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ANNA ROSENBERG

Dementia prevention in at-risk individuals

Focus on selection and engagement of target populations

DEMENTIA PREVENTION IN AT-RISK INDIVIDUALS

FOCUS ON SELECTION AND ENGAGEMENT OF TARGET POPULATIONS

Anna Rosenberg

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Author's address: Institute of Clinical Medicine, Department of Neurology
University of Eastern Finland
KUOPIO
FINLAND

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Supervisors: Professor Miia Kivipelto, M.D., Ph.D.
Division of Clinical Geriatrics
Centre for Alzheimer Research, NVS
Karolinska Institutet
STOCKHOLM
SWEDEN

Associate Professor Alina Solomon, M.D., Ph.D.
Institute of Clinical Medicine, Department of Neurology
University of Eastern Finland
KUOPIO
FINLAND

Professor Hilikka Soininen, M.D., Ph.D.
Institute of Clinical Medicine, Department of Neurology
University of Eastern Finland
KUOPIO
FINLAND

Docent Tiia Ngandu, M.D., Ph.D.
Public Health Promotion Unit
Finnish Institute for Health and Welfare (THL)
HELSINKI
FINLAND

Reviewers: Professor Elisabet Londos, M.D., Ph.D.
Department of Clinical Sciences
Lund University
MALMÖ
SWEDEN

Associate Professor of Geriatrics Minna Raivio, M.D., Ph.D.
University of Helsinki
HELSINKI
FINLAND

Opponent:

Professor John O'Brien, M.D., Ph.D.
Department of Psychiatry
University of Cambridge
CAMBRIDGE
UNITED KINGDOM

Rosenberg, Anna

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ABSTRACT

Dementia and its most common cause Alzheimer's disease (AD) are global health challenges. With no cure in sight, strategies to prevent or delay dementia onset in at-risk individuals are urgently needed, and multidomain interventions targeting multiple risk factors and mechanisms may be warranted. Several randomized controlled trials (RCT) are ongoing, but their optimal design and conduct are unclear. This thesis used data from three large, completed, pioneering prevention RCTs and a memory clinic, with the aim to offer insights into the selection and engagement of target populations in prevention RCTs. The aim was to assess the response to a multidomain lifestyle intervention in subgroups of participants to understand who benefitted the most (I) and investigate older adults' knowledge of dementia as well as their motivation and attitudes towards prevention and RCT participation (II, III). In addition, risk factors, biomarkers, and research criteria for AD were explored and their impact on disease progression was assessed in two cohorts (IV, V).

Studies I-III included participants of the 2-year Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER) RCT (N=1,260) and the multinational Healthy Aging Through Internet Counselling in the Elderly (HATICE) eHealth RCT (N=2,724). These subjects did not have significant cognitive impairment but were at risk based on their cognitive performance and/or other risk factors. In FINGER, participant baseline characteristics, including age, sex, socioeconomic status, cognitive performance, and vascular risk factors, were studied as modifiers of the intervention effects on cognition (I). In HATICE, the reasons for participation were studied in all 3 countries (Finland, France, the Netherlands) before randomization with a questionnaire (N=341), followed by semi-structured interviews (N=46) (II). A subset of interviews were analyzed in Study III (interviewees who introduced the topic of dementia, N=15). Studies IV and V included individuals with mild cognitive impairment but no dementia. Study IV focused on a sample of Karolinska University Hospital memory clinic patients (N=318) with normal cerebrospinal fluid (CSF) β -amyloid (A β 42) based on the cut-off values used at the clinic (low A β 42 typical for AD), while Study V included participants of the

LipiDiDiet RCT with International Working Group-1 (IWG-1) defined prodromal AD (impaired memory + one or several AD biomarkers; N=311, N=287 in the thesis). In the memory clinic cohort, biomarkers and other characteristics, including vascular factors, were studied as predictors of dementia (mean follow-up 3 years) (IV). In LipiDiDiet, the utility of IWG-1 as selection criteria was studied by classifying the participants according to more restrictive criteria (IWG-2, National Institute of Aging and the Alzheimer's Association (NIA-AA) 2011, NIA-AA 2018) (V). The 2-year cognitive/functional decline and progression to dementia were also assessed.

In the FINGER RCT, participant characteristics did not modify the response to intervention. Similar cognitive benefits were observed in the whole population, indicating that the intervention can be implemented in a large elderly population at increased risk of dementia. In the HATICE RCT, contributing to research, improving lifestyle, and receiving medical monitoring were identified as the most important reasons for participation. Interviews suggested some between-country differences (e.g., altruism emphasized in France, health checks in Finland). Having a family history of dementia or other first-hand experience was a recurring theme in the interviews. This was linked to increased awareness of dementia, yet uncertainty about prevention. Concerns over own health and risk were expressed, and those with a family history of dementia were highly motivated to enroll in HATICE and improve their lifestyle. In the memory clinic cohort, 38% developed dementia (mostly AD), and lower A β within the normal range was associated with a higher risk. A β improved the prediction based on age and cognition; applying a higher cut-off for abnormality did not affect the results. Most other factors did not predict dementia or improve the basic prediction. In the LipiDiDiet RCT, where brain atrophy was often the only biomarker available at screening, most participants with centrally analyzed CSF at baseline met the more restrictive AD criteria (e.g., 64% with NIA-AA 2018 AD, A+T+N+ profile). The dementia risk increased with increasing biomarker evidence.

This thesis offers new insights into dementia prevention in different at-risk groups and informs the design, recruitment, and conduct of future RCTs. This is important given the current methodological challenges and disappointing results of RCTs. The results support the use of the FINGER model and selection criteria in RCTs with a similar design. Understanding older adults' expectations and motivations to participate in RCTs will help design interventions that are perceived as attractive by the target populations. Regarding prodromal AD, less restrictive criteria work well in participant recruitment, and their use in certain RCTs could be preferred due to feasibility. In memory clinic patients, A β within the normal range may not rule out AD and risk of dementia could still be high. Future research is needed to understand if there is a window of opportunity for preventive interventions in this population.

National Library of Medicine Classification: W 84, WT 101, WT 104, WT 155, WT 160
Medical Subject Headings: Alzheimer Disease/prevention & control; Cognition; Dementia/prevention & control; Aged; Biomarkers; Health Behavior; Healthy Aging; Life Style; Motivation; Risk Factors; Qualitative Research; Patient Participation; Patient Selection; Randomized Controlled Trials as Topic; Research Design

Rosenberg, Anna

Muistisairauksien ennaltaehkäisy eri riskiryhmissä: näkökulmia tutkimusten suunnitteluun ja toteutukseen sekä tutkittavien valintaan

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TIIVISTELMÄ

Muistisairauksiin kuten Alzheimerin tautiin (AT) ei ole parantavaa hoitoa, minkä vuoksi on tärkeää tutkia ennaltaehkäisyä tai taudin hidastamisen mahdollisuutta eri riskiryhmissä. Tällä hetkellä tutkitaan erityisesti sellaisia ennaltaehkäiseviä interventioita, jotka kohdistuvat samanaikaisesti moneen eri riskitekijään, mukaan lukien elintapoihin. Eri riskiryhmien tuntemus on kuitenkin puutteellista, ja on epäselvää keille interventiot kannattaisi kohdistaa, millaisia niiden tulisi olla ja miten ikäihmiset ja osallistujat itse suhtautuvat ennaltaehkäisyyn ja tutkimuksiin. Tässä väitöskirjassa hyödynnettiin kolmen laajan, urauurtavan ennaltaehkäisy-tutkimuksen sekä muistipoliklinikan aineistoja. Tavoitteena oli selvittää, ketkä hyötyvät eniten ennaltaehkäisevästä elintapainterventiosta (I), mikä motivoi ikäihmisiä osallistumaan tutkimuksiin (II) ja miten tietämys ja asenteet muistisairauksia ja ennaltaehkäisyä kohtaan vaikuttavat motivaatioon (III). Työssä tarkasteltiin lisäksi erityyppisissä riskiryhmissä AT:n riskitekijöitä ja tautipatologiaa kuvastavia biomarkkereita (mukaan lukien uusia biomarkkereihin pohjautuvia AT:n diagnostisia tutkimuskriteerejä) sekä niiden yhteyttä taudin etenemiseen (IV, V).

Osatöiden I-III tutkimusjoukko koostui suomalaisen FINGER- (N=1260) sekä kansainvälisen HATICE-tutkimuksen osallistujista (N=2724), joilla ei ollut muisti- ja ajattelutoimintojen eli kognition heikentymää mutta joiden muistisairausriski oli kohonnut. FINGER-alaryhmäanalyysissä selvitettiin, vaikuttivatko tutkittavien ikä, sukupuoli, koulutus- ja tulotaso, alkutilanteen kognitio tai sydän- ja verisuonitautien riskitekijät kaksivuotisesta elintapainterventiosta saataviin hyötyihin (I). HATICE-tutkimuksessa kartoitettiin kyselyllä syitä osallistua Internet-pohjaiseen elintapainterventioon Ranskassa, Hollannissa ja Suomessa (N=341), ja osaa vastaajista myös haastateltiin (N=46) (II). Osatyössä III analysoitiin ne haastattelut, joissa muistisairauksista keskusteltiin haastateltavien aloitteesta (N=15). Osatöiden IV ja V tutkimusjoukko koostui henkilöistä, joilla oli jo lievää kognition heikentymää mutta ei dementiaa. Karoliinisen instituutin muistipoliklinikalla toteutetussa osatyössä (IV) tutkittiin niitä potilaita, joilla oli tyyppillisestä AT:sta poiketen normaali β -amyloidin ($A\beta$) pitoisuus likvorissa (N=318), kun taas LipiDiDiet-tutkimuksen osallistujilla

(osatyö V, väitöskirjassa N=287) oli IWG-1-tutkimuskriteerien mukainen varhainen AT (muistin heikentyminen + jokin AT:iin liittyvä biomarkkeri). Muistipoliklinikkakohortissa tutkittiin, miten AT:n eri biomarkkerit ja muun muassa sydän- ja verisuonitautien riskitekijät ennustivat dementian kehittymistä keskimäärin 3 vuoden aikana. LipiDiDiet-kohortissa IWG-1-kriteerien käyttökelpoisuutta tutkittavien valinnassa arvioitiin luokittelemalla osallistujat IWG-1:tä tiukempien tutkimuskriteerien mukaan (IWG-2, NIA-AA 2011, NIA-AA 2018) ja tarkastelemalla kognition ja toimintakyvyn muutosta sekä dementian kehittymistä 2 vuoden aikana.

FINGER-tutkimuksessa kognitio parani enemmän interventio- kuin verrokki-ryhmässä koko tutkimusjoukossa, tutkittavien alkutilanteen ominaisuuksista riippumatta. Elintapaintervention vaikutukset eivät siten kohdistuneet ainoastaan tiettyihin alaryhmiin, vaan siitä oli hyötyä laajalle joukolle ikäihmisiä, joilla oli kohonnut muistisairausriski. HATICE-tutkimuksessa halu auttaa tiedettä, parantaa elintapoja tai saada terveysseuranta olivat tärkeimmät syyt osallistua. Hieman eri seikat korostuivat eri maissa (Ranskassa auttaminen, Suomessa terveysseuranta). Haastatteluisissa, joissa keskusteltiin muistisairauksista, sukurasite oli keskeinen teema. Se kytkeytyi muun muassa siihen, kuinka kattavaa tietämys muistisairauksista oli. Ennaltaehkäisyyn liittyi epävarmuutta ja epätietoisuutta. Haastatteluisissa korostui huoli omasta terveydestä ja sairastumisriskistä, ja omakohtainen kokemus muistisairauksista motivoi osallistumaan tutkimukseen ja parantamaan elintapoja. Muistipoliklinikkatutkimuksessa 38%:lla potilaista todettiin myöhemmin dementia (usein AT) ja alhaisempi, vaikkakin viitearvojen perusteella normaali, A β oli yhteydessä korkeampaan riskiin. A β myös paransi ikään ja kognitioon perustuvaa ennustemallia toisin kuin useimmat muut tekijät. LipiDiDiet-kohortissa, jossa hippokampuksen surkastuminen oli usein ainoa käytettävissä oleva biomarkkeri tutkimuksen alussa, myös muut biomarkkerit osoittautuivat jälkikäteen analysoitaessa AT:lle tyypillisiksi ja suurin osa tutkittavista täytti tiukemmat AT-kriteerit. Mitä selkeämpi AT-biomarkkeriprofiili, sitä suurempi oli dementiariski.

Väitöskirjan tuloksia voidaan suoraan hyödyntää uusia muistisairauksien ennaltaehkäisy tutkimuksia suunniteltaessa. Tulokset tukevat ensinnäkin FINGER-interventiomallin ja tutkimuksessa käytettyjen sisäänottokriteerien soveltamista muissa samankaltaisissa tutkimuksissa. Ennaltaehkäisy tutkimuksiin kohdistuvien odotusten sekä osallistumiseen vaikuttavien syiden ymmärtäminen puolestaan auttaa suunnittelemaan tehokkaampia ja kohderyhmien näkökulmasta mielekkäitä interventioita. Varhaiseen AT:iin liittyen tulokset osoittavat, että käytännöllisemmät ja väljemmät sisäänottokriteerit saattavat soveltua hyvin tiettyihin tutkimuksiin. Lisäksi selkeän A β -patologian puuttuminen ei välttämättä poissulje varhaista AT:ia vaan dementiariski saattaa silti olla kohonnut. Jatkossa tulee selvittää, millaisia interventioita tälle potilasjoukolle voisi kohdistaa.

Yleinen suomalainen ontologia: Alzheimerin tauti; dementia; muistisairaudet; ikääntyneet; ennaltaehkäisy; riskiryhmät; riskitekijät; elintavat; terveyskäyttäytyminen; markkerit; satunnaistetut vertailukokeet; kliiniset kokeet; kvalitatiivinen tutkimus

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ABBREVIATIONS

A β	β -amyloid
A β 42	β -amyloid 1-42
A β 42/40	ratio of β -amyloid 1-42 and 1-40
ACCEPT-HATICE	ancillary substudy of the HATICE trial
ACTIVE	Advanced Cognitive Training for Independent and Vital Elderly
AD	Alzheimer's disease
ADCOMS	AD Composite Score
ADNI	Alzheimer's Disease Neuroimaging Initiative
ANU-ADRI	Australian National University AD Risk Index
APOE	apolipoprotein E
APP	amyloid precursor protein
APPLE-Tree	Active Prevention in People at risk of dementia: Lifestyle bEhaviour change and Technology to REduce cognitive and functional decline
ATN	Biomarker classification scheme (A for amyloid, T for tau, N for neuronal injury)
AU-ARROW	the AUstralian-Multidomain Approach to Reduce Dementia Risk by PrOtecting Brain Health with Lifestyle intervention

BBL-CD	Body Brain Life for Cognitive Decline
BBL-GP	Body Brain Life – General Practice
BDNF	brain-derived neurotrophic factor
BDSI	Brief Dementia Screening Indicator
BMI	body mass index
BP	blood pressure
CAIDE	Cardiovascular Risk Factors, Aging and Dementia
CDR	Clinical Dementia Rating
CDR-SB	Clinical Dementia Rating-Sum of Boxes
CERAD	Consortium to Establish a Registry for Alzheimer’s Disease
CSF	cerebrospinal fluid
CT	computerized tomography
CVD	cardiovascular disease
DHA	docosahexaenoic acid
DIAN	Dominantly Inherited Alzheimer Network
DRS	Dementia Risk Score
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, 4 th revision
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, 5 th revision
eHealth	electronic health

E.Mu.N.I	Efficacy of Multiple Nonpharmacological interventions in individuals with subjective memory decline
EPA	eicosapentaenoic acid
EPAD	European Prevention of Alzheimer’s Dementia Consortium
FDA	U.S. Food and Drug Administration agency
FDG-PET	fluoro-deoxy-glucose positron emission tomography
FINGER	Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability
GP	general practitioner
HATICE	Healthy Aging Through Internet Counselling in the Elderly
HDL	high-density lipoprotein
HS	hippocampal sclerosis
ICD-10	International Classification of Diseases, 10 th revision
ICD-11	International Classification of Diseases, 11 th revision
IDEAS	The Imaging Dementia – Evidence for Amyloid Scanning study
In-MINDD	Innovative Midlife Intervention for Dementia Deterrence
ITT	intention-to-treat

IWG	International Working Group
J-MINT	Japan-multimodal intervention trial for prevention of dementia
LATE-NC	limbic-predominant age-related TDP-43 encephalopathy neuropathologic change
LDL	low-density lipoprotein
LIBRA	the Lifestyle for Brain Health score
LIFE	The Lifestyle Interventions and Independence for Elders Study
MAPT	Multidomain Alzheimer Preventive Trial
MCI	mild cognitive impairment
mHealth	mobile health
MIND-ADmini	Multimodal Preventive Trial for Alzheimer's Disease
MIND-CHINA	Multimodal INtervention to delay Dementia and disability in rural China
mITT	modified intention-to-treat
MMSE	Mini-Mental State Examination
MRI	magnetic resonance imaging
MTA	medial temporal lobe atrophy
MYB	Maintain Your Brain
NIA-AA	National Institute of Aging and the Alzheimer's Association

NINCDS-ADRDA	National Institute of Neurological Disorders and Stroke – Alzheimer Disease and Related Disorders
NTB	neuropsychological test battery
OPAL	Older People And n-3 Long-chain polyunsaturated fatty acids
PART	primary age-related tauopathy
PENSA	Prevention of Cognitive Decline in APOE ε4 Carriers with Subjective Cognitive Decline After EGCG and a Multimodal Intervention
PET	positron emission tomography
PONDER	The Protein Omega-3 and vitamin D Exercise Research
preDIVA	Prevention of Dementia by Intensive Vascular Care
PRODEMOS	Prevention of Dementia Through Mobile Phone Applications
p-tau	phosphorylated tau
RAVLT	Rey Auditory Verbal Learning Test
RCT	randomized controlled trial
rrAD	Risk Reduction for Alzheimer’s Disease
SBP	systolic blood pressure
SCI	subjective cognitive impairment
SINGER	SINGapore intervention study to prevent cognitive impairment and disability

SMARRT	Systematic Multi-domain Alzheimer's Risk Reduction Trial
SNAP	suspected non-AD pathology
SPEAR	Study of Participant Experience of Alzheimer's disease Research
SPRINT-MIND	Systolic Blood Pressure Intervention Trial – Memory and Cognition IN Decreased Hypertension
STRENGTH	Study of the effects of adapted Tango and multidimensional intervention in pREvention of dementia in aging: developing healthy lifestyle programs
SV2A	synaptic vesicle glycoprotein 2A
TDP-43	hyperphosphorylated transactive response DNA-binding protein 43
TIA	transient ischemic attack
t-tau	total tau
U.S. POINTER	U.S. Study to Protect Brain Health Through Lifestyle Intervention to Reduce Risk
WHO	World Health Organization
WMS-r	Wechsler Memory Scale revised
WW-FINGERS	World-Wide FINGERS

1 INTRODUCTION

Dementia is an enormous global health challenge. According to the World Health Organization (WHO) (2018a), this progressive syndrome characterized by severe cognitive and functional impairment was the fifth most common overall cause of death in 2016. In the older population segment, it is a major cause of disability, institutionalization, and death. Dementia affects around nine million individuals in Europe and 50 million individuals globally, and these numbers have been estimated to double in Europe and triple worldwide in the next 30 years (Alzheimer's Disease International, 2019; Alzheimer Europe, 2020). This is due to population aging, both in Western and in low- and middle-income countries.

The development of disease-modifying therapies and a cure for dementia has been a research priority for decades. The focus has been primarily on Alzheimer's disease (AD), which is the most common underlying cause of late-life cognitive decline and dementia. So far, attempts to develop effective disease-modifying drugs have yielded little success. A key problem has been, and still is, the incomplete understanding of biological disease mechanisms. The definition of AD as a complex disease continuum is also relatively recent. AD does not equal dementia, but dementia is the endpoint of a gradual disease process that starts long before the onset of noticeable clinical symptoms (Dubois et al., 2007; Jack et al., 2010). In individuals with AD-type brain pathology but no cognitive impairment, the duration of this so-called preclinical disease phase has been estimated to be 8–13 years, depending on age (Vermunt et al., 2019a). The duration of the subsequent prodromal phase with mild symptoms has been estimated to be approximately four years, totaling 12–17 years before the onset of dementia (Vermunt et al., 2019a). With the newly proposed—and much debated—research diagnostic criteria for AD, the clinical and biological AD definitions have been separated (Albert et al., 2011; Dubois et al., 2007, 2014, 2016; Jack et al., 2018; Sperling et al., 2011). Redefining AD has major implications, not least on prevalence estimates. When also asymptomatic individuals are considered, the prevalence of AD may be three times higher in old age than previously estimated based on clinical diagnosis (Jack et al., 2019a).

This paradigm shift has also implications for randomized controlled trials (RCT) and interventions, and RCTs for AD treatment have become RCTs for dementia prevention. Trials target earlier disease stages with the aim to prevent or delay the onset of clinical symptoms or the worsening of existing symptoms, to ultimately prevent or delay dementia. Trials are also becoming increasingly complex to address the biological and clinical heterogeneity of late-life AD and cognitive impairment. Importantly, much like in cardiovascular disease (CVD), there is compelling evidence for the role of different vascular, metabolic, lifestyle-related, and other modifiable factors as risk and protective factors (Livingston et al., 2020; World Health Organization, 2019). This highlights the potential of non-pharmacological

approaches in dementia prevention. The newest generation of non-pharmacological dementia prevention RCTs mainly focus on multidomain strategies, which means that the interventions target several modifiable risk factors, lifestyle aspects, and health behaviors simultaneously. The concept of multidomain prevention has previously been successfully tested in the context of CVD (Griffin et al., 2011; Strandberg et al., 2006; Tuomilehto et al., 2001). The first large, complex, multidomain dementia prevention RCTs have been recently completed, and the results are encouraging (Andrieu et al., 2017; Ngandu et al., 2015; van Charante et al., 2016). The next wave of multidomain RCTs is currently ongoing worldwide, and many RCTs are being planned (Kivipelto et al., 2020). Of special interest are electronic health (eHealth) and mobile health (mHealth) strategies, which have a wider reach and can potentially improve the cost-effectiveness of interventions.

Dementia prevention is a fairly new research topic compared with CVD prevention, for example, and the optimal design and conduct of dementia prevention RCTs are still unclear (Richard et al., 2012). Key aspects include but are not limited to the optimal selection, recruitment, and engagement of target populations that are at risk of cognitive decline and dementia. Research is needed to understand which intervention strategies are suitable and feasible for different target populations and what the optimal participant selection criteria are for RCTs. This is important to target interventions at those who are most likely to benefit from them based on their biomarker or clinical risk profile. Additionally, it is unclear how to optimally recruit participants, especially in multinational settings where different strategies might be needed to accommodate cultural differences, and how to design the interventions to ensure optimal adherence. This is a key consideration in interventions involving risk factor self-management and changes in health behavior. In this context, the strong stigma of dementia and poor public awareness of the means to reduce the risk of dementia are a further challenge (Alzheimer's Disease International, 2019).

Using data from some of the first large, completed multidomain dementia prevention RCTs and a memory clinic, this thesis offers insights into the selection and engagement of target populations in dementia prevention RCTs. This work combines quantitative and qualitative approaches and incorporates the target population perspective. The specific aims were: 1) to assess potential heterogeneity in the response to a multidomain preventive intervention to understand which subgroups of participants benefitted the most; 2) to investigate older adults' knowledge and perceptions of dementia as well as their motivation and attitude towards prevention and RCT participation; and 3) to explore risk factors, AD biomarkers, and research diagnostic criteria for AD as well as their impact on disease progression in two different cohorts to inform participant selection for future RCTs.

2 REVIEW OF THE LITERATURE

2.1 COGNITIVE DECLINE AND DEMENTIA

2.1.1 Clinical diagnosis

Many cognitive abilities deteriorate slightly as a part of normal aging (Harada et al., 2013). These include, for example, short- and long-term memory, problem-solving skills, the ability to logically plan and execute tasks, as well as speed and flexibility of thinking, reasoning, and information processing. Pathological 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 (American Psychiatric Association, 1994). Several conditions can underlie cognitive decline and dementia. Common irreversible conditions include neurodegenerative disorders, such as AD, frontotemporal lobar degeneration, Lewy body disease, and Parkinson's disease. Other causes include depression, burnout, and other psychiatric conditions, vascular disease, head trauma, certain medications, alcohol or drug abuse, and metabolic dysfunction such as hypo- or hyperthyroidism (Langa & Levine, 2014). The leading cause of sporadic late-life cognitive impairment is AD, followed by cerebrovascular disease (Iadecola et al., 2019). With irreversible conditions, cognitive impairment tends to be progressive and the symptoms worsen gradually. At the dementia stage, the clinical symptoms and severity can be graded mild, moderate, or severe with standardized assessment tools such as the Clinical Dementia Rating (CDR) scale (Morris, 1997). Survival after a dementia diagnosis depends on the type and severity of dementia (Mueller et al., 2019; Rhodius-Meester et al., 2019), for example, but some recent studies have reported an overall median life expectancy of three to six years (Joling et al., 2020; Mayeda et al., 2017; Rhodius-Meester et al., 2019).

Cognitive decline is usually a long process, and dementia is typically preceded by more subtle cognitive dysfunction. The earliest symptomatic expression of cognitive impairment is subjective cognitive impairment (SCI, or subjective cognitive decline), initially referred to as 'memory complaints' as the term was proposed in the context of AD (Jessen et al., 2020). SCI means that individuals experience subtle cognitive difficulties and concerns, but their neuropsychological test performance does not deviate from what is expected for their age and level of education (Jessen et al., 2020). Individuals with SCI are considered cognitively unimpaired and clinically healthy, yet at increased risk of cognitive impairment. Estimates of the magnitude of risk and progression rates vary. In a study with a mean follow-up of four years, 7% of older adults with SCI progressed to dementia, while it was the case for 6% of those without SCI (Slot et al., 2019). In a meta-analysis with a mean follow-up of five years,

progression rates were 11% and 5%, respectively; the risk of progression was approximately twice as high among those with SCI (Mitchell et al., 2014).

The first stage where cognitive changes become clearly noticeable is commonly referred to as mild cognitive impairment (MCI). The concept of MCI was first proposed over 20 years ago, and it was initially considered a pre-AD state where individuals lie between normal cognition and AD-type dementia (Petersen et al., 1999). MCI criteria were mostly developed in research settings and for research purposes. Before the clinical and biological heterogeneity of MCI was fully understood, the criteria were used in AD RCTs to identify individuals who progressed rapidly to dementia (Schneider et al., 2014). Different MCI definitions and criteria have been proposed in the literature, but in essence, MCI is characterized by a subjective experience of cognitive decline and a cognitive performance that is lower than normal and expected for the age and educational level (Albert et al., 2011; Petersen, 2004; Petersen et al., 1999; Winblad et al., 2004). The subjective experience of cognitive decline is ideally verified by a family member or other informant. Preferably, neuropsychological tests with available normative data should be used to assess cognition, but none of the criteria clearly specify the most appropriate tests. Likewise, no universal, clear-cut definition for mildly abnormal performance exists.

MCI can be considered single-domain (i.e., impairment in one cognitive domain) or multi-domain (i.e., impairment in several domains) and amnesic or non-amnesic (impairment mainly in memory and learning vs. other domains such as executive functioning, processing speed, attention, visuospatial abilities, or language) (Winblad et al., 2004). Impairment in executive functioning and processing speed is considered a hallmark of vascular cognitive impairment (Iadecola et al., 2019), whereas AD is typically characterized by impairment in memory and learning. Thus, an amnesic phenotype was required for MCI diagnosis in the earliest criteria (Petersen et al., 1999). In contrast with dementia, there is only a little, if any, functional impairment in MCI (Albert et al., 2011; Petersen, 2004; Petersen et al., 1999; Winblad et al., 2004). The criteria require that independence in usual daily tasks and functioning is preserved, even if some assistance or greater effort might be required in complex tasks such as handling finances. Additionally, unlike dementia, cognitive impairment in MCI does not markedly interfere with social interaction. Nevertheless, drawing a line between MCI and dementia can be difficult in practice due to inter- and intra-individual variation in cognitive and functional performance. The decision as to whether the impairment is severe enough to interfere with everyday activities and limit independence is ultimately based on clinical assessment and judgment.

Individuals with MCI are at risk of a short-term progression to severe cognitive impairment. In a systematic review and meta-analysis by the American Academy of Neurology expert group, approximately 15% of older adults with MCI (65+ years) were diagnosed with dementia after two years (Petersen et al., 2018). Compared with older adults without MCI, the risk of both all-cause and AD dementia was approximately three times higher among those with MCI. Another meta-analysis including studies until 2008 showed that 24–32% of individuals with MCI developed

some type of dementia when followed up for a longer period (three to 10 years), depending on the exact definition of MCI (Mitchell & Shiri-Feshki, 2009). Higher progression rates were reported for memory clinics than community settings. Nevertheless, when MCI is diagnosed clinically without any information about potential underlying pathology, it can remain stable for years or even be reversible. However, individuals who have reverted might still have an increased risk of future cognitive decline (Petersen et al., 2018; Vermunt et al., 2019b).

Widely used disease coding systems and guidelines for clinical diagnosis of cognitive impairment and dementia include the International Classification of Diseases (ICD) by the WHO and the Diagnostic and Statistical Manual of Mental Disorders (DSM) by the American Psychiatric Association. These guidelines were recently updated (ICD-11 released in 2018, DSM-5 in 2013), and some conceptually important changes were introduced (American Psychiatric Association, 2013; World Health Organization, 2018b). Updates in the DSM criteria are briefly summarized next; for a detailed discussion, readers are referred to work by Sachdev et al. (2014).

First, a broader and less AD-centric definition of dementia was introduced to clearly separate the concepts of AD and dementia. In the previous version DSM-IV (American Psychiatric Association, 1994), impairment in at least two cognitive domains, one of them being memory, was obligatory for a diagnosis. In DSM-5, an impairment in only one domain is sufficient and an amnesic phenotype is no longer required. A degree of functional impairment significant enough to interfere with everyday activities remains a criterion for dementia. This broader definition might have an impact on dementia prevalence estimates: in one study, 56% of patients were diagnosed with dementia when the DSM-IV criteria were applied and 78% when the DSM-5 criteria were used (Tay et al., 2015). Second, the DSM-5 criteria introduced a new nomenclature, as the label 'dementia' was replaced with 'major neurocognitive disorder'. The terms 'AD' and 'dementia' have often been used interchangeably (Knopman et al., 2019), and the Latin-derived word 'dementia'—literally translated as 'out of mind'—has been commonly associated with old age, senility, and disability. The term 'major neurocognitive disorder' was proposed to reduce this stigma and to highlight the heterogeneous nature of the syndrome, which can affect people at different stages in life (Sachdev et al., 2014). Finally, the DSM-5 criteria better recognize milder expressions of cognitive impairment, which were grouped as 'cognitive disorders not otherwise specified' in the previous criteria. The term 'mild neurocognitive disorder' in DSM-5 is essentially equivalent to MCI (i.e., modest cognitive decline in any domain but preserved independence in everyday activities), and the main difference is in the terminology (Stokin et al., 2015). As in the previous criteria, the DSM-5 diagnosis of cognitive impairment is made in a stepwise manner. A syndrome-level diagnosis, either for a major or mild neurocognitive disorder, is made first, and a subtype is assigned at the next step (e.g., neurocognitive disorder due to AD, or vascular neurocognitive disorder). The possibility of mixed etiology is well recognized (neurocognitive disorder due to multiple etiologies). At present, biomarkers are not incorporated in these clinical diagnostic guidelines.

2.1.2 Disease concepts in evolution: the case of Alzheimer's disease

2.1.2.1 Research criteria for early, biology-based diagnosis

Many of the changes in diagnostic guidelines for cognitive impairment stem from the advances made in AD research during the past few decades. In particular, an increased understanding of AD pathophysiology as well as the development and validation of *in vivo* biomarkers have been a breakthrough. Biomarkers mirror the neuropathology and can in some cases be measured at least 15–20 years before the first clinical symptoms, as shown for AD mutation carriers (Benzinger et al., 2013; Quiroz et al., 2020). Before biomarkers were available, AD and dementia diagnoses were tightly interconnected, such that an AD diagnosis was usually not made prior to severe, dementia-level cognitive impairment. The widely used diagnostic criteria proposed in the 1980s and 1990s, i.e., DSM-IV (American Psychiatric Association, 1994) and the National Institute of Neurological Disorders and Stroke—Alzheimer Disease and Related Disorders (NINCDS-ADRDA) criteria (McKhann et al., 1984), considered AD as a disease defined by typical clinical symptoms. Progressive impairment in several cognitive domains, including memory, had to be present. Once all other apparent causes of cognitive decline were excluded based on clinical examination and medical history, those with the typical clinical phenotype were assumed to have AD-typical neuropathology (hence the term 'probable AD' in the NINCDS-ADRDA criteria). A definite diagnosis required an autopsy (McKhann et al., 1984). Biomarkers have changed this view, and a diagnosis of inclusion rather than exclusion before the onset of 'full-blown' dementia has become possible. Since 2007, several sets of research diagnostic criteria for AD have been published (Albert et al., 2011; Dubois et al., 2007, 2014, 2016; Sperling et al., 2011), the most recent of which is the 2018 research framework (Jack et al., 2018). Criteria have undergone refinements as new evidence for the specificity and temporal order of biomarkers has accumulated and assessment methods have improved. The AD-characteristic pathophysiological processes and respective biomarkers are summarized next; the new research criteria and rationale behind updating the NINCDS-ADRDA criteria are discussed thereafter.

There are several types of biomarkers that reflect the key AD-characteristic pathophysiological processes and are incorporated into the research diagnostic criteria. These include markers of 1) β -amyloid ($A\beta$) deposition, 2) tau protein buildup, and 3) neurodegeneration. Validated biomarkers do not yet exist for all the other important pathological events, such as the inflammation response and activation of microglia cells (Jack et al., 2018). A detailed description of AD pathophysiology is beyond the scope of this thesis, and readers are, for example, referred to a recent review by Long and Holtzman (2019). In brief, AD drug development and the revision of the diagnostic criteria have been guided by the amyloid cascade hypothesis (Hardy & Higgins, 1992; Selkoe & Hardy, 2016). According to this hypothesis, an imbalance in amyloid precursor protein (APP) cleavage and $A\beta$ clearance leads to an increase in levels of $A\beta$, particularly the 42-

amino acid form (A β 42). This is essentially the first key pathologic event in AD. Consequently, A β peptides aggregate and form extracellular soluble oligomers and insoluble plaques. Validated biomarkers for A β accumulation include increased cortical uptake and binding of A β -specific ligands in positron emission tomography (PET) (Clark et al., 2012), as well as decreased levels of A β 42 in the cerebrospinal fluid (CSF) (Olsson et al., 2016), the latter being an indirect measure of the cerebral A β load. The ratio of CSF A β 42 and A β 40 is also informative and might correlate better with A β PET than CSF A β 42 alone (Janelidze et al., 2016).

According to the amyloid cascade hypothesis, neuronal injury—another AD hallmark, albeit non-specific—occurs downstream in the cascade of pathological events. Through not fully understood mechanisms, A β induces hyperphosphorylation of the tau protein, formation of intracellular neurofibrillary tau tangles, and finally the spread of tau pathology from the medial temporal lobe into the other areas of the brain. Other later events in the disease process are synaptic dysfunction, impaired brain connectivity, and eventually, neuronal death and cognitive impairment (Jack et al., 2010, 2013). Biomarkers of neuronal injury include markers of tau pathology, i.e., increased CSF levels of total tau (t-tau) and phosphorylated tau (p-tau) (Olsson et al., 2016). Tau PET has become recently available (Lowe et al., 2018), and it is now incorporated into the research diagnostic criteria (Jack et al., 2018). With tau PET, it is possible to visually assess and quantify the regional distribution and load of tau tangles. Other neuronal injury markers are a decreased uptake of fluoro-deoxy-glucose (FDG) in the temporoparietal brain regions in PET (as a proxy for reduced brain glucose metabolism and synaptic impairment) (Minoshima et al., 1997) as well as medial temporal lobe atrophy (MTA) in structural magnetic resonance imaging (MRI) (Scheltens et al., 1992). MTA reflects neuronal loss. Unlike A β biomarkers, markers of neuronal injury correlate well with cognitive decline and disease progression (Jack et al., 2013).

The amyloid cascade hypothesis is not entirely undisputed, and alternative hypotheses have been proposed. Given the close correlation between tau and the disease progression and severity, as well as the fact that it can occur in the absence of A β , tau could be the key player in AD (tau hypothesis; described e.g. by Kametani and Hasegawa, 2018). Other hypotheses emphasize the interplay between A β and tau. For example, De Strooper and Karran (2016) proposed that both A β and tau accumulation might be risk factors, rather than causes, of AD. These events are possibly independent and parallel processes, which are accelerated by aging and other unknown upstream events. Impaired protein clearance and accumulation of 'proteopathic stress' leads to the 'cellular phase of AD', which is characterized by disrupted cellular homeostasis and a range of biochemical processes. These involve not only neurons but also the vasculature, blood-brain-barrier, microglia, and astroglia. The A β and tau interaction and biochemical processes in the cellular phase are all essential for the disease to progress to the clinical phase. Indeed, many studies have shown that both A β and tau are needed to cause cognitive decline (e.g., Betthausen et al., 2020; Dubois et al., 2018; Mormino et al., 2014; Sperling et al., 2019).

In addition to the classic biomarkers for A β , tau, and neuronal injury, new biomarkers are emerging. Blood-based p-tau markers seem particularly promising (Karikari et al., 2020; Palmqvist et al., 2020). Other new markers include blood-based markers of A β (Nakamura et al., 2018) and inflammation (Gross et al., 2019), neurofilament light as a marker of axonal injury (Bridel et al., 2019; Preische et al., 2019), as well as neurogranin (Portelius et al., 2018), synaptic vesicle glycoprotein 2A (SV2A) PET (Chen et al., 2018), and functional MRI (Vemuri et al., 2012) as markers of synaptic dysfunction and impaired brain functional connectivity. The utility and potential diagnostic or prognostic value of these biomarkers is not yet fully understood. Emerging technologies, such as wearable devices and sensors, could potentially give rise to digital biomarkers in the future, but literature is so far scarce (Gold et al., 2018; Kourtis et al., 2019).

The main issue with the older and purely clinical criteria for AD has been their suboptimal specificity and sensitivity, i.e., the mismatch between clinical AD diagnosis and underlying neuropathology. Autopsy (Beach et al., 2012; Boyle et al., 2018; Schneider et al., 2009; Serrano-Pozo et al., 2014) and imaging studies (Landau et al., 2016; Ossenkoppele et al., 2015) have reported an absence of classic AD-type pathology in around 12–17% of individuals diagnosed with AD dementia, and some studies have reported even greater discrepancies (Rosén et al., 2015). In the Imaging Dementia—Evidence for Amyloid Scanning (IDEAS) study, 36% of the patients were A β negative (i.e., normal) when a PET scan was performed after a clinical AD diagnosis (Rabinovici et al., 2019). At the same time, a non-AD dementia diagnosis does not equal the absence of AD-type pathology. For example, in their meta-analysis Ossenkoppele et al. (2015) showed that 42% of 75–84-year-old adults with vascular dementia had positive A β PET scans. In a recent memory clinic study, 53% of patients with a mild or major vascular cognitive disorder had abnormal (i.e., decreased) CSF A β (Leijenaar et al., 2020). Similarly, 52% of the IDEAS patients with some form of non-AD dementia had positive A β PET scans (Rabinovici et al., 2019).

All new research criteria for AD aim to improve the diagnostic specificity and sensitivity by incorporating *in vivo* biomarkers and critically assessing what—if any—cognition-related aspects should be considered in the diagnostic procedure. A comparison of the older diagnostic criteria and new research criteria is presented in Table 1. Despite some fundamental differences, which are described later in this section, all the new criteria are primarily intended for research purposes (e.g., as RCT inclusion criteria). The main differences are related to the nomenclature, types of biomarkers recognized, as well as timing of the diagnosis and its relation to the cognitive status. In essence, the criteria provide different answers to the questions of what AD is and when it starts. Does it start when the first symptoms occur and there is supportive biomarker evidence? Or does one have AD as soon as the first neuropathological changes occur? Of note, while familial forms of AD are incorporated into the research diagnostic criteria, the focus here is on sporadic AD and related terminology.

Table 1. Diagnostic criteria for AD.

	NINCDS-ADRDA 1984	IWG-1 2007 (refined in 2010)	NIA-AA 2011	IWG-2 2014	NIA-AA 2018
Intended use	Clinical use, research	Research	Clinical use (core criteria), expanded criteria for research	Research	Research
Timing of diagnosis	At dementia stage (probable AD); after death (definite AD)	At any symptomatic stage (probable AD; prodromal AD and AD dementia); after death (definite AD)	At any symptomatic stage (MCI and dementia due to AD); in research also at preclinical stage (preclinical AD)	At any symptomatic stage	AD at any stage of the cognitive continuum; Alzheimer's clinical syndrome at any symptomatic stage
Diagnostic assessments	Clinical/cognition	Clinical/cognition + biomarkers	Clinical/cognition (core criteria); Clinical/cognition + biomarkers (research criteria)	Clinical/cognition + biomarkers	Biomarkers
Cognitive criteria for AD	Dementia, amnesic phenotype required	Episodic memory impairment, no dementia required (prodromal AD)	MCI (any domain) or dementia, amnesic phenotype not required	Impairment in any domain (typical or atypical AD), no dementia required	Not required; cognitive staging can accompany diagnosis
Biomarker criteria for AD	Not included	Any abnormal marker: A+ or any neuronal injury marker + (including MTA, FDG-PET)	Different combinations reflect a different likelihood of AD High: A+ and any neuronal injury marker + (including MTA, FDG-PET) Intermediate: A+ or any neuronal injury marker + when the other one is unknown Unlikely: A- and neuronal injury - Uninformative: Biomarkers conflicting or unknown	Amyloid PET+ or CSF A+ and an abnormal marker of tau: CSF p-tau+ or t-tau+	A+ and an abnormal marker of tau: CSF p-tau+ or tau PET+
Preclinical stage recognized?	No	Yes, asymptomatic at risk for AD (2010)	Yes, preclinical AD: stage 1 (A+ and neuronal injury -), stage 2 (A+ and neuronal injury +), and stage 3 (A+ and neuronal injury + and very mild cognitive decline)	Yes, asymptomatic at risk for AD	Yes, AD is independent of cognitive status

In the first set of research diagnostic criteria, proposed by the International Working Group (IWG) in 2007 (Dubois et al., 2007) and refined a few years later to introduce new terminology (Dubois et al., 2010), a major advancement compared to the NINCDS-ADRDA criteria was the combination of cognition and biomarkers in the diagnostic procedure. These criteria (IWG-1 criteria) introduced the concept of prodromal AD to distinguish AD from dementia. Core criteria are AD-typical cognitive changes consisting of self- or informant-perceived progressive memory decline and an objectively measurable episodic memory impairment with or without impairment in non-memory domains. Biomarker abnormalities are referred to as supportive features, and at least one such feature is needed for an AD diagnosis. Equal weight is assigned to all biomarkers that were available and validated when the criteria were proposed. In other words, abnormality in any biomarker is sufficient (Table 1, p. 31).

In 2014, the IWG proposed a second set of criteria (IWG-2) (Dubois et al., 2014). These criteria distinguished the pathophysiological or diagnostic biomarkers, i.e., markers of A β and tau deposition, from the less AD-specific markers occurring later in the disease course (i.e., MTA and hypometabolism in FDG-PET). Like in the IWG-1 criteria, an AD diagnosis is based on the combination of clinical phenotype and biomarker abnormality, but the IWG-2 biomarker criteria are more restrictive. Evidence for A β accumulation is required, alone or together with evidence for tau pathology depending on which A β biomarker is used, and less AD-specific markers are not considered. The IWG-1 criteria recognize only the amnesic clinical phenotype, but the IWG-2 criteria include both typical and atypical AD (i.e., the posterior variant characterized by visuospatial dysfunction, the frontal variant characterized by executive dysfunction and behavioural symptoms, and the logopenic variant characterized by problems with language and speech). Another advancement in the IWG-2 criteria is the recognition of the preclinical disease stage. The IWG-2 defines this stage by the absence of cognitive concerns and impairment but presence of AD-type pathology. It is noteworthy that the term 'asymptomatic at risk for AD' was initially used, to indicate a high risk but absence of a full-blown disease. In 2016, the IWG revised this and proposed the term 'preclinical AD' when both A β and tau markers are abnormal; the term 'asymptomatic at risk for AD' applies when either A β or tau is abnormal (Dubois et al., 2016). Tau pathology in the absence of A β pathology is thus considered an at-risk state.

In addition to the European IWG, the National Institute of Aging and the Alzheimer's Association (NIA-AA) in the United States have contributed to updating the NINCDS-ADRDA criteria. In 2011, the NIA-AA published one set of criteria for MCI and dementia due to AD to be used in regular health care and another set of criteria including biomarker assessments to be used in research (Albert et al., 2011; McKhann et al., 2011). Research criteria were proposed separately for each disease stage: preclinical AD (Sperling et al., 2011), MCI (Albert et al., 2011), and dementia (McKhann et al., 2011). In the NIA-AA 2011 research criteria, which are based on the hypothetical dynamic biomarker model (Jack et al., 2010), biomarkers reflecting A β

accumulation are distinguished from those reflecting neuronal injury (including tau). Different biomarker combinations correspond to a different likelihood that the clinical phenotype (MCI or dementia) is caused by an AD-type pathology. The four levels of likelihood are presented in Table 1 (p. 31). The combination of an abnormal A β marker and any abnormal marker of neuronal injury confers high likelihood; AD is unlikely if markers of A β and neuronal injury are both considered normal. In contrast to the IWG-criteria, the NIA-AA 2011 criteria recognize situations in which biomarkers are discordant or not all of them are tested. In the preclinical AD criteria, three stages are outlined: stage 1 is characterized by intact cognition and isolated A β abnormality; at stage 2, both the A β and neuronal injury markers are abnormal; and at stage 3, biomarker abnormalities are accompanied by subtle cognitive changes that are considered in between normal cognition and MCI (Sperling et al., 2011). Once it became evident that a considerable proportion of cognitively healthy and mildly impaired individuals have normal A β but abnormal neuronal injury markers, the term 'suspected non-AD pathology' (SNAP) was introduced (Jack et al., 2012).

In 2018, the NIA-AA updated the 2011 criteria and proposed a research framework (Jack et al., 2018), which is based on the ATN biomarker classification scheme (Jack et al., 2016). In this biomarker scheme, 'A' stands for A β deposition, 'T' for tau pathology (specifically CSF p-tau and more recently tau PET), and 'N' for neuronal injury. Compared with all the other criteria, the NIA-AA 2018 criteria are the only ones distinguishing between AD-specific tau pathology and tau pathology reflecting general neuronal injury. In addition, these are currently the only criteria to define AD as a strictly biological construct where the diagnosis is independent from the cognitive status and clinical phenotype. Based on the ATN system, where 'A', 'T' and 'N' biomarkers are considered either abnormal or normal, an individual can be classified into one of eight possible biomarker profile categories. These profiles can be further grouped into three categories: normal AD biomarkers, non-Alzheimer's pathologic change, and the Alzheimer's continuum. The Alzheimer's continuum, characterized by A β abnormality, comprises the following profiles: Alzheimer's pathologic change (isolated A β abnormality, A+T-N-), AD (abnormal A β and tau, A+T+N \pm), and Alzheimer's and concomitant suspected non-Alzheimer's pathologic change (abnormal A β and neuronal injury but normal tau, A+T-N+). The disease is diagnosed based on biomarker evidence and only afterwards linked to cognitive performance (e.g., AD with MCI, or AD with dementia). The term 'Alzheimer's clinical syndrome' applies when the biomarker profile is unknown but AD-typical clinical symptoms are present.

Several studies have evaluated the utility of the research diagnostic criteria by applying them to different cognitively healthy (Burnham et al., 2016; Clark et al., 2018; Kern et al., 2018; Knopman et al., 2012; Soldan et al., 2016; Vos et al., 2013) and mildly impaired populations (Bertens et al., 2017; Caroli et al., 2015; Lowe et al., 2013; Petersen et al., 2013; Prestia et al., 2015; Vos et al., 2015). The proportion of individuals assigned to each category and the respective clinical progression rates varied in these studies, depending on the study setting, target population, and the choice of

biomarkers and cut-offs for abnormality. Still, the risk of progression and cognitive decline consistently increased with increasing evidence of biomarker abnormality. In a systematic review and meta-analysis focusing on preclinical AD (Parnetti et al., 2019), the prevalence of NIA-AA 2011 preclinical AD stage 1, 2, and 3 was 13%, 16%, and 5%, respectively. The prevalence of SNAP was not reported. In total, 20% (stage 1), 38% (stage 2), and 73% (stage 3) progressed to MCI or dementia over a follow-up period of one to four years. In a large multicenter study by Vos et al. (2015), the validity of the IWG and NIA-AA criteria was assessed in memory clinic MCI patients. The prevalence of prodromal AD and high AD likelihood decreased with increasing requirements for biomarker abnormality (IWG-1 prodromal AD 53%, NIA-AA 2011 high AD likelihood 46%, IWG-2 prodromal AD 40%). The three-year progression rate to AD dementia was 50% and 61% in individuals with IWG-1 and IWG-2 prodromal AD and approximately 20% in those with no prodromal AD. The risk was three to four times higher for those with prodromal AD. With respect to the NIA-AA 2011 criteria, the risk of AD dementia increased with an increasing likelihood of AD. In total, 5% of individuals in the low likelihood group progressed to AD dementia. This was the case for 22–24% in the conflicting biomarker group, 49% in the intermediate likelihood group, and 59% in the high likelihood group. Compared with the low likelihood group, the risk was approximately five, 10, and 14 times higher in the above-mentioned groups. This study was published in 2015 and did not include the NIA-AA 2018 criteria. More recently, other studies have shown that there is a correlation between the NIA-AA 2018 biomarker profile and cognitive status, and that the A+T+(N±) profiles are associated with greater cognitive deterioration and risk of dementia (Altomare et al., 2019; Dodich et al., 2020; Ebenau et al., 2020; Ekman et al., 2018; Jack et al., 2019c; Soldan et al., 2019).

Through the development of the research diagnostic criteria, steps have been taken towards a better understanding of AD. These somewhat A β -centric criteria as well as the underlying hypothetical dynamic AD biomarker model have nevertheless also been criticized (De Strooper & Karran, 2016; Morris et al., 2018). Potential drawbacks relate to how individuals are ruled in and out when considering a diagnosis of AD. Studies have suggested that the diagnostic utility of A β and tau biomarkers is somewhat uncertain, because older individuals might have pathological levels of A β and tau without any cognitive symptoms or impairment. For example, Jansen et al. (2015) showed that the prevalence of A β pathology increased with increasing age. Among cognitively healthy older adults aged 75 and 80, 28% and 33% had positive amyloid PET scans, respectively. Similarly, Jack et al. (2017) estimated an A+T+N+ biomarker profile to be present in 22% of cognitively healthy 80-year-old individuals. The causal and temporal relationship between A β and tau also remains so far unclear. The development of tau PET might solve this problem, as the simultaneous *in vivo* imaging of both pathologies now becomes possible. One study including both A β and tau PET imaging found that, unlike the common A+T- and A+T+ profiles, an A-T+ profile occurred rarely in cognitively healthy individuals (Jack et al., 2019b). These findings support the model of

biomarker ordering, but not all studies have reported similar observations (Weigand et al., 2020).

Another potential challenge associated with the research diagnostic criteria is the fact that different types of biomarkers for a specific pathology are considered equal (i.e., CSF and PET). CSF levels of A β and tau might become abnormal earlier than the respective PET scans, and biomarker discordance has been reported in the literature (De Wilde et al., 2019; Meyer et al., 2020). The optimal biomarker cut-offs are also unclear (Villeneuve et al., 2015), and using different cut-offs might change the classification, as shown for example in the study by Jack et al. (2019b). Weigand et al. (2020), who reported a high prevalence for the A-T+ profile in their study, attributed their results largely to the fact that the tau PET cut-offs were defined differently than in other studies (i.e., independently from amyloid PET cut-offs). Lastly, AD, particularly in old age, is a heterogeneous condition characterized by the presence of different co-morbid pathologies. These could potentially lower the threshold for clinically significant cognitive impairment (Kapasi et al., 2017). Thus, it remains unclear whether the same criteria and biomarker cut-offs can be applied to all individuals and to both early- and late-onset AD. The heterogeneity of cognitive impairment in old age, with a focus on AD, is discussed in detail next.

2.1.2.2 Heterogeneity of Alzheimer's disease in old age

As shown in community-based studies, a single neuropathology rarely causes cognitive impairment in old age; rather, combinations of several different pathological features (i.e., mixed pathologies) are common findings in autopsies (Brenowitz et al., 2017; Suemoto et al., 2019; White et al., 2016). This applies also to AD. Most individuals with a clinical AD diagnosis have AD-type neuropathology (Beach et al., 2012; Landau et al., 2016; Ossenkoppele et al., 2015; Schneider et al., 2009; Serrano-Pozo et al., 2014), but it rarely occurs in isolation. In one recent autopsy study, for example, pure AD pathology was reported for 17% and 22% of individuals who died with dementia and MCI, respectively, whereas mixed AD pathology was present in 73% and 55% of the individuals (Abner et al., 2017). In another large autopsy study, 65% of the individuals with an AD dementia diagnosis had AD pathology and only 9% had pure AD pathology (Boyle et al., 2018).

In AD, the most common co-morbid pathologies are cerebrovascular pathology, hippocampal sclerosis (HS), and other proteinopathies such as hyperphosphorylated transactive response DNA-binding protein 43 (TDP-43) pathology and alpha-synucleinopathy, which is usually seen in Lewy body disease (Boyle et al., 2018). Cerebrovascular pathology includes infarcts, microbleeds, cerebral amyloid angiopathy, atherosclerosis, and arteriolosclerosis (Iadecola et al., 2019). Co-occurrence of vascular pathology is particularly common and characteristic for an AD-like clinical syndrome (Beach et al., 2012; Schneider et al., 2009). In the study by Abner et al. (2017), 62% and 73% of dementia and MCI cases with mixed pathology had a co-morbid vascular pathology. Boyle et al. (2018), who investigated a broad range of different neuropathologies, concluded that vascular pathology was present

in 30–36% of the cases. TDP-43 and alpha-synuclein proteinopathies were found in this study in 35% and 10% of the individuals, respectively, and 10% had HS. The authors also reported that nearly 60% of the autopsied individuals had more than three different pathologies, and 236 different combinations were observed. For some of the neuropathological profiles, distinct terms have been proposed to better define them, one example being the limbic-predominant age-related TDP-43 encephalopathy neuropathologic change (LATE-NC) (Nelson et al., 2019). LATE-NC occurs alone or together with AD-type pathology or HS usually in old age, and it is associated with an AD-like clinical amnesic phenotype, yet symptoms progress slowly. Conditions like argyrophilic grain disease (Rodriguez et al., 2016) and primary age-related tauopathy (PART) (Bell et al., 2019; Crary et al., 2014) can also lead to a clinical phenotype that closely resembles that of typical AD, even if only minimal or no A β pathology is present. It remains somewhat controversial whether conditions like PART should be counted in the Alzheimer's disease continuum (Duyckaerts et al., 2015; Jellinger et al., 2015).

Different pathologies contribute independently to cognitive decline and dementia (Power et al., 2018), and having multiple pathologies is associated with an increased risk of dementia (also AD-type) (Arvanitakis et al., 2016; James et al., 2016; Nag et al., 2015). For example, in the Finnish Vantaa 85+ study, the odds ratio for dementia (reference group no pathology) was approximately five, 10, and 11 among those with one, two, and three pathologies, respectively (Tanskanen et al., 2017). In another study, the 90+ Study, the odds ratios for dementia were 3.5 for pure AD pathology and 13 for mixed AD pathology (Kawas et al., 2015). How exactly co-morbid pathologies contribute to neurodegeneration and cognitive decline in AD, and what the exact mechanisms are, is not well understood. One hypothesis is that if AD pathology is present but not in sufficient amounts, co-morbid pathologies like vascular pathologies could act as an additional 'hit' and lower the threshold for cognitive impairment (Kapasi et al., 2017; Toledo et al., 2013). Until recently, it has been unclear how important each of the different pathologies is exactly and what proportion of dementia cases can be explained by certain neuropathologies commonly seen in older adults. In a large autopsy cohort with longitudinal cognition data, Boyle et al. (2018) showed that AD pathology had the strongest effect, explaining approximately 50% of the cognitive decline in this population. However, there was significant inter-individual variation depending on the pathology profile. In a separate report (Boyle et al., 2019), the authors estimated first that 35% of the AD dementia cases were attributable to AD pathology, and vascular pathology and non-AD neurodegenerative pathologies accounted for approximately 22% and 27% of the cases, respectively. When adjusted for overlap, approximately seven out of 10 cases were attributable to all neuropathologies combined. This means that other so far unknown factors and pathologies could have contributed to approximately a third of all AD dementia cases.

2.1.3 Risk and protective factors

2.1.3.1 Individual factors

Several non-modifiable and modifiable factors contribute to late-life cognitive impairment. Of all these factors, age has the greatest effect. The prevalence of dementia increases rapidly from approximately 1% in the age group 65–69 years, to 8% and 22% in the age groups 75–79 and 85–89 years, respectively (Alzheimer Europe, 2020). Among genetic factors, apolipoprotein E (*APOE*) and its $\epsilon 4$ allele is the most potent known susceptibility gene: one $\epsilon 4$ copy is associated with an approximately three-fold risk and two copies with a 15-fold risk of AD dementia (Farrer et al., 1997). Conversely, *APOE* $\epsilon 2$ allele is protective (Farrer et al., 1997; Reiman et al., 2020). Recently, 50 additional relevant gene loci were found in large genome-wide association studies, yet the individual contribution of each of these genes seems to be substantially lower than that of *APOE* (Sims et al., 2020). Apart from $A\beta$ and tau biology, the identified genes are linked to biological pathways such as immunity, cholesterol metabolism, endocytosis, vascular pathways, and ubiquitination (i.e., protein processing for degradation), underlining the complexity of the disease (Sims et al., 2020). Polygenic risk scores reflecting an individual's overall genetic risk burden hold promise as risk prediction tools (Escott-Price et al., 2015).

Other relevant non-modifiable risk factors of late-life cognitive impairment include sex and ethnicity. Female sex is associated with a higher prevalence of dementia, particularly in old age (Alzheimer Europe, 2020). The longer life expectancy of women might explain this, while some other potential explanations are sex differences in educational and occupational attainment, certain sex-specific biological factors such as hormonal changes in menopause, as well as differences in vulnerability to other risk factors such as *APOE* $\epsilon 4$ (Rahman et al., 2019). With respect to race and ethnicity, African Americans, for example, have a higher risk of dementia than Caucasians (Mayeda et al., 2016), potentially due to both genetic and environmental factors.

Over the past decades, compelling evidence has accumulated from longitudinal observational studies on the role of modifiable environmental factors in the development and progression of late-life cognitive impairment. A range of vascular, metabolic, lifestyle-related, and psychosocial risk and protective factors have been identified; comprehensive overviews have been provided for example in the Lancet Commission reports (Livingston et al., 2017, 2020) and in a recently published systematic review and meta-analysis (Yu et al., 2020). As a whole, a good vascular health status and healthy lifestyle are associated with a lower risk of late-life cognitive impairment (Dhana et al., 2020; Sabia et al., 2019). Figure 1 summarizes the individual modifiable risk and protective factors for which the current evidence base is most robust. Apart from depression and hearing loss, these factors were also addressed in the complex multidomain lifestyle interventions that are described in this thesis in connection with Studies I-III.

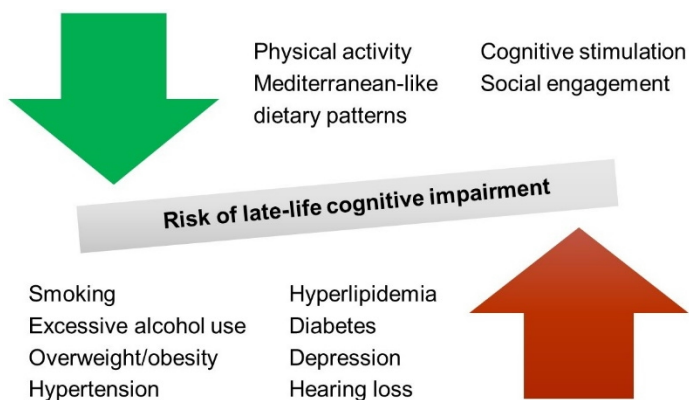


Figure 1. Modifiable risk and protective factors for late-life cognitive impairment.

Recently, the WHO appointed an expert group to assess systematic reviews of RCTs targeting the factors in Figure 1, with the aim to formulate guidelines for preventive strategies (World Health Organization, 2019). The guidelines made strong recommendations for physical activity and tobacco cessation interventions. Conditional recommendations were issued for dietary and cognitive interventions, interventions concerning alcohol use, and interventions targeting each of the vascular and metabolic risk factors (obesity, hypertension, hyperlipidemia, and diabetes). In another comprehensive systematic review, no RCT evidence was found to support any recommendations (National Academies of Sciences, Engineering, and Medicine, 2017). When observational data were also considered, this report identified cognitive and exercise interventions and blood pressure (BP) management as potentially beneficial strategies.

According to large modelling studies (Livingston et al., 2017; Norton et al., 2014), approximately 30–35% of dementia cases worldwide could be attributed to a combination of the following modifiable factors: low educational attainment (no secondary school education), hypertension, obesity, diabetes, physical inactivity, smoking, and depression (additionally hearing loss and lack of social engagement were included in the report by Livingston et al., 2017). The most recent Lancet Commission report includes three additional factors, namely the excessive use of alcohol, head injury, and pollution, and attributes 40% of dementia cases to modifiable factors (Livingston et al., 2020). These estimates are based on the elimination of all the above-mentioned factors, and for comparison, eliminating *APOE* ϵ 4 was estimated to result in a 7% reduction in dementia incidence (Livingston et al., 2017). The contribution of modifiable risk factors might be even greater in developing countries (Mukadam et al., 2019), but data on the prevalence and relevance of some risk factors are still scarce in many regions of the world (Anstey et al., 2019). Of note, while education can be considered a modifiable factor in a broad

sense, it is usually not the case on an individual level. This is because the level of formal education is unlikely to change in mid- or late-life.

The above-mentioned studies did not assess the role of unhealthy dietary patterns, and it is unclear whether the estimated proportion of cases explained by modifiable risk factors is correct or perhaps an underestimation. Methodological choices and differences in study design might also have a substantial impact on the estimations. In a Swedish cohort study, for example, only 10% of the dementia cases were attributable to the combination of the nine modifiable factors investigated by Livingston et al. (2017), and *APOE* $\epsilon 4$ alone had the greatest impact (Tomata et al., 2020).

Modifiable risk factors typically occur in clusters, as, for example, different unhealthy lifestyle habits tend to be correlated. The risk of cognitive impairment increases with an increasing risk factor burden, as shown in a recent meta-analysis of observational studies (Peters et al., 2019). Compared with no risk factors, having one, two, or at least three modifiable risk factors was associated in this study with a 1.2, 1.7, or 2.2 times higher risk of dementia, respectively. Modifiable risk factors might potentially also interact with genetic factors, but results are mixed. The observational Cardiovascular Risk Factors, Aging and Dementia study (CAIDE) reported a particularly pronounced association between lifestyle risk factors and increased dementia risk among *APOE* $\epsilon 4$ carriers (Kivipelto et al., 2008). In the Rotterdam Study, a healthy lifestyle appeared to be protective for *APOE* $\epsilon 4$ non-carriers but not carriers (Licher et al., 2019). In some studies, *APOE* and genetic risk did not modify the association between vascular health or lifestyle and the risk of dementia (Peloso et al., 2020; Samieri et al., 2018) or cognitive performance (Lyall et al., 2019; Rodriguez et al., 2018). A large study including nearly 200,000 individuals also did not find any interaction between lifestyle and a polygenic risk score (Lourida et al., 2019).

The association between many modifiable factors and the risk of cognitive impairment varies across the lifespan. Several mid-life but not necessarily late-life factors have been associated with a higher risk of cognitive impairment, and a change over time in risk factor levels can be informative. Examples of such factors are hypertension, hypercholesterolemia, and obesity (Peters et al., 2020). In fact, inverse associations have been reported, i.e., higher BP, cholesterol, or body mass index (BMI) in old age appear to be protective (e.g., Gregson et al., 2019; Kivimäki et al., 2018). This is likely because of reverse causality bias, i.e., pathophysiological processes gradually start to interfere with the regulation of BP, weight, and appetite, leading to a decline in BP and weight (Peters et al., 2020). It is also important to note that not all modifiable factors identified in a cognitively healthy population are necessarily relevant risk factors for disease progression among those who already have some cognitive impairment (Cooper et al., 2015).

The mechanisms through which vascular, metabolic, and lifestyle-related risk factors promote cognitive impairment and contribute to neurodegeneration are complex. Cerebrovascular pathologies develop when structural changes in the

vasculature reduce cerebral blood flow, induce hypoperfusion and hypoxia, and ultimately disrupt the metabolic homeostasis in the brain (e.g., reviews by Iadecola et al., 2019 and Kapasi & Schneider, 2016). Endothelial dysfunction and altered permeability of the blood-brain-barrier (i.e., impaired functioning of the neurovascular unit) contribute to oxidative stress and inflammation, detrimental processes triggered also by A β accumulation. This leads to a vicious circle where damage accumulates over time. Vascular and metabolic factors might also be directly linked to A β -related pathways. For example, hypertension could promote A β production through APP cleavage (Faraco & Iadecola, 2013), and dietary salt could induce hyperphosphorylation of tau (Faraco et al., 2019). An association between mid-life vascular risk factors and A β accumulation later in life has been reported in the literature (Gottesman et al., 2017), and vascular factors and A β have been shown to interact and synergistically promote cognitive decline (Rabin et al., 2018). However, most studies suggest that the pathways are independent and the effects of vascular factors are simply additive (e.g., Abner et al., 2016; Bos et al., 2019; Conner et al., 2019; Gustavsson et al., 2020; Lane et al., 2020; Rantanen et al., 2017; Vemuri et al., 2015).

With respect to depression, the mechanistic pathways linking it with cognitive impairment are poorly understood. The association between depression and cognitive impairment could be explained by the negative effects of depression on the vascular risk profile (indirect effects) as well as elevated levels of stress hormone cortisol, which contribute to hippocampal atrophy (direct effects) (Byers & Yaffe, 2011). Hearing loss might be linked to dementia through social isolation and depression (Livingston et al., 2020). The protective effects of cognitive stimulation and social engagement, much like those of education, can be mostly explained with increased resilience. This means a better ability to cope with disease-related brain changes and remaining cognitively intact or stable for longer than expected (Stern, 2009, 2012). The widely used term 'cognitive reserve' refers to the use of available brain resources to counteract the detrimental effects of disease pathology (Stern, 2009, 2012). In other words, the brain is flexible, and alternative compensatory strategies are used to process information and solve tasks. Cognitive stimulation is nevertheless associated also with less pronounced AD pathology, indicating increased resistance to brain pathology (Oveisgharan et al., 2020).

Mediterranean-type dietary patterns, which are characterized by a low to moderate intake of meat and dairy products but a high intake of fruit, vegetables, fish, and whole-grain foods, alleviate oxidative stress and inflammation and improve the vascular risk profile (Scarmeas et al., 2018). The protective effects of physical activity are complex and include direct biological mechanisms as well as indirect effects on other risk factors of cognitive impairment. These effects were recently described by Valenzuela et al. (2020) in a comprehensive review. First, exercise stimulates the production of neurotrophins (in particular, brain-derived neurotrophic factor BDNF) and metabolites, such as lactate and ketone bodies, which further upregulate BDNF production. This promotes hippocampal neurogenesis and

improves neuronal plasticity. Second, exercise enhances perfusion in the brain and protects against A β accumulation by alleviating oxidative stress and reducing inflammation. Finally, exercise helps reduce depressive symptoms and has positive effects on the vascular risk profile (e.g., diabetes, overweight).

2.1.3.2 Risk scores

In order to estimate an individual's overall risk of cognitive impairment, several dementia risk scores and prediction tools have been developed for different populations at different stages of life as well as for different outcomes (i.e., any type of dementia vs. AD dementia). The available risk scores combine non-modifiable and modifiable risk and protective factors, but the number and type of factors incorporated in the scores vary. In a recent systematic review, 61 different risk scores were identified: the majority, 39 scores, were intended for older populations and four were intended for middle-aged populations (Hou et al., 2019). The other prediction models were intended for use in MCI or diabetes. So far, two of the risk scores developed in the context of diabetes and five of the general mid-life and late-life risk scores have been validated. These five risk scores are briefly described below.

The CAIDE risk score for 20-year dementia risk prediction based on a mid-life risk profile was developed in the Finnish CAIDE study cohort (Kivipelto et al., 2006) and validated in the ethnically more diverse U.S. Kaiser Permanente cohort with a longer, on average 36-year, follow-up period (Exalto et al., 2014). The CAIDE score takes into account seven factors: age, sex, education, total cholesterol, BMI, systolic blood pressure (SBP), and physical activity; the *APOE* genotype is additionally incorporated in a separate version of the score (Kivipelto et al., 2006). The validation study tested whether additional risk factors, such as depression, diabetes, and smoking, could improve the predictive accuracy of the score, but no such factors were identified. The CAIDE score is informative among middle-aged individuals, but has limited utility in old age (Anstey et al., 2014; Licher et al., 2018). Recently, the CAIDE score was associated with the rate of brain atrophy before the onset of dementia (O'Brien et al., 2019). The CAIDE risk score is available as a mobile application, the CAIDE Risk Score App, which allows community-dwellers to easily test their risk (Sindi et al., 2015).

The Australian National University AD Risk Index (ANU-ADRI) was developed specifically for AD prediction (Anstey et al., 2013). It is based on a systematic literature review and not a cohort study like the CAIDE score. The ANU-ADRI score comprises 15 factors that can be easily assessed: age and sex (points for age depend on sex), education, BMI, total cholesterol, smoking status, drinking habits, social engagement, physical activity, cognitive stimulation, fish consumption, pesticide exposure, and medical conditions (depression, diabetes, and traumatic brain injury) (Anstey et al., 2013). Three different cohorts with slightly different mean ages (ranging from 53 to 75 years) and follow-up times (ranging from approximately four to six years) were used for validation (Anstey et al., 2014).

The Dementia Risk Score (DRS) for five-year dementia risk prediction among older individuals aged 60–79 years was developed and validated in a primary health care setting in the United Kingdom (Walters et al., 2016). The DRS takes into account 12 factors, all of which can be assessed by administering a questionnaire or interviewing the patient: age, sex, deprivation/socioeconomic situation, BMI, smoking status, alcohol abuse, use of medications (antihypertensive drugs, aspirin), and medical conditions (depression, diabetes, stroke/transient ischemic attack (TIA), and atrial fibrillation). The Brief Dementia Screening Indicator (BDSI) for six-year dementia risk prediction among individuals aged 65–79 years was developed based on four different U.S. cohort studies (Barnes et al., 2014). Similar to the DRS, the rationale was to use variables that were easy to collect or readily available from routine examinations in primary care settings. The BDSI includes seven factors: age, education, BMI, need for assistance with handling finances or medications, and medical conditions (depression, diabetes, and stroke).

The Lifestyle for Brain Health (LIBRA) score is the only dementia risk score to include solely modifiable risk and protective factors (Schiepers et al., 2018). Similar to the ANU-ADRI, it was developed based on a systematic literature review of modifiable environmental factors showing a consistent association with dementia risk (Deckers et al., 2015). In total, 12 factors were included in the risk score: physical activity, smoking status, obesity, total cholesterol, drinking habits, cognitive stimulation, dietary habits (adherence to the Mediterranean diet), and medical conditions (depression, hypertension, coronary heart disease, renal dysfunction, and diabetes). The predictive accuracy of the LIBRA score was tested in the Dutch Maastricht Ageing Study cohort where the mean age was 65 years and the follow-up time was 16 years (Schiepers et al., 2018). The score was also tested in the European DESCRIPA cohort with a mean follow-up of seven years (Vos et al., 2017). In the latter study, a higher LIBRA score was associated with a higher dementia risk in the age groups 55–69 and 70–79 years but not among those aged 80+ years. In the CAIDE study, higher mid-life LIBRA scores were predictive of late-life dementia, but the findings by Vos et al. (2017) concerning the predictive value even after the age of 70 years were not fully confirmed in this cohort (Deckers et al., 2020).

2.2 CLINICAL TRIALS TO PREVENT COGNITIVE DECLINE AND DEMENTIA

2.2.1 What do we mean by ‘prevention’ and ‘preventive interventions’?

Currently, there are no disease-modifying drugs to treat or reverse dementia and underlying conditions, and a growing interest in ‘prevention’ and ‘preventive’ interventions has become evident. Different pharmacological and non-pharmacological approaches and ongoing/completed RCTs are discussed in detail in the next sections. What the term ‘prevention’ exactly means and what the desired outcomes of the preventive measures are depends on the target population. Prevention, defined by the WHO (2020) as “specific population- and individual-based interventions aimed at minimizing the burden of diseases and associated risk factors”, is usually divided into primary, secondary, and tertiary prevention, depending on when in the disease continuum the intervention takes place. The aim of primary preventive measures is to reduce the occurrence of the disease and avoid it altogether, for example by limiting exposure to known risk factors and altering unhealthy habits and behavior. Given the established link between modifiable risk factors and cognitive impairment, a number of these types of preventive interventions are now ongoing. Secondary preventive measures target individuals with a manifest early-stage disease, and the focus is on early detection and diagnosis to slow down or delay the disease progression. With respect to AD, advances in biomarker research have enabled timely diagnoses and created opportunities for these types of preventive approaches, as discussed in section 2.1.2.1. Finally, tertiary preventive measures target individuals at an advanced disease stage and aim to reduce complications, improve the quality of life and coping, support independent living, and delay institutionalization.

With respect to the prevention of cognitive decline and dementia, the exact classification of RCTs can nevertheless be complicated. Whether a trial is considered a primary, secondary, or tertiary prevention RCT depends on how the underlying disease (i.e., AD) is defined. The different definitions and levels of prevention were outlined by Solomon et al. (2014). If clinical and cognitive symptoms are considered the defining feature of AD onset, the aim of primary prevention RCTs is to delay the onset of these first symptoms, regardless of the brain pathology. In this case, the aim of secondary prevention RCTs is to delay the onset of dementia. If AD is defined purely biologically, the aim of primary prevention RCTs is to prevent brain pathology, while delaying the onset of first noticeable clinical symptoms among those with brain pathology is considered a secondary prevention. Consequently, RCTs targeting cognitively impaired individuals with the aim to prevent dementia are considered tertiary prevention RCTs. Many of the current RCTs cannot be clearly defined as primary, secondary, or tertiary prevention RCTs. For example, population-based RCTs might include mixed populations in relation to both cognitive performance and disease pathology. If only those with significant cognitive impairment are excluded from the RCT, the study population might consist of both

cognitively intact older adults and those with mild symptoms and concerns. In addition, a subsample of participants at best might be tested for AD-type biomarkers in these RCTs.

A term that frequently co-occurs with 'prevention' is 'risk reduction', and these two concepts are used somewhat interchangeably in the literature. As the RCT evidence is still scarce as regards to whether the effects of modifiable risk factors are causal and whether cognitive impairment can ultimately be prevented (particularly on an individual level), the term 'risk reduction' could be preferred in some situations. For instance, it could be the preferred term when communicating to general public about the different intervention strategies and means to address the risk of cognitive impairment. The recent WHO guidelines, which are intended for health care providers/policymakers and wider implementation, also refer to risk reduction instead of prevention (World Health Organization, 2019).

2.2.2 Trends in drug development

During the past few years, the number of disease-modifying agents entering phase I and II AD RCTs has increased slightly, yet remained fairly stable in phase III (Cummings et al., 2018, 2019, 2020). This suggests that promising signals from preclinical and early clinical studies can rarely be translated into clinically meaningful results in larger target populations. Even advancing to the phase III stage does not guarantee success: several large phase III RCTs testing different promising A β focused agents have recently failed or been prematurely discontinued (Egan et al., 2019; Honig et al., 2018; Ostrowitzki et al., 2017; Wessels et al., 2020). In these RCTs, drug treatments did not lead to cognitive benefits, even though only individuals with confirmed A β pathology were selected and the biological target engagement was deemed to be achieved (Kennedy et al., 2016; Klein et al., 2019; Ostrowitzki et al., 2012; Salloway et al., 2018; Yang et al., 2019). Unexpectedly, treatment with β -secretase inhibitors, a thoroughly investigated group of agents, appeared to be associated with cognitive and functional worsening and a more frequent occurrence of neuropsychiatric symptoms (Egan et al., 2019; Henley et al., 2019; Wessels et al., 2020). The anti-A β agent that currently holds the most promise is the antibody aducanumab (Sevigny et al., 2016). Based on data from two large phase III RCTs, both of which were prematurely discontinued after an interim analysis, a decision was recently made to pursue regulatory approval (Biogen, 2019).

A β continues to be the primary therapeutic target in RCTs, but the pipeline is becoming more diverse and now includes a broad range of disease-modifying agents targeting different pathways (Cummings et al., 2020). Major pathways and mechanisms include tau pathology (targeted, e.g., with anti-tau antibodies and aggregation inhibitors), neuroprotection and synaptic plasticity (e.g., SV2A modulators such as levetiracetam), inflammation and immunomodulation (e.g., selective tyrosine kinase inhibitors such as masitinib), and metabolism (e.g., insulin and metformin) (Cummings et al., 2020). In China, an anti-inflammatory agent (GV-971) was approved in November 2019 for the treatment of AD, but there are no

completed global RCTs yet (Cummings et al., 2020). Another proposed strategy, though not yet tested in RCTs, is to target *APOE* (Long & Holtzman, 2019). Combination therapies are also considered an intriguing option. Possibilities identified so far include targeting different steps of a single pathway (e.g., combining a β -secretase inhibitor + $A\beta$ antibody) or targeting multiple different pathways (e.g., combining anti- $A\beta$ + anti-tau agents) (Gauthier et al., 2019). Combining disease-modifying drugs with non-pharmacological approaches, such as lifestyle interventions, could also be relevant. However, no such full-scale RCTs are yet ongoing.

There are also some new trends in RCT design. The selection of target populations is discussed in detail in section 2.2.4.2, but in brief, the focus is shifting towards preclinical disease and asymptomatic at-risk individuals. For example, $A\beta$ antibodies that did not demonstrate an effect in mild/prodromal AD are now being tested in cognitively healthy AD mutation carriers (Cummings et al., 2020; Tariot et al., 2018). However, based on the first results from the Dominantly Inherited Alzheimer Network (DIAN) RCT, it is unclear whether $A\beta$ -targeting agents are the appropriate treatment strategy even in this population. Despite effective $A\beta$ clearance and reduction in levels of tau and other neurodegenerative markers, no significant cognitive benefits were observed (Cummings et al., 2020; Roche, 2020). With respect to outcome measures, the need for different tools at different disease stages is increasingly well recognized. Although further validation is needed, the Preclinical Alzheimer Cognitive Composite and the Alzheimer's Prevention Initiative composite cognitive test score, for example, might be suitable to detect subtle cognitive changes at the asymptomatic stage (Schneider & Goldberg, 2020). Instruments combining cognitive and functional elements or items from several scales (e.g., Clinical Dementia Rating-Sum of Boxes CDR-SB, AD Composite Score ADCOMS) could be preferred for prodromal AD (Schneider & Goldberg, 2020). Biomarkers are now also accepted as RCT outcomes, as outlined in the recent U.S. Food and Drug Administration (FDA) guidelines (2018). At the earliest disease stage (i.e., with biomarker abnormality but an absence of cognitive and functional impairment), accelerated approval could be granted if a drug showed a positive effect on biomarkers. Biomarkers need to correlate with disease progression and clinically relevant cognitive and functional outcomes, but no biomarker so far fully meets these requirements (U.S. Department of Health and Human Services Food and Drug Administration, 2018). Finally, the concept of adaptive design has been introduced in AD RCTs. This is incorporated into the European Prevention of Alzheimer's Dementia Consortium (EPAD) (Ritchie et al., 2016) and DIAN (Bateman et al., 2017) projects, for example. Adaptive design enables the testing of multiple interventions against a shared control group, and doses can be adjusted or intervention arms can be discontinued during the RCT based on biomarker and safety data (Bateman et al., 2017; Ritchie et al., 2016).

2.2.3 Complex multidomain non-pharmacological interventions

In addition to disease-modifying drugs, lifestyle-based and other non-pharmacological approaches have been extensively investigated as potential preventive strategies. The cognitive benefits of single-domain interventions, i.e., those targeting only one risk factor or aspect of lifestyle at a time, have been studied in numerous RCTs. A comprehensive overview of these RCTs is presented in a systematic review by Andrieu et al. (2015). Many of these RCTs have been small and/or short in terms of the intervention or follow-up period. In addition, methods and interventions have not been harmonized, and the results are thus mixed overall. Some positive signals have been reported (e.g., cognitive stimulation intervention in the Advanced Cognitive Training for Independent and Vital Elderly ACTIVE study, Ball et al., 2002; Rebok et al., 2014), but as with drugs, most larger and longer-term RCTs have not been able to clearly show that a single-domain approach could reduce the risk of cognitive impairment. Examples include the Lifestyle Interventions and Independence for Elders (LIFE) study investigating a physical activity intervention (Sink et al., 2015) and the Older People And n-3 Long-chain polyunsaturated fatty acids (OPAL) study investigating a nutritional intervention (Dangour et al., 2010).

Based on recent evidence, one single-domain strategy may hold some promise, namely the intensive management of BP. In the Systolic Blood Pressure Intervention Trial (SPRINT) Memory and Cognition IN Decreased Hypertension (MIND) RCT, over 9,300 non-demented hypertensive individuals aged 50+ years with increased risk of CVD but no diabetes or history of strokes were randomized into an intensive BP control group (goal for SBP < 120 mmHg) and a standard control group (goal for SBP < 140 mmHg) (Williamson et al., 2019). Both groups received lifestyle advice and antihypertensives; any agents were allowed. After a median intervention period of approximately three and follow-up of five years, the intensive treatment group had a significantly lower risk of cognitive impairment (MCI or dementia). These results are encouraging but there are still some caveats. The SPRINT-MIND was a substudy of the SPRINT RCT in which the primary outcome was the incidence of CVD and not cognition. Once the intensive treatment showed clear benefits on vascular health, the RCT was stopped earlier than planned. Thus, it might have been underpowered to detect an effect on the incidence of dementia. It is also unclear whether the intervention had any effects on cognitive test performance.

Given that multiple risk factors contribute to late-life cognitive impairment (yet each individual factor plays a fairly small role) and these factors rarely exist in complete isolation (Livingston et al., 2020), it may not be surprising that single-domain approaches show little or no effects on cognition. Therefore, the focus has shifted towards more complex multidomain interventions, which combine elements from different single-domain interventions and address several risk factors, health behaviors, and lifestyle aspects simultaneously. This approach was previously shown to be feasible and effective in preventing CVD outcomes in individuals with type 2 diabetes but no manifest CVD (Griffin et al., 2011), as well as in those with a history of CVD (Strandberg et al., 2006). Additionally, the multidomain approach has

been successful in preventing diabetes among overweight individuals with impaired glucose tolerance (Tuomilehto et al., 2001). With respect to the prevention of cognitive impairment, several small and/or short-term multidomain RCTs with different target populations and combinations of interventions have been conducted so far. RCTs have targeted individuals with cognitive complaints but no severe impairment (Bamidis et al., 2015; Barnes et al., 2013; Diamond et al., 2015; McEwen et al., 2018), pre-frail or frail older adults (Chen et al., 2020; Romera-Liebana et al., 2018), those with vascular or other dementia risk factors (Anstey et al., 2015; Park et al., 2019; Smith et al., 2010), MCI patients (Bae et al., 2019; Blumenthal et al., 2019; Lam et al., 2015; Rovner et al., 2018), patients recovering from stroke (Bath et al., 2017; Ihle-Hansen et al., 2014; Matz et al., 2015), unselected non-demented community-dwellers (Clare et al., 2015; Lee et al., 2014; Ten Brinke et al., 2020), and mixed patient populations (Schwartz et al., 2019). Overall, the findings of these RCTs are mixed. To date, three large (>1,000 participants), long-term (>12 months), proof-of-concept RCTs have been completed, all in Europe. One of these RCTs, the Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER), reported significant beneficial effects on cognition (Ngandu et al., 2015). The French Multidomain Alzheimer Preventive Trial (MAPT) (Andrieu et al., 2017) and the Dutch Prevention of Dementia by Intensive Vascular Care (preDIVA) (van Charante et al., 2016) did not meet their primary outcomes. These three RCTs are discussed in detail below and in other relevant sections of this thesis.

FINGER was the first of the three RCTs to be completed. FINGER was conducted at six Finnish study sites among 1,260 community-dwellers aged 60–77 years. These individuals did not have significant cognitive impairment or a diagnosis of neurocognitive disorder/dementia, but they were at increased risk of cognitive decline based on their CAIDE risk score and cognitive testing (Kivipelto et al., 2013; Ngandu et al., 2014, 2015). Details of the FINGER RCT are presented in section 4.1.1. In brief, participants were randomized to receive either a multidomain lifestyle program consisting of activities related to physical exercise, nutrition, cognitive training, and management of vascular risk factors, or alternatively regular health advice (control group). The intervention was delivered in individual and group sessions face-to-face. The two-year intervention showed beneficial effects on the primary outcome (change in cognitive performance measured with a neuropsychological test battery NTB, Harrison et al., 2007): cognition improved in both groups but significantly more in the intervention group (Ngandu et al., 2015). To understand the clinical significance of these results and the long-term intervention effects on incidence of cognitive impairment, follow-up assessments took place at approximately five and seven years (three and five years after the end of the RCT). Another follow-up study will take place at approximately 10 years. After the two-year intervention period, some positive effects on clinically relevant outcomes were already observed. The intervention was associated with improved health-related quality of life (Strandberg et al., 2017) and a lower risk of developing new chronic medical conditions (Marengoni et al., 2018) or disability (Kulmala et al., 2019).

The MAPT RCT was conducted at 13 study sites across France, and it included 1,680 individuals aged 70+ years with subjective memory impairment, slow gait, and/or limitations in instrumental activities of daily living, indicating some degree of disability (Andrieu et al., 2017; Vellas et al., 2014). The participants were randomized into four groups: 1) omega-3 supplementation combined with a multidomain lifestyle program consisting of cognitive training and advice related to physical activity and nutrition; 2) a placebo product combined with a lifestyle program; 3) only omega-3 supplementation; and 4) only a placebo product. The lifestyle intervention was delivered primarily in group sessions, but individual motivational interviews and consultations were also organized. The three-year intervention did not have significant beneficial effects on the primary outcome (change in cognitive performance measured with a composite score based on four tests) (Andrieu et al., 2017). Both groups receiving the lifestyle intervention improved while the control groups declined slightly, but differences between the four randomization groups were not significant. Pooled together, the lifestyle groups showed significant improvements compared to the other two groups. The intervention did not appear to have beneficial effects on the more clinically relevant outcomes, such as cognitive-functional performance (change in CDR-SB scores), daily functioning, physical performance, or depressive symptoms.

PreDIVA is the largest and longest of the three RCTs, with an intervention period of six years. Via 116 general practices in 26 health care centers, preDIVA recruited a total of 3,526 participants aged 70–78 years; no specific inclusion criteria related to vascular and dementia risk factors were applied (Richard et al., 2009; van Charante et al., 2016). The general practices were randomized into the intervention and control groups. The intervention group received tailored lifestyle guidance and intensive management of vascular risk factors but no cognitive training or stimulation. The control group received usual care. The intervention consisted of one-on-one sessions with a nurse at the health care center. In contrast to the FINGER and MAPT RCTs, antihypertensives, lipid-lowering drugs, and other medications were initiated as part of the intervention to reduce vascular risk factors. A key difference between the preDIVA RCT and the other RCTs was the choice of the primary outcome (in preDIVA the primary outcome was the incidence of all-cause dementia). After six years, no difference was observed in the occurrence of dementia between the intervention and control groups (van Charante et al., 2016).

In addition to these three completed RCTs, other large long-term RCTs are currently ongoing worldwide in different populations. These include the two-year Agewell.de study with 1,152 German primary care patients (recruitment completed) (Zülke et al., 2019), the two-year U.S. Study to Protect Brain Health Through Lifestyle Intervention to Reduce Risk (U.S. POINTER) with a recruitment goal of 2,000 individuals (ClinicalTrials.gov identifier NCT03688126), and the Multimodal Intervention to delay Dementia and disability in rural China (MIND-CHINA) with a recruitment goal of 3,000 individuals. A five-year RCT with over 2,000 participants is currently at the planning stage in Canada (Can Thumbs Up), and an RCT with

1,400 participants is planned in Latin America (LATAM-FINGER). These RCTs are conducted within the World-Wide FINGERS (WW-FINGERS) global RCT network, and they are described in a recent article by Kivipelto et al. (2020).

A number of smaller-scale RCTs are also planned or are already underway in diverse settings and populations. These include: the Systematic Multi-domain Alzheimer's Risk Reduction Trial (SMARRT) (Yaffe et al., 2019), the Risk Reduction for Alzheimer's Disease (rrAD) (Szabo-Reed et al., 2019), and MINDSpeed (Clark et al., 2019) in the United States; the Efficacy of Multiple Nonpharmacological interventions in individuals with subjective memory decline (E.Mu.N.I) (Rolandi et al., 2020) and the Study of the effects of adapted Tango and multidimensional intervention in pREvention of dementia in aging: developing healthy lifestyle programs (STRENGTH) (Giuli et al., 2020) in Italy; the Active Prevention in People at risk of dementia: Lifestyle, bEhaviour change and Technology to REducE cognitive and functional decline (APPLE-Tree) in the United Kingdom (Cooper et al., 2020); the Body Brain Life for Cognitive Decline (BBL-CD) (McMaster et al., 2018), the RCT of Body Brain Life—General Practice (BBL-GP) and a Lifestyle Modification Programme (Kim et al., 2018), and the Protein Omega-3 aNd vitamin D Exercise Research (PONDER) (Macpherson et al., 2019) in Australia; the SYNERGIC RCT in the United Kingdom and Canada (Montero-Odasso et al., 2018); and the Efficacy of a Multicomponent Cognitive Intervention in Adults with Subjective Cognitive Decline and Mild Cognitive Impairments trial in Taiwan (ClinicalTrials.gov identifier NCT04023032). WW-FINGERS associated RCTs, described by Kivipelto et al. (2020), include: the GOIZ-ZAINDU and the Prevention of Cognitive Decline in *APOE* ϵ 4 Carriers with Subjective Cognitive Decline After EGCG and a Multimodal Intervention (PENSA) RCTs in Spain; the SINGapore intervention study to prevent cognitive impairment and disability (SINGER); the AUstralian-Multidomain Approach to Reduce Dementia Risk by PrOtecting Brain Health with Lifestyle intervention (AU-ARROW); the Japan-multimodal intervention trial for prevention of dementia (J-MINT), and the SUPERBRAIN RCT in South Korea (see also Park et al., 2020).

In addition to lifestyle interventions, the complex intervention concept can be applied also to multinutrient interventions, for example. Currently, the most investigated multinutrient combination is Fortasyn Connect™, which contains omega-3 fatty acids docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA), choline, uridine monophosphate, vitamins B6, B12, C, E, folic acid, phospholipids, and selenium (Van Wijk et al., 2014). Fortasyn Connect™ is based on the rationale that these nutrients act as precursors and cofactors for neuronal membrane phospholipid synthesis (Van Wijk et al., 2014). All of them are needed to optimally stimulate the formation of membranes, which in turn affects synaptic functioning and A β production. Due to these potentially direct disease-modifying effects, multinutrients such as Fortasyn Connect™ lie between pharmacological and non-pharmacological interventions. The cognitive effects of Fortasyn Connect™ have been investigated in mild (Scheltens et al., 2010, 2012) and mild-to-moderate AD

dementia (Shah et al., 2013), and more recently in prodromal AD in the multinational LipiDiDiet RCT (Soininen et al., 2017). Details of the LipiDiDiet RCT are presented in section 4.1.4. The LipiDiDiet medical food intervention did not have a significant effect on the primary outcome (two-year change in cognitive performance, measured with NTB) (Soininen et al., 2017). Some beneficial effects were observed on certain secondary outcomes, such as rate of hippocampal atrophy and change in CDR-SB scores. After three years, the intervention group showed significantly less decline in cognitive performance (NTB), cognitive-functional performance (CDR-SB), and brain volumes than the control group (Soininen et al., 2020).

All the above-mentioned complex multidomain interventions were or are delivered face-to-face. This is usually a resource-intensive approach because RCTs need to recruit and train experienced staff and organize suitable facilities. Moreover, this type of intervention is not easily or widely available and accessible, as only a small group of individuals residing in a specific geographic area can be invited to participate. To overcome these issues, multidomain online-based eHealth and mHealth lifestyle interventions have been designed. Online interventions have been shown to have the potential to improve the vascular risk profile in older adults (Beishuizen et al., 2016). The current programs focusing on cognitive health—most of them being relatively short with a small sample size—are summarized in a recent systematic review and meta-analysis (Wesselman et al., 2019) and they are not discussed exhaustively here. Completed or ongoing large, longer-term (at least six months) eHealth and mHealth RCTs targeting middle-aged or older at-risk individuals are discussed below.

The Healthy Ageing Through Internet Counselling in the Elderly (HATICE) RCT investigated the efficacy of an online-based and coach-supported lifestyle intervention in improving older adults' vascular risk profile and reducing their risk of CVD and dementia (Richard et al., 2016, 2019). Details of the HATICE RCT are presented in section 4.1.2. In brief, HATICE recruited 2,724 individuals aged 65+ years without significant cognitive impairment or a diagnosis of neurocognitive disorder/dementia, but with at least two vascular risk factors and/or CVD or diabetes. Participants entered the intervention arm (platform with advice on risk factor management and the possibility to interact with a coach) or the control arm (platform with general advice and no contact with a coach). The primary outcome was the change in vascular risk profile over 1.5 years, calculated as the change in a composite score of three vascular risk factors (SBP, low-density lipoprotein LDL, BMI). Other key outcomes were changes in individual vascular risk factors, the risk of CVD and dementia based on risk scores, cognitive performance, and the incidence of CVD. The vascular risk profile improved in both groups, but the intervention was reported to have significant beneficial effects (Richard et al., 2019). A reduction was observed in the dementia risk (CAIDE score), while no between-group differences were observed in relation to cognitive performance.

Another completed eHealth lifestyle intervention targeting at-risk individuals is the Innovative Midlife Intervention for Dementia Deterrence (In-MINDD), a six-

month feasibility RCT in four European countries (O'Donnell et al., 2015). In this RCT, participants were required to have at least one modifiable risk factor (a vascular risk factor, CVD, diabetes, depression, lack of cognitive stimulation, or sedentary lifestyle). In total, 451 non-demented individuals aged 40–60 years were randomized into two groups. Participants in the intervention group had the opportunity to discuss their LIBRA dementia risk score with a health care professional, and they got access to an online platform with advice on how to manage their risk factors as well as a possibility to set personal lifestyle goals. The control group received general advice. At the end of the study, the control group was also given access to the platform and all participants received information about their LIBRA scores. The primary outcome was the change in the LIBRA score. No significant difference was observed between the intervention and control groups after the six-month intervention period (Irving, no date). Other endpoints in this RCT were related to the feasibility and acceptability of the intervention.

Two large, long-term, lifestyle-based eHealth or mHealth RCTs are currently ongoing: the three-year Australian Maintain your Brain (MYB) study targeting 6,236 individuals aged 55–77 years (Heffernan et al., 2019), and the 1.5-year United Kingdom-China collaboration project Prevention of Dementia Through Mobile Phone Applications (PRODEMOS, registration number ISRCTN15986016), which plans to recruit 2,400 individuals with a similar age range to that in the MYB RCT (Prodemos Project AMC, 2018). Both RCTs target non-demented older adults with several modifiable risk factors. In the MYB RCT, participants are required to have at least two risk factors that are different enough to ensure eligibility in at least two of the four online intervention modules. Each module focuses on a different dementia risk factor or group of risk factors (physical activity, nutrition, brain training, and peace of mind dealing with depression/mental health). The control group gets access to the online platform but receives general information instead of tailored advice. In the PRODEMOS study, the focus is on individuals with low socioeconomic status and poor access to health care. The intervention resembles that of the HATICE RCT but is delivered through a mobile app.

In addition to these RCTs targeting individuals with dementia risk factors, a few large projects focus on the more unselected general population. For example, in the Dutch Brain Aging Monitor study, which was not an RCT, nearly 3,000 individuals who registered on a website were given the opportunity to set lifestyle goals based on their risk profile (Aalbers et al., 2016). In an ongoing RCT in Thailand (ClinicalTrials.gov identifier NCT02967406), a combination of a three-year digital lifestyle intervention and face-to-face support is being tested among 45–75-year-old community-dwellers without dementia and CVD. The aim is to recruit 3,600 participants and the primary outcome is the incidence of dementia after 10 years.

2.2.4 Challenges and considerations in trial design and intervention implementation

The original studies in this thesis focus on some of the widely recognized key challenges and considerations in the design, conduct, and implementation of dementia prevention interventions. These include but are not limited to the selection and recruitment of target populations, participant engagement and adherence, and attitudes towards dementia and its prevention, including poor knowledge and the stigma of dementia. These topics and recent relevant literature are discussed in the next sections. Section 2.2.4.1 focuses on the role and potential added value of qualitative research in exploring these issues in RCTs.

2.2.4.1 Complex trials call for complex methods: embedding qualitative research in trials

Qualitative research embedded in RCTs is becoming increasingly common, in particular in RCTs investigating complex interventions to change health behavior. In this type of research, interviews or focus group discussions are conducted with participants, study partners, or study staff to understand their perceptions of different trial-related aspects. Qualitative research embedded in RCTs has the potential to facilitate recruitment and generate hypotheses as to why a particular intervention did or did not show any benefits (O’Cathain et al., 2013; Richards et al., 2019).

In their systematic review of qualitative research embedded in RCTs, O’Cathain et al. (2013) identified four common topics and areas of research. First, qualitative research can aim to optimize the content and delivery of interventions by focusing on participant experiences of different intervention components, the perceived benefits of the intervention, or the feasibility, acceptability, and implementation of the intervention in practice. Second, its focus can be on the RCT design and conduct, with the aim to investigate experiences with recruitment and RCT procedures, as well as reasons for participation, non-participation, non-adherence, or drop-out. Furthermore, it can aim to identify local adaptations that could improve the RCT conduct in multinational or multicenter settings. Third, qualitative studies can deal with RCT outcomes: they can explore which outcomes participants consider important and whether individual attitudes and preferences could explain the observed differences in the response to treatment. Finally, the research questions in qualitative studies can be related to the target condition itself. These studies explore the participants’ health behaviors as well as their attitudes, beliefs, and experiences with the disease.

Depending on the research question, qualitative studies embedded in RCTs can take place before, during, or after the RCT. The latter approach is common in pilot or feasibility studies in which the results might guide the planning of larger efficacy RCTs. The systematic review mentioned above found that most embedded qualitative studies were conducted after the RCT and dealt with participant

experiences of the intervention; only 30% of the studies were conducted prior to randomization (O’Cathain et al., 2013). However, the authors speculated that qualitative studies might often be planned and undertaken in RCTs, but the results are not always published.

Qualitative research has been conducted in many lifestyle RCTs targeting different chronic health conditions and populations. For example, in an intervention designed to support older adults’ mental and physical wellbeing (Lifestyle Matters), qualitative research was undertaken to explore the participants’ perceptions of the recruitment process (Chatters et al., 2018) as well as their experiences of the intervention and its perceived effects after the RCT (Chatters et al., 2017; Mountain et al., 2020). Aspects related to intervention feasibility and acceptability and its means of delivery have been explored in RCTs focusing on chronic pain management (Nøst et al., 2016), obesity (Kozica et al., 2015), and diabetes prevention (Beasley et al., 2019), for example. In one RCT targeting older adults at risk of CVD, diabetes, or depression, qualitative studies were planned before and after the RCT to assess how the participants perceived the intervention and what their attitudes were towards lifestyle changes (Sahlen et al., 2013). In one diabetes prevention intervention among at-risk older adults, interviews were conducted to assess how the participants perceived their own health behavior and how they understood the concept of being ‘at risk’ of diabetes (Følling et al., 2016).

With respect to lifestyle-based dementia prevention interventions, only a few RCTs have reported results from qualitative substudies. In the preDIVA RCT, a subsample of participants were interviewed on average four years after the start of the intervention with the aim to understand their initial reasons for participation, and to investigate which trial- or intervention-related features were important for their active engagement in and adherence to the intervention (Ligthart et al., 2015). A qualitative substudy in the Agewell pilot RCT explored the acceptability of the intervention and potential barriers (Nelis et al., 2018). In the In-MINDD pilot RCT, interviews were conducted to understand how the LIBRA score as a measure of dementia risk was perceived by the participants and whether the awareness of this risk affected their willingness to engage in the intervention and improve their lifestyles (Irving, no date). Another aim in this project was to assess the feasibility and acceptability of the intervention and its means of delivery (i.e., an online platform). Indeed, in eHealth interventions, interviews or focus groups with the potential end-users can be helpful to ensure that the online platforms are appropriately designed and appear attractive and interesting (Jongstra et al., 2017; Wesselman et al., 2018).

2.2.4.2 Selection and recruitment of target populations

In dementia prevention RCTs, selecting and enrolling the appropriate target population is considered one of the key determinants for success. Following the frequent failures of RCTs, it has become clear that targeting mild to moderate AD patients with already substantial impairment is not an ideal strategy to investigate

disease-modifying therapies. Brain pathology is suggested to occur and accumulate as early as decades before the onset of the first symptoms (at least when measured with the currently available cognitive and functional scales) (Jack et al., 2010, 2013), which is why reducing or reversing the pathology at such an advanced stage is unlikely to result in clinical benefits. The majority of the ongoing and recently completed/terminated pharmacological RCTs have, therefore, recruited individuals at pre-dementia stages. Various enrichment and/or diagnostic confirmation strategies have been applied in order to identify homogeneous populations at a high risk of cognitive decline. The most common strategy, in particular in prodromal AD drug RCTs, is to confirm the A β status prior to enrolment. Grill et al. (2019) reviewed the eligibility criteria of all ClinicalTrials.gov registered RCTs recruiting or planning to recruit individuals with prodromal AD or MCI due to AD and concluded that 70% of the RCTs required A β positivity for eligibility. This requirement stems from experiences in the earlier RCTs, which relied on clinical inclusion criteria. In RCTs investigating A β antibodies bapineuzumab and solanezumab, for example, up to 20% of randomized participants were A β negative (Salloway et al., 2014; Siemers et al., 2016).

A β assessment has also been used to detect preclinical AD in cognitively healthy individuals (Sperling et al., 2014). Another relevant enrichment strategy in this population is selection based on an AD mutation (Bateman et al., 2017; Tariot et al., 2018) or *APOE* genotype, alone or combined with other genetic and non-modifiable factors (Burns et al., 2019; Lopez Lopez et al., 2019). In both prodromal and preclinical AD, the research diagnostic criteria for AD could facilitate recruitment and help match individuals with a desired biological profile with the right investigational therapy. Some RCTs have already incorporated these strategies (Coric et al., 2015; Ostrowitzki et al., 2017; Soininen et al., 2017; Wessels et al., 2020). Many simulation studies (Bertens et al., 2017; Holland et al., 2012; Insel et al., 2015b; Wolz et al., 2016), but not all (Schneider et al., 2010), have shown that recruiting biologically more homogeneous participants (i.e., those with the most evidence for AD-typical pathology) could reduce the sample sizes required to observe a treatment effect and lead to shorter RCTs. Most of these studies were conducted in the Alzheimer's Disease Neuroimaging Initiative (ADNI) cohort. Similar findings were reported in one study that used data from a large real-life phase III RCT targeting mild-to-moderate AD (Ballard et al., 2019). This study investigated the A β status, *APOE* genotype, and family history as potential enrichment factors.

As opposed to pharmacological RCTs where biomarker-based selection is often warranted due to the drug's specific mechanism of action, complex multidomain lifestyle interventions—particularly if community-based—can have broader and more pragmatic eligibility criteria. However, the question of the optimal target population still remains in these RCTs (Richard et al., 2012). The timing of the intervention is one key challenge. As discussed earlier in this literature review, mid-life might be the optimal time to intervene due to the time-dependent nature of many vascular risk factors, but it is not feasible to conduct such long RCTs. The few large

multidomain RCTs conducted so far all targeted older adults, although the FINGER participants were on average somewhat younger than the MAPT and preDIVA participants (69 vs. 75 years) (Andrieu et al., 2017; Ngandu et al., 2015; van Charante et al., 2016). Another consideration is the baseline cognitive performance. The FINGER, MAPT, and preDIVA RCTs all targeted individuals without significant cognitive impairment, but FINGER screened individuals with a range of cognitive tests to identify those with a cognitive performance at the mean level or slightly lower than expected for age and to exclude those with a very good performance. This was pursued in the MAPT RCT as well, by including individuals with subjective memory complaints and/or signs of frailty. In contrast, the preDIVA RCT did not apply any cognitive selection criteria. Finally, it is unclear to what extent the target population should be enriched for vascular and other modifiable risk factors of interest. In the FINGER RCT, the CAIDE score was used in participant selection, whereas modifiable risk factors were not taken into account in recruitment for the MAPT or preDIVA RCTs.

In addition to participant selection, effective recruitment is a challenge in AD and dementia RCTs. For example, in large phase III drug RCTs it can take several years to reach the recruitment goal (Cummings et al., 2016). This is partly due to extensive eligibility criteria and exclusion of a large group of older adults. For instance, older adults usually have medical conditions other than AD or cognitive impairment, but drug RCTs might exclude frail individuals or those with multiple co-morbidities and medications due to safety concerns. Contraindications for lumbar puncture or neuroimaging may prevent participation, especially in drug RCTs. Furthermore, the common requirement of a study partner to provide information about the participant's status and wellbeing excludes those without a family or close friend. A systematic review estimated that among memory clinic patients diagnosed with AD dementia, only 26% met the eligibility criteria for pharmacological RCTs (Cooper et al., 2014). Less than half of these patients (43%) were willing to participate, meaning that only approximately one out of 10 patients was ultimately enrolled in a trial.

In the new prevention RCTs that target earlier disease stages, cognitive eligibility criteria are stricter and biomarker testing is integrated into the process, and this could make recruitment particularly challenging. Requirements for abnormal biomarkers lead to fewer eligible individuals. For example, approximately 35–45% of the ADNI subjects with MCI were shown to be A β negative, depending on the study and method used to assess the A β status (CSF or PET) (Grill et al., 2019; Landau et al., 2016). Indeed, screening failure rates have been high in some of the recent phase II or III RCTs targeting early prodromal and/or mild AD: only around 20–30% of those who agreed to participate and underwent screening were randomized (Coric et al., 2015; Egan et al., 2019; Ostrowitzki et al., 2017; Wessels et al., 2020). Being biomarker negative despite having the right clinical and cognitive profile was a key reason behind the screening failure in some of these RCTs. In a recent study on participant enrichment in mild-to-moderate AD RCTs, the authors concluded that selection

based on *APOE* $\epsilon 4$ and/or $A\beta$ positivity would be the ideal strategy, but less than 20% of the subsample with data available met these criteria (Ballard et al., 2019).

The requirement for biomarker positivity not only reduces the number of eligible individuals but also affects the willingness to participate in RCTs. Risks and fear of invasive treatments and procedures, such as lumbar punctures or PET imaging, are a barrier to enrollment, especially among those with only mild symptoms or no symptoms at all (Grill et al., 2013; Nuño et al., 2017). Recruitment for complex multidomain lifestyle interventions might be slightly easier because eligibility criteria are usually kept to the minimum. In addition, attitudes might in general be more positive towards non-pharmacological than pharmacological interventions (Calamia et al., 2016). In the FINGER, MAPT, and preDIVA RCTs, approximately 45–65% of those assessed for eligibility at the screening stage were ultimately randomized (Andrieu et al., 2017; Ngandu et al., 2015; van Charante et al., 2016).

One proposed strategy to streamline recruitment in future RCTs and to potentially engage individuals who previously may not have been effectively reached is to develop large online study registries. Currently available registries include the Brain Health Registry (Weiner et al., 2018), Alzheimer’s Prevention Registry (Banner Alzheimer’s Institute, 2020; Langbaum et al., 2020), TrialMatch (Alzheimer’s Association, 2020), and GeneMatch (Langbaum et al., 2019) in the United States, Great Minds in the United Kingdom (Dementias Platform UK, 2020), and hersenonderzoek.nl in the Netherlands (Alzheimercentrum Amsterdam, no date). Registries can be quite simple or serve as detailed data repositories. Simple registries require only basic demographic information at the first stage and there are no exclusion criteria. When recruiting for an RCT, individuals who have shown an interest in studies and given permission to be contacted on this platform could be pre-screened and invited to participate.

While eligibility criteria are necessary in RCTs to ensure that the interventions are administered to the appropriate target populations, the study population should ideally be as representative of the true end users of the treatment as possible. Poor representativeness might limit the generalizability of the findings. As mentioned earlier, RCT participants tend to be healthier in general than non-participants. Moreover, individuals with AD dementia who meet the eligibility criteria and enroll in RCTs tend to be younger, more educated, and more often men than those who are ineligible (Cooper et al., 2014). Research done in preclinical AD found that individuals representing ethnic minorities might be less likely to enroll in RCTs (Zhou et al., 2017). Similar issues might be present also in complex multidomain lifestyle interventions, but little is currently known about the study population representativeness in these studies. In the FINGER RCT, those who underwent screening were younger, more often women, and had a higher level of education than those who were invited but decided not to attend (Ngandu et al., 2014). They also had fewer vascular risk factors and less often a history of CVD. In the MAPT RCT, such detailed information about the target population was not available. However, based on the high proportion of participants with a university level education

(approximately 30%), the study population might not have been entirely representative of the general older population (Andrieu et al., 2017). Issues with representativeness might occur also in eHealth interventions targeting older adults. Although Internet use is on the rise among older adults (European Union, 2019) and those familiar with the Internet might be highly interested in eHealth (Wesselman et al., 2018), individuals with no experience or a negative attitude towards using the Internet might be more skeptical and reluctant to take part (De Veer et al., 2015). Compared with non-participants, older adults participating in eHealth RCTs are more frequent Internet users and more confident in their computer skills, but also younger and more educated and socially active (Poli et al., 2019). They also have better cognition. The FINGER research team also reported that age, education level, cognition, and previous use of computers were associated with adherence to the computerized cognitive training program (Turunen et al., 2019).

2.2.4.3 Participant engagement and adherence

Participant engagement and adherence to interventions is an important consideration, in particular in dementia prevention RCTs that focus on lifestyle modification and risk factor self-management. Adherence to recommendations and the intervention protocol is a key determinant of treatment efficacy, as shown for example in type 2 diabetes prevention research (Dunkley et al., 2014). Yet, changing behavior and adopting a healthier lifestyle is difficult. Individuals also do not always perceive lifestyle changes as necessary even if risk factors are present (Brotons et al., 2012; Kotseva et al., 2020). Another challenge is to sustain healthier habits and stay engaged during the entire intervention period, which usually needs to be long in prevention RCTs that target individuals without significant cognitive impairment (Richard et al., 2012). In the FINGER, MAPT, and preDIVA RCTs, discontinuation rates tended to increase with increasing study duration. The drop-out rate was 11% in the two-year FINGER (Ngandu et al., 2015), 21% in the three-year MAPT (Andrieu et al., 2017), and 38% in the six-year preDIVA RCT (van Charante et al., 2016).

In addition to the mere discontinuation rate, in complex multidomain RCTs it is also informative to measure active participation in the different intervention domains. However, it is noteworthy that adherence to intervention activities and adherence to healthy lifestyle changes are two different aspects (the latter can also be assessed among control group participants who often receive general care or advice). Currently, there is no widely accepted definition for adherence to multidomain preventive interventions, and it is unclear how much intervention exposure is required for optimal effects—and how little would be enough to obtain some benefits. In the preDIVA, MAPT, and FINGER RCTs, adherence to the multidomain intervention decreased with increasing intervention intensity and complexity (Beishuizen et al., 2017; Coley et al., 2019). In the least demanding preDIVA intervention (i.e., only nurse consultations), the adherence rate was 78% when defined as attendance in at least two-thirds of all scheduled sessions (Beishuizen et al., 2017). In the MAPT RCT, there were two and in the FINGER RCT four separate

intervention components. Using the same definition of adherence than in preDIVA, 61% of MAPT and 19% of FINGER participants engaged simultaneously in all components (Coley et al., 2019). With respect to individual intervention components, adherence to the more passive components was high (e.g., 93% for vascular risk monitoring visits in the FINGER RCT and 76% for omega-3/placebo supplementation in the MAPT RCT), but substantially lower for activities requiring more personal effort (e.g., approximately 50% and 25% for the FINGER exercise and cognitive training sessions, respectively) (Coley et al., 2019). Some factors, including higher age, poorer cognition, depressive symptoms, and smoking, were identified as potential predictors of a lower adherence or non-adherence, but there was no consistent pattern and results varied across the RCTs and different intervention components (Beishuizen et al., 2017; Coley et al., 2019).

With respect to eHealth and mHealth interventions, measuring adherence is usually less straightforward than in face-to-face interventions. This is because it can be defined in many different ways (Sieverink et al., 2017). Examples include recording the number of logins or total time spent on the website or app, the number of webpages accessed and viewed, or the number of certain features used. Apart from In-MINDD and HATICE, the completed eHealth RCTs have not reported detailed adherence data, and the determinants of engagement are unknown (Wesselman et al., 2019). In the In-MINDD study, an algorithm was used to study which webpages related to different risk factors were most frequently visited (Irving, no date). Diet, exercise, and BP control appeared the most interesting topics, whereas only approximately 5% of all views were related to weight management and cognitive activities. The number of logins per participant or the actual use of the program for the intended purpose (e.g., the number of lifestyle goals set) was not recorded in the In-MINDD study. In the HATICE study, the median number of monthly logins in the intervention group was rather low, approximately two (Richard et al., 2019). The platform was used most frequently during the first six months, but the number of logins decreased gradually over time. Nevertheless, around 90% of the participants contacted the coach actively at least once, and around 30% sent more than 10 messages. Approximately 90% also set at least one lifestyle goal; most goals were related to weight management or physical activity. A few qualitative and mixed-method studies have explored which factors and features of an online program would facilitate its use and improve participant engagement and adherence (Jongstra et al., 2017; Wesselman et al., 2018). Important considerations identified in these studies were user-friendliness (e.g., no difficult passwords or user accounts are needed to login); a clear structure and visually pleasing layout; personalized, comprehensive, and up-to-date content; possibility to receive reminders; and positive and encouraging feedback focusing on health rather than disease (e.g., referring to risk factors as 'health factors').

Regardless of their design or means of delivery, when planning meaningful and engaging multidomain interventions, it is of interest to consider older adults' motivations and expectations towards participation. In the context of other chronic

conditions, altruistic reasons and a willingness to help, as well as obtaining personal benefits such as health gains, have been highlighted as the most important incentives to participate in RCTs (Fearn et al., 2010; Halpern et al., 2003; Nielsen & Berthelsen, 2019; Reed et al., 2013; Tolmie et al., 2004). These two reasons are also the most common motivators in AD and dementia research, but little is known about the reasons for participating specifically in multidomain prevention RCTs. Altruistic reasons identified in previous studies include the willingness to help (loved ones, future generations, or others in the same situation) (Bardach et al., 2018; Grill et al., 2013; Nuño et al., 2017) as well as benefitting society by advancing science and contributing to the development of new treatments (Calamia et al., 2016; Cox et al., 2019; Jefferson et al., 2011; Lawrence et al., 2014). Common personal reasons include receiving regular medical check-ups and feedback about one's own health; continuity of care and getting support from health care professionals; the need for more information; the desire to reduce personal dementia risk; and access to new effective medications (Calamia et al., 2016; Cox et al., 2019; Grill et al., 2013; Lawrence et al., 2014; Solomon et al., 2012). Diagnostic confirmation and being informed about one's prognosis are of particular importance for those with manifest cognitive impairment (Lawrence et al., 2014). Other reasons, such as having nothing to lose or no specific reason to decline, receiving medical care free of charge, or meeting and connecting with other people in the same situation, are usually listed as less important reasons (Bardach et al., 2018; Cox et al., 2019; Grill et al., 2013; Solomon et al., 2012).

2.2.4.4 Limited knowledge and the stigma of dementia

Older adults' poor understanding of dementia and the surrounding stigma are a major challenge to research participation as well as implementation and uptake of preventive interventions. Stigma of dementia is common, not only in the general public but also among health care professionals (Herrmann et al., 2018). Even affected individuals can experience and express a stigma (Ashworth, 2020; Xanthopoulou & McCabe, 2019). One study showed that older adults who were aware of their diagnosis experienced more anxiety and a poorer quality of life than those who were unaware of the diagnostic label, regardless of the actual symptoms and their impact on everyday life (Stites et al., 2017). Stigma as a concept refers to the myths, misconceptions, negative feelings, and stereotypes that are thought to apply to all persons sharing a specific feature, in this case a diagnosis of dementia. Dementia and related disorders are commonly associated with feelings of pity, shame, and fear, as well as social distancing and discrimination (Stites et al., 2018; Xanthopoulou & McCabe, 2019). Concerns over loss of control and competence are common, and individuals living with dementia are perceived as incapable of being involved in any decision-making concerning their own health and wellbeing (Stites et al., 2018; Xanthopoulou & McCabe, 2019). Stigma can have many negative consequences. It can discourage people to actively seek help for early symptoms and, thus, delay a timely diagnosis and early intervention (Herrmann et al., 2018; Werner

et al., 2014). Because of the stigma and fear of possible consequences, people might also be suspicious towards gene and biomarker testing (Milne et al., 2018; Stites et al., 2018). Current prevention RCTs often rely on these assessments, and stigma might therefore be a barrier to research and RCT participation.

Stigma and knowledge of dementia are tightly linked. Those with limited knowledge and understanding often express views and opinions indicating a stigma (Herrmann et al., 2018). Surveys conducted around the world have consistently reported that the general knowledge of dementia is poor (Cations et al., 2018; Farina et al., 2020; Liu et al., 2019). Dementia is often associated with high age and perceived as a natural part of getting old which cannot be prevented. According to one systematic review of surveys, approximately half of the respondents held these beliefs (Cations et al., 2018). In a recent survey on attitudes to dementia, which included nearly 70,000 respondents from 155 countries, 70% of the general public and 62% of health care professionals thought that dementia was not a disorder but a part of normal aging (Alzheimer's Disease International, 2019). In total, 25% agreed with the statement that nothing can be done to prevent dementia, and 88% of the respondents named *APOE* as a cause of the disease. Approximately half of the respondents in this survey (55%) agreed that an unhealthy lifestyle could contribute to dementia. Some other studies have suggested that people might recognize some risk and protective factors better than others (Heger et al., 2019). Lack of knowledge could be a barrier to dementia prevention and prevention research because it could hinder people from adopting a brain-healthier lifestyle (Bosco et al., 2020; Heger et al., 2019; Smith et al., 2015). Initiatives to improve knowledge are currently underway, including an RCT to investigate the efficacy of an online intervention in reducing the stigma that surrounds dementia (Kim et al., 2019). Qualitative explorations of older adults' knowledge, potential knowledge gaps, and barriers to engagement in prevention have been incorporated into some prevention RCTs (Cooper et al., 2020; Irving, no date; O'Donnell et al., 2015), but evidence is scarce.

3 AIMS OF THE STUDY

By combining quantitative and qualitative approaches, this thesis aims to offer insights into the selection and engagement of target populations in dementia prevention RCTs. The focus was on 1) assessing heterogeneity in the response to a multidomain preventive intervention to understand the prevention potential in different subgroups, 2) investigating older adults' motivations and attitudes towards prevention and participation in a prevention RCT, and 3) exploring risk factors, AD biomarkers, and research diagnostic criteria for AD as well as their impact on disease progression in two different cohorts to inform participant selection for future RCTs.

The specific aims of the studies were as follows:

I. To investigate whether participant baseline characteristics, including demographics, socioeconomic status, cognitive performance, and the vascular risk profile, modified the cognitive response to intervention in a multidomain lifestyle prevention RCT (FINGER) targeting at-risk older adults without significant cognitive impairment.

II. To investigate reasons for participation in a multinational, multidomain eHealth lifestyle prevention RCT (HATICE) targeting at-risk older adults without significant cognitive impairment.

III. To explore the knowledge of and attitudes towards dementia and prevention among older adults participating in a multinational, multidomain eHealth lifestyle prevention RCT (HATICE).

IV. To study the prognosis of memory clinic patients with MCI and normal CSF A β levels and investigate AD biomarkers, clinical characteristics, and vascular risk factors as potential predictors of progression to dementia.

V. To apply the research diagnostic criteria for AD to the prodromal AD population enrolled in the multinational LipiDiDiet RCT and investigate the impact of biomarker profiles on cognitive/functional decline and progression to dementia.

4 SUBJECTS AND METHODS

The studies presented in this thesis were conducted using data from three large prevention RCTs (Studies I–III & V) and one observational memory clinic cohort (Study IV). The study designs and methods are summarized in Table 2. The FINGER and HATICE studies are RCTs investigating the effects of a multidomain lifestyle intervention on cognition, either as a primary (FINGER) or secondary outcome (HATICE). A key difference between these RCTs is the delivery of the intervention (a traditional face-to-face vs. eHealth approach). The LipiDiDiet RCT investigated the effects of a multinutrient medical food product on cognition. Study I investigated the intervention effects in subgroups of participants (in FINGER), studies II and III focused on RCT participation and the target population perspective (in HATICE), and studies IV and V investigated biomarker profiles and disease progression in two different cohorts (the LipiDiDiet and memory clinic cohorts).

All study populations were at increased risk of cognitive decline and dementia, thus representing potentially attractive target populations for preventive strategies. The FINGER and HATICE participants were mostly community-dwelling older adults who did not have significant cognitive impairment but were at risk of future cognitive decline based on their vascular and lifestyle-related risk profile (both RCTs) as well as their cognitive performance (FINGER). The memory clinic and LipiDiDiet cohorts consisted of individuals with mild cognitive impairment and varying levels of evidence for underlying AD-type pathology. The memory clinic patients in Study IV had CSF A β within the normal range (based on laboratory cut-offs) and were assumed to have a lower risk of AD-type dementia. The LipiDiDiet participants met the IWG-1 criteria for prodromal AD and were at higher risk of AD dementia.

Table 2. Summary of subjects and methods.

Study	Setting	Design	Population	Data	Outcomes
I	FINGER RCT	Longitudinal; pre-specified subgroup analysis	Community-dwelling at-risk older adults with no significant cognitive impairment (N=1,260)	Demographics, socioeconomic status, cognition, medical history, vascular risk factors & risk profile	Change in cognition (NTB total, memory, executive function & processing speed scores)
II	HATICE RCT	Cross-sectional; substudy (ACCEPT-HATICE)	At-risk older adults with no significant cognitive impairment (N=343; N=15) ^a	Questionnaire, semi-structured interviews	Reasons for participation in the HATICE RCT
III			Semi-structured interviews	Knowledge and perceptions of dementia and prevention	
IV	University hospital memory clinic	Longitudinal; retrospective review of medical records	Patients with MCI and normal levels of CSF A β (N=318)	Demographics, cognition, medical history, vascular risk factors, <i>APOE</i> , biomarkers, CAIDE score	Progression to dementia
V	LipiDiDiet RCT	Longitudinal; post hoc analysis	Patients with prodromal AD, i.e. mild memory impairment and AD-biomarkers (N=287) ^b	Demographics, cognition, biomarkers, <i>APOE</i>	Change in cognition and function (NTB composite, total, memory, executive function & CDR-SB scores); progression to dementia

^a Subsample of HATICE participants (N=2,724); N=343 in Study II (two individuals did not fill in the questionnaire but were interviewed) and a subsample of N=15 in Study III

^b Subsample of LipiDiDiet participants (N=311); all participants with centrally analyzed biomarkers at baseline

4.1 STUDY SETTINGS AND DESIGNS

4.1.1 The FINGER trial (Study I)

The FINGER RCT targeted community-dwelling older adults who did not have any significant cognitive impairment when the RCT started, but who were at increased risk of cognitive decline (Kivipelto et al., 2013; Ngandu et al., 2015). A detailed description of participant selection and eligibility criteria can be found in section 4.2.1. Recruitment took place between 2009 and 2011, and the two-year RCT was completed in 2014. A total of 2,654 individuals were screened and 1,260 were randomized at a 1:1 ratio into the lifestyle intervention (N=631) and control groups (N=629). The primary outcome studied was the change in cognitive performance over two years, defined as a change in the NTB total score. Scores for individual cognitive domains were specified as the secondary cognitive outcomes. Other secondary endpoints were changes in individual vascular risk factors (BP, BMI, blood lipids, glucose), lifestyle (diet, physical activity), physical performance, and depressive symptoms. Safety and compliance were also assessed. The intervention demonstrated overall beneficial effects on the primary endpoint, which is why the pre-specified subgroup analyses performed in Study I were warranted to investigate participant baseline characteristics as potential modifiers of the benefits and response to the intervention.

In the FINGER RCT, the multidomain lifestyle-based intervention was delivered face-to-face by an experienced multidisciplinary team of trained nurses, physicians, psychologists, nutritionists, and physiotherapists, both individually and in small groups. Complete double-blinding was difficult to achieve due to the nature of the intervention, but outcome assessors were blinded to the randomization status and the intervention/control group allocation was not disclosed to the participants. The multidomain intervention followed national and international recommendations and guidelines (National Nutrition Council, 2005; Nelson et al., 2007; Working group appointed by the Finnish Medical Society Duodecim and the Finnish Hypertension Society, 2009; Working group appointed by the Finnish Medical Society Duodecim and the Medical Advisory Board of the Finnish Diabetes Society, 2007; Working group set up by the Finnish Medical Society Duodecim and Finnish Society of Internal Medicine, 2009) and built partly on previous studies (Dahlin et al., 2008; Komulainen et al., 2010). The focus was on four components: diet, physical activity, cognition, and improvement and management of vascular risk factors. Social engagement and support were linked to each of these components and can be considered a fifth constituent. To facilitate engagement in and adherence to the intensive lifestyle program, the intervention components were introduced gradually. The two-year intervention program included a total of 10 sessions of dietary counselling (three individual and seven group sessions), 10–11 cognitive group sessions, two six-month periods of independent computer-based cognitive training (72 sessions per period, 10–15 minutes per session), three to eight weekly exercise sessions (one to three resistance and two to five aerobic training sessions; lower

frequency at the beginning), and six additional physician or nurse consultations to further address potential vascular risk factors. The number and content of intervention sessions was similar for all participants regardless of their individual risk profile or personal interests. Nevertheless, participants received tailored instructions and advice based on their lifestyle and health status. For example, the individual dietary counselling meetings focused on each person's own dietary challenges and habits. All the intervention activities were also progressive in nature. One example were the resistance and aerobic training programs, which were regularly adjusted. Another example was cognitive training, where the tasks became increasingly difficult with improved performance. At baseline, all participants both in the intervention and control groups received advice and written material about dietary and exercise recommendations to manage vascular risk factors. Afterwards, the control group was offered regular health advice during the visits that were intended for all participants (three nurse visits for measurements and blood tests, a physician's visit at the end). As the FINGER intervention was non-pharmacological, both the intervention and control group participants were advised to contact their regular health care provider if the initiation or adjustment of medication was deemed necessary.

4.1.2 The HATICE trial and ACCEPT-HATICE substudy (Studies II & III)

Studies II & III are based on the HATICE RCT, an 18-month eHealth RCT conducted in Finland (in the Kuopio and Joensuu area in Eastern Finland), France (in the Toulouse area), and the Netherlands (in Amsterdam) (Richard et al., 2016, 2019). Recruitment took place between 2015 and 2016, and the RCT was completed in 2018. The HATICE RCT investigated the efficacy of an Internet-based multidomain lifestyle intervention in promoting vascular health and preventing CVD and cognitive decline. The primary outcome was the change in the vascular risk profile, which was defined by a composite score comprising SBP, LDL, and BMI. Secondary outcomes included changes in the individual vascular risk factors, physical activity, and CVD and CAIDE risk scores. Incident CVD and cognitive functioning were also listed as secondary outcomes. The use of the online platform and login frequency were also assessed in the study.

Like the FINGER RCT, HATICE targeted older adults who did not have any significant cognitive impairment when the RCT started, but who were at increased risk of cognitive decline and had the potential for risk reduction (for a detailed description of participant selection and eligibility criteria, see section 4.2.2). A total of 4,857 individuals were screened and 2,724 (1,471 in the Netherlands, 885 in Finland, and 368 in France) were randomized at a 1:1 ratio into the multidomain lifestyle intervention (N=1,389) and control groups (N=1,335). In contrast to the FINGER intervention, the HATICE intervention was delivered entirely online through a secure Internet platform designed for this RCT (Barbera et al., 2018; Jongstra et al., 2017). The intervention focused on seven different risk factors: hypertension, hyperlipidemia, obesity, smoking, physical inactivity, unhealthy

dietary habits, and diabetes. Recommendations followed national and European evidence-based guidelines and were tailored according to the participants' lifestyle and health status (Barbera et al., 2018). Health care professionals (referred to as lifestyle coaches in this RCT) encouraged and motivated the participants to independently manage and reduce the risk factors relevant for them. The participants were able to set concrete personal goals on the online platform, for example they could enter BP measurements or blood test results to receive feedback and track their own progress. They could also view educational content (videos, written material, games) and connect with fellow participants. Coaches monitored progress remotely. The control group participants were offered access to a website with regular generic health advice and no possibility to interact or discuss matters with a coach. All participants received an online questionnaire every three months and a phone call after one year to collect outcome-related information. During this call, the coaches motivated the intervention group participants to sustain their lifestyle changes and/or encouraged them to set new goals. Similarly to the FINGER intervention, the HATICE intervention did not have a pharmacological component, and the participants were advised to contact their regular health care provider if necessary. Like in FINGER, blinding in the HATICE RCT was pursued as much as possible. Coaches were not blinded, but group allocation was not disclosed to the participants and outcome assessors were blinded to the randomization status.

Studies II & III were conducted in a subsample of the HATICE RCT participants as part of the ACCEPT-HATICE ancillary substudy. The aim of the ACCEPT-HATICE study was to investigate potential determinants of participation and non-participation in the HATICE RCT as well as perceptions regarding CVD and dementia prevention. Data in the ACCEPT-HATICE substudy were collected in two stages. Quantitative data collection using an online questionnaire about reasons for participating in the HATICE RCT was followed by semi-structured interviews with a subsample of questionnaire respondents. Sociodemographic and other baseline variables (e.g., vascular risk factors) were collected as part of the HATICE RCT procedures. From April 2016 onwards, newly recruited HATICE participants in all three countries (Finland, France, the Netherlands) were invited to fill in the questionnaire (for a detailed description of the questionnaire, see section 4.3.2.2). There were no specific inclusion or exclusion criteria for the ACCEPT-HATICE substudy. Data from participants who did not ultimately enroll in the HATICE RCT (e.g., due to withdrawal or ineligibility) were later excluded. Participants were invited to fill in the questionnaire directly after pre-screening before the screening visit or latest before the baseline visit. Questionnaire respondents who had consented to be re-contacted were identified during June–August 2016, and a convenience sample, in all three countries, was invited for face-to-face interviews (for a detailed description of the interviews, see section 4.3.2.3). Participants who had had their baseline visit more than three months previously were not contacted. This was done to minimize the risk that trial-related activities and the intervention itself could have potentially affected their opinions.

4.1.3 The Karolinska University Hospital Memory Clinic (Study IV)

Study IV was conducted at the Karolinska University Hospital Theme Aging Memory Clinic in Stockholm, Sweden. The Memory Unit in Stockholm consists of two specialized outpatient clinics, one located in the Solna area and one in the Huddinge area. The unit examines individuals with suspected cognitive impairment referred by general practitioners (GP) or other physicians in the catchment area, and it has additional responsibility for early-onset cognitive impairment in the entire Stockholm area and hereditary cases in Sweden. Altogether, the clinics examine approximately 800 new patients per year, and at referral, most patients are diagnosed with SCI or MCI. Study IV included patients examined at the Huddinge memory clinic (hereafter referred to as the 'Memory Clinic').

Routine procedures at the Memory Clinic include the following assessments: a comprehensive medical examination and anamnesis, a neuropsychological evaluation, neuroimaging, blood chemistry to rule out somatic causes of cognitive symptoms, and CSF collection. The necessity for other assessments is evaluated on a case-by-case basis. Patients are also routinely invited, and most accept, to give their informed consent for their clinical data and samples to be included in the Karolinska University Hospital Theme Aging electronic database and biobank for clinical research. A multidisciplinary team of experts evaluates each case and reaches a consensus diagnosis usually within a few months since the patient's first visit to the clinic. After diagnosis, patients are referred to their primary care unit or followed up at the Memory Clinic, depending on the diagnosis and physician's evaluation of the patients' overall situation.

In Study IV, Memory Clinic patient records were reviewed retrospectively. Patients diagnosed with MCI at the Memory Clinic were identified in the research database, and their baseline data were collected in 2014 from electronic medical records (for a detailed description of participant selection and eligibility criteria, see section 4.2.3). Patient characteristics obtained from the medical records were chosen based on optimal data availability and included the following: the date of MCI diagnosis, demographics (age, sex, years of formal education), cognitive performance (Mini-Mental State Examination MMSE (Folstein et al., 1975) and the Rey Auditory Verbal Learning Test RAVLT (Rosenberg et al., 1984), immediate and delayed recall), CSF and imaging biomarkers (CSF A β 42, t-tau, p-tau, and visual rating of MTA), non-modifiable risk factors (*APOE* genotype, family history of dementia), depressive symptoms (Cornell Scale for Depression in Dementia score, Alexopoulos et al., 1988), use of medications and medical history (with a focus on hypertension, hyperlipidemia, and diabetes), and individual vascular risk factors (BP, smoking status, BMI). Medical records were reviewed again in 2018 for follow-up diagnoses, and the date and type of dementia diagnosis was recorded. For those who had not progressed to dementia, the date of the most recent follow-up visit was recorded.

4.1.4 The LipiDiDiet trial (Study V)

Study V is a post hoc analysis of the LipiDiDiet RCT, which is a multicenter RCT conducted at 11 study sites in Finland, Germany, Sweden, and the Netherlands (Soininen et al., 2017). Recruitment took place between 2009 and 2013, and the two-year core RCT was completed in 2015. Up to four 12-month double-blind interventional extension studies were completed at each site. The LipiDiDiet RCT investigated the efficacy of the Fortasyn Connect™ multinutrient in preventing cognitive decline. The primary outcome was the two-year change in cognitive performance, defined as a change in an NTB composite score. Changes in the individual domain-specific scores and the total NTB score were specified as the secondary cognitive outcomes. Other secondary outcomes were the change in cognitive-functional performance (CDR-SB score), rate of brain atrophy, changes in blood lipids and fatty acid profiles, as well as incident dementia after two years of intervention. Safety and compliance were also assessed.

The LipiDiDiet RCT targeted cognitively mildly impaired individuals with prodromal AD (for a detailed description of participant selection and eligibility criteria, see section 4.2.4). Participants were primarily recruited from memory clinics. A total of 382 individuals were screened and 311 were randomized at a 1:1 ratio into the intervention (N=153) and control groups (N=158). The intervention group consumed a 125 ml vanilla- or strawberry-flavored dose of the medical food product Souvenaid® (produced by Nutricia, Zoetermeer, the Netherlands) once a day. Control group participants received a 125 ml placebo product once a day, which was similar in terms of taste and consistency and contained the same number of calories. Visits with the study nurse and/or physician took place at screening/baseline, three months, six months, nine months, 12 months, 18 months, and 24 months. In addition, the study nurses contacted the participants by phone monthly for the first six months and every two months after that. Participants who were diagnosed with dementia during the two-year RCT were offered the opportunity to continue participation, and from October 2012 onwards, switch their double-blind product to an open-label active product.

4.2 STUDY POPULATIONS

4.2.1 The FINGER trial participants (Study I)

The FINGER RCT population consisted of community-dwellers aged 60–77 years at an increased risk of cognitive decline and with potential for risk reduction, but no significant cognitive impairment upon enrollment in the RCT. Risk assessment was based on the mid-life CAIDE risk score (range 0–15, higher scores reflect a higher dementia risk) as well as cognitive performance. The FINGER participants were identified and recruited from previously conducted observational population-based health monitoring surveys, including the FINRISK surveys conducted every five years during 1972–2007 and type 2 diabetes prevention program surveys conducted

in 2004 and 2007. A mid-life CAIDE score was calculated based on the data collected in the surveys to determine preliminary eligibility. Exact inclusion criteria were as follows: 1) a CAIDE score of at least six (apart from age, points were given based on risk factor levels at the time of the survey) and 2) cognitive performance at the mean level or slightly lower than expected for age based on the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) test battery (Morris et al., 1989) (a word list memory task with 19 words or less out of 30, word list recall of 75% or less out of 100%, or an MMSE with 20–26 points out of 30). As described by Ngandu et al. (2014), these inclusion criteria (i.e., the CAIDE score + cognitive tests focusing on the memory domain) identified participants with a potentially increased risk of both AD-type and vascular cognitive impairment. Individuals with diagnosed or suspected dementia, or a low MMSE (< 20), and those with any conditions that might hinder participation and adherence to the intervention (e.g., severe depression or visual impairment) were excluded.

All randomized FINGER participants with available data were included in the pre-specified subgroup analyses of Study I. Primary analyses were performed for the modified intention-to-treat (mITT) population with at least one post-baseline assessment (N=1,190); sensitivity analyses were performed for the whole intention-to-treat (ITT) population (N=1,260).

4.2.2 The HATICE and ACCEPT-HATICE participants (Studies II & III)

The HATICE RCT population consisted of community-dwellers aged 65+ years with potential for CVD and dementia risk reduction but no significant cognitive impairment at baseline. The potential for risk reduction was defined as having at least two CVD/dementia risk factors and/or a history of CVD or diabetes. The following factors were taken into account in the risk assessment: hypertension (diagnosis, ongoing medication, and/or measured BP \geq 140/90 mmHg or SBP \geq 160 mmHg depending on age); hyperlipidemia (diagnosis, ongoing medication, and/or total cholesterol \geq 5 mmol/l or LDL \geq 2.5 mmol/l); smoking; obesity (BMI \geq 30 kg/m² and/or a waist circumference \geq 102 cm for men and \geq 88 cm for women); and physical inactivity (less than 2.5 hours of moderate-intensity activity per week). A history of CVD was defined as a diagnosis of a myocardial infarction, stroke/TIA, coronary artery disease, and/or peripheral arterial disease. In addition to having the desired risk profile, participants had to be familiar with computers and the Internet, meaning that they were able to send emails and conduct basic online searches. Similar to the FINGER RCT, individuals with diagnosed or suspected dementia, a low MMSE (in HATICE below 24), or any condition that might affect their participation (e.g., visual impairment) were excluded. Recruitment strategies varied between the three countries involved in the HATICE RCT. These included the national population register (in Finland), registration lists of GPs (in the Netherlands), and registration lists of prevention units, mailing lists, and advertisements (in France). Eligibility was initially assessed in all countries during a pre-screening phone call to reduce the

number of screening failures. A face-to-face screening visit was scheduled after the call.

A total of 464 individuals were invited to participate in the ACCEPT-HATICE substudy (Studies II & III). The online questionnaire was filled in by 371 individuals (79%) of whom 341 were ultimately randomized in HATICE and included in the ACCEPT-HATICE substudy (13% of all randomized participants). In total, 67% of the questionnaires were completed before the screening visit. Of the 341 questionnaire respondents, 309 (91%) consented to be re-contacted for an interview. A total of 82 respondents were invited, and 46 were interviewed: 15 in Finland, 13 in France, and 18 in the Netherlands. In the Netherlands, two HATICE participants were interviewed despite not having filled in the questionnaire. These individuals were interviewed together with their partners who also participated in the HATICE RCT and had completed the questionnaire. The detailed ACCEPT-HATICE study flowchart is presented in the original Study II publication.

4.2.3 The Karolinska Memory Clinic cohort (Study IV)

The Memory Clinic cohort investigated in Study IV consisted of all patients who were diagnosed with MCI (Winblad et al., 2004) at the Memory Clinic in 2007–2014 and fulfilled the selection criteria for the study. These were as follows: 1) that they had provided informed consent and were included in the clinic's electronic research database; 2) the availability of medical records from the first assessment period to collect demographic and clinical data; 3) the availability of CSF results from the first assessment period; 4) at least one follow-up visit at the Memory Clinic (\geq one year after the first assessment and MCI diagnosis); and 5) CSF A β 42 levels within the normal range according to the cut-off values provided by the laboratories and employed routinely at the Memory Clinic. The study included a total of 318 patients.

4.2.4 The LipiDiDiet trial participants (Study V)

Participants in the LipiDiDiet RCT were individuals aged 55–85 years with prodromal AD according to the IWG-1 criteria (Dubois et al., 2007). Based on these criteria, participants had to have some evidence of an underlying AD-type pathology and a mild episodic memory impairment. The following biomarkers were considered: CSF A β (A β 42 < 450 pg/ml and/or A β 42/40 ratio $\times 10 < 1$), CSF t-tau (> 350 pg/ml), CSF p-tau (> 60 pg/ml), FDG-PET (hypometabolism in temporoparietal brain regions), and visually rated MTA (≥ 1) in a structural MRI. Abnormality in at least one (any) of these biomarkers was required. The evaluation of cognition for eligibility was based on the following tests: the Free and Cued Selective Reminding Test, free recall (≤ 22 points) and delayed free recall (≤ 8 points); the Wechsler Memory Scale revised (WMS-r) story delayed recall ($\leq 75\%$); the WMS-r delayed recall of figures ($\leq 75\%$); the Trail Making Test A (≥ 60 seconds) and B (≥ 150 seconds), the Symbol Digit substitution test (≤ 35 points); and the category fluency test (≤ 16 points). Cognitive impairment was defined as an abnormal performance in at least

two of the above-mentioned tests of which at least one had to be a memory-related test. Individuals with diagnosed dementia or an MMSE below 24 (below 20 if six or fewer years of education) and those using cholinesterase inhibitors or memantine were excluded. Other exclusion criteria were neuroimaging abnormalities that could potentially cause and explain the cognitive impairment (stroke, intracranial bleeding, mass lesion, or normal pressure hydrocephalus) as well as medical and other conditions that could affect participation and adherence (e.g., severe depression). Due to the nature of the intervention, individuals taking omega-3 products or large doses of vitamins B6, B12, C, E, or folic acid (>200% of the recommended daily intake) were also excluded.

For the post hoc analyses conducted in study V, all randomized participants were included whose CSF biomarkers and/or MTA had been centrally analyzed at baseline using standardized methods (N=287). The mITT population was included in the longitudinal analyses (all randomized participants with at least one post-baseline assessment, excluding data after progression to dementia and start of AD medication and/or open-label active study product).

4.3 PROCEDURES AND OUTCOMES

4.3.1 Baseline assessments

4.3.1.1 Participant characteristics analyzed in Studies I-V

In Study I (FINGER), the participant baseline characteristics that were investigated as potential modifiers of the response to intervention were collected at the screening and baseline visits. An MMSE was performed at the screening visit by a study nurse, and a study physician examined all the participants and interviewed them to obtain information about their medical history. A fasting blood sample was taken at the baseline visit by a study nurse who also measured the BP, height, and weight during this visit. The BMI (kg/m²) was calculated based on height and weight. Information about socioeconomic factors (educational attainment, annual household income) and lifestyle (e.g., smoking habits) was collected with a questionnaire. Based on these self-reported data and measurements conducted by the nurse, the participants' overall cardiovascular risk was calculated in Study I using the FINRISK score (slightly different risk algorithms were used for men and women) (Vartiainen et al., 2007, 2016). The risk score included the following factors: age, total cholesterol, SBP, high-density lipoprotein (HDL), smoking status, and diabetes. A family history of CVD was not included as this information was not collected in the FINGER RCT. The final score used in Study I was a ratio of the calculated score and the score of an age- and sex-matched person with an 'optimal' cardiovascular risk profile (total cholesterol 4.5 mmol/l, SBP 120 mmHg, HDL 1.32 mmol/l, no smoking, no diabetes; Vartiainen et al., 2007, 2016). In this way, we obtained a score solely reflecting the vascular risk profile (hereafter referred to as the 'overall cardiovascular risk'). Self-reported medical history data were also used to identify persons with an indication for

secondary CVD prevention. A history of CVD was defined as a diagnosis of a stroke, myocardial infarction, and/or diabetes.

In Studies II & III (HATICE), demographic and clinical characteristics used to describe the study population were obtained at the screening and baseline visits through questionnaires and measurements performed by the lifestyle coaches. In the LipiDiDiet RCT, demographic characteristics and the MMSE used as covariates in the Study V analyses were collected at the screening visit by a study nurse and/or physician. In Study IV, patient baseline characteristics studied as predictors of clinical progression, or included as covariates in the analyses, were collected during the first assessment period at the Memory Clinic through interviews and examinations conducted by nurses and physicians. Educational attainment, medical history, use of medications, family history of dementia (defined as having at least one affected first-degree relative), and lifestyle habits (smoking) were self-reported data. MMSE, Cornell Scale for Depression in Dementia, and measurements of height, weight, and BP were performed by a nurse or physician; RAVLT was performed by a psychologist. The BMI (kg/m²) was calculated based on height and weight. A blood sample was collected in some cases to assess the *APOE* genotype. The CAIDE risk score (versions with and without *APOE*) was calculated in Study IV based on demographic and clinical data. As opposed to the original CAIDE score, the score in Study IV did not include physical activity as this information was not systematically collected at the Memory Clinic. In addition, points for cholesterol and BP were mainly given based on a diagnosis of hyperlipidemia and hypertension. The full table showing how the CAIDE risk scores were calculated is presented in the original Study IV publication (supplementary material).

4.3.1.2 Biomarker assessments (Studies IV & V)

In Studies IV and V, CSF and MRI biomarkers were used to select and characterize the study populations and predict their cognitive decline and/or progression to dementia. Biomarkers of interest were CSF A β 42, A β 42/40 ratio (only Study V), p-tau, and t-tau, as well as MTA. In Study IV, CSF biomarker concentrations were measured with sandwich enzyme-linked immunosorbent assays (Innogenetics (Fujirebio), Ghent, Belgium) at the Karolinska University Hospital in Stockholm, Sweden (2007–2011) or at the Clinical Neurochemistry Laboratory at Sahlgrenska University Hospital in Gothenburg, Sweden (2012–2014). The cut-offs for CSF biomarker abnormality as specified by the laboratories were as follows: A β 42 < 450 pg/ml (2007–2011) or < 550 pg/ml (2012–2014); t-tau \geq 400 pg/ml; and p-tau \geq 80 pg/ml. These cut-offs were used in Study IV to select and classify individuals. MTA was visually rated by experienced radiologists based on structural MRI or computerized tomography (CT) scans. Both hemispheres were scored separately according to the Scheltens scale (0–4; 0 means no atrophy and 4 indicates severe hippocampal volume loss). In Study IV, the mean score was calculated and the cut-off for abnormality was set at > 1.

In Study V, analyses of the CSF biomarkers collected at baseline were conducted at the Clinical Neurochemistry Laboratory at Sahlgrenska University Hospital in Gothenburg, Sweden. Biomarker concentrations were measured using the MSD Abeta Triplex (A β 42 and A β 40; Meso Scale Discovery, Rockville, Maryland) and sandwich enzyme-linked immunosorbent assays (t-tau and p-tau; Fujirebio, Ghent, Belgium). The cut-offs for CSF biomarker abnormality used in the LipiDiDiet central analysis and in Study V were as follows: A β 42 < 450 pg/ml; A β 42/40 ratio $\times 10 < 1$; t-tau > 350 pg/ml; and p-tau > 60 pg/ml. MTA was visually rated based on structural MRI scans at the VU University Medical Center in Amsterdam, the Netherlands. Both hemispheres were scored separately according to the Scheltens scale. The sum of the scores was calculated and the cut-off for abnormality was set at ≥ 1 .

4.3.2 Outcome assessments

4.3.2.1 Cognitive and clinical outcomes analyzed in Study I, IV & V

In Studies I, IV, and V, the cognitive and clinical outcomes of interest were changes in cognition measured with an extensive NTB (Studies I & V), changes in cognitive-functional performance defined as a change in the CDR-SB score (Study V), and progression to dementia (Studies IV & V).

In the FINGER and LipiDiDiet RCTs, an NTB was performed by a study psychologist at baseline, one year, and two years (one additional assessment at six months in the LipiDiDiet RCT). Scores of individual cognitive tests were converted into standardized Z-scores, with higher scores reflecting better performance. In Study I (FINGER), the primary outcome NTB total score was based on 14 individual test scores covering three cognitive domains: memory, processing speed, and executive functioning. There were six memory tests (the WMS-r visual paired associates test, immediate and delayed recall; the WMS-r logical memory test, immediate and delayed recall; the CERAD 10-word list test, learning and delayed recall), three tests for processing speed (the Stroop test, condition 2; the concept shifting test, condition A; the letter digit substitution test), and five tests for executive functioning (the category fluency test; the Stroop test, interference score; the WMS-r digit span; the concept shifting test, condition C; the Trail Making Test, B-A). The NTB total and domain-specific scores were obtained by calculating the sum of individual Z-scores and dividing by the number of items available. At least three memory tests, two processing speed tests, and three executive functioning tests (in total eight) had to be completed to calculate the total and domain-specific Z-scores.

The total NTB in Study V (LipiDiDiet) consisted of 16 individual test scores, most of which were the same as in the FINGER RCT. There were some differences in how the cognitive domains and outcomes were defined. In the LipiDiDiet RCT, the memory domain included three tests (the CERAD 10-word list test, learning, delayed recall and recognition) and the executive functioning domain included four tests (the category fluency test; the WMS-r digit span; the concept shifting test, condition C; the letter digit substitution test). The nine other tests included in the NTB total score

were: the WMS-r logical memory test, immediate and delayed recall; the WMS-r visual paired associates test, immediate and delayed recall; the 30-item Boston Naming Test; the CERAD Constructional Praxis, copy and recall; and the concept shifting test, conditions A and B. The primary outcome (NTB composite score) included five tests of which at least four had to be completed (the CERAD 10-word list test, learning, delayed recall and recognition; the category fluency test; the letter digit substitution test). All three memory tests and at least three executive functioning tests had to be completed to calculate the domain-specific Z-scores. At least 12 out of 16 tests were required for the NTB total score.

The CDR-SB scores investigated in Study V were assessed by a study nurse or physician at three timepoints (baseline, one year, and two years). Dementia and AD diagnoses were made by experienced medical specialists in Studies IV & V, and diagnoses were based on the DSM-IV (American Psychiatric Association, 1994) and NINCDS-ADRDA criteria (McKhann et al., 1984), respectively.

4.3.2.2 The ACCEPT-HATICE questionnaire (Study II)

In Study II, a questionnaire was administered to explore reasons for participation in the HATICE RCT. It was based on and adapted from a previous study (Andrieu et al., 2012). The questionnaire was translated into Finnish, French, and Dutch by researchers fluent in both English and the local language (in Finland by A. Rosenberg). It was administered online, and the link was sent to the participants' personal email addresses. Each participant was able to complete the questionnaire only once. The questionnaire included 14 statements, and the participants were asked to what extent they agreed with the statements. They were also asked to indicate for each statement whether it was a reason for participation. The full list of statements is shown in the original Study II publication; an example is shown in Table 3 on page 76. Respondents also had the option to add other reasons. Respondents were allowed and encouraged to select all statements that they considered relevant to their participation. Finally, the respondents had to specify one statement that they considered their main reason (a pre-specified statement or an own reason). At the end of the questionnaire, the participants could enter their contact details (phone number) if they agreed to be potentially re-contacted for further questions and an interview.

A second questionnaire was specifically designed for people who declined the invitation to participate in the RCT. In the invitation letter to the HATICE RCT, individuals who were not interested in the RCT were asked to access an online questionnaire and provide reasons for their non-participation. In France and the Netherlands, non-participants were also identified retrospectively, when possible, and invited to fill in the questionnaire. Only a few individuals completed the questionnaire, and few non-participants were interviewed in France and the Netherlands. Due to the scarcity of data, a detailed exploration of the results was not possible. In Finland, it was not possible to actively seek contact (e.g., by post or phone) with individuals who had been approached earlier but did not respond to the

HATICE invitation letter. This was due to ethical reasons. It was also not possible to interview non-participant questionnaire respondents.

Table 3. An example of the ACCEPT-HATICE questionnaire statements.

	I agree with this statement:				This is a reason why I accepted to participate:	
	Totally agree	Somewhat agree	Somewhat disagree	Totally disagree	Yes	No
I am interested in contributing to scientific progress	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

4.3.2.3 Semi-structured interviews (Studies II & III)

Semi-structured interviews were conducted 1) to understand the reasons for participation in the HATICE RCT (Study II) and 2) to explore the HATICE participants’ knowledge and perceptions of dementia and their attitudes towards prevention in depth (Study III). Interviews were conducted in all three countries involved in the HATICE RCT (Finland, France, the Netherlands) by local researchers in the local language (in Finland by A. Rosenberg). Interviews were conducted at the local HATICE study centers, and they lasted approximately one hour each. A harmonized interview guide covering the following topics was developed and followed in a flexible and adaptive manner: 1) a general introduction, life course, and events; 2) health behavior and practices, perceived and actual health status; 3) perceptions of and attitudes towards CVD and prevention as well as the role of the Internet in health promotion; and 4) reasons for participation in the HATICE RCT. The structured interview guide did not include the topic of cognitive impairment/dementia/cognitive disorders and related questions. Whenever the interviewees spontaneously brought up the topic of cognitive impairment/dementia/cognitive disorders during the interview (hereafter ‘dementia’ for the sake of conciseness), they were additionally queried about their knowledge and perceptions of dementia and prevention. All interviewees who freely mentioned dementia were included in Study III (N=15, all the participants interviewed in Finland).

The full ACCEPT-HATICE interview guide and a detailed description of dementia-related questions are presented in the original Study II and III publications. Examples of questions asked in the interviews are listed in Box 1. The questions were open-ended, and the interviewers encouraged the interviewees to speak freely. The interviewers facilitated and guided the discussion, rather than directed it. When necessary, more detailed follow-up questions were asked to ensure that the topics were sufficiently covered. At the end, the interviewers summarized the discussion and gave the interviewees the chance to add something or clarify their views. The

questionnaire responses had not been analyzed at the time of the interviews, and the interview guide or interviewers were therefore not influenced by the quantitative results. The interviews were tape-recorded and transcribed verbatim in the local language. Repeat interviews were not conducted, and transcripts were not returned to the participants.

Box 1. Examples of questions asked during the interviews.

- Can you tell me a bit about yourself and your daily activities? How do you spend your time?
- When you have a medical problem or question about your health, what steps do you take?
- What do you think about your own health? How do you usually cope with health problems and illness?
- What do you know about CVD? What can one do to manage it or prevent it from worsening? Do you try to manage or prevent CVD yourself? If yes, how and why?
- In what way do you think the Internet could be a useful tool to improve health?
- Why did you decide to participate in HATICE? What expectations do you have? What kind of benefits, if any, are you expecting to get? What did you find particularly interesting in this trial?
- What do you know about dementia? What do you know about risk factors and prevention? Do you believe it can be prevented (why/why not)? If yes, how?
- What kind of feelings and thoughts does dementia evoke? Why?
- What motivates you towards the prevention of dementia?

4.4 DATA ANALYSIS

4.4.1 Statistical methods

Participant baseline characteristics were compared between groups of interest using a t-test (continuous variables between two independent groups) and a χ^2 test (categorical variables). In Study II, between-country comparisons of participant characteristics and reasons for participation were conducted using an analysis of variance or Kruskal-Wallis test (continuous variables; more than two independent groups) and a χ^2 test (categorical variables), as appropriate. The statistical analyses in studies I, II, and IV were performed using Stata software version 14.1 (StataCorp LP, College Station, TX). SAS software version 9.4 was used in Study V. The level of statistical significance was < 0.05 , unless otherwise specified.

The analyses in Study I were performed according to a pre-specified statistical analysis plan. Linear mixed models for repeated measures were used to explore whether participant characteristics influenced the intervention effects on the primary and secondary cognitive outcomes, i.e., the two-year change in cognitive performance measured with an NTB. Linear mixed models were chosen to account for both within-person and between-person variability over time. The models

included group allocation (intervention or control), time, characteristics of interest (e.g., age; dichotomous or continuous depending on the characteristic), and all interaction terms as predictors (e.g., group*time, group*age, time*age, and group*time*age). The study site was entered in all models as a covariate. Skewed NTB Z-scores and characteristics with continuous values were log transformed to achieve normality. As recommended in the guidelines for RCT subgroup analyses (Wang et al., 2007), coefficients for the three-way interaction terms group*time*characteristic and the corresponding p-values were shown as the main results. In other words, it was shown whether the intervention effects (group*time interaction) varied across the levels of a characteristic variable (e.g., age, or men vs. women). Estimates for the change in cognition in the intervention and control groups within each subgroup as well as the difference of these estimates were obtained from the mixed models with the linear combinations of estimators (lincom) post-estimation command. For this purpose, continuous characteristics were dichotomized based on median values to achieve approximately equal sized groups.

In Study IV, the relationship between patient characteristics and subsequent dementia diagnosis was investigated using the Cox proportional hazards model with age as the time scale. Patients were censored according to their age at the time of the dementia diagnosis or end of follow-up (last available follow-up visit). Patient characteristics were entered in the model one at a time, and all models were adjusted for age (age as the time scale), sex, years of formal education, and baseline MMSE. CSF biomarkers were log transformed and Z-standardized. After identifying potential predictors of disease progression, i.e., characteristics showing a significant or borderline significant association with progression to dementia ($p < 0.10$), their predictive performance was examined using the Harrell C (concordance) statistic. The Harrell C statistic is similar to the area under the curve (i.e., it indicates the model's ability to distinguish between positive and negative cases; values range from 0 to 1). A value of 0.5 is equal to random and 1 means a perfect prediction. No clear definition or cut-off points exist, but the terms 'poor', 'acceptable', and 'excellent' prediction have been proposed when values are below 0.7, 0.7–0.8, and greater than 0.8, respectively (Hosmer et al., 2013). Models with age, cognition (RAVLT delayed recall), and the characteristics of interest were compared to a simple model including age and cognition alone. The models were based on complete cases, and comparisons were conducted between models including the same patients.

In study V, linear mixed models for repeated measures were used to explore changes over two years in the primary and secondary cognitive outcomes (NTB) and cognitive-functional performance (CDR-SB score) among participants with different biomarker profiles at baseline. Models included the baseline score (NTB or CDR-SB), MMSE, group allocation (intervention or control), time, the group*time interaction, the biomarker profile (diagnostic criteria as categorical class variables, with number of categories depending on the criteria), and the biomarker profile*time interaction as predictors. A random intercept with a variance components covariance structure was used within sites, and a random intercept and slope for time with an

unstructured covariance structure was used within subjects. Least-squares means for the change from baseline were estimated from the models for each group, and p-values for the difference in the least-squares means over two years between each group and the respective reference group were obtained. The relationship between biomarker profiles and the risk of dementia was investigated using the Cox proportional hazards model adjusted for group allocation, MMSE, and study site.

4.4.2 Qualitative methods

A content analysis was applied to the interview data. In both studies II and III, two independent researchers in each country familiarized themselves with the interview transcripts through repeated readings and performed initial coding of the material. The codes were short descriptive phrases summarizing the core meaning of each meaning unit (phrase, sentence, or paragraph). First-level codes in Study II were generated in the local language based on the original Finnish, French, and Dutch transcripts (in Finland by A. Rosenberg and another Finnish researcher). In Study III, interview sections related to the research questions of interest were extracted and translated into English, and first-level codes were generated in Finnish (by A. Rosenberg) and English (by a non-Finnish speaking researcher). The coding in Study II was performed using a qualitative data analysis software. NVivo version 11 was used in France and Finland, and ATLAS.ti version 1.6.0 (484) was used in the Netherlands. A coding framework, created together based on the interview guide, steered the initial coding. The coding framework was developed and refined during the analysis process to ensure that it captured all the relevant aspects that emerged from the interviews. The coding in Study III was performed manually without a computer software, and it was done inductively without a pre-defined coding framework.

In both studies, the researchers compared their codes after the initial first-level coding and discussed similarities and differences between the codes. The codes were then sorted and abstracted into subcategories and further into broader categories. Table 4 shows an example of the coding performed in Study III. The analysis was an iterative process in which the researchers worked back and forth between the raw data, codes, and categories until inter-coder agreement was reached (within country and between the three countries in Study II). Core themes linking the categories and findings together represented the main results in both studies. To formulate the theme in Study II, the analysis was completed by reflecting on the qualitative and quantitative findings in parallel. Such a mixed-method approach, also referred to as methodological triangulation, enriches the understanding of a research problem by elucidating different aspects of the same phenomenon (Greene et al., 1989; O’Cathain et al., 2010). A mixed-method approach supports primarily two analytical goals: 1) convergence and corroboration and 2) elaboration, illustration, and clarification of the findings. Study II was quantitative-based, and the interpretation of the qualitative data aided the interpretation of the quantitative findings and statistically significant results (Onwuegbuzie & Leech, 2004).

Table 4. Examples of quotes, codes, and subcategories that were identified and linked to the category 'Stigma of dementia' in Study III.

Quotes	Codes	Subcategories	Category
<i>"I wouldn't want to find out yet if I'll get AD. (...) It's terrible to live with that information."</i>	Terrible to live knowing that one will get it		
<i>"Maybe it's better [not to know in advance], it [AD] comes if it's meant to be. My father's sister was 70 when she was diagnosed. And it progressed really fast. Maybe it's better not to know, it will come if it's meant to happen."</i>	Better not to know if one will get it	Better not to know about own cognitive status or risk	
<i>"These diseases are so common. That's why I wanted to participate. If I can do anything to help to reduce the burden of memory disorders, I'm willing to do it."</i>	Will to reduce the burden of dementia	Burden for society	
<i>"Mother has AD, that's what I fear the most, it's such a dreadful disease that even a sudden death would be better."</i>	Dreadful disease		Stigma of dementia
<i>"It evokes... Not quite fear but... My mother doesn't feel scared, she's alright because she doesn't remember anything. But it's sad for me to watch her."</i>	Sadness	Dementia evokes misery	
<i>"(...) If you get that kind of a disease, that's it. There is no going back. It's so sad to think about it when you're still healthy."</i>	Nothing can be done about it	Hopelessness, resignation	
<i>" (...) It's terrible. It worries me, I've always told others that if I get dementia, they should drown me."</i>	Better to die		

4.5 ETHICAL ASPECTS

The FINGER RCT received ethical approval from the coordinating ethics committee of the Helsinki and Uusimaa Hospital District. Ethical approval for the Karolinska University Hospital electronic database and biobank for clinical dementia research was granted by the Regional Ethical Review Board in Stockholm. The HATICE and LipiDiDiet RCTs were approved by the local ethics committees of the participating study centers. For LipiDiDiet, approval was obtained from the ethics committee of the Hospital District of Northern Savo in Finland, the Stockholm Regional Ethical Review Board in Sweden, the Medical Ethical Committee of the VU University Medical Center Amsterdam in the Netherlands, and the ethics committees of University of Regensburg, Eberhards-Karls-University of Tübingen and Tübingen University Hospital Clinic, Heidelberg University, the Medical faculty in Mannheim, and Saarland University in Germany. Approval for HATICE was obtained from the ethics committee of the Hospital District of Northern Savo in Finland, the Medical Ethical Committee of the Academic Medical Center in the Netherlands, and the Comité de Protection des Personnes Sud Ouest et Outre Mer in France. The ACCEPT-HATICE substudy received separate ethical approval from each ethics committee as an amendment to the HATICE RCT. All participants gave written informed consent before enrollment. None of the studies in this thesis included participants with severe cognitive impairment, and all participants were able to provide informed consent themselves. All the RCTs were conducted in accordance with the Declaration of Helsinki and the principles of Good Clinical Practice, and they were registered beforehand (the FINGER RCT was registered at ClinicalTrials.gov with identifier NCT01041989, the HATICE RCT was registered in the ISRCTN registry with identifier ISRCTN48151589, and the LipiDiDiet RCT was registered in the Netherlands Trial Registry with identifier NL1620).

5 RESULTS

5.1 BASELINE CHARACTERISTICS OF THE STUDY POPULATIONS

Table 5 provides an overview of the study populations. More detailed participant characteristics are presented in the original publications of Studies I-IV and in the Study V manuscript. The mean age was approximately 65 years in the Memory Clinic cohort, 69 years in the FINGER cohort, 70 years in the ACCEPT-HATICE cohort, and 71 years in the LipiDiDiet cohort. Both sexes were fairly equally represented in all cohorts. Vascular risk factors were prevalent in the FINGER and ACCEPT-HATICE cohorts, which was expected due to the nature of the interventions and the participant selection criteria (i.e., selection of at-risk individuals). For example, hyperlipidemia was one of the risk factors considered when assessing eligibility for the HATICE RCT, and elevated cholesterol is included in the CAIDE score, which was used to select participants for FINGER. In the CAIDE score, points are also given for lower education, potentially explaining why the proportion of highly educated individuals was lower in FINGER than in ACCEPT-HATICE (and in HATICE overall). It is also noteworthy that computer literacy was an inclusion criteria in the HATICE RCT, potentially resulting in the exclusion of some older adults with a lower level of education. With respect to biomarkers, elevated CSF t-tau and p-tau as well as MTA were more common in the LipiDiDiet than in the Memory Clinic cohort. This was expected, as the LipiDiDiet population was selected based on the IWG-1 criteria for prodromal AD, and MTA was a key biomarker used at screening.

In Studies II, III, and V, the study populations were a subsample of the HATICE (ACCEPT-HATICE substudy; Studies II & III) and LipiDiDiet (Study V) cohorts. With respect to the baseline characteristics, there were no differences between the LipiDiDiet participants who were and were not included in Study V, apart from the CDR-SB scores which were lower among those included in Study V. A detailed baseline comparison of the HATICE participants who were and were not included in the ACCEPT-HATICE substudy is presented in the original Study II publication. In summary, the ACCEPT-HATICE participants were younger and more often had a university education and a lower MMSE. They were also more often physically active and had less hypertension, diabetes, and CVD. In the ACCEPT-HATICE substudy, 56% of the participants were Finnish, 30% were French, and 14% were Dutch. In the entire HATICE population, 32% of the participants were Finnish, 14% were French, and 54% were Dutch. Between-country differences in ACCEPT-HATICE participant baseline characteristics are presented in detail in the original Study II publication. Differences were observed in age (younger participants in Finland), cognitive performance (lower MMSE in Finland), and self-reported engagement in physical activity (higher proportion of physically active participants in Finland).

Table 5. Baseline characteristics of the populations in Studies I–V.

	Study I (FINGER) N=1260	Studies II & III (HATICE sub- sample) N=341	Study IV (Memory Clinic) N=318	Study V (LipiDiDiet) N=287
Demographics				
Age, years	69.4 (4.7)	69.6 (3.9)	64.8 (9.1)	70.9 (6.6)
Male	672 (53.3%)	163 (47.8%)	144 (45.3%)	140 (48.8%)
Education				
Years	10.0 (3.4)	—	11.7 (3.7)	10.5 (3.7)
University level	116/1244 (9.3%)	173/341 (50.7%)	—	—
Cognition				
MMSE	26.7 (2.0)	28.1 (1.5)	27.1 (2.5)	26.6 (2.0)
Vascular risk factors				
Smoker	114/1255 (9.1%)	20/341 (5.9%)	41/287 (14.3%)	—
Obese (BMI ≥ 30 kg/m ²)	377/1249 (30.2%)	120/341 (35.2%)	31/205 (15.1%)	—
Physically inactive ^a	364/1247 (29.2%)	76/341 (22.3%)	—	—
Hypertension				
Diagnosis (self-reported)	821/1246 (65.9%)	—	130/318 (40.9%)	—
Diagnosis or elevated BP ^b	990/1248 (79.3%)	260/341 (76.2%)	189/277 (68.2%)	—
Hyperlipidemia				
Diagnosis (self-reported)	840/1250 (67.2%)	—	93/318 (29.3%)	—
Diagnosis or elevated cholesterol ^c	1187/1255 (94.6%)	329/341 (96.5%)	—	—
Diabetes	165/1250 (13.2%)	61/341 (17.9%)	53/318 (16.7%)	—
History of CVD ^d	261/1250 (20.9%)	66/341 (19.4%)	46/219 (21.0%)	—
CAIDE risk score, biomarkers, and APOE genotype				
CAIDE score	7.9 (1.9)	—	7.5 (2.5)	—
with APOE ^e	10.0 (2.3)	—	9.4 (2.4)	—
APOE ε4 carrier ^f	389/1175 (33.1%)	—	86/171 (50.3%)	162/260 (62.3%)
CSF Aβ ₄₂ , pg/ml	—	—	849 (294)	412 (242)
Abnormal Aβ ^g	—	—	0/318 (0%)	94/107 (87.9%)
CSF t-tau, pg/ml	—	—	336 (185)	616 (276)
Abnormal t-tau ^g	—	—	92/317 (29.0%)	92/107 (86.0%)
CSF p-tau, pg/ml	—	—	58 (25)	78 (29)
Abnormal p-tau ^g	—	—	60/317 (18.9%)	74/107 (69.2%)
MTA score	—	—	1.1 (0.8)	2.4 (1.6)
Abnormal MTA ^g	—	—	84/237 (35.4%)	241/279 (86.4%)

Data are presented as means (SD) or N (%).

^a Defined as engaging in moderate-intensity exercise less than 2.5 hours per week (HATICE) or less than twice per week (FINGER, for at least 20 minutes per session).

^b Elevated BP defined as SBP > 140 mmHg and/or diastolic BP > 90 mmHg.

^c Elevated cholesterol defined as total cholesterol \geq 5 mmol/l and/or LDL \geq 2.5 mmol/l.

^d Defined as a history of stroke, myocardial infarction, or diabetes (FINGER); a history of stroke/TIA, myocardial infarction, coronary artery disease, or peripheral artery disease (HATICE); and a history of stroke/TIA, myocardial infarction, or coronary artery disease (Memory Clinic).

^e CAIDE scores calculated without the physical activity component

^f Individuals with at least one ϵ 4 allele. Number of APOE ϵ 4/ ϵ 4 carriers was 40 in the FINGER cohort, 24 in the Memory Clinic cohort, and 49 in the LipiDiDiet cohort.

^g Abnormality refers to low CSF A β (A β 42 in Study IV; A β 42 and/or A β 42/40 ratio in Study V), high CSF t-tau, high CSF p-tau, and presence of MTA. The cut-offs used for biomarker abnormality are study-specific and are presented in section 4.3.1.2.

5.2 BASELINE PARTICIPANT CHARACTERISTICS AS MODIFIERS OF RESPONSE TO A MULTIDOMAIN LIFESTYLE INTERVENTION – STUDY I

5.2.1 Sociodemographic and -economic factors and cognition

The effect modification by participant baseline characteristics was investigated to explore whether the overall beneficial effects of the FINGER multidomain lifestyle intervention on cognition varied between different subgroups of participants. The demographic and socioeconomic factors of interest included age, sex, years of formal education, and the annual household income. The MMSE score was used as a measure of global cognitive performance in this analysis. With regard to the primary outcome (NTB total), none of the above-mentioned baseline characteristics modified the response to the intervention (all p-values for group*time*characteristic interactions > 0.05; Figure 2, p. 87). This was also observed in the sensitivity analysis and for all secondary cognitive outcomes (the results are presented in the original Study I publication). Individual estimates for the difference between the intervention and control groups in the total NTB score change were consistently positive, indicating benefits in all subgroups that were investigated: men and women; age groups < 70 and \geq 70 years; education < 9 and \geq 9 years; MMSE < 27 and \geq 27; household income < 30 000 € and \geq 30 000 € (Figure 2).

While all group*time*characteristic interactions were statistically non-significant, there was some indication of particular responsiveness to the intervention within certain subgroups, i.e., there were statistically significant differences between the intervention and control groups in the estimates for change in cognition (Figure 2). These subgroups included older participants, those with higher levels of education

and higher annual household incomes, as well as those who scored lower on the MMSE.

5.2.2 Vascular risk profile

Variables related to the vascular risk profile included individual risk factors (BMI, systolic and diastolic BP, total cholesterol, HDL, LDL, fasting glucose), cardiovascular comorbidity (the presence of manifest CVD), and the overall cardiovascular risk (the risk level compared to a low-risk person of the same age and sex). None of the individual vascular risk factors modified the response to the intervention (all p-values for group*time*characteristic interactions > 0.05; Figure 2), and the results were consistent for all cognitive outcomes (the results for secondary cognitive outcomes are presented in the original Study I publication). For processing speed, a p-value of 0.03 was observed for the group*time*diastolic blood pressure interaction; however, this result would not be significant after applying corrections for multiple testing. Manifest CVD or the overall vascular risk load did not influence the response to the intervention. Estimates for the difference between the intervention and control groups in the total NTB score change were consistently positive in all subgroups: BMI < 27.4 and ≥ 27.4 kg/m²; SBP < 140 and ≥ 140 mmHg; diastolic BP < 80 and ≥ 80 mmHg; total cholesterol < 5.1 and ≥ 5.1 mmol/l; LDL < 3.04 and ≥ 3.04 mmol/l; HDL < 1.4 and ≥ 1.4 mmol/l; fasting glucose < 5.9 and ≥ 5.9 mmol/l; manifest CVD and no manifest CVD; overall cardiovascular risk < 1.4 and ≥ 1.4 (the risk level compared to a low-risk person of the same age and sex).

While all group*time*characteristic interactions were statistically non-significant, differences between the intervention and control groups were again observed within certain subgroups (Figure 2). These included participants with higher SBP, cholesterol (total, HDL, LDL), and fasting glucose. In addition, statistically significant differences between the intervention and control groups were observed among those with lower BMI and diastolic BP, as well as those with no manifest CVD.

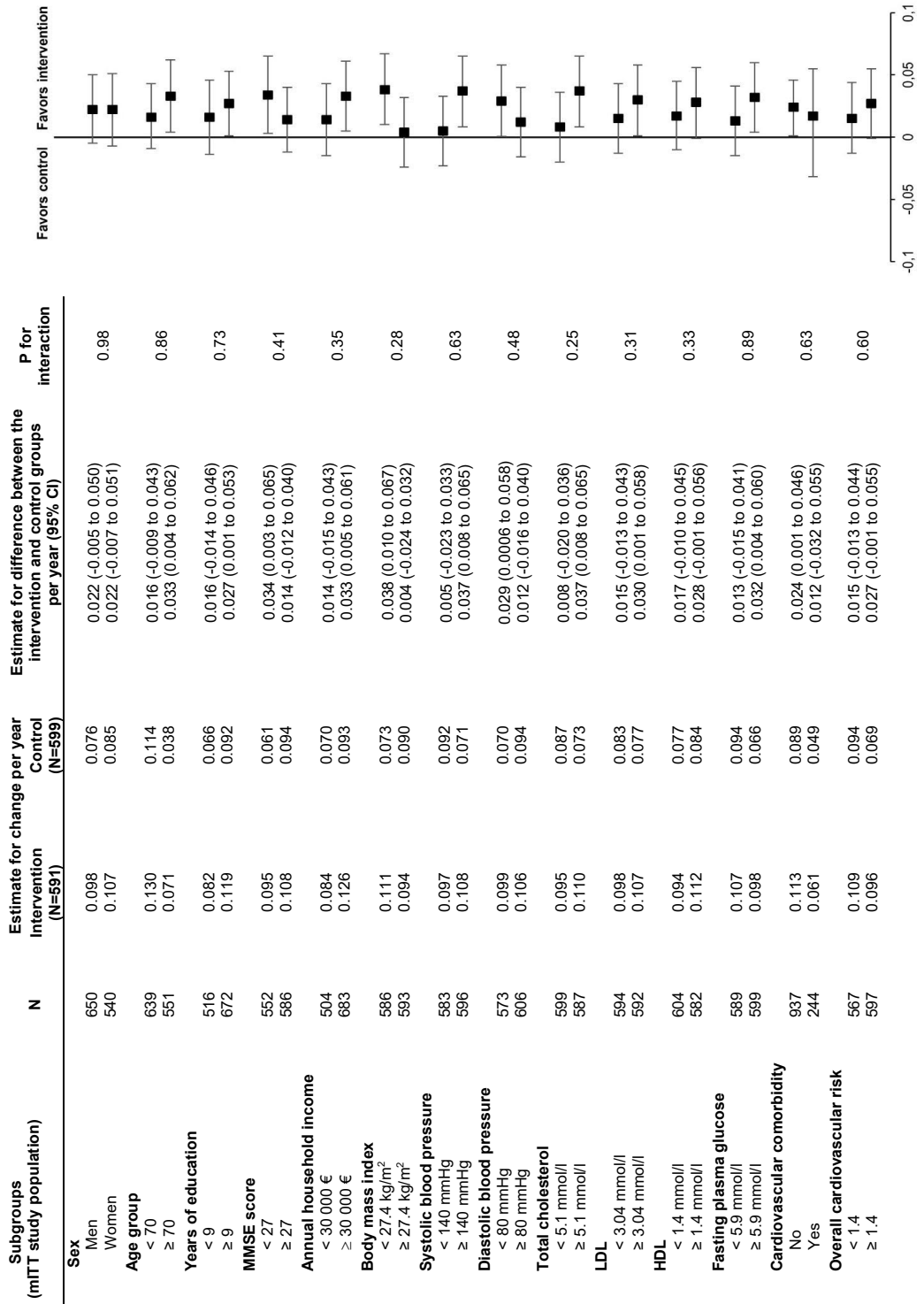


Figure 2. Effects of the FINGER intervention on the primary outcome (change in NTB total score) across subgroups.

P-values are shown for the group*time*characteristic interactions (continuous variables except for sex, household income, and cardiovascular comorbidity). P-values for interaction > 0.05 indicate that the intervention effects on cognition did not vary by baseline characteristics. Positive estimates for the difference between the intervention and control groups within subgroups indicate that the effect was in favor of the intervention group.

5.3 REASONS FOR PARTICIPATING IN A MULTIDOMAIN LIFESTYLE TRIAL – STUDY II

5.3.1 Questionnaire responses

Questionnaire statements and the proportions of participants (total and per country) naming each item as a reason for participation in the HATICE RCT are shown in Figure 3. In the whole study population, the most common reasons for participation were: 1) the willingness to contribute to research (selected by 85% of all respondents); 2) the possibility to gain health benefits through lifestyle improvements (84%); and 3) the possibility to receive additional medical monitoring (79%). These reasons were followed by the willingness to improve dietary and exercise habits (71% and 60%, respectively) and personal health concerns (54%). Overall, 53% of the respondents stated that they decided to participate in the HATICE RCT because it was both a fun and effective way to improve their health. All other pre-specified reasons were selected by fewer than 50% of the respondents.

In France and the Netherlands, altruism was the most frequently mentioned reason for participation (96% and 94%, respectively), while in Finland it was the third most common reason (77%). The most frequently named reason in Finland was to obtain health benefits through lifestyle improvement (91%), which was selected more often as a reason in Finland and in France (82%) than in the Netherlands (62%). Dutch respondents were also less likely to emphasize diet- or exercise-related aspects. A similar proportion of respondents in all three countries indicated medical monitoring and personal health concerns as reasons for participation.

With regard to Internet-related reasons, no between-country differences were observed in the proportion of respondents indicating that the HATICE RCT was a fun or effective way to improve their health. However, French respondents were particularly prone to emphasize the flexibility and user-friendliness of the Internet (58% in France, 44% in Finland, 28% in the Netherlands), and Finnish respondents showed more interest than others in an eHealth study like HATICE because they wanted to appear modern (38% in Finland, 27% in France, 19% in the Netherlands).

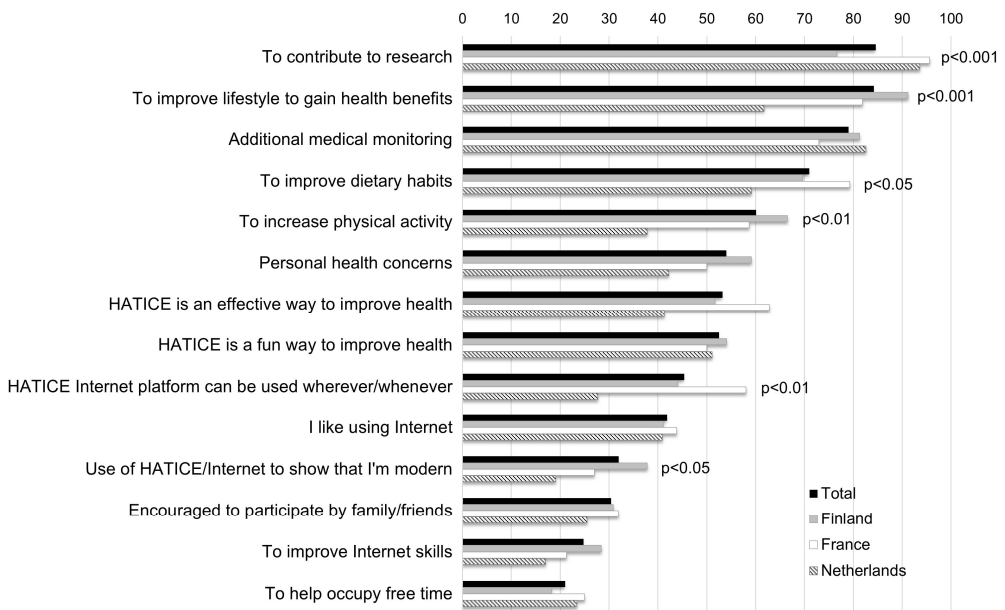


Figure 3. The percentage of respondents (total and per country) indicating each statement as a reason for participation in the HATICE RCT.

The proportions of participants (total and per country) naming each item as their main reason for participation in the HATICE RCT are shown in Figure 4. In the whole population, the most frequently mentioned main reasons were the contribution to research (32%), health benefits through lifestyle improvement (24%), and additional medical monitoring (19%). Being worried about health was selected by 8% of the respondents. Altruistic reasons appeared to be more important in France (51%) and the Netherlands (37%) than in Finland (23%). Medical monitoring was emphasized as a main reason particularly in Finland (24% vs. 13% in the Netherlands and 11% in France). Personal health concerns were selected as the main reason by 10% of the Finnish and 11% of the Dutch respondents, whereas they were hardly mentioned in France (1%). While the attitude towards the Internet was overall positive and it was considered a fun and effective tool to improve health, only approximately 4% of all respondents mentioned any Internet-related reason as their main reason for participation. In total, 12 individuals specified 'other reason' as their main reason for participation. In addition to reasons which fall under the categories of altruism, lifestyle improvement, and medical monitoring, the following aspects were also mentioned: curiosity, interest in health and memory-related topics, being advised to participate by a GP, and the non-pharmacological nature of the intervention (i.e., health advice instead of drug treatment).

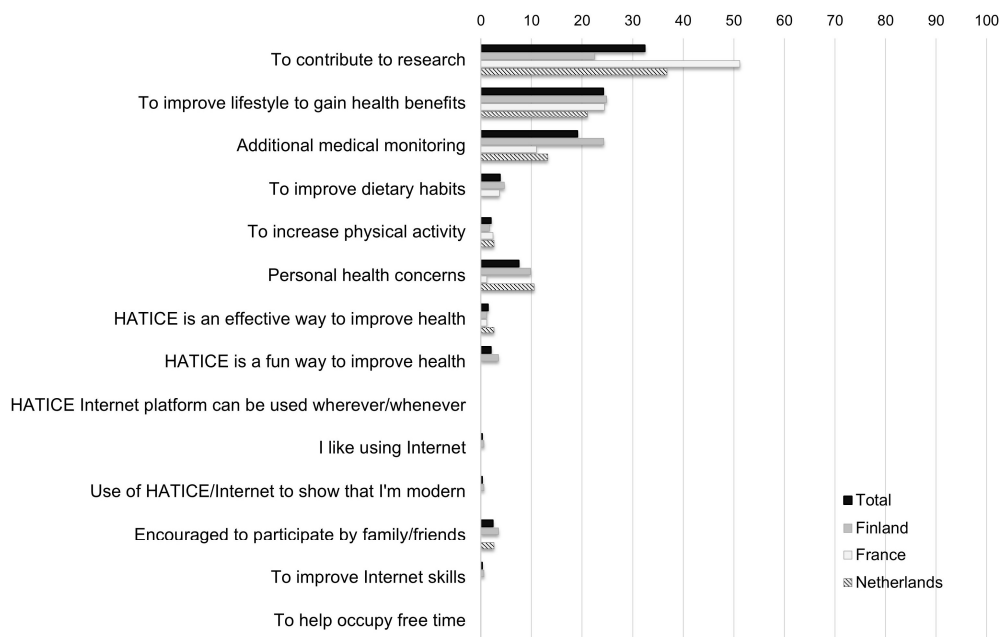


Figure 4. The percentage of respondents (total and per country) indicating each statement as the main reason for participation in the HATICE RCT.

A total of just 32 individuals completed the non-participation questionnaire (10 in Finland, 19 in France, 3 in the Netherlands). Common reasons for non-participation written in the free-text field included the following: lack of time, having other commitments, having already a healthy lifestyle, participation in another study, receiving already sufficient medical care, and self-exclusion (i.e., the person considered that the trial eligibility criteria listed in the invitation letter were not met).

5.3.2 Interviews

In line with the questionnaire responses, a willingness to contribute to research, the desire to change lifestyle to gain health benefits, and an interest in additional medical monitoring emerged in the interviews as the most common reasons for participation in HATICE. Through the content analysis, a desire to maintain independence, wellbeing, and the ability to function in old age was identified as the main theme: it appeared to be a key incentive underlying the decision to participate (Figure 5).

With respect to altruistic reasons, the interviewees frequently expressed concerns over aging and health deterioration, and it shaped their perceptions of medical research. Such individuals were motivated to contribute to research specifically focused on older adults' health and wellbeing. Although the interviewees talked selflessly about helping others or society, and considered participation as a duty and privilege, increased awareness of aging-related health issues and the importance of research was in some cases linked to personal concerns and experiences with severely ill family members or institutionalized relatives. Altruistic reasons were

expressed particularly in France, whereas they seemed mostly subordinate to other more important reasons in Finland and in the Netherlands.

Lifestyle improvement through the HATICE RCT was discussed in detail mostly in Finland and in the Netherlands. The interviewees tended to recognize where they had room for improvement and often gave concrete examples of risk factors or unhealthy behaviors they wanted to focus on. Participation was commonly envisioned as having a personal trainer who would provide support and tailored advice for sustained lifestyle changes and boost motivation. Rather than being free of disease or infirmity, the main motivation towards lifestyle change was to keep in shape in order to lead an active, socially fulfilling, and mobile life now and later in old age. A wish to avoid disability and institutionalization was frequently expressed.

With respect to medical monitoring, some interviewees expressed a need for reassurance, and some considered it an add-on to their current care (e.g., more frequent monitoring of blood lipids or glucose). Some, on the other hand, perceived it as a simple, low-threshold way to share their concerns with health care professionals and to learn about their health status and risk. Early detection of health issues and better monitoring of existing diseases were considered important in order to lead an independent and disability-free life. Medical monitoring and health concerns were emphasized particularly in Finland, where the interviewees frequently mentioned difficulties in accessing health care. Other issues were also raised, such as the lack of continuity in care and lack of contact with an own assigned GP. Medical monitoring was mentioned to a lesser extent in the Netherlands, and in France these aspects were not spontaneously mentioned as reasons for participation.

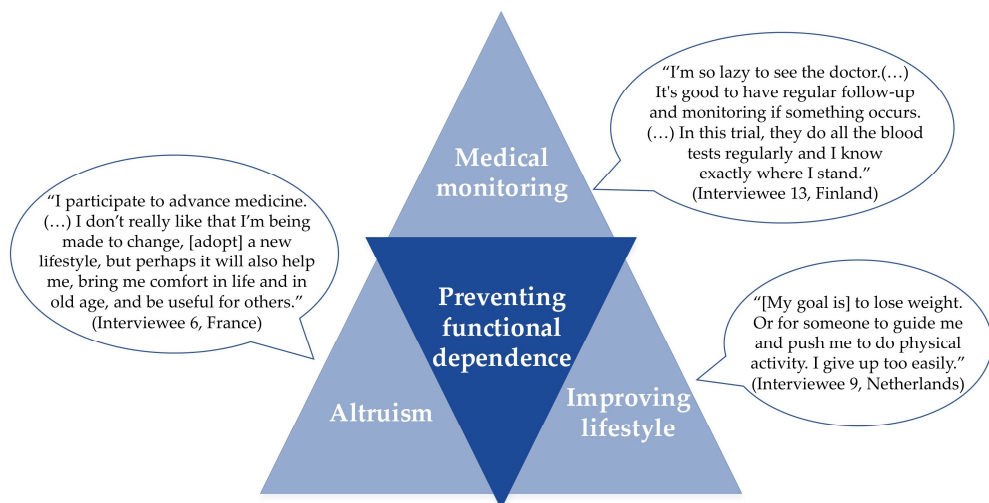


Figure 5. The most common reasons for participation in HATICE based on the interviews.

The light blue triangles represent the most important reasons expressed by the participants; examples of quotes are shown for each reason. The dark blue triangle represents the main theme and underlying motivation for participation.

5.4 KNOWLEDGE OF AND ATTITUDE TOWARDS DEMENTIA AND PREVENTION AMONG PARTICIPANTS IN A MULTIDOMAIN LIFESTYLE TRIAL – STUDY III

Through the content analysis, categories were generated to describe each of the three pre-defined research questions: 1) knowledge of dementia and prevention, 2) perceptions and feelings associated with dementia, and 3) attitudes towards dementia prevention. The research questions and categories are presented in Figure 6 on page 95. Having a family history of dementia or other indirect experiences through friends or acquaintances was identified as the theme. Personal experiences were linked to each of the research questions: 1) what the participants knew and thought about dementia, 2) what kinds of emotions dementia evoked, and 3) how the participants perceived the possibility and usefulness of prevention and the potential benefits of participating in a prevention RCT (Figure 6). In the following paragraphs, the main results are presented, and examples of illustrative quotes are given. Additional quotes can be found in the original Study III publication.

Overall, the interviewees appeared to have partial understanding of the cause and risk/protective factors of dementia. A clear need for practical, concrete advice and information from a reliable source was expressed. Old age and genetic factors were frequently emphasized as key risk factors, especially by interviewees reporting a family history of dementia or other first-hand experiences with affected people. In contrast, the role of a healthy lifestyle and management of vascular risk factors were discussed in a superficial manner, if at all. While those reporting a family history of dementia tended to have reasonable knowledge of some risk factors, they also expressed uncertainty and hesitation because of their conflicting experiences.

“Only the normal type of dementia occurs in my family, the type that comes with high age. It is very likely that I will get it as well.” (Interviewee 5, female, 68 years)

“I don’t really know if there is any link [between CVD and dementia]. (...) I don’t know if the risk factors are the same or different.” (Interviewee 1, female, 71 years).

“I feel sorry for my brother, he was a picture of health and had a healthy diet for his whole life. No alcohol, cigarettes, or anything. He was slim, worked hard, exercised, and still he got diabetes and AD.” (Interviewee 2, female, 70 years)

Psychosocial factors, such as stress, depression, and lack of social engagement, were the most widely recognized modifiable risk factors of dementia. In addition, the most common answer interviewees provided as ways to reduce dementia risk was engaging in socially and cognitively stimulating activities. Yet, participants did not appear to have strong confidence in prevention. Discrepant opinions and doubts about the possibility of prevention were frequently expressed, and such reservations

were again related to conflicting personal experiences among interviewees with a family history of dementia or other relationship with affected people.

“I’ve been thinking whether I’m preventing dementia when I use the computer? I’ve read a lot about prevention; solve crossword puzzles, do this and do that, and you will supposedly prevent dementia. I’m skeptical about that. (...) I’m not sure whether it’s possible to have an impact on the brain. Whether our own actions can have an effect. Damn, if the frontal lobe shuts down, it will shut down.” (Interviewee 13, female, 66 years)

In general, the interviewees often perceived dementia as a part of normal aging or as a hereditary condition which “comes if it’s meant to be and nothing can be done about it” (Interviewee 10, female, 67 years). However, many believed that the onset of dementia could potentially be postponed (in their case or in general), even if avoiding the disease altogether might not be possible. Driven by fear of dementia and a perceived high personal risk of falling ill, some of these individuals reported high motivation and a proactive attitude towards lifestyle and behavior changes.

(Interviewer: Is there anything one can do when it comes to dementia?) “I don’t know, I don’t think so. (...) I guess it happens slowly. I don’t know, maybe it can be slowed down a little bit by exercising and training memory... By keeping the brain active and solving different tasks and problems.” (Interviewer: Brain training?) “Yes exactly, brain training is the right word.” (Interviewee 6, male, 66 years)

(Interviewer: What motivates you towards prevention of dementia?) “Fear, having seen in my parents how severe these diseases are.” (Interviewee 1, female, 71 years)

Getting diagnosed and treated with available symptomatic medications as early as possible, as well as regular medical follow-ups, were considered crucial for slowing down the disease progression. This topic was particularly elaborated on by some interviewees who disclosed a family history of dementia or other indirect experiences.

“Of course, it’s not possible to stop or prevent it [AD], if it happens to me too. But at least... (...) Our mother started the medication quite late (...). I don’t know if it’s possible to detect it [the disease] myself, but at least when others notice that there’s something wrong with me... It would be possible to intervene earlier. To get the medication early. I think that the medication was crucial in my mother’s case. God knows how fast the disease would have progressed without it.” (Interviewee 7, female, 67 years)

Fear and concern were often mentioned when the interviewees described what kinds of emotions the topic of dementia evoked. When the interviewees tried to explain why they felt scared and worried about dementia, they tended to talk about its progressive and incurable nature and described it as a burden. Dementia was also

commonly associated with loss of independence and autonomy. Fear and concern were expressed even by those who tended to have an otherwise positive and carefree outlook on aging and health. Those with personal experiences with affected people, such as caregivers to relatives or family members, shared their emotional and often negative stories, and these seemed to shape their perceptions of dementia. Commonly described feelings of despair and hopelessness indicated a stigma.

“I guess it [dementia] can be slowed down but eventually, it will happen if it’s meant to be. I guess what everyone fears the most is that one becomes faulty. That others need to look after you and you can’t take care of yourself.” (Interviewee 4, male, 66 years)

“It’s such a burden for others. An immense burden. It’s terrible. It worries me, I’ve always told others that if I get dementia, they should drown me.” (Interviewee 13, female, 66 years)

“I know how hard the final stages are for the family. Our grandmother didn’t recognize anyone else but me, and when she saw her reflection in the mirror, she asked who that stranger was. (...) Then she became physically unable to function. Dirtied places with her feces (...). I wouldn’t wish that for myself.” (Interviewee 10, female, 67 years).

In addition to being generally worried about dementia and its societal burden, many interviewees stated being specifically concerned over their own cognitive status and risk of dementia. This was particularly evident among those disclosing a family history or other indirect experiences of dementia. Such individuals also frequently appeared to be interested in the HATICE RCT. This was either because they were interested in the topic of dementia and wanted more information about it, or because they were curious to learn specifically about their current health status and future risk through different tests and assessments. Diagnostic and prognostic tests, for example genetic and other assessments not in use in regular health care, were thought to be available in research settings.

“[I expect to learn] what causes it and which factors have an impact on it and whether I have this burden [disease] too.” (Interviewee 10, female, 67 years).

“What interests me the most is whether they detect anything [in my memory] ... Memory is the most mysterious thing for me. (...) Memory interests me in particular. The other things [lifestyle-related] are more on the side. (...)” (Interviewee 15, male, 67 years)

“I thought that since they run genetic tests I will find out if I carry dementia genes. But apparently that’s not the case.” (Interviewee 3, female, 67 years)

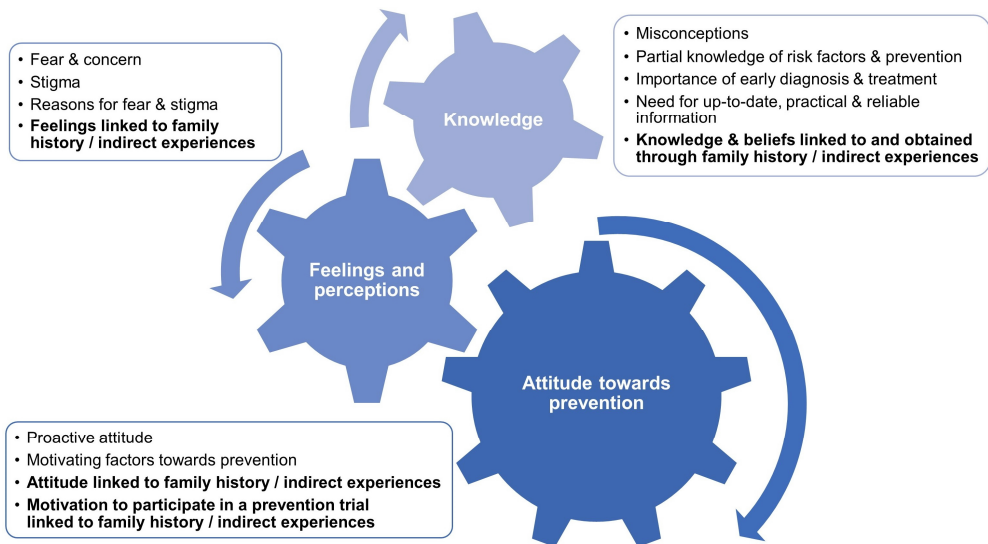


Figure 6. Categories identified to describe the participants' knowledge and perceptions of and attitude towards dementia and prevention.

The cogwheels represent the three pre-defined research questions; the text boxes contain the categories identified through the analysis. Categories marked in bold constitute the main theme that was linked to all research questions.

5.5 DISEASE PROGRESSION IN PATIENTS WITH MILD COGNITIVE IMPAIRMENT AND NORMAL CSF AMYLOID – STUDY IV

5.5.1 Progression to dementia and biomarker profiles

In the memory clinic MCI population with CSF A β 42 within the normal range, a total of 121 out of 318 patients (38.1%) progressed to dementia after a mean follow-up time of three years (range 1-10 years). AD was specified as the underlying cause of dementia in 75% of the cases (91/121). Other etiologies were vascular dementia, frontotemporal dementia, unspecified dementia, and Parkinson's disease dementia. A detailed baseline comparison between those who did and did not progress to dementia is shown in the original Study IV publication. In summary, those who developed dementia were on average older when they were first examined at the Memory Clinic and more often *APOE* ϵ 4 carriers. Their performance in the RAVLT immediate and delayed recall tests was poorer, they had more pronounced MTA, and their CSF t-tau and p-tau levels were higher and A β 42 levels lower, although all patients had A β 42 levels within the normal range. No differences were observed in

the level of education, sex distribution, CAIDE score, or individual vascular risk factors, apart from SBP (higher among those who progressed to dementia).

The patients' baseline biomarker profiles and progression rates to dementia within each group are shown in Table 6. Among patients with a full biomarker profile available (t-tau and p-tau in CSF, and MTA; N=236), 87 (36.9%) had one, 35 (14.8%) two, and 13 (5.5%) three abnormal biomarkers. All biomarkers were considered normal in 101 patients (42.8%). Approximately a quarter of patients with normal biomarkers progressed to dementia (26 out of 101), while 84.6% of those with three abnormal biomarkers developed dementia (11 out of 13).

Table 6. Biomarker profiles and progression to some type of dementia.

Biomarker profile	N (%)	Progression to dementia within group N (%)
0 abnormal biomarkers		
P-tau- T-tau- MTA-	101 (42.8)	26 (25.7)
1 abnormal biomarker		
P-tau+ T-tau- MTA-	4 (1.7)	0 (0.0)
P-tau- T-tau+ MTA-	22 (9.3)	13 (59.1)
P-tau- T-tau- MTA+	61 (25.9)	26 (42.6)
2 abnormal biomarkers		
P-tau+ T-tau+ MTA-	25 (10.6)	12 (48.0)
P-tau+ T-tau- MTA+	0 (0.0)	0 (0.0)
P-tau- T-tau+ MTA+	10 (4.2)	8 (80.0)
3 abnormal biomarkers		
P-tau+ T-tau+ MTA+	13 (5.5)	11 (84.6)

5.5.2 Predictors of progression

Hazard ratios (95% confidence intervals) for the associations between biomarkers, cognitive performance, *APOE* $\epsilon 4$ genotype, family history of dementia, and the risk of progression to any type of dementia are shown in Figure 7. Higher baseline CSF $A\beta 42$ levels were associated with a reduced dementia risk (HR 0.65), indicating that lower $A\beta 42$ levels—although still normal according to the laboratory cut-offs—were linked to an increased risk of disease progression. A one SD increase in t-tau and p-tau levels was associated with an approximately two-fold and 1.5-fold risk of dementia, respectively. An increased risk was also observed among those with MTA. Having the *APOE* $\epsilon 4$ genotype (at least one $\epsilon 4$ allele) approximately doubled the risk of dementia, but a family history of dementia was not predictive. Due to the small number of *APOE* $\epsilon 4/\epsilon 4$ carriers (N=24), the $\epsilon 4/\epsilon 4$ group was not considered separately. Better baseline cognitive performance (a higher RAVLT score) was associated with a lower risk. The results were similar for AD dementia as an outcome as well as when a higher cut-off was applied for $A\beta$ abnormality. These results are presented in the original Study IV publication.

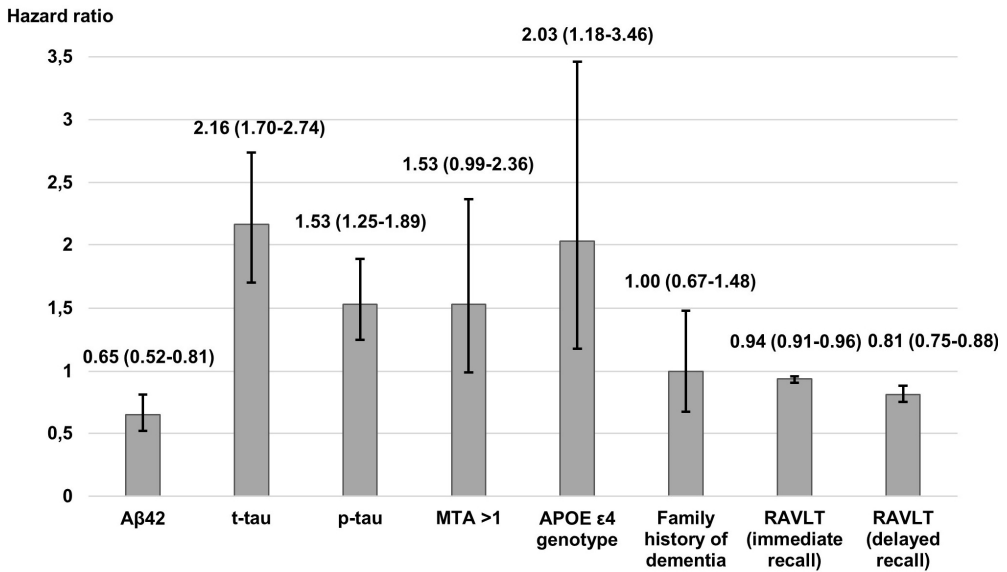


Figure 7. Association of biomarkers, cognitive performance, and non-modifiable risk factors with the risk of progression to any type of dementia.

Hazard ratios (95% confidence intervals) for the associations between vascular factors, depressive symptoms, CAIDE score, and the risk of progression to any type of dementia are shown in Figure 8. A higher SBP was associated with a higher risk of progression to dementia, while a higher BMI and depressive symptoms (a higher Cornell score) appeared to be protective. Diastolic BP, smoking habits, hypertension, hyperlipidemia, diabetes, or the CAIDE score (with and without *APOE*) were not associated with the risk of progression to dementia. The results were similar for AD dementia as an outcome as well as when a higher cut-off was applied for Aβ abnormality. These results are presented in the original Study IV publication.

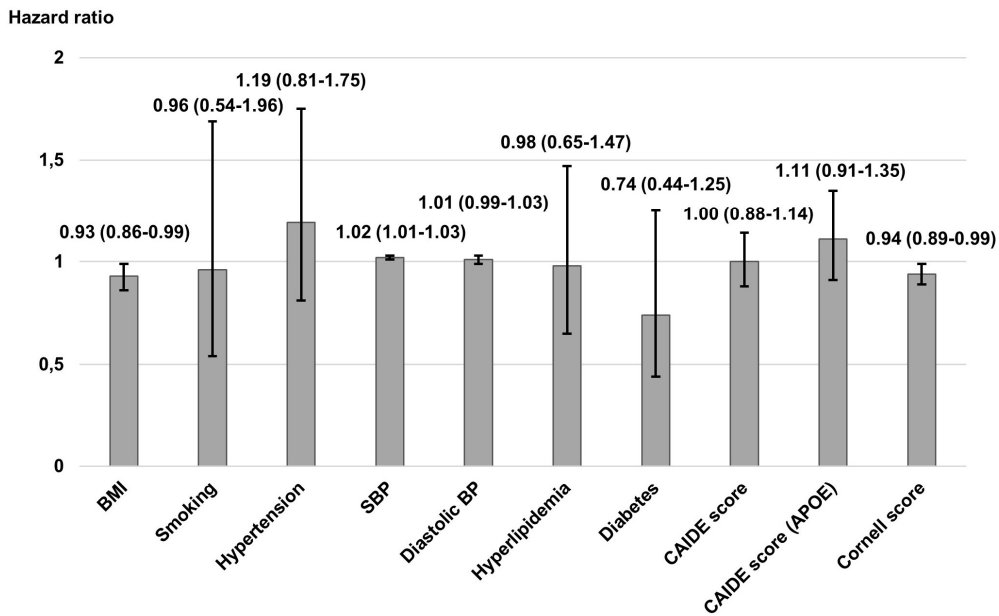


Figure 8. Association of vascular factors, depressive symptoms, and the CAIDE score with the risk of progression to any type of dementia.

Predictive performance of the basic models (age, cognition) and models with additional predictors are shown in Table 7. In the main analysis including all patients with normal A β 42 (based on the laboratory cut-offs), A β 42 improved the prediction of progression based on age and cognition alone. Adding p-tau or t-tau further improved the prediction, and a model with age and cognition together with all three CSF biomarkers was the best. Similar results were obtained in the sensitivity analyses where a higher cut-off was applied for A β abnormality (Table 7): A β 42 alone improved the basic model and was highly predictive in combination with p-tau and/or t-tau (Harrell C values over 0.80 for both outcomes).

In the main analysis, the *APOE* ϵ 4 genotype improved the basic prediction model and the magnitude of the effect was comparable to that of A β 42. MTA, vascular factors, or the Cornell score did not markedly add predictive value, meaning that the prediction based on age and cognition alone was largely similar. In the sensitivity analysis, these factors seemed to improve the prediction, but the effect was smaller than that of CSF biomarkers.

Table 7. Predictive performance of the basic models and models including additional predictors.

Prediction model	N	Harrell C for all A β 42 normal		N	Harrell C for A β 42 > 696 pg/ml		
		Dementia	AD dementia		Dementia	AD dementia	
Basic model vs. CSF biomarkers	Age, RAVLT(basic)	234	0.69	0.69	140	0.74	0.74
	Basic + A β 42		0.73	0.75		0.79	0.79
	Basic + A β 42,p-tau		0.75	0.78		0.80	0.82
	Basic + A β 42/p-tau		0.74	0.78		0.78	0.82
	Basic + A β 42,t-tau		0.76	0.81		0.82	0.87
	Basic + A β 42/t-tau		0.76	0.81		0.81	0.86
	Basic + A β 42, p-tau, t-tau		0.78	0.83		0.83	0.88
Basic model vs. MTA	Age, RAVLT(basic)	171	0.71	0.72	101	0.74	0.75
	Basic + MTA		0.71	0.72		0.77	0.78
Basic model vs. APOE ϵ 4 genotype	Age, RAVLT(basic)	133	0.68	0.68	72	0.73	0.71
	Basic + APOE		0.72	0.72		0.77	0.78
Basic model vs. SBP	Age, RAVLT(basic)	182	0.69	0.71	109	0.73	0.75
	Basic + SBP		0.70	0.71		0.77	0.78
Basic model vs. BMI	Age, RAVLT(basic)	141	0.72	0.71	82	0.78	0.82
	Basic + BMI		0.74	0.74		0.80	0.83
Basic model vs. depressive symptoms	Age, RAVLT(basic)	183	0.69	0.72	105	0.74	0.78
	Basic + Cornell		0.70	0.74		0.77	0.81

5.6 BIOMARKER PROFILES AND DISEASE PROGRESSION IN PRODROMAL AD – STUDY V

5.6.1 Classification according to the research criteria for AD

Of the 287 LipiDiDiet participants included in the analyses, 180 had only an MTA score available at baseline. These individuals had either not undergone a lumbar puncture or CSF biomarkers were not centrally analyzed. Of the 107 participants with centrally analyzed baseline CSF biomarker data available, both CSF and MTA data were available for 99 participants. The majority of the participants had abnormal CSF A β levels (87.9%), and a similar proportion of the participants had abnormal CSF t-tau levels (86.0%) and MTA (86.4%) (Table 5, p. 84). CSF p-tau levels were considered abnormal in 69.2% of the participants (Table 5, p. 84). The classification of the participants according to the IWG-2, NIA-AA 2011, and NIA-AA 2018 criteria is shown in Table 8.

Table 8. Classification of the participants according to the research diagnostic criteria for AD based on the baseline biomarker profiles.

Diagnostic criteria	Biomarker profile	N (%) within diagnostic criteria
NIA-AA 2011 (N=287)		
Low AD likelihood	Normal A β + normal p-tau, t-tau, MTA	0 (0.0%)
Isolated amyloid pathology	Abnormal A β + normal p-tau, t-tau, MTA	1 (0.3%)
Suspected non-AD pathology (SNAP)	Normal A β + abnormal p-tau, t-tau and/or MTA	13 (4.5%)
High AD likelihood	Abnormal A β + abnormal p-tau, t-tau and/or MTA	93 (32.4%)
Intermediate AD likelihood	CSF biomarkers not available, abnormal MTA	155 (54.0%)
Inconclusive/uninformative	CSF biomarkers not available, normal MTA	25 (8.7%)
IWG-2 (N=107)		
No prodromal AD	Normal A β + normal/abnormal p-tau, t-tau, MTA OR Abnormal A β + normal p-tau, t-tau, MTA	26 (24.3%)
Prodromal AD	Abnormal A β + abnormal p-tau and/or t-tau	81 (75.7%)
NIA-AA 2018 (N=107)		
Normal AD biomarkers	Normal A β + normal p-tau, t-tau, MTA	0 (0.0%)
Alzheimer's pathologic change	Abnormal A β + normal p-tau, t-tau, MTA	1 (0.9%)
Non-Alzheimer's pathologic change	Normal A β + abnormal p-tau, t-tau and/or MTA	13 (12.1%)
Alzheimer's and concomitant suspected non-Alzheimer's pathologic change	Abnormal A β + normal p-tau + abnormal t-tau and/or MTA	25 (23.4%)
AD	Abnormal A β + abnormal p-tau + normal/abnormal t-tau and/or MTA	68 (63.6%)

In the NIA-AA 2011 criteria, MTA is acknowledged as a biomarker along with the CSF biomarkers, meaning that individuals with missing CSF biomarker information can be classified. In our study, 54.0% of the participants (155/287) were thus classified in the NIA-AA 2011 intermediate AD likelihood group (Table 8). Approximately a third of the participants (32.4%, 93/287) had a high AD likelihood. The inconclusive/uninformative group comprised 8.7% of the participants (25/287). The remaining participants had conflicting biomarkers: 4.5% (13/287) were classified as SNAP and 0.3% (1/287) as isolated amyloid pathology.

The subsample of participants with available CSF biomarkers was classified according to the IWG-2 and NIA-AA 2018 research criteria (Table 8). In total, 75.7%

(81/107) had IWG-2 defined prodromal AD; approximately a quarter of the participants (24.3%, 26/107) did not. According to the NIA-AA 2018 criteria, 63.6% of the participants (68/107) were classified in the AD group. The remaining participants had conflicting biomarker evidence and were categorized as follows: 23.4% (25/107) were assigned to the Alzheimer's and concomitant suspected non-Alzheimer's pathologic change group, 12.1% (13/107) to the non-Alzheimer's pathologic change group, and 0.9% (1/107) to the Alzheimer's pathologic change group. There were no participants in the normal AD biomarker group. However, even a slight adjustment of the CSF p-tau cut-off (> 55 pg/ml instead of > 60 pg/ml) had an impact on the classification: in this case, 72.0% of the participants (77/107) were classified in the AD group and 15.0% (16/107) in the Alzheimer's and concomitant suspected non-Alzheimer's pathologic change group. A Venn diagram illustrating the participants' biomarker profiles according to the ATN classification scheme (original biomarker cut-offs) is shown in Figure 9. All participants in the AD group had an A+T+N+ biomarker profile, i.e., all individuals with abnormal CSF A β and p-tau levels also had abnormal CSF t-tau levels and/or MTA.

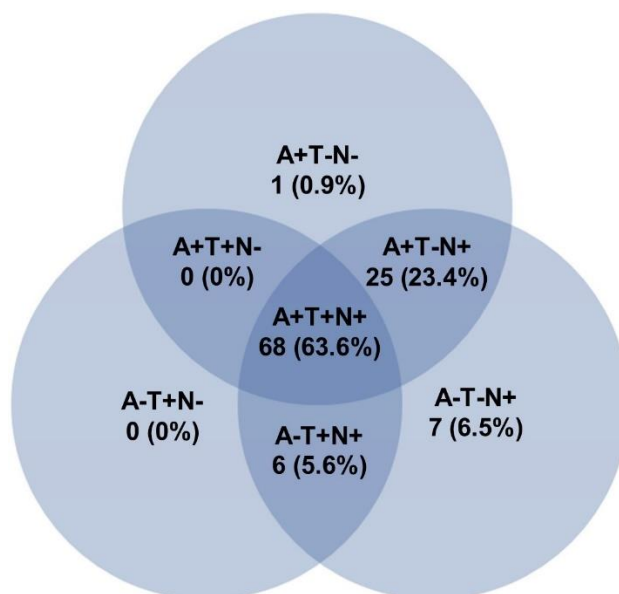


Figure 9. Biomarker profiles according to the ATN classification scheme among participants with available CSF (N=107).

A+ refers to abnormal A β (low CSF A β 42 levels and/or A β 42/40 ratio), T+ to abnormal p-tau (high CSF p-tau levels), and N+ to abnormal t-tau (high CSF t-tau levels) and/or abnormal MTA (Scheltens scale, visual rating, ≥ 1).

5.6.2 Cognitive and functional decline and progression to dementia

Estimates for the two-year changes in cognitive (NTB) and cognitive-functional (CDR-SB) performance, two-year progression rates to dementia, and hazard ratios for dementia risk are shown in Table 9 for each set of research criteria.

With respect to the IWG-2 criteria, the changes in NTB scores were modest overall in both groups, and no significant between-group differences were observed. For CDR-SB, there was more worsening in the prodromal AD group (estimate for change 1.17 points vs. 0.42 points; $p=0.03$), and this group also had a higher risk of progression to dementia (progression rate 42.0% vs. 26.9%; HR 4.7, 95% CI 1.6–13.7).

Similar to the IWG-2 groups, the changes in NTB scores were modest in all NIA-AA 2011 groups. No significant differences were observed between the reference group SNAP and the other groups, apart from the intermediate AD likelihood group, which showed a higher rate of decline in the NTB memory and total scores ($p=0.04$). No significant differences were observed between the intermediate and high AD likelihood groups, indicating a similar pattern of decline in these groups. The high AD likelihood group was more likely to progress to dementia than the SNAP group (43.0% vs. 7.7%; HR 7.5, 95% CI 1.0–55.0). There was no difference in the risk of progression between the high and intermediate AD likelihood groups.

With regard to the NIA-AA 2018 criteria, the changes in NTB scores were again small across all groups. The AD group consistently showed the highest rate of decline, but the changes did not significantly differ from those of the reference group, i.e., non-Alzheimer's pathologic change. The CDR-SB scores worsened more in the AD group than in the reference group (estimate for change 1.40 points vs. 0.50 points; $p=0.03$) and in the Alzheimer's and concomitant suspected non-Alzheimer's pathologic change group (estimate for change 1.40 points vs. 0.44 points; $p=0.01$). The Alzheimer's and concomitant suspected non-Alzheimer's pathologic change group did not differ from the reference group. The AD group was more likely to progress to dementia than the reference group (44.1% vs. 7.7%; HR 9.4, 95% CI 1.2–72.7) and the Alzheimer's and concomitant suspected non-Alzheimer's pathologic change group (44.1 % vs. 40.0%; HR 2.7, 95% CI 1.0–7.0). No difference in the progression rate was found between the Alzheimer's and concomitant suspected non-Alzheimer's pathologic change group and the reference group.

Table 9. Changes in NTB and CDR-SB scores and progression to dementia according to the IWG-2, NIA-AA 2011, and NIA-AA 2018 criteria.

Diagnostic criteria	N	Change in NTB composite		Change in NTB memory		Change in NTB executive functioning		Change in NTB total		Change in CDR-SB		Progression to dementia	
		Estimate	p	Estimate	p	Estimate	p	Estimate	p	Estimate	p	N (%)	HR (95% CI)
IWG-2													
No prodromal AD	24	-0.010	ref	0.010	ref	-0.081	ref	0.066	ref	0.42	ref	7/26 (26.9)	ref
Prodromal AD	76	-0.244	0.11	-0.238	0.12	-0.098	0.91	-0.100	0.10	1.17	0.03	34/81 (42.0)	4.7 (1.6-13.7)
NIA-AA 2011													
SNAP	13	0.099	ref	0.155	ref	-0.044	ref	0.069	ref	0.55	ref	1/13 (7.7)	ref
Inconclusive/uninformative	22	0.112	0.94	0.053	0.63	0.024	0.71	0.101	0.82	0.24	0.55	4/25 (16.0)	2.1 (0.2-19.0)
Intermediate AD likelihood	135	-0.189	0.06	-0.203	0.04	-0.148	0.49	-0.168	0.04	1.28	0.08	64/155 (41.3)	6.7 (0.9-49.2)
High AD likelihood	86	-0.190	0.07	-0.183	0.07	-0.080	0.82	-0.083	0.20	1.09	0.21	40/93 (43.0)	7.5 (1.0-55.0)
NIA-AA 2018													
Non-Alzheimer's pathologic change	13	0.067	ref	0.083	ref	-0.091	ref	0.057	ref	0.50	ref	1/13 (7.7)	ref
Alzheimer's and concomitant suspected non-Alzheimer's pathologic change	22	-0.138	0.32	-0.099	0.41	-0.111	0.92	0.044	0.92	0.44	0.90	10/25 (40.0)	3.5 (0.4-29.5)
AD	64	-0.267	0.07	-0.274	0.08	-0.088	0.99	-0.126	0.16	1.40	0.03	30/68 (44.1)	9.4 (1.2-72.7)

Estimates for change in the NTB and CDR-SB scores are least-squares means for change from baseline over two years within each group. Negative values indicate a decline over time, except for CDR-SB where positive values indicate decline. P-values are shown for the difference in the least-squares means over two years between each group and the reference group. Numbers of participants are as per the mITT analysis. Isolated amyloid pathology (NIA-AA 2011) and Alzheimer's pathologic change (NIA-AA 2018) were excluded from the analyses (N=1). CDR-SB data were missing for 9 participants (IWG-1, NIA-AA 2018) and 32 participants (NIA-AA 2011).

6 DISCUSSION

To successfully plan and conduct the next generation dementia prevention RCTs, lessons should be learned from the RCTs completed so far. This thesis offers practical insights into the selection and engagement of target populations for future RCTs. Studies I, IV, and V dealt with questions related to target population selection; Studies II and III focused on the target population perspective and dealt mainly with engagement.

Study I is so far the only study to examine heterogeneity in the response to a multidomain lifestyle intervention in an RCT that met its primary outcome and reported significant positive effects on cognition. Exploring which subgroups of participants are most likely to benefit from a multidomain lifestyle intervention has direct implications for future RCT design and participant selection. Study IV adds to the growing body of literature that calls attention to the issue of dichotomizing $A\beta$ and using this information to potentially rule out AD and future risk of disease progression. Preventive approaches need to be developed and tailored for different at-risk populations, and our findings may have implications for participant selection in future RCTs. Study V is so far the only study to apply and assess the currently available research diagnostic criteria for AD in a real-life RCT setting, both cross-sectionally and longitudinally. These criteria were specifically designed to facilitate RCT recruitment, and our work may inform certain types of prevention RCTs about the most feasible and appropriate participant selection criteria. Finally, Studies II and III were the first to comprehensively explore the target population perspective in a multidomain dementia prevention RCT. The focus was on the reasons for participation and older adults' knowledge of and attitudes towards dementia and prevention. Another novel aspect was the exploration of potential between-country differences as well as the role of eHealth in the decision to participate. Qualitative interviews allowed us to expand on the quantitative findings and gain an even better understanding of the participant perspective. The findings of these studies can be used to inform future RCT design (e.g., recruitment strategies, intervention content and delivery).

6.1 SELECTING TARGET POPULATIONS FOR DEMENTIA PREVENTION TRIALS

6.1.1 Community-dwelling at-risk older adults as a target population

FINGER is the first and—so far—only large long-term RCT to demonstrate that community-dwelling at-risk older adults benefitted from a multidomain lifestyle intervention designed to prevent cognitive impairment. In a pre-specified subgroup analysis, we assessed whether the overall beneficial effects of the intervention were evident also in different subgroups of participants and whether there was any effect

modification by the participant baseline characteristics. This was done to understand if the FINGER eligibility criteria were sufficient, or if a further stratification or enrichment based on the risk profile would have led to better effects. We found no statistically significant heterogeneity in the intervention effects or response, suggesting that the participants benefitted from the intervention regardless of their age, sex, education, socioeconomic status, cognitive performance, and vascular risk profile. The estimated differences in the change in cognition between the intervention and control groups were consistently positive in all subgroups (in favor of the intervention group, indicating more improvement).

Subgroup analyses of RCTs are common. Even in RCTs reporting overall non-significant results, as in many AD/dementia RCTs, they can be useful to generate further hypotheses and inform future RCTs about the optimal selection of target populations. Subgroup analyses can be complex and difficult to evaluate, and cautious interpretations of the results are always warranted. Lack of appropriate interaction analyses and drawing conclusions based on p-values within subgroups are common issues (e.g., effect modification is considered to occur when $p < 0.05$ in one subgroup but not the other) (Wang et al., 2007). In addition, the absence of statistically significant interaction effects does not rule out the possibility of effect modification, because few RCTs are powered to detect such effects in subgroup analyses (Wang et al., 2007). On the other hand, studying multiple subgroups and outcomes increases the probability of finding significant effects by chance. For example, we conducted a total of 56 analyses (14 subgroups x four cognitive outcomes), which by chance alone would result in up to two significant interaction terms at a significance level of $p=0.05$ (one was indeed found). Another problem in subgroup analyses is that they can suggest a lack of effect in some subgroups when the RCT results are overall positive (Rothwell, 2005). We did not observe this, and the estimates within the subgroups were consistently positive and in line with the main FINGER results. Therefore, while effect modification by participant baseline characteristics cannot be fully ruled out in the FINGER RCT, it seems that the intervention likely benefitted the entire at-risk study population. The positive effects were not limited to certain subgroups of participants, such as those at highest risk of future cognitive decline based on their age or vascular risk profile.

It is still plausible that individuals who have more room for improvement in some aspect of the lifestyle or vascular profile could benefit more from an intervention designed to target that specific factor. For example, even if no interaction effects were reported in the subgroup analyses of the SPRINT-MIND BP control RCT, a strong beneficial effect was observed within the subgroup with the highest BP at baseline (Williamson et al., 2019). In the LIFE exercise RCT, the subgroup analyses suggested benefits among individuals with a poorer physical performance (Sink et al., 2015). Likewise, there was some indication of particularly pronounced intervention benefits in certain high-risk subgroups within our FINGER study population. These included those who were older, those who had MMSE scores below the median, and those with higher levels of vascular risk factors (e.g., SBP and cholesterol above the

median). Some of the subgroups seemed somewhat counterintuitive, such as those with lower BMI or lower diastolic BP and those with no history of CVD. These findings underline that it can be challenging to interpret results of subgroup analyses, and importantly this demonstrates that assessing the risk of cognitive decline in older adults is not straightforward. With respect to CVD, it is also possible that participants with a diagnosed disease already had close contact with regular health care and their risk factors were well controlled and monitored outside this RCT.

In the context of large multidomain dementia prevention RCTs, in addition to our FINGER study, subgroup analyses have been conducted in the MAPT and preDIVA RCTs, both of which reported non-significant overall results. In the MAPT RCT, pre-specified analysis included subgrouping by baseline cognitive performance; exploratory subgroups were based on the *APOE* genotype, frailty, CAIDE score, A β status in PET, and blood fatty acid profile (due to the omega-3 intervention) (Andrieu et al., 2017; Chhetri et al., 2018). The authors reported significant interaction effects and intervention benefits among A β positive participants and those with a CAIDE score of at least six, the cut-off used in the FINGER RCT to select participants. Other baseline characteristics did not modify the response to intervention. With respect to *APOE*, a significant difference between the intervention and control groups (indicating an intervention benefit) was observed within the ϵ 4 carrier subgroup (Andrieu et al., 2017). Interestingly, Solomon et al. (2018) reported a similar pattern in the FINGER RCT. Again, the interpretation of within-subgroup results is challenging, especially when the overall interaction effects are non-significant. Nevertheless, these results collectively suggest that the effects of a multidomain lifestyle intervention are not limited to *APOE* ϵ 4 non-carriers, and lifestyle changes can support and improve cognitive performance also among individuals with a genetic susceptibility to AD.

In the preDIVA RCT, effect modification was investigated in subgroups based on age, sex, *APOE* genotype, and the baseline vascular risk profile (CVD, hypertension, and hyperlipidemia) (van Charante et al., 2016). Effect modification was investigated also separately in ITT and per protocol analyses (the latter included only participants who adhered to the study visits and the protocol). Formal tests of interactions were not shown, but based on the per protocol analysis the authors concluded that there were intervention benefits among those with no history of CVD as well as among those with untreated hypertension (a diagnosis but no ongoing treatment). With respect to risk scores, the preDIVA research group investigated potential effect modification by the LIBRA score (van Middelaar et al., 2018b). Unlike for MAPT, the authors reported that the effects of the preDIVA intervention did not vary by the level of dementia risk at baseline. In other words, there was no indication that higher-risk individuals would have benefitted from the intervention.

Overall, it is difficult to assess whether the significant positive results in the FINGER and the non-significant results in the MAPT and preDIVA RCTs are attributable to the selection of the target populations. This is because many additional

factors such as intervention content and intensity likely played an important role. Nevertheless, our findings suggest that the FINGER recruitment strategy was successful. The MAPT and preDIVA subgroup analyses, as well as previous experiences in diabetes prevention RCTs (Lindström et al., 2008; Sussman et al., 2015), further support the hypothesis that recruiting at-risk individuals and enriching the study population for vascular risk might be the preferred approach in multidomain lifestyle prevention RCTs. Indeed, many of the new ongoing or planned dementia prevention RCTs, which are discussed in the literature review in section 2.2.3, target different types of at-risk, rather than unselected, populations. For example, the U.S. POINTER RCT is recruiting physically inactive older adults with a family history of dementia, and the South Korean SUPERBRAIN and Australian MYB RCTs are targeting individuals with at least one or two modifiable risk factors, respectively (Kivipelto et al., 2020). The CAIDE risk score is also being used as an inclusion criterion, for example in the APPLE-Tree RCT (Cooper et al., 2020). As in the FINGER study, the requirement in this RCT is a score of at least six.

While the FINGER RCT targeted an at-risk population, the inclusion criteria were overall fairly pragmatic. The cognitive criteria excluded only extreme performers (significant cognitive impairment or very good cognition), and the CAIDE cut-off score was fairly lenient, ruling out only individuals with a very low dementia risk. In fact, more than 80% of the individuals in the population-based surveys, which were used to identify potentially eligible FINGER participants, had a CAIDE score of at least six (Ngandu et al., 2014). In the MAPT RCT, the CAIDE score was not used in recruitment, but 87% of the participants still had a score of at least six (Andrieu et al., 2017). More restrictive criteria are applied in some ongoing RCTs, for example in the German Agewell.de RCT (Zülke et al., 2019), to select a population at an even higher risk of dementia. In this RCT, a CAIDE score of at least nine is required. While this might, in theory, seem a better approach to maximize the chance of clear intervention benefits—especially in community-dwelling older adults without any significant cognitive impairment—recruitment could become an issue when fewer individuals meet the eligibility criteria. The generalizability of the results could also suffer, which has implications for the implementation of successful prevention strategies into clinical practice. In this regard, it is relevant to consider previous experiences and findings in CVD research. In CVD prevention, a broad population-based strategy to address risk factors has potentially the biggest impact on public health (Jousilahti et al., 2016). According to the so-called prevention paradox, most disease cases occur in a large population at low or moderate risk, and thus, a small risk reduction in this large low/moderate risk population has more impact than a large risk reduction in a small population of high-risk individuals (Rose, 1981). This also means that interventions could have great public health impacts, even if the benefits experienced by an individual would be fairly small.

6.1.2 Cognitively impaired individuals with and without AD-pathology as target populations

The NIA-AA recently proposed a purely biological definition of AD in the 2018 research framework (Jack et al., 2018). Regardless of cognitive performance and clinical symptoms, AD could be defined by a specific biomarker profile, the key biomarker being $A\beta$. The research framework and the related ATN biomarker classification scheme (Jack et al., 2016) rely on biomarker dichotomization as ‘normal’ and ‘abnormal’, based on certain cut-off values. A typical AD biomarker profile equals a higher risk of cognitive deterioration, and individuals without a clear $A\beta$ pathology are assumed to have a non-AD pathology and to develop a non-AD dementia should their cognition even decline over time. We investigated the prognosis of this less studied at-risk population in a memory clinic study including MCI patients. Approximately 38% of these patients with CSF $A\beta$ levels within the normal range (based on laboratory cut-offs) developed dementia during a fairly short mean follow-up period of three years, the majority of the cases being the AD-type. Expectedly, given that markers of neuronal injury correlate with cognitive decline and disease progression (Jack et al., 2010), we found that these markers were associated with a higher dementia risk, but interestingly, a lower CSF $A\beta$ within the normal range was also associated with a higher risk (both all-type and AD dementia). Compared to a minimal set of basic, commonly available clinical predictors (age, test of episodic memory), CSF biomarkers—including $A\beta$ —and particularly the combination of all three markers also slightly improved the prediction (Harrell C approximately 0.7 (borderline acceptable) for the basic model; 0.75 for the model including also $A\beta$; and 0.8 (borderline excellent) for the full model). Our findings suggest that lower $A\beta$ levels might not be benign even in patients with $A\beta$ within the normal range, and the possibility of AD should not be ruled out in this population.

Abnormality of both $A\beta$ and neuronal injury markers is associated with a greater risk of clinical progression and faster cognitive decline in MCI than abnormality of neuronal injury markers alone, but a number of $A\beta$ -normal, ‘lower-risk’ individuals still develop AD-type dementia over time (Caroli et al., 2015; Petersen et al., 2013; Prestia et al., 2013; Vos et al., 2015). The association between continuous CSF biomarkers and the risk of disease progression in this type of population has previously been investigated in one study (Tijms et al., 2017). This study was conducted in a mixed SCI/MCI memory clinic population and the findings are largely similar to ours (lower normal $A\beta$ levels were associated with an increased risk). It has been somewhat unclear whether the association could mainly be driven by individuals with $A\beta$ levels only slightly above the cut-off value. For example, one study found that MCI patients with SNAP, who later progressed to dementia, tended to have subthreshold $A\beta$ (Vos et al., 2015). If this was the case, the issue might be solved by updating the current biomarker cut-offs, which are indeed controversial, in particular when it comes to CSF $A\beta$ (Schindler et al., 2018). In the sensitivity analysis of our study, we applied a higher threshold for normal $A\beta$, resulting in the exclusion of patients in the gray zone. Largely comparable results were obtained,

indicating that the findings were not driven by individuals with A β just above the cut-off value. The study by Tijms et al. (2017) supports our conclusions. To select the A β -normal participants for this study, the researchers used a research-based cut-off that was stricter than the one used in routine clinical practice. Collectively, these findings suggest that simply adjusting the current A β cut-offs may not be the optimal solution, and a clear-cut threshold to identify individuals with and without underlying AD may not exist at all.

The accumulation of brain pathology is a complex and dynamic process that should be viewed as a continuum with no sharp boundaries between normal and abnormal, or disease and no disease—even if cut-offs are useful in certain situations to identify high-risk individuals. A growing body of literature highlights the importance of studying A β as a continuous rather than only a dichotomous measure. One PET study concluded that a continuous measure of the A β burden (in this case the standardized A β tracer uptake value ratio in PET) might be more informative than a simple dichotomization when predicting the rate of cognitive decline in middle-aged cognitively healthy individuals (Farrell et al., 2017). A greater A β burden, mainly among A β -positive individuals, was associated with more decline over time in this study. Other PET studies, also in cognitively healthy individuals, showed that the accumulation of A β within the normal range might be related to subsequent cognitive decline (Farrell et al., 2018; Landau et al., 2018). ADNI studies in cognitively healthy and MCI individuals have reported substantial changes in neuronal injury markers and cognitive performance even below the A β positivity threshold (Insel et al., 2015a, 2016, 2017). A perspective paper that was published approximately at the same time as our study, also called attention to the problem with A β dichotomization (McRae-McKee et al., 2019). In this study, cognitively healthy ADNI participants were classified as A β positive or negative according to the established cut-offs for A β PET positivity in the ADNI cohort. The difference between the observed value and cut-off value was calculated for each participant (indicative of how much the value is below or above the cut-off). The authors found that the cognitive trajectories were largely similar when excluding individuals with any extreme values and focusing on those with values close to the threshold (comprising 40% of the whole sample).

In our so-called amyloid-normal memory clinic cohort, we also investigated factors other than CSF biomarkers as potential predictors of subsequent dementia. Factors included in the analysis were cognitive performance (episodic memory), MTA, the *APOE* genotype, a family history of dementia, the Cornell test score as a measure of depressive symptoms, the CAIDE score, and vascular factors including BP, BMI, smoking habits, and vascular conditions. A poorer episodic memory, *APOE* ϵ 4 genotype, and higher SBP showed an association with a higher dementia risk, while higher BMI and depressive symptoms were associated with a lower risk. Other vascular factors, smoking, or the CAIDE score were not associated with the risk of disease progression. None of the factors markedly improved the prediction of dementia based on age and cognition alone. However, it is noteworthy that some

variables were only available for a subset of patients, potentially limiting the statistical power of the analyses.

Overall, previous findings on modifiable risk factors as predictors of progression from MCI to dementia are mixed. While important in mid-life, these factors might have a less straightforward role in old age and when the follow-up period is fairly short. They could potentially also have only limited relevance in a cognitively impaired patient population. In one meta-analysis, lower BMI, hypertension, and diabetes were identified as risk factors for progression, while smoking and hyperlipidemia did not show an association with subsequent dementia (Li et al., 2016). Another meta-analysis evaluated the evidence and reported findings separately for amnesic/non-amnesic/any MCI and for AD dementia/any dementia as outcomes (Cooper et al., 2015). In this study, a lower BMI and excessive use of alcohol were identified as risk factors for progression from any MCI to any dementia; metabolic syndrome was a risk factor for progression from amnesic MCI to any dementia; and diabetes was a risk factor for progression from amnesic and other types of MCI to both AD and any dementia. Physical activity was associated with a lower dementia risk (progression from any MCI to any dementia), as was a Mediterranean-type diet (progression from amnesic MCI to AD dementia). Inconsistent evidence or a lack of association was reported for depression, smoking, hypertension, and hyperlipidemia (Cooper et al., 2015). In these meta-analyses, the predictors were not assessed separately in $A\beta$ negative and positive patients. In one large multicenter study investigating predictors of cognitive decline, individuals were classified according to the IWG-2 and NIA-AA 2011 criteria (Bos et al., 2017). In this study, alcohol consumption was identified as the only modifiable predictor for disease progression in MCI, whereas smoking habits, depression, obesity, and vascular comorbidities (hypertension, hyperlipidemia, diabetes, stroke, and atherosclerosis) did not predict future decline. No effect modification by the biomarker profile was observed.

Prior to our study, the potential utility of the CAIDE score as a prediction tool in memory clinic settings has been investigated in another Karolinska University Hospital Memory Clinic study where the population was a mixed group of SCI and MCI patients (Enache et al., 2016). These patients were not selected or classified according to their biomarker profiles. The authors of this study concluded that the CAIDE score (with and without *APOE*) was a fairly poor short-term predictor of dementia (areas under the curve approximately 0.6). It is likely that other prediction models and tools are needed for memory clinic populations. Ideally, these could be more personalized than the current tools and include continuous biomarkers instead of a categorization as abnormal or normal. Recently, such models were proposed for memory clinic MCI patients and they were also validated externally (van Maurik et al., 2017, 2019). These models did not include any vascular, lifestyle-related, or other potentially modifiable risk factors, which is typical for prediction models that are intended for individuals with MCI. A recent meta-analysis identified 15 different models for prediction of progression from MCI to AD dementia, all of which relied

on cognitive tests and biomarkers and none of which included modifiable factors (Hou et al., 2019). Prediction tools with more than simply fixed components would have the advantage of including factors that could be managed and monitored by the patients themselves and targeted with preventive interventions.

With respect to memory clinic MCI populations, including those without a clear AD-type pathology, it remains unclear what the most relevant risk factors are for disease progression and whether improving them could actually slow down cognitive decline or delay the onset of dementia. In our study, higher BP and lower BMI were associated with an increased dementia risk, but these factors did not markedly improve the prediction based on age and cognition alone. In this already cognitively impaired patient population, it is possible that a change over time in these factors, for instance weight loss, could have been more informative than the absolute values at the time of the baseline assessment. However, this information was not available. Other potentially relevant modifiable factors that were not available for our analyses include for example physical activity, dietary habits, and engagement in cognitive and social activities. In addition to the limited data availability, our clinic-based study also has other important limitations. First, there was variation in the follow-up time and number of memory clinic visits, and because of the relatively short mean follow-up period, it is possible that some patients will progress to dementia at a later stage. Second, follow-up visits at the Memory Clinic are arranged based on the clinician's assessment and judgment, and higher-risk individuals might be more likely to be re-examined at the clinic after their first diagnosis. Finally, as the clinicians were not blinded to the CSF biomarker data, bias introduced due to circularity cannot be fully ruled out. However, lumbar puncture and CSF collection is a part of the routine examination protocol at the Memory Clinic (i.e., it is performed for all patients who can safely undergo the procedure, not just for those with suspected AD).

Considering the positive signals in the SPRINT-MIND BP control RCT (Williamson et al., 2019), the association we observed between BP and the risk of dementia in our study population could be interesting and should be further explored. With respect to weight and nutritional status, some RCTs are already investigating the possibility to slow down cognitive decline by supporting the nutritional status and improving nutritional deficiency at the pre-dementia stage. One example is the LipiDiDiet RCT investigating a multinutrient medical food product (Soininen et al., 2017). Another example is the Multimodal Preventive Trial for Alzheimer's Disease (MIND-ADmini) pilot RCT (ClinicalTrials.gov identifier NCT03249688), which is based on the LipiDiDiet and FINGER RCTs and targets prodromal AD (Kivipelto et al., 2020). The MIND-ADmini study is evaluating the feasibility of a lifestyle-based, FINGER-type multidomain intervention, alone and together with the multinutrient medical food product used in the LipiDiDiet RCT. This approach addresses many different modifiable risk factors simultaneously. Several other initiatives to address modifiable risk factors in MCI are also ongoing, as discussed in the literature review in section 2.2.3.

The above-mentioned LipiDiDiet and MIND-ADmini RCTs, as well as drug RCTs and many other ongoing and planned RCTs, focus specifically on the early prodromal stages of AD rather than more heterogeneous MCI populations. However, it remains unclear what the ideal criteria are to identify the prodromal AD population. Optimal selection criteria depend on the RCT, but in general, the criteria should be specific enough to reliably identify a population with underlying AD-pathology and a high short-term risk of disease progression, yet be pragmatic enough to ensure efficient recruitment. The LipiDiDiet RCT is one of the first prevention RCTs to use the IWG-1 criteria for prodromal AD in participant selection, and it offers a rare opportunity to apply and assess all the so far proposed research diagnostic criteria for AD in a real-life RCT setting. This is because the study population selected based on the less restrictive criteria could be re-classified according to the more restrictive criteria. In our study, we examined the LipiDiDiet participants' baseline biomarker profiles, classified them according to the IWG-2, NIA-AA 2011, and NIA-AA 2018 criteria, and investigated the rate of cognitive/functional decline and risk of progression to dementia over two years. We found that the majority of the participants could be classified as having prodromal AD (IWG-2), a high AD likelihood (NIA-AA 2011), and AD (NIA-AA 2018), even though MTA was often the only biomarker analyzed at screening. Nearly nine out of 10 participants were A β positive, and most participants had an A+T+N+ biomarker profile.

Previous studies have shown that the newer research diagnostic criteria tend to be more specific than the IWG-1 criteria (Prestia et al., 2015; Vos et al., 2015). Still, our findings suggest that the IWG-1 criteria may reliably capture an early symptomatic AD population, even though these criteria are more pragmatic and require less comprehensive biomarker evidence than the more recently proposed criteria. It is still noteworthy that approximately a quarter of the participants with available CSF data had a normal p-tau and an A+T-N+ profile, indicating either subthreshold level tauopathy or amyloidosis in combination with comorbid non-AD pathologies which might drive neurodegeneration (Botha et al., 2018; Jack et al., 2019c; Nelson et al., 2019). We observed that even a small adjustment of the CSF p-tau cut-off changed the classification, suggesting that several LipiDiDiet participants with an A+T-N+ profile had subthreshold levels of tau. Similar to our study among memory clinic patients with A β in the normal range (Study IV), this finding underlines the issue with using sharp dichotomous cut-offs to classify individuals.

In the longitudinal analysis of disease progression, we observed that the decline in cognition (i.e., NTB) and cognitive-functional performance (i.e., CDR-SB) tended to be steeper in the prodromal AD (IWG-2), high and intermediate AD likelihood (NIA-AA 2011), and AD (NIA-AA 2018) groups. However, few significant differences were observed between these and the respective reference groups. It is likely that we lacked the statistical power to detect between-group differences because of the small sample size and limited number of observations in groups reflecting lower certainty of AD (e.g., reference groups 'low AD likelihood' and 'SNAP'). Another explanation is that the cognitive changes were modest overall and

smaller than expected during the first two years of the LipiDiDiet RCT, as discussed by Soininen et al. (2017). We observed here that the changes in the NTB scores were modest even among those with both abnormal A β and neuronal injury markers. However, after three years, Soininen et al. (2020) reported that the change in cognition in the whole LipiDiDiet population was closer to what was initially expected. With respect to CDR-SB, we found that the increase (i.e., worsening) was more pronounced in the NIA-AA 2018 AD group (A+T+N+) than in the Alzheimer's and concomitant suspected non-Alzheimer's pathologic change group (A+T-N+). This supports the distinction between markers of tau (e.g., p-tau) and other neuronal injury markers. The LipiDiDiet extension studies will shed light on the longer-term cognitive and cognitive-functional trajectories and prognosis across the different biomarker profiles.

In terms of progression to dementia, the rates of progression increased with increasing evidence for AD-type pathology and the risk was higher among participants with IWG-2 prodromal AD, NIA-AA 2011 high AD likelihood, and NIA-AA 2018 AD. Progression in these three groups was very similar, highlighting the overlap between the criteria and the groups. Overall, our findings are in line with studies showing that MCI individuals with IWG-2 prodromal AD or NIA-AA 2011 high AD likelihood, i.e., those with abnormal A β and neuronal injury markers, might have an increased risk of disease progression compared to those with normal/conflicting biomarkers or only abnormal A β (Bertens et al., 2017; Vos et al., 2015). The few available longitudinal studies investigating the NIA-AA 2018 criteria have also reported an increased risk of decline for the AD biomarker profiles, both in MCI (Altomare et al., 2019; Ekman et al., 2018) and among cognitively healthy individuals (Ebenau et al., 2020; Jack et al., 2019c; Soldan et al., 2019).

The evaluation of participant eligibility in the LipiDiDiet RCT was often based on the assessment of MTA rather than CSF biomarkers, due to feasibility reasons. A large group of participants included in our study were, thus, classified in the NIA-AA 2011 intermediate AD likelihood group. Notably, we observed that the rate of disease progression was consistently similar in this group and in the high AD likelihood group (A β abnormality required). This is an encouraging result, given that the assessment of only one biomarker (usually MTA in widely available MRI) is a common scenario. The currently used methods for measuring A β are invasive (lumbar puncture) and costly (PET), limiting their application in routine clinical practice and in RCTs conducted in diverse settings and diverse populations. While CSF and PET assessments are currently necessary to verify the biomarker status in RCTs investigating A β - or tau-targeting therapies, less restrictive selection criteria could be considered due to feasibility in RCTs investigating non-pharmacological lifestyle interventions or combination therapies, for example. These interventions may not directly target specific disease pathologies but exert their effects through multiple mechanisms of action. Such RCTs are increasingly relevant, and many are currently ongoing or planned in different settings and populations (Kivipelto et al., 2020).

6.2 ENGAGING TARGET POPULATIONS IN DEMENTIA PREVENTION TRIALS

6.2.1 Altruism and personal benefit as key reasons for participation

When the HATICE RCT participants were asked to specify the relevant reasons for participation, multiple items were frequently selected, but three common motivating factors emerged from the questionnaires and interviews: 1) the desire to contribute to scientific progress (altruistic reason), 2) the possibility to improve one's own health through lifestyle changes (personal reason), and 3) access to additional medical monitoring in the trial (personal reason). Each of these statements was selected in the questionnaire by 80–85% of the participants, and each of them was indicated as the single main reason by approximately 20–30% of the participants. Approximately half of the population indicated another personal reason, namely health concerns, as a reason for participation and it was the main reason for 8% of the participants. In the interviews, aspects such as societal benefit, helping other older people, and dutifulness were mentioned as altruistic motives. Making lifestyle changes such as losing weight or increasing physical activity was considered useful to manage existing CVD and risk factors and to potentially avoid medications in the future. Individuals emphasizing medical monitoring perceived HATICE as an easy and convenient way to confirm good health or address specific health concerns, which were often related to cognitive performance and personal risk of developing cognitive impairment.

Different altruistic and personal reasons are important incentives for older adults in RCTs dealing with nutrition (Fearn et al., 2010), cancer (Nielsen & Berthelsen, 2019), CVD prevention (Cheung et al., 2008; Halpern et al., 2003; Tolmie et al., 2004), and self-management of chronic conditions (Reed et al., 2013). Similarly, studies investigating participation in hypothetical AD RCTs (Calamia et al., 2016; Cox et al., 2019; Grill et al., 2013, 2016; Lawrence et al., 2014; Nuño et al., 2017), real-life drug RCTs (Bardach et al., 2018; Solomon et al., 2012), dementia research registries (Avent et al., 2013; Jefferson et al., 2011), and longitudinal cohort studies such as the Whitehall II (Mein et al., 2012) and Gothenburg H70 Birth Cohort Studies (Dahlin-Ivanoff et al., 2019) have identified altruistic reasons and personal benefits as the most common motivations. Recently, the mixed-method Study of Participant Experience of Alzheimer's disease Research (SPEAR) within EPAD reported that nearly all the participants selected helping others as a somewhat or very important reason to enroll in this trial-readiness cohort study; access to new therapies in the future and learning about their health were selected by approximately 50% and 30%, respectively (Brenman & Milne, 2020). These results have been published as a report and not yet as a research article. Prior research on older adults' reasons for enrolling specifically in dementia prevention RCTs is scarce, but in line with our findings, the preDIVA and In-MINDD RCTs also highlighted the importance of personal benefit. Regular medical check-ups including physical and cognitive assessments were perceived as highly useful and reassuring in the preDIVA study (Ligthart et al., 2015),

and the In-MINDD participants mentioned general interest in personal risk factors and the possibility to reduce dementia risk as a reason (Irving, no date). Similarly to the SPEAR study, the In-MINDD results are currently available only as a preliminary report. Regarding the preDIVA RCT, the interviews took place four years after randomization, and it is thus unclear whether and how the intervention and other procedures, such as study visits, had affected the participants' views on their participation. An advantage of our study was that it was conducted in a real-life RCT and importantly, during the recruitment phase. A key limitation is the scarcity of quantitative and qualitative data on non-participation. A detailed exploration of reasons for non-participation could have strengthened our study by offering additional insights into how the target population perceived the RCT (Dahl et al., 2018; Foster et al., 2015; Hughes-Morley et al., 2016; Kandola et al., 2018).

Whether personal benefits and the desire to help research are equally important incentives for older adults, or whether more importance is given to one or the other, is unclear. This could depend on the study design (observational studies vs. interventions), the target population (patients vs. others), and the research methodology (quantitative vs. qualitative). In some survey studies, respondents selected both altruistic and personal reasons, but they were not asked to specify the main reason (e.g. Bardach et al., 2018; Calamia et al., 2016). According to some studies, altruism might weigh more than personal benefit in the decision-making (Avent et al., 2013; Jefferson et al., 2011; Solomon et al., 2012). In the qualitative substudy of the Whitehall II study, participants gave more importance to medical check-ups than altruistic motives, although the study staff believed the opposite (Mein et al., 2012). Our qualitative findings suggest that altruism was an important incentive for the HATICE RCT participants, but it was rarely the tipping point. Rather, it often appeared subordinate to other reasons. Even those who emphasized altruism as the most important reason were not willing to selflessly help any research. Research aiming to improve older adults' quality of life, care, and health services was a priority, as the participants considered it relevant for themselves in the future. Helping others or society is thought to be important, but older adults may be unlikely to participate unless they feel they will benefit in some way. This has been observed also in qualitative studies embedded for example in epilepsy and gastro-oesophageal reflux disease RCTs (Canvin & Jacoby, 2006; McCann et al., 2010). McCann et al. (2010) described that while helping others was the reason behind the initial interest in participation, the final decision was made only after weighing the perceived personal benefits, disadvantages, and risks.

A desire to prevent disability and maintain an active and independent life in old age was a key underlying motivation for participation in the HATICE RCT. It appeared in the background, regardless of whether the participants named altruistic or personal reasons as their main motivations. Persons reporting altruistic reasons appeared to be particularly concerned over functional deterioration and loss of autonomy in old age. The ascertainment of a good health status, careful monitoring of pre-existing conditions, and early identification of any new disease were

considered important to be able to lead a fulfilling life for as long as possible. Finally, a desire to prevent disability and discomfort, rather than any specific disease as such, motivated some participants to make lifestyle changes. As one interviewee mentioned, “it is normal to eat pills in old age, they don’t cause any worry or inconvenience. When I don’t feel sick, I don’t perceive myself as being sick”. This view on successful aging has been reported also in some previous studies. For example, in the Finnish Vitality 90+ study in the oldest-old population, the interviewees rarely referred to physical health when describing good aging, but emphasized aspects such as being free of pain and disability, being able to continue living independently, and maintaining a meaningful social life and friendships (Nosraty et al., 2012, 2015). When motivating older adults to make lifestyle changes and adhere to lifestyle interventions, the possibility to prevent functional deterioration and disability could be emphasized even more.

6.2.2 The Internet: facilitator or barrier to participation in eHealth trials?

In the future, a number of preventive interventions will be eHealth- or mHealth-based. Therefore, it is important to understand how older adults perceive the digital aspect of the intervention and whether it could affect their willingness to participate. In our study, a positive attitude towards the Internet and interest in improving computer skills were selected as a reason for participation by approximately 40% and 25% of the questionnaire respondents, respectively. Nearly half of the participants appreciated the flexibility associated with an online intervention. However, the digital means of intervention delivery did not play a key role in the decision to enroll in the HATICE RCT: Internet-related reasons were the main motivation only for less than 5% of the participants. As suggested by previous studies (Foster et al., 2015; Kandola et al., 2018), it is possible that the Internet was, in fact, an important reason to not enroll in the trial, but we were not able to explore this issue as the data on non-participation were insufficient.

With respect to the potential usefulness of the Internet in health promotion and risk factor self-management, the interviewees’ opinions varied. Especially those using computers regularly in their everyday lives saw benefits, but some were doubtful whether health information found online is reliable. The HATICE program as such was perceived as trustworthy because it was offered by a reliable party (i.e., a university). Consistent with a previous mixed-method study investigating facilitators and barriers to participation in a hypothetical eHealth dementia prevention RCT (Wesselman et al., 2018), many of our study participants also wondered if they had sufficient computer skills to successfully engage in the intervention and complete the program. Another common finding in both studies was that older adults have concerns over the reliability and inconsistency of information found online. Health information is scattered, and it is hard to determine what is relevant. In another recent study, older adults appeared to have little trust in dementia-related information presented in the media, and current recommendations and evidence for risk factors and prevention were perceived as inconsistent and

inconclusive (Bosco et al., 2020). In recent years, the Internet has become a key source of brain health related information for many people (Heger et al., 2019; Wesselman et al., 2018), and for example in the Alzheimer's Disease International (2019) survey, 36% of the respondents stated that they would seek help and advice on the Internet if they were worried about their cognition. Yet, older adults might not be able to assess the credibility of online information as well as younger individuals (Liao & Fu, 2014), and with regard to information about AD prevention, the quality of online articles and websites has been shown to vary greatly (Robillard & Feng, 2016). An eHealth platform should, therefore, be a one-stop-shop for reliable, evidence-based, and up-to-date information about dementia and prevention.

Consistent with population-based surveys (Cations et al., 2018), we found that the HATICE participants included in our study appeared to have a poor overall knowledge of dementia and prevention. For example, we identified a misconception that dementia is a part of normal aging and entirely attributable to non-modifiable factors. The link between vascular factors and cognitive impairment was unclear; some described that dementia could at most be slowed down but not prevented completely by improving certain modifiable risk factors. Cognitive activities and stimulation were mentioned more often as beneficial than physical activity and healthy dietary habits, which is in line with previous findings. For example, in the Dutch Mijnbreincoach (My Brain Coach) survey, being cognitively active, engaging in physical activity, and having a healthy diet were identified correctly as protective factors by approximately 50–80% of the people surveyed (Heger et al., 2019). The role of vascular disease and risk factors, such as coronary artery disease, hypertension, and hyperlipidemia, was recognized less often (by approximately 20-30% depending on the factor). The HATICE interviewees in our study reported hearing and reading about the topic of dementia prevention, but their understanding seemed superficial. Both our study and a previous qualitative study (Kim et al., 2015) suggest that, even if many older adults could name risk factors correctly in surveys, they might not fully comprehend what these factors actually mean, or how they could be managed in practice. Online platforms offered by health care units or universities could be an attractive and convenient way to access tangible and understandable information about health and dementia prevention.

eHealth and mHealth tools are designed for independent use, but studies investigating facilitators and barriers to engagement have shown that older adults might appreciate human contact also in remote interventions. Interaction with other participants might not be very important (Wesselman et al., 2018), but the possibility to communicate with a health care professional, ask questions, and get personal support is essential (Jongstra et al., 2017; van Middelaar et al., 2018a). This could increase older adults' initial interest in the program, but also boost their motivation to continue its use (van Middelaar et al., 2018a). The HATICE interviewees in our study similarly mentioned that they expected and wished to also interact with the coaches in face-to-face consultations or on the phone. The wishes and needs of older

adults for personal interaction, feedback, and hands-on guidance with computers could be a challenge in future large-scale online prevention interventions.

6.2.3 Impact of the setting and recruitment strategies on the motivation to participate

The multinational RCT setting allowed us to investigate potential between-country differences in older adults' reasons for participation in the HATICE RCT. The three motivations discussed in section 6.2.1 were the main reasons in all three countries, but the importance given to each of them varied slightly between the countries. In the questionnaire, the willingness to contribute to research was the most frequently mentioned reason for participation in France and in the Netherlands, whereas in Finland it was the third most common reason. Each of the three reasons was selected as the main reason by approximately 25% of the Finnish participants, whereas around 40% of the Dutch and 50% of the French participants selected altruism. Approximately one in three Finnish and one in four Dutch participants indicated that being worried about their health or being interested in receiving medical monitoring was their main reason, whereas it was the case for only approximately 10% of the French participants. These differences were evident also in the interviews.

While the role of cultural differences cannot be fully ruled out, it is likely that the different HATICE recruitment strategies explain many of these findings. In Finland, participants were recruited from a population register (65+ year-old individuals living in the area were identified and invited) and in the Netherlands the recruitment was carried out via GP practices (GPs invited 65+ year-old patients). In France, participants were recruited among those who had attended CVD consultations at a local prevention center. In the interviews, many French participants described that they had a close and trustworthy relationship with their physician, and they had experienced only minor, if any, problems accessing health care services. Dutch participants showed interest in the possibility to receive medical monitoring in the HATICE RCT, but mostly to confirm a good health status. Finnish participants, on the other hand, described various problems with health care and found it difficult to access treatment or get consultation. Some of them wanted to participate in the HATICE RCT to simply confirm that they did not have underlying health issues, but many had specific health concerns. A decrease in satisfaction with regular health care services and in the perceived access to these services has been reported in Finland (Raivio et al., 2014), and unmet medical needs are more common in Finland than in many other European countries (OECD/European Observatory on Health Systems and Policies, 2017). Participants in the Swedish Gothenburg H70 Birth Cohort Study were also reported to have similar concerns and doubts about health care (Dahlin-Ivanoff et al., 2019). Getting better-quality health care and monitoring to detect if anything is wrong, i.e., "accessing health services through the back door" as described by Townsend and Cox (2013), was identified as a key motivation to participate in this study. Taken together, personal reasons for study participation, such as having medical check-ups, might be less relevant when older adults have a

stable relationship with a physician and feel that their health issues are taken care of. In contrast, the possibility to discuss concerns with health care professionals and receive medical check-ups might be one important incentive when access to regular care is—or at least is perceived to be—limited.

6.2.4 Personal experiences of dementia as a reason for participation

In the interviews where the topic of cognition and dementia was discussed with the participants, having a family history of dementia or other first-hand experiences with affected people emerged as a recurrent theme. Personal experience was linked to sensitivity and receptiveness to issues related to brain health and prevention, and it was one important factor underlying the decision and motivation to engage in prevention and participate in the HATICE RCT. As shown before (Glynn et al., 2017), those with a family history or other experience with dementia seemed somewhat more knowledgeable about the condition and had a better understanding of the protective effects of physical activity, a healthy and balanced diet, and social and cognitive stimulation. Great emphasis was nevertheless placed on genes and heredity as the determinants of illness. Some were uncertain whether prevention would be possible, especially if their loved ones living with dementia had no apparent modifiable risk factors. The participants' beliefs and knowledge, acquired from the media, for example, were often related back to and weighed against their own first-hand experiences. Feelings of fear, hopelessness, and anxiety were expressed when the topic of dementia was discussed, and concerns and distress were often related to the personal cognitive performance of the participants and the risk of future impairment. Some participants monitored themselves closely and a family history of dementia had increased their awareness of their cognition. As reported before (Robinson et al., 2018), neurocognitive disorders and dementia were described as life-threatening and incurable illnesses, and they were perceived as clearly distinct from other conditions prevalent among older adults (e.g., cancer or CVD) in the sense that a person with dementia would eventually lose their personhood and become useless. As one participant of another study described, "with Alzheimer's you stop being you" (Milne et al., 2018). In this study, individuals with a family history of dementia were interviewed regarding their potential interest in learning about their biomarker profiles.

Personal experiences and exposure, as well as negative emotions such as fear, are known to affect how an individual perceives the risk of a specific health-related threat (Ferrer & Klein, 2015). According to previous literature, a family history of dementia shapes the understanding and perception of personal dementia risk (Caselli et al., 2014; Lock et al., 2006; Milne et al., 2018; Roberts et al., 2014). In the study by Milne et al. (2018), many interviewees with a family history of dementia already considered themselves at high risk and did not think that learning about their biomarker profile or other clinically relevant information could change their view. Importantly, the perception of disease risk is a key determinant of health behavior (Ferrer & Klein, 2015), and a key finding in our study was that fear and a family

history or other experiences with dementia appeared to be linked to an increased motivation towards prevention (i.e., lifestyle improvement) and a willingness to participate in the HATICE RCT. A few other studies in the context of dementia (Bosco et al., 2020; Milne et al., 2018) and diabetes (Følling et al., 2016) also reported that individuals who considered themselves at high risk showed great interest in prevention. However, the evidence is mixed. A perceived risk might motivate some individuals, but discourage others (Claassen et al., 2010; Prom-Wormley et al., 2019). A systematic review concluded that *APOE* genotype disclosure to first-degree relatives of AD patients might lead to at least short-term lifestyle changes (Bemelmans et al., 2016); however, a meta-analysis did not find any link between genetic risk disclosure and lifestyle change (Hollands et al., 2016). In future prevention RCTs, it would be relevant to explore how participants perceive their own risk of dementia and address any potential false beliefs or concerns (e.g., prevention is not possible due to the family history). This is important, given the recent evidence that lifestyle changes are likely to be beneficial even among individuals with a genetic susceptibility to AD (Lourida et al., 2019; Solomon et al., 2018).

One key incentive for participation in the HATICE RCT was to learn about one's own cognitive health and risk of dementia through clinical and cognitive assessments. This was true especially for those with a family history of dementia or other first-hand experience with affected individuals. Genetic testing and disclosure were mistakenly expected by some participants. For some, the HATICE RCT appeared to be a convenient way to confirm that nothing was wrong; some emphasized the early detection of AD. A few participants thought that frequent monitoring of their health status and cognitive performance in an RCT could accelerate access to early treatment and care, a finding reported also by Milne and colleagues (2018). Overall, public interest in learning about the likelihood of developing AD is high, especially when a person has a family history of AD and they perceive the risk as high (Roberts et al., 2014; Tang et al., 2017; Wikler et al., 2013). This also increases the interest in RCT participation (Grill et al., 2013, 2016; Lawrence et al., 2014). However, not all individuals are willing to receive information about their own risk (Brenman & Milne, 2020; Lawrence et al., 2014; Ott et al., 2016), and biomarker disclosure, for example, may evoke anxiety and stress (Milne et al., 2018). Some of our participants also expressed reservations and mentioned not wanting to know yet if they would develop dementia in the future.

For some older adults, a family history of dementia or other first-hand experiences with affected individuals could nevertheless be one reason to seek medical advice and information about their health and dementia risk in an RCT. Should fear and the stigma of dementia prevent some people from seeking help in regular health care (Akenine et al., 2020), participation in an RCT (e.g., a lifestyle RCT with little risk associated with the intervention) could be an easy way to address health-related concerns. Medical monitoring to complement health care could be emphasized in future prevention RCTs to facilitate recruitment, but it is important to address any potentially unrealistic expectations older adults may have regarding

diagnostic or risk assessments. Disappointment in the intervention content or study visits and assessments could increase the risk of drop-out and non-adherence (Skea et al., 2019).

It is possible that learning more about one's own health might be a relevant reason to participate in RCTs when individuals are not necessarily in regular contact with a health care or prevention unit. In our study, this was the case at the Finnish study site. In the interviews, the topic of dementia was explored only when the interviewees introduced it themselves, for instance, when they mentioned dementia or related aspects as a reason for participation in the HATICE RCT. Only the Finnish participants spontaneously mentioned the topic of dementia, and it was not discussed in France or the Netherlands. This could reflect the impact of different HATICE recruitment strategies. Not including the topic of dementia in the original ACCEPT-HATICE core interview guide is a key limitation of Study III, as it would have allowed us to explore potential between-country differences in knowledge and perceptions, like in Study II.

6.2.5 Recommendations for future trial design and conduct

Based on the findings of Studies II and III, some recommendations can be proposed for the future design and conduct of complex multidomain dementia prevention RCTs including a lifestyle component. These are listed in Box 2.

Box 2. Recommendations for future dementia prevention RCTs targeting older adults.

Recruitment in RCTs could potentially be facilitated by:

- Highlighting personal benefits, e.g., medical check-ups and tests to ensure a good health status and to monitor vascular and cognitive health.
But: participation does not replace regular care and unrealistic expectations should be managed.
- Highlighting the scientific and societal impact of the RCT; explaining its purpose and linking it with concrete outcomes relevant for older adults.
Emphasizing the quality of life and prevention of disability and functional impairment.
- Targeting older adults with a family history of dementia or other experiences with affected individuals as they could be more motivated and receptive to the topic.
- Tailoring recruitment strategies; emphasizing different aspects in different settings (e.g., medical monitoring when participants do not have regular contact with a health care unit).

The following aspects could be considered to improve the design of interventions:

- Understandable, evidence-based information about health, prevention, and risk factors, with a focus on common misconceptions (the role of age and genes) and the link between vascular and cognitive health.
- Communicating about recent research findings; using risk scores or other tools to illustrate the risk of dementia and potential of risk reduction.
- Tailored support to improve lifestyles; practical advice and tips; active coaching and follow-up as some people want to feel accountable to stay motivated.
- The possibility to communicate with the study staff and fellow participants also in real life (eHealth RCTs).
- Encouragement and hands-on support with the platform and devices (eHealth RCTs).

7 CONCLUSIONS

In general, the findings of this thesis support the notion that conducting large-scale and multinational dementia prevention RCTs is feasible. Careful selection of participants and understanding their motivations and expectations may further increase the efficacy and participant engagement.

The following conclusions can be drawn based on the studies in this thesis:

- (1) In the FINGER RCT, in which the CAIDE dementia risk score and cognitive testing were used to select a population at increased risk of cognitive decline, beneficial intervention effects were not limited to any subgroups of participants but were observed in the whole population. No further stratification or enrichment was necessary to obtain better effects. Targeting an at-risk, rather than unselected, population is likely to be the optimal strategy in multidomain prevention RCTs. The use of the FINGER model and selection criteria is feasible and appropriate in RCTs with a similar design.
- (2) Memory clinic patients with MCI and 'normal' CSF A β are at risk of short-term progression to AD-type dementia, despite the absence of clear AD-typical pathology. AD should not be ruled out in this population, and biomarkers should ideally be treated as continuous rather than dichotomous measures when assessing and predicting the risk of disease progression. Given that these individuals are often ineligible for drug RCTs, the potential for prevention and suitable interventions should be further studied in this at-risk population.
- (3) The IWG-1 criteria have the potential to identify a prodromal AD population with typical AD pathology, even though they require less extensive biomarker evidence than the more recently proposed criteria. These less restrictive and more pragmatic selection criteria could be preferred due to feasibility in certain RCTs, for example in diverse settings where access to CSF or PET might be limited. The criteria could also be used in multidomain RCTs, which may not directly target any single or specific disease pathologies.
- (4) Altruistic reasons and personal benefits motivated older adults to participate in a multidomain eHealth prevention RCT. Depending on culture, context (e.g., health care setting), and recruitment strategy, different aspects of the trial and intervention could be emphasized to facilitate participant recruitment and engagement (e.g., access to additional medical monitoring, the possibility to receive information about dementia and prevention, or scientific impact).

- (5) In a multidomain eHealth prevention RCT, the means of intervention delivery (i.e., online instead of face-to-face) was not an important reason for participation. Personal contact and real-life interaction, as well as sufficient support with the online platform and devices are crucial for older adults' engagement in an eHealth intervention.
- (6) Knowledge of dementia and prevention was limited and superficial among the participants of a multidomain prevention RCT, and there was little confidence in the possibility to prevent dementia. Incorporating reliable, understandable, and up-to-date information about dementia and prevention into the intervention programs is important to facilitate engagement and adherence.
- (7) People with a family history of dementia or other first-hand experiences with affected people were highly aware of and receptive to the topic of dementia and prevention. Because of their high motivation towards prevention and RCT participation, these individuals could represent an attractive target population for certain prevention RCTs.

8 FUTURE PERSPECTIVES

AD and dementia research is at a crossroads. While the clinical and biological understanding of AD has improved over the years, the disappointing results of pharmacological RCTs have revealed that not enough is known about the factors and pathways driving the disease pathogenesis and progression. Recently, it has been emphasized that in old age, AD and cognitive impairment are typically not only characterized by amyloid or tau but various other pathologies as well (Boyle et al., 2018, 2019). This challenges the current view of what truly characterizes AD and late-life cognitive impairment. In future research, it is necessary to look beyond the obvious and explore other factors and pathways, with the help of new emerging technologies and methods such as proteomics, genomics, and metabolomics (Badhwar et al., 2020; Johnson et al., 2020). Developing multifactorial disease models could allow precise subtyping and characterization of individuals, much like in cancer, such that individuals would no longer be assigned under the broad umbrella term of 'AD' irrespective of their risk profile and characteristics. This could open the door to tailored risk prediction and novel treatment and prevention strategies. In this context, not only risk factors but also protective factors could be relevant. If eliminating specific disease pathologies or risk factors does not lead to clinically relevant benefits, increasing the resistance against these pathologies by enhancing protective factors (or mimicking their effects with drugs) could be an attractive strategy. Observational cohort studies with long follow-up periods offer opportunities to study such factors (Barbera et al., 2020). For instance, it is of interest to investigate what characterizes the oldest old individuals who show no cognitive deterioration despite their high age.

The fact that late-life AD and dementia are heterogeneous conditions, and the determinants of disease development and progression might be different in different individuals, calls for personalized preventive strategies. The next generation of prevention RCTs needs to consider that one size may not fit all, and differences in target populations, their risk profiles, and individuals' personal interests and motivations have to be taken into account in the RCT and intervention design. Importantly, different target populations (i.e., those at short-term vs. long-term risk of cognitive decline) are likely to require different strategies for successful prevention. To this aim, there is a need to bridge the gap between non-pharmacological and pharmacological approaches. While there could still be a window of opportunity for prevention in individuals with mild cognitive impairment and pathological brain changes, simply targeting modifiable factors even in a multidomain manner might not be enough. Rather, a multimodal strategy could be warranted (e.g., a combination of disease-modifying drugs and a multidomain non-pharmacological intervention) (Kivipelto et al., 2020).

With respect to the delivery of complex multidomain preventive interventions, eHealth and mHealth tools will be highly relevant in the future, as older adults

become increasingly familiar with technology and the Internet. It is likely that at least certain components of many interventions will be offered in an online environment or mobile app, and remote assessments and study visits are another plausible future scenario. The current COVID-19 pandemic might speed up this transition, and similar outbreaks will likely recur in the future (Editors of *Alzheimer's & Dementia*, 2020). When appropriately designed in terms of both technical aspects and content, Internet-based tools can be a powerful and cost-effective strategy—not just to test interventions, but also to implement any successful preventive strategies and to educate people about dementia and prevention. Even though it has been argued that there may not be enough dementia-specific RCT evidence yet to support public health campaigns about the role of lifestyle in prevention (National Academies of Sciences, Engineering, and Medicine, 2017), the new Lancet Commission report emphasizes the importance of being ambitious about prevention and encourages people to take action (Livingston et al., 2020). Research is needed to obtain more evidence, but recommendations should not wait. Moreover, several modifiable risk factors are shared between dementia and other non-communicable diseases, and their monitoring and management improves health as a whole. Increasing the public awareness of dementia and the possible means to prevent or postpone it should, therefore, remain one of the priorities in dementia research.

Methodological issues in RCTs have been highlighted as a key challenge when evaluating the evidence on dementia prevention (National Academies of Sciences, Engineering, and Medicine, 2017; World Health Organization, 2019). Drawing definite conclusions can be difficult because of differences in study populations and exposures (i.e., intervention content, intensity, and duration). Thus, it is essential to improve and align the methodology, design, and conduct of future prevention RCTs. Dementia is a rapidly increasing global challenge, and ideally, researchers worldwide should collaborate and work together to develop preventive strategies. To this aim, the WW-FINGERS global network of multidomain dementia prevention was launched in 2017 (Kivipelto et al., 2020). This initiative enables the testing and adaptation of FINGER-type preventive interventions in diverse settings and populations. Importantly, to address and overcome many of the challenges in the current prevention RCTs, a key aim of WW-FINGERS is to harmonize RCT methodology and provide a platform for data sharing and pooling. Regardless of their outcomes per se, the WW-FINGERS RCTs will generate urgently needed knowledge about feasible and effective strategies to reduce the global burden of AD and dementia.

REFERENCES

- Aalbers, T., Qin, L., Baars, M.A.E., De Lange, A., Kessels, R.P.C., & Rikkert, M.G.M.O., 2016. Changing behavioral lifestyle risk factors related to cognitive decline in later life using a self-motivated ehealth intervention in Dutch adults. *J. Med. Internet Res.* 18, e171. <https://doi.org/10.2196/jmir.5269>
- Abner, E.L., Kryscio, R.J., Schmitt, F.A., Fardo, D.W., Moga, D.C., Ighodaro, E.T., et al., 2017. Outcomes after diagnosis of mild cognitive impairment in a large autopsy series. *Ann. Neurol.* 81, 549–559. <https://doi.org/10.1002/ana.24903>
- Abner, E.L., Nelson, P.T., Kryscio, R.J., Schmitt, F.A., Fardo, D.W., Woltjer, R.L., et al., 2016. Diabetes is associated with cerebrovascular but not Alzheimer’s disease neuropathology. *Alzheimer’s Dement.* 12, 882–889. <https://doi.org/10.1016/j.jalz.2015.12.006>
- Akenine, U., Barbera, M., Beishuizen, C.R., Fallahpour, M., Guillemont, J., Rosenberg, A., et al., 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* 10, e037050. <https://doi.org/10.1136/bmjopen-2020-037050>
- Albert, M.S., DeKosky, S.T., Dickson, D., Dubois, B., Feldman, H.H., Fox, N.C., et al., 2011. The diagnosis of mild cognitive impairment due to Alzheimer’s disease: recommendations from the National Institute on Aging-Alzheimer’s Association workgroups on diagnostic guidelines for Alzheimer’s disease. *Alzheimer’s Dement.* 7, 270–279. <https://doi.org/10.1016/j.jalz.2011.03.008>
- Alexopoulos, G.S., Abrams, R.C., Young, R.C., & Shamoian, C.A., 1988. Cornell Scale for Depression in Dementia. *Biol. Psychiatry* 23, 271–284. [https://doi.org/10.1016/0006-3223\(88\)90038-8](https://doi.org/10.1016/0006-3223(88)90038-8)
- Altomare, D., De Wilde, A., Ossenkoppele, R., Pelkmans, W., Bouwman, F., Groot, C., et al., 2019. Applying the ATN scheme in a memory clinic population: The ABIDE project. *Neurology* 93, e1635–e1646. <https://doi.org/10.1212/WNL.00000000000008361>
- Alzheimer’s Association, 2020. About TrialMatch: Clinical Trial Matching Service for Alzheimer’s and Other Dementia [WWW Document]. Retrieved from https://alz.org/alzheimers-dementia/research_progress/clinical-trials/about-clinical-trials (accessed 07/27/2020).
- Alzheimer’s Disease International, 2019. World Alzheimer Report 2019: Attitudes to dementia. London:Alzheimer’s Disease International.
- Alzheimer Europe, 2020. Dementia in Europe Yearbook 2019 - Estimating the prevalence of dementia in Europe.
- Alzheimercentrum Amsterdam, no date. Hersen onderzoek nl [WWW Document]. Retrieved from <https://hersenonderzoek.nl/> (accessed 07/27/2020).
- American Psychiatric Association, 1994. Diagnostic and Statistical Manual of Mental Disorders, 4th ed. Washington, DC.

- American Psychiatric Association, 2013. Diagnostic and Statistical Manual of Mental Disorders, 5th ed. Washington, DC.
- Andrieu, S., Coley, N., Gardette, V., Subra, J., Oustric, S., Fournier, T., et al., 2012. Representations and practices of prevention in elderly populations: investigating acceptance to participate in and adherence to an intervention study for the prevention of Alzheimer's disease (ACCEPT study)--the need for a multidisciplinary approach. *J. Nutr. Health Aging* 16, 352–354. <https://doi.org/10.1007/s12603-012-0045-9>
- Andrieu, S., Coley, N., Lovestone, S., Aisen, P.S., & Vellas, B., 2015. Prevention of sporadic Alzheimer's disease: Lessons learned from clinical trials and future directions. *Lancet Neurol.* 14, 926–944. [https://doi.org/10.1016/S1474-4422\(15\)00153-2](https://doi.org/10.1016/S1474-4422(15)00153-2)
- Andrieu, S., Guyonnet, S., Coley, N., Cantet, C., Bonnefoy, M., Bordes, S., et al., 2017. Effect of long-term omega 3 polyunsaturated fatty acid supplementation with or without multidomain intervention on cognitive function in elderly adults with memory complaints (MAPT): a randomised, placebo-controlled trial. *Lancet Neurol.* 16, 377–389. [https://doi.org/10.1016/S1474-4422\(17\)30040-6](https://doi.org/10.1016/S1474-4422(17)30040-6)
- Anstey, K.J., Bahar-Fuchs, A., Herath, P., Kim, S., Burns, R., Rebok, G.W., et al., 2015. Body brain life: A randomized controlled trial of an online dementia risk reduction intervention in middle-aged adults at risk of Alzheimer's disease. *Alzheimer's Dement. Transl. Res. Clin. Interv.* 1, 72–80. <https://doi.org/10.1016/j.trci.2015.04.003>
- Anstey, K.J., Cherbuin, N., & Herath, P.M., 2013. Development of a New Method for Assessing Global Risk of Alzheimer's Disease for Use in Population Health Approaches to Prevention. *Prev. Sci.* 14, 411–421. <https://doi.org/10.1007/s11121-012-0313-2>
- Anstey, K.J., Cherbuin, N., Herath, P.M., Qiu, C., Kuller, L.H., Lopez, O.L., et al., 2014. A self-report risk index to predict occurrence of dementia in three independent cohorts of older adults: The ANU-ADRI. *PLoS One* 9, e86141. <https://doi.org/10.1371/journal.pone.0086141>
- Anstey, K.J., Ee, N., Eramudugolla, R., Jagger, C., & Peters, R., 2019. A Systematic Review of Meta-Analyses that Evaluate Risk Factors for Dementia to Evaluate the Quantity, Quality, and Global Representativeness of Evidence. *J. Alzheimer's Dis.* 70, S165–S186. <https://doi.org/10.3233/JAD-190181>
- Arvanitakis, Z., Capuano, A.W., Leurgans, S.E., Bennett, D.A., & Schneider, J.A., 2016. Relation of cerebral vessel disease to Alzheimer's disease dementia and cognitive function in elderly people: a cross-sectional study. *Lancet Neurol.* 15, 934–943. [https://doi.org/10.1016/S1474-4422\(16\)30029-1](https://doi.org/10.1016/S1474-4422(16)30029-1)
- Ashworth, R., 2020. Perceptions of stigma among people affected by early- and late-onset Alzheimer's disease. *J. Health Psychol.* 25, 490–510. <https://doi.org/10.1177/1359105317720818>
- Avent, C., Curry, L., Gregory, S., Marquardt, S., Pae, L., Wilson, D., et al., 2013. Establishing the motivations of patients with dementia and cognitive

- impairment and their carers in joining a dementia research register (DemReg). *Int. Psychogeriatrics* 25, 963–971. <https://doi.org/10.1017/S1041610213000252>
- Badhwar, A., McFall, G.P., Sapkota, S., Black, S.E., Chertkow, H., Duchesne, S., et al., 2020. A multiomics approach to heterogeneity in Alzheimer's disease: focused review and roadmap. *Brain* 143, 1315–1331. <https://doi.org/10.1093/brain/awz384>
- Bae, S., Lee, Sangyoon, Lee, Sungchul, Jung, S., Makino, K., Harada, Kazuhiro, et al., 2019. The effect of a multicomponent intervention to promote community activity on cognitive function in older adults with mild cognitive impairment: A randomized controlled trial. *Complement. Ther. Med.* 42, 164–169. <https://doi.org/10.1016/j.ctim.2018.11.011>
- Ball, K., Berch, D.B., Helmers, K.F., Jobe, J.B., Leveck, M.D., Marsiske, M., et al., 2002. Effects of cognitive training interventions with older adults: a randomized controlled trial. *JAMA - J. Am. Med. Assoc.* 288, 2271–2281. <https://doi.org/10.1001/jama.288.18.2271>
- Ballard, C., Atri, A., Boneva, N., Cummings, J.L., Frölich, L., Molinuevo, J.L., et al., 2019. Enrichment factors for clinical trials in mild-to-moderate Alzheimer's disease. *Alzheimer's Dement. Transl. Res. Clin. Interv.* 5, 164–174. <https://doi.org/10.1016/j.trci.2019.04.001>
- Bamidis, P.D., Fissler, P., Papageorgiou, S.G., Zilidou, V., Konstantinidis, E.I., Billis, A.S., et al., 2015. Gains in cognition through combined cognitive and physical training: The role of training dosage and severity of neurocognitive disorder. *Front. Aging Neurosci.* 7, 152. <https://doi.org/10.3389/fnagi.2015.00152>
- Banner Alzheimer's Institute, 2020. Alzheimer's Prevention Registry [WWW Document]. Retrieved from <https://www.endalznow.org/> (accessed 07/27/2020).
- Barbera, M., Kulmala, J., Lisko, I., Pietilä, E., Rosenberg, A., Hallikainen, I., et al., 2020. Third follow-up of the Cardiovascular Risk Factors, Aging and Dementia (CAIDE) cohort investigating determinants of cognitive, physical, and psychosocial wellbeing among the oldest old: the CAIDE85+ study protocol. *BMC Geriatr.* 20, 238. <https://doi.org/10.1186/s12877-020-01617-5>
- Barbera, M., Mangialasche, F., Jongstra, S., Guillemont, J., Ngandu, T., Beishuizen, C., et al., 2018. Designing an Internet-Based Multidomain Intervention for the Prevention of Cardiovascular Disease and Cognitive Impairment in Older Adults: The HATICE Trial. *J. Alzheimer's Dis.* 62, 649–663. <https://doi.org/10.3233/JAD-170858>
- Bardach, S.H., Holmes, S.D., & Jicha, G.A., 2018. Motivators for Alzheimer's disease clinical trial participation. *Aging Clin. Exp. Res.* 30, 209–212. <https://doi.org/10.1007/s40520-017-0771-2>
- Barnes, D.E., Beiser, A.S., Lee, A., Langa, K.M., Koyama, A., Preis, S.R., et al., 2014. Development and validation of a brief dementia screening indicator for primary care. *Alzheimer's Dement.* 10, 656–665.e1. <https://doi.org/10.1016/j.jalz.2013.11.006>
- Barnes, D.E., Santos-Modesitt, W., Poelke, G., Kramer, A.F., Castro, C., Middleton,

- L.E., et al., 2013. The Mental Activity and eXercise (MAX) trial: a randomized controlled trial to enhance cognitive function in older adults. *JAMA Intern. Med.* 173, 797–804. <https://doi.org/10.1001/jamainternmed.2013.189>
- Bateman, R.J., Benzinger, T.L., Berry, S., Clifford, D.B., Duggan, C., Fagan, A.M., et al., 2017. The DIAN-TU Next Generation Alzheimer’s prevention trial: Adaptive design and disease progression model. *Alzheimer’s Dement.* 13, 8–19. <https://doi.org/10.1016/j.jalz.2016.07.005>
- Bath, P.M., Scutt, P., Blackburn, D.J., Ankolekar, S., Krishnan, K., Ballard, C., et al., 2017. Intensive versus Guideline Blood Pressure and Lipid Lowering in Patients with Previous Stroke: Main results from the pilot prevention of Decline in Cognition after Stroke trial (PODCAST) randomised controlled trial. *PLoS One* 12, e0164608. <https://doi.org/10.1371/journal.pone.0164608>
- Beach, T.G., Monsell, S.E., Phillips, L.E., & Kukull, W., 2012. Accuracy of the clinical diagnosis of Alzheimer disease at National Institute on Aging Alzheimer Disease Centers, 2005–2010. *J. Neuropathol. Exp. Neurol.* 71, 266–273. <https://doi.org/10.1097/NEN.0b013e31824b211b>
- Beasley, J.M., Kirshner, L., Wylie-Rosett, J., Sevick, M.A., Deluca, L., & Chodosh, J., 2019. BRInging the Diabetes prevention program to GEriatric populations (BRIDGE): A feasibility study. *Pilot Feasibility Stud.* 5, 129. <https://doi.org/10.1186/s40814-019-0513-7>
- Beishuizen, C.R.L., Coley, N., Moll van Charante, E.P., van Gool, W.A., Richard, E., & Andrieu, S., 2017. Determinants of Dropout and Nonadherence in a Dementia Prevention Randomized Controlled Trial: The Prevention of Dementia by Intensive Vascular Care Trial. *J. Am. Geriatr. Soc.* 65, 1505–1513. <https://doi.org/10.1111/jgs.14834>
- Beishuizen, C.R.L., Stephan, B.C.M., Van Gool, W.A., Brayne, C., Peters, R.J.G., Andrieu, S., et al., 2016. Web-based interventions targeting cardiovascular risk factors in middle-aged and older people: A systematic review and meta-analysis. *J. Med. Internet Res.* 18, e55. <https://doi.org/10.2196/jmir.5218>
- Bell, W.R., An, Y., Kageyama, Y., English, C., Rudow, G.L., Pletnikova, O., et al., 2019. Neuropathologic, genetic, and longitudinal cognitive profiles in primary age-related tauopathy (PART) and Alzheimer’s disease. *Alzheimer’s Dement.* 15, 8–16. <https://doi.org/10.1016/j.jalz.2018.07.215>
- Bemelmans, S.A.S.A., Tromp, K., Bunnik, E.M., Milne, R.J., Badger, S., Brayne, C., et al., 2016. Psychological, behavioral and social effects of disclosing Alzheimer’s disease biomarkers to research participants: a systematic review. *Alzheimer’s Res. Ther.* 8, 46. <https://doi.org/10.1186/s13195-016-0212-z>
- Benzinger, T.L.S., Blazey, T., Jack, C.R., Koeppe, R.A., Su, Y., Xiong, C., et al., 2013. Regional variability of imaging biomarkers in autosomal dominant Alzheimer’s disease. *Proc. Natl. Acad. Sci. U. S. A.* 110, e4502–4509. <https://doi.org/10.1073/pnas.1317918110>
- Bertens, D., Tijms, B.M., Vermunt, L., Prins, N.D., Scheltens, P., & Visser, P.J., 2017. The effect of diagnostic criteria on outcome measures in preclinical and

- prodromal Alzheimer's disease: Implications for trial design. *Alzheimer's Dement. Transl. Res. Clin. Interv.* 3, 513–523. <https://doi.org/10.1016/j.trci.2017.08.005>
- Bethausser, T.J., Kosciak, R.L., Jonaitis, E.M., Allison, S.L., Cody, K.A., Erickson, C.M., et al., 2020. Amyloid and tau imaging biomarkers explain cognitive decline from late middle-age. *Brain* 143, 320–335. <https://doi.org/10.1093/brain/awz378>
- Biogen, 2019. Biogen plans regulatory filing for aducanumab in Alzheimer's disease based on new analysis of larger dataset from phase 3 studies. [WWW Document]. Retrieved from <https://investors.biogen.com/news-releases/news-release-details/biogen-plans-regulatory-filing-aducanumab-alzheimers-disease> (accessed 07/28/2020).
- Blumenthal, J.A., Smith, P.J., Mabe, S., Hinderliter, A., Lin, P.H., Liao, L., et al., 2019. Lifestyle and neurocognition in older adults with cognitive impairments: A randomized trial. *Neurology* 92, e212–e223. <https://doi.org/10.1212/WNL.0000000000006784>
- Bos, I., Vos, S.J., Frölich, L., Kornhuber, J., Wiltfang, J., Maier, W., et al., 2017. The frequency and influence of dementia risk factors in prodromal Alzheimer's disease. *Neurobiol. Aging* 56, 33–40. <https://doi.org/10.1016/j.neurobiolaging.2017.03.034>
- Bos, I., Vos, S.J.B., Schindler, S.E., Hassenstab, J., Xiong, C., Grant, E., et al., 2019. Vascular risk factors are associated with longitudinal changes in cerebrospinal fluid tau markers and cognition in preclinical Alzheimer's disease. *Alzheimer's Dement.* 15, 1149–1159. <https://doi.org/10.1016/j.jalz.2019.04.015>
- Bosco, A., Jones, K.A., Di Lorito, C., Stephan, B.C.M., Orrell, M., & Oliveira, D., 2020. Changing lifestyle for dementia risk reduction: Inductive content analysis of a national UK survey. *PLoS One* 15, e0233039. <https://doi.org/10.1371/journal.pone.0233039>
- Botha, H., Mantyh, W.G., Graff-Radford, J., Machulda, M.M., Przybelski, S.A., Wiste, H.J., et al., 2018. Tau-negative amnesic dementia masquerading as Alzheimer disease dementia. *Neurology* 90, e940–e946. <https://doi.org/10.1212/WNL.0000000000005124>
- Boyle, P.A., Yu, L., Leurgans, S.E., Wilson, R.S., Brookmeyer, R., Schneider, J.A., et al., 2019. Attributable risk of Alzheimer's dementia attributed to age-related neuropathologies. *Ann. Neurol.* 85, 114–124. <https://doi.org/10.1002/ana.25380>
- Boyle, P.A., Yu, L., Wilson, R.S., Leurgans, S.E., Schneider, J.A., & Bennett, D.A., 2018. Person-specific contribution of neuropathologies to cognitive loss in old age. *Ann. Neurol.* 83, 74–83. <https://doi.org/10.1002/ana.25123>
- Brenman, N., & Milne, R., 2020. A Study of Participant Experience of Alzheimer's disease Research (SPEAR) - Final report [WWW Document]. Retrieved from http://ep-ad.org/wp-content/uploads/2020/07/SPEAR-Report_Final_26-June-20.pdf (accessed 07/20/2020).
- Brenowitz, W.D., Keene, C.D., Hawes, S.E., Hubbard, R.A., Longstreth, W.T.J., Woltjer, R.L., et al., 2017. Alzheimer's disease neuropathologic change, Lewy

- body disease, and vascular brain injury in clinic- and community-based samples. *Neurobiol. Aging* 53, 83–92. <https://doi.org/10.1016/j.neurobiolaging.2017.01.017>
- Bridel, C., Van Wieringen, W.N., Zetterberg, H., Tijms, B.M., Teunissen, C.E., Alvarez-Cermeño, J.C., et al., 2019. Diagnostic Value of Cerebrospinal Fluid Neurofilament Light Protein in Neurology: A Systematic Review and Meta-analysis. *JAMA Neurol.* 76, 1035–1048. <https://doi.org/10.1001/jamaneurol.2019.1534>
- Brotons, C., Bulc, M., Sammut, M.R., Sheehan, M., Manuel da Silva Martins, C., Björkelund, C., et al., 2012. Attitudes toward preventive services and lifestyle: the views of primary care patients in Europe. the EUROPREVIEW patient study. *Fam. Pract.* 29 Suppl 1, i168–i176. <https://doi.org/10.1093/fampra/cmr102>
- Burnham, S.C., Bourgeat, P., Doré, V., Savage, G., Brown, B., Laws, S., et al., 2016. Clinical and cognitive trajectories in cognitively healthy elderly individuals with suspected non-Alzheimer’s disease pathophysiology (SNAP) or Alzheimer’s disease pathology: a longitudinal study. *Lancet Neurol.* 15, 1044–1053. [https://doi.org/10.1016/S1474-4422\(16\)30125-9](https://doi.org/10.1016/S1474-4422(16)30125-9)
- Burns, D.K., Chiang, C., Welsh-Bohmer, K.A., Brannan, S.K., Culp, M., O’Neil, J., et al., 2019. The TOMMORROW study: Design of an Alzheimer’s disease delay-of-onset clinical trial. *Alzheimer’s Dement. Transl. Res. Clin. Interv.* 5, 661–670. <https://doi.org/10.1016/j.trci.2019.09.010>
- Byers, A.L., & Yaffe, K., 2011. Depression and risk of developing dementia. *Nat. Rev. Neurol.* 7, 323–331. <https://doi.org/10.1038/nrneurol.2011.60>
- Calamia, M., Bernstein, J.P.K., & Keller, J.N., 2016. I’d do anything for research, but i won’t do that: Interest in pharmacological interventions in older adults enrolled in a longitudinal aging study. *PLoS One* 11, e0159664. <https://doi.org/10.1371/journal.pone.0159664>
- Canvin, K., & Jacoby, A., 2006. Duty, desire or indifference? A qualitative study of patient decisions about recruitment to an epilepsy treatment trial. *Trials* 7, 32. <https://doi.org/10.1186/1745-6215-7-32>
- Caroli, A., Prestia, A., Galluzzi, S., Ferrari, C., Van Der Flier, W.M., Ossenkoppele, R., et al., 2015. Mild cognitive impairment with suspected nonamyloid pathology (SNAP): Prediction of progression. *Neurology* 84, 508–515. <https://doi.org/10.1212/WNL.0000000000001209>
- Caselli, R.J., Langbaum, J., Marchant, G.E., Lindor, R.A., Hunt, K.S., Henslin, B.R., et al., 2014. Public perceptions of presymptomatic testing for Alzheimer disease. *Mayo Clin. Proc.* 89, 1389–1396. <https://doi.org/10.1016/j.mayocp.2014.05.016>
- Cations, M., Radisic, G., Crotty, M., & Laver, K.E., 2018. What does the general public understand about prevention and treatment of dementia? A systematic review of population-based surveys. *PLoS One* 13, e0196085. <https://doi.org/10.1371/journal.pone.0196085>
- Chatters, R., Newbould, L., Sprange, K., Hind, D., Mountain, G., Shortland, K., et al., 2018. Recruitment of older adults to three preventative lifestyle improvement

- studies. *Trials* 19, 121. <https://doi.org/10.1186/s13063-018-2482-1>
- Chatters, R., Roberts, J., Mountain, G., Cook, S., Windle, G., Craig, C., et al., 2017. The long-term (24-month) effect on health and well-being of the Lifestyle Matters community-based intervention in people aged 65 years and over: A qualitative study. *BMJ Open* 7, e016711. <https://doi.org/10.1136/bmjopen-2017-016711>
- Chen, L.-K., Hwang, A.-C., Lee, W.-J., Peng, L.-N., Lin, M.-H., Neil, D.L., et al., 2020. Efficacy of multidomain interventions to improve physical frailty, depression and cognition: data from cluster-randomized controlled trials. *J. Cachexia. Sarcopenia Muscle* 11, 650–662. <https://doi.org/10.1002/jcsm.12534>
- Chen, M.K., Mecca, A.P., Naganawa, M., Finnema, S.J., Toyonaga, T., Lin, S.F., et al., 2018. Assessing Synaptic Density in Alzheimer Disease with Synaptic Vesicle Glycoprotein 2A Positron Emission Tomographic Imaging. *JAMA Neurol.* 75, 1215–1224. <https://doi.org/10.1001/jamaneurol.2018.1836>
- Cheung, A.M., Lee, Y., Kapral, M., Scher, J., Ho, I., Lui-Yee, D., et al., 2008. Barriers and motivations for women to participate in cardiovascular trials. *J. Obstet. Gynaecol. Canada JOGC* 30, 332–337. [https://doi.org/10.1016/S1701-2163\(16\)32802-X](https://doi.org/10.1016/S1701-2163(16)32802-X)
- Chhetri, J.K., De Souto Barreto, P., Cantet, C., Pothier, K., Cesari, M., Andrieu, S., et al., 2018. Effects of a 3-Year Multi-Domain Intervention with or without Omega-3 Supplementation on Cognitive Functions in Older Subjects with Increased CAIDE Dementia Scores. *J. Alzheimer's Dis.* 64, 71–78. <https://doi.org/10.3233/JAD-180209>
- Claassen, L., Henneman, L., Janssens, A.C.J.W., Wijdenes-Pijl, M., Qureshi, N., Walter, F.M., et al., 2010. Using family history information to promote healthy lifestyles and prevent diseases; a discussion of the evidence. *BMC Public Health* 10, 248. <https://doi.org/10.1186/1471-2458-10-248>
- Clare, L., Nelis, S.M., Jones, I.R., Hindle, J. V., Thom, J.M., Nixon, J.A., et al., 2015. The Agewell trial: A pilot randomised controlled trial of a behaviour change intervention to promote healthy ageing and reduce risk of dementia in later life. *BMC Psychiatry* 15, 25. <https://doi.org/10.1186/s12888-015-0402-4>
- Clark, C.M., Pontecorvo, M.J., Beach, T.G., Bedell, B.J., Coleman, R.E., Doraiswamy, P.M., et al., 2012. Cerebral PET with florbetapir compared with neuropathology at autopsy for detection of neuritic amyloid- β plaques: A prospective cohort study. *Lancet Neurol.* 11, 669–678. [https://doi.org/10.1016/S1474-4422\(12\)70142-4](https://doi.org/10.1016/S1474-4422(12)70142-4)
- Clark, D.O., Xu, H., Moser, L., Adeoye, P., Lin, A.W., Tangney, C.C., et al., 2019. MIND food and speed of processing training in older adults with low education, the MINDSpeed Alzheimer's disease prevention pilot trial. *Contemp. Clin. Trials* 84, 105814. <https://doi.org/10.1016/j.cct.2019.105814>
- Clark, L.R., Berman, S.E., Norton, D., Kosciak, R.L., Jonaitis, E., Blennow, K., et al., 2018. Age-accelerated cognitive decline in asymptomatic adults with CSF β -Amyloid. *Neurology* 90, e1306–e1315. <https://doi.org/10.1212/WNL.0000000000005291>
- Coley, N., Ngandu, T., Lehtisalo, J., Soininen, H., Vellas, B., Richard, E., et al., 2019.

- Adherence to multidomain interventions for dementia prevention: Data from the FINGER and MAPT trials. *Alzheimer's Dement.* 15, 729–741. <https://doi.org/10.1016/j.jalz.2019.03.005>
- Conner, S.C., Pase, M.P., Carneiro, H., Raman, M.R., McKee, A.C., Alvarez, V.E., et al., 2019. Mid-life and late-life vascular risk factor burden and neuropathology in old age. *Ann. Clin. Transl. Neurol.* 6, 2403–2412. <https://doi.org/10.1002/acn3.50936>
- Cooper, C., Aguirre, E., Barber, J.A., Bass, N., Brodaty, H., Burton, A., et al., 2020. APPLE-Tree (Active Prevention in People at risk of dementia: Lifestyle, bEHaviour change and Technology to REDUCE cognitive and functional decline) programme: Protocol. *Int. J. Geriatr. Psychiatry* 35, 811–819. <https://doi.org/10.1002/gps.5249>
- Cooper, C., Ketley, D., & Livingston, G., 2014. Systematic review and meta-analysis to estimate potential recruitment to dementia intervention studies. *Int. J. Geriatr. Psychiatry* 29, 515–525. <https://doi.org/10.1002/gps.4034>
- Cooper, C., Sommerlad, A., Lyketsos, C.G., & Livingston, G., 2015. Modifiable predictors of dementia in mild cognitive impairment: A systematic review and meta-analysis. *Am. J. Psychiatry* 172, 323–334. <https://doi.org/10.1176/appi.ajp.2014.14070878>
- Coric, V., Salloway, S., van Dyck, C.H., Dubois, B., Andreasen, N., Brody, M., et al., 2015. Targeting Prodromal Alzheimer Disease With Avagacestat: A Randomized Clinical Trial. *JAMA Neurol.* 72, 1324–1333. <https://doi.org/10.1001/jamaneurol.2015.0607>
- Cox, C.G., Ryan B A, M.M., Gillen, D.L., & Grill, J.D., 2019. A Preliminary Study of Clinical Trial Enrollment Decisions Among People With Mild Cognitive Impairment and Their Study Partners. *Am. J. Geriatr. Psychiatry* 27, 322–332. <https://doi.org/10.1016/j.jagp.2018.10.016>
- Crary, J.F., Trojanowski, J.Q., Schneider, J.A., Abisambra, J.F., Abner, E.L., Alafuzoff, I., et al., 2014. Primary age-related tauopathy (PART): a common pathology associated with human aging. *Acta Neuropathol.* 128, 755–766. <https://doi.org/10.1007/s00401-014-1349-0>
- Cummings, J., Aisen, P.S., Dubois, B., Frölich, L., Jack, C.R., Jones, R.W., et al., 2016. Drug development in Alzheimer's disease: The path to 2025. *Alzheimer's Res. Ther.* 8, 39. <https://doi.org/10.1186/s13195-016-0207-9>
- Cummings, J., Lee, G., Ritter, A., Sabbagh, M., & Zhong, K., 2019. Alzheimer's disease drug development pipeline: 2019. *Alzheimer's Dement. Transl. Res. Clin. Interv.* 5, 272–293. <https://doi.org/10.1016/j.trci.2019.05.008>
- Cummings, J., Lee, G., Ritter, A., Sabbagh, M., & Zhong, K., 2020. Alzheimer's disease drug development pipeline: 2020. *Alzheimer's Dement. Transl. Res. Clin. Interv.* 6, e12050. <https://doi.org/10.1002/trc2.12050>
- Cummings, J., Lee, G., Ritter, A., & Zhong, K., 2018. Alzheimer's disease drug development pipeline: 2018. *Alzheimer's Dement. Transl. Res. Clin. Interv.* 4, 195–214. <https://doi.org/10.1016/j.trci.2018.03.009>

- Dahl, M., Lindholt, J., Søgaard, R., Frost, L., Andersen, L.S., & Lorentzen, V., 2018. An interview-based study of nonattendance at screening for cardiovascular diseases and diabetes in older women: Nonattendees' perspectives. *J. Clin. Nurs.* 27, 939–948. <https://doi.org/10.1111/jocn.14018>
- Dahlin-Ivanoff, S., Sterner, T.R., Blennow, K., Skoog, I., & Erhag, H.F., 2019. Was it worth it? Older adults' experiences of participating in a population-based cohort study—a focus group study. *BMC Geriatr.* 19, 224. <https://doi.org/10.1186/s12877-019-1238-4>
- Dahlin, E., Neely, A.S., Larsson, A., Bäckman, L., & Nyberg, L., 2008. Transfer of learning after updating training mediated by the striatum. *Science (80-.)*. 320, 1510–1512. <https://doi.org/10.1126/science.1155466>
- Dangour, A.D., Allen, E., Elbourne, D., Fasey, N., Fletcher, A.E., Hardy, P., et al., 2010. Effect of 2-y n-3 long-chain polyunsaturated fatty acid supplementation on cognitive function in older people: A randomized, double-blind, controlled trial. *Am. J. Clin. Nutr.* 91, 1725–1732. <https://doi.org/10.3945/ajcn.2009.29121>
- De Strooper, B., & Karran, E., 2016. The Cellular Phase of Alzheimer's Disease. *Cell* 164, 603–615. <https://doi.org/10.1016/j.cell.2015.12.056>
- De Veer, A.J.E., Peeters, J.M., Brabers, A.E.M., Schellevis, F.G., Rademakers, J.J.D.J.M., & Francke, A.L., 2015. Determinants of the intention to use e-health by community dwelling older people. *BMC Health Serv. Res.* 15, 103. <https://doi.org/10.1186/s12913-015-0765-8>
- De Wilde, A., Reimand, J., Teunissen, C.E., Zwan, M., Windhorst, A.D., Boellaard, R., et al., 2019. Discordant amyloid- β PET and CSF biomarkers and its clinical consequences. *Alzheimer's Res. Ther.* 11, 78. <https://doi.org/10.1186/s13195-019-0532-x>
- Deckers, K., Barbera, M., Köhler, S., Ngandu, T., van Boxtel, M., Rusanen, M., et al., 2020. Long-term dementia risk prediction by the LIBRA score: A 30-year follow-up of the CAIDE study. *Int. J. Geriatr. Psychiatry* 35, 195–203. <https://doi.org/10.1002/gps.5235>
- Deckers, K., Van Boxtel, M.P.J., Schiepers, O.J.G., De Vugt, M., Sánchez, J.L.M., Anstey, K.J., et al., 2015. Target risk factors for dementia prevention: A systematic review and Delphi consensus study on the evidence from observational studies. *Int. J. Geriatr. Psychiatry* 30, 234–246. <https://doi.org/10.1002/gps.4245>
- Dementias Platform UK, 2020. Great Minds [WWW Document]. Retrieved from <https://www.greatmindsfordementia.uk/> (accessed 07/27/2020).
- Dhana, K., Evans, D.A., Rajan, K.B., Bennett, D.A., & Morris, M.C., 2020. Healthy lifestyle and the risk of Alzheimer dementia: Findings from 2 longitudinal studies. *Neurology* 95, e374–e383. <https://doi.org/10.1212/WNL.0000000000009816>
- Diamond, K., Mowszowski, L., Cockayne, N., Norrie, L., Paradise, M., Hermens, D.F., et al., 2015. Randomized controlled trial of a healthy brain ageing cognitive training program: effects on memory, mood, and sleep. *J. Alzheimer's Dis.* 44,

- 1181–1191. <https://doi.org/10.3233/JAD-142061>
- Dodich, A., Mendes, A., Assal, F., Chicherio, C., Rakotomiaramanana, B., Andryszak, P., et al., 2020. The A/T/N model applied through imaging biomarkers in a memory clinic. *Eur. J. Nucl. Med. Mol. Imaging* 47, 247–255. <https://doi.org/10.1007/s00259-019-04536-9>
- Dubois, B., Epelbaum, S., Nyasse, F., Bakardjian, H., Gagliardi, G., Uspenskaya, O., et al., 2018. Cognitive and neuroimaging features and brain β -amyloidosis in individuals at risk of Alzheimer's disease (INSIGHT-preAD): a longitudinal observational study. *Lancet Neurol.* 17, 335–346. [https://doi.org/10.1016/S1474-4422\(18\)30029-2](https://doi.org/10.1016/S1474-4422(18)30029-2)
- Dubois, B., Feldman, H.H., Jacova, C., Cummings, J.L., DeKosky, S.T., Barberger-Gateau, P., et al., 2010. Revising the definition of Alzheimer's disease: A new lexicon. *Lancet Neurol.* 9, 1118–1127. [https://doi.org/10.1016/S1474-4422\(10\)70223-4](https://doi.org/10.1016/S1474-4422(10)70223-4)
- Dubois, B., Feldman, H.H., Jacova, C., DeKosky, S.T., Barberger-Gateau, P., Cummings, J., et al., 2007. Research criteria for the diagnosis of Alzheimer's disease: revising the NINCDS-ADRDA criteria. *Lancet Neurol.* 6, 734–746. [https://doi.org/10.1016/S1474-4422\(07\)70178-3](https://doi.org/10.1016/S1474-4422(07)70178-3)
- Dubois, B., Feldman, H.H., Jacova, C., Hampel, H., Molinuevo, J.L., Blennow, K., et al., 2014. Advancing research diagnostic criteria for Alzheimer's disease: The IWG-2 criteria. *Lancet Neurol.* 13, 614–629. [https://doi.org/10.1016/S1474-4422\(14\)70090-0](https://doi.org/10.1016/S1474-4422(14)70090-0)
- Dubois, B., Hampel, H., Feldman, H.H., Scheltens, P., Aisen, P., Andrieu, S., et al., 2016. Preclinical Alzheimer's disease: Definition, natural history, and diagnostic criteria. *Alzheimer's Dement.* 12, 292–323. <https://doi.org/10.1016/j.jalz.2016.02.002>
- Dunkley, A.J., Bodicoat, D.H., Greaves, C.J., Russell, C., Yates, T., Davies, M.J., et al., 2014. Diabetes prevention in the real world: Effectiveness of pragmatic lifestyle interventions for the prevention of type 2 diabetes and of the impact of adherence to guideline recommendations - A systematic review and meta-analysis. *Diabetes Care* 37, 922–933. <https://doi.org/10.2337/dc13-2195>
- Duyckaerts, C., Braak, H., Brion, J.P., Buée, L., Del Tredici, K., Goedert, M., et al., 2015. PART is part of Alzheimer disease. *Acta Neuropathol.* 129, 749–756. <https://doi.org/10.1007/s00401-015-1390-7>
- Ebenau, J.L., Timmers, T., Wesselman, L.M.P., Verberk, I.M.W., Verfaillie, S.C.J., Slot, R.E.R., et al., 2020. ATN classification and clinical progression in subjective cognitive decline: The SCIENCe project. *Neurology* 95, e46–e58. <https://doi.org/10.1212/WNL.00000000000009724>
- Editors of Alzheimer's & Dementia, 2020. Alzheimer's Disease Research Enterprise in the Era of COVID-19/SARS-CoV-2. *Alzheimer's Dement.* 16, 587–588. <https://doi.org/10.1002/alz.12093>
- Egan, M.F., Kost, J., Voss, T., Mukai, Y., Aisen, P.S., Cummings, J.L., et al., 2019. Randomized trial of verubecestat for prodromal Alzheimer's disease. *N. Engl.*

- J. Med.* 380, 1408–1420. <https://doi.org/10.1056/NEJMoa1812840>
- Ekman, U., Ferreira, D., & Westman, E., 2018. The A/T/N biomarker scheme and patterns of brain atrophy assessed in mild cognitive impairment. *Sci. Rep.* 8, 8431. <https://doi.org/10.1038/s41598-018-26151-8>
- Enache, D., Solomon, A., Cavallin, L., Kåreholt, I., Kramberger, M.G., Aarsland, D., et al., 2016. CAIDE Dementia Risk Score and biomarkers of neurodegeneration in memory clinic patients without dementia. *Neurobiol. Aging* 42, 124–131. <https://doi.org/10.1016/j.neurobiolaging.2016.03.007>
- Escott-Price, V., Sims, R., Bannister, C., Harold, D., Vronskaya, M., Majounie, E., et al., 2015. Common polygenic variation enhances risk prediction for Alzheimer’s disease. *Brain* 138, 3673–3684. <https://doi.org/10.1093/brain/awv268>
- European Union, 2019. Ageing Europe. Looking at the lives of older people in the EU, 2019 edition. Publications Office of the European Union, Luxembourg. <https://doi.org/10.2785/811048>
- Exalto, L.G., Quesenberry, C.P., Barnes, D., Kivipelto, M., Biessels, G.J., & Whitmer, R.A., 2014. Midlife risk score for the prediction of dementia four decades later. *Alzheimer’s Dement.* 10, 562–570. <https://doi.org/10.1016/j.jalz.2013.05.1772>
- Faraco, G., Hochrainer, K., Segarra, S.G., Schaeffer, S., Santisteban, M.M., Menon, A., et al., 2019. Dietary salt promotes cognitive impairment through tau phosphorylation. *Nature* 574, 686–690. <https://doi.org/10.1038/s41586-019-1688-z>
- Faraco, G., & Iadecola, C., 2013. Hypertension: a harbinger of stroke and dementia. *Hypertension* 62, 810–817. <https://doi.org/10.1161/HYPERTENSIONAHA.113.01063>
- Farina, N., Suemoto, C.K., Burton, J.K., Oliveira, D., & Frost, R., 2020. Perceptions of dementia amongst the general public across Latin America: a systematic review. *Aging Ment. Heal.* 1–10. <https://doi.org/10.1080/13607863.2020.1725738>
- Farrell, M.E., Chen, X., Rundle, M.M., Chan, M.Y., Wig, G.S., & Park, D.C., 2018. Regional amyloid accumulation and cognitive decline in initially amyloid-negative adults. *Neurology* 91, e1809–e1821. <https://doi.org/10.1212/WNL.0000000000006469>
- Farrell, M.E., Kennedy, K.M., Rodrigue, K.M., Wig, G., Bischof, G.N., Rieck, J.R., et al., 2017. Association of longitudinal cognitive decline with amyloid burden in middle-aged and older adults: Evidence for a dose-response relationship. *JAMA Neurol.* 74, 830–838. <https://doi.org/10.1001/jamaneurol.2017.0892>
- Farrer, L.A., Cupples, L.A., Haines, J.L., Hyman, B., Kukull, W.A., Mayeux, R., et al., 1997. Effects of age, sex, and ethnicity on the association between apolipoprotein E genotype and Alzheimer disease. A meta-analysis. APOE and Alzheimer Disease Meta Analysis Consortium. *JAMA - J. Am. Med. Assoc.* 278, 1349–1356. <https://doi.org/doi:10.1001/jama.1997.03550160069041>
- Fearn, P., Avenell, A., Mccann, S., Milne, A.C., & Maclennan, G., 2010. Factors influencing the participation of older people in clinical trials - Data analysis from the MAVIS trial. *J. Nutr. Heal. Aging* 14, 51–56. <https://doi.org/>

10.1007/s12603-010-0009-x

- Ferrer, R.A., & Klein, W.M.P., 2015. Risk perceptions and health behavior. *Curr. Opin. Psychol.* 5, 85–89. <https://doi.org/10.1016/j.copsyc.2015.03.012>
- Følling, I.S., Solbjør, M., Midthjell, K., Kulseng, B., & Helvik, A.S., 2016. Exploring lifestyle and risk in preventing type 2 diabetes—a nested qualitative study of older participants in a lifestyle intervention program (VEND-RISK). *BMC Public Health* 16, 876. <https://doi.org/10.1186/s12889-016-3559-y>
- Folstein, M.F., Folstein, S.E., & McHugh, P.R., 1975. “Mini-mental state”. A practical method for grading the cognitive state of patients for the clinician. *J. Psychiatr. Res.* 12, 189–198. [https://doi.org/10.1016/0022-3956\(75\)90026-6](https://doi.org/10.1016/0022-3956(75)90026-6)
- Foster, A., Horspool, K.A., Edwards, L., Thomas, C.L., Salisbury, C., Montgomery, A.A., et al., 2015. Who does not participate in telehealth trials and why? A cross-sectional survey. *Trials* 16, 258. <https://doi.org/10.1186/s13063-015-0773-3>
- Gauthier, S., Alam, J., Fillit, H., Iwatsubo, T., Liu-Seifert, H., Sabbagh, M., et al., 2019. Combination Therapy for Alzheimer’s Disease: Perspectives of the EU/US CTAD Task Force. *J. Prev. Alzheimer’s Dis.* 6, 164–168. <https://doi.org/10.14283/jpad.2019.12>
- Giuli, C., Paoloni, C., Santillo, E., Baliotti, M., Fabbietti, P., Postacchini, D., et al., 2020. Study of the effects of adapted Tango and multidimensional intervention in pREvention of dementia in agiNG: developing healthY lifestyle programs (STRENGTH Project)—the experimental protocol of a prospective randomised controlled trial. *Aging Clin. Exp. Res.* Epub Mar 2. <https://doi.org/10.1007/s40520-020-01504-4>
- Glynn, R.W., Shelley, E., & Lawlor, B.A., 2017. Public knowledge and understanding of dementia—evidence from a national survey in Ireland. *Age Ageing* 46, 865–869. <https://doi.org/10.1093/ageing/afx082>
- Gold, M., Amatniek, J., Carrillo, M.C., Cedarbaum, J.M., Hendrix, J.A., Miller, B.B., et al., 2018. Digital technologies as biomarkers, clinical outcomes assessment, and recruitment tools in Alzheimer’s disease clinical trials. *Alzheimer’s Dement. Transl. Res. Clin. Interv.* 4, 234–242. <https://doi.org/10.1016/j.trci.2018.04.003>
- Gottesman, R.F., Schneider, A.L.C., Zhou, Y., Coresh, J., Green, E., Gupta, N., et al., 2017. Association Between Midlife Vascular Risk Factors and Estimated Brain Amyloid Deposition. *JAMA - J. Am. Med. Assoc.* 317, 1443–1450. <https://doi.org/10.1001/jama.2017.3090>
- Greene, J.C., Caracelli, V.J., & Graham, W.F., 1989. Toward a Conceptual Framework for Mixed-Method Evaluation Designs. *Educ. Eval. Policy Anal.* 11, 255–274. <https://doi.org/https://doi.org/10.3102/01623737011003255>
- Gregson, J., Qizilbash, N., Iwagami, M., Douglas, I., Johnson, M., Pearce, N., et al., 2019. Blood pressure and risk of dementia and its subtypes: a historical cohort study with long-term follow-up in 2.6 million people. *Eur. J. Neurol.* 26, 1479–1486. <https://doi.org/10.1111/ene.14030>
- Griffin, S.J., Borch-Johnsen, K., Davies, M.J., Khunti, K., Rutten, G.E., Sandbæk, A., et al., 2011. Effect of early intensive multifactorial therapy on 5-year

- cardiovascular outcomes in individuals with type 2 diabetes detected by screening (ADDITION-Europe): A cluster-randomised trial. *Lancet* 378, 156–167. [https://doi.org/10.1016/S0140-6736\(11\)60698-3](https://doi.org/10.1016/S0140-6736(11)60698-3)
- Grill, J.D., Karlawish, J., Elashoff, D., & Vickrey, B.G., 2013. Risk disclosure and preclinical Alzheimer's disease clinical trial enrollment. *Alzheimer's Dement.* 9, 356-359.e1. <https://doi.org/10.1016/j.jalz.2012.03.001>
- Grill, J.D., Nuño, M.M., & Gillen, D.L., 2019. Which MCI Patients Should be Included in Prodromal Alzheimer Disease Clinical Trials? *Alzheimer Dis. Assoc. Disord.* 33, 104–112. <https://doi.org/10.1097/WAD.0000000000000303>
- Grill, J.D., Zhou, Y., Elashoff, D., & Karlawish, J., 2016. Disclosure of amyloid status is not a barrier to recruitment in preclinical Alzheimer's disease clinical trials. *Neurobiol. Aging* 39, 147–153. <https://doi.org/10.1016/j.neurobiolaging.2015.11.007>
- Gross, A.L., Walker, K.A., Moghekar, A.R., Pettigrew, C., Soldan, A., Albert, M.S., et al., 2019. Plasma Markers of Inflammation Linked to Clinical Progression and Decline During Preclinical AD. *Front. Aging Neurosci.* 11, 229. <https://doi.org/10.3389/fnagi.2019.00229>
- Gustavsson, A.-M., van Westen, D., Stomrud, E., Engström, G., Nägga, K., & Hansson, O., 2020. Midlife Atherosclerosis and Development of Alzheimer or Vascular Dementia. *Ann. Neurol.* 87, 52–62. <https://doi.org/10.1002/ana.25645>
- Halpern, S.D., Karlawish, J.H.T., Casarett, D., Berlin, J.A., Townsend, R.R., & Asch, D.A., 2003. Hypertensive patients' willingness to participate in placebo-controlled trials: implications for recruitment efficiency. *Am. Heart J.* 146, 985–992. [https://doi.org/10.1016/S0002-8703\(03\)00507-6](https://doi.org/10.1016/S0002-8703(03)00507-6)
- Harada, C.N., Natelson Love, M.C., & Triebel, K.L., 2013. Normal cognitive aging. *Clin. Geriatr. Med.* 29, 737–752. <https://doi.org/10.1016/j.cger.2013.07.002>
- Hardy, J.A., & Higgins, G.A., 1992. Alzheimer's disease: The amyloid cascade hypothesis. *Science (80-)*. 256, 184–185. <https://doi.org/10.1126/science.1566067>
- Harrison, J., Minassian, S.L., Jenkins, L., Black, R.S., Koller, M., & Grundman, M., 2007. A neuropsychological test battery for use in Alzheimer disease clinical trials. *Arch. Neurol.* 64, 1323–1329. <https://doi.org/10.1001/archneur.64.9.1323>
- Heffernan, M., Andrews, G., Fiatarone Singh, M.A., Valenzuela, M., Anstey, K.J., Maeder, A.J., et al., 2019. Maintain Your Brain: Protocol of a 3-Year Randomized Controlled Trial of a Personalized Multi-Modal Digital Health Intervention to Prevent Cognitive Decline among Community Dwelling 55 to 77 Year Olds. *J. Alzheimer's Dis.* 70, S221–S237. <https://doi.org/10.3233/JAD-180572>
- Heger, I., Deckers, K., Van Boxtel, M., De Vugt, M., Hajema, K., Verhey, F., et al., 2019. Dementia awareness and risk perception in middle-aged and older individuals: Baseline results of the MijnBreincoach survey on the association between lifestyle and brain health. *BMC Public Health* 19, 678. <https://doi.org/10.1186/s12889-019-7010-z>
- Henley, D., Raghavan, N., Sperling, R., Aisen, P., Raman, R., & Romano, G., 2019. Preliminary Results of a Trial of Atabecestat in Preclinical Alzheimer's Disease.

- N. Engl. J. Med.* <https://doi.org/10.1056/NEJMc1813435>
- Herrmann, L.K., Welter, E., Leverenz, J., Lerner, A.J., Udelson, N., Kanetsky, C., et al., 2018. A Systematic Review of Dementia-related Stigma Research: Can We Move the Stigma Dial? *Am. J. Geriatr. Psychiatry* 26, 316–331. <https://doi.org/10.1016/j.jagp.2017.09.006>
- Holland, D., McEvoy, L.K., Desikan, R.S., & Dale, A.M., 2012. Enrichment and Stratification for Predementia Alzheimer Disease Clinical Trials. *PLoS One* 7, e47739. <https://doi.org/10.1371/journal.pone.0047739>
- Hollands, G.J., French, D.P., Griffin, S.J., Prevost, A.T., Sutton, S., King, S., et al., 2016. The impact of communicating genetic risks of disease on riskreducing health behaviour: Systematic review with meta-analysis. *BMJ* 352, i1102. <https://doi.org/10.1136/bmj.i1102>
- Honig, L.S., Vellas, B., Woodward, M., Boada, M., Bullock, R., Borrie, M., et al., 2018. Trial of solanezumab for mild dementia due to Alzheimer’s disease. *N. Engl. J. Med.* 378, 321–330. <https://doi.org/10.1056/NEJMoa1705971>
- Hosmer, D., Lemeshow, S., & Sturdivant, R., 2013. Applied Logistic Regression, chapter Assessing the Fit of the Model, 3rd ed. John Wiley & Sons.
- Hou, X.H., Feng, L., Zhang, C., Cao, X.P., Tan, L., & Yu, J.T., 2019. Models for predicting risk of dementia: a systematic review. *J. Neurol. Neurosurg. Psychiatry* 90, 373–379. <https://doi.org/10.1136/jnnp-2018-318212>
- Hughes-Morley, A., Young, B., Hempel, R.J., Russell, I.T., Waheed, W., & Bower, P., 2016. What can we learn from trial decliners about improving recruitment? Qualitative study. *Trials* 17, 494. <https://doi.org/10.1186/s13063-016-1626-4>
- Iadecola, C., Duering, M., Hachinski, V., Joutel, A., Pendlebury, S.T., Schneider, J.A., et al., 2019. Vascular Cognitive Impairment and Dementia: JACC Scientific Expert Panel. *J. Am. Coll. Cardiol.* 73, 3326–3344. <https://doi.org/10.1016/j.jacc.2019.04.034>
- Ihle-Hansen, H., Thommessen, B., Fagerland, M.W., Øksengård, A.R., Wyller, T.B., Engedal, K., et al., 2014. Multifactorial vascular risk factor intervention to prevent cognitive impairment after stroke and TIA: A 12-month randomized controlled trial. *Int. J. Stroke* 9, 932–938. <https://doi.org/10.1111/j.1747-4949.2012.00928.x>
- Insel, P.S., Mattsson, N., Donohue, M.C., Mackin, R.S., Aisen, P.S., Jack, C.R.J., et al., 2015a. The transitional association between β -amyloid pathology and regional brain atrophy. *Alzheimer’s Dement.* 11, 1171–1179. <https://doi.org/10.1016/j.jalz.2014.11.002>
- Insel, P.S., Mattsson, N., Mackin, R.S., Kornak, J., Nosheny, R., Tosun-Turgut, D., et al., 2015b. Biomarkers and cognitive endpoints to optimize trials in Alzheimer’s disease. *Ann. Clin. Transl. Neurol.* 2, 534–547. <https://doi.org/10.1002/acn3.192>
- Insel, P.S., Mattsson, N., Mackin, R.S., Schöll, M., Nosheny, R.L., Tosun, D., et al., 2016. Accelerating rates of cognitive decline and imaging markers associated with β -amyloid pathology. *Neurology* 86, 1887–1896. <https://doi.org/10.1212/WNL.0000000000002683>

- Insel, P.S., Ossenkoppele, R., Gessert, D., Jagust, W., Landau, S., Hansson, O., et al., 2017. Time to amyloid positivity and preclinical changes in brain metabolism, atrophy, and cognition: Evidence for emerging amyloid pathology in Alzheimer's disease. *Front. Neurosci.* 11, 281. <https://doi.org/10.3389/fnins.2017.00281>
- Irving, K., no date. In-MINDD Project - Final Report Supporting Document [WWW Document]. Retrieved from <https://cordis.europa.eu/project/id/304979/reporting> (accessed 06/20/2020).
- Jack, C.R., Bennett, D.A., Blennow, K., Carrillo, M.C., Dunn, B., Haeberlein, S.B., et al., 2018. NIA-AA Research Framework: Toward a biological definition of Alzheimer's disease. *Alzheimer's Dement.* 14, 535–562. <https://doi.org/10.1016/j.jalz.2018.02.018>
- Jack, C.R., Bennett, D.A., Blennow, K., Carrillo, M.C., Feldman, H.H., Frisoni, G.B., et al., 2016. A/T/N: An unbiased descriptive classification scheme for Alzheimer disease biomarkers. *Neurology* 87, 539–547. <https://doi.org/10.1212/WNL.0000000000002923>
- Jack, C.R., Knopman, D.S., Jagust, W.J., Petersen, R.C., Weiner, M.W., Aisen, P.S., et al., 2013. Tracking pathophysiological processes in Alzheimer's disease: an updated hypothetical model of dynamic biomarkers. *Lancet Neurol.* 12, 207–216. [https://doi.org/10.1016/S1474-4422\(12\)70291-0](https://doi.org/10.1016/S1474-4422(12)70291-0)
- Jack, C.R., Knopman, D.S., Jagust, W.J., Shaw, L.M., Aisen, P.S., Weiner, M.W., et al., 2010. Hypothetical Pathological Cascade in Alzheimer's Disease. *Lancet Neurol.* 9, 1–20. [https://doi.org/10.1016/S1474-4422\(09\)70299-6](https://doi.org/10.1016/S1474-4422(09)70299-6).
- Jack, C.R., Knopman, D.S., Weigand, S.D., Wiste, H.J., Vemuri, P., Lowe, V., et al., 2012. An operational approach to National Institute on Aging-Alzheimer's Association criteria for preclinical Alzheimer disease. *Ann. Neurol.* 71, 765–775. <https://doi.org/10.1002/ana.22628>
- Jack, C.R., Therneau, T.M., Weigand, S.D., Wiste, H.J., Knopman, D.S., Vemuri, P., et al., 2019a. Prevalence of Biologically vs Clinically Defined Alzheimer Spectrum Entities Using the National Institute on Aging-Alzheimer's Association Research Framework. *JAMA Neurol.* 76, 1174–1183. <https://doi.org/10.1001/jamaneurol.2019.1971>
- Jack, C.R., Wiste, H.J., Botha, H., Weigand, S.D., Therneau, T.M., Knopman, D.S., et al., 2019b. The bivariate distribution of amyloid- β and tau: Relationship with established neurocognitive clinical syndromes. *Brain* 142, 3230–3242. <https://doi.org/10.1093/brain/awz268>
- Jack, C.R., Wiste, H.J., Therneau, T.M., Weigand, S.D., Knopman, D.S., Mielke, M.M., et al., 2019c. Associations of Amyloid, Tau, and Neurodegeneration Biomarker Profiles with Rates of Memory Decline among Individuals Without Dementia. *JAMA - J. Am. Med. Assoc.* 321, 2316–2325. <https://doi.org/10.1001/jama.2019.7437>
- Jack, C.R., Wiste, H.J., Weigand, S.D., Therneau, T.M., Knopman, D.S., Lowe, V., et al., 2017. Age-specific and sex-specific prevalence of cerebral β -amyloidosis,

- tauopathy, and neurodegeneration in cognitively unimpaired individuals aged 50-95 years: a cross-sectional study. *Lancet Neurol.* 16, 435–444. [https://doi.org/10.1016/S1474-4422\(17\)30077-7](https://doi.org/10.1016/S1474-4422(17)30077-7)
- James, B.D., Wilson, R.S., Boyle, P.A., Trojanowski, J.Q., Bennett, D.A., & Schneider, J.A., 2016. TDP-43 stage, mixed pathologies, and clinical Alzheimer's-type dementia. *Brain* 139, 2983–2993. <https://doi.org/10.1093/brain/aww224>
- Janelidze, S., Zetterberg, H., Mattsson, N., Palmqvist, S., Vanderstichele, H., Lindberg, O., et al., 2016. CSF A β 42/A β 40 and A β 42/A β 38 ratios: better diagnostic markers of Alzheimer disease. *Ann. Clin. Transl. Neurol.* 3, 154–165. <https://doi.org/10.1002/acn3.274>
- Jansen, W.J., Ossenkoppele, R., Knol, D.L., Tijms, B.M., Scheltens, P., Verhey, F.R.J., et al., 2015. Prevalence of cerebral amyloid pathology in persons without dementia: a meta-analysis. *JAMA - J. Am. Med. Assoc.* 313, 1924–1938. <https://doi.org/10.1001/jama.2015.4668>
- Jefferson, A.L., Lambe, S., Chaisson, C., Palmisano, J., Horvath, K.J., & Karlawish, J., 2011. Clinical research participation among aging adults enrolled in an Alzheimer's Disease Center research registry. *J. Alzheimers. Dis.* 23, 443–452. <https://doi.org/10.3233/JAD-2010-101536>
- Jellinger, K.A., Alafuzoff, I., Attems, J., Beach, T.G., Cairns, N.J., Crary, J.F., et al., 2015. PART, a distinct tauopathy, different from classical sporadic Alzheimer disease. *Acta Neuropathol.* 129, 757–762. <https://doi.org/10.1007/s00401-015-1407-2>
- Jessen, F., Amariglio, R.E., Buckley, R.F., van der Flier, W.M., Han, Y., Molinuevo, J.L., et al., 2020. The characterisation of subjective cognitive decline. *Lancet Neurol.* 19, 271–278. [https://doi.org/10.1016/S1474-4422\(19\)30368-0](https://doi.org/10.1016/S1474-4422(19)30368-0)
- Johnson, E.C.B., Dammer, E.B., Duong, D.M., Ping, L., Zhou, M., Yin, L., et al., 2020. Large-scale proteomic analysis of Alzheimer's disease brain and cerebrospinal fluid reveals early changes in energy metabolism associated with microglia and astrocyte activation. *Nat. Med.* 26, 769–780. <https://doi.org/10.1038/s41591-020-0815-6>
- Joling, K.J., Janssen, O., Francke, A.L., Verheij, R.A., Lissenberg-Witte, B.I., Visser, P.J., et al., 2020. Time from diagnosis to institutionalization and death in people with dementia. *Alzheimer's Dement.* 16, 662–671. <https://doi.org/10.1002/alz.12063>
- Jongstra, S., Beishuizen, C., Andrieu, S., Barbera, M., Van Dorp, M., Van De Groep, B., et al., 2017. Development and Validation of an Interactive Internet Platform for Older People: The Healthy Ageing Through Internet Counselling in the Elderly Study. *Telemed. e-Health* 23, 96–104. <https://doi.org/10.1089/tmj.2016.0066>
- Jousilahti, P., Laatikainen, T., Peltonen, M., Borodulin, K., Männistö, S., Jula, A., et al., 2016. Primary prevention and risk factor reduction in coronary heart disease mortality among working aged men and women in eastern Finland over 40 years: Population based observational study. *BMJ* 352, 1–8. <https://doi.org/>

10.1136/bmj.i721

- Kametani, F., & Hasegawa, M., 2018. Reconsideration of Amyloid Hypothesis and Tau Hypothesis in Alzheimer's Disease. *Front. Neurosci.* 12, 25. <https://doi.org/10.3389/fnins.2018.00025>
- Kandola, D.K., Banner, D., Araki, Y., Bates, J., Hadi, H., & Lear, S.A., 2018. The Participant Recruitment Outcomes (PRO) study: Exploring contemporary perspectives of telehealth trial non-participation through insights from patients, clinicians, study investigators, and study staff. *Contemp. Clin. Trials Commun.* 11, 75–82. <https://doi.org/10.1016/j.conctc.2018.05.005>
- Kapasi, A., DeCarli, C., & Schneider, J.A., 2017. Impact of multiple pathologies on the threshold for clinically overt dementia. *Acta Neuropathol.* 134, 171–186. <https://doi.org/10.1007/s00401-017-1717-7>
- Kapasi, A., & Schneider, J.A., 2016. Vascular contributions to cognitive impairment, clinical Alzheimer's disease, and dementia in older persons. *Biochim. Biophys. Acta* 1862, 878–886. <https://doi.org/10.1016/j.bbadis.2015.12.023>
- Karikari, T.K., Pascoal, T.A., Ashton, N.J., Janelidze, S., Benedet, A.L., Rodriguez, J.L., et al., 2020. Blood phosphorylated tau 181 as a biomarker for Alzheimer's disease: a diagnostic performance and prediction modelling study using data from four prospective cohorts. *Lancet Neurol.* 19, 422–433. [https://doi.org/10.1016/S1474-4422\(20\)30071-5](https://doi.org/10.1016/S1474-4422(20)30071-5)
- Kawas, C.H., Kim, R.C., Sonnen, J.A., Bullain, S.S., Trieu, T., & Corrada, M.M., 2015. Multiple pathologies are common and related to dementia in the oldest-old: The 90 + Study. *Neurology* 85, 535–542. <https://doi.org/10.1212/WNL.0000000000001831>
- Kennedy, M.E., Stamford, A.W., Chen, X., Cox, K., Cumming, J.N., Dockendorf, M.F., et al., 2016. The BACE1 inhibitor verubecestat (MK-8931) reduces CNS b-Amyloid in animal models and in Alzheimer's disease patients. *Sci. Transl. Med.* 8, 1–14. <https://doi.org/10.1126/scitranslmed.aad9704>
- Kern, S., Zetterberg, H., Kern, J., Zettergren, A., Waern, M., Höglund, K., et al., 2018. Prevalence of preclinical Alzheimer disease: Comparison of current classification systems. *Neurology* 90, e1682–e1691. <https://doi.org/10.1212/WNL.0000000000005476>
- Kim, S., McMaster, M., Torres, S., Cox, K.L., Lautenschlager, N., Rebok, G.W., et al., 2018. Protocol for a pragmatic randomised controlled trial of Body Brain Life-General Practice and a Lifestyle Modification Programme to decrease dementia risk exposure in a primary care setting. *BMJ Open* 8, e019329. <https://doi.org/10.1136/bmjopen-2017-019329>
- Kim, S., Sargent-Cox, K.A., & Anstey, K.J., 2015. A qualitative study of older and middle-aged adults' perception and attitudes towards dementia and dementia risk reduction. *J. Adv. Nurs.* 71, 1694–1703. <https://doi.org/10.1111/jan.12641>
- Kim, S., Werner, P., Richardson, A., & Anstey, K.J., 2019. Dementia Stigma Reduction (DESeRvE): Study protocol for a randomized controlled trial of an online intervention program to reduce dementia-related public stigma. *Contemp. Clin.*

- Trials Commun.* 14, 100351. <https://doi.org/10.1016/j.conctc.2019.100351>
- Kivimäki, M., Luukkonen, R., Batty, G.D., Ferrie, J.E., Pentti, J., Nyberg, S.T., et al., 2018. Body mass index and risk of dementia: Analysis of individual-level data from 1.3 million individuals. *Alzheimer's Dement.* 14, 601–609. <https://doi.org/10.1016/j.jalz.2017.09.016>
- Kivipelto, M., Mangialasche, F., Snyder, H.M., Allegri, R., Andrieu, S., Arai, H., et al., 2020. World-Wide FINGERS Network: A global approach to risk reduction and prevention of dementia. *Alzheimer's Dement.* 16, 1078–1094. <https://doi.org/10.1002/alz.12123>
- Kivipelto, M., Ngandu, T., Laatikainen, T., Winblad, B., Soininen, H., & Tuomilehto, J., 2006. Risk score for the prediction of dementia risk in 20 years among middle aged people: a longitudinal, population-based study. *Lancet Neurol.* 5, 735–741. [https://doi.org/10.1016/S1474-4422\(06\)70537-3](https://doi.org/10.1016/S1474-4422(06)70537-3)
- Kivipelto, M., Rovio, S., Ngandu, T., Kåreholt, I., Eskelinen, M., Winblad, B., et al., 2008. Apolipoprotein E 4 magnifies lifestyle risks for dementia : a population-based study. *J. Cell. Mol. Med* 12, 2762–2771. <https://doi.org/10.1111/j.1582-4934.2008.0296.x>
- Kivipelto, M., Solomon, A., Ahtiluoto, S., Ngandu, T., Lehtisalo, J., Antikainen, R., et al., 2013. The Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER): study design and progress. *Alzheimer's Dement.* 9, 657–665. <https://doi.org/10.1016/j.jalz.2012.09.012>
- Klein, G., Delmar, P., Voyle, N., Rehal, S., Hofmann, C., Abi-Saab, D., et al., 2019. Gantenerumab reduces amyloid- β plaques in patients with prodromal to moderate Alzheimer's disease: A PET substudy interim analysis. *Alzheimer's Res. Ther.* 11, 101. <https://doi.org/10.1186/s13195-019-0559-z>
- Knopman, D.S., Jack, C.R., Wiste, H.J., Weigand, S.D., Vemuri, P., Lowe, V., et al., 2012. Short-term clinical outcomes for stages of NIA-AA preclinical Alzheimer disease. *Neurology* 78, 1576–1582. <https://doi.org/10.1212/WNL.0b013e3182563bbe>
- Knopman, D.S., Petersen, R.C., & Jack, C.R., 2019. A brief history of “Alzheimer disease”: Multiple meanings separated by a common name. *Neurology* 92, 1053–1059. <https://doi.org/10.1212/WNL.0000000000007583>
- Komulainen, P., Kivipelto, M., Lakka, T.A., Savonen, K., Hassinen, M., Kiviniemi, V., et al., 2010. Exercise, fitness and cognition – A randomised controlled trial in older individuals: The DR's EXTRA study. *Eur. Geriatr. Med.* 1, 266–272. <https://doi.org/https://doi.org/10.1016/j.eurger.2010.08.001>
- Kotseva, K., De Backer, G., De Bacquer, D., Rydén, L., Hoes, A., Grobbee, D., et al., 2020. Primary prevention efforts are poorly developed in people at high cardiovascular risk: A report from the European Society of Cardiology EURObservational Research Programme EUROASPIRE V survey in 16 European countries. *Eur. J. Prev. Cardiol.* Epub Mar 2, 2047487320908698. <https://doi.org/10.1177/2047487320908698>
- Kourtis, L.C., Regele, O.B., Wright, J.M., & Jones, G.B., 2019. Digital biomarkers for

- Alzheimer's disease: the mobile/wearable devices opportunity. *NPJ Digit. Med.* 2, 9. <https://doi.org/10.1038/s41746-019-0084-2>
- Kozica, S.L., Lombard, C.B., Ilic, D., Ng, S., Harrison, C.L., & Teede, H.J., 2015. Acceptability of delivery modes for lifestyle advice in a large scale randomised controlled obesity prevention trial Health behavior, health promotion and society. *BMC Public Health* 15, 699. <https://doi.org/10.1186/s12889-015-1995-8>
- Kulmala, J., Ngandu, T., Havulinna, S., Levälähti, E., Lehtisalo, J., Solomon, A., et al., 2019. The Effect of Multidomain Lifestyle Intervention on Daily Functioning in Older People. *J. Am. Geriatr. Soc.* 67, 1138–1144. <https://doi.org/10.1111/jgs.15837>
- Lam, L.C.W., Chan, W.C., Leung, T., Fung, A.W.T., & Leung, E.M.F., 2015. Would older adults with mild cognitive impairment adhere to and benefit from a structured lifestyle activity intervention to enhance cognition?: A cluster randomized controlled trial. *PLoS One* 10, e0118173. <https://doi.org/10.1371/journal.pone.0118173>
- Landau, S.M., Horng, A., Fero, A., & Jagust, W.J., 2016. Amyloid negativity in patients with clinically diagnosed Alzheimer disease and MCI. *Neurology* 86, 1377–1385. <https://doi.org/10.1212/WNL.0000000000002576>
- Landau, S.M., Horng, A., & Jagust, W.J., 2018. Memory decline accompanies subthreshold amyloid accumulation. *Neurology* 90, e1452–e1460. <https://doi.org/10.1212/WNL.0000000000005354>
- Lane, C.A., Barnes, J., Nicholas, J.M., Sudre, C.H., Cash, D.M., Malone, I.B., et al., 2020. Associations between Vascular Risk Across Adulthood and Brain Pathology in Late Life: Evidence from a British Birth Cohort. *JAMA Neurol.* 77, 175–183. <https://doi.org/10.1001/jamaneurol.2019.3774>
- Langa, K.M., & Levine, D.A., 2014. The diagnosis and management of mild cognitive impairment: A clinical review. *JAMA - J. Am. Med. Assoc.* 312, 2551–2561. <https://doi.org/10.1001/jama.2014.13806>
- Langbaum, J.B., High, N., Nichols, J., Kettenhoven, C., Reiman, E.M., & Tariot, P.N., 2020. The Alzheimer's Prevention Registry: A Large Internet-Based Participant Recruitment Registry to Accelerate Referrals to Alzheimer's-Focused Studies. *J. Prev. Alzheimer's Dis.* <https://doi.org/10.14283/jpad.2020.31>
- Langbaum, J.B., Karlawish, J., Roberts, J.S., Wood, E.M., Bradbury, A., High, N., et al., 2019. GeneMatch: A novel recruitment registry using at-home APOE genotyping to enhance referrals to Alzheimer's prevention studies. *Alzheimer's Dement.* 15, 515–524. <https://doi.org/10.1016/j.jalz.2018.12.007>
- Lawrence, V., Pickett, J., Ballard, C., & Murray, J., 2014. Patient and carer views on participating in clinical trials for prodromal Alzheimer's disease and mild cognitive impairment. *Int. J. Geriatr. Psychiatry* 29, 22–31. <https://doi.org/10.1002/gps.3958>
- Lee, K.S., Lee, Y., Back, J.H., Son, S.J., Choi, S.H., Chung, Y.K., et al., 2014. Effects of a multidomain lifestyle modification on cognitive function in older adults: An eighteen-month community-based cluster randomized controlled trial. *Psychother. Psychosom.* 83, 270–278. <https://doi.org/10.1159/000360820>

- Leijenaar, J.F., Groot, C., Sudre, C.H., Bergeron, D., Leeuwis, A.E., Cardoso, M.J., et al., 2020. Comorbid amyloid- β pathology affects clinical and imaging features in VCD. *Alzheimer's Dement.* 16, 354–364. <https://doi.org/10.1016/j.jalz.2019.08.190>
- Li, J.-Q., Tan, Lan, Wang, H.-F., Tan, M.-S., Tan, Lin, Xu, W., et al., 2016. Risk factors for predicting progression from mild cognitive impairment to Alzheimer's disease: a systematic review and meta-analysis of cohort studies. *J. Neurol. Neurosurg. Psychiatry* 87, 476–484. <https://doi.org/10.1136/jnnp-2014-310095>
- Liao, Q.V., & Fu, W.T., 2014. Age differences in credibility judgments of online health information. *ACM Trans. Comput. Interact.* 21. <https://doi.org/10.1145/2534410>
- Licher, S., Ahmad, S., Karamujić-Čomić, H., Voortman, T., Leening, M.J.G., Ikram, M.A., et al., 2019. Genetic predisposition, modifiable-risk-factor profile and long-term dementia risk in the general population. *Nat. Med.* 25, 1364–1369. <https://doi.org/10.1038/s41591-019-0547-7>
- Licher, S., Yilmaz, P., Leening, M.J.G., Wolters, F.J., Vernooij, M.W., Stephan, B.C.M., et al., 2018. External validation of four dementia prediction models for use in the general community-dwelling population: a comparative analysis from the Rotterdam Study. *Eur. J. Epidemiol.* 33, 645–655. <https://doi.org/10.1007/s10654-018-0403-y>
- Ligthart, S.A., Van Den Eerenbeemt, K.D.M., Pols, J., Van Bussel, E.F., Richard, E., & Moll Van Charante, E.P., 2015. Perspectives of older people engaging in nurse-led cardiovascular prevention programmes: A qualitative study in primary care in the Netherlands. *Br. J. Gen. Pract.* 65, e41–e48. <https://doi.org/10.3399/bjgp15X683149>
- Lindström, J., Peltonen, M., Eriksson, J.G., Aunola, S., Hämäläinen, H., Ilanne-Parikka, P., et al., 2008. Determinants for the effectiveness of lifestyle intervention in the finnish diabetes prevention study. *Diabetes Care* 31, 857–862. <https://doi.org/10.2337/dc07-2162>
- Liu, D., Cheng, G., An, L., Gan, X., Wu, Y., Zhang, B., et al., 2019. Public knowledge about dementia in China: A national wechat-based survey. *Int. J. Environ. Res. Public Health* 16, 1–14. <https://doi.org/10.3390/ijerph16214231>
- Livingston, G., Huntley, J., Sommerlad, A., Ames, D., Ballard, C., Banerjee, S., et al., 2020. Dementia prevention, intervention, and care: 2020 report of the Lancet Commission. *Lancet* S0140-6736, 30367–6. [https://doi.org/10.1016/S0140-6736\(20\)30367-6](https://doi.org/10.1016/S0140-6736(20)30367-6)
- Livingston, G., Sommerlad, A., Orgeta, V., Costafreda, S.G., Huntley, J., Ames, D., et al., 2017. Dementia prevention, intervention, and care. *Lancet* 390, 2673–2734. [https://doi.org/10.1016/S0140-6736\(17\)31363-6](https://doi.org/10.1016/S0140-6736(17)31363-6)
- Lock, M., Freeman, J., Sharples, R., & Lloyd, S., 2006. When it runs in the family: Putting susceptibility genes in perspective. *Public Underst. Sci.* 15, 277–300. <https://doi.org/10.1177/0963662506059259>
- Long, J.M., & Holtzman, D.M., 2019. Alzheimer Disease: An Update on Pathobiology and Treatment Strategies. *Cell* 179, 312–339. <https://doi.org/10.1016/>

- Lopez Lopez, C., Tariot, P.N., Caputo, A., Langbaum, J.B., Liu, F., Riviere, M.E., et al., 2019. The Alzheimer's Prevention Initiative Generation Program: Study design of two randomized controlled trials for individuals at risk for clinical onset of Alzheimer's disease. *Alzheimer's Dement. Transl. Res. Clin. Interv.* 5, 216–227. <https://doi.org/10.1016/j.trci.2019.02.005>
- Lourida, I., Hannon, E., Littlejohns, T.J., Langa, K.M., Hyppönen, E., Kuzma, E., et al., 2019. Association of Lifestyle and Genetic Risk With Incidence of Dementia. *JAMA - J. Am. Med. Assoc.* 322, 430–437. <https://doi.org/10.1001/jama.2019.9879>
- Lowe, V.J., Peller, P.J., Weigand, S.D., Quintero, C.M., Tosakulwong, N., Vemuri, P., et al., 2013. Application of the national institute on aging-alzheimer's association AD criteria to ADNI. *Neurology* 80, 2130–2137. <https://doi.org/10.1212/WNL.0b013e318295d6cf>
- Lowe, V.J., Wiste, H.J., Senjem, M.L., Weigand, S.D., Therneau, T.M., Boeve, B.F., et al., 2018. Widespread brain tau and its association with ageing, Braak stage and Alzheimer's dementia. *Brain* 141, 271–287. <https://doi.org/10.1093/brain/awx320>
- Lyall, D.M., Celis-Morales, C., Lyall, L.M., Graham, C., Graham, N., Mackay, D.F., et al., 2019. Assessing for interaction between APOE ϵ 4, sex, and lifestyle on cognitive abilities. *Neurology* 92, e2691–e2698. <https://doi.org/10.1212/WNL.0000000000007551>
- Macpherson, H., Brownell, S., Duckham, R.L., Meyer, B., Mirzaee, S., & Daly, R.M., 2019. Multifaceted intervention to enhance cognition in older people at risk of cognitive decline: study protocol for the Protein Omega-3 and Vitamin D Exercise Research (PONDER) study. *BMJ Open* 9, e024145. <https://doi.org/10.1136/bmjopen-2018-024145>
- Marengoni, A., Rizzuto, D., Fratiglioni, L., Antikainen, R., Laatikainen, T., Lehtisalo, J., et al., 2018. The Effect of a 2-Year Intervention Consisting of Diet, Physical Exercise, Cognitive Training, and Monitoring of Vascular Risk on Chronic Morbidity-the FINGER Randomized Controlled Trial. *J. Am. Med. Dir. Assoc.* 19, 355-360.e1. <https://doi.org/10.1016/j.jamda.2017.09.020>
- Matz, K., Teuschl, Y., Firlinger, B., Dachenhausen, A., Keindl, M., Seyfang, L., et al., 2015. Multidomain lifestyle interventions for the prevention of cognitive decline after ischemic stroke randomized trial. *Stroke* 46, 2874–2880. <https://doi.org/10.1161/STROKEAHA.115.009992>
- Mayeda, E., Glymour, M., Quesenberry, C., Johnson, J., Pérez-Stable, E., & Whitmer, R., 2017. Survival after dementia diagnosis in five racial/ethnic groups. *Alzheimer's Dement.* 13, 761–769. <https://doi.org/10.1016/j.jalz.2016.12.008>
- Mayeda, E.R., Glymour, M.M., Quesenberry, C.P., & Whitmer, R.A., 2016. Inequalities in dementia incidence between six racial and ethnic groups over 14 years. *Alzheimer's Dement.* 12, 216–224. <https://doi.org/10.1016/j.jalz.2015.12.007>
- McCann, S.K., Campbell, M.K., & Entwistle, V.A., 2010. Reasons for participating in randomised controlled trials: Conditional altruism and considerations for self. *Trials* 11, 31. <https://doi.org/10.1186/1745-6215-11-31>

- McEwen, S.C., Siddarth, P., Abedelsater, B., Kim, Y., Mui, W., Wu, P., et al., 2018. Simultaneous Aerobic Exercise and Memory Training Program in Older Adults with Subjective Memory Impairments. *J. Alzheimer's Dis.* 62, 795–806. <https://doi.org/10.3233/JAD-170846>
- McKhann, G., Drachman, D., Folstein, M., Katzman, R., Price, D., & Stadlan, E.M., 1984. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. *Neurology* 34, 939–944. <https://doi.org/10.1212/wnl.34.7.939>
- McKhann, G.M., Knopman, D.S., Chertkow, H., Hyman, B.T., Jack, C.R.J., Kawas, C.H., et al., 2011. The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimer's Dement.* 7, 263–269. <https://doi.org/10.1016/j.jalz.2011.03.005>
- McMaster, M., Kim, S., Clare, L., Torres, S.J., D'este, C., & Anstey, K.J., 2018. Body, brain, life for cognitive decline (BBL-CD): Protocol for a multidomain dementia risk reduction randomized controlled trial for subjective cognitive decline and mild cognitive impairment. *Clin. Interv. Aging* 13, 2397–2406. <https://doi.org/10.2147/CIA.S182046>
- McRae-McKee, K., Udeh-Momoh, C.T., Price, G., Bajaj, S., de Jager, C.A., Scott, D., et al., 2019. Perspective: Clinical relevance of the dichotomous classification of Alzheimer's disease biomarkers: Should there be a "gray zone"? *Alzheimer's Dement.* 15, 1348–1356. <https://doi.org/10.1016/j.jalz.2019.07.010>
- Mein, G., Seale, C., Rice, H., Johal, S., Ashcroft, R.E., Ellison, G., et al., 2012. Altruism and participation in longitudinal health research? Insights from the Whitehall II Study. *Soc. Sci. Med.* 75, 2345–2352. <https://doi.org/10.1016/j.socscimed.2012.09.006>
- Meyer, P.F., Pichet Binette, A., Gonneaud, J., Breitner, J.C.S., & Villeneuve, S., 2020. Characterization of Alzheimer Disease Biomarker Discrepancies Using Cerebrospinal Fluid Phosphorylated Tau and AV1451 Positron Emission Tomography. *JAMA Neurol.* 77, 508–516. <https://doi.org/10.1001/jamaneurol.2019.4749>
- Milne, R., Diaz, A., Badger, S., Bunnik, E., Fauria, K., & Wells, K., 2018. At, with and beyond risk: expectations of living with the possibility of future dementia. *Sociol. Heal. Illn.* 40, 969–987. <https://doi.org/10.1111/1467-9566.12731>
- Minoshima, S., Giordani, B., Berent, S., Frey, K.A., Foster, N.L., & Kuhl, D.E., 1997. Metabolic reduction in the posterior cingulate cortex in very early Alzheimer's disease. *Ann. Neurol.* 42, 85–94. <https://doi.org/10.1002/ana.410420114>
- Mitchell, A.J., Beaumont, H., Ferguson, D., Yadegarfar, M., & Stubbs, B., 2014. Risk of dementia and mild cognitive impairment in older people with subjective memory complaints: Meta-analysis. *Acta Psychiatr. Scand.* 130, 439–451. <https://doi.org/10.1111/acps.12336>
- Mitchell, A.J., & Shiri-Feshki, M., 2009. Rate of progression of mild cognitive

- impairment to dementia - Meta-analysis of 41 robust inception cohort studies. *Acta Psychiatr. Scand.* 119, 252–265. <https://doi.org/10.1111/j.1600-0447.2008.01326.x>
- Montero-Odasso, M., Almeida, Q.J., Burhan, A.M., Camicioli, R., Doyon, J., Fraser, S., et al., 2018. SYNERGIC TRIAL (SYNchronizing Exercises, Remedies in Gait and Cognition) a multi-Centre randomized controlled double blind trial to improve gait and cognition in mild cognitive impairment. *BMC Geriatr.* 18, 93. <https://doi.org/10.1186/s12877-018-0782-7>
- Mormino, E.C., Betensky, R.A., Hedden, T., Schultz, A.P., Amariglio, R.E., Rentz, D.M., et al., 2014. Synergistic effect of β -amyloid and neurodegeneration on cognitive decline in clinically normal individuals. *JAMA Neurol.* 71, 1379–1385. <https://doi.org/10.1001/jamaneurol.2014.2031>
- Morris, G.P., Clark, I.A., & Vissel, B., 2018. Questions concerning the role of amyloid- β in the definition, aetiology and diagnosis of Alzheimer's disease. *Acta Neuropathol.* 136, 663–689. <https://doi.org/10.1007/s00401-018-1918-8>
- Morris, J., 1997. Clinical dementia rating: a reliable and valid diagnostic and staging measure for dementia of the Alzheimer type. *Int. psychogeriatrics* 9, 173–178. <https://doi.org/10.1017/s1041610297004870>
- Morris, J.C., Heyman, A., Mohs, R.C., Hughes, J.P., van Belle, G., Fillenbaum, G., et al., 1989. The Consortium to Establish a Registry for Alzheimer's Disease (CERAD). Part I. Clinical and neuropsychological assessment of Alzheimer's disease. *Neurology* 39, 1159–1165. <https://doi.org/10.1212/wnl.39.9.1159>
- Mountain, G., Sprange, K., & Chatters, R., 2020. Lifestyle matters randomized controlled trial of a preventive health intervention for older people: Qualitative sub study with participants and intervention facilitators. *Clin. Interv. Aging* 15, 239–253. <https://doi.org/10.2147/CIA.S232108>
- Mueller, C., Soysal, P., Rongve, A., Isik, A.T., Thompson, T., Maggi, S., et al., 2019. Survival time and differences between dementia with Lewy bodies and Alzheimer's disease following diagnosis: A meta-analysis of longitudinal studies. *Ageing Res. Rev.* 50, 72–80. <https://doi.org/10.1016/j.arr.2019.01.005>
- Mukadam, N., Sommerlad, A., Huntley, J., & Livingston, G., 2019. Population attributable fractions for risk factors for dementia in low-income and middle-income countries: an analysis using cross-sectional survey data. *Lancet Glob. Heal.* 7, e596–e603. [https://doi.org/10.1016/S2214-109X\(19\)30074-9](https://doi.org/10.1016/S2214-109X(19)30074-9)
- Nag, S., Yu, L., Capuano, A.W., Wilson, R.S., Leurgans, S.E., Bennett, D.A., et al., 2015. Hippocampal sclerosis and TDP-43 pathology in aging and Alzheimer disease. *Ann. Neurol.* 77, 942–952. <https://doi.org/10.1002/ana.24388>
- Nakamura, A., Kaneko, N., Villemagne, V.L., Kato, T., Doecke, J., Doré, V., et al., 2018. High performance plasma amyloid- β biomarkers for Alzheimer's disease. *Nature* 554, 249–254. <https://doi.org/10.1038/nature25456>
- National Academies of Sciences, Engineering, and Medicine, 2017. Preventing Cognitive Decline and Dementia: A Way Forward. The National Academies Press, Washington, DC. <https://doi.org/https://doi.org/10.17226/24782>

- National Nutrition Council, 2005. Finnish nutrition recommendations: diet and physical activity in balance. Edita Publishing, Helsinki.
- Nelis, S.M., Thom, J.M., Jones, I.R., Hindle, J. V., & Clare, L., 2018. Goal-setting to Promote a Healthier Lifestyle in Later Life: Qualitative Evaluation of the AgeWell Trial. *Clin. Gerontol.* 41, 335–345. <https://doi.org/10.1080/07317115.2017.1416509>
- Nelson, M.E., Rejeski, W.J., Blair, S.N., Duncan, P.W., Judge, J.O., King, A.C., et al., 2007. Physical activity and public health in older adults: Recommendation from the American College of Sports Medicine and the American Heart Association. *Circulation* 116, 1094–1105. <https://doi.org/10.1161/CIRCULATIONAHA.107.185650>
- Nelson, P.T., Dickson, D.W., Trojanowski, J.Q., Jack, C.R., Boyle, P.A., Arfanakis, K., et al., 2019. Limbic-predominant age-related TDP-43 encephalopathy (LATE): Consensus working group report. *Brain* 142, 1503–1527. <https://doi.org/10.1093/brain/awz099>
- Ngandu, T., Lehtisalo, J., Levälähti, E., Laatikainen, T., Lindström, J., Peltonen, M., et al., 2014. Recruitment and baseline characteristics of participants in the finnish geriatric intervention study to prevent cognitive impairment and disability (FINGER)—A randomized controlled lifestyle trial. *Int. J. Environ. Res. Public Health* 11, 9345–9360. <https://doi.org/10.3390/ijerph110909345>
- Ngandu, T., Lehtisalo, J., Solomon, A., Levälähti, E., Ahtiluoto, S., Antikainen, R., et al., 2015. A 2 year multidomain intervention of diet, exercise, cognitive training, and vascular risk monitoring versus control to prevent cognitive decline in at-risk elderly people (FINGER): A randomised controlled trial. *Lancet* 385, 2255–2263. [https://doi.org/10.1016/S0140-6736\(15\)60461-5](https://doi.org/10.1016/S0140-6736(15)60461-5)
- Nielsen, Z.E., & Berthelsen, C.B., 2019. Cancer patients' perceptions of factors influencing their decisions on participation in clinical drug trials: A qualitative meta-synthesis. *J. Clin. Nurs.* 28, 2443–2461. <https://doi.org/10.1111/jocn.14785>
- Norton, S., Matthews, F.E., Barnes, D.E., Yaffe, K., & Brayne, C., 2014. Potential for primary prevention of Alzheimer's disease: An analysis of population-based data. *Lancet Neurol.* 13, 788–794. [https://doi.org/10.1016/S1474-4422\(14\)70136-X](https://doi.org/10.1016/S1474-4422(14)70136-X)
- Nosraty, L., Jylhä, M., Raittila, T., & Lumme-Sandt, K., 2015. Perceptions by the oldest old of successful aging, Vitality 90+ Study. *J. Aging Stud.* 32, 50–58. <https://doi.org/10.1016/j.jaging.2015.01.002>
- Nosraty, L., Sarkeala, T., Hervonen, A., & Jylhä, M., 2012. Is there successful aging for nonagenarians? the vitality 90+ study. *J. Aging Res.* 2012, 868797. <https://doi.org/10.1155/2012/868797>
- Nøst, T.H., Steinsbekk, A., Bratås, O., & Grønning, K., 2016. Expectations, effect and experiences of an easily accessible self-management intervention for people with chronic pain: Study protocol for a randomised controlled trial with embedded qualitative study. *Trials* 17, 325. <https://doi.org/10.1186/s13063-016-1462-6>
- Nuño, M.M., Gillen, D.L., Dosanjh, K.K., Brook, J., Elashoff, D., Ringman, J.M., et al.,

2017. Attitudes toward clinical trials across the Alzheimer's disease spectrum. *Alzheimer's Res. Ther.* 9, 81. <https://doi.org/10.1186/s13195-017-0311-5>
- O'Brien, J.T., Firbank, M.J., Ritchie, K., Wells, K., Williams, G.B., Ritchie, C.W., et al., 2019. Association between midlife dementia risk factors and longitudinal brain atrophy: The PREVENT-Dementia study. *J. Neurol. Neurosurg. Psychiatry* 91, 158–161. <https://doi.org/10.1136/jnnp-2019-321652>
- O'Cathain, A., Murphy, E., & Nicholl, J., 2010. Three techniques for integrating data in mixed methods studies. *BMJ* 341, c4587. <https://doi.org/10.1136/bmj.c4587>
- O'Cathain, A., Thomas, K.J., Drabble, S.J., Rudolph, A., & Hewison, J., 2013. What can qualitative research do for randomised controlled trials? A systematic mapping review. *BMJ Open* 3, e002889. <https://doi.org/10.1136/bmjopen-2013-002889>
- O'Donnell, C.A., Browne, S., Pierce, M., McConnachie, A., Deckers, K., van Boxtel, M.P.J., et al., 2015. Reducing dementia risk by targeting modifiable risk factors in mid-life: Study protocol for the Innovative Midlife Intervention for Dementia Deterrence (In-MINDD) randomised controlled feasibility trial. *Pilot Feasibility Stud.* 1, 40. <https://doi.org/10.1186/s40814-015-0035-x>
- OECD/European Observatory on Health Systems and Policies, 2017. Finland: Country Health Profile 2017, State of Health in the EU. OECD Publishing, Paris/European Observatory on Health Systems and Policies, Brussels. <https://doi.org/http://dx.doi.org/10.1787/9789264283367-en>
- Olsson, B., Lautner, R., Andreasson, U., Öhrfelt, A., Portelius, E., Bjerke, M., et al., 2016. CSF and blood biomarkers for the diagnosis of Alzheimer's disease: a systematic review and meta-analysis. *Lancet Neurol.* 15, 673–684. [https://doi.org/10.1016/S1474-4422\(16\)00070-3](https://doi.org/10.1016/S1474-4422(16)00070-3)
- Onwuegbuzie, A.J., & Leech, N.L., 2004. Enhancing the Interpretation of "Significant" Findings: The Role of Mixed Methods Research. *Qual. Rep.* 9, 770–792. Retrieved from <https://nsuworks.nova.edu/tqr/vol9/iss4/10>
- Ossenkoppele, R., Jansen, W.J., Rabinovici, G.D., Knol, D.L., van der Flier, W.M., van Berckel, B.N.M., et al., 2015. Prevalence of amyloid PET positivity in dementia syndromes: a meta-analysis. *JAMA - J. Am. Med. Assoc.* 313, 1939–1949. <https://doi.org/10.1001/jama.2015.4669>
- Ostrowitzki, S., Deptula, D., Thurffjell, L., Barkhof, F., Bohrmann, B., Brooks, D.J., et al., 2012. Mechanism of amyloid removal in patients with Alzheimer disease treated with gantenerumab. *Arch. Neurol.* 69, 198–207. <https://doi.org/10.1001/archneurol.2011.1538>
- Ostrowitzki, S., Lasser, R.A., Dorflinger, E., Scheltens, P., Barkhof, F., Nikolcheva, T., et al., 2017. A phase III randomized trial of gantenerumab in prodromal Alzheimer's disease. *Alzheimer's Res. Ther.* 9, 95. <https://doi.org/10.1186/s13195-017-0318-y>
- Ott, B.R., Pelosi, M.A., Tremont, G., & Snyder, P.J., 2016. A survey of knowledge and views concerning genetic and amyloid positron emission tomography status disclosure. *Alzheimer's Dement. Transl. Res. Clin. Interv.* 2, 23–29.

<https://doi.org/10.1016/j.trci.2015.12.001>

- Oveisgharan, S., Wilson, R.S., Yu, L., Schneider, J.A., & Bennett, D.A., 2020. Association of Early-Life Cognitive Enrichment With Alzheimer Disease Pathological Changes and Cognitive Decline. *JAMA Neurol.* Epub Jun 2, e201941. <https://doi.org/10.1001/jamaneurol.2020.1941>
- Palmqvist, S., Janelidze, S., Quiroz, Y.T., Zetterberg, H., Lopera, F., Stomrud, E., et al., 2020. Discriminative Accuracy of Plasma Phospho-tau217 for Alzheimer Disease vs Other Neurodegenerative Disorders. *JAMA - J. Am. Med. Assoc.* Epub Jul 2. <https://doi.org/10.1001/jama.2020.12134>
- Park, H.K., Jeong, J.H., Moon, S.Y., Park, Y.K., Hong, C.H., Na, H.R., et al., 2020. South Korean study to prevent cognitive impairment and protect brain health through lifestyle intervention in at-risk elderly people: Protocol of a multicenter, randomized controlled feasibility trial. *J. Clin. Neurol.* 16, 292–303. <https://doi.org/10.3988/jcn.2020.16.2.292>
- Park, J.E., Jeon, S.Y., Kim, S.A., Kim, J.H., Kim, S.H., Lee, K.W., et al., 2019. A Multidomain Intervention for Modifying Lifestyle Habits Reduces the Dementia Risk in Community-Dwelling Older Adults: A Single-Blinded Randomized Controlled Pilot Study. *J. Alzheimer's Dis.* 70, 51–60. <https://doi.org/10.3233/JAD-190016>
- Parnetti, L., Chipi, E., Salvadori, N., D'Andrea, K., & Eusebi, P., 2019. Prevalence and risk of progression of preclinical Alzheimer's disease stages: A systematic review and meta-analysis. *Alzheimer's Res. Ther.* 11, 7. <https://doi.org/10.1186/s13195-018-0459-7>
- Peloso, G.M., Beiser, A.S., Satizabal, C.L., Xanthakis, V., Vasani, R.S., Pase, M.P., et al., 2020. Cardiovascular health, genetic risk, and risk of dementia in the Framingham Heart Study. *Neurology* Epub Jul 2. <https://doi.org/10.1212/WNL.00000000000010306>
- Peters, R., Booth, A., Rockwood, K., Peters, J., D'Este, C., & Anstey, K.J., 2019. Combining modifiable risk factors and risk of dementia: A systematic review and meta-analysis. *BMJ Open* 9, e022846. <https://doi.org/10.1136/bmjopen-2018-022846>
- Peters, R., Peters, J., Booth, A., & Anstey, K.J., 2020. Trajectory of blood pressure, body mass index, cholesterol and incident dementia: systematic review. *Br. J. Psychiatry* 216, 16–28. <https://doi.org/10.1192/bjp.2019.156>
- Petersen, R.C., 2004. Mild cognitive impairment as a diagnostic entity. *J. Intern. Med.* 256, 183–194. <https://doi.org/10.1111/j.1365-2796.2004.01388.x>
- Petersen, R.C., Aisen, P., Boeve, B.F., Geda, Y.E., Ivnik, R.J., Knopman, D.S., et al., 2013. Mild cognitive impairment due to Alzheimer disease in the community. *Ann. Neurol.* 74, 199–208. <https://doi.org/10.1002/ana.23931>
- Petersen, R.C., Lopez, O., Armstrong, M.J., Getchius, T.S.D., Ganguli, M., Gloss, D., et al., 2018. Practice guideline update summary: Mild cognitive impairment report of the guideline development, dissemination, and implementation. *Neurology* 90, 126–135. <https://doi.org/10.1212/WNL.00000000000004826>

- Petersen, R.C., Smith, G.E., Waring, S.C., Ivnik, R.J., Tangalos, E.G., & Kokmen, E., 1999. Mild cognitive impairment: Clinical characterization and outcome. *Arch. Neurol.* 56, 303–308. <https://doi.org/10.1001/archneur.56.3.303>
- Poli, A., Kelfve, S., & Motel-Klingebiel, A., 2019. A research tool for measuring non-participation of older people in research on digital health. *BMC Public Health* 19, 1487. <https://doi.org/10.1186/s12889-019-7830-x>
- Portelius, E., Olsson, B., Höglund, K., Cullen, N.C., Kvartsberg, H., Andreasson, U., et al., 2018. Cerebrospinal fluid neurogranin concentration in neurodegeneration: relation to clinical phenotypes and neuropathology. *Acta Neuropathol.* 136, 363–376. <https://doi.org/10.1007/s00401-018-1851-x>
- Power, M.C., Mormino, E., Soldan, A., James, B.D., Yu, L., Armstrong, N.M., et al., 2018. Combined neuropathological pathways account for age-related risk of dementia. *Ann. Neurol.* 84, 10–22. <https://doi.org/10.1002/ana.25246>
- Preische, O., Schultz, S.A., Apel, A., Kuhle, J., Kaeser, S.A., Barro, C., et al., 2019. Serum neurofilament dynamics predicts neurodegeneration and clinical progression in presymptomatic Alzheimer’s disease. *Nat. Med.* 25, 277–283. <https://doi.org/10.1038/s41591-018-0304-3>
- Prestia, A., Caroli, A., van der Flier, W.M., Ossenkoppele, R., Van Berckel, B., Barkhof, F., et al., 2013. Prediction of dementia in MCI patients based on core diagnostic markers for Alzheimer disease. *Neurology* 80, 1048–1056. <https://doi.org/10.1212/WNL.0b013e3182872830>
- Prestia, A., Caroli, A., Wade, S.K., van der Flier, W.M., Ossenkoppele, R., Van Berckel, B., et al., 2015. Prediction of AD dementia by biomarkers following the NIA-AA and IWG diagnostic criteria in MCI patients from three European memory clinics. *Alzheimer’s Dement.* 11, 1191–1201. <https://doi.org/10.1016/j.jalz.2014.12.001>
- Prodemos Project AMC, 2018. Project outline [WWW Document]. Retrieved from <https://www.prodemos-project.eu/project/> (accessed 06/26/2020).
- Prom-Wormley, E.C., Clifford, J.S., Bourdon, J.L., Barr, P., Blondino, C., Ball, K.M., et al., 2019. Developing community-based health education strategies with family history: Assessing the association between community resident family history and interest in health education. *Soc. Sci. Med.* 112160. <https://doi.org/10.1016/j.socscimed.2019.02.011>
- Quiroz, Y.T., Zetterberg, H., Reiman, E.M., Chen, Y., Su, Y., Fox-Fuller, J.T., et al., 2020. Plasma neurofilament light chain in the presenilin 1 E280A autosomal dominant Alzheimer’s disease kindred: a cross-sectional and longitudinal cohort study. *Lancet Neurol.* 19, 513–521. [https://doi.org/10.1016/S1474-4422\(20\)30137-X](https://doi.org/10.1016/S1474-4422(20)30137-X)
- Rabin, J.S., Schultz, A.P., Hedden, T., Viswanathan, A., Marshall, G.A., Kilpatrick, E., et al., 2018. Interactive Associations of Vascular Risk and β -Amyloid Burden With Cognitive Decline in Clinically Normal Elderly Individuals: Findings From the Harvard Aging Brain Study. *JAMA Neurol.* 75, 1124–1131. <https://doi.org/10.1001/jamaneurol.2018.1123>

- Rabinovici, G.D., Gatsonis, C., Apgar, C., Chaudhary, K., Gareen, I., Hanna, L., et al., 2019. Association of Amyloid Positron Emission Tomography with Subsequent Change in Clinical Management among Medicare Beneficiaries with Mild Cognitive Impairment or Dementia. *JAMA - J. Am. Med. Assoc.* 321, 1286–1294. <https://doi.org/10.1001/jama.2019.2000>
- Rahman, A., Jackson, H., Hristov, H., Isaacson, R.S., Saif, N., Shetty, T., et al., 2019. Sex and Gender Driven Modifiers of Alzheimer's: The Role for Estrogenic Control Across Age, Race, Medical, and Lifestyle Risks. *Front. Aging Neurosci.* 11, 315. <https://doi.org/10.3389/fnagi.2019.00315>
- Raivio, R., Jääskeläinen, J., Holmberg-Marttila, D., & Mattila, K.J., 2014. Decreasing trends in patient satisfaction, accessibility and continuity of care in Finnish primary health care - a 14-year follow-up questionnaire study. *BMC Fam. Pract.* 15, 98. <https://doi.org/10.1186/1471-2296-15-98>
- Rantanen, K., Strandberg, A.Y., Salomaa, V., Pitkälä, K., Tilvis, R.S., Tienari, P., et al., 2017. Cardiovascular risk factors and glucose tolerance in midlife and risk of cognitive disorders in old age up to a 49-year follow-up of the Helsinki businessmen study. *Ann. Med.* 49, 462–469. <https://doi.org/10.1080/07853890.2017.1290821>
- Rebok, G.W., Ball, K., Guey, L.T., Jones, R.N., Kim, H.-Y., King, J.W., et al., 2014. Ten-year effects of the advanced cognitive training for independent and vital elderly cognitive training trial on cognition and everyday functioning in older adults. *J. Am. Geriatr. Soc.* 62, 16–24. <https://doi.org/10.1111/jgs.12607>
- Reed, R.L., Barton, C.A., Isherwood, L.M., Baxter, J.M.O., & Roeger, L., 2013. Recruitment for a clinical trial of chronic disease self-management for older adults with multimorbidity: A successful approach within general practice. *BMC Fam. Pract.* 14, 125. <https://doi.org/10.1186/1471-2296-14-125>
- Reiman, E.M., Arboleda-Velasquez, J.F., Quiroz, Y.T., Huentelman, M.J., Beach, T.G., Caselli, R.J., et al., 2020. Exceptionally low likelihood of Alzheimer's dementia in APOE2 homozygotes from a 5,000-person neuropathological study. *Nat. Commun.* 11, 667. <https://doi.org/10.1038/s41467-019-14279-8>
- Rhodijs-Meester, H.F.M., Tijms, B.M., Lemstra, A.W., Prins, N.D., Pijnenburg, Y.A.L., Bouwman, F., et al., 2019. Survival in memory clinic cohort is short, even in young-onset dementia. *J. Neurol. Neurosurg. Psychiatry* 90, 726–728. <https://doi.org/10.1136/jnnp-2018-318820>
- Richard, E., Andrieu, S., Solomon, A., Mangialasche, F., Ahtiluoto, S., Van Charante, E.P.M., et al., 2012. Methodological challenges in designing dementia prevention trials - The European Dementia Prevention Initiative (EDPI). *J. Neurol. Sci.* 322, 64–70. <https://doi.org/10.1016/j.jns.2012.06.012>
- Richard, E., den Heuvel, E. Van, Moll van Charante, E.P., Achthoven, L., Vermeulen, M., Bindels, P.J., et al., 2009. Prevention of Dementia by Intensive Vascular Care (PreDIVA). *Alzheimer Dis. Assoc. Disord.* 23, 198–204. <https://doi.org/10.1097/wad.0b013e31819783a4>
- Richard, E., Jongstra, S., Soininen, H., Brayne, C., Moll Van Charante, E.P., Meiller,

- Y., et al., 2016. Healthy Ageing Through Internet Counselling in the Elderly: The HATICE randomised controlled trial for the prevention of cardiovascular disease and cognitive impairment. *BMJ Open* 6, e010806. <https://doi.org/10.1136/bmjopen-2015-010806>
- Richard, E., Moll van Charante, E.P., Hoevenaar-Blom, M.P., Coley, N., Barbera, M., van der Groep, A., et al., 2019. Healthy ageing through internet counselling in the elderly (HATICE): a multinational, randomised controlled trial. *Lancet Digit. Heal.* 1, e424–e434. [https://doi.org/10.1016/S2589-7500\(19\)30153-0](https://doi.org/10.1016/S2589-7500(19)30153-0)
- Richards, D.A., Bazeley, P., Borglin, G., Craig, P., Emsley, R., Frost, J., et al., 2019. Integrating quantitative and qualitative data and findings when undertaking randomised controlled trials. *BMJ Open* 9, e032081. <https://doi.org/10.1136/bmjopen-2019-032081>
- Ritchie, C.W., Molinuevo, J.L., Truyen, L., Satlin, A., Van der Geypen, S., & Lovestone, S., 2016. Development of interventions for the secondary prevention of Alzheimer's dementia: the European Prevention of Alzheimer's Dementia (EPAD) project. *The Lancet Psychiatry* 3, 179–186. [https://doi.org/10.1016/S2215-0366\(15\)00454-X](https://doi.org/10.1016/S2215-0366(15)00454-X)
- Roberts, J.S., McLaughlin, S.J., & Connell, C.M., 2014. Public beliefs and knowledge about risk and protective factors for Alzheimer's disease. *Alzheimer's Dement.* 10, S381-9. <https://doi.org/10.1016/j.jalz.2013.07.001>
- Robillard, J.M., & Feng, T.L., 2016. Health advice in a digital world: Quality and content of online information about the prevention of Alzheimer's disease. *J. Alzheimer's Dis.* 55, 219–229. <https://doi.org/10.3233/JAD-160650>
- Robinson, L., Dickinson, C., Magklara, E., Newton, L., & Prato, L., 2018. Proactive approaches to identifying dementia and dementia risk ; a qualitative study of public attitudes and preferences. *BMJ Open* 8, e018677. <https://doi.org/10.1136/bmjopen-2017-018677>
- Roche, 2020. Roche provides topline results from investigator-led Phase II/III trial with gantenerumab in rare inherited form of Alzheimer's disease [WWW Document]. Retrieved from <https://www.roche.com/dam/jcr:51c98f25-7482-4ad7-89e0-1436e2b51302/en/roche-media-release-10022020-en.pdf> (accessed 06/15/2020).
- Rodriguez, F.S., Schroeter, M.L., Arélin, K., Veronica Witte, A., Baber, R., Burkhardt, R., et al., 2018. APOE e4-genotype and lifestyle interaction on cognitive performance: Results of the LIFE-adult-study. *Heal. Psychol.* 37, 194–205. <https://doi.org/10.1037/hea0000515>
- Rodriguez, R.D., Suemoto, C.K., Molina, M., Nascimento, C.F., Leite, R.E.P., De Lucena Ferretti-Rebustini, R.E., et al., 2016. Argyrophilic Grain Disease: Demographics, clinical, and neuropathological features from a large autopsy study. *J. Neuropathol. Exp. Neurol.* 75, 628–635. <https://doi.org/10.1093/jnen/nlw034>
- Rolandi, E., Dodich, A., Galluzzi, S., Ferrari, C., Mandelli, S., Ribaldi, F., et al., 2020. Randomized controlled trial on the efficacy of a multilevel non-pharmacologic

- intervention in older adults with subjective memory decline: design and baseline findings of the E.Mu.N.I. study. *Aging Clin. Exp. Res.* 32, 817–826. <https://doi.org/10.1007/s40520-019-01403-3>
- Romera-Liebana, L., Orfila, F., Segura, J.M., Real, J., Fabra, M.L., Möller, M., et al., 2018. Effects of a primary care-based multifactorial intervention on physical and cognitive function in frail, elderly individuals: A randomized controlled trial. *Journals Gerontol. - Ser. A Biol. Sci. Med. Sci.* 73, 1668–1674. <https://doi.org/10.1093/gerona/glx259>
- Rose, G., 1981. Strategy of prevention: lessons from cardiovascular disease. *Br. Med. J. (Clin. Res. Ed)*. 282, 1847–1851. <https://doi.org/10.1136/bmj.282.6279.1847>
- Rosén, C., Farahmand, B., Skillbäck, T., Nägga, K., Mattsson, N., Kilander, L., et al., 2015. Benchmarking biomarker-based criteria for Alzheimer’s disease: Data from the Swedish Dementia Registry, SveDem. *Alzheimer’s Dement.* 11, 1470–1479. <https://doi.org/10.1016/j.jalz.2015.04.007>
- Rosenberg, S.J., Ryan, J.J., & Prifitera, A., 1984. Rey Auditory-Verbal Learning Test performance of patients with and without memory impairment. *J. Clin. Psychol.* 40, 785–787. [https://doi.org/10.1002/1097-4679\(198405\)40:3<785::aid-jclp2270400325>3.0.co;2-4](https://doi.org/10.1002/1097-4679(198405)40:3<785::aid-jclp2270400325>3.0.co;2-4)
- Rothwell, P.M., 2005. Treating individuals 2. Subgroup analysis in randomised controlled trials: importance, indications, and interpretation. *Lancet* 365, 176–186. [https://doi.org/10.1016/S0140-6736\(05\)17709-5](https://doi.org/10.1016/S0140-6736(05)17709-5)
- Rovner, B.W., Casten, R.J., Hegel, M.T., & Leiby, B., 2018. Preventing Cognitive Decline in Black Individuals With Mild Cognitive Impairment: A Randomized Clinical Trial. *JAMA Neurol.* 75, 1487–1493. <https://doi.org/10.1001/jamaneurol.2018.2513>
- Sabia, S., Fayosse, A., Dumurgier, J., Schnitzler, A., Empana, J.-P., Ebmeier, K.P., et al., 2019. Association of ideal cardiovascular health at age 50 with incidence of dementia: 25 year follow-up of Whitehall II cohort study. *BMJ* 366, 14414. <https://doi.org/10.1136/bmj.l4414>
- Sachdev, P.S., Blacker, D., Blazer, D.G., Ganguli, M., Jeste, D. V., Paulsen, J.S., et al., 2014. Classifying neurocognitive disorders: The DSM-5 approach. *Nat. Rev. Neurol.* 10, 634–642. <https://doi.org/10.1038/nrneurol.2014.181>
- Sahlen, K.G., Johansson, H., Nyström, L., & Lindholm, L., 2013. Health coaching to promote healthier lifestyle among older people at moderate risk for cardiovascular diseases, diabetes and depression: A study protocol for a randomized controlled trial in Sweden. *BMC Public Health* 13, 199. <https://doi.org/10.1186/1471-2458-13-199>
- Salloway, S., Honigberg, L.A., Cho, W., Ward, M., Friesenhahn, M., Brunstein, F., et al., 2018. Amyloid positron emission tomography and cerebrospinal fluid results from a crenezumab anti-amyloid-beta antibody double-blind, placebo-controlled, randomized phase II study in mild-to-moderate Alzheimer’s disease (BLAZE). *Alzheimer’s Res. Ther.* 10, 96. <https://doi.org/10.1186/s13195-018-0424-5>

- Salloway, S., Sperling, R., Fox, N.C., Blennow, K., Klunk, W., Raskind, M., et al., 2014. Two phase 3 trials of bapineuzumab in mild-to-moderate Alzheimer's disease. *N. Engl. J. Med.* 370, 322–333. <https://doi.org/10.1056/NEJMoa1304839>
- Samieri, C., Perier, M.C., Gaye, B., Proust-Lima, C., Helmer, C., Dartigues, J.F., et al., 2018. Association of cardiovascular health level in older age with cognitive decline and incident dementia. *JAMA - J. Am. Med. Assoc.* 320, 657–664. <https://doi.org/10.1001/jama.2018.11499>
- Scarmeas, N., Anastasiou, C.A., & Yannakoulia, M., 2018. Nutrition and prevention of cognitive impairment. *Lancet Neurol.* 17, 1006–1015. [https://doi.org/10.1016/S1474-4422\(18\)30338-7](https://doi.org/10.1016/S1474-4422(18)30338-7)
- Scheltens, P., Kamphuis, P.J.G.H., Verhey, F.R.J., Olde Rikkert, M.G.M., Wurtman, R.J., Wilkinson, D., et al., 2010. Efficacy of a medical food in mild Alzheimer's disease: A randomized, controlled trial. *Alzheimer's Dement.* 6, 1-10.e1. <https://doi.org/10.1016/j.jalz.2009.10.003>
- Scheltens, P., Leys, D., Barkhof, F., Huglo, D., Weinstein, H.C., Vermersch, P., et al., 1992. Atrophy of medial temporal lobes on MRI in "probable" Alzheimer's disease and normal ageing: diagnostic value and neuropsychological correlates. *J. Neurol. Neurosurg. Psychiatry* 55, 967–972. <https://doi.org/10.1136/jnnp.55.10.967>
- Scheltens, P., Twisk, J.W.R., Blesa, R., Scarpini, E., Von Arnim, C.A.F., Bongers, A., et al., 2012. Efficacy of souvenaid in mild alzheimer's disease: Results from a randomized, controlled trial. *J. Alzheimer's Dis.* 31, 225–236. <https://doi.org/10.3233/JAD-2012-121189>
- Schiepers, O.J.G., Köhler, S., Deckers, K., Irving, K., O'Donnell, C.A., van den Akker, M., et al., 2018. Lifestyle for Brain Health (LIBRA): a new model for dementia prevention. *Int. J. Geriatr. Psychiatry* 33, 167–175. <https://doi.org/10.1002/gps.4700>
- Schindler, S.E., Sutphen, C.L., Teunissen, C., McCue, L.M., Morris, J.C., Holtzman, D.M., et al., 2018. Upward drift in cerebrospinal fluid amyloid β 42 assay values for more than 10 years. *Alzheimer's Dement.* 14, 62–70. <https://doi.org/10.1016/j.jalz.2017.06.2264>
- Schneider, J.A., Arvanitakis, Z., Leurgans, S.E., & Bennett, D.A., 2009. The neuropathology of probable Alzheimer disease and mild cognitive impairment. *Ann. Neurol.* 66, 200–208. <https://doi.org/10.1002/ana.21706>
- Schneider, L.S., & Goldberg, T.E., 2020. Composite cognitive and functional measures for early stage Alzheimer's disease trials. *Alzheimer's Dement. Diagnosis, Assess. Dis. Monit.* 12, e12017. <https://doi.org/10.1002/dad2.12017>
- Schneider, L.S., Kennedy, R.E., & Cutter, G.R., 2010. Requiring an amyloid-beta1-42 biomarker for prodromal Alzheimer's disease or mild cognitive impairment does not lead to more efficient clinical trials. *Alzheimer's Dement.* 6, 367–377. <https://doi.org/10.1016/j.jalz.2010.07.004>
- Schneider, L.S., Mangialasche, F., Andreasen, N., Feldman, H., Giacobini, E., Jones, R., et al., 2014. Clinical trials and late-stage drug development for Alzheimer's

- disease: An appraisal from 1984 to 2014. *J. Intern. Med.* 275, 251–283. <https://doi.org/10.1111/joim.12191>
- Schwartz, H.E.M., Bay, C.P., McFeeley, B.M., Krivanek, T.J., Daffner, K.R., & Gale, S.A., 2019. The Brain Health Champion study: Health coaching changes behaviors in patients with cognitive impairment. *Alzheimer's Dement. Transl. Res. Clin. Interv.* 5, 771–779. <https://doi.org/10.1016/j.trci.2019.09.008>
- Selkoe, D.J., & Hardy, J., 2016. The amyloid hypothesis of Alzheimer's disease at 25 years. *EMBO Mol. Med.* 8, 595–608. <https://doi.org/10.15252/emmm.201606210>
- Serrano-Pozo, A., Qian, J., Monsell, S.E., Blacker, D., Gómez-Isla, T., Betensky, R.A., et al., 2014. Mild to moderate Alzheimer dementia with insufficient neuropathological changes. *Ann. Neurol.* 75, 597–601. <https://doi.org/10.1002/ana.24125>
- Sevigny, J., Chiao, P., Bussière, T., Weinreb, P.H., Williams, L., Maier, M., et al., 2016. The antibody aducanumab reduces A β plaques in Alzheimer's disease. *Nature* 537, 50–56. <https://doi.org/10.1038/nature19323>
- Shah, R.C., Kamphuis, P.J., Leurgans, S., Swinkels, S.H., Sadowsky, C.H., Bongers, A., et al., 2013. The S-Connect study: Results from a randomized, controlled trial of Souvenaid in mild-to-moderate Alzheimer's disease. *Alzheimer's Res. Ther.* 5, 59. <https://doi.org/10.1186/alzrt224>
- Siemers, E.R., Sundell, K.L., Carlson, C., Case, M., Sethuraman, G., Liu-Seifert, H., et al., 2016. Phase 3 solanezumab trials: Secondary outcomes in mild Alzheimer's disease patients. *Alzheimer's Dement.* 12, 110–120. <https://doi.org/10.1016/j.jalz.2015.06.1893>
- Sieverink, F., Kelders, S.M., & Gemert-Pijnen, V., 2017. Clarifying the concept of adherence to ehealth technology: Systematic review on when usage becomes adherence. *J. Med. Internet Res.* 19, e402. <https://doi.org/10.2196/jmir.8578>
- Sims, R., Hill, M., & Williams, J., 2020. The multiplex model of the genetics of Alzheimer's disease. *Nat. Neurosci.* 23, 311–322. <https://doi.org/10.1038/s41593-020-0599-5>
- Sindi, S., Calov, E., Fokkens, J., Ngandu, T., Soininen, H., Tuomilehto, J., et al., 2015. The CAIDE Dementia Risk Score App: The development of an evidence-based mobile application to predict the risk of dementia. *Alzheimer's Dement. Diagnosis, Assess. Dis. Monit.* 1, 328–333. <https://doi.org/10.1016/j.dadm.2015.06.005>
- Sink, K.M., Espeland, M.A., Castro, C.M., Church, T., Cohen, R., Dodson, J.A., et al., 2015. Effect of a 24-Month Physical Activity Intervention vs Health Education on Cognitive Outcomes in Sedentary Older Adults: The LIFE Randomized Trial. *JAMA - J. Am. Med. Assoc.* 314, 781–790. <https://doi.org/10.1001/jama.2015.9617>
- Skea, Z.C., Newlands, R., & Gillies, K., 2019. Exploring non-retention in clinical trials: A meta-ethnographic synthesis of studies reporting participant reasons for drop out. *BMJ Open* 9, e021959. <https://doi.org/10.1136/bmjopen-2018-021959>
- Slot, R.E.R., Sikkes, S.A.M., Berkhof, J., Brodaty, H., Buckley, R., Cavedo, E., et al.,

2019. Subjective cognitive decline and rates of incident Alzheimer's disease and non-Alzheimer's disease dementia. *Alzheimer's Dement.* 15, 465–476. <https://doi.org/10.1016/j.jalz.2018.10.003>
- Smith, B.J., Ali, S., & Quach, H., 2015. The motivation and actions of Australians concerning brain health and dementia risk reduction. *Heal. Promot. J. Aust.* 26, 115–121. <https://doi.org/10.1071/HE14111>
- Smith, P.J., Blumenthal, J.A., Babyak, M.A., Craighead, L., Welsh-Bohmer, K.A., Browndyke, J.N., et al., 2010. Effects of the dietary approaches to stop hypertension diet, exercise, and caloric restriction on neurocognition in overweight adults with high blood pressure. *Hypertension* 55, 1331–1338. <https://doi.org/10.1161/HYPERTENSIONAHA.109.146795>
- Soininen, H., Solomon, A., Visser, P.J., Hendrix, S.B., Blennow, K., Kivipelto, M., et al., 2017. 24-month intervention with a specific multinutrient in people with prodromal Alzheimer's disease (LipiDiDiet): a randomised, double-blind, controlled trial. *Lancet Neurol.* 16, 965–975. [https://doi.org/10.1016/S1474-4422\(17\)30332-0](https://doi.org/10.1016/S1474-4422(17)30332-0)
- Soininen, H., Solomon, A., Visser, P.J., Hendrix, S.B., Blennow, K., Kivipelto, M., et al., 2020. 36-month LipiDiDiet multinutrient clinical trial in prodromal Alzheimer's disease. In-press.
- Soldan, A., Pettigrew, C., Cai, Q., Wang, M.-C., Moghekar, A.R., O'Brien, R.J., et al., 2016. Hypothetical Preclinical Alzheimer Disease Groups and Longitudinal Cognitive Change. *JAMA Neurol.* 73, 698–705. <https://doi.org/10.1001/jamaneurol.2016.0194>
- Soldan, A., Pettigrew, C., Fagan, A.M., Schindler, S.E., Moghekar, A., Fowler, C., et al., 2019. ATN profiles among cognitively normal individuals and longitudinal cognitive outcomes. *Neurology* 92, e1567–e1579. <https://doi.org/10.1212/WNL.0000000000007248>
- Solomon, A., Akenine, U., Andreasen, N., Mangialasche, F., Wimo, A., Jelic, V., et al., 2012. Practical lessons from amyloid immunotherapy trials in Alzheimer disease. *Curr. Alzheimer Res.* 9, 1126–1134. <https://doi.org/10.2174/156720512804142958>
- Solomon, A., Mangialasche, F., Richard, E., Andrieu, S., Bennett, D.A., Breteler, M., et al., 2014. Advances in the prevention of Alzheimer's disease and dementia. *J. Intern. Med.* 275, 229–250. <https://doi.org/10.1111/joim.12178>
- Solomon, A., Turunen, H., Ngandu, T., Peltonen, M., Levälähti, E., Helisalmi, S., et al., 2018. Effect of the Apolipoprotein E Genotype on Cognitive Change During a Multidomain Lifestyle Intervention: A Subgroup Analysis of a Randomized Clinical Trial. *JAMA Neurol.* 75, 462–470. <https://doi.org/10.1001/jamaneurol.2017.4365>
- Sperling, R.A., Aisen, P.S., Beckett, L.A., Bennett, D.A., Craft, S., Fagan, A.M., et al., 2011. Toward defining the preclinical stages of Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease.

- Alzheimer's Dement.* 7, 280–292. <https://doi.org/10.1016/j.jalz.2011.03.003>
- Sperling, R.A., Mormino, E.C., Schultz, A.P., Betensky, R.A., Papp, K. V, Amariglio, R.E., et al., 2019. The impact of amyloid-beta and tau on prospective cognitive decline in older individuals. *Ann. Neurol.* 85, 181–193. <https://doi.org/10.1002/ana.25395>
- Sperling, R.A., Rentz, D.M., Johnson, K.A., Karlawish, J., Donohue, M., Salmon, D.P., et al., 2014. The A4 study: stopping AD before symptoms begin? *Sci. Transl. Med.* 6, 228fs13. <https://doi.org/10.1126/scitranslmed.3007941>
- Stern, Y., 2009. Cognitive reserve. *Neuropsychologia* 47, 2015–2028. <https://doi.org/10.1016/j.neuropsychologia.2009.03.004>
- Stern, Y., 2012. Cognitive reserve in ageing and Alzheimer's disease. *Lancet Neurol.* 11, 1006–1012. [https://doi.org/10.1016/S1474-4422\(12\)70191-6](https://doi.org/10.1016/S1474-4422(12)70191-6)
- Stites, S.D., Karlawish, J., Harkins, K., Rubright, J.D., & Wolk, D., 2017. Awareness of Mild Cognitive Impairment and Mild Alzheimer's Disease Dementia Diagnoses Associated with Lower Self-Ratings of Quality of Life in Older Adults. *Journals Gerontol. - Ser. B Psychol. Sci. Soc. Sci.* 72, 974–985. <https://doi.org/10.1093/geronb/gbx100>
- Stites, S.D., Rubright, J.D., & Karlawish, J., 2018. What features of stigma do the public most commonly attribute to Alzheimer's disease dementia? Results of a survey of the U.S. general public. *Alzheimer's Dement.* 14, 925–932. <https://doi.org/10.1016/j.jalz.2018.01.006>
- Stokin, G.B., Krell-Roesch, J., Petersen, R.C., & Geda, Y.E., 2015. Mild Neurocognitive disorder: An old wine in a new bottle. *Harv. Rev. Psychiatry* 23, 368–376. <https://doi.org/10.1097/HRP.0000000000000084>
- Strandberg, T.E., Levälähti, E., Ngandu, T., Solomon, A., Kivipelto, M., Kivipelto, M., et al., 2017. Health-related quality of life in a multidomain intervention trial to prevent cognitive decline (FINGER). *Eur. Geriatr. Med.* 8, 164–167. <https://doi.org/10.1016/j.eurger.2016.12.005>
- Strandberg, T.E., Pitkala, K.H., Berglind, S., Nieminen, M.S., & Tilvis, R.S., 2006. Multifactorial intervention to prevent recurrent cardiovascular events in patients 75 years or older: The Drugs and Evidence-Based Medicine in the Elderly (DEBATE) study: A randomized, controlled trial. *Am. Heart J.* 152, 585–592. <https://doi.org/10.1016/j.ahj.2006.02.006>
- Suemoto, C.K., Leite, R.E.P., Ferretti-Rebustini, R.E.L., Rodriguez, R.D., Nitrini, R., Pasqualucci, C.A., et al., 2019. Neuropathological lesions in the very old: results from a large Brazilian autopsy study. *Brain Pathol.* 29, 771–781. <https://doi.org/10.1111/bpa.12719>
- Sussman, J.B., Kent, D.M., Nelson, J.P., & Hayward, R.A., 2015. Improving diabetes prevention with benefit based tailored treatment: Risk based reanalysis of diabetes prevention program. *BMJ* 350, 1–10. <https://doi.org/10.1136/bmj.h454>
- Szabo-Reed, A.N., Vidoni, E., Binder, E.F., Burns, J., Cullum, C.M., Gahan, W.P., et al., 2019. Rationale and methods for a multicenter clinical trial assessing exercise and intensive vascular risk reduction in preventing dementia (rrAD

- Study). *Contemp. Clin. Trials* 79, 44–54. <https://doi.org/10.1016/j.cct.2019.02.007>
- Tang, W., Kannaley, K., Friedman, D.B., Edwards, V.J., Wilcox, S., Levkoff, S.E., et al., 2017. Concern about developing Alzheimer’s disease or dementia and intention to be screened: An analysis of national survey data. *Arch. Gerontol. Geriatr.* 71, 43–49. <https://doi.org/10.1016/j.archger.2017.02.013>
- Tanskanen, M., Mäkelä, M., Notkola, I.-L., Myllykangas, L., Rastas, S., Oinas, M., et al., 2017. Population-based analysis of pathological correlates of dementia in the oldest old. *Ann. Clin. Transl. Neurol.* 4, 154–165. <https://doi.org/10.1002/acn3.389>
- Tariot, P.N., Lopera, F., Langbaum, J.B., Thomas, R.G., Hendrix, S., Schneider, L.S., et al., 2018. The Alzheimer’s Prevention Initiative Autosomal-Dominant Alzheimer’s Disease Trial: Study of crenezumab versus placebo in preclinical PSEN1 E280A mutation carriers to evaluate efficacy and safety in the treatment of autosomal-dominant Alzheimer’s disease. *Alzheimer’s Dement. Transl. Res. Clin. Interv.* 4, 150–160. <https://doi.org/10.1016/j.trci.2018.02.002>
- Tay, L., Lim, W.S., Chan, M., Ali, N., Mahanum, S., Chew, P., et al., 2015. New DSM-V neurocognitive disorders criteria and their impact on diagnostic classifications of mild cognitive impairment and dementia in a memory clinic setting. *Am. J. Geriatr. Psychiatry* 23, 768–779. <https://doi.org/10.1016/j.jagp.2015.01.004>
- Ten Brinke, L.F., Best, J.R., Chan, J.L.C., Ghag, C., Erickson, K.I., Handy, T.C., et al., 2020. The effects of computerized cognitive training with and without physical exercise on cognitive function in older adults: An 8-week randomized controlled trial. *Journals Gerontol. - Ser. A Biol. Sci. Med. Sci.* 75, 755–763. <https://doi.org/10.1093/gerona/glz115>
- Tijms, B.M., Bertens, D., Slot, R.E., Gouw, A.A., Teunissen, C.E., Scheltens, P., et al., 2017. Low normal cerebrospinal fluid A β 42 levels predict clinical progression in nondemented subjects. *Ann. Neurol.* 81, 749–753. <https://doi.org/10.1002/ana.24921>
- Toledo, J.B., Arnold, S.E., Raible, K., Brettschneider, J., Xie, S.X., Grossman, M., et al., 2013. Contribution of cerebrovascular disease in autopsy confirmed neurodegenerative disease cases in the National Alzheimer’s Coordinating Centre. *Brain* 136, 2697–2706. <https://doi.org/10.1093/brain/awt188>
- Tolmie, E.P., Mungall, M.M.B., Loudon, G., Lindsay, G.M., & Gaw, A., 2004. Understanding why older people participate in clinical trials: The experience of the Scottish PROSPER participants. *Age Ageing* 33, 374–378. <https://doi.org/10.1093/ageing/afh109>
- Tomata, Y., Li, X., Karlsson, I.K., Mosing, M.A., Pedersen, N.L., & Hägg, S., 2020. Joint impact of common risk factors on incident dementia: A cohort study of the Swedish Twin Registry. *J. Intern. Med.* 288, 234–237. <https://doi.org/10.1111/joim.13071>
- Townsend, A., & Cox, S.M., 2013. Accessing health services through the back door: A qualitative interview study investigating reasons why people participate in

- health research in Canada. *BMC Med. Ethics* 14, 40. <https://doi.org/10.1186/1472-6939-14-40>
- Tuomilehto, J., Lindström, J., Eriksson, J.G., Valle, T.T., Hämäläinen, H., Ilanne-Parikka, P., et al., 2001. Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. *N. Engl. J. Med.* 344, 1343–1350. <https://doi.org/10.1056/NEJM200105033441801>
- Turunen, M., Hokkanen, L., Bäckman, L., Stigsdotter-Neely, A., Hänninen, T., Paajanen, T., et al., 2019. Computer-based cognitive training for older adults: Determinants of adherence. *PLoS One* 14, e0219541. <https://doi.org/10.1371/journal.pone.0219541>
- U.S. Department of Health and Human Services Food and Drug Administration, 2018. Early Alzheimer’s Disease: Developing Drugs for Treatment - Draft Guidance for Industry [WWW Document]. Retrieved from <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/alzheimers-disease-developing-drugs-treatment-guidance-industry> (accessed 06/20/2020).
- Valenzuela, P.L., Castillo-García, A., Morales, J.S., de la Villa, P., Hampel, H., Emanuele, E., et al., 2020. Exercise benefits on Alzheimer’s disease: State-of-the-science. *Ageing Res. Rev.* 62, 101108. <https://doi.org/10.1016/j.arr.2020.101108>
- van Charante, E.P.M., Richard, E., Eurelings, L.S., van Dalen, J.W., Ligthart, S.A., van Bussel, E.F., et al., 2016. Effectiveness of a 6-year multidomain vascular care intervention to prevent dementia (preDIVA): a cluster-randomised controlled trial. *Lancet* 388, 797–805. [https://doi.org/10.1016/S0140-6736\(16\)30950-3](https://doi.org/10.1016/S0140-6736(16)30950-3)
- van Maurik, I.S., Vos, S.J., Bos, I., Bouwman, F.H., Teunissen, C.E., Scheltens, P., et al., 2019. Biomarker-based prognosis for people with mild cognitive impairment (ABIDE): a modelling study. *Lancet Neurol.* 18, 1034–1044. [https://doi.org/10.1016/S1474-4422\(19\)30283-2](https://doi.org/10.1016/S1474-4422(19)30283-2)
- van Maurik, I.S., Zwan, M.D., Tijms, B.M., Bouwman, F.H., Teunissen, C.E., Scheltens, P., et al., 2017. Interpreting Biomarker Results in Individual Patients With Mild Cognitive Impairment in the Alzheimer’s Biomarkers in Daily Practice (ABIDE) Project. *JAMA Neurol.* 74, 1481–1491. <https://doi.org/10.1001/jamaneurol.2017.2712>
- van Middelaar, T., Beishuizen, C.R.L., Guillemont, J., Barbera, M., Richard, E., & Moll van Charante, E.P., 2018a. Engaging older people in an internet platform for cardiovascular risk self-management: a qualitative study among Dutch HATICE participants. *BMJ Open* 8, e019683. <https://doi.org/10.1136/bmjopen-2017-019683>
- van Middelaar, T., Hoevenaar-Blom, M.P., van Gool, W.A., Moll van Charante, E.P., van Dalen, J.-W., Deckers, K., et al., 2018b. Modifiable dementia risk score to study heterogeneity in treatment effect of a dementia prevention trial: a post hoc analysis in the preDIVA trial using the LIBRA index. *Alzheimer’s Res. Ther.* 10, 62. <https://doi.org/10.1186/s13195-018-0389-4>
- Van Wijk, N., Broersen, L.M., De Wilde, M.C., Hageman, R.J.J., Groenendijk, M.,

- Sijben, J.W.C., et al., 2014. Targeting synaptic dysfunction in Alzheimer's disease by administering a specific nutrient combination. *J. Alzheimer's Dis.* 38, 459–479. <https://doi.org/10.3233/JAD-130998>
- Vartiainen, E., Laatikainen, T., Peltonen, M., & Puska, P., 2016. Predicting Coronary Heart Disease and Stroke: The FINRISK Calculator. *Glob. Heart* 11, 213–216. <https://doi.org/10.1016/j.gheart.2016.04.007>
- Vartiainen, E., Laatikainen, T., Salomaa, V., Jousilahti, P., Peltonen, M., & Puska, P., 2007. Sydäninfarkti- ja aivohalvausriskin arviointi FINRISKI-tutkimuksessa. *Suom. Lääkäril.* 62, 4507–4513.
- Vellas, B., Carrie, I., Gillette-Guyonnet, S., Touchon, J., Dantoine, T., Dartigues, J.F., et al., 2014. MAPT study: A Multidomain Approach for preventing Alzheimer's Disease: Design and Baseline Data. *J Prev Alzheimers Dis* 1, 13–22.
- Vemuri, P., Jones, D.T., & Jack, C.R., 2012. Resting state functional MRI in Alzheimer's disease. *Alzheimer's Res. Ther.* 4, 2. <https://doi.org/10.1186/alzrt100>
- Vemuri, P., Lesnick, T.G., Przybelski, S.A., Knopman, D.S., Preboske, G.M., Kantarci, K., et al., 2015. Vascular and amyloid pathologies are independent predictors of cognitive decline in normal elderly. *Brain* 138, 761–771. <https://doi.org/10.1093/brain/awu393>
- Vermunt, L., Sikkes, S.A.M., van den Hout, A., Handels, R., Bos, I., van der Flier, W.M., et al., 2019a. Duration of preclinical, prodromal, and dementia stages of Alzheimer's disease in relation to age, sex, and APOE genotype. *Alzheimer's Dement.* 15, 888–898. <https://doi.org/10.1016/j.jalz.2019.04.001>
- Vermunt, L., van Paasen, A.J.L., Teunissen, C.E., Scheltens, P., Visser, P.J., & Tijms, B.M., 2019b. Alzheimer disease biomarkers may aid in the prognosis of MCI cases initially reverted to normal. *Neurology* 92, e2699–e2705. <https://doi.org/10.1212/WNL.0000000000007609>
- Villeneuve, S., Rabinovici, G.D., Cohn-Sheehy, B.I., Madison, C., Ayakta, N., Ghosh, P.M., et al., 2015. Existing Pittsburgh Compound-B positron emission tomography thresholds are too high: Statistical and pathological evaluation. *Brain* 138, 2020–2033. <https://doi.org/10.1093/brain/aww112>
- Vos, S.J.B., Van Boxtel, M.P.J., Schiepers, O.J.G., Deckers, K., De Vugt, M., Carrière, I., et al., 2017. Modifiable Risk Factors for Prevention of Dementia in Midlife, Late Life and the Oldest-Old: Validation of the LIBRA Index. *J. Alzheimer's Dis.* 58, 537–547. <https://doi.org/10.3233/JAD-161208>
- Vos, S.J.B., Verhey, F., Frölich, L., Kornhuber, J., Wiltfang, J., Maier, W., et al., 2015. Prevalence and prognosis of Alzheimer's disease at the mild cognitive impairment stage. *Brain* 138, 1327–1338. <https://doi.org/10.1093/brain/aww029>
- Vos, S.J.B., Xiong, C., Visser, P.J., Jasielec, M.S., Hassenstab, J., Grant, E.A., et al., 2013. Preclinical Alzheimer's disease and its outcome: A longitudinal cohort study. *Lancet Neurol.* 12, 957–965. [https://doi.org/10.1016/S1474-4422\(13\)70194-7](https://doi.org/10.1016/S1474-4422(13)70194-7)
- Walters, K., Hardoon, S., Petersen, I., Iliffe, S., Omar, R.Z., Nazareth, I., et al., 2016. Predicting dementia risk in primary care: Development and validation of the Dementia Risk Score using routinely collected data. *BMC Med.* 14, 6.

- <https://doi.org/10.1186/s12916-016-0549-y>
- Wang, R., Lagakos, S.W., Ware, J.H., Hunter, D.J., & Drazen, J.M., 2007. Statistics in medicine - Reporting of subgroup analyses in clinical trials. *N. Engl. J. Med.* 357, 2189–2194. <https://doi.org/10.1056/NEJMSr077003>
- Weigand, A.J., Bangen, K.J., Thomas, K.R., Delano-Wood, L., Gilbert, P.E., Brickman, A.M., et al., 2020. Is tau in the absence of amyloid on the Alzheimer's continuum?: A study of discordant PET positivity. *Brain Commun.* 2, fcz046. <https://doi.org/10.1093/braincomms/fcz046>
- Weiner, M.W., Nosheny, R., Camacho, M., Truran-Sacrey, D., Mackin, R.S., Flenniken, D., et al., 2018. The Brain Health Registry: An internet-based platform for recruitment, assessment, and longitudinal monitoring of participants for neuroscience studies. *Alzheimer's Dement.* 14, 1063–1076. <https://doi.org/10.1016/j.jalz.2018.02.021>
- Werner, P., Goldstein, D., Karpas, D.S., Chan, L., & Lai, C., 2014. Help-Seeking for Dementia: a systematic review of the literature. *Alzheimer Dis. Assoc. Disord.* 28, 299–310. <https://doi.org/10.1097/wad.0000000000000065>
- Wesselman, L.M.P., Hooghiemstra, A.M., Schoonmade, L.J., De Wit, M.C.J., Van Der Flier, W.M., & Sikkes, S.A.M., 2019. Web-based multidomain lifestyle programs for brain health: Comprehensive overview and meta-analysis. *J. Med. Internet Res. Ment. Heal.* 6, e12104. <https://doi.org/10.2196/12104>
- Wesselman, L.M.P., Schild, A.K., Coll-Padros, N., van der Borg, W.E., Meurs, J.H.P., Hooghiemstra, A.M., et al., 2018. Wishes and preferences for an online lifestyle program for brain health—A mixed methods study. *Alzheimer's Dement. Transl. Res. Clin. Interv.* 4, 141–149. <https://doi.org/10.1016/j.trci.2018.03.003>
- Wessels, A.M., Tariot, P.N., Zimmer, J.A., Selzler, K.J., Bragg, S.M., Andersen, S.W., et al., 2020. Efficacy and Safety of Lanabecestat for Treatment of Early and Mild Alzheimer Disease: The AMARANTH and DAYBREAK-ALZ Randomized Clinical Trials. *JAMA Neurol.* 77, 199–209. <https://doi.org/10.1001/jamaneurol.2019.3988>
- White, L.R., Edland, S.D., Hemmy, L.S., Montine, K.S., Zarow, C., Sonnen, J.A., et al., 2016. Neuropathologic comorbidity and cognitive impairment in the Nun and Honolulu-Asia Aging Studies. *Neurology* 86, 1000–1008. <https://doi.org/10.1212/WNL.0000000000002480>
- Wikler, E.M., Blendon, R.J., & Benson, J.M., 2013. Would you want to know? Public attitudes on early diagnostic testing for Alzheimer's disease. *Alzheimer's Res. Ther.* 5, 43. <https://doi.org/10.1186/alzrt206>
- Williamson, J.D., Pajewski, N.M., Auchus, A.P., Bryan, R.N., Chelune, G., Cheung, A.K., et al., 2019. Effect of Intensive vs Standard Blood Pressure Control on Probable Dementia: A Randomized Clinical Trial. *JAMA - J. Am. Med. Assoc.* 321, 553–561. <https://doi.org/10.1001/jama.2018.21442>
- Winblad, B., Palmer, K., Kivipelto, M., Jelic, V., Fratiglioni, L., Wahlund, L.O., et al., 2004. Mild cognitive impairment - Beyond controversies, towards a consensus: Report of the International Working Group on Mild Cognitive Impairment. *J.*

- Intern. Med.* 256, 240–246. <https://doi.org/10.1111/j.1365-2796.2004.01380.x>
- Wolz, R., Schwarz, A.J., Gray, K.R., Yu, P., & Hill, D.L.G., 2016. Enrichment of clinical trials in MCI due to AD using markers of amyloid and neurodegeneration. *Neurology* 87, 1235–1241. <https://doi.org/10.1212/WNL.0000000000003126>
- Working group appointed by the Finnish Medical Society Duodecim and the Finnish Hypertension Society, 2009. Hypertension: current care summary. The Finnish Medical Society Duodecim, Helsinki.
- Working group appointed by the Finnish Medical Society Duodecim and the Medical Advisory Board of the Finnish Diabetes Society, 2007. Diabetes: current care summary. The Finnish Medical Society Duodecim, Helsinki.
- Working group set up by the Finnish Medical Society Duodecim and Finnish Society of Internal Medicine, 2009. Dyslipidaemias: current care summary. The Finnish Medical Society Duodecim, Helsinki.
- World Health Organization, 2018a. Global Health Estimates 2016: Deaths by Cause, Age, Sex, by Country and by Region, 2000-2016. World Health Organization, Geneva.
- World Health Organization, 2018b. International Classification of Diseases, 11th revision. World Health Organization, Geneva.
- World Health Organization, 2019. Risk reduction of cognitive decline and dementia: WHO guidelines. World Health Organization, Geneva.
- World Health Organization, 2020. Health promotion and disease prevention through population-based interventions, including action to address social determinants and health inequity [WWW Document]. Retrieved from <http://www.emro.who.int/about-who/public-health-functions/health-promotion-disease-prevention.html> (accessed 07/28/2020).
- Xanthopoulou, P., & McCabe, R., 2019. Subjective experiences of cognitive decline and receiving a diagnosis of dementia: Qualitative interviews with people recently diagnosed in memory clinics in the UK. *BMJ Open* 9, e026071. <https://doi.org/10.1136/bmjopen-2018-026071>
- Yaffe, K., Barnes, D.E., Rosenberg, D., Dublin, S., Kaup, A.R., Ludman, E.J., et al., 2019. Systematic Multi-Domain Alzheimer's Risk Reduction Trial (SMARRT): Study Protocol. *J. Alzheimer's Dis.* 70, S207–S220. <https://doi.org/10.3233/JAD-180634>
- Yang, T., Dang, Y., Ostaszewski, B., Mengel, D., Steffen, V., Rabe, C., et al., 2019. Target engagement in an alzheimer trial: Crenezumab lowers amyloid β oligomers in cerebrospinal fluid. *Ann. Neurol.* 86, 215–224. <https://doi.org/10.1002/ana.25513>
- Yu, J.-T., Xu, W., Tan, C.-C., Andrieu, S., Suckling, J., Evangelou, E., et al., 2020. Evidence-based prevention of Alzheimer's disease: systematic review and meta-analysis of 243 observational prospective studies and 153 randomised controlled trials. *J. Neurol. Neurosurg. Psychiatry* Epub Jul 2. <https://doi.org/10.1136/jnnp-2019-321913>
- Zhou, Y., Elashoff, D., Kremen, S., Teng, E., Karlawish, J., & Grill, J.D., 2017. African

Americans are less likely to enroll in preclinical Alzheimer's disease clinical trials. *Alzheimer's Dement. Transl. Res. Clin. Interv.* 3, 57–64. <https://doi.org/10.1016/j.trci.2016.09.004>

Zülke, A., Luck, T., Pabst, A., Hoffmann, W., Thyrian, J.R., Gensichen, J., et al., 2019. AgeWell.de - study protocol of a pragmatic multi-center cluster-randomized controlled prevention trial against cognitive decline in older primary care patients. *BMC Geriatr.* 19, 203. <https://doi.org/10.1186/s12877-019-1212-1>



ANNA ROSENBERG

Dementia is an enormous global health challenge. With no cure in sight, identifying strategies to prevent or delay its onset in different at-risk populations is a priority. This thesis used data from three large, completed, pioneering dementia prevention trials and a memory clinic, with the aim to offer insights into the selection and engagement of target populations in prevention trials. The findings inform the design and conduct of the next generation dementia prevention trials.



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