Secondary Prevention for Alzheimer Disease

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Chapter 1

General introduction

Alzheimer disease (AD) is the most common cause of dementia, accounting for 50-70% of the estimated 46 million patients with dementia world-wide [1, 2]. AD dementia is a main cause of disability and death, and has a major impact on the lives of patients and their families [3, 4]. The disease is defined by amyloid plaque and tau tangle formation in the brain, which are accompanied by neurodegeneration and cognitive decline [5]. Dementia is the end-stage of AD [6]. There is currently no treatment to slow or halt the disease. Despite significant investments of pharmaceutical companies, investigators, study participants and their caregivers, all clinical trials thus far have failed [3]. The simple explanation for the negative results would be that all treatment compounds were ineffective. Still, in retrospect, there can also have been shortcomings in the design of the trials, in particular the participant selection and timing of the interventions [7].

1.1 Clinical trials in relation to biomarker developments

One major issue hampering clinical trials in AD in the past was diagnostic uncertainty. According to screening data of previous clinical trials 10-25% of patients with a clinical diagnosis of AD-type dementia did not have evidence amyloid plaque accumulation in the brain [8-10]. This is particularly problematic for experimental treatment studies, because many of the compounds target amyloid plaques [11]. During the past two decades, biomarkers became available that can measure amyloid accumulation during life using cerebrospinal fluid (CSF) or positron emission tomography (PET) imaging. The use of these biomarkers allows confirmation of AD pathophysiology in patients with AD dementia at study enrolment, which ensures that the right patients are treated.

Using AD biomarkers, it became clear that AD pathology may be present long before the onset of dementia [12, 13]. Individuals with amyloid pathology may be treated during this period to delay or prevent the onset of dementia [14-16]. Another explanation for the lack of treatment effects is that the interventions were initiated too late in the disease process. An hypothesis is that equivalent interventions may be effective when started earlier, e.g., in pre-dementia AD [17]. In a new branch of research into pre-dementia AD, individuals without dementia undergo AD biomarker measurements and are followed over time. To conduct trials in pre-dementia AD, we need to understand when to intervene, how to find suitable participants, and develop methods to evaluate effectiveness in pre-dementia AD. Those are topics investigated in this thesis.

This chapter has the following structure: (2) a brief summary of the current hypothesis on the development of AD and explanation of relevant terminology and methods, which both provide background for the following chapters, (3) progress and challenges in clinical trials for AD, (4) project descriptions, (5) the specific aims and outline of this thesis.

2 Understanding and defining Alzheimer disease

2.1 Biological progression model of Alzheimer disease

In 1992, Hardy and Higgins pose the amyloid cascade hypothesis [18], which Jack and colleagues adapt into the disease progression model of AD, based on early biomarker studies [19]. According to this hypothesis, AD dementia develops in a sequential order of biomarker and clinical abnormality over decades. The first sign is amyloid accumulation, followed by neuronal injury and dysfunction, neurodegeneration, cognitive decline, and functional decline (Figure 1). Several publications support this AD progression model. Firstly, early biomarker studies show that 30% of

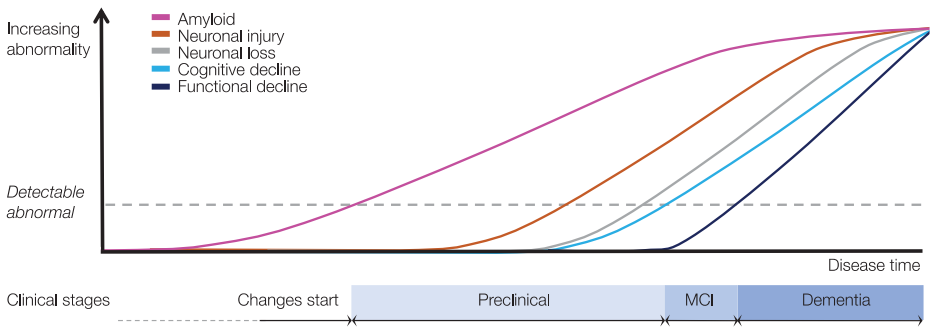

Figure 1 Alzheimer disease progression model and clinical stages
Adapted from Jack et al. 2013 [5].

individuals, who are older than 65 years have evidence of amyloid accumulation in their brain, but have no dementia [20], which is also conform neuropathology studies. It indicates that pathophysiological changes start before symptoms are present [5]. Second, there is a gap of ~20 to 30 years between the increases of amyloid accumulation and AD-type dementia prevalence [20]. Based on amyloid accumulation rates, the pre-dementia period is estimated to be approximately 17 years [21]. Lastly, in the presence of AD pathology, cognitively normal individuals show higher progression rates to mild cognitive impairment and dementia compared to individuals without AD pathology [22-25]. This evidence suggests that there is a long pre-dementia period as window of opportunity for interventions to prevent dementia, warranting further investigation.

2.2 Clinical stages of Alzheimer disease

To study pre-dementia stages of AD, research expert groups developed criteria which divide AD into clinical stages [14, 26, 27]. These criteria have been updated several times over the past 10 years. In this thesis, I use an amyloid-centric definition: if amyloid accumulation is present, this is referred to as AD. Preclinical AD refers then to individuals without any signs of cognitive impairment. Prodromal AD and mild cognitive impairment (MCI) due to AD are both referring to the mild cognitive impairment stage, in which there is cognitive impairment, but no functional impairment. In AD dementia, patients have become dependent on others in their activities of daily living, as a result of progressive cognitive impairment [6]. AD dementia has a mild, moderate and severe dementia stage, according the level of functional dependence on others.

Clinically, most individuals progress from normal cognition via mild cognitive impairment to dementia, but the duration of the stages has not been well-described (see Ch. 2.1 of this thesis). Some individuals revert to less severe stages or fluctuate between clinical stages [28]. This clinically deviating group of patients are interesting to study as they might inform us on the prognostic factors for clinical progression of AD (Ch. 2.2).

2.3 Risk factors for Alzheimer disease

Many risk and protective factors for AD dementia have been identified, including genetic and environmental factors [2]. In less than 1% of patients, AD is caused by a genetic mutation in the PSEN1, PSEN2 or APP gene. The most common genetic risk factor for AD dementia is the presence of one or two *APOE ε4* alleles. There are also many risk and protective factors found in epidemiological studies of which the mechanisms are unknown. Risk factors for AD type-dementia include female sex, lower level of education, hypertension, and depressive symptoms. More exercise and more social and intellectual engagement seem protective. The effect of these risk factors can also be stage-specific (Ch. 2.1) Unraveling risk factors for AD dementia can help to target treatments or stratify clinical trial enrolment and evaluation of outcomes (Ch. 3.2).

2.4 Structural neuroimaging and connectivity

In AD, patients have neurodegenerative changes that can be detected and characterized with structural brain imaging. For clinical trials, structural magnetic resonance imaging (MRI) can be useful for selecting participants most likely to undergo cognitive decline, or to measure treatment response [29]. The temporal cortex appears preferentially vulnerable to atrophy in AD. Well-established techniques for assessing temporal lobe atrophy include visual medial temporal lobe atrophy (MTA) rating scale and automated volumetrics [30-32]. More recent studies are able to measure cortical thickness in multiple brain regions, suggesting that cortical thinning in multiple brain regions, including in the parietal lobe, may be a sensitive marker of AD-related changes [33]. Growing evidence also suggests disruptions in grey matter connectivity as an early feature of AD [34-36].

In this thesis, we apply the single-subject whole-brain grey matter covariance network approach (Ch. 4) [37]. This method is based on the fact that brain structures develop and maintain in an organized manner, which results in similarity between brain areas and that is correlated to healthy brain function [38, 39]. This similarity can be described as a network using graph theory properties, such as the number of nodes and connections, the average path length between nodes and the level of clustering (see Box 1 Chapter 4.1 on page 116 for details). The networks have previously been shown to be disrupted in AD dementia patients [36]. Additionally, in cognitively healthy individuals grey matter network disruptions are associated with amyloid accumulation levels [40, 41]. This suggests that network changes occur early in the disease and that this may be developed into an endpoint for clinical trials in pre-dementia AD. Studying brain connectivity can also be useful to better understand the development of the disease.

2.5 Cerebrospinal fluid biomarkers

CSF protein levels are used to diagnose AD, as well as to study biological changes (Ch. 4.2). The proteins used for diagnosis AD include reflections of β-amyloid (Aβ) and tau (phosphorylated [pTau], total [tTau]) accumulation. More biological processes can be reflected in the CSF by protein levels, such as amyloid processing, neurodegeneration, inflammation and synaptic damage [42-47]. We use the ratio of $A\beta_{42/40}$ as a marker of amyloid aggregation, $A\beta_{40}$ for amyloid processing, pTau for hyperphosphorylation of tau and tTau for neuronal injury. Neuronal calcium-sensor protein (VILIP1) reflects neuronal death and neurofilament light chain (NfL) axonal degeneration. Furthermore, levels of chitinase-3-like protein 1 (YKL-40), an astrocyte marker, and soluble TREM2, a microglia marker, are assessed to detect inflammation. SNAP-25 is used to detect presynaptic damage and neurogranin (Ng) to detect postsynaptic damage. Combining CSF markers with grey matter connectivity may allow delineation of which processes contribute to network disruptions over the AD trajectory (Ch. 4.2).

3 Clinical trials

3.1 Clinical trials for prevention of AD

Three types of prevention exist in medicine. The first type is primary prevention, referring to a preventive treatment for individuals without pathological signs of the disease. In AD, one testable hypothesis can be to prevent amyloid accumulation by intervening in the amyloid production. Secondary prevention applies to individuals with pathological signs of the disease, who do not yet exhibit symptoms, i.e., preclinical AD (no cognitive impairment) or MCI due to AD (no dementia). An AD-specific example is to aim to delay the onset of cognitive impairment, for example by the removal of amyloid. Finally, tertiary prevention applies to individuals with both pathological signs and symptoms, and should prevent further complications or decline of the disease, i.e., stabilize or improve AD dementia. Depending on how symptomatic is defined, prevention of further decline in MCI due to AD can be considered tertiary prevention (prevention of decline in symptomatic disease), but it can also fall under secondary prevention (delay of the onset of dementia). The scope entails secondary prevention aimed at disease-modification. This means to change the disease course, as opposed to a symptomatic treatment suppressing disease symptoms. The phase 2 proof-of-concept trials is when target engagement needs to be proven.

3.2 Prevention trials using AD biomarker inclusion criteria

Prevention trials with AD biomarker-inclusion criteria emerge from 2009, affecting enrolment and screening procedures (Figure 2). The first prevention trial to require abnormality in a biological marker related to AD in the trial selection criteria is the Lipididiet study, starting March 2009 [48]. Shortly thereafter, in May 2009, another prevention trial in MCI is the first to specifically require evidence of amyloid accumulation, operationalized as either abnormal CSF Aβ, or an abnormal CSF Aβ to tau ratio [49].

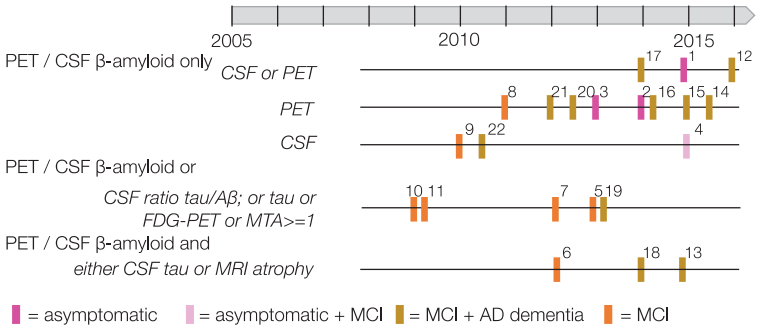

Figure 2 Biomarker inclusion criteria for clinical trials by start date
Every tickmark represents a study: 1) NCT02569398; 2) NCT02008357; 3) NCT02000583; 4) NCT02547818; 5) NCT01953601 6) NCT01522404; 7) NCT01429623; 8) NCT01227564; 9) NCT01224106 10) NCT00890890; 11) NTR1705; 12) NCT02670083 13) NCT02389413; 14) NCT02477800; 15) NCT02322021; 16) NCT02292238; 17) NCT02245737; 18) NCT02054208; 19) ACTRN12613000777796; 20) NCT01767311; 21) NCT01561430; 22) NCT01255163

The requirement of an abnormal amyloid PET scan, aside of an MCI diagnosis, is used for the first time in the trial testing ACC-001+QS21 (active Aβ immunization) in 2011. The first secondary prevention study in cognitively normal individuals with amyloid accumulation is an exercise trial in 2013 [50]. The first pharmaceutical trial in this group is the 'Anti-Amyloid Treatment in Asymptomatic Alzheimer's study' (A4 study) in 2014 [51].

3.3 Challenges of secondary prevention trials in Alzheimer disease

Participants for trials in preclinical AD, such as A4, do not present in large quantities in memory clinics, because most of them do not experience complaints. Therefore, they need to be recruited from the general population, where the biomarker status is unknown. Additionally, trials have strict eligibility criteria on co-morbidities and require a serious commitment from participants. This is a novel challenge for recruitment, finding and screening these individuals, which can lead to major delays in trial completion or even unfinished studies [52] (Ch. 3).

Traditional endpoints include decline on cognitive and functional measures, but in the pre-dementia stages in AD these measures may not be sensitive enough to detect decline over time during the trial [53]. Yet, without a functional endpoint, it is difficult to define the clinical benefit for patients. This is another reason, why a more comprehensive understanding of the total course of AD would be useful to inform clinical trial design and guide the implementation of future treatments. There are two large international consortia, both including academic and private sector partners, aimed at understanding the development of AD dementia and the execution of interventions that play a major role in this thesis, the European prevention of Alzheimer Dementia (EPAD) project and the Dominantly Inherited Alzheimer disease network (DIAN).

4 Consortia in sporadic and autosomal dominant Alzheimer disease

4.1 EPAD project

In 2015, the EPAD project, funded through the Innovative Medicine Initiative (IMI), is initiated with a dual purpose of setting up a framework to execute secondary prevention trials and in parallel study pre-dementia AD [53, 54]. The goal is to set up a platform trial structure, which allows multiple compounds to be investigated according the same protocol. In a platform-trial, sponsors can share placebo-groups, and less participants are needed per study. Additionally, individuals are first included in a 'trial-ready' cohort, in which they are phenotyped, with clinical and cognitive tests, neuroimaging and blood and CSF collection, and are followed over time. About 25% of participants in the trial-ready cohort are expected to participate in a clinical trial during the time frame of the project. Data collected in the trial-ready cohort may be used as run-in data to increase the power of the trial.

In addition, individuals for the trial-ready cohort should be recruited from other studies, enabling preselection. As part of this thesis, we investigate this novel method

of participant recruitment for AD studies. We set up a virtual registry, to which the pre-existing studies can be linked, and have participants that qualify join the EPAD trial-ready cohort (Ch. 3). The idea is that this approach results in less recruitment delay and less screen failures.

4.2 DIAN project

In 2008, the DIAN project starts collecting data for its observational study of carriers of an autosomal dominantly inherited genetic mutation of AD and their family members [55]. In this form of AD, the age of onset of dementia is usually between 40 and 50 years of age [56]. As the age of symptom onset is similar within the mutation type, we can use the estimated years to symptom onset (EYO) as an alternative time scale (irrespective of mutation status). This allows exact staging of individuals including the pre-symptomatic persons, and that is not yet possible in sporadic AD. For example, if someone is 35 years and for the mutation in their family, the average age of onset of dementia is 50, the EYO is minus 15.

The participants undergo regular clinical and cognitive tests, neuroimaging and blood and lumbar puncture for CSF [57]. All family members were included, such that noncarriers are a natural control group. Figure 3 shows how we compare mutation carriers, and non-carrier family members over the disease trajectory. Previous work in this study demonstrated divergence between mutation carriers and noncarriers in CSF Aβ more than 20 years, CSF tau 10 years, and memory decline seven years before dementia onset [57]. The DIAN project also encompasses an intervention study, which is shaped as a platform clinical trial structure and started in 2012 with the first two trial arms [58]. Results of the DIAN observational study are used to design that trial. We use the data of the DIAN observational study to investigate when and how grey matter network change in autosomal dominant AD (ADAD). As disruptions of structural grey matter networks are seen early in sporadic AD, these networks may provide an alternative endpoint for clinical trials in pre-dementia AD. Therefore, we attempt to validate those findings in this pure form of AD, and also investigate the biological correlates of grey matter networks (Ch. 4).

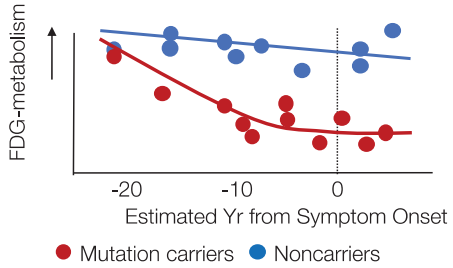

Figure 3 Illustration of comparison by years to symptom onset
Adapted from Bateman et al. NEJM [57]

5 Aim and outline

The purpose of the thesis is to use biomarker and clinical measurements to provide new input into how clinical trials should be structured that aim to evaluate novel secondary prevention strategies for AD. This includes the duration of pre-dementia AD and influencing factors, recruitment and selection of participants, and the development of endpoints to measure treatment response in trials.

The studies address three specific aims:

1. Improve the understanding of the clinical course of Alzheimer disease (2.1,2.2).
2. Set up the EPAD virtual registry for participant recruitment for the EPAD trial-ready cohort and trials, and evaluate learnings (3.1,3.2).
3. Understand how grey matter networks change with disease progression and identify biological correlates in autosomal dominant Alzheimer disease (4.1,4.2).

5.1 Thesis outline

First, we tie together the short-term follow-up of individuals of all AD clinical stages, using the multi-state model technique, to estimate the duration of each stage and of the complete disease course, which can provide information on prognosis (2.1). In the second chapter, we investigate the value of AD biomarkers for the prognosis of a clinically diverting group. Individuals with initially mild cognitive impairment, who improved to normal cognition were continued to be followed on clinical markers. This group is known to be at an increased risk for dementia, and we hypothesize that the underlying cause was AD (2.2). The second topic of this thesis is the set-up of EPAD Registry, a project for linking existing cohorts to enable engagement and selection of participants for EPAD cohort study and secondary prevention trials, and we then evaluate this novel method (3.1,3.2). The final topic addresses changes of structural grey matter networks over the course of AD, to study their use as a potential clinical trial endpoint. We investigate if findings on grey matter network disruptions in sporadic AD translate to individuals with autosomal dominant AD (4.1), and which biological processes, as measured in CSF, may be underlying the disruptions (4.2).

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