oslo University Hospital, Ullevål and Innlandet Hospital Trust included 352 patients in the NorCog register between May 2009 and June 2012 who met the inclusion criteria for the PADR study. They were contacted and asked to participate in a follow-up assessment for the PADR study. From the memory clinics affiliated with NorCog, 212 participants with MCI or dementia at baseline agreed to undergo the follow-up assessment.

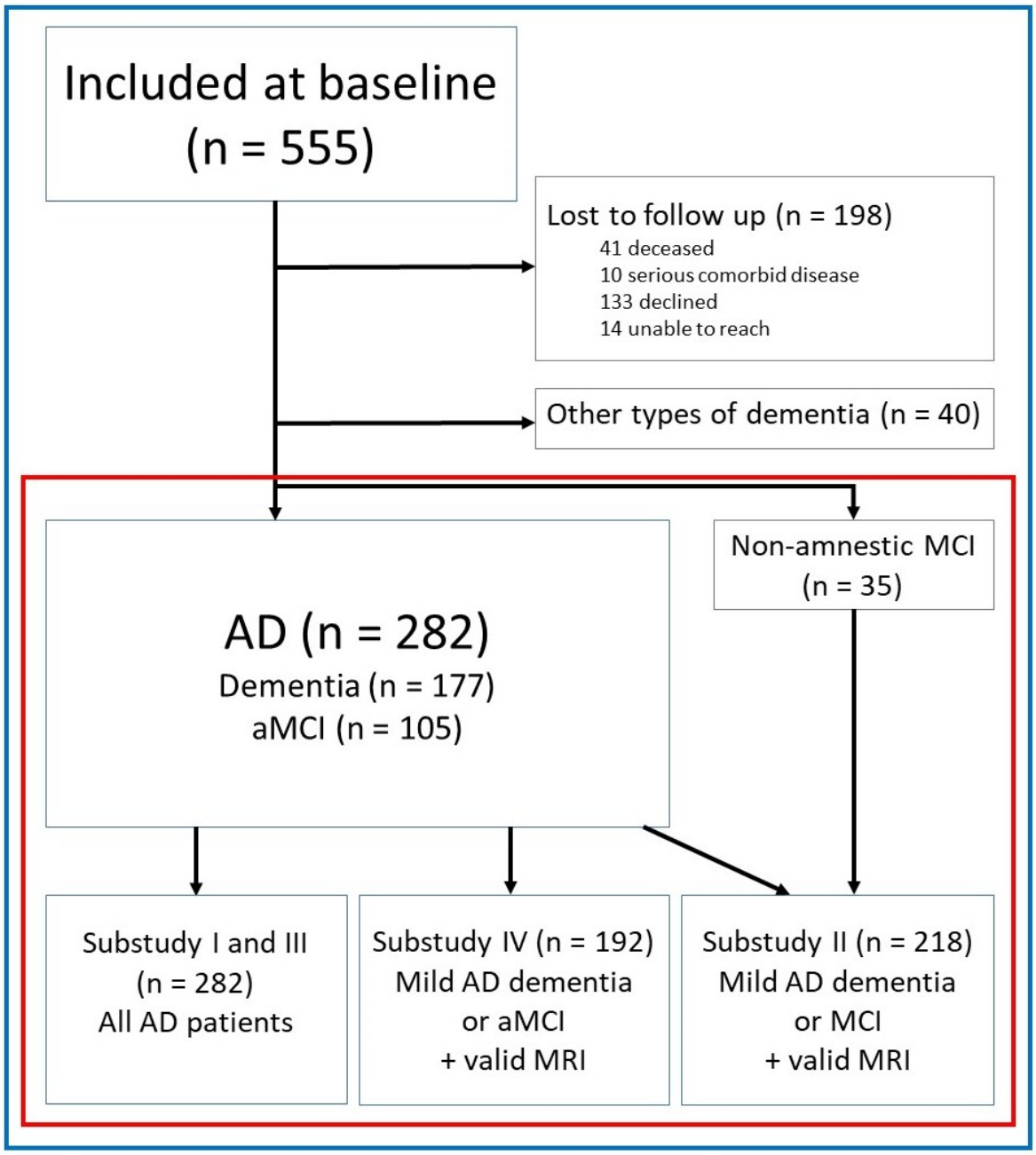
In addition to the NorCog patients, the memory clinic at the geriatric department at St. Olavs Hospital, Trondheim University Hospital prospectively recruited 203 patients for the PADR study between February 2010 and February 2014. These patients were asked to participate in the PAR study at the time of diagnostic workup at the memory clinic and informed that they would be contacted again for a follow-up assessment. Of these 203 patients, 128 individuals underwent a follow-up assessment. For 17 additional patients who were not able to meet for the follow-up assessment due to their medical condition, information was collected from caregivers only.

Substudies I and III were based on all patients in the PADR study who had a diagnosis of AD dementia or aMCI (n = 282) (Figure 1). Substudy IV included patients with mild AD dementia or aMCI who had an MRI with T2-weighted scans taken within 6 months of the baseline examination (n = 192). Substudy II included patients with mild AD dementia or MCI (amnestic or non-amnestic) who had been assessed by a coronal-section MRI of the brain within 6 months of the baseline examination (n = 218). Baseline characteristics of the different substudies are given in Table 2.

3.2.3 Diagnostic criteria, diagnoses and procedures for making the diagnoses

The ICD-10 criteria for research were used to diagnose dementia and the Winblad criteria to diagnose MCI (165). The NINCDS-ADRDA criteria were used for AD dementia. MCI patients with impaired memory as an early and predominant symptom and a score equivalent to or below 1.5 SD on at least one memory test were classified as aMCI, in accordance with the Petersen criteria (3). This applied to both patients with impairment of memory alone (single-domain MCI) and patients with impairment of

Figure 1. Study flowchart for the Progression of Alzheimer's Disease and Resource use (PADR) study and the present study. The blue frame represents the PADR study and the red frame the present study.



AD: Alzheimer's disease; aMCI: amnestic mild cognitive impairment; MCI: mild cognitive impairment; MRI: magnetic resonance imaging

other cognitive domains in addition to memory (multi-domain MCI). Primarily, the CERAD Word List Memory test, delayed recall task (described in Section 3.2.4) was the memory test used to distinguish aMCI from non-amnestic MCI. The group of aMCI patients was categorised as AD (without dementia).

Table 2. Baseline characteristics in the different substudies

	Substudy I and III	Substudy II	Substudy IV
Number of patients	282	218	192
Site of inclusion			
Oslo University Hospital, Ullevål	136	116	99
St. Olavs Hospital, Trondheim University Hospital	130	95	89
Innlandet Hospital Trust	16	7	4
Age, years (SD)	73.3 (8.8)	71.7 (9.2)	72.7 (8.3)
Females, n (%)	153 (54.3)	116 (53.2)	104 (54.2)
Education, years (SD)	11.7 (3.6)	12.1 (3.6)	12.0 (3.6)
MMSE (SD)	23.7 (4.4)	24.3 (4.4)	24.0 (4.4)
Diagnosis			
AD dementia, n	177	124	117
amnestic MCI, n	105	76	75
non-amnestic MCI, n	**0**	**18**	**0**

AD: Alzheimer's disease; MCI: mild cognitive impairment; MMSE: Mini-Mental State Examination; SD: Standard deviation

For differential diagnosis, we used the following criteria to separate AD from other brain disorders that can cause dementia: The McKeith criteria were used for dementia with Lewy bodies (282) and the Neary criteria for frontotemporal dementia (283). Patients with pre-existing Parkinson's disease were diagnosed with Parkinson's disease dementia when they met the ICD-10 criteria for dementia. Vascular dementia was diagnosed according to the ICD-10 criteria for research (165). Patients who met the NINCDS-ADRDA criteria for AD and also had vascular changes were classified as AD. Information on ApoE status was not available in the diagnostic process. CSF biomarkers were available only for a subset of patients: 110/282 patients (39%) in substudy I and III, 97/218 in substudy II (44%), and 88/192 patients (46%) in substudy IV. Decreased Aβ-42 and/or elevated p-tau or t-tau in CSF supported an AD diagnosis.

Study researchers were experienced physicians with clinical experience in geriatric medicine and old-age psychiatry. Two study researchers diagnosed all included patients

from St. Olavs Hospital, Trondheim University Hospital and from Innlandet Hospital Trust in consensus. For patients from Oslo University Hospital, Ullevål, an interrater reliability analysis was performed between two of the researchers, showing substantial to very good interrater agreement for MCI (kappa 0.66) and AD diagnoses (kappa 0.73 for early-onset AD and 0.85 for late-onset AD). Because of the high kappa, patients from the memory clinic at Oslo University Hospital, Ullevål were diagnosed by one researcher (physician) alone. Only two of the centres assigned the research diagnoses (Oslo University Hospital, Ullevål, and St. Olavs Hospital, Trondheim University Hospital) and an interrater reliability analysis between these two centres showed substantial agreement for all diagnoses (kappa 0.66 for MCI, 0.65 for early-onset AD, and 0.71 for late-onset AD). The same study researchers diagnosed patients at follow-up at St.Olavs Hospital, Trondheim University Hospital and Oslo University Hospital, Ullevål, while one physician, with research experience in multicentre studies, diagnosed patients in Innlandet Hospital Trust at follow-up.

3.2.4 Assessments

The baseline assessments of patients and the interviews with caregivers were performed as regular consultations by consultants and nurses employed at each memory clinic and standardised in a case-record form. Patients underwent comprehensive neuropsychological and physical examinations at baseline, with most of the tests repeated at follow-up (Table 3). The evaluation included measurements of height, weight, systolic and diastolic blood pressure, blood tests, and in most cases an electrocardiogram (ECG). Demographic data, smoking status and medications in current use were recorded. Medical history was obtained from hospital records, from referral letters from general practitioners, and from interviews with patients and relatives.

The study researchers performed the follow-up assessments after a mean of 24 months (range 16–37, 80% between 20 and 28 months). If possible, patients living in nursing homes at the time of follow-up assessments were visited at the nursing home. Otherwise, information was collected through telephone interviews with caregivers. Most assessments from baseline were repeated at follow-up. Ongoing use of cholinesterase inhibitors and/or memantine at follow-up was registered.

Table 3. Assessments performed at baseline and follow-up

	Baseline	Follow-up
Sociodemographic characteristics	x	x
Current medications	x	x
Smoking status (never/former versus current)	x	
Previous disorders		
Stroke	x	
Transient ischemic attack	x	
Hypertension	x	
Heart disease	x	
Atrial fibrillation	x	
Peripheral artery disease	x	
Diabetes	x	
Hypercholesterolemia	x	
Measurements		
Systolic and diastolic blood pressure (mm Hg)	x	x
Height (cm), weight (kg), and body mass index (kg/m^2)	x	x
Blood sample	x	
ApoE status	x	
ECG	x	
Brain imaging		
MRI (CT)	x	
Cognitive assessments		
MMSE-NR	x	x
Word-List Learning Test (from CERAD)	x	x
The clock drawing test	x	x
Trail Making Test A and B	x	x
Neuropsychiatric assessments		
Cornell Scale for Depression in Dementia	x	x
Neuropsychiatric Inventory Questionnaire	x	x
Proxy information		
Duration of symptoms	x	
Physical Self-Maintenance Scale (Lawton and Brody)	x	x
Instrumental Activities of Daily Living (Lawton and Brody)	x	x
Clinical Dementia Rating Scale score*	**x**	**x**

**Scoring was based on all available information from the patient and from the proxy. PADR: Progression of Alzheimer's Disease and Resource Use; ApoE: Apolipoprotein E; ECG: electrocardiogram; MRI: magnetic resonance imaging; CT: computer tomography; MMSE-NR: Mini-Mental State Examination-Norwegian Revised Version; CERAD: Consortium to Establish a Registry for Alzheimer's Disease*

3.2.4.1 Primary outcome: the Clinical Dementia Rating Scale (CDR)

The **Clinical Dementia Rating Scale** (CDR) was used as the primary outcome measure in the PADR study. Although designed primarily for carers and proxies, the CDR allows for all sources of information to be used to score the patient. This is one of the

most widely used measures of dementia severity, assessing six different areas: memory, orientation, judgment and problem solving, community affairs, home and hobbies

personal care, with scores 0, 0.5, 1, 2, or 3 (with higher scores denoting poorer function). A global score of 0–3 is calculated based on an algorithm that weights memory as the primary domain, returning a global score of 0–3 (284). Zero is the best possible score, indicating no cognitive impairment; 0.5 translates to uncertain or subtle cognitive impairment; and 1, 2, and 3 indicate mild, moderate, and severe dementia, respectively. However, a CDR score of 0.5 does not equate to MCI, as CDR is a severity rating scale and not a diagnostic instrument. Patients with a CDR score of 0.5 may meet the diagnostic criteria for MCI, or they may have mild dementia (3).

For research, the score of each item can be summed, constructing a continuous scale 0–18 (higher scores denoting poorer function), the CDR Sum of Boxes (CDR-SB). As an outcome measure, trials with CDR-SB require smaller sample sizes to detect a significant difference compared to trials with cognitive outcome measures (285). It has been suggested that since each change in item score of 1 or 0.5 points represents a clinically recognisable decline in an area of AD symptomatology, a change of 1 (or even 0.5) point in the CDR-SB could be clinically relevant (286). We have not been able to determine whether this has been verified in studies; neither have we found any study examining the minimal clinically important difference of the CDR-SB. It may be argued that the minimal clinically important difference is likely to be less than the difference between the CDR stages, as there are distinct clinical differences between normal cognition, MCI, and mild, moderate and severe dementia. Studies staging dementia based on the CDR-SB have proposed scores of 0.5–2.0 for questionable impairment, 2.5–4.0 for very mild dementia, 4.5–9.0 for mild dementia, 9.5–15.5 for moderate dementia and 16.0–18.0 for severe dementia (287). From this perspective, a clinically important difference may be no more than 2 or 3 points, possibly less. As the CDR score is derived from an algorithm giving preference to the memory item, there is no direct translation between the CDR-SB and CDR scores. However, when comparing CDR-SB scores with CDR scores, a CDR-SB of 0.5–4.0 corresponds to a CDR score of 0.5 in most cases, while CDR-SB of 4.5–9.0 corresponds to CDR 1, CDR-SB 9.5–15.5 corresponds to CDR 2, and CDR-SB 16.0–18.0 corresponds to CDR 3.

The CDR was originally developed as a staging instrument, and thus, it is unlikely that an increase from 1 to 2 in an item score represents twice as much change as an increase from 0.5 to 1, and the change of one point in an item score does not necessarily equal a one-point change in a different item.

The CDR is a well-validated instrument with high interrater reliability (218). It has been proposed as the primary outcome measure for clinical trials in early AD, as it comprehensively assesses both cognitive and functional disability in AD patients and thus has the potential to detect change throughout the disease course (219, 288). CDR is less affected by age than cognitive tests (289). Some studies have explored the items of CDR with factor analysis, finding that the first three items load to a "cognitive" factor and the last three to a "functional" factor (218, 219).

All study researchers underwent online training as recommended by the Washington University Alzheimer's Disease Research Center, which created the CDR, and all fulfilled the requirements for certification as "CDR raters" (290). The study researchers independently scored all patients on the CDR based on all information available from the baseline assessments, both from patients and proxies, and the same certified researchers assessed the patients at follow-up.

3.2.4.2 Cognitive assessments

Cognition was measured with a comprehensive test battery performed at baseline, with the majority of tests repeated at follow-up as shown in Table 3.

The **Mini-Mental State Examination (MMSE)** is the most widely used performance-based cognitive screening instrument (203, 291). This brief tool assesses orientation, attention, registration, calculation, recall, language, and construction in 20 items, with a maximum score of 30. The Norwegian version was introduced in 1984 and has good validity for dementia (292). The Mini-Mental State Examination-Norwegian Revised Version (MMSE-NR), introduced by Strobel and Engedal in 2008, was used in this study. Traditionally, scores above 24 have been considered normal, but they are influenced by age and education, and other cut-off points have been proposed (293).

The test is designed for repeated testing with specific instructions for retesting; however, practice effects have been seen in non-demented subjects (294). Limited

response ranges are causes of floor and ceiling effects, limiting the test's utility in advanced dementia as well as for detecting early cognitive deficits. The test is not very sensitive to change but might be most sensitive to changes in the middle to late stages of AD (295, 296). Furthermore, there is little consensus on what constitutes an appropriate threshold for determining a decline in the patient's cognitive status. Different attempts have been made to address this issue, ranging from expert opinions to statistical methods of estimating significant differences; most studies have found that a change in MMSE score must be above 2–4 points to be clinically meaningful (297, 298).

The **CERAD Word List Memory test**, also called the 10-word test, from the Consortium to Establish a Registry for Alzheimer's Disease (CERAD), is used to assess memory (206). This test has three different tasks that investigate different aspects of memory: learning, delayed recall, and recognition. The present study used the two first tasks. In the **learning** task, the patient is presented with 10 words and asked to name them afterwards, and this is done three times, giving a score from zero to a maximum of 30 if all words are recalled each time. After 10 minutes, the patient is asked to recall as many of the 10 words as possible in the **delayed recall** task (score 0–10). Finally, the patient is asked to recognise the 10 words when presented together with 10 new words (score 0-20). For all tasks scores increase with education and decrease with age; thus, scores are interpreted based on normative data. Both learning and delayed recall are sensitive to impairments of memory as seen in early AD, and the delayed recall test, especially, has been found to be useful for the early detection of disease (299). A change in test scores from 4 to 8 points in the learning task or a change of 2 to 4 points in delayed recall has been found to be outside what could be ascribed to practice effects, measurement error, and/or normal age-related cognitive decline (300).

The **clock drawing test** is a widely used cognitive screening test involving many cognitive functions, including attention, working memory, visual memory, visuospatial abilities, and executive function (291). The test was administered and scored in the version described by Shulman, which requires the patient to place numbers on a pre-drawn circle, said to represent a clock face, and then set the time at "10 past 11". The test is rated on a scale ranging from 0–5, with higher scores denoting better functioning (301). Research on whether the clock drawing test is able to differentiate between MCI

and normal cognition has identified conflicting results, and the test is more sensitive to the cognitive decline associated with dementia (302). The clock drawing test was included in substudy I, but due to high correlation with other cognitive tests, was omitted from multiple regression analyses.

The **Trail Making Test** (TMT) **A and B** is among the most frequently administered cognitive tests; part A is believed to assess visual scanning and psychomotor speed, while part B is believed to assess these abilities in addition to working memory and divided attention (303). The test measures the time in seconds it takes a patient to complete each of two tasks. In part A, the task is to draw lines connecting consecutively numbered circles from 1 to 25, whereas in part B, the same number of consecutively numbered and lettered circles must be connected, alternating between numbers and letters. We measured the time patients needed to complete each test. Shorter time indicates better psychomotoric speed and executive function. Patients who were unable to complete the tests because of cognitive impairment were given the maximum time of 180 (TMT A) and 360 seconds (TMT B) in analyses. Normal scores in the Trail Making Test decline with age and may be influenced by education (304, 305). Patients' scores were interpreted based on age-stratified normative data.

3.2.4.3 Instrumental activities of daily living

Instrumental activities of daily living (IADL) were assessed using the scale by Lawton and Brody, designed originally to guide the choice of living arrangements for elderly people (207). The scale evaluates the ability to manage eight activities, based on questions: to use the telephone, shop, prepare food, clean the house, do laundry, handle transportation, take care of one's own medications and handle finances. Each IADL item can be scored as "0" (dependent) or "1" (independent). The test has gender and cultural biases. In our study, three of the items ("prepare food", "housecleaning", and "laundry") were not applicable to many of the patients, especially men, and were omitted from analyses. The sum score was divided by the number of items evaluated, giving a score ranging from 0 (completely dependent) to 1 (completely independent). The scale has been criticised for inconsistencies in the scoring of single items and for having ceiling effects, and the minimal clinically important difference has not been explored in studies (306). However, the minimal clinically important difference is not

known for other IADL scales either, and generally, many IADL scales have moderate or low measurement quality of measurement properties (306).

3.2.4.4 Neuropsychiatric assessments

Depressive symptoms were assessed in interviews with caregivers using the **Cornell Scale for Depression in Dementia** (CSDD). The scale is designed specifically to assess depressive symptoms among elderly patients with dementia and assesses 19 items with scores of 0–2, for a total score of 0–38, where higher scores indicate the presence of more depressive symptoms (307). The scale is validated for use in elderly subjects both with and without dementia, and a previous study in Norwegian memory clinics has identified a cut-off of ≥6 for depression (308-310).

Behavioural change was assessed with the **Neuropsychiatric Inventory Questionnaire** (NPI-Q). This 12-item informant scale rates the severity of neuropsychiatric symptoms on a scale of 0–3, for a total score of 0–36; higher scores indicate the presence of more or more-severe neuropsychiatric symptoms (311). The minimum clinically meaningful change in the NPI-Q has been found to be around 3 points in patients with dementia (312). The NPI-Q was included in substudy II, but since few patients displayed these symptoms (39 of 218), the variable was not included in further analyses.

3.2.4.5 Biological measurements

Blood-sample analyses were done for standard assessments, including cholesterol, creatinine and glucose. Apolipoprotein E (ApoE) genotyping was conducted using the Illumina Infinium OmniExpress v1.1 chip at deCODE Genetics, Reykjavik, Iceland, and the result was dichotomised based on the presence of at least one ApoE epsilon 4 (ApoE ε4) allele into carriers and non-carriers of ApoE ε4.

Cerebrospinal fluid (CSF) was drawn in 110 of the 282 patients with AD (34% of aMCI patients and 42% of patients with AD dementia) and analysed for A42, T-tau, and P-tau.

3.2.4.6 Vascular risk factors and vascular burden

VRFs were classified based on medical history and records, medication use, and findings at baseline. Patients were considered as having hypertension when it was reported in their medical records, if using antihypertensives (angiotensin-converting enzyme inhibitors, angiotensin II receptor antagonists, beta blockers, diuretics, or

calcium antagonists), or if they had a blood pressure of >140 systolic or >90 diastolic at baseline. Patients were classified as having hypercholesterolaemia if this was reported in the medical history, used statins, or had a total cholesterol level of ≥ 6.5 mmol/l at baseline. Diabetes was registered by medical history or use of any antidiabetic drug. Being overweight was defined as having a body mass index ≥ 25 kg/m^2, and patients were registered as smokers if they smoked at baseline, regardless of former smoking history. Atrial fibrillation (AF) was recorded from the medical history and ECGs. Information on previous strokes, transient ischemic attacks, heart disease (angina pectoris, myocardial infarction, heart failure, or valvular disease), and peripheral artery disease was retrieved from the hospitals' medical records.

To assess the vascular burden of each patient, the Framingham Stroke Risk Profile (FSRP) was calculated (313) (Table 4). The score integrates the effects of age, gender, and measurements of systolic blood pressure; the use of antihypertensive treatment; diabetes mellitus; current smoking status; prevalent cardiovascular disease; current or previous AF; and the presence or absence of left-ventricular hypertrophy on ECG.

Cardiovascular disease is defined in this risk score as a history of myocardial infarction, angina pectoris, intermittent claudication, or congestive heart failure. ECGs were examined for left-ventricular hypertrophy according to the Framingham criteria (314). In addition to the original FSRP, risk scores for all patients were calculated with the recently published revised FSRP, based on more current data on stroke risk factors, with a lower impact of AF and prevalent cardiovascular disease (315).

Blood-pressure measurements were missing for 3, smoking status for 7, weight and height for 26, creatinine for 10, cholesterol measurements for 48, and ECG for 71 patients. When measurements were not available, VRF status was based on medical history and drug use alone.

3.2.4.7 Structural brain imaging

Structural brain imaging was performed for all patients at baseline, using magnetic resonance imaging (MRI) in most cases; however, some patients underwent CT scans because of pacemakers or claustrophobia. The MRI examinations were regular clinical examinations conducted at several different centres using different MRI protocols.

Table 4. The Framingham Stroke Risk Profile

Men	Points										
	0	**+1**	**+2**	**+3**	**+4**	**+5**	**+6**	**+7**	**+8**	**+9**	**+10**
Age (years)	54–56	57–59	60–62	63–65	66–68	69–72	73–75	76–78	79–81	82–84	85
Untreated SBP (mm Hg)	97–105	106–115	116–125	126–135	136–145	146–155	156–165	166–175	176–185	186–195	196–205
Treated SBP (mm Hg)	97-105	106–112	113–117	118–123	124–129	130–135	136–142	143–150	151–161	162–176	177–205
Diabetes	No		Yes								
Smoking	No			Yes							
Cardiovascular disease	No				Yes						
Atrial fibrillation	No				Yes						
Left ventricular hypertrophy	No					Yes					

Women	Points										
	0	**+1**	**+2**	**+3**	**+4**	**+5**	**+6**	**+7**	**+8**	**+9**	**+10**
Age (years)	54–56	57–59	60–62	63–64	65–67	68–70	71–73	74–76	77–78	79–81	82–84
Untreated SBP (mm Hg)		95–106	107–118	119–130	131–143	144–155	156–167	168–180	181–192	193–204	205–216
Treated SBP (mm Hg)		95–106	107–113	114–119	120–125	126–131	132–139	140–148	149–160	161–204	205–216
Diabetes	No			Yes							
Smoking	No			Yes							
Cardiovascular disease	No		Yes								
Atrial fibrillation	No						Yes				
Left ventricular hypertrophy	No				Yes						

Probability of stroke within 10 years in relation to points scored on the Framingham Stroke Risk Profile

Points	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**	**27**	**28**	**29**	**30**
Men, 10-year probability, %	3	3	4	4	5	5	6	7	8	10	11	13	15	17	20	22	26	29	33	37	42	47	52	57	63	68	74	79	84	88
Women, 10-year probability, %	1	1	2	2	2	3	4	4	5	6	8	9	11	13	16	19	23	27	32	37	43	50	57	64	71	78	84			

From D'Agostino et al. 1994 (313). SBP: systolic blood pressure. Left-ventricular hypertrophy defined by ECG criteria. The given points are for each of the seven variables age, systolic blood pressure (either for untreated or treated, depending on the use of antihypertensive medication), diabetes, smoking, cardiovascular disease, atrial fibrillation and left-ventricular hypertrophy.

Only MRIs performed within six months before or after the clinical assessment at baseline were included for analyses (mean 2.3 months (SD 1.5), within < 4 months for 88% of participants). Due to the examination of MTA and WMHs, only those with MRIs with coronal sections were selected for substudy II; those with T2 weighted images were selected for substudy IV.

An experienced neuroradiologist examined the MRI scans blinded to all clinical data and diagnostic information. This evaluation took place after patient recruitment was complete. MTA was rated using Scheltens MTA scale (142), which includes evaluation of the choroid fissure, the temporal horn of the lateral ventricle, and the height of the hippocampus, yielding a score of 0-4 (higher score denoting more atrophy). MTA was assessed on the left and right sides separately, and the mean score was calculated. WMHs were evaluated using the Fazekas scale, rating severity of WMHs in the periventricular and subcortical regions combined on a scale of 0–3 (316). The presence and number of lacunes (≤10 mm) and cortical infarcts were recorded.

3.2.5 Statistics

Data were analysed using IBM SPSS Statistics for Windows, versions 22.0, 23.0, 24.0, and 25.0, Armonk, NY, USA. In general, data in all substudies were normally distributed. When in doubt, normality plots were discussed with a statistician, taking into account the total number of subjects. Categorical variables were compared using Pearson's χ^2 test and continuous data compared with independent samples t-tests. In all substudies, a p value below 0.05 was used as a threshold for statistical significance. No adjustment for multiplicity was made.

Sample size estimations

Based on registry data from NorCog, where 40% of patients were registered with at least one of the VRFs, including hypertension, hypercholesterolaemia, hyperhomocysteinaemia, or diabetes, we estimated that 50% of the patients would have VRFs or established vascular disease when the list of conditions was extended to include cerebrovascular events and heart disease. Based on suggestions in the literature and on clinical experience, we estimated that a difference in the CDR-SB score of 2 points would be clinically significant. From the literature, we estimated the expected

CDR-SB progression to be 1.6 points per year, which translates to 3.2 points in the course of 24 months of follow-up. We expected that patients with AD with concomitant vascular disease or VRFs would progress 5 points on the CDR-SB in 24 months. If 50% of AD patients have VRFs or vascular diseases, in order to detect a difference in progression rates between AD patients with and without VRFs of 1.8 points, with $\alpha = 0.05$ and beta = 0.10, we estimated that 63 patients would be needed in each group, for a total of 126 patients. Due to high attrition rates in studies of elderly people with cognitive impairment and in order to enable subgroup analyses, we calculated that we needed to double this number, i.e. 252 patients with AD.

The smallest sample size in the four substudies was 192 patients. This sample size ensures at least 90% power to detect group differences of 0.5 standard deviations (SD) or larger. If true differences are small, however, the power will be low. In all substudies, a p-value of < 0.05 was used as the threshold for statistical significance.

In substudy I, multiple linear regression was used to explore which baseline variables predicted progression, as measured by CDR-SB change per year of follow-up. Intercorrelations between independent variables were checked using the Spearman rho coefficient, and variables with > 0.5 were not included. Tolerance statistics and variance inflation factor were used to check for multicollinearity. The external responsiveness for annual changes in the scores for the CDR-SB, MMSE, and IADL were examined with Spearman correlation coefficients, and the analysis was extended to examine "cognitive" and "functional" domains of the CDR-SB, based on factor analyses in the literature.

The MMSE was missing for some patients because they had been assessed only by telephone interview, with an informant at follow-up. In order to check the validity of the primary analyses, missing cognitive data on the MMSE were imputated for these patients. Imputations were based on age, education, baseline MMSE, and baseline CDR-SB, as well as dementia diagnosis, place of residence (nursing home or own home), and CDR-SB at follow-up.

In substudy II, logistic and linear regression analyses were conducted to explore which variables predicted conversion from MCI to dementia and progression rate in patients

with MCI or AD dementia. Bivariate and multiple regression models were estimated. All multiple regression models were reduced by Akaike's information criteria (AIC), where a smaller value implies a better model and were adjusted for age and gender. As the study included three centres, a logistic regression model for hierarchical data and a linear mixed model were estimated to adjust for a potential clustering effect. The clustering effect appeared to be negligible in adjusted models. In the second part of the study, a growth mixture model was estimated on the CDR-SB measured at baseline and follow-up to identify unknown groups of patients following distinct trajectories. Groups were defined as distinct if the average probability of belonging to a group exceeded 0.7, and 95% confidence intervals for trajectories were non-overlapping. The identified trajectory groups were compared with ANOVA and the χ^2 test. Nominal logistic regression analysis was conducted to assess predictors of group belonging.

In substudy III, linear regression analyses were conducted to explore the association between vascular factors and disease progression, as measured by annual CDR-SB change, and analyses were adjusted for age and gender.

In substudy IV, several multiple linear regression analyses were performed to explore the effect of concomitant cerebrovascular disease on cognitive test results, depressive symptoms, and MTA in AD.

3.2.6 Ethical considerations

The study was conducted according to the Helsinki Declaration; participation was voluntary; and patients received oral and written information and gave written consent to participate. Only patients with the capacity to consent at baseline were recruited. Patients' capacities to consent were evaluated in connection with the cognitive assessment at baseline. Due to their lack of capacity to consent, the study did not include any patients with severe dementia. The Regional Committee for Medical and Health Research Ethics in Southeast Norway approved the study (REC number 2011/531).

4 Results

4.1 Substudy I – Progression of Alzheimer's disease

General results

Patients who were reassessed in the study had characteristics similar to those who were lost to follow-up, with the following exceptions: they had less formal education, were more often smokers and living alone, and a higher proportion of them received the lowest scores on the Trail Making Test, part B.

A mean increase (worsening) in CDR-SB score of 1.6 points/year (SD 1.8, cut-points for highest and lowest quartiles 0.3 and 2.2 points per year), a mean decline in MMSE scores of 1.9 points/year (SD 2.6, cut-points for highest and lowest quartiles 0 and 3.1 points/year), and a mean decline in IADL of -0.13/year (SD 0.14) were found. Users of choline esterase inhibitors or memantine did not differ in progression rates from non-users. MMSE values were missing at follow-up for some patients who were unable to come back to the memory clinic and for whom assessment was done as a telephone interview with their caregiver. Multiple imputations of these missing MMSE values at follow-up rendered an annual loss of 2.1 points on the MMSE instead of 1.9 points.

Slow and rapid progression

Applying a definition of slow progression as less than a 1-point worsening on the CDR-SB per year, 47% of the patients were slow progressors, of these 11% had better scores at follow-up, 7% unchanged score, and 28% less than one point annual worsening. The proportion of patients having slow progression on the MMSE (<1 point per year) was 44. For IADL functions, 60% of patients showed little decline, with independence lost on no more than one item from baseline to follow-up.

Slow progressors were present in all disease stages examined. A total of 52% of the patients with a CDR of 0.5, 44% of the patients with a CDR of 1 and 27% of those with a CDR of 2 at baseline had a less than 1-point worsening on the CDR-SB per year. Slow progressors were younger at diagnosis ($p < 0.001$), had more formal education, better IADL function, and scored better on cognitive tests (MMSE, word-list delayed recall, clock drawing test, and Trail Making Test B, all $p < 0.001$).

Rapid progression, as defined by a decrease in the MMSE score of 6 points or more per year, was found in 7% of patients.

Predictors of progression

In unadjusted regression analyses, significant associations were found between age (p = 0.001), number of medications taken regularly (p = 0.050), Trail Making Test B scores (p < 0.001), CERAD word-list delayed recall score (p < 0.001), and change in the CDR-SB. In the adjusted analysis, including age, ApoE ε4 carrier status, Trail Making Test B score, word-list delayed recall score, history of hypertension, and number of medications taken regularly, only the Trail Making Test B score remained significant (p < 0.001). The model including these variables explained R^2 = 17% of the variance of the change in CDR-SB score.

Correlations analyses between measures of progression

The correlation between change in the CDR-SB and change in IADL was somewhat stronger than the correlation between the CDR-SB change and MMSE change. Dividing CDR-SB into cognitive and functional subscores, changes in both subscores correlated more strongly with IADL change than with MMSE change. The weakest correlation was found between MMSE change and IADL change. When analysed separately by CDR group, correlations were generally strongest for the CDR 1 group, followed by the CDR 0.5 group.

4.2 Substudy II – Visual evaluation of medial temporal lobe atrophy as a predictor of progression

General results

Comparisons of patients with a valid MRI at baseline with patients without a valid MRI showed that patients without MRI had lower MMSE and higher CDR-SB scores at baseline; fewer had hypertension; and a larger proportion had AD dementia (57% versus 40%, p = 0.012). Patients with MRIs had higher annual progression rates as measured with the CDR-SB (p = 0.013), but the proportion of patients converting from MCI to dementia did not differ (56% versus 43%, p = 0.151).

MCI patients had an annual increase in CDR-SB of 0.91 (SD 1.55), while patients with mild AD dementia had an annual change of 2.14 (SD 2.01). The annual conversion rate from MCI to dementia was 27%.

Medial temporal lobe atrophy as a predictor of progression

An unadjusted regression model with CDR-SB as outcome identified an interaction between visually assessed MTA and diagnosis (whether the patient was diagnosed with MCI or AD dementia). In an adjusted model, only age ($p = 0.034$) and word-list delayed recall ($p = 0.029$) were significant predictors. For MTA scores below two, the association between MTA and progression differed between patients with MCI diagnosis and with AD dementia diagnosis, with the annual CDR-SB change being higher in patients with AD than in patients with MCI.

Visually assessed MTA was found to be a predictor of MCI conversion in an unadjusted model ($p = 0.001$) but not in the adjusted model ($p = 0.075$). In the adjusted model, only word-list delayed recall ($p < 0.001$) and ApoE ε4 carrier status ($p = 0.043$) were significant predictors.

Trajectory analysis

A trajectory analysis was performed and identified four distinct groups that differed in progression rate. Two of these groups had a quite stable course, including a total of 73% of patients. The group with the lowest baseline CDR-SB and little progression (group 1) was used as the reference in a nominal regression model comparing the groups. In the adjusted model, a diagnosis of AD dementia, lower scores on the word-list delayed recall, and advanced age were predictors of membership in a group with more progression. The CSDD score was found to be a predictor of being in a group with higher (worse) CDR-SB baseline scores but with limited further decline (group 2; $p = 0.021$). MTA was not found to be a significant predictor of group membership in the adjusted model.

4.3 Substudy III – Association between vascular comorbidity and progression of Alzheimer's disease

General results

VRFs were prevalent among the AD patients of this study, where 83% had hypertension, 53% hypercholesterolaemia, and 9% diabetes; 41% were overweight; and 10% were smokers. Only 6% of the patients referred to in this substudy had none of these VRFs, whereas 24% had one, 45% had two, 20% had three, and five percentages had four of these VRFs; no patient had all five of them. A history of vascular disease was reported for 33% of the patients, the most common being heart disease (16%) and cerebrovascular events (15%). On MRI, 16% had lacunar and four percentages had cortical infarcts. WMHs with a Fazekas score of 2 and 3 were present in 26% and 33%, respectively.

Vascular risk factors and diseases as predictors of disease progression in Alzheimer's disease

Unadjusted regression analyses revealed no significant associations between any individual VRF and progression of AD. There was a trend for patients with BMI above the normal range to progress less quickly than others ($p = 0.09$).

The Framingham Stroke Risk Profile was calculated to estimate the vascular burden of importance for brain health, and analyses were repeated with the newly revised version of this risk tool, based on risk factors and stroke incidence in recent decades. The revised FSRP scores gave significantly lower stroke-risk estimates, but neither the revised nor the original FSRP scores showed any significant association with AD progression.

The existence of cerebrovascular disease on MRI, as infarcts (cortical or lacunar) or WMHs, was not found to predict progression in AD.

Additional subgroup analyses on patients with untreated hypertension, hypercholesterolaemia or diabetes did not reveal any association with progression of AD.

4.4 Substudy IV – Symptom profile in Alzheimer's disease with and without concomitant cerebrovascular disease

General results

In this substudy, 63% of the AD patients had concomitant CVD, as defined by the presence of any cortical or lacunar infarctions on MRIs or WMHs with Fazekas 2 or 3. In unadjusted analyses, patients with concomitant CVD were older (75.4 versus 68.1 years, $p < 0.001$) and more likely to report a history of a cerebrovascular event (24/121 versus 4/71 patients, $p = 0.007$) than patients without CVD. The group with CVD had higher CDR-SB scores (4.1 versus 3.4 points, $p = 0.024$), poorer results on the Trail Making A ($p = 0.015$) and B tests ($p = 0.011$) and the word-list immediate recall test ($p = 0.031$). No significant differences in delayed recall or MMSE scores were found, nor in depressive symptoms as measured with the CSDD.

When adjusting for age and gender, there were no significant associations between CVD and the results of cognitive tests or depressive symptoms. Adjusting for CDR-SB score in addition to age and gender did not change the results. Subgroup analyses were performed for aMCI and mild dementia. Numerically, the effects seemed to be weaker in the dementia group, but no significant difference between the aMCI and the dementia group was observed.

The association between CVD and MTA

The group with CVD had more-pronounced MTA (2.1 versus 1.5 points, $p < 0.001$). The association between CVD and MTA was significant in the adjusted analysis ($p = 0.011$).

5 Discussion

In the present descriptive study recruiting patients from three different memory clinics, we studied predictors of progression in AD in general and with a particular focus on how comorbid vascular diseases and VRFs influence disease progression. We examined the association of VRFs, vascular diseases, and vascular burden with disease progression and explored the ability of baseline characteristics, cognitive test results, and MTA on MRI to predict the progression of AD. We examined AD patients with and without cerebrovascular disease for differences in symptom profile. We found that baseline cognition and age predicted progression rate but explained a small fraction of the variance in progression. Vascular comorbidity was not associated with progression of AD. The degree of MTA was not associated with progression of AD. Few predictors of progression of AD were identified, and most of the variance remained unexplained. Concomitant cerebrovascular disease in AD patients was associated with different results on cognitive tests in unadjusted analyses, but this association disappeared after adjusting for age. Contrary to our expectations, AD patients with concomitant CVS had more-pronounced MTA.

5.1 Results

5.1.1 Progression of Alzheimer's disease and predictors of disease progression

As AD is a neurodegenerative disease, progression is expected in all patients. The mean annual progression of AD of 1.6 points on the CDR-SB was comparable to the results of similar studies in memory clinics as well as in a population-based study (214, 220, 222, 224, 317). The annual proportion converting from MCI to AD dementia was 27%. This number is high but still falls within the range of what has been reported from studies in memory clinics previously (318). We identified almost half of the patients as slow progressors, as defined by a less than one-point increase in CDR-SB per year. Few studies have investigated slow progression in AD, but our results are in line with their findings (214, 224, 317).

Our study identified 7% of patients as rapid progressors, based on changes in their MMSE scores. Definitions of rapid progression vary, and the prevalence detected varies with follow-up periods and cut-offs applied. A shorter follow-up time could possibly identify a larger number of patients as rapid progressors, while our study identified few

rapid progressors when the criterion was for them to lose six points per year (226). The majority of studies have assessed rapid progression based on a follow-up of 3–12 months, while we used the average annual progression over two years. A study identifying patients with rapid, intermediate and slow progression after a year and extending follow-up for another three years did not find group differences in decline for the rapid progressors compared to the others (227).

In substudy I, we found that worse cognition at baseline predicted more-rapid progression, which is in line with most but not all studies (227). Some of this might be explained by the fact that patients entered the study at different stages, as more-rapid disease-progression rates are observed in more-advanced stages. Additionally, lower scores on cognitive tests at baseline might represent more disseminated brain pathology, in which case it is unsurprising if patients with lower test results are registered with faster progression. Early impairment in executive functions has been associated with more-rapid progression (227). Finally, CDR as a global measurement scale might not be detailed enough to discern these differences between patients in the early stages of the disease process.

Studies applying trajectory analyses have found that baseline MMSE, CDR-SB score, and education could predict trajectory groups for most patients with relatively good accuracy, i.e. foreseeing whether the patient was likely to experience fast, intermediate or slow progression during follow-up (237, 317). However, results from trajectory analyses cannot be directly compared to regression analyses determining the amount of variation in progression explained by different factors.

Other factors commonly found to predict progression are age and education, with most studies identifying younger age and higher education as predictors of more-rapid decline (221, 230). Contrary to this, in our study older age was found to be a predictor of cognitive deterioration in an unadjusted analysis but the effect of age disappeared in a model adjusting for ApoE ε4 carrier status, cognitive test results, history of hypertension and the number of medications in use. We found no effect of education on progression.

Regarding age, early-onset AD has been found to progress more rapidly than late-onset disease (319).By contrast, the oldest old tend to decline faster than other patients with AD, possibly as a result of more comorbidities (320). What seems to be an effect of age for the latter group might, therefore, be an effect of a different factor not properly controlled for in analyses, such as comorbidities. Our study had no comorbidity index but medications in use might indicate the number of other conditions present, and having a history of hypertension might have led to more cardiovascular disease. The effect of age on progression disappeared in a model where these factors were adjusted for. Given the divergent effects of age on disease progression in the youngest and oldest AD patients, the distribution of age in the AD population studied might affect what association is identified.

Substudy II found that MTA was associated with disease progression in unadjusted analyses. However, when adjusting for other factors, MTA was no longer significant, while memory impairment at baseline was a significant predictor. In other studies, MTA has been found to predict progression from MCI to dementia with a sensitivity of 51% and a specificity of 69%, indicating limited clinical usefulness (321, 322). CSF biomarkers, amyloid PET, and FDG-PET may all perform better than MTA in predicting progression from MCI to AD dementia, while markers of neuronal injury may be better at predicting disease-progression rates in general in AD (240, 241, 244, 323). For MCI patients, a combination of biomarkers performs better than individual biomarkers in identifying individuals who have underlying AD pathology, thus predicting which MCI patients are likely to progress to AD dementia. As a biomarker of neurodegeneration, MTA is not specific for AD but is sensitive to multiple other conditions (324). Since the specificity of MTA for underlying AD pathology is inferior to that of amyloid and tau biomarkers, this may explain why MTA does not perform as well in identifying those MCI patients who will progress to AD dementia. However, disease progression in general in AD is more closely associated with neurodegeneration than with amyloid biomarkers, which may be the reason why markers of neuronal injury may be better at predicting disease-progression rates (126).

Contrary to our hypothesis, our study did not find any association between vascular comorbidities and disease progression in AD. The hypothesis that VRFs and diseases

could be of importance for disease progression in AD is based on the many links between VRFs and AD. VRFs are associated with the development of AD and also with a decline in cognitive test results within the normal range, both in mid-life and late-life (325-327). Furthermore, the falling age-adjusted incidence of dementia observed in several high-income countries over the last decades has been partially attributed to changes in the prevalence of VRFs (8-10). Various VRFs and vascular diseases have been associated with disease progression in AD in previous studies, as shown in Table 1. Vascular diseases and risk factors could impact disease progression in AD either through the accelerated accumulation of AD neuropathology or by causing cerebrovascular injuries to the brain, which in combination with AD neuropathology may result in more-severe impairment.

We found no effect of a history of strokes or CVD on MRI on the rate of progression in AD. This was unexpected, as the resulting loss of neuronal tissue may lower the threshold for AD symptoms, and incident strokes in AD patients may accelerate decline (328, 329). Furthermore, we had expected an association between AF and AD progression since embolism due to AF might lead to clinical or silent strokes, and anticoagulation is associated with reduced incidence of dementia in AF. Previous studies have shown that AF is associated with lower scores on cognitive tests and reduced hippocampal volume, even in stroke-free individuals, and their risk of cognitive decline increases with longer exposure to AF, possibly indicating that other mechanisms may be involved, such as cerebral hypoperfusion damaging nerve cells (330-332). As cerebral hypoperfusion can occur with coronary heart disease or heart failure, we had anticipated that this could influence AD progression in heart disease (332-335). However, we found no associations between any of the vascular diseases and the rate of progression in AD.

The lack of association between hypertension and disease progression in AD was surprising as hypertension is closely associated with CVD and brain health, and many of the patients in our study had a history of hypertension. Hypertension may lead to changes in vessel walls, inducing arterial stiffness and increased pulse pressure, which may damage microcirculation (336). Diabetes may also cause microcircular damage, neurotoxicity, inflammation, and disruption of the blood–brain barrier, and we had

expected that this could be of relevance to the rate of progression in AD (337). Hypercholesterolaemia is associated with an accumulation of Aβ, in addition to being a contributor to atherosclerosis (59). Smoking is another driver of atherosclerosis, and current smoking has been associated with progression of cerebral SVD (338). Based on these potential mechanisms and given the fact that several other studies have identified associations between VRFs and disease progression in AD, our findings are surprising.

The limited influence of each vascular disease or VRF alone could be a possible explanation for this. However, we had expected that their compound effects, measured as vascular burden, could influence progression in AD; contrary to our expectations, vascular burden was not associated with disease progression in AD.

There are several possible explanations for the lack of association between vascular comorbidities and disease progression in our study. There is no clear consensus on how VRFs should be defined or measured to study their impact on the progression of AD. Neither is it clear whether VRFs or vascular diseases are the most-relevant entities to study, nor how single VRFs or diseases add up to a composite exposure. VRFs may be present for decades before a patient develops AD (8, 42, 47, 339). Potentially, the duration and timing of exposure, how much the risk factors deviated from normal or optimal levels, and whether they were treated or not are all aspects that should be considered when examining the influence of VRFs. This historical information is seldom available in clinical studies. VRFs in mid-life have been associated with the risk of developing AD in late-life (33, 68, 340). However, it is not known whether VRFs in late-life affect the disease process in AD, as they are associated neither with the risk of receiving an AD diagnosis nor with amyloid accumulation (8, 68). This may indicate that either a long duration or a specific timing of exposure may be required to observe an effect of VRFs on AD. Judging from the time lag between mid-life and the average age when AD symptoms begin to appear, it might be that the exposure would have to persist for decades (34, 47). There are indications that the duration of exposure to VRFs may contribute to the risk of developing dementia, but to the best of our knowledge, whether the duration of exposure to VRFs is of importance for progression of AD has not been studied (34).

Additionally, several other aspects make it difficult to assess the impact of VRFs. Information about former treatment and its effects on risk factors is usually not available. Adding to the complexity, the declining levels of blood pressure, cholesterol, weight, and physical activity that are observed for years before a diagnosis of AD is made complicate analyses on the association between VRFs and progression. In late-life, low blood pressure has been linked to cognitive impairment, and some have suggested that the relationship of blood pressure and cognitive impairment may be U- or J-shaped in this group, and that a decline in blood pressure may contribute to reduced perfusion, cerebral ischemia, and accumulation of β-amyloid (44, 107, 341). Studies indicate that β-amyloid aggravates cerebrovascular changes and vice versa (107). The levels of VRFs measured when the patient has developed cognitive impairment or dementia are, in many cases, different from those to which the same individual was exposed in previous decades. It is thus unclear whether it is more relevant to use medical history or current levels of VRFs when exploring for a potential association with disease progression in AD. To the best of our knowledge, this has not been examined in studies. As information on VRFs is often limited, most studies, including ours, have dichotomised VRFs based on a given cut-off, which may vary among studies. This may have reduced power in statistical analyses, limiting the chances of identifying associations between VRFs and the progression of AD. We repeated our analyses applying different definitions of VRFs; using medical history, drug use and measurements isolated and in different combinations, and analysed within subgroups of patients with untreated hypertension, hypercholesterolemia and diabetes, but identified no association with progression of AD for any variant of VRFs.

As VRFs contribute to the development of vascular diseases, many patients will have both. It is not known whether the vascular diseases or the underlying VRFs are more relevant for the progression of AD. VRFs, such as hypertension, may lead to vascular diseases but might also have independent effects on the disease process in AD. Cerebrovascular disease may directly affect cognition, and many of the effects of VRFs on AD are mediated through vascular changes in the brain (342). Thus, it might be expected that cerebrovascular disease would be associated with the progression of AD. Incident strokes may influence the progression of AD, and aggravation of WMHs is

associated with worsened cognition (328, 343). Our study found no association between CVD at baseline and disease progression in AD.

As MRI scans were done only at baseline, we were not able to assess whether AD progression was associated with an increase in CVD. A recent study indicated that the cognitive decline attributed to WMHs was not related to baseline levels but rather to the development of new lesions (344). In our study, treatment administered to prevent CVD may have reduced the incidence of new strokes and prevented aggravation of other forms of CVD, which in turn could have led to less progression of cognitive impairment.

Patients often have more than one VRF or vascular disease. Some studies have used the number of abnormal risk factors as a simple way of calculating increased risk. Several compound measures have been developed to assess composite vascular risk, or vascular burden (313, 345, 346). The development of mathematical algorithms allows for differentiated weighting of individual risk factors. Most scales were developed using occurrence of VRFs in mid-life, with strokes, heart disease, or cardiovascular disease in general as outcomes. Estimations of vascular burden have been associated with risk of subsequent cognitive decline, all-cause dementia, and AD (42, 339, 345, 346). However, the majority of risk scales were designed with cardiovascular disease as the outcome and only a few with dementia or AD (256, 339, 346, 347). Compound risk estimates typically use cross-sectional data for levels of VRFs. As levels of VRFs observed in late-life may differ from those in mid-life, this may render the risk scales less suitable for use in late-life. We chose to use the FSRP, as this is a commonly used vascular risk score for brain health, cognition, and dementia.

Vascular risk scores are one way of calculating the net effect of several risk factors combined. Apart from this, our study used multiple regression models to estimate the joint effect of multiple factors. A multiple regression model with cognitive test results together with age, ApoE ε4 carrier status, history of hypertension and the number of medications taken regularly explained only 17% of the variation in disease-progression rates. The second substudy identified MTA as a predictor of conversion from MCI to

AD dementia in an unadjusted model but not in an adjusted model. MTA did not predict progression in the AD group as a whole.

In the PADR study, we have also studied whether depression, inflammation, and medication use impact disease progression in AD. In general, the study identified either no effect or only a modest effect from the range of factors explored for their association with progression (236, 348-350) (results on inflammation and drug use have not been published yet). Adding these factors to the multiple regression model described in paper I did not lead to more than a minor improvement in the predictive ability of the model (not shown). As we were unable to foresee more than a fraction of the progression observed in the study, our results raise important questions about whether progression in AD is predictable, and if that is the case, which factors can determine the disease course.

Studies on predictors of disease progression show great variability in their results, with many of them identifying one or a few factors, with small or moderate effect sizes, and predictors typically explaining only a minor part of the variation in progression rates. In addition, only a minority of studies have been population-based, and few predictors are consistent between studies. To the best of our knowledge, no risk calculator exists for disease progression in AD, although a prognosis score to predict mortality based on age, gender and loss of ADL functions has been constructed (351, 352). Recently, a model predicting trajectories of cognitive test results has been developed using machine-learning techniques on longitudinal data for cognitive test scores and MRI measures (353).

As ours and other studies find few and weak predictors of progression in AD, questions to be considered are why few predictors are consistent across studies and why they explain just a minor part of the variance in progression. Some of the discrepancies between studies may reflect differences in study populations, with a considerable variation in mean values and range for predictors studied, such as participants' ages, education levels, the prevalence of hypertension or diabetes, and the percentage being smokers. Thus, the relative importance of risk factors may differ between study

populations, which may be one explanation for the heterogeneity in predictors of progression.

Other explanations for studies finding few and weak predictors for progression is that AD is a multifactorial disease, which is also supported by the many risk factors identified for developing AD, as described in Section 2.1.3. No single biomarker mapping AD progression in the individual patient has been identified, which may suggest that there might not be one single underlying process determining AD progression but rather that the disease process is the result of many factors. Although a common underlying AD pathology of amyloid plaques and neurofibrillary tangles has been displayed, there are probably several subtypes and these might have different progression. MRI assessments of the brain demonstrate heterogenic patterns of regional brain atrophy in AD patients, and this heterogeneity has been associated with differences in disease progression (354). Atypical presentations of AD display different patterns of hypometabolism on FDG-PET compared to typical AD (355). The genetic contribution to AD development spans from autosomal dominant inheritance with high penetrance to gene variants with low impact on AD risk in the individual (8). Neuroinflammation may also contribute to the pathogenesis of AD, and some gene variants for immune receptors are associated with AD (356). These differences indicate that there might be subtypes of AD with different progression rates.

Although AD was formerly regarded as a clinicopathological entity, studies have identified varying severity of underlying AD pathology. The threshold for when AD pathology becomes symptomatic is influenced both by concomitant brain pathology, such as vascular brain injury, and by cognitive reserve (32, 106). Educational level is often used in studies as a measure of cognitive reserve and is associated with the ability to tolerate more AD pathology before symptoms develop. However, it has also been associated with more-rapid disease progression in AD. This has been interpreted as a buffering capacity of cognitive reserve for brain pathology, and when this is exceeded, a more-rapid clinical deterioration is observed. This diverse effect of education illustrates how disease progression might have to be interpreted in a multifactorial model, taking into account both the underlying pathology and factors related to risk and resilience. Although patients may appear to be at the same stage of the disease, for instance,

diagnosed with mild dementia in AD, there may be substantial individual variation in these underlying factors. In turn, this might explain why it is so difficult to identify common determinants of the disease course.

Numerous studies have attempted to reduce disease progression in AD, but there is still no drug available for AD that can halt or reverse the disease process (178). Drug trials for AD are moving towards testing medications in very early stages (178). A lack of effect in the symptomatic stages of AD is also the case for intervention studies treating VRFs to halt the progression of AD at the MCI or dementia stage, for treatment of both single and multiple VRFs (357-359). However, a multi-domain intervention including treatment of VRFs in a population estimated to be at risk of cognitive decline showed a positive effect on cognition (360). In the symptomatic stages of AD, no treatments aiming to influence disease progression have yet been shown to have an effect. This raises the question of whether symptomatic AD might represent a disease state for which intervention in the disease course is difficult or impossible. Alternatively, it may be that studies have failed because the heterogeneity of AD has prevented interventions from showing significant effects in large groups of patients.

We found no difference in progression rates between AD patients with and without cerebrovascular disease. Little is known about the progression of cognitive impairment caused by cerebrovascular disease, especially in combination with AD pathology (361-363). A study assessing cognition in clinically normal elderly individuals found that a composite measure of vascular burden and amyloid positivity both was associated with slowly declining cognitive trajectories, while the combination of VRFs and amyloid β was associated with a more-rapid cognitive decline (325). Longitudinal studies with post-mortem examinations suggest that the cognitive effects of cerebrovascular disease in many AD cases are moderate and fairly stable over time (121). This might indicate that, in most patients, the accrual of cerebrovascular pathology is a slow process, possibly too slow for significant differences in cognition to manifest themselves during the follow-up time of most clinical studies in dementia (343, 364).

5.1.2 The influence of concomitant cerebrovascular disease on symptom profile in Alzheimer's disease

Diagnostic criteria for AD and vascular cognitive impairment (VCI) describe typical symptoms and cognitive deficits for these conditions. Thus, we had expected AD patients with concomitant CVD to show additional symptoms associated with vascular pathology. Comparing the groups in unadjusted analyses, we observed differences in symptoms between AD patients with and without concomitant CVD. However, no difference was found in analyses adjusted for age and gender, which might indicate that the observed differences were related to age rather than to CVD. Age is a strong risk factor for cerebrovascular disease, and there was an age difference between the groups of AD patients with and without CVD. Thus, age might be a confounder in studies of symptom profiles resulting from CVD.

As we observed no differences in symptoms in the adjusted analyses, our findings do not support the idea that symptoms can be used to distinguish between these groups. The literature is conflicting on whether concomitant cerebrovascular disease in AD leads to distinct cognitive deficits (115-117). Even when comparing AD with vascular dementia (VaD), the cognitive symptom profile has been shown to be similar, although VaD patients may have better memory and worse executive functioning (365). The cognitive symptoms among patients with SVD may be heterogeneous and not particularly distinct, and neuropsychological profiles have only a modest ability to distinguish between AD and subcortical VaD (114, 118). Subcortical infarcts have been associated not only with reduced processing speed and impaired executive function but also with reduced episodic memory (366). These discrepancies could be related to individual differences in the distribution of pathology in the brain.

Individual differences in the location, extent, and nature of CVD could be part of the explanation for differences in symptom profiles. Although different types and amounts of CVD have been associated with cognitive impairment and dementia, how much CVD is required in order to cause cognitive impairment is still undetermined (367). When a major stroke leads directly to dementia in a previously unimpaired person, it may be clear that the stroke was the cause of cognitive impairment. However, this is less clear

among patients with cognitive impairment if there is no history of stroke, and MRI or CT scan shows cerebrovascular disease.

Adding to the complexity of cerebrovascular disease, microinfarcts have been shown to have a strong association with cognitive impairment but are invisible on MRIs (368, 369). Determining the amounts, locations and types of CVD sufficient to explain cognitive deficits in the individual patient is challenging even when CVD appears to be the only aetiology of cognitive impairment (104, 113, 367). In AD with CVD, it may be even more difficult to disentangle how much of the cognitive impairment is attributable to each aetiology in the individual patient (121, 369).

There are indications that a certain amount of vascular pathology may be required to produce distinct symptoms (370). Threshold effects may be a reason why studies on cognition in AD and concomitant CVD come to different results. By contrast, in the late stages of AD, the effect of AD pathology on symptoms may be so strong that it overwhelms the influence of other pathologies (104). Depending on disease stage in AD and cerebrovascular burden, different studies may thus reach conflicting results.

In our study, many of the patients classified as not having CVD had some degree of WMHs on MRI (Fazekas score of 1), and most had one or more VRFs (349). Therefore, the group of AD patients not classified with CVD may have had some CVD. On the contrary, for some of our patients classified as having CVD based on findings such as a single lacune or a moderate degree of WMHs (Fazekas score of 2) on MRI, this may have represented CVD that did not affect cognition. Thus, the way patients were classified in groups with and without CVD may be the explanation for not finding a difference in symptom profile. Other studies exploring the effect of CVD on cognition vary widely in the manifestations of CVD included and the cut-offs applied, making comparisons challenging.

WMHs were the most common type of CVD in our study. Although WMHs are strongly associated with SVD, they may also result from other processes, such as inflammation or other non-ischemic changes. In dominantly inherited AD, WMHs are found before symptom onset, suggesting that they might be part of the disease process. Higher WMH volumes have been independently associated with smaller entorhinal

cortex volumes in aMCI, an effect observed in patients without significant CVD (371) . Even in normal controls, WMHs are associated with hippocampal atrophy, also when controlling for CSF biomarkers, VRFs, and concurrent brain atrophy (372).

We observed that CVD in AD was associated with more-pronounced MTA than AD without CVD. Visual assessment of MTA has reasonably good specificity and sensitivity in separating AD from normal ageing but does not perform as well in separating different types of dementia (324). As a biomarker for neurodegeneration, MTA is not specific for AD but is sensitive to multiple other conditions (324). Additionally, not all patients with AD have MTA (324).

However, disease progression in AD, in general, is more closely associated with neurodegeneration than with amyloid biomarkers, which may be the reason markers of neuronal injury may be better at predicting disease-progression rates (126). The nature of the underlying process leading to MTA cannot be determined with certainty from structural imaging or other biomarkers. In healthy controls, MTA has been associated with age, ApoE carrier status, cerebrovascular disease, and comorbid psychiatric disease (324). The hippocampus is vulnerable not only to AD pathology but also to vascular damage (373-375). Therefore, the more-pronounced MTA in AD with CVD may be a result of the joint influence of both pathologies.

In conclusion, our study indicates that although MTA is a characteristic feature of AD, it might not have the ability to distinguish between underlying pathologies. Further, the study indicates that cognitive symptom profiles cannot be used to make assumptions about the coexistence of CVD in AD patients.

5.2 Methods

5.2.1 Study design and selection of patients

This is an observational study conducted in memory clinic patients. They are a select patient group compared to the general dementia population, with higher levels of education, better treatment of other diseases, less comorbidity, younger age, and in earlier disease stages on average (376). Therefore, the results of studies conducted at memory clinics may not be valid for the general dementia population. However, our study population also included patients from a geriatric memory clinic with older

patients with more comorbidities, bringing the study population closer to the general dementia population. Studies examining the progression of AD in population samples have found slower progression than reported in memory clinic studies (214).

Many similar studies on disease progression in AD have identified more or stronger predictors of disease progression in AD than we were able to detect. Although the PADR study recruited a sufficient number of patients based on our power analyses, and this number was comparable to the sample sizes in many other studies, we identified few predictors of disease progression. A possible explanation for this is that our population may have been more heterogeneous compared to other samples, possibly reflecting the diversity of people with dementia but, at the same time, reducing the predictive value of several factors. Studying a patient group less heterogeneous in age, disease stage, education, or comorbidity burden would possibly have facilitated the identification of predictors valid for a more-restricted sample. Unfortunately, our sample size was not large enough to perform such subgroup analyses.

As in similar studies, the attrition rate in our study was high and represents a major weakness. However, the rate was comparable to other studies in memory clinics (220, 222). Patients lost to follow-up had more cognitive impairment at baseline, which is a predictor of progression and it is probable that patients experiencing severe progression would be more likely to drop out of a follow-up assessment. Therefore, we visited many patients in nursing homes at follow-up, which represents a strength of our study compared to studies that assessed only those patients who were able to return to the memory clinic. We do not have information on the causes of death for those who died, but it is well known that mortality rates increase with severity of AD, vascular disorders, and rapid progression, and the impact of VRFs and vascular diseases may have been overlooked in these patients (221, 377).

In summary, the attrition of patients more likely to decline, including those who died before follow-up, may have led to an underestimation of the progression. By contrast, our memory clinic population may have had more-rapid progression than the general dementia population. To the best of our knowledge, only one population-based study on AD progression has been conducted, identifying a mean progression rate similar to ours

(214). Therefore, we believe that our results, although influenced by study design and attrition, are valid for an AD population.

Studies on progression of AD vary widely in length of follow-up and number of examinations. Our follow-up period of a mean of two years is longer than that of some studies. Calculating mean progression over this time span makes estimations of progression more reliable than with a shorter follow-up. However, the length of our follow-up period could still have been too short to assess relevant differences. Several factors could impact the disease course through slow processes and require more than two years to demonstrate an effect. This could be the case for VRFs, where some other studies may have been superior to ours in their ability to detect predictors of progression through longer observation periods (249, 257). Many dementia studies have repeated serial assessments. Having more than two assessments adds valuable information about patients who are lost to follow-up before the final study visit, enabling comparison with patients who shared the same trajectories initially.

In terms of statistics, with only two assessments our study was limited to linear analyses. Mathematically, three or more observations allow for other analytic methods, with flexible curves. This may be an advantage in dementia studies, as the literature describes that disease progression is slower in the initial stages than in more-advanced stages (214). Our study found no significant differences in progression rates between disease stages.

The power calculation of the study was based on the assumption of a difference in progression rates between AD patients with and without VRFs. Despite including far more patients in the study than suggested as necessary by the power calculation, no group differences in progression were detected. Although a larger study might have improved our chances of finding a difference between groups, it may be argued that our study is sufficiently powered to identify a clinically significant difference. The study assessed more than twice the number of patients suggested by the power calculation but still identified no differences in progression rates between AD patients with and without VRFs. Our study should have sufficient power to detect modest group differences, and it may be argued that it is sufficiently powered to identify a clinically significant

difference. However, it may be that a longer follow-up would have been needed in order to identify differences between groups.

Substudy IV was done as post-hoc analyses, which is a limitation, as data were not gathered with the intention of comparing these groups, and this should be regarded as hypothesis-generating research. The inclusion of gait parameters and data on urinary incontinence would have improved the study in regard to differences in symptom profiles, but unfortunately, these data were not available.

5.2.2 Choice of progression measures in Alzheimer's disease

As AD is a heterogeneous condition, in terms of both its presentation and its progression, the choice of progression measures in AD studies is challenging. Research in AD has discovered biomarkers and mapped their typical change over time but no biological correlate to clinical disease progression in the individual has been identified thus far. However, there have been approaches to disease-progression modelling that aim to reconstruct biomarker trajectories across the disease progression in AD. Models have been constructed for biomarker trajectories, for MRI change, and for disease mechanisms (378-382). Although models have been tested on some existing datasets few have been tested for their ability to predict future decline (383).

Whereas it is clear that AD pathology accumulates over time, there is no clear link between the amount of AD pathology and the severity of symptoms (126). The multifactorial nature of the disease is probably part of the reason it is difficult to align clinical progression with underlying biological processes. The lack of a measurable underlying process to which the clinical severity scores can be compared is a problem in the field, as there is no "gold standard" for the comparison of measures. Thus, all measures of progression can be compared only to each other, and validation against a biomarker showing disease progression is, thus far, not feasible.

An ideal clinical-progression measure should have good psychometric properties; be sensitive to change across all disease stages, preferably with an even distribution of scores across the disease spectrum; and reflect clinically meaningful changes (288, 384). Many studies have relied only on cognitive measures of progression, but deteriorations in function or behaviour may occur even with unchanged results on

cognitive tests (215). Decline in function and altered behaviour are related to quality of life in people with dementia (180). An ideal progression measure should encompass all relevant aspects of progression. Alternatively, several aspects of progression could be assessed concomitantly. Furthermore, an ideal progression measure could be scored without having to complete extensive and time-consuming forms or interviews and should not be influenced by educational level or comorbidities. No instruments meet all these criteria, and as patients' symptoms vary during the course of dementia, it is difficult to design assessments that are suitable for all disease stages.

Our study chose the annual change in a global measure to assess progression in AD. The CDR-SB is widely used, well-validated, sensitive to change across the disease spectrum, requires smaller sample sizes than cognitive tests to detect differences, and has high interrater reliability (218, 219, 285, 288). Limitations in the use of the CDR-SB include its dependence on a reliable proxy, a time-consuming interview, and scales that require judgment. The score emphasises the memory item above others. A limitation in the use of the CDR-SB is that the CDR was originally developed as a staging instrument. As the scoring system was not developed for continuous use, a change of one point in one item is not necessarily of equal importance across the scale. The CDR score integrates several aspects of cognition and function, but behavioural changes that do not affect function are not captured. The choice of the CDR-SB as an outcome measure allows for detection of small changes, but as the minimal clinically important difference is unknown, the relevance of the smallest changes may be unclear. However, the CDR-SB may require smaller sample sizes than other clinical scales and has been recommended as a primary outcome measure (219, 285). As there is no gold standard for "clinical progression", it is impossible to establish what measure would be the best. Many trials have used the CDR-SB, but clinical trials in early stages of AD have developed composite measures of cognition and function as an alternative (385).

The MMSE as a global cognitive test was used as a secondary outcome measure for progression. The strength of the MMSE is that it is very well-known, used in numerous studies, and has been designed to allow repeated testing (384, 386). The main limitations are floor and ceiling effects, both of which were visible in our study; the limited number of cognitive domains assessed; practice effects; limited sensitivity to

change; and an uneven distribution of points lost across the different stages of dementia (296) (ref). Reliance on cognitive tests alone would not capture all relevant changes in AD as function and behaviour are not assessed.

The IADL score was used as a secondary outcome measure for progression. The strength of using an IADL scale is that function is a central aspect of dementia, and functional losses may thus be more relevant to disease progression than decreasing scores on a cognitive test. How much ADL and quality of life are affected by AD will, in many cases, be more important both to the person living with dementia and his or her family members than how cognitive skills are affected. ADL are also very important for the societies, as they are closely linked to care needs and related costs. The IADL scale by Lawton and Brody has been used for many years, enabling comparisons with other studies; however, it has several major limitations (183). These include gender and culture biases, with several items rated as not applicable for many of the patients in our study. For this reason, we based IADL scores on five instead of eight items, but the scale still measured changes in the IADL items that were relevant for all participants. For each item, patients were rated as dependent ("0") or independent ("1"), according to the original scale. However, the point of transition between independence and dependence is not necessarily consistent and comparable across items on this scale. For instance, a person who needs a companion in order to travel on public transportation is still counted as independent, while someone who is able to prepare adequate meals when supplied with the necessary ingredients is regarded as dependent. With dichotomised scoring, the test is less sensitive to change. Moreover, the test is now dated and thus misses elements of modern life, while some elements appear outdated. The test has ceiling effects, which we observed among our patients at baseline, but at follow-up, there were also floor effects, as some patients had scored 0 in all IADL functions.

The inclusion of basic ADL functions in the outcome measure in this study could have helped avoid the floor effect of IADL measures seen in advanced dementia. Generally, many IADL scales have moderate or low quality measurement properties, limiting their usefulness both when diagnosing cognitive impairment or dementia and when following patients longitudinally (306). Our results may have been limited by the use of an old

scale with poor psychometric qualities, having limited sensitivity to change. An updated IADL scale with better psychometric qualities could have improved our study (306, 387).

5.2.3 MRI and biomarkers

Our study used clinical MRIs to explore visual assessment of MTA as a predictor of progression and to assess cerebrovascular disease. Clinical MRIs performed in different locations were used in the study, and thus the study did not have a standardised MRI protocol. The lack of a standardised protocol is a major limitation of the study. Most MRIs were performed using a 1.5 T scanner. A strength of the study is that an experienced neuroradiologist performed the visual ratings.

Other studies exploring the effect of CVD on cognition vary widely in regard to which manifestations of CVD they include and which cut-offs they apply, making comparisons challenging. A more thorough examination of cerebrovascular disease, including other types of CVD and distinguishing between periventricular and deep WMHs, could have improved our ability to discern between injuries of importance for cognition and other cerebrovascular manifestations. Several studies have attempted to grade SVD based on a score for SVD burden. Standardised MRI protocols, including assessments for cerebral microbleeds and periventricular spaces, and separate ratings of periventricular and deep WMHs, would have allowed the calculation of SVD burden (388). A graded scale of SVD might have improved our ability to detect associations between cerebrovascular disease and symptom profile and progression of AD. Alternatively, assessing cerebrovascular disease by measuring the affected brain volume could have provided a graded estimate of vascular injury. As studies suggest that location, volume, and type of cerebrovascular damage may be relevant for cognitive effects, all these methods should probably be considered rough estimates of the underlying cerebrovascular disease (367).

Another limitation of the MRI scans is that only one assessment was performed. The addition of an MRI scan at follow-up would have allowed for the evaluation of change in MTA and in cerebrovascular disease in relation to disease progression. However, this was not possible due to a lack of funding.

5.2.4 Diagnoses

The AD diagnoses in this study were based on clinical criteria. The NINCDS-ADRDA criteria are known to misclassify 10–30% of patients, even when applied by experts in the field. As many of our patients were of advanced age, a substantial proportion is likely to have had multiple brain pathologies causing cognitive impairment. We cannot exclude the possibility that some of the aMCI patients included in the analyses as having AD could have had a different aetiology of cognitive impairment. This might have impaired our ability to identify predictors of disease progression. However, the clinical evaluation was performed by experienced clinicians; the diagnostic workup was standardised; and patients were diagnosed in consensus between two clinicians.

The use of CSF biomarkers for the diagnosis of AD could have improved diagnostic precision in the study but these were available only for a subset of the patients. However, for the oldest patients in the study, biomarker positivity would have contributed less to diagnostic accuracy, as biomarkers are frequently positive in this age group, even among people with normal cognition (136-138). Optimally, dementia diagnoses in a study are verified by autopsy, which was not an option in our study.

Regarding MCI, the Winblad criteria are broad, allowing the inclusion of even conditions that do not represent the prodromal phase of any dementia disorders, among them depression. This may explain why some MCI patients were stable or even improved. Another problem is that differentiation between MCI and AD dementia is sometimes difficult to make because there are no sharp distinctions.

In this study, patients with aMCI were included in the analyses of progression and symptom profile together with patients diagnosed with AD dementia. For memory clinic patients with aMCI and no indications of another underlying pathology, AD will, however, often be the cause of MCI, which is also supported by the fact that here was a high conversion rate from MCI to dementia (18). That these patients did not receive a diagnosis of AD at baseline and were not diagnosed with newer research criteria that apply biomarkers to identify MCI patients with a high likelihood of AD aetiology may be a point of criticism. Thus, this approach may have included patients without AD as the underlying cause of cognitive impairment in the analyses, which could potentially

hamper our ability to identify significant predictors and explain the high proportion of subjects with slow progression. However, separate analyses for AD dementia and MCI did not support this being the case. We should also bear in mind that there are studies showing that only about 70% of patients with aMCI who progress to dementia meet the neuropathological criteria for AD (389, 390).

5.2.5 Statistical issues

With patients from three study centres, there is a potential risk of a clustering effect, which was adjusted for only in substudy II. As the problem related to not adjusting for a clustering effect may be that a predictor is overestimated, it is unlikely to have influenced our results in substudy III or IV, where results were negative.

Substudy IV was done post hoc and included many multiple regression analyses, which increases the risk of chance findings. Our finding of an association between concomitant CVD and MTA may, therefore, be due to a type I error (rejecting a null hypothesis that is true).

6 General conclusions

6.1. Clinical implications

This study generally identified few predictors of progression in AD, and these predictors explained only a small proportion of the variation in progression rates. Based on our findings, more-severe cognitive impairment at the time of diagnosis may predict more-rapid progression, but the effect is weak. VRFs or cerebrovascular disease on MRI does not imply a different prognosis, at least in a population where most risk factors are treated.

The study identified that a considerable proportion of the patients had no or little progression over two years. This is welcome news for patients and their families, implying that the most common disease course is a slow progression.

The effect of cerebrovascular disease in AD patients was not recognisable by symptom profile. Diagnostic criteria based on symptom profiles often fail to discern the aetiology of cognitive impairment, and many patients with mixed aetiologies fulfil clinical criteria for AD without showing symptoms associated with cerebrovascular disease. MTA does not seem to be a reliable biomarker

6.2 Proposals for future research

The progression of distinct subgroups of AD patients should be studied in order to establish whether there are differences in progression for example between early-onset AD, without other brain pathologies, and late-onset AD.

Studies of progression in AD using patient-reported outcome measures are lacking. Further studies should involve patients and families or user organisations in order to establish what outcome measures for dementia progression they find most relevant.

Studies of progression should be conducted as trajectory analyses with repeated serial measurements.

Studies on the effects of VRFs for the progression of AD should examine whether there is a difference between previous and current risk factors. It should also be explored how duration and severity of VRFs impact on the risk of developing AD and whether this is of relevance for progression.

More research is needed on the link between symptoms and underlying pathology in the brain when AD is combined with vascular or other aetiologies. Longitudinal prospective studies with repeated MRI scans and clinical assessments should be conducted in order to disentangle these links.

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