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Chapter 5

Summary and general discussion

Secondary prevention trials in Alzheimer disease (AD) aim to delay, or even prevent, the onset of dementia. Most novel, and challenging, are clinical trials intervening in the preclinical stage, when disease signs are subtle and outcome measures have been shown to have insufficient sensitivity. How to optimally design and conduct these types of trials is thus a timely topic of scientific debate. Our incomplete insight in the natural course of pre-dementia AD (preclinical + prodromal) complicates creating appropriate selection criteria and outcomes to measure effectiveness. In addition, a good enrolment rate is essential, but it is not yet established how to find and screen these potential participants, who present in insufficient numbers in memory clinics. This thesis contains several studies relevant for secondary prevention of AD. We estimated the duration of preclinical, prodromal, and dementia stages of AD (Ch. 2.1,2.2); studied strategies for recruitment and selection of participants for secondary prevention studies (Ch. 3.1,3.2); and investigated grey matter network disruption as a potential outcome measure (Ch. 4.1,4.2).

The main findings are:

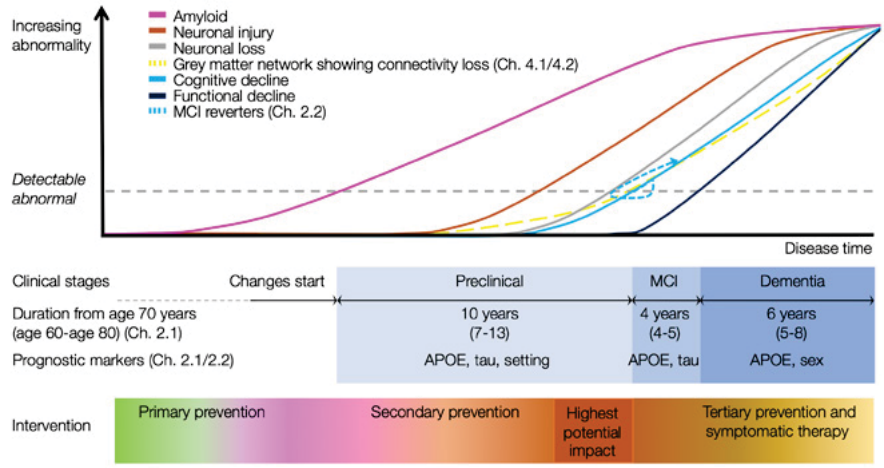

Figure 1 Thesis results incorporated in AD progression model with prevention strategy
Adapted from Jack et al. 2013 [49].

(1) Clinical course of AD

- Total AD duration varied between 24 years for an individual aged 60, and 15 years for an individual aged 80.
- For an individual aged 70 with preclinical AD, estimated duration of preclinical AD was 10 years, of prodromal AD 4 years, and of dementia 6 years.
- The duration of AD stages is dependent on age, setting, sex, *APOE*, and CSF tau.

(2) Recruitment for Alzheimer disease research

- We set up the virtual EPAD Registry to show the feasibility to preselect individuals from ongoing studies for future AD prevention studies.
- Lower age, higher education, male sex, and a family history of dementia were associated with an increased willingness and ability to participate in future AD prevention studies.
- Higher age and *APOE* ε4 carriership was associated with an increased risk for amyloid pathology.

(3) Grey matter network analysis is a potential surrogate endpoint for trials

- Individuals who carry an autosomal dominant AD mutation show increased decline over time in grey matter connectivity 6 years before the estimated time of symptom onset.
- Loss of grey matter connectivity correlates with cognitive decline.
- Loss of grey matter connectivity was associated with CSF markers of tau, synaptic and axonal degeneration, and astrocyte activation.

This chapter has the following structure: (1) a summary of the studies with context, (2) relevance and implications of the findings for trials and future treatment, (3) methodological considerations, and (4) future directions for clinical research on secondary prevention of AD and conclusion.

1 Summary of the thesis and context

1.1 Clinical course of AD

Duration of clinical AD stages and prognostic factors

In Chapter 2.1, we estimated duration of the preclinical (amyloid-positive normal cognition), prodromal (amyloid-positive MCI), and dementia stages of AD according the individuals' age, sex, *APOE* genotype, CSF tau levels and the setting (clinic or research). The estimates were based on multi-cohort data of 3,268 individuals. The overall duration of AD from amyloid-positivity ranged from 24 years at age 60 to 15 years at age 80. The estimates for an individual with preclinical AD, aged 70, were 10 years in the preclinical AD stage, 4 years in the prodromal AD stage, and 6 years in the dementia stages. Comparable to our study, one previous study estimated that pre-dementia AD is 17 years based on amyloid accumulation rates [1]. Lower age-specific durations of preclinical and prodromal AD were driven by higher mortality, faster decline, and lower reversion from MCI. This is in concordance with an exponential increase in AD dementia prevalence with age [2]. Higher progression rates at higher ages may be driven by a longer exposure duration at baseline or lower resilience [3].

We found a pronounced effect of cohort: for example preclinical AD, at age 70, had in a research setting a duration of 11 years, which was almost 3 times larger than the duration in clinical setting of 4 years. The shorter pre-dementia stages in the memory clinic patients compared to research participants may have two reasons. Individuals are longer in that stage at entry or those with more aggressive disease present more frequent at memory clinics. Compared to non-carriers, *APOE* ε4 carriers had a shorter duration of preclinical (~ -1.5 to -4 years) and prodromal AD (~-1 year). The shorter pre-dementia duration in *APOE* ε4 carriers is in line previous studies showing higher amyloid accumulation rates and an earlier dementia onset in *APOE* ε4 carriers [4-6]. When CSF tau was abnormal at baseline, preclinical AD was ~3 years and prodromal AD ~2.5 years shorter. The shortened preclinical and prodromal AD stages for individuals with elevated CSF tau levels at baseline is also in accordance with many studies showing to faster cognitive decline and neurodegeneration in those groups [7-10]. In conclusion, the estimations of AD duration improve when age, sex, *APOE* genotype, tau and setting are taken into account.

MCI reverters

Not all individuals with MCI progress to dementia. Ten to 30 percent of individuals with MCI show improvement to normal cognition [11], which seems a positive event. However, others had shown that MCI reverters remain at increased risk for dementia [12, 13]. We postulated this increased risk could be due to underlying AD.

In Chapter 2.2, we investigated which baseline factors, i.e., demographics, cognition, CSF and imaging markers, were associated with decline to MCI or dementia after initial reversion. We selected two independent samples of MCI reverters, the Alzheimer Disease Neuroimaging Initiative (ADNI) and Amsterdam Dementia Cohort. We found that the MCI reverters who subsequently showed decline were older and had abnormal amyloid PET and CSF tau levels more often compared to those who remained normal. In this clinically diverting group, AD biomarkers aid in distinguishing, a good prognosis, the stable MCI reverters, from those that are likely to decline again.

1.2 Strategies for recruitment and prescreening for studies on prevention of AD dementia

Trials for a secondary prevention strategy for AD have started to involve the search for individuals with normal cognition and evidence of amyloid pathology (EARLY and A4 trial) [14], or genetic risk factors, *APOE* ε4 and/or TOMM40 (TOMMORROW and Generation I&II trial). As individuals from the general population have a relatively low prevalence of amyloid accumulation or AD risk alleles as well as contra-indications for trial participation, these studies are facing high (pre)screen failure rates [15]. In the A4 trial, the total screen failure rate was 83% [16]. We set up the EPAD Registry, as an alternative to memory clinic referrals, outreach and advertisement. The aim was to facilitate recruitment and reduce screen failure for the EPAD longitudinal cohort study by enabling prescreening of individuals from existing studies. A subset of the EPAD participants will enroll in future clinical trials, thus general contra-indications for trials are checked, but amyloid-positivity is not required to pass the screening (Chapter 3.1). We compared the enrolment from 4 settings (memory clinic, general population, online and in-person volunteers research). Participation rates were highest in the memory clinic (59%) and lowest in the population-based cohort (3%). Despite the difference in participation rates, the total recruitment numbers were similar between settings as cohorts with a low participation rate had the largest number of participants in our study.

The percentages amyloid-positive individuals were around 30% in both the A4 trial screening and the EPAD trial-ready cohort participants. In Chapter 3.2, we assessed whether the presence of AD risk factors influenced participation rates and prevalence of amyloid positivity across the different settings of the recruitment sources. We found that individuals who were relatively young, had a higher education, male sex, and a family history of dementia were more often willing and able to participate in the EPAD trial-ready cohort. Among those who enrolled in the EPAD trial-ready cohort, the prevalence of amyloid positivity was higher for those who were at baseline relatively old and those carrying the *APOE* ε4 allele. These predictors were robust across settings.

1.3 Grey matter networks as potential surrogate endpoint for trials

Grey matter network changes align with progression in autosomal dominant AD

For a reliable measurement of treatment effects in secondary prevention, we need outcome measures that can track change in pre-dementia stages. In chapter 4.1, we studied a novel marker of AD progression, i.e., grey matter network measures. We tested whether, and how, such networks declined over the disease course in individuals carrying an autosomal dominant AD (ADAD) mutation compared to their noncarrier family members, as a function of estimated years to symptom onset. Mutation carriers had an increased rate of decline of the global grey matter network measures from 6 years before symptom onset. This was the first study to show that network disruptions decline within individuals with AD over time. The speed of grey matter network decline was predicted by the rate of amyloid accumulation, and closely associated to other markers of neurodegeneration on MR, FDG-PET and to cognitive decline. It provides a validation of grey matter network measures as a marker for disease progression in AD.

What are the biological correlates of grey matter networks disruption in AD?

In chapter 4.2, we further investigated the biological mechanisms underlying grey matter network disruptions in ADAD. To this end, we studied how grey matter network disruptions related to pathological markers in CSF that are known to be involved in AD, covering amyloid and tau aggregation, neuronal death, synaptic and axonal injury, and inflammation. We found that more abnormal levels of the CSF markers correlated with network disruptions. For elevated levels of markers of synaptic injury, tau, and neuronal death the associations with network disruption were specific for the mutation carriers, while the associations were also present in the noncarriers for axonal injury (NfL) and astrocyte activation. Higher NfL levels were most strongly associated with disrupted networks, which supports that axonal integrity plays a role in grey matter networks [17]. When comparing biomarker trajectories by the estimated years to symptom onset, we found that amyloid, tau, synaptic, and neuronal death markers diverged between the mutation carriers and noncarriers before, and axonal injury and astrocyte activation around the same time as grey matter network measures. The findings suggest that grey matter network disruptions may reflect loss of axonal connectivity in AD, occurring downstream from synaptic and neuronal injury.

2 Relevance of the findings for design of secondary prevention studies

2.1 Implications for trial design and inclusion criteria

Our finding that the pre-dementia period was 12 to 17 years has several implications. Trials in younger subjects with preclinical AD would take 15-20 years before the effect on progression to dementia can be assessed, which may make prevention trials challenging. A solution for this problem is to use surrogate endpoints [18]. The A4 and EARLY trial have a cognitive composite, but surrogate endpoints could also be biomarkers of disease progression, such as connectivity loss. When the disease

trajectory is well established, health economic models, taking into account age and setting, can extrapolate treatment effects, as measured at intermediate time points to estimate outcomes relevant for patients and/or society. In addition, the prognostic information on amyloid-positivity and MCI reversion forms an improvement for the previously available information for (potential) trial participants.

Enrichment and stratification with *APOE* and tau within amyloid-positive individuals

The pre-dementia period was influenced by age, *APOE*, CSF tau, meaning that further stratification by these factors could increase the power of secondary prevention trials. Enrichment for the *APOE* ε4 allele may result in more short-term progression and faster decline [4]. An advantage of stratification by *APOE* ε4 is that it increases the etiological and phenotypical homogeneity of the sample. However 40% of individuals with AD do not carry this allele and a treatment is also needed for them [19]. Enrichment with abnormal CSF tau would also increase the power to detect clinical and cognitive decline in amyloid-positive individuals without dementia [9]. Moreover, individuals who improve spontaneously are detrimental for the power of trial. Individuals with amyloid and tau-positive MCI rarely revert to normal cognition, and if so, are at increased risk to decline again. Of note, enrichment by markers related to fast decline will not necessarily increase the likelihood for trial success, in case an enrichment marker negatively affects the treatment response. For example: while a decreased cortical thickness is prognostic for faster cognitive decline, individuals with more atrophy at baseline could respond worse to a specific treatment. Therefore, it is important to take hypotheses on the relation between enrichment factors and the mode of action of the compound into consideration for the design of trial.

Detection of late-stage preclinical AD

We found that within amyloid-positive individuals a clinical visit, generally prompted by complaints of the patient or their relatives, is a strong prognostic factor for clinical progression. The finding suggests that these individuals are in late-stage preclinical AD, which would be a window of high potential impact of a preventive treatment (Figure 1). It also supports the pursuit to delineate which subjective signs and complaints reflect very early clinical progression of AD [20-22] in order to refine selection of individuals who may have clinical benefit from a treatment.

2.2 Implications for recruitment and prescreening for studies on prevention of AD dementia

Registries for participant selection and engagement

The EPAD Registry approach successfully kick-started enrolment for the project, with low screen failure due to contra-indications. However, we noted an issue with sustainability, as existing cohorts became depleted if not continuously enrolling new participants. A registry with continued enrollment, with a wider purpose seems more sustainable; either facilitating more studies and/or including data collection. In the

Netherlands, we performed a small pilot, modelled after the Brain Health Registry in USA [23]. The mature version of this participant registry was launched launched in 2019 [Zwan et al. in preparation]. Initiatives with related scopes include: TrialMatch (USA), JoinDementiaResearchUK (UK), and StepUP (Australia). We found that the set-up and maintenance require expertise in AD, online recruitment and engagement, and technological aspects. A generic registry is thus associated with substantial costs, but reduces the recruitment efforts in other projects, and probably even improves the percentage of studies with successfully completed enrolment. Nonetheless, it may be difficult to prove efficacy of registries, as recruitment effort and time tend to be underestimated [15].

Implementation of strategies for trial screening

Another implication of our studies on recruitment and screening was that currently available predictors for amyloid positivity have a modest predictive value. To obtain lower screen failure rates based on amyloid negativity, the population that qualifies for screening should to be massively restricted. If additional selection criteria beyond amyloid-positivity were to be included, as suggested in previous paragraphs, the prevalence of eligible individuals will be even lower, which proportionally increases the recruitment challenge [24]. A powerful way to decrease the screening burden is the commonly applied step-wise screening approach. In light of the recent developments in blood tests for Abeta and neurodegeneration [25-28], a blood test as a first step during screening could reduce the number of PET scans or CSF collections. A potential advantage of using a biological state marker, rather than a risk factor such as family history for dementia, is that larger proportion of individuals who may qualify can have access to the study screening. When these participants are drawn from a participant registry, and they subsequently screen fail for one study, the collected information can be (re)used for prescreening in future studies. Participants can then apply for re-screening, when a biomarker retest is sensible, after comorbidities have resolved, or personal circumstances have changed. In addition, the registry can enable the participants to share their data with multiple scientists, minimizing tedious repetition for the participant.

2.3 Implications for grey matter networks as surrogate endpoint

The investigation of grey matter networks in ADAD showed with respect to the potential use as a surrogate endpoint for trials that the networks decline within individuals over time in AD. However, most of the pure extracted measures, network degree, connectivity density and path length showed large variations within individuals over time. This intra-individual variability limits its use as an endpoint in clinical trials. In contrast, normalization to a reference network seemed to increase the ability to track change over time. Therefore, these small world measures are better suited as potential endpoints. Grey matter networks measures predicted future cognitive decline and neurodegeneration, which suggests that reduced decline of the grey matter

connectivity, or even improvement, may point towards robust disease modification. Our investigations should be extended by power calculations, as well as testing which of network metric(s) is superior and whether network measures have added value compared to current surrogate outcomes on cognition. It may also be possible to identify an optimal combination of structural grey matter markers with increased statistical power to detect change over time.

3 Methodological considerations

3.1 Staging and duration of the disease course of AD

A problem of studying a slowly progressive disease as AD is that the 'exposure duration' differs between individuals at study entry. The rate and the degree of preceded brain damage are unknown, while these influence the speed of progression [29]. Staging models intent to align individuals better on the disease severity [30-35]. The assumption is that when the staging within preclinical AD is more precise, disease-related abnormalities stand out. For all new modeling approaches, the balance between identification of plausible, relevant patterns, without over-specification towards the hypothesis presents a challenge. This is for example a risk when we include variables that are also part of the diagnostic criteria for MCI and dementia as predictors in classification modeling. In our ADAD project, we used the mutation-specific age at dementia onset as a surrogate timeline [36]. For interpreting an EYO of divergence between mutation carriers and noncarriers, it is important keep in mind that this time point is influenced by sample size, model specifications, the exact definition of EYO, as well as between subject variability, floor- and ceiling-effects of the investigated disease markers. In addition, longitudinal analyses do not always overlap completely with the cross-sectional trajectories [37]. In our study on grey matter networks decline over time was detectable later, likely due to a lower sample size. Still, the shape of the curves overlapped, pointing consistently towards an accelerating rate of decline of grey matter networks over the disease course.

In chapter 2.1, we used short-term longitudinal data of amyloid-positive individuals to estimate the AD clinical stage durations [38, 39]. Here, it is also important to remember the assumptions made. An assumption in our MSM model was that we presume that everyone who is amyloid-positive is on a trajectory to AD dementia. A limitation was that we could not include a separate tau stage in preclinical AD, due to few repeated measurements of tau. Mortality risk can be accounted for by multi-state or competitive risk models, but has mostly been ignored in AD studies. The primary reason for not incorporating mortality in prognostic studies with biomarkers is often because it is simply not systematically checked after attrition or completion of study visits. This was also a limitation in our study, and may be an explanation for the low mortality proportion in the preclinical AD group. Repeating this analysis with longer follow-up until death would improve the accuracy, and may allow further refinement of the model with additional covariates or stages.

3.2 Study population

We found low MCI reversion rates in the memory clinic cohort, and a shorter duration of pre-dementia stages in a clinical compared a research setting. This is in concordance with setting effects on the incidence of MCI and dementia, in amyloid biomarkers confirmed individuals with normal cognition or MCI, respectively [10, 40, 41]. Improved phenotyping may lead to better alignment between different cohort types, but at this stage, the different absolute risk estimates across populations warrants cautiousness when extrapolating results, for example in economic models.

We also studied the ADAD population. By definition, ADAD and sporadic AD differ in genetic causes, leading to questions on the generalizability of findings in ADAD. An advantage of studying the development of AD in mutation carriers of ADAD is the limited aging effects, due to the relatively young age of dementia onset. Grey matter network disruptions were consistent between the forms of AD. With regards to treatment development it is critical to learn whether causative cascades between these forms of AD converge, and based on our findings this convergence is likely to be upstream from grey matter network disruptions.

4 Future perspectives and conclusion

Studying the disease course of AD

Utilizing the larger datasets and increasingly follow-up durations, researchers started to apply more advanced methods to better understand progression of AD in the pre-dementia stages. Yet, repeated biomarkers measurements over long time periods, and observations of biomarker transitions at still rare [32, 42]. Information on biomarkers during early and mid-life is also sparse, though important, because early-life changes or a disequilibrium from an early-life homeostasis may relate to the development of AD in late-life. Another restriction in the advancement of prevention trial design are challenges with regards to the markers available for the disease monitoring. First, while most markers have a good diagnostic value, most are less suitable for predicting and monitoring disease progression. As it is unlikely that we can find one perfect disease marker for progression, the development of a practical toolbox seems more realistic, to which grey matter network measure can be added. Secondly, aging individuals can have multiple pathologies contributing to the speed of decline. Therefore, good markers for the other pathologies are important for AD modeling, to enable accounting for other factors. With a precise individual prognosis, we would be able to offer a future treatment to the appropriate persons at the right disease stage [43].

Run-in data for selection and treatment evaluation in trials

With regards to treatment evaluation, a run-in period (without any treatment) has been shown to have the potential to increase the power over cross-sectional baseline values [44, 45]. A run-in period is already implemented in DIAN-TU and the EPAD project to reduce the number of participants needed. Future trials should continue to refine and optimize the use of a run-in period.

Selection criteria intent to restrict the inclusion to individuals with potential benefit from a treatment [43]. While selection criteria on clinical, cognitive and biological signs with cross-sectional cut-offs are practical, the premorbid levels of those markers differ between individuals. Therefore, a cross-sectional value within the normal range does not exclude decline from the premorbid levels. In future trials, longitudinal inclusion criteria may facilitate selection of the appropriate individuals. Further investigations should clarify the pros and cons of essentially restricting enrolment to those who demonstrated decline (or no improvement) over time on specific markers before the start of trial.

Research participants motivation and engagement, why and how?

Prevention trial participation will not fit everyone's personal circumstances, life style and personality. Motivations include aspects of: having an affected family member or partner, altruism, help the next generation, passion for science, worries about cognition, curiosity about their body, meaningful activity, prospect of frequent check-ups, or hope for personal benefit. The population in clinical trials in Europe and the USA, and also in EPAD, is very homogenous Caucasian and higher-than-average educated. While upholding the appreciation for those participating, it would be better for the generalizability and recruitment rates if clinical trial populations had more diverse backgrounds. Increasing diversity requires specific adaptations to the trial design and recruitment strategy [46]. Interaction with the new type of research participants can teach us what drives individuals to join AD studies and which practical aspects of clinical trials may hamper participation. An alternative way to increase the recruitment (and retention) may be to lower the burden for participants [47]. This could include for example to develop cognitive tests that are less boring to complete, or replacing site visits by teleconferencing or home visits. Another practicality is the requirement for an informant about the participants daily functioning, which can preclude (trial) participation and cause attrition. Possibly the development of clinical trial robots, similar to care robots [48], could offer an alternative to a human informant for the trial, and by home observations reduce the number of tests and site visits needed.

4.1 Conclusion

In this thesis, we have investigated the trajectory of AD with different methods and figure 1 places these findings in the context of AD pathological cascade. This knowledge is important for understanding the development of AD, how to structure future trials in different stages, as well as for the implementation of treatments when these become available. Most previous secondary prevention trials targed amyloid, also the focus in our studies. Relatively new is that novel leads are more diverse and now include anti-tau compounds. Therefore, the maturation of participant registries and better blood-based screening markers will allow flexibility for adaptions in selection criteria. With our modern tools, tireless efforts of researchers and participants, and inspired by recent treatment successes in neurological diseases, a break-though could be around the corner. When this will happen is a matter of speculation.

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