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PERSPECTIVES ON PARTICIPATION IN DEMENTIA PREVENTION CLINICAL TRIALS

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PERSPECTIVES ON PARTICIPATION IN DEMENTIA PREVENTION CLINICAL TRIALS

THESIS FOR DOCTORAL DEGREE (Ph.D.)

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ABSTRACT

Dementia is an enormous global health challenge with a rapid increase in the number of people affected. There is an urgent need for research to find effective treatments and preventive strategies. Dementia prevention research is undergoing rapid development with novel approaches and techniques used. Both pharmacological and multimodal lifestyle randomized controlled trials (RCTs) have become longer, more complex, and target people earlier in the disease continuum. For the participants in clinical trials, this means new challenges.

The overall aim of this thesis was to explore the experiences of participation in dementia prevention clinical trials among study participants, study partners, and specialized personnel/ staff. Furthermore, the aim was to further understand their attitudes and knowledge about dementia and related diagnoses. All studies used qualitative method. Data from different kind of RCTs was collected with questionnaires including open-ended questions, focus groups and individual interviews. Content analysis and Grounded theory were used.

Study I Questionnaire with open-ended questions to 19 participants and 20 study partners in immunotherapy Alzheimer´s disease (AD) phase I-II RCTs and group interview with eight staff members in the clinical trial unit were used. Staff members highlighted the high burden for the participants. The main motives for participation were a willingness to help research and the benefits of access to specialized care. The main disadvantages were that participating was time-consuming and perceived distress in connection to some investigations.

Study II Focus group interviews were conducted within the Healthy Ageing Through Internet Counselling in the Elderly (HATICE) study with expert nurses (n=13) in cardiovascular disease (CVD) prevention in Finland and in the Netherlands. The purpose was to describe nurses' best experiences and practices with supporting CVD prevention and describe their suggestions on how to integrate their experiences into an online eHealth platform. Important aspects were to establish a relationship of trust, awareness and expectation management, and appropriate time and monitoring.

Study III Focus groups interviews with older “at risk” adults (presence of CVD risk factors) in Finland, The Netherlands, and France were conducted as part of the HATICE study (n=44). The purpose was to explore attitudes of older adults at increased risk of CVD and dementia and engagement in an eHealth self-management prevention program as well as facilitators and barriers. The results were represented in three categories: access to reliable information about CVD and dementia, trust in the healthcare provider, and burden and stigma of dementia.

Study IV Individual interviews with participants in multimodal dementia prevention MIND-AD_{MINI} trial among persons with prodromal AD (n=8) were conducted. The participants' experience of participating in the trial is presented as a dynamic process. Previous knowledge, their motives, and the received information guide the participants'

decision to take part in the trial. The trial was well tolerated and received even though the participants initially experienced high burden and difficulties managing information provided.

Conclusions: Despite differences in the trials and target populations, the participants presented similar motives for participating in dementia prevention trials including altruistic, hope for personal benefits of the interventions, and access to specialized care. There are differences in the participants' preferences and need for support in a trial, between the participating countries, and along the disease continuum. To address this, a more person-centred approach in the conduction of the trials is suggested. This may improve participant´s situation and the quality of RCTs which is important given the increasing complexity and new methods used in dementia prevention trials.

LIST OF SCIENTIFIC PAPERS

I. Solomon A, **Akenine U**, Andreasen N, Mangialasche F, Wimo A, Jelic V, Kivipelto M, Winblad B (2012) Practical Lessons from Amyloid Immunotherapy Trials in Alzheimer Disease. *Current Alzheimer Research, 2012, 9, 1126-1134*

II. Beishuizen C, **Akenine U**, Barbera M, Rosenberg A, Fallah Pour M, Richard E, Soininen H, Mangialasche F, Kivipelto M, Pols J, Moll van Charante E (2019) Integrating nurses' experiences with supporting behaviour change for cardiovascular prevention into a selfmanagement internet platform in Finland and the Netherlands: a qualitative study. *BMJ Open 2019;9:e023480. doi:10.1136/ bmjopen-2018-023480*

III. **Akenine U**, Barbera M, Beishuizen C, Fallah Pour M, Guillemont J, Rosenberg A, Coley N, Mangialasche F, Salo L, Savy S, Pols J, Andrieu S, Richard E, Soininen H, Moll van Charante E, Kivipelto M (2020) Attitudes of at-risk older adults about prevention of cardiovascular disease and dementia using eHealth: a qualitative study in a European context *BMJ Open 2020;10:e037050. doi:10.1136/ bmjopen-2020-037050*

IV. **Akenine U**, Thunborg C, Kivipelto M, Fallah Pour M. Experiences of participation in a multimodal lifestyle preventive trial MIND-AD_{MINI} among persons with prodromal Alzheimer's disease of: A qualitative interview study (submitted)

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LIST OF ABBREVIATIONS

AD	Alzheimer's disease
APOE	Apolipoprotein E
CA	Content Analysis
CAIDE risk score	Cardiovascular Risk Factors, Ageing and Dementia – CAIDE Dementia Risk Score
CSF	Cerebrospinal fluid
CT	Computed tomography
CSR	Cerebrospinal fluid
CRF	Case Report Form
CVD	Cardiovascular Disease
DoH	Declaration of Helsinki
DMT	Disease modifying therapies
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, 5th edition
DMT	Disease modifying therapy
EPAD	European Prevention of Alzheimers Dementia Consortium
FINGER	Finnish Geriatric Intervention Study to prevent Cognitive Impairment and Disability
FTD	Frontotemporal dementia
GCP	Good Clinical Practice
GP	General practitioner
GT	Grounded Theory
HATICE	The Healthy Agening Through Internet Conselling in the Elderly
ICD-9	International Classification of Disease
ICH	International Conference on Harmonization
IWG-1	International Working Group -criteria
LBD	Dementia with Lewy bodies
MDC	Medical decision-making capacity
MIND-AD	Multimodal preventive trial for AD

MAPT	Multidomain Alzheimer Preventive Trial
MCI	Mild cognitive impairment
MMSE	Mini mental state examination
MRI	Magnetic resonance imaging
NCD	Neurocognitive disorder
NTB	Neuropsychological test battery
NMDA	N-metyl-D-asparate receptor
MDC	Medical Decision
PC	Person Centered
PET	Positron emission tomography
preDIVA	Prevention of Dementia by Intensive Vascular Care
VaD	Vascular Dementia
WMA	World Medical Association
WHO	World Healt Organization
WW-FINGERS	Worls Wide FINGERS global RCT network

1 INTRODUCTION

This thesis is written in this context of the rapid development and of dementia prevention and risk reduction research and randomized controlled trials (RCT) trials, providing participants, study-partners, and specialized personnel perspectives on participating in trials in different settings. Dementia caused by Alzheimer's disease (AD) was, until 1970, regarded as untreatable. After discovering cholinergic deficiency in the cortex of AD patients, a number of RCTs aimed at increasing acetylcholine levels. The first cholinesterase inhibitors were introduced in the market in the mid-1990s. These symptomatic drugs are still used and are the main treatments options for AD together with NMDA receptor antagonist (1). Ethical issues discussed at this time around 1980, were disclosure of the diagnose to the person affected, the use of placebo in clinical trials, and patients' competency to consent to research (2). In the search for disease-modifying therapies, several drugs have been tested in RCTs during the last decades with no or limited success (3). During the last decade, there has been positive signals and increasing interest for non-pharmacological interventions to prevent or postpone the onset of dementia (4). Since then, new diagnostic criteria, primarily developed for research (5), has made it possible to target more early phases of AD with different interventions. The knowledge about AD is continuously developing (6), and the disease is now considered as a biological entity having a preclinical, prodromal, and dementia phase (7). However, this development is followed by new ethical issues, such as disclosure of AD diagnosis to asymptomatic or minimally symptomatic persons, the uncertainty of biomarker-based diagnoses, and social stigma in AD and dementia (8). In many non-pharmacological interventions, the target population is “at-risk” general population, eg, earlier and broader than the specific AD research criteria.

Disease-modifying therapies (DMTs) aim to prevent or delay the onset or progression of cognitive impairment. DMTs with different approaches (e.g. targeting amyloid and, tau, neuroprotection, anti-inflammatory, and metabolic interventions) have been tested in several pharmacological phase III studies, but they have failed to achieve clinical endpoints (9).

Biomarkers such as advanced brain imaging, results from cerebrospinal fluid (CSF) testing, and genetic testing, play an increasingly important role in AD drug development (10), and is also important for an earlier and more accurate diagnosis. The new possibilities to detect disease pathology in persons with very mild symptoms or even without any symptoms has created the target group at risk for dementia from the biomarker perspective. This has the potential to be helpful, but as the therapeutic paradigm shifts from symptom management to prevention, disclosure and communicating the meaning of biomarkers and risk prediction to potential trial participants become areas where many ethical issues have been identified (11, 12).

Multidomain lifestyle interventions address the etiology of cognitive impairment, dementia, and AD as multifactorial and with several potentially modifiable risk factors and protective factors, table 1, including vascular lifestyle-related factors (13-15).

Table 1. Proposed modifiable risk and protective factors for dementia

Risk factors	**Protective factors**
Diabetes High blood pressure at mid life Obesity at midlife Physical inactivity Depression Smoking Low education Hearing loss Traumatic Brain Injery High alcohol consumption Social isolation Air pollution	Healty Diet Education Physical activity Mental activity Social activity
Other new risk factors	
Loneliness Hopelessness Stress Sleep disturbances Impaired oral health Infections? Covid-19?	

During the last decades, there has been increasing evidence linking various modifiable risk factors throughout the life-course to dementia and AD (16). The recent Lancet Commission paper estimated that 40% of dementia globally is related to modifiable risk factors (modified list, see table 1). It is important to acknowledge that the evidence level for these risk factors is varying. For some (e.g. vascular risk factors and physical activity), it is already quite strong but for others (eg social isolation and hearing loss) it is still more limited and more studies are needed (17). There are also 'novel' risk factors which have been getting more interest recently e.g. feelings of loneliness and hopelessness (not only depression), stress and sleep disturbances. There is also intensive research going on to analyze the possible long-term impact of covid-19 infection for the risk of cognitive impairment and eventually dementia (18).

Most of the evidence concerning modifiable risk factors comes from epidemiological and experimental studies and it has been more challenging to get evidence from RCTs. The previous single domain interventions targeting modifiable risk factors have yielded modest or negative trials (16) Multimodal prevention trials target several risk factors simultaneously for optimal preventive effect, e.g., exercise, nutritional guidance, cognitive training, social activity, and monitoring of metabolic and vascular risk factors (4). The first multidomain RCT, the Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER), showed a beneficial effect of the intervention on the primary outcome, change in cognition on neuropsychological test battery (NTB) (19). The FINGER model has been adapted to local, geographical, ethnical, and cultural differences, and new trials have started

worldwide in the World-Wide FINGERS network (20). Other novel strategies in dementia research are, for example, preparing readiness-cohorts, adaptive designs(21), and the use of internet or eHealth tools for prevention trials (22, 23), which has increasing relevance in the current covid-19 pandemic landscape.

When researcher and various stakeholders formulate goals for future biomedical and pharmaceutical research, they stress the need for a more holistic approach in dementia research, future directions are suggested to focus on prevention, early diagnosis, and personalized care, and strong involvement of the patient and user perspective (24). Among these recommendations are topics concerning knowledge and awareness of dementia/AD and risk reduction, including different professional stakeholders and professions in research, and a need to facilitate collaboration across research domains and geographical locations (25). In the future, dementia prevention and personalized care are suggested to work closer with the vascular and other non-communicable disease (NCD) prevention field (integrated interventions) and public health for developing, evaluate and implementing brain health services (26). The interprofessional perspective are highlighted as essential in the development of the research field. A multiprotection aspect is present through this thesis, from the aim to present different perspectives form different groups, to the composition of the reseach groups, with a strong multi professional representation.

The purpose with this thesis is to describe different perspectives and experiences of dementia prevention clinical trials: pharmacological trials, lifestyle interventions, and the usage of new technology in prevention trials targeting persons at risk for developing dementia, prodromal AD, and mild dementia, study partners, and expert health care professionals. Knowledge about this different perspective can help to safeguard the wellbeing of participants in these trials. Furthermore, this knowledge can be helpful in design, conduction, and evaluation of dementia preventive trials.

2 BACKGROUND

2.1 DEMENTIA

Neurocognitive disorder (NCD) is the term that is used in the latest version of the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5) (American Psychiatric Association, DSM 5) for what are used to be called dementia. The word dementia, from Latin, means "a being out of one's mind" is slowly replaced, but such changes take time. In this thesis, both terms will be used as they both are used in general population, clinical settings and in research. The term Dementia is still the one most used and understood by the public, patients, and healthcare staff, although it might be more stigmatizing than the newer term, Neurocognitive disorder (27).

Historically, dementia has been considered a part of normal aging rather than a disease. This reflects in the previous use of the diagnose "senile dementia" in the ninth edition of the

International Classification of Disease (ICD-9) used in Sweden until 1997. Even if dementia is primarily age related (28) several other factors contribute to the risk of developing dementia, including cardiovascular morbidity, psychiatric diseases, and genetic factors (29-31). Major neurocognitive disorders or dementia is a syndrome diagnose for a set of symptoms where the cognitive impairment affects the ability to be independent in everyday activities and decline over time, caused by a group of neurodegenerative diseases and do not take biological background into account. The most common forms of dementia are AD with 60-70% of all cases, followed by Vascular dementia (VaD) 15%, Dementia with Lewy bodies (LBD), and Frontotemporal dementia (FTD) (32) (33). The primary cause of VaD is cerebrovascular disease with disturbed function of blood vessels in the brain by several pathologies causing cognitive impairment (34).

Dementia is an enormous global health challenge. According to the World Health Organization (WHO) (17), this progressive syndrome characterized by severe cognition and functional impairment was the fifth most common overall cause of death in 2016. I the older population segment, it is a major cause of disability, institutionalization, and death.

50 million people worldwide, and 9 million in Europe, are estimated to be affected by dementia. Within 30 years, this number is expected to double in Europa (35) and triple worldwide (36). This is due to an ageing population in both Western and low- and middle-income countries. The greatest increase in dementia cases is expected in the low- and middle-income countries. The World Health Organization (WHO) acknowledged this trend, sometimes described in terms of a fast-growing epidemic, and highlighted dementia and its prevention as a global public health priority (17). Alzheimer's disease is not equal to dementia, although dementia is the end state of the disease that gradual progress, but starts long before clinical symptoms are evident (37, 38).

Symptoms of dementia are associated with a cognitive deficit in multiple domains and functional deterioration in parallel with behavioral and psychological symptoms (39, 40). Cognitive deficits commonly affect memory functions, executive functions, learning, language, visuospatial functions, motor functions, and attention (29). The possibility of mixed etiology is well recognized (dementia neurocognitive disorder due to multiple etiologies) especially among the older age groups.

2.2 COGNITIVE IMPAIRMENT

In normal aging, some deterioration of cognitive abilities such as memory, problem solving, and the ability to plan and execute tasks, can be considered as normal, as well as some deterioration in speed and flexibility of thinking, reasoning and processing information (41). When the deterioration in these areas progress faster and become more severe than expected due to aging, it is a pathological impairment (27).

Pathological cognitive impairment occurs when the changes are more pronounced and rapid than can be expected from aging alone. The most severe expression of pathological cognitive impairment is dementia, which is characterized by an intra-individual cognitive decline severe

enough to compromise functioning and cause disability. Mild cognitive impairment (MCI) is a term used to describe clinical state of minor impairment in one or several cognitive functions, while others may be unimpaired. There are multiple underlying causes of MCI and some may be reversable such as medication side effects or depression. However, some MCI patients may progress to AD and some to other dementia diagnosis while others will not decline further in cognition (42, 43).

Cognitive abilities are very important for the capacity to comprehend information and make informed medical decision, and to understand the consequences of different decisions (44). Understanding, reasoning, and appreciating are essential for the ability to evaluate risk and benefits (45).

2.3 ALZHEIMER´S DISEASE

Alzheimer's disease (AD) was first described by the German psychiatrist and neuropathologist Alois Alzheimer after examining his patient Auguste Deter in 1901. Auguste suffered from progressive memory loss, disorientation, and hallucination. After her death, Dr. Alzheimer performed postmortem autopsy studies of her brain and described cerebral atrophy and protein deposits representing the classic manifestations of AD.

AD is the most common cause of dementia. The typical disease progression is gradual over a long period of time, and the pathological changes in the brain may start to develop decades before dementia diagnosis can be made. In recent years, new methods, diagnostic tools, and research diagnostic criteria have been developed, including biomarkers' usage before clinical signs of disease appear (46). The RTCs have now shifted from later stages in the disease continuum towards targeting the earlier stages of preclinical or prodromal AD (47). With this shift in defining the disease and development of new criteria, trials for AD treatment has become RCTs for dementia prevention.

AD is considered a multifactorial disease probably driven by both environmental and genetic factors (48). Several studies have reported an increased risk for dementia and AD in association with vascular, metabolic, and lifestyle-related risk factors besides age and genetic factors. These include e.g., obesity, hypertension, hypercholesterolemia, especially at midlife, and diabetes mellitus (46). Unhealthy dietary habits, smoking, alcohol drinking, and lack of physical activity also add to the increased dementia risk. On the other hand, an active lifestyle including physical, social, and cognitive activities and education have been suggested as protective factors (4, 49). Dementia risk scores, e.g., the CAIDE risk score (49), that combine several modifiable risk factors now make it possible to identify people who have an increased risk of developing dementia and who may benefit most from interventions targeting vascular lifestyle factors (4, 50).

Today, different biomarkers are used in research and clinical settings to identify persons with a high risk of developing AD dementia. CSF biomarkers (low beta-amyloid, and high total tau and phosporilated tau levels) and neuroimaging-based biomarkers (PET, MRI) are part of the proposed research diagnostic criteria for AD (37, 51). The clinical use of biomarkers helps with

an early and more accurate diagnosis, and in research studies, biomarkers can help select the most suitable individuals for clinical trials. The new possibilities to detect disease pathology in persons with very mild symptoms (prodromal AD), or even without any symptoms (preclinical AD) have created the target group at risk for dementia from the biomarker perspective (47).

3 DEMENTIA PREVENTION CLINICAL TRIALS

The terms prevention and risk reduction are sometimes used interchangeably in the literature. WHO uses the term risk reduction in their guidelines: Risk reduction of cognitive decline and dementia (36)

WHO defines the term “prevention” as *"specific population and individual-based interventions aimed to minimize the burden of diseases and associated risk factors." (52)*

Dementia prevention RCTs may not always be easy to put in the well-recognized categories of primary, secondary, and tertiary preventions. Dementia primary prevention aims to reduce disease incidence by addressing disease mechanisms or increasing resistance to disease by targeting persons in the population at a time when they do not yet bear either disease markers or clinical impairment. Dementia secondary prevention aims to detect and target clinically normal individuals with biomarker evidence of disease to delay or prevent symptom onset. Tertiary dementia prevention aims to target patients with clinical impairment to reduce the impact of progressive symptomatic decline (36, 46).

The paradigm shifts towards the recognition that neurobiology changes occur long before cognitive symptoms AD and the RCTs targeting the disease in earlier stages, has entailed that trials has become increasingly complex in design, longer and more burdensome for participants. Dementia preventive trial faces many challenges, and one of the major challenges is selecting and recruit a target population most likely to benefit from the intervention. Pharmacological trials with a disease-modifying approach have failed repeatedly, targeting mild to moderate Alzheimer's disease. The failures in pharmacological trials has contributed to highlight the need of non-pharmacological approaches targeting different vascular, metabolic, lifestyle related, and other modifiable risk and protective factors (53). The shift to target the earlier stages of the diseases, has resulted in a majority of new trials are recruiting the participants at a pre-dementia stage (54).

The use of biomarkers in the recruitment process is often required and the participants also have to fulfill certain cognitive eligibility criteria. Using biomarkers in preclinical disease entails ethical challenges. A person's right to know and not know their biomarkers as they prefer must be ensured (55). Recruitment of the large numbers of participants is challenging for most trials. Even when all the inclusion criteria are met, not all possible candidates are willing to participate in long demanding trials. Further barriers for recruitment in dementia prevention trials are insufficient knowledge among the public about dementia and the possibility for prevention and perceived disease stigma (56).

New strategies in dementia preventive research are developed continuously. Adaptive design, for example, where changes can be done during the RCT, doses can be adjusted, arms with different interventions can be discontinued during the trial if the preliminary results is not satisfying, and a control group can be shared between several investigations, has been applied in a few studies, e.g., European Prevention of Alzheimer's Dementia Consortium (EPAD) (57).

Another new strategy likely to be seen in the future is combining disease-modifying drugs with lifestyle interventions in RCTs and eHealth solutions. This rapid development is likely to affect how participation in clinical trials are experienced. Perspectives form the participants, study partners and personnel with hand on experiences with conduction of trials or expertise in the area, can have sustainable value in further development of dementia prevention reseach.

The interest for the participants motives and experiences of taking part in clinical trial has increased as trials are getting longer and more complex. To participate in long trials with many study visits and with intense or invasive interventions are burdensome for the participants (58).

Motives for participating in clinical trials has been previously investigated, and altruism is the most common described reason for participation in trials where there is no expected benefits of the interventions for the participants, although further participation seems to be unlikely if there is no personal benefits (59-64). To be able to help others in the future, and to bring hope to future generations and supporting reseach was important for the participants. The feeling of being part of finding a solution was described by participants and care givers in qualitative interview and survey studies (60, 64). Other important motives for participating in a clinical trial were extra medical monitoring and expected health benefits from taking part in a lifestyle intervention trial (65).

Many studies have described recruitment and retention of participants to dementia prevention trials, and described facilitators, barriers and different strategies (66-70). A survey study shows that recruitment may be more challenging in trials with high-burden and high-risk in MCI population compared to a dementia population (58). A telephone interview study among RCT centers in UK showed that complicated trial information constitutes a major barrier for recruitment to AD clinical trials and highlighted the need for clear and concise study information (70). Participants in a qualitative study revealed low awareness of the cause and risk factors of cognitive disorders and prevention (71) and to increase public awareness and attitudes towards research is described as essential to meet future need in participant recruitment of dementia RCTs (66). Some studies have investigated experiences and attitudes from participants in clinical trials, but many are done in hypothetical research situations.

In many current and future trials, participants will have to learn their genetic and or biomarker status to be eligible for clinical trials and the risk and means of discussing genetic or biomarker results to participants is discussed in several studies, especially in pre-clinical or prodromal phases of the Alzheimer continuum (72-75). Although the ethical discussion of biomarker disclosure is outside the scoop of this theses, some aspects of this ethical dilemma are present in this project.

This thesis highlights the need for more knowledge on how to increase awareness in the public, reduce stigma, and provide understandable information to the participants, and the need to adapt trial protocols to the needs of the participants. The studies provide perspectives on three different types of multinational dementia preventive trials: Pharmacological trials in early phase, eHealth trial and multimodal lifestyle trial.

3.1 PHARMACOLOGICAL CLINICAL TRIALS

Drug discovery is in general complicated, and especially in neuroscience, with an estimated failure rate greater than 95% (76). The clinical need for symptomatic and disease-modifying therapies (DMTs) is enormous and combined with a potentially big world market for pharmaceutical companies, which drives the research and development of disease treatment (3). In the 1980s and 1990s, the cholinergic hypothesis drove drug development and the trials in the search for AD therapy, even if interests in other agents such as neuroprotective, anti-inflammatory, and nutritional, emerged in the late 1990s. Four cholinesterase inhibitors have been marked for AD treatment and none since 2002 in Europe. The amyloid cascade hypothesis, presented in 1991(77), has since dominated the field (78). The first anti-amyloid drugs were tested in late-stage trials in 2001(79). RCTs during this time were substantially less burdensome for the participants with shorter trials of 3-6-month duration, less invasive investigations with no lumbar punctures, and only 2-3 MRI or CTs.

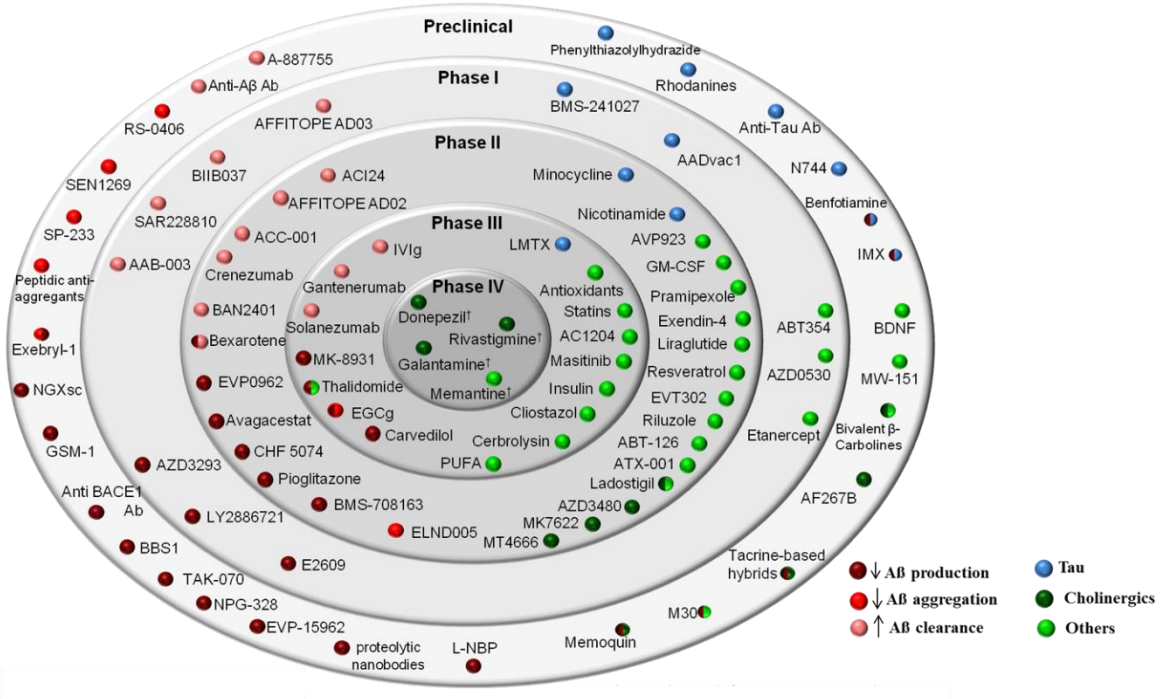

Figure 1. Disease- Modifying Drugs tested in RCTs 2013. Modified from Lancet Neurology 2010. Mangialasche, Kivipelto et al.

Development of new drugs takes many years and after preclinical research the clinical RCTs are described in three phases. Very few trials reach phase III. Most trials in phase I and II do

not show satisfying effect, but some trials had to be prematurely discontinued du to acceleration of deterioration in cognition or side effects such as elevated liver enzymes (80).

Phase I is when a new substance is first tested in a human being. Usually, the participants are healthy volunteers, but in some drugs with specific targets, the tests need to be performed in patients with a specific disease. The medical supervision is strict, and these trials are conducted in specialized medical units, phase I units. The trial's purpose is to determine whether the participants tolerate the drug and whether it behaves in the body in the manner indicated by the animal studies and other research. Patients with AD (including dementia) are often included in phase I trials.

Phase II is usually the first time the drug is given to patients with the relevant disease. Different doses are tested to see how the drug affects the disease or its symptoms, determine the dose to be used in large-scale testing, and evaluate possible side effects. The number of patients recruited in Phase II trials is relatively limited.

Phase III studies include a large number of patients, sometimes thousands, to assess efficacy, effectiveness, and safety. The large number is necessary to obtain a satisfactory basis for statistical analyses. (81, 82)

In February 2020 there were 121 agents in ongoing clinical trials for AD therapy were registered in ClinicalTrials.gov, and 97 of them were classified as disease modification agents intended to change the underlying biology of Alzheimer's disease. In phase I, there were 27 trials for AD therapy; 18 of these were DMT. Phase I trials had an average duration of 116 weeks, including recruitment and treatment, and a mean number of 43 participants. There were 73 phases II trials ongoing witch of 55 were DMTs. The mean treatment time was 43 weeks, with an average of 131 participants in each trial. Phase III trials included a mean of 554 participants and had a mean treatment exposure of 64 weeks. DMT trials were longer and larger than symptomatic agents, with 98 weeks of treatment and including an average of 689 participants. In February 2020, those trials required 31 314 participants (83).

Study I was conducted with participants and their study partners included in early phase I- II pharmacological trials.

3.2 E-HEALTH PREVENTION STUDIES

One major future challenge is how to reach a large population with health-promoting interventions, and novel approaches are needed. Patient self-management has been suggested as a useful tool for CVD risk reduction. eHealth models can potentially increase adherence to therapy in CVD risk reduction, provide opportunities for individualized intervention strategies and serve as a platform for information and education (84, 85). Previous reviews show beneficial effects of coach-supported eHealth interventions on individual risk factors (86-88). The recent years' rapid development of eHealth for self-management has increased the opportunities for large-scale RTC in the area of lifestyle interventions targeting CVD risk factors and prevention of cognitive decline. E-health solutions may be a future way to reach lager population groups for dementia prevention. More knowledge is needed in RCT trials on

the effectiveness and feasibility of such solutions and qualitative data are needed on the preferences of the target groups. Study II and II investigated aspects of an eHealth solution.

3.2.1 The HATICE trial

The Healthy Aging Through Internet Counselling in the Elderly (HATICE) trial was an 18 moth eHealth RCT conducted in Finland, France, and the Netherlands (23, 89). This trial recruited 2724 individuals aged over 65 years, without cognitive impairment, but with at least two vascular factors and/or CVD or diabetes. Participants in the intervention arm received access to the platform with advice on risk management and the possibility of interacting with a coach within the platform design. The control group had access to a platform with general health advice and no access to a coach. The primary outcome was a change in the composite score of three vascular risk factors. Other outcome measures were cognitive performance, changes in CVD risk and dementia based on risk scores, and CVD incidence. Both groups showed significant beneficial effects, but no difference in cognitive performance was reported (89). Sub studies described participants experiences of the HATICE trial (65, 71).

Study II and III are embedded qualitative studies within the HATICE trial, conducted before and during the design (22) of the eHealth platform.

3.3 NON-PHARMACOLOGICAL MULTIMODAL PREVENTIVE TRIALS

Lifestyle related factors such as hypertension, diabetes, smoking, obesity, physical inactivity, depression, and low education, are attributed to one third of AD cases (90). Given the multifactorial etiology of AD, a multimodal intervention approach, targeting multiple risk factors are a promising prevention strategy. In Europe, several RCTs have been testing multimodal preventive interventions (4). The Multidomain Alzheimer Preventive Trial, MAPT (91), included 1680 individuals aged over 70 years with subjective memory impairment in a three-year multicenter study in France. Three groups received combinations of lifestyle interventions and a nutritional supplement, and a control group received placebo. The primary outcome was change in cognitive performance, but no significant differences were found between the groups. The Dutch Prevention of Dementia by Intensive Vascular Care, preDIVA (92) recruited 3526 participants without dementia aged 70-80 years from general practices. The intervention group received tailored lifestyle guidance and monitoring and treatment of vascular risk factors. The primary outcome was incidence of dementia. No difference was shown after six years. The Finnish FINGER trial (19) was the first multidomain lifestyle based RCT reporting that it is possible to prevent cognitive decline and impairment. The 2-year trial included 1260 participants at 6 study sites in Finland. Age range was 60-77 years. The participants did not show any significant cognitive impairment at inclusion, but they had an increased risk of cognitive decline based on the Cardiovascular Risk Factors, Aging and Dementia (CAIDE) Risk Score(49) and cognitive testing. Participants were randomized into an intervention and control group. The intervention group received: a) nutritional guidance according to national recommendations in Finland; b) physical exercise training in groups; c) cognitive training provided by a computer program; and d) monitoring and management of

vascular risk factors. The control group received regular health advice. The results showed an increase in overall cognitive functions. World-Wide FINGERS (WW-FINGERS) global RCT network (20) was launched in 2017. Multidomain lifestyle interventions for risk reduction in more than 30 countries will investigate feasibility and efficacy of the FINGER intervention model targeting vascular, metabolic and lifestyle factors. The network aims to harmonize and adapt multidomain intervention across various geographical, cultural, and economic stings and facilitate data sharing and analysis.

Future possibilities for prevention in individuals with mild cognitive impairment, where targeting modifiable risk factors may not enough, might be a combination of disease modifying drugs and non-pharmacological interventions (20).

3.3.1 The MIND-AD$_{MINI}$ trial

The MIND-AD trial was a 6-month multinational parallel-group randomized controlled trial conducted in Finland, Sweden, France, and Germany. In Sweden, a 6-month extension was conducted. The study included in total 93 participants with prodromal AD using the International Working Group -1 criteria (IWG-1) (37). Other important inclusion criteria were vascular and lifestyle-related risk factors. Participants were randomized into three arms: a) multimodal lifestyle/vascular intervention; b) multimodal lifestyle/vascular intervention and medical food; and c) control or regular health advice/care. The primary outcome was feasibility and safety. Secondary outcomes were adherence to the individual intervention domains and healthy lifestyle changes. The multimodal lifestyle/vascular intervention included several components. 1) *Nutritional guidance* was delivered in 3-4 group sessions, and 3 individual face to face sessions with careful assessment of individual needs and providing individually tailored advice. Study partners were invited to participate in all visits. Recommendations were adapted to the respective national recommendations. 2) *Physical exercise program* was provided in groups of 4-6 participants twice a week. Physiotherapists or personal trainers led the groups. The exercise program was tailored to the participants' individual capacity. 3) *Cognitive training* included group sessions twice a week for about 20 minutes and the possibility to train using the computerized training program at home. A psychologist or occupational therapist led the group sessions. The web-based training program was in-house developed with an increasing level of difficulty. The program targeted executive functions, working memory, episodic memory, and mental speed. 4) *Intensive management of metabolic and vascular risk factors* was adapted to national guidelines. Additional meetings were scheduled with a study nurse to measure blood pressure, weight, BMI, hip and waist circumference, and further lifestyle management recommendations. If medication was necessary, the study physician wrote a prescription, or the participant was referred to regular health care. 5) *Social activities* were planned in connection to study visits. The arm with lifestyle/vascular intervention and medical food received also the study product Souvenaid, a 125 ml milk-based drink daily. In total 93 participants were randomized. The study was completed in December 2019.

Study IV is an embedded qualitative study within the MIND-AD$_{MINI}$ protocol.

4 GENERAL THEORETICAL PERSPECTIVES

4.1 PERSON CENTEREDNESS

Already Florence Nightingale described the importance of involving patients in the processes of care (93). Carl Rodgers introduced the term Person-Centered (PC) in the 1940th. The core of this theory is that each individual has several qualities and can draw strength from available resources and find way to remedy difficulties (94). Many followed, and among those were well-known theorist, Dorothea Orem, who focused on person-centered care (95) and her theory is today implemented in care settings worldwide.

A PC approach focuses on the biological, social, psychological, cultural and spiritual dimensions of a person (96), and a person centered care- (PCC) means acknowledging the persons´ beliefs and values, the respect for the person, right to self-determination and mutual respect as the cornerstones (96).

In regular health care, old routines and traditions and health care systems have not yet adapted to PCC, where focus is on the individual patient´s needs, preferences and values (97).

Key components of a PC-approach are described by Ekman et.al (97) as a partnership between the person receiving care, their families, and health care professionals. This is not unlike the relationship between the researcher/study-team and the participant, including study partner in an RCT setting. Furthermore, Ekman describes that this partnership builds on mutual respect for each parties' knowledge about living with the disease, care, treatment, and rehabilitation.

Person-centered care emphasizes the patients' perspective and involvement, resulting in a shift from a model where patients are objects of care, to a model where they are involved as active partners in the decision-making process (98). For patients to be active participants in the decision-making process, they need to have sufficient and relevant knowledge, which can only be provided by continuous person-centered information. Patients' needs and whishes need to be systematically assessed by health care professionals (99). In an RCT setting participants knowledge, need for information and decision-making processes are central for deciding to participate in a clinical trial, although these are seldom addressed.

In an RCT context, applying a PC approach could mean a more careful examination of the participants' motives for participating, including knowledge and awareness of the participants situation, previous experiences, fears, and stigma related issues, and addressing the differences in individual needs and expectations.

The perspective of person-centeredness has not, to our knowledge, previously been used when discussing participants' situations in dementia prevention RCTs. During the work with this thesis, it became evident that both the theoretical and more practical perspectives of person-

centeredness are constantly present in the findings of different studies. During the design and conduction of the studies, a general perspective of person-centered frameworks such as the one presented by WHO 2007, *People-centered health care: a policy framework* (100) has been applied.

In the Declaration of Helsinki (DoH), International Conference on Harmonization (IHC), and Good Clinical Practice (GCP) documents, people who are included in trials are referred to as study subjects. In the PCC the term patients is often replaced with the term person to shift focus from the disease to the person. In this thesis, the term participants is used. Participating, in this context, mean taking part in a randomized controlled trial.

4.2 DECLARATION OF HELSINKI

Declaration of Helsinki (DoH) is a set of ethical principles developed by World Medical Association (WMA), regarding human experimentation and research on human material and data. It is regarded as the cornerstone document on human research ethics. The declaration was originally adopted in June 1964 in Helsinki, Finland, and has been revised several times, most recently in 2013. DoH addresses the informed consent as one of the basic principles. Another is that the investigator's duty is solely to the patient, and while there is always a need for research, the subject's welfare must always take precedence over the interests of science and society, and ethical considerations must always take precedence over laws and regulations. The declaration also addresses risks, burdens, and benefits. Vulnerable groups and individuals included in the research are discussed. The first paragraph states that the declaration is intended to be read as a whole and that all paragraphs are depended on each other, and a single paragraph should not be applied without consideration of all relevant paragraphs (101-103).

The Belmont report from 1978, is another important document in the history of medical research ethics and is regarded as a landmark in the field. The Belmont report defines three important ethical principles in research on human subjects: 1) *Respect for persons* - individuals should be treated as autonomous agents; 2) *Beneficence* – a) do no harm; b) maximize possible benefits and minimize possible harm; and 3) *Justice* "Who ought to receive the benefits of research and bear its burdens?" - a) To each person an equal share, b) to each person according to individual need, and c) to each person according to individual effort.

The Belmont report finally discusses these principles' applications and highlights three important elements in research with human subjects. 1) *Informed Consent* - the three components of the informed consent process are information, comprehension, and voluntariness; 2) *Assessment of risks and benefits* - the report discusses several aspects of risks and benefits, including when research includes vulnerable populations. The judgment includes the nature and degree of risk and the nature and level of the anticipated benefits; and 3) *Selections of subjects* - the selection of subjects should be fair to the individual and within the social context. Participation in potentially beneficial research should be fairly distributed. Research with potentially higher risk should not be offered only to less desirable subjects (104).

The fourths of the maim ethical principles for biomedical reseach; non-malefience, is not discussed in the Belmont report, but are an important principle in the DoH.

Today the Belmont report is regarded as an important historical document that provides the moral framework for understanding the regulation on the use of humans in research in the United States(105, 106).

4.2.1 Good Clinical Practice

Good Clinical Practice (GCP) is an international quality standard that is provided by the International Conference on Harmonization (ICH). GCP defines a set of standards for clinical trials involving human subjects. GCP presents guidelines on the ethical aspects of clinical studies. The objectives of GCP are to safeguard the rights and wellbeing of the trial subjects and include protection of human rights for participants in clinical trials. GCP aims to ensure the credibility and accuracy of clinical data generated during clinical trials. Furthermore, GCP aims to ensure that studies are scientifically authentic and that procedures are properly documented to assure the safety and efficacy of the new compounds (107).

The tree first principles are regarded as the most important.

1. Clinical trials shall be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with GCP and the applicable regulatory requirements.

2. Foreseeable risks and inconvenience shall be weighed against the anticipated benefit to justify the risk.

3. Rights, safety, and wellbeing of the subjects are the most important consideration and shall prevail over the interests of science and society.

This thesis embraces the ethical principles described in the DoH and the studies are conducted according to the guidelines built on DoH. Knowledge generated in this thesis connects to several areas of the principles such as informed consent, risk/benefit, and to ensure the wellbeing of the subjects.

5 RATIONALE

To face the challenges of recruitment for future trials, there is a need to know more about the individuals' motives for participating. To reduce dropouts and keep participants active and adherent in the trials, we need to listen to their experiences and understand how we can meet their expectations on trial participation in the best possible way. There is a need to understand what interventions are feasible for both participants and relatives/study partners across the AD continuum in lifestyle trials. New technology, such as internet platforms and eHealth models, will be increasingly used in research and the implementation of results, and thus, input from participants and end-users, will be crucial in this development.

With substantial recent shifts in the dementia/AD field in clinical practice and research, changes have occurred in how clinical trials are performed and which target groups they now aim to include. A diversity of new questions has thus arisen. When studies become larger and are conducted internationally, protocols may need to be adapted to local settings. With local differences in social and health service systems, people from many different cultures, with different knowledge and understanding of disease and prevention, will be included in trials following a single main protocol. To facilitate this adaptation to local settings, increased understanding of the impact of cultural diversity regarding participants' attitudes and knowledge on prevention, disease, and research will be necessary.

Ethical questions and decisions are frequently present in AD/dementia research. When shifting focus from patients with AD dementia to prodromal AD and across the AD continuum to preclinical non-symptomatic biomarker-positive and at-risk individuals, multiple ethical dilemmas arise. For example, if, when, and how information on biomarkers and dementia risk should be communicated in the best possible way, when used for inclusion in clinical trials.

This knowledge will promote research and facilitate the implementation of research findings in clinical practice and society at large. Therefore, the main focus for this project is to illuminate different perspectives and experiences of -dementia preventive clinical trials: pharmacological trials, lifestyle interventions, and usage of new technology, focusing on persons at risk for developing dementia, prodromal AD, and mild dementia in different settings, study partners, and expert health care professionals.

6 RESEARCH AIM

6.1 GENERAL AIM

The overall aim was to develop new knowledge regarding participation in clinical trials among study participants in the field of dementia prevention by exploring experiences of participation in dementia prevention clinical trials among study participants, study partners, and specialized personnel. Furthermore, the aim was to further understand their attitudes and knowledge about dementia and related diagnoses.

6.2 SPECIFIC AIMS

Study I

To investigate practical experiences of staff, participants, and study-partners in immunotherapy RCTs.

Study II

To explore nurses' best practices with behavior change guidance for cardiovascular (CVD) prevention, including the potential for dementia prevention, in order to learn how to optimally integrate these into a coach-supported internet-platform.

Study III

This study aimed to explore knowledge of and attitudes towards prevention among older adults at risk of CVD and dementia, and to describe the facilitators and barriers for engagement in eHealth self-management prevention programs.

Study IV

To explore and describe the experiences of participation in the Multimodal preventive trial for AD (MIND-AD_{MINI}) among persons with prodromal Alzheimer's disease.

7 METHOD

Qualitative methods are defined as a detailed investigation of a phenomenon through the collection of rich narrative materials, using flexible research approaches such as interviews, focus groups or observations (108).

The goal for qualitative research is to generate knowledge that helps us understand the phenomenon as experienced by the participants themselves in their natural context (109, 110). Qualitative studies are useful for studying new or complex phenomena that cannot be quantitatively measured. Qualitative methods involve systematically collecting and interpreting of data. In this project, the interviews gave the participants an opportunity to express their situation, experiences, and attitudes with focus on their needs and values. Individual interviews were conducted to capture the perspectives of the person and that person's unique experiences, create meaning and create knowledge about the person´s context. Focus groups were used to increase the variety of perspectives when allowing the participants to interact and reflect upon others´ responses (111). A person-centered approach was applied during the project. The notion that there are several interpretations of the reality, influenced by the researcher's knowledge, values and beliefs of the phenomenon, is the core of the constructivist paradigm (108), from which the point of view in this thesis is derived.

7.1 QUALITATIVE METHODS STUDIES EMBEDDED IN RCTs

As randomized controlled trials are getting more complex, there is increasing use of qualitative methods within RTCs to address a wide range of aspects. In an extensive systematic mapping review, O'Chathain describes the most common areas for qualitative studies within RCTs, the design, the measures used in the trial, the outcomes of the trial, and the target condition of the trial. The qualitative methods have been used in all stages in RCTs before, during the conduction of the trial, and after the trial. This review identified a number of potential values for using qualitative methods within RCTs, such as improving the external validity of trials by identifying barriers for recruitment, exploring contextual issues, and facilitating transferability important for implementation (112).

7.2 GROUNDED THEORY

Grounded Theory (GT) is a systematic method used to construct an explanatory model or theory about a phenomenon (113, 114) which is grounded in data that have been systematically collected and analyzed. GT was first developed by sociologist Glaser and Straus in 1967, California, USA (115). Strauss later modified his perspective on GT in his work with Corbin (113, 114). Over time three different perspectives have emerged and are frequently used in the research area of health care. Glaser, Corbin and Strauss, and Charmaz methods have many similarities in method and terminology although there are several differences. While Glaser's classical GT-, and even Strauss and Corbin´s, has its roots in a positivistic perspective, Charmaz introduced a constructivist perspective (116). Strauss and Corbin shifted to a more

postpositivist position in their later work and Corbin acknowledged the co-construction of meaning between researcher and participants in the generation of data during unstructured interviews (117).

GT is described as being useful in research areas where there is little previous knowledge, and where new perspectives might be beneficial (118). GT is also a suitable method when there is a process involved in the phenomenon under investigation, although process is not always a necessary element to GT (116).

In GT the data collection and the analyses occur simultaneously. The first step in the data analytic phase is coding of the data, where segments of data are preliminary sorted into similar categories. In the axial coding phase, the categories are brought together into groups or themes. The themes generally represent a new way of understanding the phenomenon investigated. In the selective coding, the researcher organizes and integrates the categories and theme in a way that represent an understanding or a theory (117).

7.3 CONTENT ANALYSIS

The first descriptions of qualitative content analyses related to a positivistic paradigm (119). The content analysis method has over time, been developed from a method of counting content, to a more interpretative method within the hermeneutic paradigm (120), characterized by multiple subjective realities (121). Content analysis is a systematic method to analyze qualitative data. This method can analyze manifest and descriptive content, resulting in categories and latent and interpretative content, resulting in themes (120, 122). The analytic process involves descriptions and interpretations of various levels of abstraction. No descriptions are free from interpretations (123). Content analysis can be performed in various ways, depending on the study aim, the quality of data and the knowledge and experience of the researcher, but the process of content analysis is characterized by de-contextualization and re-contextualization. In the non-linear process, data are divided in to pieces meaning units, condensing and coding the units (120). In the re-contextualization phase, codes are sorted and compared by their similarities and differences and then abstracted into sub-categories. When data are combined, new patterns emerge allowing deeper understanding of the data (122).

Table 2. Overview of methods

7.4 OVERVIEW OF METHODS

	Study I	**Study II**	**Study III**	**Study IV**
Design	Qualitative	Qualitative	Qualitative	Qualitative
Aim	To investigate practical experiences of staff, participants, and study-partners in immunotherapy RCTs	To explore nurses' best practices with behavior change guidance for cardiovascular (CVD) prevention, including the potential for dementia prevention, in order to learn how to optimally integrate these into a coach-supported internet-platform	To explore knowledge of and attitudes towards prevention among older adults at risk of CVD and dementia, and to describe the facilitators and barriers for engagement in eHealth self-management prevention programs.	To explore and describe the experiences of participation in the Multimodal preventive trial for AD (MIND-D_{MINI}) among persons with prodromal Alzheimer's disease
Data collection	Questionnaires, open ended questions	Focus groups Interviews	Focus groups Interviews	Individual Interviews
Data analysis	Content analysis	Grounded Theory	Grounded Theory	Content analysis
Context	Pharmacological phase I-II trials Clinical Trial Research Unit, Memory Clinic, Karolinska University Hospital Sweden	e-Health prevention Embedded qualitative study in the design phase of the HATICE trial Finland Netherlands	eHealth prevention Embedded qualitative study in the design phase of the HATICE trial Finland Netherlands France	Multidomian lifestyle prevention Embedded qualitative study in the conduction and evaluation phase of the MIND-AD_{MINI} trial Sweden

7.4.1 Participants and settings

7.4.2 Study I

The study investigated experiences related to amyloid immunotherapy RCTs from the Clinical Trial Research Unit of the Memory Clinic at Karolinska University Hospital, Huddinge, Sweden. The Clinical Trial Research Unit carried out over 50 AD trials from 2001 and until the time of study I in 2011. During the period 2005 until the end of 2011, 14 amyloid

immunotherapy RCTs were carried out in the unit, including 154 participants. Eight trials were passive immunotherapy trials, of which 6 of this were phase I-II and 2 trials were phase III trial. A total of 90 participants were included. Three active immunotherapy trials in phase I-II included 64 participants. All trials are described in study I (124). Participants at the Clinical Trial Research Unit were recruited mainly from patients referred to the Memory Clinic for cognitive evaluation, but referrals from other memory clinics in Sweden were possible

Staff Members in study I included, three physicians, one psychologist, and four research nurses at the Clinical Trial Research Unit. All staff members were experienced in clinical trials and had 4-15 years of trial experience. Two physicians and the psychologist worked part-time with patients referred to the Memory Clinic at Karolinska University Hospital for cognitive assessments. All research nurses worked full time at the unit.

Patients with AD and study partners in study I were enrolled in Phase I/II amyloid immunotherapy RCTs at the Clinical Trial Research Unit. Twenty patients recruited as a consecutive sample and their caregivers who had been involved in phase I/II immunotherapy RCTs for up to one year were asked to participate in the study. This sample represented all participants meeting the criteria at that time. Nineteen patients, 9 women, and 10 men, were included. All 20 of the caregivers accepted participation. Patients' mean MMSE score was 23 points at inclusion in the RCT and their mean age was 66 years.

Amyloid immunotherapy RCTs trials were demanding for patients and caregivers. A visit could be as long as six hours, and caregivers had to be present at each visit. The RCTs' duration was 12-18 months and required in average 22 visits at the clinic. During that time, the participants took part in 8 evaluations of their cognition, 40-70 blood-samples were drawn, and 10 EEGs, 2-3 lumbar punctures, 2-3 PET-scans, and up to 12 MRI investigations were performed.

Studies II and III

Study II and study III were part of the Healthy Ageing Through Internet Counselling in the Elderly (HATICE) study (ISRCTN48151589), a European randomised controlled trial that tested the efficacy of an eHealth multimodal intervention in a coach-supported internet platform for self-management risk factors for CVD and Dementia in older people to prevent CVD and cognitive decline. The HATICE study was conducted in Finland, the Netherlands, and France. Study II was conducted in Finland and the Netherlands. Study III was conducted in Finland, France, and the Netherlands.

Study II and III were embedded in the HATICE study and were conducted in parallel with the development and design of the HATICE e-health platform, and several reports from the studies were delivered to the technical team to incorporate the results from the studies in the design.

Study II participants

Field experts recruited for Study II included *Dutch primary care nurses, and Finnish*

occupational healthcare nurses experienced in CVD preventive care. The places of recruitment were selected to find nurses experienced in prevention care, within the two countries´ health care systems.

Fourteen nurses working in a semiprivate healthcare center in Kuopio (Eastern Finland) were invited by email and telephone. Six nurses (43%), all were female, consented to participate. Working as occupational health nurses, they cared mostly for patients of working age. Duration of clinical experience with CVD prevention ranged from 2 to 35 years.

Thirty-two nurses experienced in CVD preventive care working in general practices in two urban areas in the centre of the Netherlands were invited by email and telephone. Seven female nurses (22%) agreed and gave their consent to participate. The participating Dutch nurses gave care services for patients of all ages. Duration of clinical experience with CVD prevention ranged from 3 to 11 years.

The reasons for non-participation by Finnish and Dutch nurses was lack of time.

Study III Participants

Forty-four *older adults at risk of CVD* were recruited in Finland, France, and the Netherlands. In Finland, the participants were recruited from a previous trial cohort. In France and in the Netherlands, the participants were recruited from general practices.

A simplified but comprehensive version of the HATICE trial criteria was used to identify a population as similar to the HATICE trial as possible: age over 65 years, basic internet literacy defined as the use of email, self-reported cardiovascular risk factors such as hypertension and dyslipidemia, active smoking, lack of physical exercise defined based on the WHO guidelines, self-reported history of CVD such as stroke/transient ischaemic attack, myocardial infarction, angina pectoris and/or peripheral arterial disease, and self-reported diagnosis of diabetes mellitus.

Study IV

This study was part of a larger project, the Multimodal preventive trial for Alzheimer disease (MIND-AD$_{MINI}$) (ClinicalTrials.gov NCT03249688), a 6-month multinational, randomized controlled trial. The objective of MIND-AD$_{MINI}$ was to evaluate the feasibility of an adapted FINGER-based multimodal lifestyle intervention among individuals with prodromal AD, diagnosed using the International Working Group-1 criteria. Other inclusion criteria in the RCT were vascular and lifestyle-related risk factors.

The MIND-AD$_{MINI}$ trial had three parallel arms: (i) multimodal lifestyle/vascular intervention, (ii) multimodal lifestyle/vascular intervention + medical food; and (iii) control. The lifestyle intervention consisted of the following main components: (i) nutritional guidance, (ii) physical exercise, (iii) cognitive training, (iv) social activity, as well as (v) monitoring of metabolic/vascular risk. The primary outcomes were feasibility and safety, and secondary outcomes were adherence to the interventions and lifestyle changes.

The MIND-AD$_{MINI}$ study was conducted in Sweden, Germany, France and Finland. Participants in study IV were recruited among participants from one of the Swedish study-sites at the Clinical Trial Research Unit of the Memory Clinic at Karolinska University Hospital, Huddinge, Sweden. Persons with prodromal AD who participated in MIND-AD$_{MINI}$ and provided consent-to-be-contacted forms, were provided information about the interview study and eight persons gave their informed consents and agreed to participate in the study. All interviews were conducted at the study-site at the Karolinska University Hospital. Mean age of Study IV participants was 66 years (range 62-75 years), 62.5% were female, mean MMSE score was 27 points, and mean formal education level was 14.5 years (range 9-18.5 years).

Table3. Overview of participants

	Study I	**Study II**	**Study III**	**Study IV**
Number of participants	Staff n=8 RCT participants n=19 Study partners n=20	Nurses n=13	Older adults at risk n=44	RCT participants n=8
Inclusion criteria	Patients included in pharmacological trials phase I-II	Purposive sample Field experts Nurses experienced in CVD prevention	Purposive sample Similar to HATICE, age 65 or older, basic internet literacy, self-reported CVD risk factors or events, lack of physical activity, diabetes	Participants included in MIND-AD$_{MINI}$
Mean age (years)	66	48	72	66
Cognitive status	Mild AD dementia Mean MMSE =23 (RCT participants)	NA	No known deficits At risk status	Prodromal AD Mean MMSE=27

7.4.3 Data collection and analysis

Study I

Questionnaires with open and structured questions were sent to 20 participants enrolled in phase I-II amyloid immunotherapy RCTs. Similar questionnaires were sent to their study-partners. The questionnaire was designed to be easy to answer, even with mild AD dementia. Questions with graded answer alternatives and given answer alternatives were used. 19 questionnaires from the participants were sent back and 20 from the study-partners. The results from the graded questions were summarized and presented in tables. Content analysis was used to analyse the answers as the method is suitable for a variety of data (125). Two

members of the group independently read all the text and selected meaning units that corresponded to the reseach question. The meaning units were condensed and coded. The codes and categories were thorough discussed in the research group and revised several times when going back and comparing the data (120, 122).

Study II

Two focus groups were conducted, one in the Netherlands and one in Finland. In both countries the focus groups were facilitated by experienced qualitative researchers and an assistant took detailed notes. A topic list was used to guide the discussion and the nurses could interact and respond to each other's statements. After the first Dutch focus group, the topic list was refined, and some questions were added where more information was needed or for being clarification. In both countries experiences of working with CVD prevention were discussed, and in Finland the nurses were also asked about their experiences with prevention for dementia. The focus groups lasted for approximately 2 hours each. The discussions were audio recorded and transcribed. -In Finland the transcriptions were translated into English since not all researchers were Finnish speaking. The analyses followed the principles of Grounded Theory (113, 114). In the Netherlands and in Finland 2 researchers coded the data and identified initial themes. Thereafter the codes and initial themes were compared and thorough discussed until consensus was reached. All data from Finland were then cross checked by the Finnish focus group moderator. At this point all Dutch themes and quotes were translated into English for further analysis. During the following iterative analysis phase, the data were compared and both teams returned to their data and the themes were merged and refined. The whole research team had two face to face meetings and multiple mail and phone conversations. The differences in the health care systems became evident during the analysis and therefor a description of both systems was developed and used to help the understanding during the analysis and in the presentation of the results. The results were returned to the participants for feedback.

Study III

Data were collected in three rounds of focus groups with a total of eight focus groups, three in Finland, three in the Netherlands and two in France. Semi- structured focus group interviews were conducted following an interview guide with the main topics described. The interviews were conducted by experienced members of the local research team in the native language. The interviews were audio recorded and detailed notes were taken. Two of the recordings, one in Finland and one in France failed due to technical issues, and the detailed notes were analysed. The remaining recordings were transcribed verbatim.

Studies II and III were conducted according to grounded theory approach (113). The analysis followed the analytic steps of initial, focused, axial, and selective coding in an inductive and deductive approach. Constant comparison was used throughout by comparing data for similarities and differences. This process of comparison was extra important in the data sets from different countries throughout the whole analysis process. Initially two researchers in each country identified codes and compared those before combined them in the axial-coding phase. This process was conducted in the local language within the local research team. In

Finland, where not all researchers were Finnish speaking, all data were translated into English. The translations were crosschecked by two researchers, fluent in both Finnish and English. When all the six first sessions were finished in the three countries, the findings were translated and combined in English. Numerous telephone meetings were held with the different research teams, as well as two face-to-face meetings.

Study IV

8 participants in the MIND-AD$_{MINI}$ trial were interviewed twice, in the beginning of the study and after 6 months of participating in the trial resulting in 16 interviews in total. The interviews were divided between two researchers who each interviewed 8 participants. All interviews took place in the hospital facilities in connection to a planned MIND-AD intervention visit, according to the preference of the participants. A semi structured interview guide was used to ensure that the topics of the research questions were covered. All interviews were audio-recorded and transcribed verbatim. Content Analysis was used for the analysis (120, 122, 123). The transcriptions were read several times to get a fist sense of the data. This reading sometimes required relistening to the recordings to get an understanding of the text. Meaning units were identified. At this stage, a colour code was introduced to identify meaning units belonging to all the intervention components in the MIND-AD$_{MINI}$ trial and some meaning units concerning the logistics of the trial. These colour codes were then used in a later stage to sort the data according to different interventions components. The meaning units were condensed and coded. The codes were then sorted and compared on their similarities and their differences and sorted into categories that were further discussed in the research team. Although the data during the collection were presumed to be thin, they proved to be rich and allowed a higher degree of abstraction and interpretation of the whole dataset. The colour codes provided a possibility to describe more concrete pros and cons related to the participants´ experiences of the separate study-related intervention components. This way the colour codes became a way not to lose important content when all data were condensed and became more abstract. During the analysis, variation in the data was strived for.

7.5 ETHICAL CONSIDERATIONS

The studies in these theses are approved by the Ethical committees in each country.

Study I

Sweden 2011/1987-31/4. 43/03

Study II

Finland 35//2014 The Netherlands NL48261.018.14

Study III

Finland 35//2014 The Netherlands NL48261.018.14 France 2014/68 2014-A01287-40

Study IV

Sweden 2016/2605-31/1

All studies followed and were guided by the DoH and the ethical principles for medical research.

All participants received oral and written information about the study and had opportunity to ask questions to the researchers. All participants gave their own informed consent to participate.

Participants in study I and IV were all included in an RCT. When informing the participants about the qualitative studies extra considerations were taken to address the risk of misunderstanding about the different studies. Additional and repeated information were provided to emphasize that their participation in the RCT would not be affected by taking part in the qualitative study. In Study I the participants answered the questionnaire anonymously to ensure that they could answer freely. In study IV the interviewing researchers were members of the RCT team with no/little direct involment in intervention activities, and interviews were decided to be the most suitable method for addressing the questions.

All data are handled and stored according to regulations in Karolinska Institutet and the universities in the participating countries.

8 FINDINGS

8.1 STUDY I

Staff members experienced in amyloid immunotherapy RCTs emphasized the high burden for the participants and their study-partners, often spouses or children, to participate in the trial. Especially demanding for the participants was the repeated cognitive testing, particularly when they experienced repeated failures. The staff members also discussed the written informed consent form as a struggle for the participants since it often was long, hard to understand, and demanded multiple signatures from the participants for separate study-related procedures.

The participants' motives for participating in the RCTs were described as a strong wish to contribute to research and the hope of receiving an effective drug to cure or slow down the progression of the disease. Participants and their caregivers described that they felt safe and trusted that they would not be exposed to unnecessary risks during the trial. The caregivers worried about the possibility of receiving placebo while this did not seem to be a concern for the participants. Both caregivers and the participants described that they had received enough information about the trial, but they wanted more information about the disease and other treatment opportunities.

Receiving professional support and regular health checks and the feelings of safety when being looked after by the study-team were mentioned as major advantages of participating, both by participants and study-partners. Participating in a trial also allowed meeting other people in a

similar situation, which was experienced as positive. Participants described few disadvantages while their study-partners stated that participation was time-consuming and burdensome for the participants, with pain and distress connected to some investigations.

8.2 STUDY II

The results are reported in two parts. The first part describes the nurses' experiences and practices with supporting the process of behaviour change for CVD prevention, including the potential for dementia prevention. The second part describes the nurses' suggestions on how to integrate their experiences in an online-support setting, stimulated by a demonstration of the HATICE platform.

Part 1and Part 2 together identify three main themes that can be understood as *the nurses' preconditions for effective behaviour change guidance in their patients:*

Establishing a relationship of trust

Part 1: The nurses in Finland and the Netherlands emphasized that the key element of behaviour change support is in establishing a relationship of trust with the patient. This relationship develops over time when the person feels respected and comfortable enough to discuss lifestyle and behaviour issues. To personalize and tailor support to each individual's needs facilitated the trusting relationship. Some differences between nurses in the two countries became evident in their preferences regarding the ideal mode of communication. The Dutch nurses expressed that repeated face-to-face contact was essential to establish a good relationship. The Finnish nurses experienced that an initial face-to-face contact could be sufficient to establish a relationship that could be followed up remotely.

Part 2: When discussing the novel platform, the nurses regarded a coach as essential for optimizing personal support. An initial face-to-face consultation with the coach and the patient could strengthen the establishment of a good relationship. The Finnish nurses felt that online coaching could successfully establish a relationship of trust, provided that the coach was a real person, and regarded the online platform as a step forward in innovating healthcare. The Dutch nurses expressed more hesitance that the platform and coach cold substitute their personal guidance.

Awareness and expectation management

Part 1: To manage the patient's awareness and expectations was described as a second precondition. In both countries (and especially in Finland due to a long-standing tradition of community-based CVD prevention), the nurses experienced that most patients had considerable knowledge of general CVD prevention but were less aware of their personal CVD risk status. To check the patients' level of knowledge and expectations regarding prevention and personal CVD risk were important steps in preventive work. The Finnish nurses acknowledged that CVD risk was also related to the potential for dementia prevention. They experienced that many patients feared dementia and lacked knowledge about the disease and

treatment and prevention options, creating a stigma towards dementia. The nurses were aware of the link between CVD and dementia but felt they lacked sufficient knowledge and training to provide proper support.

2: In both countries, the nurses regarded the internet platform as a suitable means to raise awareness and increase health literacy. Furthermore, the nurses expressed the importance of managing expectations related to online support, as they expected that misunderstandings could arise more easily through this method.

Appropriate timing and monitoring

Part 1: To provide support at the right time was regarded as crucial by the nurses to support their patients' lifestyle changes. Regular contacts and follow-ups promoted adherence and increased motivation. In both countries the nurses experienced that monitoring gave them opportunity to provide support when patients experienced obstacles or failures. The nurses put the patients in charge of preventive lifestyle changes and regarded their own role as supportive. However, the Dutch nurses preferred to have more control over the medical components of the prevention, for example, control of hypertension and diabetes, while the Finnish nurses regarded their patients as capable of staying in charge and described their own role as mentors.

Part 2: In an online platform, the nurses speculated that the patient would be in charge of the timing of support and monitoring of progress. Even if the coach would have a reactive role, providing support would be in response to the patient's demand. However, the nurses felt the coach also needed to be proactive, for example when persons experience loss of motivation. This would require insight into people's activities on the platform. Both groups thought the platform should be aligned to regular healthcare.

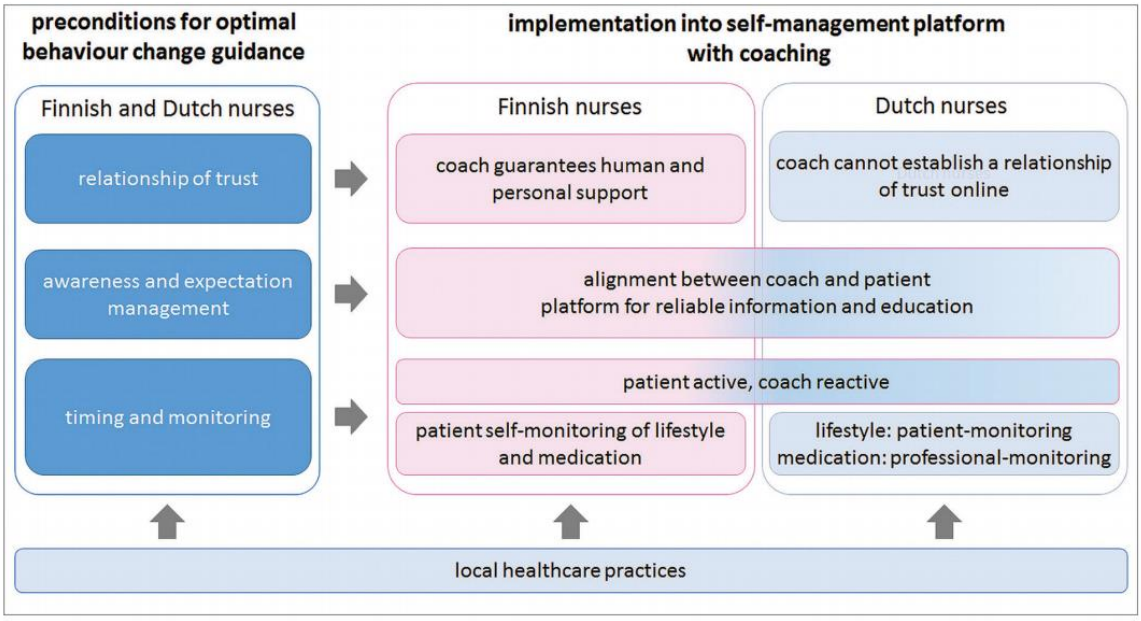

Figure1: Main themes and their preconditions. Differences and similarities between Finnish and Dutch nurses are shown to the left. Below is shown the impact of local healthcare practices.

8.3 STUDY III

Three categories were identified, and a core category was developed, representing the attitudes of older adults at increased risk of CVD and dementia regarding engagement in eHealth self-management prevention programs, and the facilitators and barriers.

Access to reliable information about CVD and dementia

In this study, the participants described that they experienced some confusion regarding prevention in general and even more concerning prevention of CVD and dementia. Participants in all three countries, Finland, the Netherlands, and France, expressed a need for reliable information about CVD and dementia and about how to put recommendations into practice. Superficial knowledge on prevention represented a significant barrier, and access to reliable information was regarded as essential for them to take steps towards prevention actions. Not being able to distinguish trustworthy from untrustworthy sources was identified as another barrier, especially concerning health-related information received from the Internet. The participants stressed that an eHealth platform could help provide trustworthy information from authorized sources tailored to individual needs.

Trust in the healthcare provider

The participants emphasized that trust in their primary healthcare providers, including their GPs and nurses, and trust in the received health-related information and the healthcare system is crucial to engage in prevention programs. In France and the Netherlands, the participants highlighted the importance of having a good relationship with their primary healthcare providers to engage in prevention programs, including those delivered through eHealth tools. They expressed a strong preference for an eHealth prevention program managed by their own primary healthcare provider. The Finnish participants acknowledged the role of trust in the eHealth lifestyle coach and data integrity when managing personal information as motivating factors to actively participate in eHealth prevention programs.

The Finnish participants stressed the importance of their autonomy and own responsibility for their health and prevention, expressing their pronounced interest in health self-management. Dutch and French participants strongly relied on their GPs advice.

Burden and stigma of dementia

The participants compared the possibilities for prevention of CVD with those of dementia and described CVD as having good treatment options and a possibility to recover, compared with dementia as a condition with no possibility for recovery. Participants associated feelings of fear, shame, and hopelessness in anticipation of developing dementia with no available treatment. Dementia was described as a great burden caused by loss of one's independence due to loss of cognitive and physical capabilities and loss of social relationships. The participants described the burden of dementia that affected the person with dementia, their families, and society.

Participants expressed a pessimistic attitude towards the prevention of dementia as opposed to CVD. However, being physically, cognitive, and socially active were described as potential preventive factors. The fact that dementia shares many risk factors with CVD was not generally known or expressed by the participants. The participants' scepticism towards prevention of dementia was closely linked to attribution of the role of genetic factors.

The stigma connected with dementia was described by the Finnish participants as a barrier to obtaining reliable information, and that the fear of dementia made it more difficult to talk about and consult a doctor about it, compared with CVD. The participants at the same time described fear as an encouraging factor to engage more in the prevention of dementia than of CVD.

From the three categories, a core category was developed: *the interactive process of the three identified categories influencing engagement in the self-management prevention program.*

The three categories were interconnected through an interactive process and were strongly influenced by the local healthcare culture and context, which shaped them differently. To minimize the stigma, there is a need to receive relevant, reliable information and trust healthcare providers. However, the burden and stigma of dementia were described as a barrier to receiving reliable information and trusting healthcare providers.

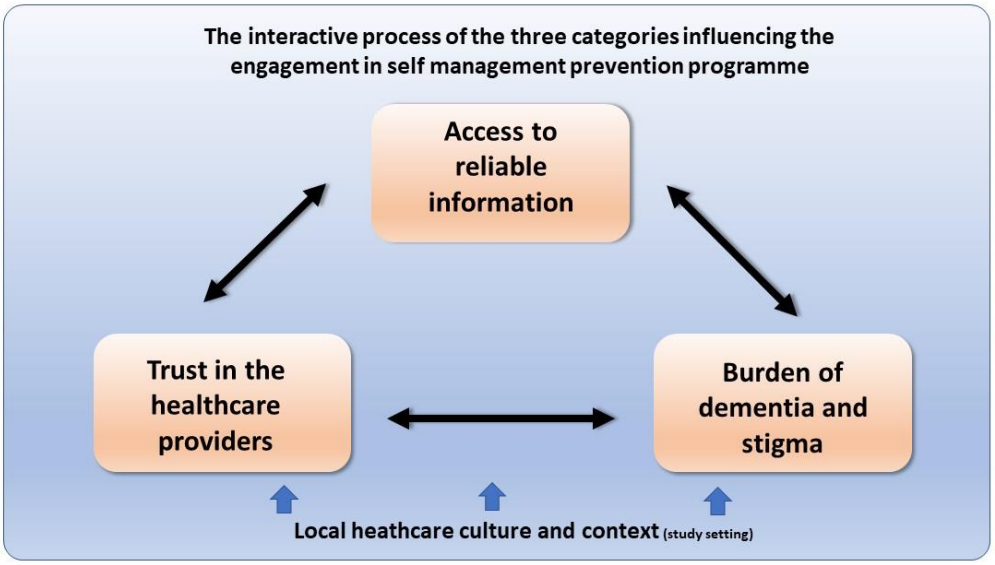

Figure 2. Presentation of the core category and the interactions between categories.

8.4 STUDY IV

The results of the study are presented in terms of a dynamic process, as demonstrated in Figure 3. The results are presented as (i) *Knowledge of Alzheimer's disease and prevention*, (ii) *Motives*, (iii) *Experiences of the received information*, (iv) *Decision-making*, (v) *Expectations*, (vi) *Experiences of participation in the MIND-AD$_{MINI}$* and (vii) *Individual and external factors*. Participants' knowledge about Alzheimer's disease and prevention, their motives to take part in the prevention trial, and their experiences of the received information regarding the prevention

trial led them to make the decision to take part in the trial and formulated their expectations. Several individual and external factors influenced participation in the study.

Since the interviews were performed twice during the intervention period (i.e., in the beginning and the end), the results are presented as a dynamic process where the contents of the categories are developed during the participants' participation in the trial. The last phase in the process described participants' experiences of their participation in the prevention trial MIND-AD$_{MINI}$.

Motives for participating were altruistic with a high wish to help research. To be an active part in the trial was important for the participants. Other motives were related to personal benefits such as access to specialized health care and direct health benefits from the intervention. The participants' belief in the intervention effect on the progression of their disease increased during the trial. The physical exercise component was the most appreciated, while being confronted with failures during cognitive training or testing were perceived as disadvantages of participating in the trial.

The results show that the MIND-AD$_{MINI}$ trial was well tolerated by the participants. Although they early in the study experienced high burden with many visits at the study-centre, and difficulties with managing the extensive amount of information provided, they later in the study accepted the amount of tasks included in the trial.

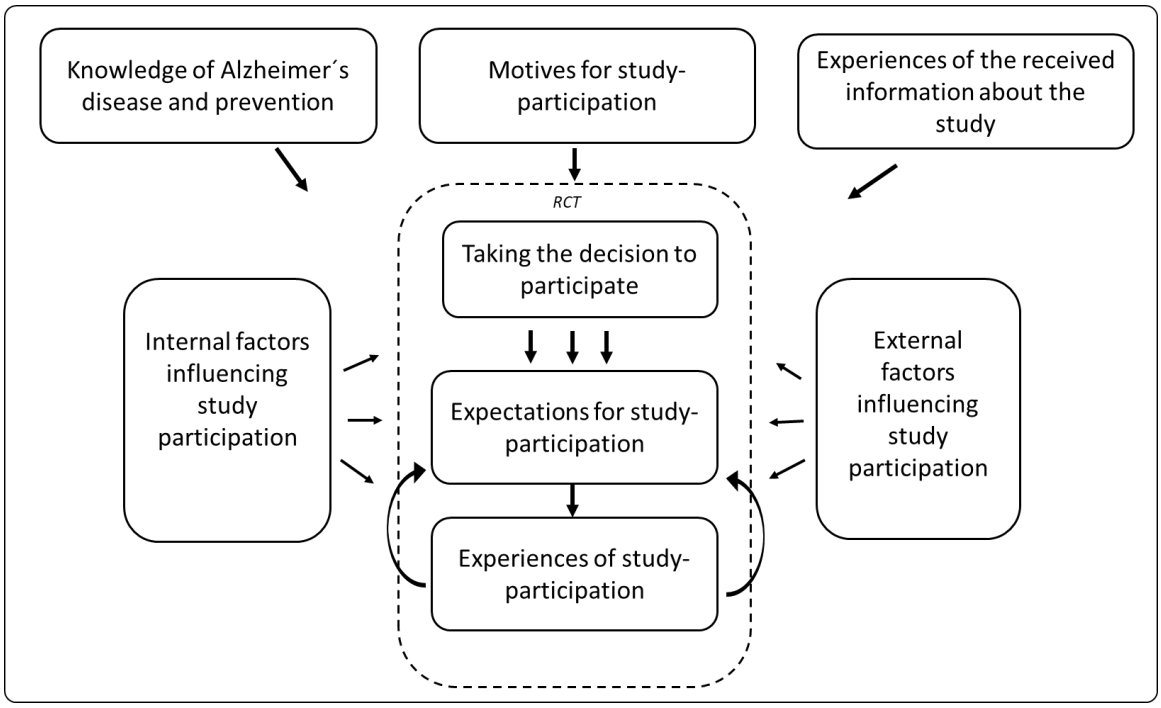

Figure 3. Dynamic process of participation in the MIND-AD$_{MINI}$ prevention trial

9 DISCUSSION

9.1 FINDINGS

The overall aim for this thesis was to develop new knowledge regarding participation in clinical trials among study participants in the field of dementia prevention by exploring experiences of participation in dementia prevention clinical trials among study participants, study partners, and specialized personnel/staff. Furthermore, the aim was to further understand their attitudes and knowledge about dementia and related diagnoses and their experiences of participation in the dementia prevention clinical trials.

In recent years, there has been a rapid development in dementia and AD prevention research. A shift to a more biological definition of the disease and acknowledging a life course perspective have led to the development of new diagnostic criteria and, new approaches when designing protocols, and the trials are targeting new populations (4, 18). In this rapid development, it is essential to ensure that the basic ethical principles for medical research are followed. According to DoH (101), this responsibility is shared among all of those involved in a trial, local laws and regulations, and ethical committees, but also by researchers, physicians and study personnel, participants, and their representatives. The results in this thesis provide knowledge that is closely connected to several of the fundamental principles of research ethics described in the DoH, for example article 25 and 26 that discuss the informed consent. The participant has a right to be informed, but the researcher also has a responsibility to ensure that participants understand the given information. Study IV explored the understanding of the informed consent over time, which is highly relevant in long trials that include participants with cognitive decline. Several articles in the declaration discuss the risks, burdens, and benefits of study participation. In dementia prevention trials the risks, the burden of participation and the potential benefits of participation variety. To follow the DoH we need to evaluate and explore the participants attitudes and experiences and include this knowledge in future studies.

The findings in this project highlight key topics that can be noted across the four studies as described below.

Knowledge about dementia related diagnoses and prevention:

The public knowledge about AD or other dementia related diagnoses, and the possibility for prevention have increased over time. However, the level of knowledge is still described as inadequate with several shortages. Knowledge is often limited to and highly dependent on personal experiences of the disease (71). In study III the participants confirmed the importance of personal experiences and describe how the fear of dementia made them take different actions. This fear could serve as a trigger to seek medical advice and initiate prevention strategies but could also prevent them from contacting medical health care and talk about their concerns. Lack of awareness about early symptoms and stigma can be barriers to early diagnosis (126). Experienced nurses working in prevention health care in study II identified public lack of knowledge about prevention, particularly the possibility of dementia prevention

in connection to CVD risk factors. They recognized themselves as educators in this matter but experienced a need for more information material and more education to be able to raise awareness among their patients. Even participants in study IV with the diagnosis of prodromal AD consider their knowledge about AD as low. A number of participants in study IV expressed a wish for getting more information, while others showed reluctance to learn more and expressed confusion on what diagnosis they had received. Prodromal AD is still mainly a research diagnosis and usually not commonly used in clinical practice, and it is unclear what information the participants had received in their regular care in the clinic. However, this makes it evident that the communication and information delivered to the patients must be clear and tailored to individual needs, especially when recruiting participants to clinical trials using research diagnostic criteria.

The need and access to information:

Patients and their caregivers need and actively seek information in relation to their diagnosis, (127, 128), and in study I and III this became evident when participants described the wish for information about the disease and treatment options, as a motive for participating in a clinical trial. Finding trustworthy information about AD, dementia and prevention was perceived as challenging by participants in this project, especially finding reliable information on the internet. Participants in study III particularly emphasized the challenge of evaluating the information and put trust in the publisher as a guarantee for quality.

Patients and caregivers usually experienced a need for support after diagnosis. Advice, social and psychological support (129) and the access to information needs to be continuous over time and adapted to different needs in time and format (126, 130). In study I and IV the participants pointed out that one of the advantages of participating in a clinical trial was the access to specialized staff at the study center.

Understanding of provided information:

Information provided, especially in clinical trials, may be perceived as hard to understand, especially for persons with cognitive deficits. Informed consent information is often long and perceived as complicated (70), which was confirmed in studies I and IV. Long and complicated information about the trial has also been described as a barrier for recruitment. Participants had questions about the key aspects of the trials. Previous literature has described it as a facilitator for recruitment of participants to clinical trials if research is embedded in patients' regular care with an established contact between clinicians and researchers (70).

Medical decision-making capacity (MDC) is a person's ability to make decisions and choices in a medical context that aligns with one's values and preferences (45, 131). Cognitive abilities, such as understanding the related information, reasoning regarding risks and benefits, and ability to communicate wishes and decisions made are essential (45).

The capacity to make one's own decisions is fundamental to the ethical principle of respect for autonomy and is a crucial component of informed consent to medical treatment and research

(101). Different terms are used in the literature to specify what type of medical decision the MCD refers to. Here, the concept MDC is used to describe participation in research and includes formulations such as "informed consent capacity" and research consent capacity (132). It is well described that MDC is affected and decreased in persons with cognitive impairment as they have a lower ability to evaluate, reason, and understand compared to healthy controls (133-135). A study examining the decisional capacity for participating in research found decreased MDC already in patients with MCI (136). In persons with early AD dementia, decreased MDC is well described (135, 137).

In study IV, we specifically asked how the participants with prodromal AD understood the informed consent given information. At two time points the participants were asked to talk about the aim and the content of the study they had consented to participated in. A few weeks after the consent, the participants were able to give a reasonably good description of the study's aim. After six months of participating in the trial, they gave a vaguer description of the study's aim, and a few participants failed in describing the aim. Interestingly they perceived themselves as well informed and connected the given information to the trustful relationship with the study team. These results indicate the need to evaluate the understanding and MDC during lengthy studies to ensure that informed consent exists.

The capacity to understand provided information is crucial for the participant to be able to give consent to participate in a clinical trial according to DoH, but is also necessary for the process of forming expectations on the participation in the trial. The expected probability for clinical benefits in early phases of pharmacological trials is low. However, unrealistic optimism for positive intervention effects in early phases of pharmacological trials has been previously described (138). Expectations on the burden of a lengthy trial with many visits and demanding interventions and risks and benefits are based on understanding the information provided. In an RCT, the participants receive many types of information that they need to manage. Researchers need to be aware of the individuals´ differences in their capacity to understand the provided information in the trial, to avoid misunderstandings and unrealistic expectations among the participants.

Trust

The frequent study visits built a trusting relationship with the study team, and the participants in study I expressed a feeling of being looked after. Trust was also evident in study IV; both studies were conducted in Sweden. In both trials, experienced personnel provided the participants with information, answered questions, and guided them to different support types tailored to individual needs.

Participants' trust in the study team and the institutions that provide the studies contributes to the decision to participate in an trial (60). In study III the participants emphasized that the trust in healthcare personnel and in the information provided, and that trust influenced their actions towards participation in a prevention trial. The results in study III highlighted the importance of existing trust, but also indicated that trust is expressed differently in the three countries. In

study I, participants trusted that they were not being exposed to any unnecessary risks when receiving drugs tested in humans for the first time. They trusted the sponsoring companies, the ethics board's regulations, and the study team to keep them safe. Several times in the different studies, the participants referred to this trust as a safeguard when they could not understand given information or discuss risks and benefits. Also, in study IV, participants described how they could not remember essential parts of information about the study given in the informed consent, but they trusted the physician and considered themselves well informed. Consequently, this indicates that if participants state that they are is satisfied with the provided information, it does not necessarily mean that they have understood the information, and there is a need for caution especially if the information is intended for consent. In a recent review of qualitative studies exploring patients' perspectives on participating in clinical trials, trust was an identified theme describing patients' trust in staff, physicians, and institutions. Trust was important for the initial decision to participate as well as for the retention of the participants (97) and patients and their study-partners often described the importance of the fact that the study is university-led when deciding to participate (70).

Stigma

Fear of stigma in the population at risk, or in preclinical AD has been reported as relatively low (139), while other studies have highlighted that stigma in preclinical phases of the disease is connected to further cognitive decline and its consequences rather than to the label of the disease itself (140). Furthermore, low public knowledge about AD and dementia is a substantial contributing factor to the stigma surrounding this disease (71, 139, 141). In study III the participants described that the fear of dementia made it harder to talk about the disease compared to CVD. The stigma also represented a barrier to obtain reliable information. In clinical trials, where repeated cognitive testing or cognitive training is a part of the protocol, the participants might be confronted with their personal shortcomings and become aware of further decline in their cognitive functions. In studies I and IV, the participants describe this as very stressful and one of the most pronounced disadvantages of participating in the trial. In trials with repeated cognitive testing and situations where participants risk being confronted with their cognitive decline symptoms, testing should be conducted with caution by well trained staff knowledgeable to meet the participants' reactions. Cognitive training in clinical trials should be designed to prevent participants from experience failure and self-stigma.

Motives for participating in a dementia prevention trial

Studies I and IV explored the participants' motives for participation in dementia prevention trials. In study I, individuals with mild AD participated in early phase pharmacological trials. In study III, potential participants at risk for CVD and dementia were asked about their motives to participate in a hypothetical e-Health prevention trial, and in study IV, participants with prodromal AD in a multimodal prevention trial shared their motives for participation. The three trials represent different approaches to dementia prevention and target populations at different stages along the disease continuum, from at-risk populations to mild AD. Interestingly, despite this difference, the participants in the trials presented similar motives for participating.

Altruistic motives were most pronounced in the participants that actually participated in trials. These participants were also further progressed in their disease. To help research and be a part of developing new knowledge, and hopefully new treatment possibilities were important for the participants. Many participants were concerned for their relatives and felt obligated to contribute in research in order to minimize the risk for their children or the next generation to suffer from the same condition. To contribute to research and help others have been indicated in an wider description of hope in early stages of AD (142). Several studies have investigated the motives of persons in the AD continuum for participating in clinical trials, but most studies have focused on investigating people's attitudes and interests in hypothetical trial situations. Altruism, and a willingness to help research, and the future generation, have been reported as some of the most important components to participating in clinical trials (61, 64, 143).

Personal benefits were the other main theme of motives for participation. Although the interventions in the trials differed, the participants hoped that they could benefit from them to some extent. In study I, some participants expressed strong hope and belief in the drug to have an effect on the disease, although most of the participants and most study partners showed more realistic expectations on the effect of the drug. In study IV, the participants expected general health benefits from the intervention but initially expressed skepticism about the interventions effects on the disease. Interestingly their belief in the interventions potential effect on delaying the worsening of symptoms increased during the trial participation. Other personal benefits in common for the three trials were access to reliable information and specialized healthcare support. The participant's motives for engaging in a dementia preventive trial were influenced by their previous knowledge and attitudes about dementia and prevention, the perceived trust in the healthcare provider, and the trust in the conductor of the trial. Fear and stigma could potentially hinder the participants from seeking health care and limit their access to clinical trials. These results were more nuanced in study III, probably because participants did not suffer from any significant cognitive decline and were not yet included in any trial. The knowledge of the participants motives for participating in a trial has been used and discussed in the context of recruitment strategies (62, 64-66, 68, 70, 144). However, the interaction with previous knowledge and the understanding of provided information should be acknowledged when discussing participants' decision to participate in trials. During the recruitment phase of the HATICE trial (23), a mixed-method study was conducted investigating the participants' motives for participating. In a real-life setting, this study showed that the main reasons for persons to participate in the e-health prevention study were an interest in contributing to scientific knowledge and personal health benefits. The third reason for participation was access to additional medical monitoring. The study showed differences in how participants described their motives in the three countries in the trial, related to differences in the health care systems, the perceived access to care, and the trust in the GP's recommendations (65). McCann described these findings as Conditional Altruism when participants initially tend to participate in a trial based on willingness to help others, but this unlikely to lead to further participation if there are no personal benefits (59). In study I, among participants who stated altruism as

motives for entering a trial, helping others gave them a sense of hope for future generations. Helping others as an expression of hope has been described earlier (142).

Participating in a dementia prevention trial

To participate in clinical trials has been described as demanding (58, 145). Pharmaceutical trials protocols allow very few deviations, and the total number of visits at the clinic might seem overwhelming. Many investigations such as MRI scans, CSF and blood samplings add to the effort, and early phase I and II drug trials are commonly associated with a potentially lower personal benefit and higher risk for side effects. Prevention trials targeting lifestyle factors may also be demanding. Several visits to the gym and regular attendance at different intervention activities and dietary changes may be challenging for the participants. Meanwhile, the personal benefits are regarded as high, and the risks are low.

The fact that participation in AD trials is burdensome and requires study partners to accompany the participant to the study site and be willing to support and provide information, influences the potential participant's willingness to participate. The requirement of having a study partner is a barrier for participating in a lengthy trial as it is burdensome for family members or friends with frequent visits during working hours (68, 70). In study IV another aspect of the demand on a study partner was revealed. In studies that recruit person with prodromal AD, not all participants had informed their families or friend about their diagnosis, which complicated the inclusion process as there were demands of a having a study partner to be able to participate in the trial. People do not always want to disclose their diagnosis to family or other networks (146) and this needs to be addressed in future trials.

Although participants in studies I and IV emphasized that it was burdensome to participate in a clinical trial, they also felt that they had been given an opportunity. They described this as winning the lottery. The foremost perceived disadvantages of participating were that it was very time consuming and hindered them from other activities. Participants in pharmacologic trials also referred to extensive investigations with many invasive procedures such as lumbar punctures, repeated MRI scans and blood samples. In common for participants in pharmacological and lifestyle trials, were the negative experiences of repeated cognitive testing, or exposure to situations where they were confronted with cognitive difficulties and in worse cases, evidence of continuous loss of cognitive functions. In future trials, unnecessary testing should be avoided, and interventions should be delivered in a way that minimizes the participants' risk of facing their cognitive shortcomings.

There are many challenges in the design and conduction of dementia prevention trials: identifying the right participants, recruitment of large numbers of participants, retaining these participants, and keeping them adherent and engaged in the interventions.

Identifying eligible participants for early dementia prevention trials is a major challenge (147, 148) and biomarkers are becoming more important in clinical trials, both for selecting participants and assessing the efficacy and safety of novel treatments along the AD continuum (10). While inclusion based on biomarkers is becoming increasingly important in

pharmacological trials, the significance of biomarkers-based identification of participants in lifestyle intervention trials may less strict as these trials target multiple mechanisms of action (20). Studies reporting persons' attitudes on disclosure of biomarkers and risk factors for AD have been mainly conducted among persons with AD not participating in clinical trials or in healthy controls, who were asked to reflect upon a hypothetical situation (74, 75, 149). These studies suggest that the persons are interested in information about risk and biomarkers. The participants also emphasized the process in which risk information was disclosed and the need for information on individualized risk assessment, follow up and care. There is growing evidence that disclosure of genetic risk based on apolipoprotein E (APOE) genotyping to volunteer populations who are asymptomatic does not increase the risk for psychosocial harm (72). The perceived benefits of genetic testing are the possibility of advanced planning for the future, and the negative effect is often connected to how the results may affect family members (139). To use different tools to estimate dementia risk is another strategy to select the right participants for prevention trials, mainly targeting lifestyle-factors. Several models have shown promising results (150).

Recruitment of participants in clinical trials has been previously discussed in the literature. Successful recruitment of study participants is often based on factors of different variety (58, 151). For example, Stormoen et al. showed that persons with AD dementia were more likely to participate in clinical trials with high risk than persons with mild cognitive impairment (MCI) or healthy controls. Stormoen et al. suggested that this might relate to the fact that persons with AD dementia may have a lower understanding of clinical trials' risk/benefit issues. Also, Nuno et al. suggested that there might be difficulties in recruiting participants in future trials focusing on preclinical or prodromal AD target groups since it becomes more common to include participants based on AD biomarkers, and the disclosure discussion has broadened. Several studies have explored people's expectations and experiences of such disclosures and discussed the consequences (149, 152-154). Study IV showed that the level of knowledge and previous experiences, the motives for participating and the participants understanding of the study related information are factors that influence the decision to participate. Even for the participants in a trial targeting prodromal AD where cognition is less affected, the situation and the information provided may be complex and hard to understand.

Retaining participants in clinical trials is important to minimizing bias and error (155) and many different strategies are described in previous literature (69, 156). Those previous studies have focused on different strategies used and the number of used strategies by the trial-centres and seldom investigated the participants' preferences or needs. If the burden is too high, there is a risk that the participant gets too tired or does not engage fully in the intervention. Several studies have shown decreasing adherence to the interventions with increasing burden and complexity (157, 158). The cognitive difficulties that effect memory, attention, and decision processes are also barriers to the conduction of the trials (159). The findings in this project emphasize the importance of incorporating the preferences and the needs of the study participants in the stages of designing, conducting and evaluating clinical trials.

Applying a person-centered approach

As personalized medicine becomes more and more important in dementia prevention research, there is a need for tailoring interventions according to an individual´s biological status. A person-centered approach describes the persons' situation based on their history, their knowledge, preferences and their strength and weaknesses. In regular health care a person-centered approach indicates a shift of focus from the disease to the person with strength, weaknesses, needs and preferences (97). In a RCT setting this could mean shift of focus from the participants as being passive study subject, to active participants and partners in the conduction of the trial.

Person centeredness emphasizes the person´s perspective and active involvement in a decision-making process. A prerequisite for the person to be able to be active in this process , is access to sufficient ant relevant information (99). Other aspects of PC include that the person is listened to, and their knowledge, experiences and wishes are made visible. Person-centered care and three main principles for implementation are described by Ekman (97) (97) and has resulted in recommendations for implementation consisting of: 1) initiating the partnership, the patient's narrative; 2) working the partnership, shared decision making; and 3) safeguarding the partnership, documenting the narrative. The findings in this research project suggest the potential benefits of adapting and implementing a structured model into the conduction of dementia preventive trials.

Declaration of Helsinki in dementia prevention trials

DoH described early ethical principles for research in human subjects. The document has continuously been updated to reflect contemporary research as clinical research has become more advanced and complex, and new knowledge has been developed, and these principles are today still very relevant. The declaration emphasize thar research is necessary to understand and develop knowledge on causes, development of diseases, and improve preventive, diagnostic and therapeutic interventions. The current existing interventions must be evaluated continually for effectiveness, accessibility, and safety. This statement supports the need to constantly evaluate ongoing research from the participants' perspective to ensure and protect their health and rights according to the declaration. Many studies are conducted in a multinational research setting with a number of local regulations and laws. DoH still offers a framework across countries, in different cultures, healthcare, and political systems (104). Good Clinical Practice (GCP) is an international quality standard that is provided by the International Conference on Harmonization (ICH).This guidelines are used in the conduction of trials and all personnel in study-sites are regularly trained in GCP. The principles form DoH and PC, share many ethical standpoints and do exist side by side in most care settings. In a clinical trial setting, PCC needs clearly formulated guidelines to be put into practice.

DoH and PCC both have their origins in fundamental ethical principles that guide and tell us *why* we do things in certain ways. Both require guidelines on *how* to complete tasks according to these principles. GCP provides strict guidelines for medical research. Many of this guideline

have served as foundations for national laws and regulations. European standards for PCC are under development. Patient involvement in healthcare – minimal requirements for person-centered care (CEN450). PCC is often an accepted and sometimes required position in the health care systems where medical research is conducted. A structured PCC model, adapted for use in RCTs, could benefit participants on a personal level in ongoing RCTs and on a more strategic level to ensure quality and develop new research studies.

With an understanding of the history of the development of medical research ethics, the failures the history presents, and knowledge about the fundamental documents that have led to today's guidelines and laws, we can also understand the need to continually evaluate and improve the safety and wellbeing of research participants (105, 160, 161). Today, in the times of a global pandemic, Covid-19, ethical questions regarding research on humans face new challenges. Old documents, such as the Belmond report with its fundamental ethical principles, are still referred to in discussing how to manage this new situation (162). Several of these principles are now regulated in laws, but ethical principles still have an important role in ensuring participants' rights and safety in rapidly advancing medical research. There is an urgent need from society to find solutions to handle the increasing cases of dementia worldwide, which propels the development and novelties in methods in the field of dementia prevention research. With understanding of the ethical background of the perspectives of DoH and a PCC, and developing frameworks for them to coexist in an RCT setting, could benefit research, patients on a group level and the situation for the individual participating in a trial.

9.2 METHODOLOGICAL CONSIDERATIONS

This project provides insights regarding on participation in dementia prevention trials, from the perspectives of participants, study partners and specialized personnel. The different studies included in the project were conducted within different types of prevention research such as pharmacological trials in early phase to multimodal lifestyle preventive trials, and trials that address the use of novel techniques as means of delivery of lifestyle prevention interventions. The trials targeted research populations in different stage along the Alzheimer’s disease continuum.

An increasing number of embedded qualitative studies in RCTs have explored complex investigations from different perspectives, such as participants, study partners, and study personnel (112). In a review of qualitative research embedded in RCTs, O'Cathain described four common research areas: 1) Optimization of the content and delivery of interventions, 2) RCT design and conduct, 3) RCT outcomes, and 4) Target the condition or disease itself. According to the review, the research questions in these four areas focus on participants' experiences of different intervention components and their perceived benefits or the feasibility and acceptability of the intervention. Reasons for participation in a trial and adherence to the interventions and which outcomes the participants consider most important are other questions. Furthermore, qualitative studies embedded in RCTs are used to explore attitudes, beliefs, and experiences of the disease. Another important task for qualitative research is to identify local adaptions that could improve RCT conduct in a multinational setting (112).

Long complicated prevention trials are dependent on large enough numbers of participants wanting to participate. Dropouts are not only very expensive but also increase the risk of bias in the trial. Furthermore, the trials become more and more dependent on participants being compliant to the interventions. In lifestyle multimodal preventions trials this means that participants must make changes in their everyday life and really put an effort into the intervention. In pharmacological trials, the overall burden of participating in the trial, with many and invasive investigations has to be feasible in relation to the participants' capacity. To be able to adapt the trials to participants' conditions and wishes, there is an increasing use of qualitative studies in the design of new prevention trials (159). The literature supports the use of qualitative methods in the design of eHealth interventions. Input from end-users is valuable to make the product attractive and easy to use (163, 164) in order to keep the participants engaged. Study I and IV confirms the high burden of participating in the trials. Bothe the pharmacological trials and the multimodal prevention trial were perceived as time consuming. In the pharmacological trial the high burden was connected to discomfort during procedures and testing, while the prevention study demanded high engagement in the interventions with many visits in the study center.

In study IV participants with prodromal AD were interviewed. There are several challenges with interviewing persons with AD. Even if their cognitive functions are expected to be largely unaffected, the participants were sometimes struggling with word finding, abstract reasoning and fluctuating awareness which have been described in early stages in the disease (165, 166). The participants were sometimes unable to stay on the topic of the conversation and repeatedly needed to be redirected by the interviewer. The researcher needs to be knowledgeable with these preconditions for communication and able to use strategies to minimize the distress for the participant, and to retrieve as high-quality data as possible. When analyzing the data, the transcriptions may at first seem thin, and demand multiple readings before the researcher can get a sense of the data as whole (167).

In study I, participants were recruited from several ongoing pharmacologic trials; they were all recruited form one study site. This may have affected the results, which may have reflected the situation at this study site. Furthermore, the participants in this study were asked to answer a questionnaire. The open-ended questions were feasible for the participants to answer, but the questions with alternatives seemed to have caused some confusion and this needed to be taken into account when presenting the results. Even if some participants struggled with writing the answers on paper and some had help from relatives, the time to reflect and formulate answers seemed to be beneficial and the data was rich. 19 out of 20 participants answered the questionnaire and 20 out of 20 study partners, which might reflect the participants' positive attitude towards research. Individual interviews might have been an even more suitable method to collect data, but in order for the participants to be able to answer the questions anonymously, the questionnaire was considered the most suitable method. As the participants would have easily been identified, and it was important that they felt safe to discuss freely, the anonymous questionnaire was a good choice.

Study II and III were conducted in a multinational setting. Participants and researchers came from 4 countries and were native speakers of 4 different languages, with English as a common work language. This was in some parts challenging and time demanding but was overcome with a rigorous planning and communication scheme. Data collection was performed in each country in the native language and initially analyzed within the local research group. In Finland, all data were translated into English as the researchers were not native Finnish speakers. Translations were cross-checked with the focus group leader who was native Finnish and fluent English speaking. Each country's research team was trained and experienced in the area of research as well as the methods used. After each step in the process meetings were held within the larger international research group. Essential parts of data were translated into English for cross comparison. During this phase, all researchers from the different teams returned to their data and added, merged, and refined the themes until agreement was achieved. Although language barriers were a major challenge in this project and nuances in data might have been lost, a well-planned and structured research processes with high competence in research groups in each country and frequent meetings with all participating researchers ensured quality and minimized these risks. Furthermore, the frequent and intensive work with merging data facilitated methodological discussions and increased the understanding of the different health care contexts in the participating countries.

Sample size in study II was limited, but the purposeful sampling resulted in rich data. In study III the large number of participants and the number of focus groups conducted, together with a thorough planning and collaborations within the large research group ensured trustworthiness. The large multi professional research group with broad experiences, the many discussions and the structured conduction of the project according to the chosen method, ensure trustworthiness. To conduct qualitative projects embedded in larger RCT studies entails even more challenges. All phases of the qualitative study have to be coordinated with the main time plan for the RCT. Study II and III were conducted during the design phase of the HATICE trial and all reporting had to be finished to be implemented in the final platform before the RCT study start. From a learning perspective, to be part of this process, study II and, to partly coordinate this work in a multidisciplinary, international setting were challenging, intense and rewarding with knowledge and experience beyond the scope of a doctoral education.

The method for studies II and III, Grounded Theory, was chosen based on its suitability for projects with limited previous knowledge, when studying processes (113, 116). The ambition was to follow the method according to Straus and Corbin (113), but as the project developed a more constructivist perspective influenced the work, with influences from Charmaz (116). As the project advanced, the frequent contacts between the research groups facilitated all the phases in project. Coding and analyses were thoroughly discussed in the group, ensuring a mutual understanding for the whole material. At the same time, these meetings helped overcome language barriers and facilitated the understanding of the differences in the contexts. In study III it became evident that one concept needed further exploration and a third round of focus groups were conducted. A theory is developed by a set of organized categories that are systematically integrated through statements of relationships that form the theoretical

framework explaining the phenomenon (113). Studies II and III did not aim to develop a theory alone but may contribute to theory development in the future together with knowledge from studies I, IV and future studies. Participating in dementia prevention clinical trials is, as a phenomenon, complex and further knowledge is needed to explain what, how, when, where and why of participating in trials and to develop an overarching explanatory concept.

In studies I and IV content analysis was used. This method was decided to be relevant to meet the aims and describe the experiences of participants (study I, IV) and study-partners and specialized personnel (study I). In study II, 16 interviews resulted in 20 hours of recorded material and hundreds of pages transcribed material. The challenges with interviewing persons with cognitive deficits, discussed above, extended to the transcription parts of the study and continued in the analysis. To transcribe an interview with an impaired language is very demanding and takes a long time. In study II the person who did the interviews also performed the transcriptions, which was a considerable advantage. Knowledge about the context of the interviews was helpful to understand the content. Experiences in communication with persons having cognitive deficits facilitated the process of the interviews. In the first part of selecting meaning units and condensing them the quality of the language needed to be considered. With paying close intention in this phase of the analysis, the data proved to be richer than first assumed. The multi-professional research teams in studies I and IV were highly experienced in research and clinical work with patients and caregivers in the field of AD but also in the conduction of RTCs. Regular discussions during all of the phases in the studies ensured credibility in these studies. The findings in this thesis are all related to unique settings within different dementia prevention RTCs and reflect our current understanding. Transferability, with the possibility to extend these findings to other populations in other settings(108, 121), must be assessed by the reader, but the descriptions of the settings and participants in the different studies will support this process. Reflexivity was used in all projects, by discussion in the research groups and using memos to reflect on philosophical standpoints, assumptions about the research, study design, codes and categories and the many procedural decisions taken during the analysis. Although memo writing is most used in GT, it is a helpful tool in all qualitative methods to develop thoughts, analytic skills, theoretical sensitivity and maintain an audit trail connected to the development of the project.

Credibility refers to a systematic and rigorous field work, but also the systematic analysis of the data. Credibility also refers to the researcher's knowledge and skills (111). The multidisciplinary research teams in the different studies represented a broad expertise in the research field as well as in qualitative research. U. Akenine is an experienced nurse with many years' experience from working with dementia research, which of course may have influenced the results, but was essential in identifying the knowledge gaps and formulating the research questions, and an asset when analyzing the data.

Finally, this project explored perspectives from active participants and potential participants and did not include persons that were willing to participate but were not eligible, or those who declined participation or participants who dropped out of a trial. Experiences and attitudes

about trial participation from these groups would be highly interesting, but outside the scope of this project.

10 FUTURE DIRECTIONS

The studies within this thesis have with the use of qualitative methods contributed with new knowledge and perspectives on participating in dementia prevention clinical trials. The results have already been used to evaluate and ensure quality in ongoing projects, to develop new platform or technologies, and have been part of a feasibility RCT. Many more trials with new technology and new interventions will follow. Future studies should focus on developing a model for gathering and evaluating different perspectives on participating in RCTs to ensure a development in the field and high quality RCTs, according to ethical principles of DoH.

Future studies could focus on wider range of participants, those who were not eligible, non-participants (if they give consent), and those who dropped out after inclusion in a clinical trial. This would give important insights about more general population and facilitate implementation of the results (eg lifestyle interventions, new technology) beyond clinical trials setting.

Longitudinal qualitative studies are also needed to explore changes in motives, expectations, and experiences of participants in long trials.

Further explorations of how the cultural and context differences affect participation will be essential in multinational trials. This is especially important given that many large-scale efficacy RCTs are multi-center, multi-national studies.

Collecting user feedback and participants experiences using digital tools and new technology (e.g. E-FINGERS concept) is needed. New technology may facilitate individualized interventions and effective and sustainable implementation (especially important during and post-covid period), but user feedback and patient-public involvement (PPI) is central already early during the project.

One important area is disclosure and communication of AD and AD risk status and involving patient in the decision process. Some ongoing projects (e.g. EURO-FINGERS consortium) will focus on these aspects.

Finally, to develop a structured model to apply a more person-centered approach and incorporate this in studies and clinical setting is needed.

New planned projects will use psychological interventions for patients with cognitive impairment to increase psychological wellbeing and flexibility which may also add adherence to multidomain lifestyle-based intervention (eg PIPCI trial). This will be increasingly important in future more complex trials combining multidomain lifestyle-based interventions and potential disease modifying drugs.

11 SVENSK SAMMANFATTNING

Demenssjukdomar innebär en enorm global hälsoutmaning med en snabb ökning av antalet drabbade personer. Det finns ett akut behov av forskning för att hitta effektiva behandlingar och förebyggande strategier. Demensforskningen utvecklas snabbt där nya metoder och tekniker som används. Både farmakologiska och multimodala livsstils studier för demensprevention har blivit längre, mer komplexa och inkluderar personer tidigare i sjukdomsförloppet. För deltagarna i kliniska prövningar innebär detta nya utmaningar.

Det övergripande syftet I detta projekt var att utforska erfarenheterna från deltagande i kliniska prövningar bland studiedeltagare, studiepartner och specialiserad personal. Dessutom var målet att ytterligare öka förståelsen om deras attityder och kunskap om demens och relaterade diagnoser. Alla studier använde kvalitativ metod. Data har samlats in från olika typer av randomiserade kliniska studier med hjälp av frågeformulär innehållande öppna frågor, fokusgrupper och individuella intervjuer. De använda metoderna är Content analysis och Grounded Theory.

Studie I Frågeformulär med öppna frågor skickades till deltagarna i immunterapi RCT fas I-II och studiepartners samt fokusgrupper genomfördes med specialiserad personal. Personalen betonade den höga bördan för deltagarna. Huvudmotiven för deltagande var en vilja att hjälpa forskningen. Fördelarna med deltagande var tillgång till specialvård. De största nackdelarna var att delta var tidskrävande och upplevt obehag i samband med vissa undersökningar.

Studie II Fokusgruppsintervjuer hölls med expertsjuksköterskor (n= 13) inom CVD-prevention Finland och i Nederländerna, för att beskriva sjuksköterskors erfarenheter och metoder för CVD-preventivt arbete, och att beskriva deras förslag på hur man integrerar dessa erfarenheter i en online e-häla plattform. Viktiga aspekter var att skapa en *relation av förtroende, hantering av kunskap och förväntningar* och *monitorering i rätt tid*.

Studie III Fokusgrupper intervjuer genomfördes med äldre personer "i riskzonen" (förekomst av CVD-riskfaktorer) i Finland, Nederländerna och Frankrike som en del av HATICE projektet (n=44) om deras attityder till CVD och demens och engagemang i preventionsprogram via en e-hälsa plattform samt hindrande och underlättande faktorer. Resultaten prepresenterades i tre kategorier, *tillgång till tillförlitlig information om CVD och demens, förtroende för vårdgivaren, börda och stigmatisering av demens.*

Studie IV Individuella intervjuer med deltagare i multimodal livsstils studie för demensprevention, MIND-AD_{MINI} för deltagare med prodramal AD (n=8). Deltagarnas erfarenhet av att delta i studien presenteras som en dynamisk process. Tidigare kunskaper, deras motiv och den mottagna informationen styr deltagarnas beslut att delta. Studien tolererades väl, men deltagarna upplevde initialt hög börda och svårigheter att hantera den givna informationen i studien.

Slutsatser: Motiven för att delta var altruistiska men också med hopp om personliga fördelar av interventionerna samt tillgång till specialiserad vård. Det finns skillnader i deltagarnas

preferenser och behov av stöd i en studie, dels i de deltagande länderna och i olika faser av sjukdomsutvecklingen. För att adressera detta, föreslås en mer personcentrerad metod applicerad i genomförandet av kliniska prövningar. Detta kan hjälpa till att förbättra situationen för deltagarna och höja kvalitén i studierna vilket är viktigt när studierna blir mer komplexa och nya metoder används i studier för demensprevention.

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