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TIMO PEKKALA

MULTIMODAL PREDICTION OF DEMENTIA AND BRAIN PATHOLOGY

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Timo Pekkala

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ABSTRACT

Dementia and associated brain pathology take years to develop. Effective interventions to prevent dementia have not been found, in part because interventions are targeted at individuals in a relatively late stage of dementia progression. This thesis aims to develop prediction models for identifying persons at risk at an earlier stage. Prediction targets included incident dementia as well as common brain pathologies underlying progressive cognitive disorders in different elderly age cohorts. An additional aim was to investigate the association of blood markers of type two diabetes (DM2) and brain amyloid deposition, a hallmark of Alzheimer's disease (AD).

Dementia was predicted in the Finnish population based Cardiovascular Risk Factors, Aging and Dementia (N=709 and 1,009) and Vantaa 85+ (N=245) study populations of cognitively healthy younger-old individuals (mean age 70 years) and oldest-old individuals (88 years), respectively. Multimodal predictors were used to predict incident dementia over a period of five to ten years using a Disease State Index (DSI) machine learning system. Incidences of common brain pathology were predicted in a Vantaa 85+ subpopulation (N=163, 89 years) over a four year follow up, and the prevalence of brain amyloid deposition on positron emission tomography (PET) was predicted in a Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER) subpopulation (N=48) of cognitively healthy younger-old individuals (71 years) with elevated cardiovascular risks and cognition at or slightly below population norms. Both prediction models were built using the DSI. A further FINGER-PET subpopulation (N=41) was used for the analysis of blood DM2 markers using a logistic regression.

Prediction of dementia in the younger-old population succeeded well (area under the curve 0.75–0.79), and in the oldest-old population almost at the same level (0.73). Predictors of dementia for the younger old and the oldest old were different, with age and vascular health achieving less effective predictions for the older cohort. For the oldest old, dementia could be predicted more accurately than most types of brain pathology (0.61–0.72). Amyloid deposition was predicted well for the younger old (0.78) using among other modalities magnetic resonance imaging, but the prediction results were better than for the oldest old even without imaging. Cognition was

a better predictor of dementia than pathology, and the apolipoprotein E genotype was a better predictor of pathology than dementia. Out of the DM2 markers, low levels of insulin resistance markers and a low concentration of plasminogen activator inhibitor-1 were associated with a positive brain amyloid deposition status.

These results indicate that at-risk persons could be identified years before a diagnosis of dementia is given, and interventions could be targeted at those who benefit the most. Different risk factors may have to be considered when targeting dementia or specific pathologies. Prediction models for brain pathology—especially amyloid—could be used to enrich study populations with persons with a specific pathology to save costs and invasive assessments in clinical trials.

Medical Subject Headings: Aged; Alzheimer Disease; Amyloid; Brain/pathology; Cognition; Cognitive Dysfunction; Decision Support Systems, Clinical; Dementia; Diabetes Mellitus, Type 2; Early Medical Intervention; Incidence; Longitudinal Studies; Neuropathology; Risk Factors

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TIIVISTELMÄ

Dementia ja sen taustalla vaikuttavat aivojen patologiset muutokset kehittyvät useiden vuosien aikana. Tehokkaita keinoja dementian ehkäisemiseksi ei vielä ole löydetty. Osin tämä saattaa johtua siitä, että ehkäisytoimia on tähän mennessä tutkittu dementian melko myöhäisessä kehitysvaiheessa. Tämä väitöstyö pyrki kehittämään ennustemalleja, joilla voitaisiin aiemmin tunnistaa henkilöt, joilla on suurentunut dementiariski. Työssä pyrittiin ennustamaan toisaalta dementian ja toisaalta yleisimpien aivojen dementiaan liitettyjen patologisten muutosten ilmaantumista. Ennustemalleja sovellettiin eri-ikäisiin vanhuusiän kohortteihin. Lisäksi väitöstyössä selvitettiin tyypin kaksi diabeteksen verimerkkiaineiden pitoisuuksien yhteyttä aivojen amyloidiproteiinikertymien esiintyvyyteen. Amyloidiproteiinin kertyminen aivokudokseen on yksi Alzheimerin taudin tyypillisistä muutoksista.

Dementian ilmaantuvuutta ennustettiin kahden suomalaisen väestöpohjaisen tutkimuksen aineistolla. Cardiovascular Risk Factors, Aging and Dementia -tutkimuksen (N=709 ja 1 009) koehenkilöt olivat kognitiivisesti terveitä keskimäärin 70-vuotiaita nuoria ikääntyneitä ja Vantaa 85+ -tutkimuksen (N=245) henkilöt taas keskimäärin 88-vuotiaita vanhoja ikääntyneitä. Malleilla ennustettiin ilmaantuvuutta viidestä kymmeneen vuoden ajanjaksolla ja ennustetekijöinä käytettiin eri terveyden osa-alueilta mitattuja monityyppisiä tekijöitä. Mallit toteutettiin Disease State Index (DSI) koneoppimisjärjestelmällä. Aivojen patologisten muutosten ilmaantumista ennustettiin Vantaa 85+ -tutkimuksen ruumiinavausosapopulaatiossa (N=163, ikä keskimäärin 89 vuotta) keskimäärin neljän vuoden seurantajaksolla. Amyloidiproteiinin esiintymistä positroniemissiotomografiassa (PET) ennustettiin Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability -tutkimuksen (FINGER) pienessä osapopulaatiossa (N=48). FINGER-tutkimuksen koehenkilöt oli valittu siten, että he olivat kognitiivisesti terveitä, mutta heidän kognition tasonsa oli mittauksissa väestökeskiarvon mukainen tai hieman heikompi. Lisäksi heillä oli suurentunut sydän- ja verisuonisairauksien riski. Myös patologian ennustemallit perustuivat DSI-järjestelmään. Tyypin kaksi diabeteksen merkkiaineiden ja amyloidin suhdetta tutkittiin logistisella regressiolla hieman pienemmässä FINGER-tutkimuksen osajoukossa (N=41).

Dementian ennustaminen nuorten ikääntyneiden ryhmässä onnistui hyvin (AUC 0.75–0.79) ja vanhojen ikääntyneiden ryhmässä lähes yhtä hyvin (0.73). Tärkeimmät ennustetekijät poikkesivat toisistaan eri ikäryhmissä: ikä ja verisuonielimistön terveydentila olivat huonompia ennustetekijöitä vanhojen ikääntyneiden ryhmässä. Vanhojen ikääntyneiden ryhmässä dementian ilmaantumista pystyttiin ennustamaan tarkemmin kuin useimpien patologisten muutosten ilmaantumista (0.61–0.72). Amyloidiproteiinin esiintymistä aivokuvantamisessa pystyttiin ennustamaan hyvin nuorten ikääntyneiden ryhmässä (0.78), kun ennustetekijänä käytettiin muun muassa aivojen magneettikuvaustuloksia. Tulokset olivat tosin parempia nuorten ikääntyneiden ryhmässä verrattuna vanhojen ikääntyneiden ryhmään, vaikka magneettikuvaustuloksia ei olisi ollut käytettävissä. Kognition taso ennusti paremmin dementian kuin aivopatologian ilmaantuvuutta. Apolipoproteiini E:n genotyyppi taas ennusti paremmin patologian kuin dementian ilmaantuvuutta. Tyypin kaksi sokeritaudin merkkiaineista matalaan insuliiniresistenssiin viittaavat merkkiainepitoisuudet ja matala PAI-1-pitoisuus (plasminogeeni aktivaattori-1:n inhibiittori) olivat yhteydessä positiiviseen amyloidilöydökseen.

Nämä tulokset osoittivat, että suuremman dementiariskin henkilöt voidaan tunnistaa vuosia ennen sairastumista. Tänä diagnoosia edeltävänä ajanjaksona voitaisiin toteuttaa interventioita niille, jotka niistä eniten hyötyisivät. Kohdennettavat riskitekijät tulisi valita sen mukaan, pyritäänkö ehkäisemään dementian tai tiettyjen patologisten muutosten ilmaantumista. Patologisten muutosten ennustemalleilla voitaisiin rikastaa tutkimuspotilaita tietyn patologian—etenkin amyloidiproteiinin—suhteen kustannusten ja kajoavien toimenpiteiden vähentämiseksi kliinisissä tutkimuksissa.

Yleinen suomalainen asiasanasto: aikuistyypin diabetes; aivot; Alzheimerin tauti; dementia; ennaltaehkäisy; ennusteet; ikääntyneet; ilmaantuvuus; kognitio; pitkittäistutkimus; päätöksentukijärjestelmät; riskitekijät

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II Hall A, Pekkala T, Polvikoski T, van Gils M, Kivipelto M, Lötjönen J, Mattila J, Kero M, Myllykangas L, Mäkelä M, Oinas M, Paetau A, Soininen H, Tanskanen M and Solomon A. Prediction models for dementia and neuropathology in the oldest old: the Vantaa 85+ cohort study. Alzheimer's Research & Therapy 11, 2019.

III Pekkala T, Hall A, Ngandu T, van Gils M, Helisalmi S, Hänninen T, Kemppainen N, Liu Y, Lötjönen J, Paajanen T, Rinne J O, Soininen H, Kivipelto M, Solomon A. Detecting amyloid positivity in elderly with increased risk of cognitive decline. Submitted to journal for publication.

IV Pekkala T, Hall A, Mangialasche F, Kemppainen N, Mecocci P, Ngandu T, Rinne J O, Soininen H, Tuomilehto J, Kivipelto M and Solomon A. Association of peripheral insulin resistance and other markers of type 2 diabetes mellitus with brain amyloid deposition in healthy individuals at risk of dementia. Submitted to journal for publication.

CONTENTS

ABBREVIATIONS

Aβ	amyloid beta protein
AD	Alzheimer's disease
ADDTC	Alzheimer's Disease Diagnostic and Treatment Centers
ADL	activities in daily living
ADNI	Alzheimer's Disease Neuroimaging Initiative
AF	atrial fibrillation
ANU-ADRI	Australian National University Alzheimer's Disease Risk Index
APOE	Apolipoprotein E gene
APP	amyloid precursor protein
AT(N)	amyloid, tau, and neurodegeneration
AUC	area under the receiver operating characteristic curve
BACE	beta-secretase
BBB	blood–brain barrier
BDI	Beck Depression Inventory
BMI	body mass index
BP	blood pressure
CAA	cerebral amyloid angiopathy
CAD	coronary artery disease
CAIDE	Cardiovascular Risk Factors, Aging and Dementia
CARTS	cerebral age-related TDP-43 with sclerosis
CDR	clinical dementia rating
CERAD	Consortium to Establish a Registry for Alzheimer's Disease
CHD	coronary heart disease
CI	confidence interval
CN	cognitively normal

CRF	cardiorespiratory fitness
CSF	cerebrospinal fluid
CVD	cerebrovascular disease
DBP	diastolic blood pressure
DLB	dementia with Lewy bodies
DM	diabetes mellitus
DSI	Disease State Index
DSM-5	fifth revision of the DSM
DSM-IV-TR	Diagnostic and Statistical Manual of Mental Disorders, 4th, revised, edition
DT	decision tree
EPAD	European Prevention of Alzheimer's Dementia
FCSRT-FR	free and cued selective reminding test, free recall
FINGER	Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability
FINMONICA	Finnish part of Monitoring Trends and Determinants in Cardiovascular Disease
FTD	frontotemporal dementia
GIP	gastric inhibitory polypeptide
GLP-1	glucagon-like peptide-1
HbA1c	glycated hemoglobin
HDL	high-density lipoprotein
HIV	human immunodeficiency virus
HOMA-IR	homeostasis model assessment for insulin resistance
HS	hippocampal sclerosis
IADL	Instrumental Activities of Daily Living
ICD-10	International Classification of Diseases 10th revision
ICH	intracerebral hemorrhage
IDE	insulin-degrading enzyme

In-MINDD	Innovative Midlife Intervention for Dementia Deterrence
IR	insulin resistance
IWG	International Working Group
LDL	low-density lipoprotein
LIBRA	Lifestyle for Brain health
LR	logistic regression
MAPT	Multidomain Alzheimer's Prevention Trial
MCI	mild cognitive impairment
MMSE	Mini-Mental State examination
mNTB	modified version of the Neuropsychological Test Battery
MRI	magnetic resonance imaging
MTA	medial temporal atrophy
NCD	neurocognitive disorder
NIA-AA	National Institute on Aging and the Alzheimer's Association
NIA-RIA	National Institute for Aging and Ronald and Nancy Reagan Institute of the Alzheimer's Association
NINCDS-ADRDA	National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association
NINDS-AIREN	National Institute of Neurological Disorders and Stroke–Association Internationale pour la Recherche et l'Enseignement en Neurosciences
NSAID	nonsteroidal anti-inflammatory drug
PAI-1	plasminogen activator inhibitor-1
PC	Principal component
PCA	principal components analysis
PD-D	Parkinson's disease dementia
PET	positron emission tomography
PIB	Pittsburgh compound B
PPA	primary progressive aphasia

PPV	positive predictive value
PreDIVA	Prevention of Dementia by Intensive Vascular Care
RCT	randomized controlled trial
RF	random forest model
ROC	Receiver operating characteristics
SBP	systolic blood pressure
SMQ	Subjective Memory Questionnaire
SPMSQ	Short portable mental status questionnaire
SPRINT	Systolic Blood Pressure Intervention Trial
SVM	support vector machine
TDP-43	TAR DNA-binding protein with molecular weight 43 kDa
THIN	Taiwanese Health Improvement Network
TIA	transient ischemic attack
TRIPOD	Transparent Reporting of a multi- variable prediction model for Individual Prognosis Or Diagnosis
VaD	vascular dementia
VASCOG	International Society of Vascular Behavioural and Cognitive Disorders
VCD	vascular cognitive disorders
VCI	vascular cognitive impairment
WM	white matter

1 INTRODUCTION

Despite efforts to develop disease-modifying interventions to prevent Alzheimer's disease (AD), dementia and the underlying diseases are still prevalent. Additionally, with populations growing older in many parts of the world, total prevalence is expected to grow further. There are, however, signs that the age-specific incidence might be decreasing in some regions (Seblova et al., 2018). Why this is exactly is not clear, but improvements in living standards and reductions of certain risk factors of dementia in the population may be partly responsible. Research into modifiable risk factors of dementia has remained in focus as AD drug trials have so far failed, and trials aiming to prevent cognitive decline and dementia have gained in importance. Interventions targeting single risk factors have often not proven successful, but new multimodal interventions have shown promise (Kivipelto et al., 2018). Globally, dementia prevention has been set as a priority, and the World Health Organization has just recently published public health guidelines for prevention that are suitable for integration into multifaceted health promotion initiatives (World Health Organization, 2019).

A problem with both disease-modifying and preventive interventions is the long time frame of dementia development. Intervention would probably have to be undertaken at an early stage to be effective. Recognizing at-risk individuals up to decades earlier is challenging, although risk scores have been used to this end. One objective of this thesis is to build and validate such models for the purposes of future trials. An important feature of such models is also to communicate the determinants of risk, which may be beneficial at an individual level.

Progress is being made not only on the epidemiological level with risk factors and their mitigation, but also with the pathophysiology of AD and other primary dementias. Measuring brain pathology via imaging and other markers offers early information on the disease process, and may also indicate disease severity more precisely than the clinical state. Additionally, measurement of pathology can be a useful indicator of intervention efficacy. One of the objectives of this thesis is to predict the presence and incidence of brain pathology. Such a prediction tool could be useful in guiding persons for further investigations, or for example to invite persons to an intervention trial targeting that specific pathology.

Type two diabetes, like dementia, is a growing problem in modern aging societies, and the two share risk factors. Diabetes is thought to be a risk factor for dementia, but causality and the possible mechanisms are not yet fully clear. For example, diabetes increases vascular brain pathology, but findings have been conflicting regarding direct causal associations with AD pathology. Other shared, rather than direct, causal factors have also been suggested to underlie the diabetes–AD association. E.g. hypercortisolemia associated with early stages of AD may provoke disturbances in glucose metabolism (Notarianni, 2017). Pre-diabetes with elevated insulin resistance may share pathological pathways with AD, and understanding these may aid in de-

signing interventions. Thus, this thesis also investigates the association of metabolic changes preceding DM2 and brain amyloid accumulation.

2 REVIEW OF THE LITERATURE

2.1 COGNITIVE DECLINE AND DEMENTIA

The aging process involves changes in brain function and cognition, but these normal changes allow an individual to age with autonomy and a well-functioning everyday life. Cognitive impairment in this context is seen as a deviation from this path. Classically, mild cognitive impairment (MCI) is a term used to describe early steps towards the pathological, where a subjective experience of cognitive decline can be backed up with objectively measured impairment of cognition (Roberts and Knopman, 2013). In the case of progressive cognitive disorders, MCI usually progresses to dementia, which in turn is characterized by considerable functional disability due to increasing cognitive impairment.

The term dementia referring to a form of extreme mental incapacity goes back to the 1520s, and accounts of dementia as a mental state go back to antiquity. The term *dementia* has historically been used for both senile dementia—dementia occurring in old age—and for dementia due to a somatic or psychiatric cause such as schizophrenia or syphilis. Contemporary clinical practice tends towards retiring the term due to the associated stigma in favour of *neurocognitive disorder*, or in the Finnish case the term *muistisairaus*, *memory disorder*. Furthermore, as knowledge about the underlying diseases progresses, more disease-specific terminology is being increasingly used.

The diagnostic criteria for dementia—irrespective of etiology—in different diagnostic systems have evolved in the past decades. The Diagnostic and Statistical Manual of Mental Disorders, 4th, revised, edition from 2000 (DSM-IV-TR; American Psychiatric Association, 2000), characterizes dementia as deterioration of cognition in multiple domains. Memory deficit is a required criterion, in addition to impairment of language skills, impairment of motor function, agnosia, or impaired executive functioning. The impairment should represent a decline from the previous level and be so severe that occupational or social functioning is harmed, that is, activities in daily living (ADL) are impaired. DSM-IV-TR emphasizes cognitive testing for determining the deficits. The International Classification of Diseases 10th revision (ICD-10; World Health Organization, 1993) defines dementia similarly primarily as a deficit of memory.

In the fifth revision of the DSM from 2013 (DSM-5; American Psychiatric Association, 2013) six distinct domains of cognition are specified, and memory deficit is not a requirement anymore. The term dementia has also been rephrased as a *major neurocognitive disorder* (NCD). To represent less severe cognitive impairment that has previously been characterized as MCI and prodromal dementia, a new diagnostic category of mild NCD was introduced. The diagnosis of major NCD as opposed to mild NCD requires a lack of independent ADL.

The National Institute on Aging and the Alzheimer's Association (NIA-AA) workgroup criteria for all-cause dementia (McKhann et al., 2011) require neuropsychiatric

symptoms that interfere with at least two practical categories of daily living. The criteria allow deficits to be determined based on patient or informant history and a simple clinical assessment. Similarly to the DSM-5, a memory deficit is not an absolute requirement.

Neuropsychological testing is used to quantify deficits in cognition (Salmon and Bondi, 2009), and validated methods exist to screen for and to assess the severity of dementia. The Clinical Dementia Rating (CDR; Berg, 1988; Morris, 1993) is commonly used to identify dementia stages from very mild to severe dementia on a four ladder scale. The assessment is based on an interview that focuses on memory and five other cognitive domains with the emphasis on memory deficits. The Mini-Mental State examination (MMSE; Folstein et al., 1975) is used for screening for cognitive decline in different outpatient care settings and to gauge the development of diagnosed memory disorders. It consists of a 19-item-long test battery that tests several cognitive domains and can be administered with little training. The quality of cognitive deficits is commonly measured using The Consortium to Establish a Registry for Alzheimer's Disease (CERAD; Morris et al., 1989) neuropsychological battery, which is well suited as a first line of assessment for persons with suspected AD. More nuanced neuropsychological assessments are used to either characterize very mild symptoms or to perform differential diagnostics (Salmon and Bondi, 2009).

Dementia, as defined above, is thought of as a syndrome that is distinctly removed from healthy aging. The syndrome is defined as a symptomatic entity, and it can have any of the several specific underlying pathologies as a cause. The following chapters introduce the main causative pathologies, of which Alzheimer's disease is the most common and widely known.

2.2 ALZHEIMER'S DISEASE

Alzheimer's disease was first defined as a clinical dementia entity. The first section gives an overview of the classical phenotype-oriented diagnostic frameworks. Then, a summary of AD pathology and associated biomarkers and examination possibilities is given. The last section presents newer diagnostic frameworks that use biomarker data at their core to define AD.

2.2.1 Clinical presentation and criteria for clinical diagnosis

The National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ARDRA) guidelines for clinical AD diagnosis (McKhann et al., 1984) are based on strictly clinical findings for *probable AD* diagnoses, and neuropathological evidence is needed for the diagnosis of *definite AD*. Deficits in two or more domains of cognition are required and neurophysiological testing is emphasized in determining the deficits. The age of disease onset should be at 40–90 years. A category of *possible AD* was introduced to describe atypical disease presentations with no other likely cause. DSM-IV-TR, similar to NINCDS-ARDRA, recognizes dementia of the Alzheimer's type with a disease-

specific requirement of advancing cognitive decline with a gradual onset. Early-onset AD-dementia (<65 years) is recognized as an additional entity, as are four subtype qualifiers (delirium, delusions, depression, uncomplicated). Impairment of ADL is required, in contrast to the NINCDS-ADRDA guidelines where ADL impairment is listed as supportive for probable AD.

In 2011 the NIA-AA workgroup (McKhann et al., 2011) published updated diagnostic criteria for dementia with the aim of incorporating state-of-the-art scientific knowledge on AD as causative for dementia. The core NIA-AA dementia criteria (section 2.1) are mandated for AD diagnosis. The suggested diagnostic procedure recognizes several levels of diagnostic certainty and variability in phenotype specifically not requiring a strict amnestic representation. As opposed to the NINCDS-ARDRA guidelines, the criteria are more specific to AD and information on biomarkers and genetics can optionally be included. DSM-5 was updated with the NIA-AA criteria in mind, and with its new category of NCDs it introduced mild NCD as a parallel to the NIA-AA's MCI due to AD. In DSM-5, attributing NCD to AD still requires a memory deficit, and biomarkers do not play a role.

More evidence on the pathophysiology of AD and a better understanding of the decades-long disease development process have led to the need to set diagnostic criteria for AD that do not necessitate full-blown dementia. Such criteria could be used to identify *prodromal AD*, a disease state preceding dementia. The intention would be to diagnose a specific disease, and not to start with incident dementia and retroactively phenotype the dementia. That is, the idea would be to move away from the traditional two-stage diagnosis. New criteria incorporate biomarker information, a subject introduced in more detail in the following chapters. An International Working Group (IWG1; Dubois et al., 2007) revised the NINCDS-ADRDA criteria by concentrating on AD-specific cognitive deficits accompanied by supporting biomarker findings indicative of AD disease progress. The criteria are research-focused, require equipment for biomarker analysis, and are tuned to be more specific than earlier criteria. The IWG1 criteria for *probable AD* are summarized as follows:

Core set of criteria A: Presence of an episodic memory impairment that 1) is reported to have progressed gradually over a period of at least six months, 2) can be verified objectively by testing, and 3) can be the solitary symptom or can be associated with other cognitive deficits. At least one supportive feature associated with known AD pathology is additionally required: B) a specific form of brain atrophy, C) biomarker evidence in the cerebrospinal fluid, D) specific changes in amyloid protein neuroimaging, or E) AD autosomal mutation in the family. Exclusion criteria include early onset or prominent non-AD symptoms, focal neurological symptoms or early extrapyramidal symptoms, and other sufficiently severe neurological conditions. Diagnosis of *definite AD* is warranted by the IWG1 criteria if the clinical evidence is supported by either histopathological findings or the patient is shown to have an AD autosomal mutation.

The older criteria have been used both in research and in clinical practice over the last 30–40 years. The newer criteria are more aimed at research. At least in Fin-

land, making use of other biomarker information than structural brain imaging has been constrained to more challenging cases requiring detailed differential diagnoses (Seppälä et al., 2013).

Better understanding of the disease and improved technology in imaging, for example, have emphasized new challenges in defining AD. The current debate revolves around defining AD as a biological disease entity with a certain pathological cascade versus defining the disease in terms of clinical symptoms that also covers early stages of the disease. The latter approach coincides with the approach of the more recent diagnostic frameworks presented in this section, and the former relies more strongly on detailed biomarker profiles introduced in the following section.

2.2.2 Pathophysiology

Recognition of AD as a discrete disease identity was coupled with finding distinct pathological lesions in the brain of the first patient to be diagnosed with Alzheimer's disease, Auguste D. Under the microscope Dr. Alois Alzheimer observed senile plaques and neurofibrillary tangles that he recognized as a separate entity from vascular lesions. The senile—or neuritic—plaques consist of extracellular aggregated amyloid beta (Aβ) peptides and are indeed typical to AD. The neurofibrillary tangles are formed by the aggregation of phosphorylated tau protein in microtubules inside neurons, a process which is not entirely specific to AD. Vascular lesions have later been presumed not to be linked to AD itself, but to cause cognitive decline and dementia independently. Other microscopic findings include general loss of neurons and amyloid angiopathy. (Erkinjuntti et al., 2015; Engelhardt and Grinberg, 2015; Bondi et al., 2017)

Scientific research into AD has as of yet not produced a consensus on the exact pathway for the occurrence of pathologic changes, or even if the recognized pathological changes are causative of the disease or if they are themselves downstream effects. Recent epidemiological studies suggest Alzheimer's dementia pathology to be heterogenous with a good share of cases being attributable to non-AD-type pathological profiles (Boyle et al., 2019). Amyloid pathology is hypothesized as the first-mover process, and neuritic plaques can be found in the brain decades before the appearance of first symptoms (Jack et al., 2013). The amyloid precursor protein (APP) is a membrane-bound protein found in neurons as well as other tissues. The purpose of APP is not fully understood. As the name suggests, the protein is best known for the end products of its cleavage, namely Aβ peptides. APP is cleaved by β secretases (BACE1 and -2) and γ secretase. Aβ40 and Aβ42 are the most common resulting oligomers, and Aβ42 is prone to misfolding and thus implicated in AD pathology. Aβ peptides are water soluble and can be found in cerebrospinal fluid (CSF), urine, and plasma. With increasing age, these Aβ peptides are known to aggregate as diffuse plaques in the neocortex. In AD, however, plaque formation is distinctly characterized by dense plaque cores surrounded by a detritus of dead neurons within a more diffuse plaque. These are neuritic plaques. Astrocytes and microglial cells are often associated with neuritic plaques indicating an inflammatory response. Aβ

is also known to accumulate in the walls of small arteries to cause cerebral amyloid angiopathy (CAA), a condition known to predispose patients towards bleeds and ischemia. (Erkinjuntti et al., 2015)

Aβ oligomers are thought to have neurotoxic and proinflammatory effects. These effects may be partially responsible for the hyperphosphorylation of tau, a protein typically stabilizing the structure of microtubules in cells. Hyperphosphorylated tau is dysfunctional and aggregates pathologically in helical filaments inside the cell. These neurofibrillary tangles are insoluble and disturb the functioning of the cell resulting ultimately in neuronal loss. Tau and hyperphosphorylated tau are however soluble, and can be measured in CSF, for instance. (Erkinjuntti et al., 2015)

Markers of both amyloid and tau pathology are used to reach a more accurate AD diagnosis, as the purely clinical diagnostic criteria of the previous section only warrant a likely diagnosis. The sensitivity of a clinical diagnosis is in the range 71–87% (Beach et al., 2012). Tau pathology is thought to progress in a manner better matching the clinical presentation of AD. The Braak staging (Braak and Braak, 1991) is a six step staging classification describing the spread of tangles from the entorhinal cortex through the limbic system—including the hippocampus—to the associative and primary visual cortices. The patient is thought to be symptomatic first at the limbic stages III–IV, and stages V–VI are usually associated with clinical AD. The pattern of neuritic plaque formation is different, starting usually from smaller areas of the cortex and spreading throughout the cortex into subcortical and subtentorial structures. This spreading pattern corresponds less reliably to the clinical stage of the disease than the spread of tangles. Therefore Aβ pathology is commonly quantified using the CERAD criteria for neuropathology (Mirra et al., 1991) that simply report the frequency of neuritic plaques in the neocortex (class 0 for none and A–C for sparse–frequent). The CERAD frequency is sometimes adapted by considering clinical data such as age. The two types of pathology are combined under the National Institute for Aging and Ronald and Nancy Reagan Institute of the Alzheimer's Association (NIA-RIA) guidelines (NIA-RIA, 1997), which determine three stages of AD probability based purely on pathological findings.

2.2.3 AD biomarkers and biomarker-based diagnosis

Several biomarkers for characteristic AD pathologies are in use today. In-vivo markers for AD pathology can provide support in diagnosis making in conjunction with the clinical presentation. The development of biomarkers is keenly ongoing with aim to identify AD in its earliest stages when AD pathology is present but no symptoms have yet appeared. The established biomarkers of AD are proxies for Aβ pathology, tau pathology, and general neurodegeneration. Whereas earlier these pathologies could be assessed by analyzing CSF, nowadays imaging modalities have made it possible to gauge the brain less invasively and gain topographical information. Positron emission tomography (PET) using common amyloid-binding ligands (e.g. Pittsburgh compound B, PIB) correlate well with post-mortem Aβ findings (Dubois et al., 2014). Amyloid PET is somewhat lacking in specificity in regard to AD, as a number of

subjects show amyloid-PET positivity with no symptoms of AD (Dubois et al., 2014).

The focus on the wider AD disease course has led to the development of criteria for the disease stages preceding the distinct cognitive deficits of AD dementia. Historically, MCI has covered conditions where subjects suffer mild subjective and objective cognitive symptoms that do not affect ADL. The term is agnostic to etiology and does not imply any kind of progression of the impairment. Preclinical AD and prodromal AD (Dubois, 2000) are terms that are used to specifically describe the stages of AD that precede dementia: in the preclinical phase AD-specific pathology exists, but no symptoms are present. In prodromal AD symptoms appear, but not at an intensity warranting diagnosis of dementia. Patients would typically be classified as having MCI. In prodromal AD the emphasis is on the biomarker profile.

Further development of definitions and criteria for presymptomatic AD (Dubois and Albert, 2004; Dubois et al., 2010; Sperling et al., 2011) is ongoing. Recently, the International Working Group criteria from 2014 (IWG2) published criteria for two entities of preclinical AD (Dubois et al., 2014). The first criterion focuses on those who are *asymptomatic at risk* of AD with either Aβ on PET or with both Aβ and tau abnormalities in CSF. Here the priority of Aβ is evident, and imaging is seen as more reliable than CSF analysis. Second, *presymptomatic AD* is defined in terms of genetic susceptibility in the form of one of the three autosomal dominant genes or other proven genes. Notably, in the IWG2 criteria the biomarkers for Aβ and tau represent diagnostic markers—that is, upstream stages of the disease process—and are preferred over downstream progression markers such as cortical atrophy or brain glucose metabolism. Additionally, the criteria enable the diagnosis of AD without restrictions to the phenotype. To further clarify the terminology, in 2016 the term *preclinical AD* was suggested to be defined in terms of particularly high AD risk with both Aβ and tau pathology present, as opposed to asymptomatic-at-risk representing a state of lower risk with only one type of pathology present (Dubois et al., 2016).

The NIA-AA workgroup updated the 2011 criteria in 2018 with the aim to define AD as a biological entity purely in terms of the pathologic disease progress (Jack et al., 2018). The definition relies on the biomarker status as defined by the amyloid, tau, and neurodegeneration (AT(N)) status. Table 1 summarizes this grouping of biomarkers. The CSF total tau is seen here as a marker of neurodegeneration rather than a marker of tauopathy as opposed to the IWG2 criteria. The framework defines an AD continuum in terms of the AT(N) profile by requiring a positive Aβ finding—a priority as with the IWG2 criteria—and letting T and N vary.

Some biomarkers are better suited for monitoring disease progression than for diagnostics, as they represent downstream changes and lack specificity. Measurement of medial temporal atrophy (MTA) using magnetic resonance imaging (MRI) is a good marker for the development of AD dementia in prodromal AD, and longitudinal MRI measurements are good predictors of disease progression. Hypometabolism on PET is a good tool for differential diagnostics and the determination of AD the subtype as well as a good estimate of the remaining brain function in AD patients with high cognitive reserve. (Dubois et al., 2014)

The recent advances in biomarker research and clinical studies in cohorts representing pre-AD or very mild AD individuals have led to a discussion on how to conceptualize AD. Dubois et al. (2018) frame the staging of AD around symptoms, defining the preclinical stage of sporadic AD as asymptomatic at risk. Here the phase before the AD-threshold—symptoms—is an at-risk state, not a part of the disease. Jack and Vemuri (2018) on the other hand, with the AT(N) classification scheme aim to frame AD as a biological entity that takes its pathological course and only in the end manifests itself as a clinical syndrome. In this framework, the at-risk stage of Dubois et al. corresponds with ongoing AD in the preclinical stage.

2.3 VASCULAR COGNITIVE DISORDERS

2.3.1 Clinical presentation and diagnostic criteria

Impaired blood supply to the brain may lead to cognitive deficits and dementia, a spectrum of disorders called vascular cognitive impairment (VCI; Erkinjuntti and Gauthier, 2009). Current guidelines identify several subtypes of vascular disorders based on arterial anatomy and disease etiology. Disease presentation varies according to etiology: disease in the large vessels typically causes severe symptoms abruptly, and cognitive deficits may be more or less apparent after treatment and/or rehabilitation. Additionally smaller, initially subclinical, events may cause lesions, such as white matter lesions, that eventually lead to gradual cognitive deficits. Risk fac-

Table 1: AD biomarkers in the NIA-AA 2018 guidelines.

Type of pathology	Biomarker	Biomarker positive finding	Topography included	Other conditions linked to biomarker positivity
Aβ	CSF Aβ42	Low concentration	No	HIV encephalitis, multiple system atrophy
	Amyloid PET	High ligand uptake	Yes	Acute traumatic brain injury
Tau	CSF p-tau	High concentration	No	—
	Tau PET	High ligand uptake	Yes	Unknown
Neurodegeneration	CSF total tau	High concentration	No	Acute traumatic brain injury, stroke, CJD
	Metabolic PET	Low uptake in AD-typical pattern	Yes	CVD, corticobasal degeneration, PPA
	Structural MRI	Expert assessment of atrophy	Yes	CVD, epilepsy, anoxia, hippocampal sclerosis

Table adapted from Jack et al. (2016, 2018). **Key**: Aβ amyloid β protein, CJD Creutzfeldt–Jakob disease, CSF cerebrospinal fluid, CVD cerebrovascular disease, HIV human immunodeficiency virus, MRI magnetic resonance imaging, PET positron emission tomography, p-tau phosphorylated tau protein, PPA primary progressive aphasia.

tors for vascular health are also risk factors for VCI via their effect on arteries and possibly also through other mechanisms (Erkinjuntti et al., 2015). These risk factors are discussed in more detail in section 2.6.

Vascular dementia (VaD) has been recognized since the 1960s as a disease entity and nowadays it is seen as a part of the VCI spectrum. The International Society for Vascular Behavioral and Cognitive Disorders (VASCOG; Sachdev et al., 2014) proposed improvements on the then current guidelines on VaD, resulting in expanded new guidelines for vascular cognitive disorders (VCD). The four sets of commonly used criteria for VaD, The National Institute of Neurological Disorders and Stroke Association Internationale pour la Recherché et l'Enseignement en Neurosciences (NINDS-AIREN; Román et al., 1993), the State of California Alzheimer's Disease Diagnostic and Treatment Centers (ADDTC; Chui et al., 1992), the DSM-IV (American Psychiatric Association, 1994), and the ICD-10 (World Health Organization, 1993) criteria, start off with a classical notion of dementia with memory impairment, diagnosis being further specified in various ways by stroke history details, neuroimaging, and the specific features of cognitive impairment. The ADDTC criteria differ from the others somewhat. The 2014 VASCOG criteria improve on these criteria by modifying the cognitive domain criteria to better take into account the frontal-executive-type deficits over memory deficits, recognize pre-dementia-level cognitive disability, define impairment due to mixed etiology, and define the types of vascular pathology more broadly.

According to the VASCOG criteria a diagnosis requires one or more of the following cognitive domains to be affected: attention and processing speed, frontal-executive function, learning and memory, language, visuoconstructional-perceptual ability, body conception, and social cognition. The deficit is defined as mild or major—corresponding to VaD—based on objective domain measurements and on the disability caused by the impairment. The diagnosis also requires evidence of significant cerebrovascular disease. Neuroimaging is emphasized in determining brain lesions and to rule out other disorders. Imaging results are to be interpreted in light of the clinical presentation and the temporal development of symptoms, and the result is a diagnosis of *probable VCD*. Sufficient evidence from a stroke incident or a clear finding from a neurological examination are permitted as substitutes when imaging is not available thus warranting a diagnosis of *possible VCD*. In VCDs, cognitive symptoms often present more severely in the acute phase and symptoms may be alleviated later. A period of 3 months is set as a threshold value for persistent symptoms. The rate of progression and fluctuation of symptoms may vary due to the specific etiology, e.g. small vessel disease may present with fluctuating symptoms due to several successive events. Exclusion criteria include features such as memory deficit as the early leading cognitive impairment as well as Parkinsonism.

It is common to find multiple processes impairing cognition at the same time. Alzheimer's pathology is often accompanied with vascular changes, and vascular pathology decreases the threshold for clinical Alzheimer's disease. The VASCOG guidelines recognize this clinical challenge and encourage choosing the most promi-

nent diagnosis, recognizing the uncertainty of the diagnosis, and acknowledging other contributing pathologies.

2.3.2 Pathophysiology

Large vessel disease affects the larger arteries at the cortical level and is typically caused by an atherosclerotic plaque or a cardiac embolus. This leads to a relatively large single cortical infarction or to several smaller downstream infarctions. In many cases focal neurological deficits are apparent alongside cognitive symptoms. *Small vessel disease* refers to the stenosis of smaller perforating arteries in the brain parenchyma. Resulting ischemic changes take the form of lacunar infarcts, white matter lesions, perivascular space dilatation, microinfarcts, and microhemorrhages. Typically, small vessel disease impairs executive functioning and the speed of processing. Depression and gait disturbances can occur. Progression is typically more gradual and focal neurological symptoms are less frequent. Arterial wall defects lead to intracerebral or subarachnoid hemorrhages. Prolonged hypoperfusion can lead to sclerosis, typically of the hippocampus, or take the form of laminar cortical sclerosis. (Erkinjuntti et al., 2015)

No biomarker measured in CSF is specific to VCI. High total tau is indicative of neuronal damage that can be associated with VaD. Brain lesions typical to VaD can be determined using MRI. Bleeds of different calibres are visible, as is thinning of cortical grey matter in small vessel disease. White matter lesions seen on an MRI are typically quantified using the Fazekas scale (Fazekas et al., 1987).

Other angiopathies known to affect arterial function as listed by Sachdev et al. (2014) include e.g. vasculitis, hereditary angiopathies, berry aneurysms, and CAA. In CAA accumulation of Aβ in the walls of small vessels often leads to microhemorrhages or microinfarctions. An in-vivo diagnosis of CAA is based on the localization of microhemorrhages in the cortical and subcortical regions on MRI. Amyloid-PET imaging does not differentiate between Aβ in brain tissue and in the arteries (Gorelick et al., 2011). CAA is a very common vascular pathology found in AD patients (Smith and Greenberg, 2009) and the severities of AD and CAA pathologies are significantly correlated (Attems et al., 2005). Some studies indicate that a higher CAA load may impair cognition independent of other pathologies (Brenowitz et al., 2015). More specifically, CAA on neuroimaging has been associated with cognitive decline before the first clinically presenting intracerebral hemorrhage (Banerjee et al., 2018).

2.4 LEWY BODY DEMENTIAS

Lewy body dementias comprise of the disease identities *dementia with Lewy bodies* (DLB) and *Parkinson's disease dementia* (PD-D), conditions that account for a significant portion of dementia cases in older age groups. Dementia prevalence increases with time past the Parkinson's disease diagnosis reaching 50% at 10 years post-diagnosis. The prevalence of DLB in patients with a dementia diagnosis is estimated to be up to 23%. It is estimated that DLB is an underdiagnosed condition, probably due to

difficulties in differentiating between it and AD. (Walker et al., 2015)

According to the 2005 DLB Consortium criteria (McKeith et al., 2005), in addition to dementia-level functional impairment, a DLB diagnosis requires the presence of core DLB features: fluctuating cognition, recurrent visual hallucinations, and spontaneous parkinsonism. Supporting features include disturbances in sleep structure, changes on brain metabolism imaging, and specific changes on electroencephalography. These criteria have been proven to be specific but not very sensitive (Walker et al., 2015). DSM-V defines *major neurocognitive disorders with Lewy bodies* similarly. PD-D is diagnosed according to criteria published in 2007 (Emre et al., 2007). In addition to established Parkinson's disease the criteria require impairment in attention, executive function, visuospatial function, or free recall; and supporting features such as apathy, depression, and delusions are acknowledged. To differentiate DLB from PD-D, dementia should not present more than one year after the start of Parkinsonism. In general, cognitive deficits in Lewy body dementias are characterized by impaired executive function and visuospatial capabilities in contrast to AD-dementia episodic memory impairment. (Erkinjuntti et al., 2015)

α-synuclein, a protein functional in presynaptic terminals in the brain, is the primary component of Lewy bodies. The pathological mechanism of the formation of these bodies is unclear similarly to the accumulation of Aβ in AD. No clear picture has emerged on risk factors of α-synuclein accumulation. The bodies are associated with neuronal dysfunction in their vicinity, but whether the formation of these inclusions has a protective effect or if they represent upstream pathological processes is unknown. In PD-D, α-synuclein pathology is thought to be more strongly associated with dementia than in DLB, where mixed etiology with Aβ is thought to play a significant role. The severity of dementia in PD-D and DLB is associated with the level of AD-type pathology present, whereas there is little evidence of concurrent vascular pathology having an effect. There are known autosomal dominant mutations that lead to Lewy body dementias or Parkinson's disease, and there is some evidence of additional familial clustering of DLB not explained by them. The APOE ϵ4 allele is associated with elevated risk of Lewy body dementias but not to the extent of AD. (Walker et al., 2015)

Imaging of α-synuclein pathology is currently not possible, but single photon emission computer tomography and metabolic PET for hypoperfusion and hypometabolism have shown distinct occipital-lobe patterns in Lewy body dementias that are not seen in AD (Minoshima et al., 2001). These tests are recognized as supportive features in the 2005 DLB criteria, and they can aid in the differential diagnosis of α-synucleinopathies and AD. α-synuclein levels in cerebrospinal fluid have been shown to some extent discriminate between dementia with Lewy bodies and AD, whereas CSF Aβ has been shown not to (Walker et al., 2015).

2.5 OTHER DEMENTIAS

Frontotemporal dementia (FTD) refers to a variety of syndromes which affect the frontal and temporal neocortices. The clinical phenotype varies according to the exact region that is affected, and the type of neuropathology also varies. Generally, the syndromes are characterized by behavioral changes, executive dysfunction, and difficulties in language. The clinical presentation can be similar to psychiatric conditions, and a differential diagnosis may be difficult. Clinical subtypes include *behavioural-variant* FTD with a prefrontally and temporally dominated pathology, and *primary progressive aphasia* of the *non-fluent variant* with a left-frontotemporal dominated pathology and of the *semantic variant* with temporally dominated pathology. As the disease progresses, the symptoms of the subtypes tend to converge as the pathology spreads. Neuropathologically, three types of pathology are recognized: 30–50% of cases are tau dominated, in 50% of the cases TAR DNA-binding protein with a molecular weight 43 kDa (TDP-43) is found in the form of intracellular inclusions, and about 10% show fused-in-sarcoma protein inclusions. Structural MRI and metabolic PET show regional cortical atrophy and metabolism, and amyloid PET is used to differentiate FTD and AD. FTD has a higher relative incidence in younger age groups compared to other types of dementia, and a number of risk genes have been recognized. Most of the inherited disease cases are due to the genes C9orf72 and GRN, resulting in TDP proteinopathy, and MAPT, resulting in tauopathy. (Bang et al., 2015; Erkinjuntti et al., 2015)

Hippocampal sclerosis (HS) is a somewhat unspecific pathological finding that has a relatively high prevalence in the very old. Historically, in cases where HS had clearly dominated typical AD pathology and an amnestic impairment was present, the term hippocampal sclerosis dementia was used (Cykowski et al., 2017). More recently HS has been strongly associated with cortical TDP-43 accumulation, and has been shown to also commonly present with AD and LBD pathology (Nag et al., 2015). HS without other neuropathology seems to be rare (Kero et al., 2018), and HS without TDP-43 pathology seems to not be associated with cognitive decline (Nag et al., 2015). Discussion is ongoing on how to conceptualize HS-related syndromes: HS dementia has been suggested to be an amnestic variant of frontotemporal degeneration due to similarities in pathology (Onyike et al., 2013). To differentiate from other degenerative disorders, Nelson et al. (2016) suggest the term *cerebral age-related TDP-43 with sclerosis* (CARTS) to be used independently for this type of pathology. Cykowski et al. (2017) suggest further to differentiate between CARTS and AD or FTD with concomitant TDP-43 pathology.

2.6 RISK FACTORS FOR DEMENTIA AND BRAIN PATHOLOGY

Epidemiological studies have revealed risk factors for cognitive decline and dementia, and for certain specific disease etiologies. In general, pathological processes leading to dementia are still largely unclear, which is reflected in the difficulties of linking risk factors to a specific pathological process, or to dementia or declining cognition

more broadly. Dementia shares well-known risk factors with e.g. cardiovascular disease, but the exact underlying mechanisms are not yet fully known.

For dementia, several risk factors have been recognized. Incidence of all-cause dementia increases exponentially with age (Jorm and Jolley, 1998). The incidence pattern for AD is similar, but for VaD there is greater variability in different populations. The incidence of AD in very old age is higher in women, and the VaD incidence is higher in younger men (Jorm and Jolley, 1998). There is clear evidence of familial susceptibility to dementia (Loy et al., 2014), partly due to the effect of specific risk genes that have been identified.

Age and genes are immutable personal characteristics that cannot be influenced. Research into preventable risk factors has produced a large number of tentative risk factors related to somatic and mental health, socioeconomic status, and lifestyle. The data are mostly observational, but randomized controlled trials do exists for some, like blood pressure and hypercholesterolemia. However, in many cases the results are mixed. Table 2 lists a number of potentially preventable risk factors for dementia and gives an estimate made by the Alzheimer's Association on the level of evidence concerning the association with dementia (Baumgart et al., 2015). In 2017, the National Academies of Sciences, Engineering, and Medicine and Health released a report outlining recommendations on interventions for some well-established risk factors and also outlined research priorities for risk factors with insufficient data. Three interventions were indicated as promising based on the current status of evidence: cognitive training, blood pressure control in midlife, and increasing physical activity. The National Academies of Sciences assessments have also been included in Table 2.

2.6.1 Education

A person's history of education and cognitive exertion seems to be associated with the timing and rapidity of cognitive decline in advanced age. A low level of education has been linked to AD-dementia risk in a comprehensive meta-analysis (Caamaño-Isorna et al., 2006). A later systematic review by Meng and D'Arcy (2012) confirmed this for the risk of AD-dementia, VaD, and unspecified dementia. In that review, most of the substudies reporting on brain pathology also found more severe pathological changes in individuals with a higher education. These findings are in line with the cognitive reserve hypothesis stating that high education and other forms of cognitive training lead to higher resilience of the brain against pathological lesions and that this elevates the threshold level at which cognition is impaired.

There is some evidence to suggest that cognitive reserve may have a slowing effect on the accumulation of Aβ itself (Lo et al., 2013; Yasuno et al., 2015). Studies have also shown an association between altered brain structure and certain surrogate markers of cognitive reserve (Xu et al., 2015) and a higher cognitive reserve has also been linked to changes seen in functional MRI (Anthony and Lin, 2018).

Table 2: Dementia risk factors and protective factors. Alzheimer's Association (AA) assessment of level of evidence on association (Baumgart et al., 2015) and National Academies of Sciences, Engineering, and Medicine and Health (NAS) recommendation on intervention (National Academies of Sciences, Engineering, and Medicine and Health, 2017).

Effect	Factor	Level of evidence on association (AA assessment)	Recommendation for intervention (NAS assessment)
Risk factors	Traumatic brain injury	Strong	—
	Midlife obesity	Moderate	—
	Midlife hypertension	Moderate	Intervention supported[†]
	Current smoking	Moderate	—
	Diabetes	Moderate	Priority for research[‡]
	History of depression	Unclear	Priority for research[‡]
	Sleep disturbances	Unclear	Priority for research[‡]
	Hyperlipidemia	Unclear	Priority for research[‡]
	Vitamin B12 deficiency[1]	—	Priority for research[‡]
	Hearing loss[2]	—	—
	Particulate air pollutants[2]	—	—
Protective factors	Years of formal education	Strong	—
	Physical activity	Moderate	Intervention supported[†]
	Mediterranean diet	Lower	Priority for research[‡]
	Cognitive training	Lower	Intervention supported[†]
	Moderate alcohol consumption	Unclear	—
	Social engagement	Unclear	Priority for research[‡]

[†]: Evidence of intervention to prevent Alzheimer's-type cognitive decline is encouraging but inconclusive. Recommendation based on evidence, neurobiological plausibility, and benefits to general health. [‡]: Insufficient evidence to recommend intervention, additional research needed. —: No statement made on risk factor. For additional references see [1]: (Ford and Almeida, 2019), [2]: (Livingston et al., 2017), and [3]: (Baumgart et al., 2015).

2.6.2 Risk genes and causal mutations

Apolipoprotein E (APOE) gene polymorphism has been linked to the incidence of AD (Saunders et al., 1993). APOE in peripheral tissue takes part in the uptake of lipoproteins such as high-density lipoprotein (HDL) and low-density lipoprotein (LDL) in the liver. APOE does not cross the blood–brain barrier (BBB). APOE found in the brain and the CSF is produced by the brain parenchymal cells, but its function is unclear. Three major alleles can be found in the population: the major type is $\epsilon 3$, while $\epsilon 4$ is the second most common, and $\epsilon 2$ is the most infrequent. The $\epsilon 4$ allele is the risk allele. A heterozygous $\epsilon 4$ genotype increases the risk of AD threefold and a homozygous genotype 8–12-fold, and $\epsilon 4$-carrying AD patients are typically younger than noncarriers (Alzheimer's Association, 2016). $\epsilon 2$ may be AD-protective (Corder et al., 1994). Frequencies of the risk allele $\epsilon 4$ in populations around the world range between 8% and 31% (Eichner et al., 2002). APOE is an important consideration in dementia research, and the effect of its polymorphism is routinely taken into account in the study of dementia risk factors. The other known risk genes are known to be associated with the metabolism of APP and lipids, and with the immune system (Erkinjuntti et al., 2015). An AD-protective variant of the APP gene has also been found (Jonsson et al., 2012). The protective effect is mediated by altered β secretase cleavage.

For non-sporadic AD, causal gene mutations have been found in the APP, PSEN1 and PSEN2 genes. Changes in the APP amino acid sequence increase the proportional output frequency of the Aβ42 subtype, and so do mutations in the γ secretase coding PSEN1 and PSEN2 genes. Down syndrome patients frequently show neuropathology similar to AD patients (Mann, 1988), possibly due to them having three alleles of APP.

2.6.3 Cardiovascular risk factors

There is an established link between the health of the cardiovascular system and the risk factors affecting it, and cognitive decline, dementia, and some of the specific underlying diseases (Power et al., 2011).

Hypertension

The association between hypertension and dementia has long been studied in cross-sectional and longitudinal studies. Age-specific effects have been found, but the results have to an extent been mixed. Some studies report on dementia overall, while some report separate results for AD and VaD, and the data is either measured or self-reported. A meta-analysis by Power et al. (2011) investigated populations with baseline mean ages 50-74 and found no association between the reported hypertension history or current hypertension and AD. Three studies investigated mid-life ($<$65 years) measured hypertension in association with AD and only one of those reported a positive association between highly elevated mid-life systolic blood pressure (SBP) and incident AD (Kivipelto et al., 2001b). Another study included in the review found suggestive evidence for a nonlinear effect where both low and high SBP indicated

higher risk of AD (Launer et al., 2000). An adverse effect of increased mid-life diastolic hypertension on incident AD was suggested by the pooled analysis, although no single study reached statistical significance. In their study, Launer et al. (2000) verified the effect of high mid-life SBP on higher incidence of VaD, whereas with diastolic blood pressure (DBP) there was no effect. A systematic review by Sharp et al. (2011) looking specifically at hypertension and VaD found a history of hypertension and measured hypertension to be clearly associated with both a higher prevalence and higher incidence. For all-cause dementia, a recent study found hypertension at a relatively low cut-off value of SBP>130 mmHg at 50 years of age to be associated with increased risk and this was independent of other cardiovascular diseases (Abell et al., 2018).

For late-life-measured BP, three studies with measured values in the meta-analysis by Power et al. (2011) reported a consistent but nonsignificant protective effect of high DBP. SBP measures indicated a similar effect but less consistently. A 9-year-follow-up of over-85-year-olds (Rastas et al., 2010) reported a protective effect of history of hypertension on incident dementia, however measured baseline BP did not show this association. A 3-year follow-up study of subjects over the age of 65 by Hayden et al. (2006) reported a positive association between hypertension and incident VaD in women and a negative association between hypertension and AD in both genders. More recently, Corrada et al. (2017) found the self-reported onset of hypertension only after the age of 80 and 90 to be associated with decreasing incidence rates of dementia compared to controls with no hypertension.

Walker et al. (2019) found two mid-life–late-life BP profiles to be associated with high dementia risk: both sustained hypertension from mid-life to late-life and the development of mid-life to late-life hypotension indicated elevated risk.

Observational studies have shown the use of antihypertensive drugs to reduce the risk of both VaD and AD (Rouch et al., 2015). Interventions treating elevated BP have shown a positive effect on cognitive decline, but not conclusively on dementia. Less than half of 11 randomized trials analysed by Rouch et al. (2015) found a significant effect on cognitive decline or dementia with a maximal follow-up time of 4.5 years within the trials. A large SPRINT MIND trial recently showed a benefit of aggressive BP control over traditional BP targets in terms of incidence of MCI and incidence of either dementia or MCI, but was only suggestive for lower incidence of dementia (SPRINT MIND Investigators for the SPRINT Research Group, 2019). In the same study, more aggressive treatment was associated with a lesser increase of white matter (WM) lesion volume and greater a decrease in brain volume (SPRINT MIND Investigators for the SPRINT Research Group, 2019).

There is other supporting neuropathological evidence for the association of brain lesions with BP. A longitudinal study by Petrovitch et al. (2000) on the effect of midlife hypertension on brain pathology during a 36 year follow up provided insights into the underlying brain changes: in those with elevated mid-life SBP, more Aβ plaques were found in the neocortex and the hippocampus, and the brain weight was also lower. Elevated DBP was associated with increased counts of neurofibrillary tan-

gles in the hippocampus. A more recent cross-sectional study by Jeon et al. (2019) in a stratified analysis showed differences in the association of hypertension with brain pathology in cognitively normal subjects and in those with AD-dementia: hypertension in cognitively normal APOE-ϵ4 noncarriers was associated with a lower cortical thickness in AD signature regions, but not Aβ accumulation, whereas ϵ4 carriers with hypertension had a higher rate of Aβ accumulation. Among AD-dementia subjects, hypertension was associated with lower Aβ deposition irrespective of the APOE genotype.

Kennelly et al. (2009) summarize the mechanisms by which elevated BP—in combination with other cardiovascular risk factors—causes VaD-related pathology. Damage to the arterial wall in the form of reactive thickening of the media and development of atheromatous material predispose the vessel for local thrombi. Cardiac failure and atrial fibrillation are cardiac outcomes of hypertension that may lead to embolus formation and infarctions.

Hypercholesterolemia

Changes in cholesterol metabolism have been associated with all-cause dementia and especially with AD-dementia. High midlife total cholesterol has consistently been associated with a higher rate of incident all-cause dementia in later life in systematic reviews (Kivipelto and Solomon, 2006; Anstey et al., 2017). For late-life cholesterol, these reviews showed no association with incident dementia. Anstey et al. (2008) analysed studies that established normal cognition at the baseline and had available data on dementia etiology at the follow up. Although such studies consistently found a link between mid-life high cholesterol and AD-dementia specifically, no association with VaD was found. A later study did find an association with both AD and VaD in a 30-year follow up (Solomon et al., 2009). A decline in cholesterol levels from midlife into old age has been associated with higher AD rates (Anstey et al., 2017). Studies looking at other dyslipidemias do not form a uniform body of evidence. Some studies have reported not finding an association between cognitive decline/dementia or high triglycerides and high density lipoprotein (Anstey et al., 2017).

Four trials targeting individuals with high cholesterol found no effect on cognitive performance or incident dementia in follow-ups ranging from 6 months to 5 years (National Academies of Sciences, Engineering, and Medicine and Health, 2017). Combination therapy where statins are accompanied by drugs inhibiting gut cholesterol uptake did not produce better results. Geifman et al. (2017) found evidence for potential intervention benefits in homozygous APOE ϵ4 carriers in subgroup analyses.

Cholesterol metabolism is essential for brain function, and brain cholesterol has been linked to neurodegenerative diseases including AD (Björkhem, 2006). APOE is closely related to cholesterol metabolism. Although the brain and peripheral cholesterol pools are separated by the blood-brain barrier, they can interact via metabolites such as oxysterols (Björkhem, 2006). Hypercholesterolemia may also increase the risk of dementia through the vascular pathway, i.e. increased risk of cardio- and cere-

brovascular disease.

Obesity

Obesity has a high comorbidity with other cardiovascular risk factors, most importantly metabolic syndrome, type 2 diabetes, and hypertension. Meta-analyses and systematic reviews have reported on the effect of body composition throughout the life course. Midlife overweight (body mass index, BMI, in $\mathrm{kg/m^2}$ from 25.0–27.5 to 30.0) and/or obesity (BMI $>$30) has been found to be associated with all-cause dementia (Anstey et al., 2011), AD (Beydoun et al., 2008; Profenno et al., 2010; Anstey et al., 2011), and VaD (Anstey et al., 2011). A stable BMI into old age was not associated with dementia (Anstey et al., 2011), but weight gain seemed to be (Beydoun et al., 2008). Beydoun et al. (2008) found associations with AD and VaD to be stronger with longer follow-up times and younger baseline populations. Midlife underweight has been associated with all-cause dementia (Beydoun et al., 2008) and AD (Anstey et al., 2011). Old-age overweight has been found to be associated with a lower risk of dementia (Baumgart et al., 2015). A large meta-analysis of BMI and incident dementia over different time periods demonstrated this reversion of association: BMI was shown to be a risk factor over decades-long follow-up periods and protective over periods of less than ten years (Kivimäki et al., 2018). The authors hypothesize that over shorter periods weight loss may be caused by preclinical dementia showing a pattern of reversed causality.

Trials investigating the effect of increased physical activity on dementia have been promising (National Academies of Sciences, Engineering, and Medicine and Health, 2017), but the extent to which the effect is due to body weight is unclear. Other potential mechanisms include improved insulin sensitivity, reduction in hypertension or high cholesterol, or neurological effects (Livingston et al., 2017).

Cardiovascular conditions

Specific cardiac conditions have been studied in association with cognitive decline and dementia. Atrial fibrillation (AF) is a risk factor for dementia not only through its association with stroke (5-fold risk of stroke in AF), but also independent of prior stroke (Aldrugh et al., 2017). Non-stroke hypothesized causal explanations include cerebral hypoperfusion and possibly associated altered Aβ metabolism, vascular inflammation, small vessel disease, and brain atrophy. Similar mechanisms may underlie the association between dementia and heart failure, a condition often secondary to a coronary conditions like coronary heart disease (CHD) or AF. Systematic reviews have confirmed the positive association between heart failure and cognitive impairment (Cannon et al., 2017) and dementia (Wolters et al., 2018), and also that between CHD and dementia (Wolters et al., 2018).

Cardiorespiratory fitness

Overall cardiorespiratory fitness (CRF) as measured by the maximum oxygen consumption has been associated with better measured cognition in a cross-sectional analysis (Freudenberger et al., 2016) as well as in a longitudinal follow-up setting (Pentikäinen et al., 2019). A study by Schultz et al. (2015) was able to link this effect to AD pathology in that they found better CRF to be protective of the harmful effects of Aβ accumulation. CRF—an aggregate measure—has been associated with hypercholesterolemia, impaired fasting glucose, diabetes mellitus, hypertension, and a high BMI (Erez et al., 2015). The association between CRF and cardiac outcomes during follow-up was shown to be mediated by hypercholesterolemia, diabetes mellitus, and obesity.

2.6.4 Insulin resistance and diabetes

Diabetes mellitus (DM) is a growing problem in modern societies, especially type two diabetes (DM2) with its overall prevalence rising due to an aging population and changing lifestyles. The pattern is similar to dementia in terms of the aging population. Additionally, the conditions share etiological features. The APOE $\epsilon 4$ allele is a known risk factor of AD, and the APOE gene is a regulator of glucose and lipid metabolism (Cheng et al., 2012). Two meta-analyses have confirmed higher dementia incidence rates to be associated with DM (Cheng et al., 2012; Gudala et al., 2013). The effect was reported for all-type dementia, AD-dementia, and VaD, but the relative risk was clearly higher for VaD in both studies. Micro- and macrovascular diseases are well-known complications of DM, and thus the association with VaD is understandable. The effect was not mediated by APOE status. The mechanisms linking DM and AD are still unclear. Hypotheses include vascular and metabolic processes including insulin resistance, but no definitive link to disease progression or pathology has been made (Gudala et al., 2013). Ahtiluoto et al. (2010) found older individuals with DM to have higher dementia incidence rates, and in autopsy to have lower levels of Aβ and tau pathology and more vascular pathology. An analysis by Moran et al. (2015) across different diagnostic groups found DM2 to intensify tau pathology but not Aβ. Roberts et al. (2014) linked DM diagnosis with AD-type brain hypometabolism patterns but found no association with AD-type Aβ accumulation.

Insulin resistance in peripheral tissue is a hallmark of DM2. In recent years research has been done on insulin resistance in the periphery and also in the central nervous system in relation to neurodegeneration. Peripheral insulin resistance (IR) is typically quantified using the homeostasis model assessment for insulin resistance (HOMA-IR=[Insulin] $\cdot$ [Glucose] $\cdot$ constant) index value. For brain IR, a new tentative blood biomarker has been suggested (Kapogiannis et al., 2015). In prediabetic and diabetic subjects higher peripheral IR has been linked to similar brain hypometabolism patterns on PET as seen in AD patients (Baker et al., 2011), a result which is analogous to findings for DM. No association has been found between late-life IR in cognitively healthy elderly and CSF Aβ (Laws et al., 2017) or Aβ on PET (Ekblad

et al., 2018). There does not seem to be an Aβ association in MCI or AD subjects either (Laws et al., 2017). Results in younger populations have been mixed (Willette et al., 2015; Westwood et al., 2017; Ekblad et al., 2018). An association between long-lasting IR and neurodegenerative changes on MRI—including hippocampal atrophy—has been reported (Korf et al., 2006).

Association with brain insulin metabolism

Brain glucose metabolism is regulated in part by insulin-independent glucose transporters at the BBB and also by insulin-dependent transporters at the BBB and in plasma membranes of parenchymal brain cells. It is nowadays known that insulin plays a role in brain metabolism and signaling, whereas before the brain was thought to be indifferent to insulin signaling. Insulin presents itself manyfold in the central nervous system: peripheral insulin is transported through the BBB, there are insulin-activated signaling pathways through the BBB, and there is endogenous insulin production in certain regions of the brain. Insulin receptors of the BBB are known to decrease in number with aging and long-term blood hyperinsulinemia. It is hypothesized, that constant peripheral IR and associated hyperinsulinemia are linked to a decrease in brain insulin-dependent glucose intake. Furthermore, the pattern of insulin transporter types varies by brain region and some regions may be more dependent on insulin-dependent glucose intake. This may make these regions more sensitive to other pathological insults such as those seen in AD. The reason for and mechanism of brain insulin production and uptake are still unclear, but it is hypothesized that insulin signaling might be linked to neuroprotective mechanisms. Brain insulin resistance may be linked to brain degradation through these mechanisms. Another hypothesis suggests brain IR to promote oxidative stress, possibly a catalyst of Aβ and tau pathology. Oxidative stress is also linked to metabolic syndrome and obesity, which are upstream stages of the IR–DM progression. (Diehl et al., 2017)

Some insight into the interplay between insulin and Aβ has been gained in mice. In a healthy brain insulin has been shown to promote amyloid clearing. Aβ seems to suppress insulin receptor levels as well as interfere with insulin receptor function thus downregulating the effect of insulin in the brain and resulting in lower Aβ clearance. Furthermore, Aβ and insulin are both cleaved by the insulin-degrading enzyme (IDE). Hyperinsulinemia may thus lead to lower levels of Aβ cleavage. IDE also apparently only cleaves monomeric Aβ. It has also been confirmed that in APOE ϵ4 positive AD patients hippocampal IDE levels are lower than in controls. (Diehl et al., 2017)

2.6.5 Lifestyle

Several lifestyle factors seem to be associated with dementia. Smoking in old age has been linked to incident dementia according to several studies (Baumgart et al., 2015), and mid-life heavy smoking was a strong predictor of late-life dementia according to Rusanen et al. (2011). Meta-analyses have found higher physical activity to be protective against cognitive decline (Sofi et al., 2011) and also protective against dementia

and AD (Hamer and Chida, 2009). A more recent review found leisure time physical activity to be more important than work-related activity in terms of AD incidence (Stephen et al., 2017a). There is evidence from a meta-analysis of light to moderate alcohol consumption being protective against all-cause dementia, AD, and VaD, when compared to no consumption (Anstey et al., 2009), but these results may partly be due to selection bias and due to the fact that most studies do no differentiate between abstainers and persons who have quit drinking.

Some nutrients and food groups have been associated with dementia, although evidence is weaker than for some other risk factors modalities (Baumgart et al., 2015). In case of cognitive decline more broadly, a Mediterranean diet as a dietary pattern and B vitamins, some antioxidants, vitamin D, and unsaturated fatty acids as specific nutrients have been associated with a protective effect on cognition in many studies (Scarmeas et al., 2018).

2.6.6 Psychosocial

Depression is a comorbid state related to dementia, and depression is associated with a two-fold prevalence of dementia in old age (Cherbuin et al., 2015). Study of the causality of the two is difficult. However, depression in midlife has been associated with increased dementia incidence in late life supporting the view that depression might be a preventable risk factor (Byers and Yaffe, 2011). A feeling of hopelessness—a very common symptom of depression—in midlife also had a similar association (Håkansson et al., 2015). Depression may be a result of minor damage due to cerebrovascular disease coinciding with cognitive impairment of the vascular type. Depression and dementia are also linked through several risk factors, such as physical inactivity, metabolic syndrome, and low-grade inflammation. As for AD-related pathology, depression is linked to elevated cortisol levels, and cortisol may induce atrophy of the hippocampus. Additionally, AD patients with depression have been reported to have higher Aβ accumulation in the hippocampus compared with nondepressed patients possibly due to increased cortisol. (Byers and Yaffe, 2011)

The CSF Aβ profile of older adults with depression resembled that of AD patients in a meta-analysis (Nascimento et al., 2015). There is no good-quality data on the effects of treatment of depression on the dementia incidence. Observational studies with very short follow-up times have shown both improvement and impairment of cognition (National Academies of Sciences, Engineering, and Medicine and Health, 2017).

Low social participation, loneliness, and infrequent social contacts have been associated with impaired cognition in a meta-analysis (Kuiper et al., 2015). A higher level of social activity has been suggested to be protective, but no prevention study data is available for the isolated effect of improved social engagement on cognition and dementia (National Academies of Sciences, Engineering, and Medicine and Health, 2017).

Table 3: Examples of risk factor combinations in midlife and late life modulating the risk of dementia.

	Potentiating combinations	Attenuating combinations
Midlife effects	– High alcohol consumption, smoking, low physical activity and saturated-fat intake have higher effect in APOE ϵ4 carriers. – Concurrent hypertension, obesity, high cholesterol, and low physical activity all add to risk independently.	– Education somewhat mitigates the risk increase due to APOE ϵ4. – Physical activity reduces the risk due to APOE ϵ4. – Risk due to low education is affected by complexity of occupational activity.
Late-life effects	– Chronic heart failure, low pulse pressure, and low DBP contribute to brain hypoperfusion and higher risk. – High SBP, DM or prediabetes, and stroke indicate atherosclerosis/vascular damage and higher risk of dementia.	– Risk due to APOE ϵ4 is mitigated by leisure time activities and lack of vascular risk factors.

Table adapted from Solomon et al. (2014a). **Key**: APOE apolipoprotein E, DBP and SBP diastolic and systolic blood pressure, DM diabetes mellitus.

2.7 A MULTIMODAL APPROACH TO DEMENTIA RISK MANAGEMENT

The interactions between the aforementioned risk factors is an important field of study, especially with future preventive interventions in mind. Prevention trials targeting a single risk factor have shown no clear benefits in terms of dementia as a primary outcome, nevertheless, a positive effect on cognition has been seen in the case of BP, for example. A multimodal approach to dementia risk management may be needed in the future. Solomon et al. (2014a) list examples of observed combination effects of risk factors. Table 3 shows how the effects of vascular risk factors vary along the life course and APOE gene polymorphism interacts with life-style and cardiovascular risk factors.

The recommendation report by the National Academies of Sciences, Engineering, and Medicine and Health (2017) not only stated priorities for single-domain interventions (see Table 2), but also indicated that multidomain interventions are needed to investigate effective dementia prevention strategies. The aim would be to target multiple risk factors concurrently and possibly affect several pathological disease processes. Several large-scale controlled trials with multidomain intervention strategies are underway, or have already published results. The Prevention of Dementia by Intensive Vascular Care (PreDIVA) randomized controlled trial (RCT) tested the efficacy of a nurse-led interventions targeting several cardiovascular, metabolic and lifestyle risk factors in an older age group in a primary health care setting, but the study failed to show an effect on dementia as the primary outcome during the 6 year follow up (Moll van Charante et al., 2016). The Finnish Geriatric Intervention Study to Pre-

vent Cognitive Impairment and Disability (FINGER) combined further domains in an RCT targeting at-risk individuals as discussed in more detail in section 4.3. The intervention group was given cognitive training and provided with social activities, guidance on nutrition, an exercise program at the gym, and monitoring and management of cardiovascular and metabolic risk factors. The first results did show a statistically significant benefit to cognition as a primary outcome, and some subdomains of cognition were also positively affected (Ngandu et al., 2015). In the Multidomain Alzheimer's Prevention Trial (MAPT) cognitive training and increased physical training were combined with nutritional guidance and an omega-3 fatty acid supplement, but in this older population with baseline subjective memory complaints there were no significant differences in the primary cognitive outcome between any of the three intervention groups and the placebo group (Andrieu et al., 2017). However, post-hoc analyses of high-risk groups defined in terms of elevated Cardiovascular Risk Factors, Aging and Dementia (CAIDE) dementia risk score (Chhetri et al., 2018) and brain Aβ positivity (Delrieu et al., 2019) indicated positive effects. Another ongoing trial is trying to reduce the cardiovascular risk and maintain cognitive function with a coach-supported interactive internet-based intervention for good diet, physical activity, and smoking cessation (Barbera et al., 2018).

Trials with positive findings have been able to show benefits to cognition as measured by a global index, or in specific subdomains of cognition. No study has been able to demonstrate an effect on incident dementia. Out of the large multidomain RCTs only PreDIVA was designed to do that within a 6-year follow-up time. They found effects in at-risk subpopulations that were not evident in the general intervention population. These observations highlight the need for more efficient population enrichment procedures. One future priority for intervention trials is to improve the subject-selection methods by identifying those at increased risk of incident dementia or possibly those with subclinical disease pathology who are likely to benefit from the specific intervention (National Academies of Sciences, Engineering, and Medicine and Health, 2017). Disease-specific biomarkers of pathology may prove to be valuable in subject selection, but they can also be helpful in monitoring intervention effects. Further research is needed in linking biomarker-characterized pathology and clinical outcomes (National Academies of Sciences, Engineering, and Medicine and Health, 2017).

2.8 DEMENTIA RISK MODELS AND SCORES

2.8.1 Definition of the prediction problem in a medical context

Risk modeling in medicine is multifaceted and has clinical applications for example in diagnostics, patient selection and outcome prediction, primary prevention targeting, and prediction of disease progression. Practical examples include the Systematic Coronary Risk Evaluation (SCORE; Perk et al., 2012) for prediction of cardiovascular fatality over 10 years, the Ottawa ankle rule for prediction of fracture and the need for a radiograph in acute trauma (Stiell et al., 1992), and the quick Sequential [Sepsis-

related] Organ Failure Assessment (qSOFA; Singer et al., 2016) for prediction of high mortality risk in septic patients. The term prediction is used here for the deduction of an outcome (e.g. fracture yes/no, probability of survival at 5 years) based on a single data point or by combining multifactorial data on the patient. The algorithm producing this mapping between multifactorial data (predictors) and the outcome is here defined as a *prediction model*. The outcome is often expressed as a binary result, but it should be noted that the context of the prediction model gives it a statistical interpretation in terms of the model's sensitivity, specificity, positive predictive power etc. The time perspectives of prediction models vary: models predicting the future are called *prognostic*, and models in a cross-sectional setting are referred to as *diagnostic* (Collins et al., 2015). There are no methodological differences in the construction of the two types of models, but the interpretation of the outcome measure determines the time frame (e.g. logistic regression). Other models, the Cox's proportional hazards model for example, incorporate time explicitly to form prognostic predictions.

Inputs of the model ultimately determine the quality of prediction. There are broadly two approaches to prediction model building. Predictors may be meaningfully determined a priori based on knowledge on the biological process or on epidemiological data on association with the outcome being modelled. In data-driven model building, an algorithm determines the inclusion and weighting of candidate predictors. In prognostic models the inclusion of a predictor naturally suggests a causative relationship with the outcome, but this does not necessarily have to be the case. In diagnostic models the association between predictors and the outcome can be mediated by causation, disease symptoms, or biological markers of the disease process, for example.

In the case of prognostic disease prediction models, predictors often include risk factors that have been associated with the condition in epidemiological studies. In the best case causality may have been established in an RCT. In the medical field, however, patient data is usually difficult to obtain due to ethical considerations, costs, or data quality issues. This puts constraints on the selection of model inputs, and models differ in terms of breadth and complexity of data. Demographic and patient-record data can be obtained without physical contact, and self-reported data and basic clinical measurements can be gathered by lower-skilled staff. More complex laboratory and imaging analyses requires higher-skilled medical staff. From the patient's point of view some examinations are more invasive and may bear risks in form of complications or radiation dose. Indeed, some prediction models are designed to reduce the need for additional analyses, and the Ottawa ankle rule is an example. The complexity of a prediction model is determined by the set of predictors. Complex multidomain models may incorporate predictors from multiple domains (e.g. demographic, imaging, and laboratory), whereas a simpler single-domain model could include only disease genealogy, for instance.

Prediction models are constructed in a specific research setting with a specific subject population and known method restrictions. The characteristics of the target cohort in terms of age, demographic background, and risk factor profile are an

important part of the definition of the model and should be properly communicated. These, and other requirements are defined in the Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis (TRIPOD) Initiative statement aimed at improving reporting standards in the field (Collins et al., 2015).

Prediction models are not only useful in a clinical setting, but also in research. For early phase drug trials, for example, the identification and enrolment of high-risk individuals could increase power of the trial, reduce the number of participants required, or reduce the intervention duration. A well-grounded prediction model can be useful in enriching a study population beyond what can be achieved with the classical approach of defining threshold values for selected risk factors. Solomon et al. (2019) outline two more scenarios where prediction models could be useful. Dementia prevention interventions could be fitted to match specific risk profiles instead of a blanket intervention targeting a broader cohort. Additionally, utilizing prediction model risk estimates as trial outcomes could mitigate the need for long follow-up times. These estimates may prove be useful also in cases where the true outcome is very rare.

2.8.2 Diagnostics of a prediction model

The quality of a prediction model is expressed using established statistical measures including sensitivity, specificity, positive and negative predictive value, and accuracy. These statistics should be used and reported together, as the choice of prediction model parameters and the tuning of the balance between sensitivity and specificity is to some extent arbitrary. The intended use of the model should guide the setting of parameters and threshold values. For example, in some cases false negative predictions may be potentially life threatening and should be avoided at the cost of specificity. On the contrary, before executing a costly and laborious intervention a very specific model may be preferred for population enrichment.

When setting threshold values for dichotomous yes/no prediction outcomes is not justified, a more general measure of model quality is used. The *receiver operating characteristic curve* is a graphical presentation of model performance in the sensitivity–specificity space used to describe the model's ability to *discriminate* between individuals. The area under the curve (AUC) quantifies the information in this graph in a single index value in the range 0.5–1, where a value of 0.5 equates to a random prediction and 1 indicates perfect prediction. According to the statistical interpretation, AUC represents the probability that the prediction model assigns a randomly chosen true positive case a higher risk estimate than a randomly chosen negative case (Hanley and McNeil, 1982). Hosmer et al. (2013) suggest an experience-based general rule of thumb for AUC interpretation as follows: values less than 0.7 indicate "poor" discrimination, values between 0.7 and 0.8 "acceptable", values between 0.8 and 0.9 "excellent", and values greater than 0.9 "outstanding". The C-statistic (or concordance statistic) for a dichotomous outcome is an analogous measure originally defined in terms of logistic regression (Hosmer et al., 2013). These measures are valid for prediction of a binary outcome at a specific time point. Variations have been

developed for other applications such as survival analysis, for instance.

In the building stage the model is estimated using a *training population*, which is a group of individuals matching the intended cohort characteristics of the model. As a general rule, the prediction performance of the estimated model will typically be superior in the training population compared to what it would be in other data sets (Harrell et al., 1996). Additionally, many model types can be tuned to predict at an arbitrarily high performance level by increasing the model complexity. Hereby the *model fit* increases, but not necessarily the model's usefulness in a general setting. The model needs to be validated against an independent set of data. In *internal validation* the study cohort itself is used by splitting it into a separate training population and a *test population*, against which the performance of the model is reported. For more generalizable and reliable assessment, *external validation* is performed by testing the performance in another, independent, cohort. Studies analyzing the validation procedures used in medical prediction studies have shown deficiencies, and the TRIPOD guidelines also aim to standardize validation reporting (Collins et al., 2015).

2.8.3 Statistical methods underlying prediction models

Regression models are typical underlying statistical methods of prediction models. *Logistic regression* or *Cox proportional hazards models* are ways to quantify associations between predictors and outcomes, and the resulting regression coefficients are good candidates for prediction model weights. In recent decades machine learning methods have increasingly been applied in the medical field leading towards more data-driven models.

A *support vector machine* (SVM) is an example of a statistical method used to categorize multidimensional data into prediction groups. The method relies on setting up a *hyperplane* in the multidimensional space defined by predictor variables in a way that separates groups appropriately—that is, while avoiding overfitting. The hyperplane is set up in reference to the closest data points which the algorithm defines using *support vectors*. In a simpler case a separation in space is obtained using a linear hyperplane, but more complex hyperplanes can be set up by using so called nonlinear *kernel functions*. (Noble, 2006; Suthaharan, 2015)

A data-driven and somewhat more abstract machine learning subspecialty are algorithms consisting of nets or trees. An *artificial neural network* consists conceptually of net nodes and their connections— neurons and synapses. Data flows through the net: model inputs enter the net from one side and an outcome exits the net on the other. Data is transformed at each node. *Decision trees* similarly facilitate processing of the model inputs at branching points starting at the trunk, and consecutive decisions leading towards different outcome categories are represented by leaves. Each branching point represents an item of input data, and at each point a decision is made about the following step. The decision is made based on a threshold value, which is a parameter of the model. The complexity of the models varies depending on the number of layers of nodes/branches. For additional complexity, decision trees can for example be joined to form a *random forest*, in which parallel outcomes of

many trees are consolidated to a consensus outcome, or are vetted against each other in a voting step. These models are fitted to training data. They produce typically black-box-type models without the ability to carry out intuitive interpretations for coefficients. (Graupe, 2007; Suthaharan, 2015)

Whatever the underlying technology of the model, internal validation is needed to assess the generalizability of the model. In *cross-validation* the study population is divided randomly in a set proportion. One subpopulation is used to train the model and the other, nominally independent subpopulation, is used to test the model. In 10-fold cross-validation, for example, 9 out of 10 equally sized portions are used for training and the single leave-out portion for testing. Then, each of the 9 remaining portions are used as the testing population in sequence. This algorithm is repeated a set number of times resulting in 10×10 cross-validation, for example.

Principal components analysis (PCA) is a statistical method used to reduce the dimensionality of high-dimension data. Conveniently, the resulting principal components (PCs) often have conceptual interpretations. A PCA on n-dimensional data results in a set of n PCs. Mathematically, PCs are linear combinations (weighted sums) of original variables with the additional condition that PCs are uncorrelated to each other. PCs are constructed in a way that the first PC attains values (PC scores) that explain a maximal amount of variance in the data. The next PCs are constructed similarly to maximize the coverage of the residual variance. In a typical case, a few of the first PCs together can explain most of the variance in a dataset. Being linear combinations of original variables, PCs often combine original features in a way that may be driven by external—although not necessarily obvious—factors. Examination of PC loadings (weights of the linear combination) can help in assigning interpretations to the PCs. (Dunteman, 1989)

2.8.4 Prognostic prediction of dementia

Prognostic prediction models have been constructed to estimate the risk of incident cognitive impairment of varying severity and in different settings. Models have been developed for predicting the conversion from MCI to AD (AUCs in the range 0.60–0.93), all-cause dementia based on late-life predictors and midlife predictors, specific dementias in late life, dementia in individuals with DM, and dementia in individuals from different educational backgrounds (Hou et al., 2019; Tang et al., 2015). A systematic review by Tang et al. (2015) of models published in the preceding five years (21 articles assessed) found an overwhelming majority of models to be built around a scoring system derived from logistic regression or Cox proportional hazards models. Two were constructed using a priori epidemiological evidence. The authors recognized nine distinct predictor modalities: demographic, subjective cognitive complaints, neuropsychological testing, health (symptoms, diagnoses, and measurements), lifestyle, diet, gene analytics, and MRI. Some models included predictors outside of these categories, for instance family history of dementia or cognitive activity.

A recent review by Hou et al. (2019) identified 46 studies predicting incident de-

mentia in cognitively healthy individuals. Seven of these had been externally validated in terms of their discrimination performance. These seven models are summarized in Table 4. Most are intended for a general population, but two models are built to predict dementia in individuals with DM2, a known risk factor of dementia. The Cardiovascular Risk Factors, Aging and Dementia (CAIDE; Kivipelto et al., 2006) risk score models the midlife risk of developing incident dementia in late life, while most of the other studies predict late-life dementia on a shorter time span of 3–10 years. The Australian National University Alzheimer's Disease Risk Index (ANU-ADRI; Anstey et al., 2013) has an age-adaptable design in that the scores given to predictors are age-dependent in cases where prior research supports this approach. For example, overweight and high cholesterol only increase risk at ages below 60. Additionally, age-related risk is stratified according to sex.

Most models have been built using a data-driven approach, where model predictors have been chosen from an available opportunistic set of variables using statistical testing. Four studies use the Cox proportional hazards model which allows for convenient treatment of attrition in the older cohorts. Two studies utilize a priori evidence on dementia risk factors and build models directly using predetermined predictors. ANU-ADRI is based on a systematic review of potential risk factors and model weights are determined from earlier published estimates. The complexity of the models varies a lot. The most focused prediction model consists of the free-recall score of the Free and Cued Selective Reminding Test (FCSRT-FR)—this model is also among the best performing. Most models include age, but it should be noted that the FCSRT-FR does not. An analysis by Mura et al. (2017) showed that combining age with free recall did not improve the results. Another well-performing model is the Taiwanese Health Improvement Network (THIN; Walters et al., 2016) registry-based model that identified about 930,000 patients for the training cohort and 260,000 patients for the test cohort, and analysed easily available demographic, life-style, prescription, and diagnosis data for effects. The performance was good in the 60–79 age group, but a model trained with 80+ individuals had practically no predictive power. The other general-population late-life models—ANU-ADRI and the Dementia Screening Indicator (Barnes et al., 2014)—performed both only moderately despite ANU-ADRI's multimodal extensive predictor set and evidence-based selection methodology. The models built for DM2 populations both included diabetes-related comorbidities, and the other additionally laboratory measurements and medication information, and both had relatively long prediction horizons. They performed equally at an acceptable performance level.

The CAIDE score combines demographic factors with cardiovascular health factors for prediction over a longer time frame. The acceptable performance of the original study was replicated in a validation study with nearly double the follow-up time (Exalto et al., 2013a). The validation also showed the model to work well in Asian, black, and white cohorts (AUCs respectively 0.81, 0.75, and 0.74). However, the performance was clearly worse in older cohorts (Anstey et al., 2014), most likely due to the varied effect of BMI and cholesterol in those age groups. The CAIDE score ver-

Table 4: Prognostic dementia prediction models with externally validated discrimination performance. Identified from Hou et al. (2019).

Model	Baseline age, yr.	Population criterion	Follow up, mean yr.	Predictors included	Predictor selection	AUC original	AUC validation
CAIDE (Kivipelto et al., 2006; Exalto et al., 2013b)[1]	Midlife	None	21 (validation 36)	Age, education, sex, SBP, BMI, cholesterol, physical inactivity (and APOE)	Data-driven (LR)	0.77 (0.78 w. APOE)	0.75
FCSRT-FR (Grober et al., 2010; Derby et al., 2013; Mura et al., 2017)	>65	None	3–5	Free recall score	A priori evidence	—	0.81–0.89
ANU-ADRI (Anstey et al., 2013, 2014)	All ages	None	4–6	Age, sex, education, DM, traumatic brain injury, cognitive activity, social engagement, smoking, alcohol, physical activity, fish intake, depressive symptoms	A priori evidence	—	0.65–0.73[2]
Dementia Screening Indicator[3] (Barnes et al., 2014)	>65	None	6[4]	Age, education, BMI, DM, stroke, needs help with money/medication, depressive symptoms	Data-driven (Cox)	—	0.68–0.78
THIN[5] (Walters et al., 2016)	60–79	None	5	Age, sex, deprivation, BMI, antihypertensive medication, smoking, alcohol, DM, depression, stroke/TIA, AF, aspirin use	Data-driven (Cox)	—	0.84
	80–95	None	5	As above, but excluding deprivation, and adding SBP, lipid ratio, anxiolytics, NSAID	Data-driven (Cox)	—	0.56
DSDRS (Exalto et al., 2013a)	>60	DM2	10	Age, education, cerebrovascular or cardiovascular disease, depression, diabetic complications	Data-driven (Cox)	0.74	0.75
NDCMP (Li et al., 2018)	>50	DM2	8	Age, sex, DM2 duration, BMI, variation of fasting glucose and HbA1c, stroke, hypoglycemia, CAD, DM medication	Data-driven (Cox)	0.76	0.75[6]

Key: AF atrial fibrillation, AUC area under the ROC curve, BMI body mass index, CAD coronary artery disease, Cox Cox proportional hazards model, DM diabetes, HbA1c glycated hemoglobin, LR logistic regression, NSAID nonsteroidal anti-inflammatory drug, SBP systolic blood pressure, TIA transient ischemic attack, — not available. **Models**: CAIDE Cardiovascular Risk Factors, Aging and Dementia; FCSRT-FR Free and Cued Selective Reminding Test, free recall; ANU-ADRI Australian National University AD Risk Index; THIN The Health Improvement Network; DSDRS Diabetes Specific Dementia Risk Score; NDCMP National Diabetes Care Management Program. **Footnotes**: [1]: Validation in matching cohorts only. [2]: Some predictors missing. [3]: Semi-external validation, predictors and weights determined by pooling over cohorts. [4]: A computational Kaplan-Meier survival. [5]: Retrospective registry study. [6]: Cohort split training/testing, 10-yr risk estimate

sion with APOE ϵ4 status as a predictor performed marginally better than the basic version.

The increasing prominence of brain pathology and biomarkers in dementia research has not yet penetrated into prognostic modeling. Models exist with MRI imaging predictors and genetic information (Tang et al., 2015), but amyloid or tau markers, or markers of LBD pathology for that matter, have not been incorporated. As for the validation of these current and future advanced models, finding external cohorts with the same expensive and possibly cumbersome biomarker analysis and long follow-up times is difficult. Tang et al. (2015) point out that only few studies take into consideration the costs associated with gathering predictor data, and that the problem of high costs is especially amplified in a population-based setting. It would be desirable to aim for a minimal predictor set while maintaining good prediction performance. The analysis of validated models (Table 4) showed top results for a simple score showing the impairment of free recall. The predictor was not supported by any other predictor modality. Additionally, increasing the model complexity did not always seem to improve prediction performance. The CAIDE score was not significantly improved by the inclusion of APOE ϵ4 status, nor did it show any higher performance when additional midlife predictors were added (Exalto et al., 2013b).

Key methodological challenges of prognostic dementia prediction models were identified in a recent review (Goerdten et al., 2019). 33% of models were not validated externally or internally, and only 10% were validated externally. A large portion of the studies (44%) were built on ADNI data making the results less generalizable, especially when external validation is not performed. The authors also commented the specific problems with machine learning models, which is the most common model type with a 43% share of all models used. Although they are efficient and accurate, these data-driven models rely strongly on the selected data source. This may make them difficult to apply in other settings. Indeed, only one externally validated model identified in Table 4 used a machine learning model. Typically the case frequency is also higher in study populations than in a real-world setting. Models using regression were noted to frequently not check underlying data assumptions, such as linearity.

It has been suggested that prediction efforts should in the future take into account subtle disease-induced changes in clinical testing, biomarker evidence of early disease stages, and the changing nature of biomarkers during the life course (Ritchie and Muniz-Terrera, 2019). Furthermore, opportunities provided by modern statistical approaches such as machine learning algorithms should be investigated more thoroughly. Future prediction studies will show if incorporating new factors more closely linked to specific disease pathologies will allow for more precise results. Such an approach narrows the gap between purely associative risk factors and diagnostic markers of disease, and such models would start resembling diagnostic models or models of disease progression. In prediction models for advanced age the diagnostic and prognostic models are easily intertwined, as the disease process is more likely already ongoing even if symptoms are not showing.

2.8.5 Prediction of brain amyloid

No prognostic prediction models for brain Aβ accumulation have so far been published. Diagnostic models do exist to predict Aβ pathology as confirmed by PET imaging or analysis of CSF, but no systematic review has been published on the results. Terminology on the subject varies in the literature and the prediction problem has, among other terms, been framed as "imputation" or "ascertainment". A literature search was performed on PubMed.gov on 9 May 2019. Study titles were reviewed, and when necessary abstracts were investigated for relevance. The search was performed with the following search query:

```
(AD OR Alzheimer's OR CSF OR PET)
AND (amyloid OR Aß OR beta-amyloid OR
     amyloid-beta OR amyloidosis)
AND (prediction OR pre-screening OR
     imputation OR ascertainment)
```

The search produced 407 results. 11 studies were identified, and two more based on references in other reports. The results are presented in Table 5. Target populations included cognitively normal (CN), MCI, and AD participants, but stratified results were not reported. The youngest cohort consisted of over-50-year-olds, although most were older. Many studies used Alzheimer's Disease Neuroimaging Initiative (ADNI) subcohorts that included at least 55-year-old participants. The Aβ status was determined either by CSF analysis or PET. Some studies used a population with Aβ CSF for training and a PET population for validation, or vice versa. Six of the models used external validation, others used either an internal validation only or no validation at all. External validation was acknowledged only if the prediction model was completely estimated in the training set. It did not, for example, suffice that a data-driven MRI classifier was estimated using a separate cohort, but the weights of the multimodal model were estimated in the test cohort (Tosun et al., 2013). Some studies saved a portion of their study population for external validation instead of using an independent cohort. These cases have been highlighted in the table. All studies were diagnostic, although some did use longitudinal data on cognition as a predictor. Three of the older studies used a logistic regression to build the models, whereas the newer models mostly used machine learning techniques. Ansart et al. (2019) tested a random forest model, logistic regression, SVM, adaptive logistic regression, and an adaptive boosting model (AdaBoost) on different cohorts and found the random forest to have the best overall performance. A random forest model was also used by two other studies, and one study used a simpler decision tree model. An SVM was used in three studies. Two studies did not report an AUC value but reported accuracy and positive prediction value instead.

The prediction performance varied according to the severity of the diagnoses included in the study population, as would be expected. AUCs were at the lowest levels in the pure-CN populations (0.77 and 0.74, non-validated) and at the highest in mixed MCI/AD cohorts (0.87–0.88). Demographic information was included in most mod-

Table 5: Diagnostic prediction models for Aβ pathology.

Study	Age group	Prediction cohort	Model type	Modalities included						AUC (or alternative)	
				Demo.	Cogn.	APOE	sMRI	Blood	Other	Internal/no validation	External validation
Mielke et al. (2012)[1]	70–92	CN	LR	x		x			Memory complaint	0.70	
				x	x	x			Memory complaint	0.70	
Bahar-Fuchs et al. (2013)	>60	MCI	LR		x					0.77–0.86	
Tosun et al. (2013)	>55	MCI	LR			x				0.81	
							x			0.70	
						x	x			0.88	
Burnham et al. (2014)[1]	>60	CN/MCI/AD	RF	x				x		0.81	0.69
				x		x		x		0.84	0.82
				x		x		x	CDR	0.88	0.85
Tosun et al. (2014)[1]	>55	MCI	LR	x		x	x			0.83 (CA)	
				x		x			ASL-MRI	0.80 (CA)	
Haghighi et al. (2015)	>55	CN/MCI	DT		x						0.76[2]
								x			0.74[2]
					x			x			0.87[2]
Apostolova et al. (2015)	>55	MCI	SVM	x	x	x	x	x		0.80	0.78[2]
Insel et al. (2016)[1]	>55	CN	RF	x	x	x			Cognitive change	0.65 (PPV)	
Lee et al. (2018)	>55	MCI/AD	LR	x		x				0.80	0.72
				x	x					0.74	0.70
				x	x	x			Hypertension	0.87	0.80
Westwood et al. (2018)	64–71[3]	CN/MCI/AD	SVM					x		0.67–0.69	
ten Kate et al. (2018)[1]	>50	CN	SVM	x	x	x	x			0.74	
		MCI		x	x	x	x			0.81	
Palmqvist et al. (2019)	>60	CN/MCI	LR	x	x	x				0.81–0.83	0.81–0.82
				x	x	x		x		0.83–0.85	0.83
Ansart et al. (2019)[1]	>55–70	CN/MCI	RF[4]	x	x	x	x			0.67–0.83	
				x	x	x			Cognitive change	0.72–0.89	
				x		x	x			0.61–0.68	0.62–0.66

Key for prediction cohort: CN cognitively normal, MCI mild cognitive impairment, AD Alzheimer's disease. **Prediction model types**: LR logistic regression, RF random forest model, DT decision tree model, SVM support vector machine. **Alternative performance measures**: CA classification accuracy, PPV positive predictive value. **Other**: ASL-MRI arterial spin labelling MRI, APOE apolipoprotein E, AUC area under the ROC curve, CDR Clinical Dementia Rating, sMRI structural MRI. **Footnotes**: [1]: Some models with fewer predictor modalities omitted, [2]: Cohort split for external validation, [3]: Range of population mean ages, [4]: RF best among 4 other methods tested.

els. The APOE genotype was an important predictor, especially in the cognitively impaired. In a CN population APOE added alongside demographic information improved the AUC from 0.62 (not shown in table) to 0.70 (Mielke et al., 2012), and in an MCI cohort it improved a structural MRI predictor from AUC 0.70 to 0.88 (Tosun et al., 2013). In an MCI/AD cohort iterative reporting of performance measures with increasing model complexity seemed to indicate APOE as a strong predictor (complete model AUC 0.87 non-validated, 0.80 validated; Lee et al., 2018). the objective measurement of cognition had a predictive value in MCI subjects as a solitary predictor (Bahar-Fuchs et al., 2013). Adding a 24-month cognitive change could improve on the cross-sectional measure somewhat in a CN population (not shown in table; Insel et al., 2016). Among older CN individuals objective cognitive scores were equal to subjective memory complaints in terms of predictive power (Mielke et al., 2012). In a cohort with MCI participants cognition and a blood assay had similar performances on their own (AUC 0.74–0.76 validated), but the multimodal model achieved AUC 0.87 (Haghighi et al., 2015). Structural MRI data was included in five models, and its added benefit to the model was demonstrated in two studies reporting performance for parallel models (Tosun et al., 2013, 2014). Ansart et al. (2019) concluded that cognitive scores were superior to MRI as an alternative and that adding MRI with the cognitive scores did not improve results significantly—an important finding considering costs and practicality of the model. Structural MRI was demonstrated to be more effective in predicting than arterial spin labeling MRI measuring brain blood flow (Tosun et al., 2014).

2.8.6 Prediction models in prevention trials

Three dementia prediction models have so far been used in intervention trials. The CAIDE risk score was used to select at-risk individuals to take part in the Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER; Ngandu et al., 2015, see section 4.3) RCT. The target cohort was designed to include individuals with an increased risk of incident dementia based on preventable cardiovascular risk factors and with below-average cognitive performance, yet no substantial cognitive impairment. The CAIDE score threshold of ≥ 6 amounted to a very mild enrichment: 84% of the available population met this requirement (Ngandu et al., 2014) with the lowest individual late-life dementia risk of 1.9% (95% confidence interval 0.2–3.5; Kivipelto et al., 2006) at the threshold level.

Another midlife life-style intervention trial, the Innovative Midlife Intervention for Dementia Deterrence (In-MINDD), utilized a risk score of modifiable risk factors constructed based on a literature search (O'Donnell et al., 2015). In this study the score was used as an educational tool to inform participants of their individual risk profile. The personalized Lifestyle for Brain health (LIBRA) score takes into account coronary disease/hypertension and factors affecting those, obesity/diabetes and associated life-style practices (physical activity and diet), renal disease, and alcohol consumption. The individual risk profiles were used to motivate the proper management of chronic diseases and to communicate in which areas lifestyles could be

improved.

Recently, a genetic risk model was used to stratify subjects into low and high risk groups in a delay-of-disease RCT (TOMMORROW) testing a DM2 medication on the incidence of MCI due to AD in the high-risk group (ClinicalTrials.gov, 2018). The risk model combines the APOE genotype, translocase of outer mitochondrial membrane 40 homolog genotype, and age to produce the risk class prediction (Lutz et al., 2016), which in turn is used as a 5-year prognosis. The prediction model had previously been externally validated for short term risk prediction. The trial was partly designed to validate the performance of the model by comparing a low-risk group and a high-risk placebo group, but the trial was terminated prematurely following a futility analysis.

Prediction models in future dementia research

Ongoing research initiatives aim to build large well-managed and well-phenotyped cohorts with a variety of risk factor information. For example, the European Prevention of Alzheimer's Dementia (EPAD) project aims to internationally improve the use of current cohorts and develop a longitudinal cohort for research of future interventions (Ritchie et al., 2016). Good quality and comprehensive risk factor coverage as well as the inclusion of biomarker data will allow for novel prediction models, which furthermore aid in designing new interventions. Prediction models for pathology may in the future be helpful in cost-effectively identifying target individuals with pathology for secondary prevention (i.e. diagnostic models) or for primary prevention (i.e. models more tuned for prognostic prediction).

3 AIMS OF THE STUDY

The general aim of this thesis was to develop prediction models for dementia and brain pathology and to investigate associations between brain amyloid accumulation and diabetes-related markers. Prediction models may potentially be useful in identifying at-risk individuals, targeting interventions, and finding optimal participants to dementia research projects. Diabetes-related markers are particularly relevant in this context given the increasing diabetes prevalence and potential mechanistic links to dementia diseases. The specific aims were:

1 To predict incident dementia over a ten year period in a late-life cognitively healthy population with multimodal predictors and a novel machine learning algorithm (Study I).

2 To predict dementia and brain pathology in a population-based cohort of the oldest of old using multimodal predictors and a novel machine learning algorithm (Study II).

3 To predict the presence of in-vivo amyloid pathology in a cognitively healthy elderly population at risk of dementia with multimodal predictors and a novel machine learning algorithm (Study III).

4 To study the associations of insulin resistance and other markers of type-two diabetes with brain amyloid pathology in vivo in a cognitively healthy elderly population at risk of dementia (Study IV).

4 SUBJECTS AND METHODS

Three separate study populations were used in this thesis project to build and validate prediction models. In the two observational studies CAIDE and Vantaa 85+, prognostic prediction models were built for dementia and brain pathology. Baseline data from the FINGER intervention trial was used in diagnostic prediction of brain amyloid (FINGER-PET) and to assess associations between brain amyloid status and metabolic markers of insulin resistance and diabetes (FINGER IR/DM). These studies and the respective outcome measures are summarized in Table 1.

4.1 THE CAIDE STUDY OF YOUNGER OLD INDIVIDUALS

The longitudinal, observational, population-based Cardiovascular Risk Factors, Aging and Dementia (CAIDE) study is an extension of cardiovascular surveys conducted in the 1972–1987 within the North Karelia Project and the Finnish part of the Monitoring Trends and Determinants in Cardiovascular Disease (FINMONICA) study (Puska et al., 1979, 1983; Vartiainen et al., 1994). These surveys were targeted at middle-aged persons with a mean age of 50.6 years at the initial visit. Later, for the purposes of the CAIDE study (Kivipelto et al., 2001a,b), a random sample of 2,000 individual participants aged 65–79 years were invited to a re-examination. The structure of the study is described in more detail in Figure 1. 1,449 persons took part in this first late-life re-examination in 1998. A second late-life follow-up was conducted in 2005–2008. This time 1,426 participants out of the initial 2,000 were still alive, and 909 participated. Late-life visits were conducted at median ages 71.3 and 78.6 years. The CAIDE study was approved by the local ethics committee of Kuopio University

Table 1: Outcome measures in prognostic/diagnostic prediction by category in the three study cohorts of the thesis.

Prediction outcome by category		CAIDE N=709&1,009 (prognostic)	Vantaa 85+ N=163&97 (prognostic)	FINGER N=48&41 (diagnostic)
Incident dementia		+	+	-
AD pathology	Aβ plaques	-	Post mortem	In vivo
	Tau tangles	-	Post mortem	-
Vascular pathology	Cerebral microinfarcts	-	Post mortem	-
	Cerebral macroinfarcts	-	Post mortem	-
	Cortical macroinfacts	-	Post mortem	-
	WM macroinfarcts	-	Post mortem	-
Other pathology	α-synuclein	-	Post mortem	-
	CAA	-	Post mortem	-
	Hippocampal sclerosis	-	Post mortem	-
	TDP-43 protein	-	Post mortem	-

Key: AD Alzheimer's disease, CAA Cerebral amyloid angiopathy, WM White matter

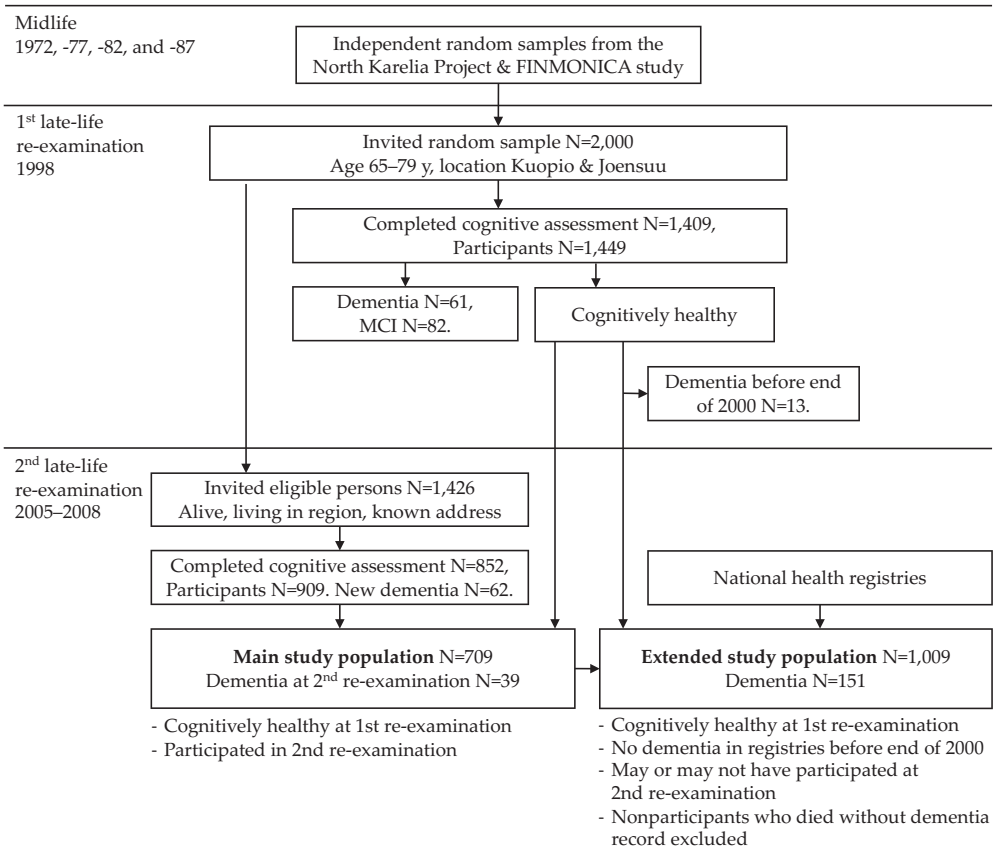


Figure 1: CAIDE study design and formation of the study cohorts.

Hospital, and written informed consent was obtained from all participants.

Study I of this thesis predicted dementia in the participants of the first late-life visit in 1998 who were verified to be cognitively healthy—that is those with no MCI or dementia diagnosis. 709 of that cohort also participated in the 2005–2008 re-examination after a mean follow-up time of 8.3 years. This cohort formed the main study population of Study I. An extended study population was formed by augmenting this with health registry data. For an additional 300 individuals who did not participate in the later re-examination register information on dementia diagnoses and mortality was used. Any relevant record in the Hospital Discharge Register, Drug Reimbursement Register, or Cause of Death Register before the end of 2008 led the individual to be classified as having dementia. These registers have been found to have a good positive predictive value, but lower sensitivity (Solomon et al., 2014b). Surviving nonparticipants without a diagnosis were counted as not having dementia, and those that had died without a diagnosis before 2008 were excluded. Additionally, individuals who had a recorded dementia diagnosis before the end of 2000 were excluded. The mean follow-up time in this extended population was 9.0 years.

Table 2: Baseline factors evaluated for model inclusion by category in the three study cohorts.

Population type and factors by category		CAIDE	Vantaa 85+	FINGER
N		709 & 1,009	245 & 163	48 & 41
Age criterion		Late-life	> 85	60–77
Population type		General population	General population	At-risk CN
Demographic[1]	Education	+	+	+
	Social class	−	+	−
Cognition	MMSE or SPMSQ	+	+	−
	Neuropsychological testing	−	−	+
	Subjective complaints	+	+	−
	Activities of daily living	−	+	−
APOE genotype		+	+	+
Comorbidities	Cardiovascular[2]	+	+	−
	Diabetes mellitus	+	+	+
	Stroke/TIA	+	+	−
Vascular/DM	Blood pressure	+	+	+
	Blood pressure change	+	−	−
	Lipids	+	+	−
	Cholesterol change	+	−	−
	Body mass index	+	+	+
	Body mass index change	+	−	−
	Waist-hip ratio	+	−	−
	Smoking	+	+	−
	Self-rated fitness	+	−	−
	Physical activity	+	−	−
	Insulin resistance	−	−	+
	HbA1c	−	−	+
	Blood assay of DM markers	−	−	+
Psychosocial	Depression	+	+	−
	Hopelessness	+	−	−
Structural MRI		−	−	+
Other	Alcohol use	+	+	−
	Self-rated health	+	−	−

Key: APOE apolipoprotein E, CN cognitively normal, DM diabetes mellitus, HbA1c glycated hemoglobin, MMSE Mini mental state examination, SPMSQ Short portable mental status questionnaire, TIA transient ischemic attack. **Footnotes**: [1]: All studies include age and sex, [2]: Includes angina pectoris, atrial fibrillation, coronary heart disease, heart failure, hypertension, myocardial infarction, and arteriosclerosis obliterans.

The CAIDE late-life visits utilized a three-step procedure to assess cognition. During the screening phase the participants were interviewed, and a set of tests were conducted to assess different cognitive domains: general cognitive screening with the Mini-Mental State Examination (MMSE; Folstein et al., 1975), *episodic memory* with the immediate word recall test (Nyberg et al., 1997; Heun et al., 1998), *semantic memory* with the category fluency test (Borkowski et al., 1967), *psychomotor speed* with the bimanual Purdue Peg Board test (Tiffin, 1968) and the letter digit substitution test (Wechsler, 1944), *executive function* with the Stroop test (Stroop, 1935), and *prospective memory* with a prospective memory task (Einstein et al., 1997).

An MMSE score of $\leq$24 indicated a referral to the clinical assessment phase, and in 2005–2008 this was also indicated by a decrease of $\geq$3 points, a delayed recall word list score $\leq$70% of the Finnish CERAD, or an informant claim of cognitive decline (2005–2008 criteria were sensitized to identify MCI better). A review board assessed the results from detailed somatic and neuropsychological testing, and when necessary used blood analysis, imaging, and in some cases a CSF analysis in the differential diagnosis phase. Dementia was diagnosed according to DSM-IV and specific dementias were identified according to established criteria. Dementia at the second CAIDE re-examination was the prediction target in Study I. The prediction targets in all studies of this thesis are summarized in Table 1.

Extensive data on health and behavior related factors were collected at each late-life visit in addition to the cognitive assessments. Self-administered questionnaires on sociodemographic characteristics, medical history, and health related behavior were used. Depression was assessed using the Beck Depression Inventory (BDI; Beck et al., 1961) and self-rated memory was assessed by administering the Subjective Memory Questionnaire (SMQ; Powell, 1980). The APOE genotype was assessed from leukocytes using a polymerase chain reaction and HhaI digestion (Tsukamoto et al., 1993). Table 2 lists all the available factor modalities and factors from the 1998 visit that were considered as potential predictors in Study I.

4.2 THE VANTAA 85+ STUDY OF OLDEST OLD INDIVIDUALS

The Vantaa 85+ study is a longitudinal observational study of cognition and post mortem neuropathology in the oldest of the old (Polvikoski et al., 1995; Rastas et al., 2010; Ahtiluoto et al., 2010). Residents of Vantaa—a city in southern Finland—aged $\geq$85 years were invited to participate in the study 1991. The study structure is outlined in Figure 2. The participation rate was very high at 98%. The baseline clinical examination was successfully completed for 553 persons. A cohort of 339 individuals completing the baseline examination who were assessed not to have dementia constituted the cohort from which the two study populations of Study 2 were derived. All participants gave their written informed consent to participate in the baseline examination, and nearest relatives of the deceased signed written consent for the autopsies. The study was approved by the ethics committee of the Health Centre of the City of Vantaa.

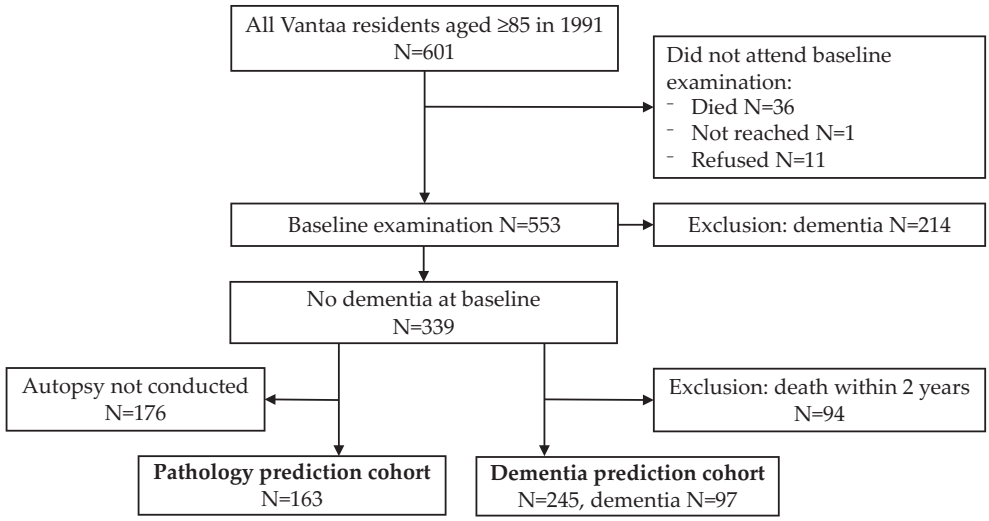


Figure 2: Vantaa 85+ study design and formation of the study cohorts.

The dementia prediction cohort consisted of those taking part in re-examinations in 1996, 1999, and 2001 to assess dementia. In addition, diagnoses were recorded for 101 participants prior to death. 94 participants who died within a two year window from the baseline visit were excluded in order to limit differences in the time to death for dementia/non-dementia participants. The dementia prediction cohort consisted of 245 individuals.

The pathology prediction cohort of 163 persons consisted of those who did not have dementia at the baseline and had autopsy data available. Within the Vantaa 85+ study altogether 304 autopsies were performed, and 16 out of these were on individuals who died before the baseline visit.

Dementia was diagnosed by a two-party consensus based on somatic, cognitive, and functioning assessments during visits and available health records. Data was gathered at the baseline visit by a physician and a trained nurse. The baseline factors assessed for eligibility as a predictor are listed in Table 2. The MMSE and the Short Portable Mental Status Questionnaire (SPMSQ; Pfeiffer, 1975) were used for a cognitive assessment, and functioning was assessed with the activities of daily living questionnaire and with the Instrumental Activities of Daily Living Scale (ADL and IADL; Katz et al., 1963; Lawton and Brody, 1969). Competence in daily activities was quantified on a self-rated scale of 1–6 (from *independent* to *needs help in all activities*). Subjective memory complaint was assessed as *no*, *a little*, or *yes*. Depression was assessed using the Zung Self-Rating Depression Scale (Zung et al., 1965). For surveyed comorbidities, the category noted as Cardiovascular in Table 2 included angina pectoris, heart infarction, atrial fibrillation, heart failure, arteriosclerosis obliterans, and hypertension. HDL and LDL were determined from blood samples using enzymatic methods (Rastas et al., 2010). The APOE genotype was determined using DNA

minisequencing and amplification through a polymerase chain reaction followed by restriction enzyme digestion with HhaI (Hixson and Vernier, 1990; Syvänen et al., 1993). DSM-III criteria were used for dementia, and appropriate established criteria for specific dementias.

Several pathological features were identified and classified in brain autopsies. These features are grouped in Table 1 by the pathology type. Aβ pathology (Polvikoski et al., 1995) was classified using the CERAD protocol, and tau pathology (Myllykangas et al., 1999) was classified by using Braak staging. Macroscopic and microscopic infarcts were identified as previously described (Tanskanen et al., 2012). Additionally, cerebral amyloid angiopathy (Tanskanen et al., 2012), FTD-related α-synuclein pathology (Oinas et al., 2009), hippocampal sclerosis (Kero et al., 2018), and TDP-43 accumulation (Kero et al., 2018) were assessed.

4.3 THE FINGER TRIAL

The Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER) was a blinded, randomized controlled trial with the aim to test a multidomain life-style intervention in the prevention of cognitive decline and dementia (Kivipelto et al., 2013; Ngandu et al., 2014, 2015). The study had a multicentre design and included a population-based sample of elderly persons who were at risk of cognitive decline. The sample originated from Finnish health surveys from 1972–2007 as shown in Figure 3. Along with an age criterion, participants were required to have a CAIDE risk score (Kivipelto et al., 2006) greater than or equal to six to be invited to a screening visit. In more detailed testing, candidate participants had to meet CERAD criteria that demonstrated cognitive performance at a mean level or somewhat lower than the Finnish general population (Hänninen et al., 2010). The specific criteria were word list learning task of ten times three words score less than or equal to 19, word list recall less than or equal to 75%, or an MMSE score less than or equal to 26. Exclusion criteria included dementia, substantial cognitive decline, MMSE less than 20, and conditions preventing safe engagement in intervention activities (Kivipelto et al., 2013). The subsequent multidomain intervention included diet guidance, exercise, cognitive training, and vascular monitoring over a two year period. Results have been published showing a benefit on overall cognition (Ngandu et al., 2015), and extended follow-ups of the study participants are still ongoing. The study was approved by the coordinating ethics committee of the hospital District of Helsinki and Uusimaa. Participants gave written informed consent at the screening and baseline visits.

A subset of the participants in the Turku area—a city in south-western part of Finland—was invited to take part in an amyloid-PET/MRI substudy. In total 48 individuals underwent PET imaging using ^{11}C-Pittsburgh compound B (PIB) after the baseline visit. Details on the imaging are presented by Kemppainen et al. (2017). The FINGER-PET participants were somewhat older (mean age 70.8 vs. 69.3) than the parent cohort due to the later initiation of the recruitment process in Turku. No other

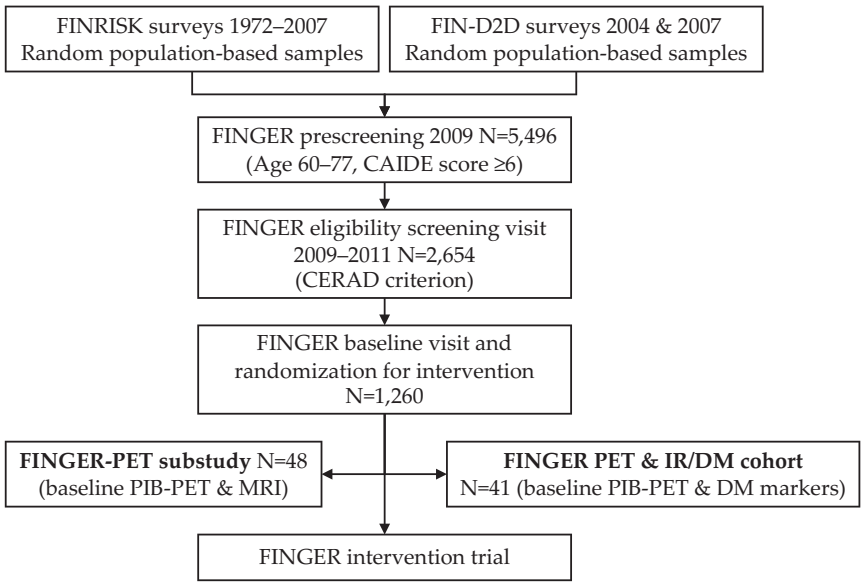


Figure 3: FINGER study design and formation of the FINGER-PET study population and the PET & IR/DM cohort.

significant differences were noted. PIB images were analysed by two experienced readers and a consensus visual assessment of amyloid positivity (Aβ+) was made. Aβ+ individuals typically showed cortical retention predominantly in AD-typical regions, and Aβ- persons displayed nonspecific accumulation in white matter. This cohort constituted the prediction cohort of Study III with amyloid positivity on PIB-PET as a prediction outcome. See Table 1 for comparison of cohorts.

Participant health data was gathered at the baseline/randomization visit by a study physician and nurse. Cognition was measured using a modified version of the Neuropsychological Test Battery (mNTB; Harrison et al., 2007). Subscores were used for the executive functioning, memory, and processing speed cognitive domains. Scores of individual cognitive tests were transformed into standardized Z scores and then the sum scores for the NTB total and sub-domains were calculated (Kivipelto et al., 2013). The APOE genotype was determined by polymerase chain reaction using TaqMan genotyping assays for 2 single-nucleotide polymorphisms and an allelic discrimination method (De la Vega et al., 2005).

All participants of the FINGER-PET cohort in Turku underwent at baseline a brain 3T MRI with T1-weighted sagittal sequences and FLAIR coronal sequences (Kemppainen et al., 2017). The cortical thickness by region and brain region volumes were attained using the Freesurfer image analysis suite (version 5.0.3). A measure of AD-type cortical thinning was calculated as an average of the entorhinal, inferior temporal, middle temporal, and fusiform regions (Jack et al., 2015a). Medial temporal lobe atrophy (MTA) was assessed on the Scheltens scale (Scheltens et al., 1992) by one blinded specialist from T1-weighted images (Stephen et al., 2017b).

41 of the FINGER-PET participants had data available on IR- and DM-related blood markers. Fasting blood glucose, insulin, HbA1c, and a 12-item Bio-Plex Pro Human Diabetes assays were analysed. The assays included adiponectin, adispin, C-peptide, ghrelin, GIP, GLP-1, glucagon, insulin, leptin, PAI-1, resistin, and visfatin. The HOMA-IR was calculated based on insulin and glucose measures. These individuals constituted the study cohort of Study IV (see Figure 3).

4.4 DISEASE STATE INDEX

The Disease State Index (DSI) is a machine learning algorithm designed to discriminate populations in terms of a condition. The discrimination is based on an index value that—as the name implies—aims to represent the state of an underlying disease based on a body of patient data. The DSI value is a continuous value allowing a more precise assessment of the disease state than a dichotomous algorithm would. The version of DSI used in this thesis classifies a subject as having a disease versus not having it, but newer versions allow classification into more than two categories. The algorithm was originally developed at the state-run VTT Technical Research Centre of Finland as a back end to a clinical decision support system, which allows a clinician to graphically examine operation of the algorithm in terms of different model predictors. The system has been further developed by Combinostics Ltd as part of the EU-funded PredictAD and PredictND tools, clinical decision support systems for AD diagnosis and differential diagnosis of dementia, respectively.

The DSI has previously been successfully used to discriminate between AD and CN (Mattila et al., 2011) and FTD and CN/MCI (Muñoz-Ruiz et al., 2013), predict MCI–dementia conversion (Mattila et al., 2011, 2012b; Hall et al., 2015; Rhodius-Meester et al., 2016), and classify dementias based on structural MRI (Koikkalainen et al., 2016) and multimodally (Tolonen et al., 2018). The model has been previously described in detail by Mattila et al. (2011, 2012a). The algorithm is trained on a set of individuals with empirical predictor value distributions and binary outcomes. Figure 4 shows example distributions of a predictor for positive and negative outcome cases. In respect to this pair of distributions, a fitness function is defined:

$$fitness(a) = \frac{L_P(a)}{L_P(a) + R_C(a)} = \frac{FN(a)}{FN(a) + FP(a)}$$

Here $L_P(a)$ is the left integral of the positive outcome distribution at a and $R_C(a)$ is the right integral of the negative outcome distribution. These correspond to the cases with false negative and false positive predictions, respectively. The function is monotonic with increasing values of a being assigned increasing values and a_{max} being assigned the maximal value of 1. Using the figure as a visual aid, it is intuitively easy to see how the ratio of the red shaded area at the left side will grow in proportion to the sum of the shaded areas when a moves to the right. Each predictor is assigned a function $fitness_i$.

The predictors' ability to discriminate between the outcomes varies and is re-

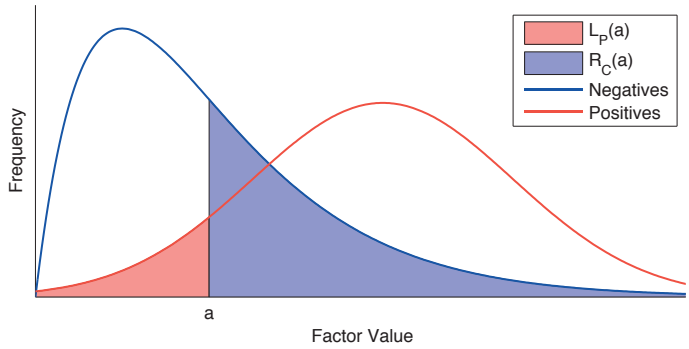


Figure 4: Derivation of the fitness function from the empirical outcome distributions. $L_P(a)$ represents the left integral of the positive outcome distribution at a (false negative prediction at threshold level a) and $R_C(a)$ represents the right integral of the negative outcome distribution (false positive prediction).

flected in the empirical distributions. The relevance of a predictor for the prediction task is defined as

$$\begin{aligned} relevance(b) &= max\left(0, L_C(b) + R_P(b) - 1\right) \\ &= max\left(0, specificity(b) + sensitivity(b) - 1\right), \end{aligned}$$

where b is the decision threshold for the factor, $L_C(b)$ is the left integral of the negative outcome distribution, and $R_P(b)$ is the right integral of the positive outcome distribution at b. The integrals can readily be interpreted as the specificity and the sensitivity of the classifier, respectively. The decision threshold b denotes the value of the factor at which the fitness function reaches 0.5. Relevance assumes values in the range 0–1 which is similar to the fitness function. For categorial variables the relevance is calculated similarly, but the comparison of groups is limited to the individuals who share the same category value.

Predictor-specific fitness function values and relevance values are combined in the model by weighting the function values with relevance values. The composite DSI value for an individual with its set of predictor values is defined as a weighted sum over each predictor i:

$$DSI = \frac{\sum_i relevance_i \times fitness_i}{\sum_i relevance_i}$$

Being an average of fitness values, DSI assumes values in the interval 0–1.

The DSI can be calculated for the complete model as described above, but also for a smaller subset of predictors or individual predictors. Conceptually linked predictors can be grouped together to assess their combined effect. Cardiovascular health, for example, can be modelled by combining blood pressure measurements, lipid values, and smoking habits under one category.

4.5 DATA ANALYSIS AND PREDICTION MODELS

Differences between prediction outcome groups—that is, incidence of dementia and ascertainment of pathology—were tested for statistical significance using the χ^2 test for categorical factors and the Mann-Whitney U test for continuous and ordered factors. In the two FINGER studies (Studies III and IV) the Mann-Whitney U test was used for all factors.

In the CAIDE model (Study I), the APOE genotype was modelled both in terms of the $\epsilon 4$ carrier status and as a variable describing genotype risk order $\epsilon 2\epsilon 2 < \epsilon 2\epsilon 3 < (\epsilon 2\epsilon 4 = \epsilon 3\epsilon 3) < \epsilon 3\epsilon 4 < \epsilon 4\epsilon 4$ (Corder et al., 1993, 1994). In Vantaa 85+ (Study II), the APOE genotype was modelled in four parallel ways by including $\epsilon 2$ and $\epsilon 4$ carrierships as binary factors, $\epsilon 3$ homozygousness as a binary factor, and all genotypes as a categorical factor. In the FINGER PET and IR/DM studies (Studies III and IV) the APOE genotype was modelled simply as dichotomous $\epsilon 4$ carrier status.

In the FINGER-PET study (Study III), volumetric MRI measures were expressed in relation to the intracranial volume and bilateral measures were consolidated into an average.

In order to analyse the relationship of different pathologies and dementia in the Vantaa 85+ study (Study II), a dimension-reduction step was performed. Principal components (PCs) were estimated for all dementia prediction cohort individuals, and for dementia and no-dementia individuals separately. PC loadings were used to identify interrelationships between pathology types. The PC analysis was done on MATLAB R2015b.

4.5.1 Prediction and validation

Model predictors were identified from a group of candidate predictors by analyzing the group mean value differences. This step reduces noise and generally improves the DSI prediction results. Given that the empirical predictor value distributions are close to continuous and have approximately the same variance, no significant predictor should be excluded based on this criterion. A p-value threshold of 0.05 for statistical significance was set in the CAIDE and Vantaa 85+ studies. Additionally, the choice of model building parameters was investigated using a spectrum of p-value threshold values used to filter factors according to their significance. In the smaller-population FINGER-PET prediction model all candidate factors were used.

Predictor grouping was utilized in the CAIDE and FINGER DSI models to form broad groups for socio-demographic features, cardiovascular health, cognition, self-rated health measures, and MRI findings. A somewhat more granular approach was taken in the Vantaa 85+ DSI model, in which groups were formed to gather all plasma lipid types together, for instance, and also to group parallel APOE genotype categorizations together. The grouping was held constant in all the Vantaa 85+ pathology prediction models, but the predictor set varied according to the p-values in regard to the specific pathology. In the reduced-dimensionality pathology prediction model the unmodified principal component scores were used as singular predictors without

using the DSI.

Prediction models built with the DSI were all internally validated. The CAIDE model was trained and tested using cross-validation with the data divided into 50×5-folds, the Vantaa 85+ models using 10×10 cross-validation for both dementia and pathology, and the FINGER model using 100×5 cross-validation. Prediction performance against the binary outcome in each case was reported as the AUC. The AUCs are reported as mean values from the cross-validation folds, and dispersion values were also reported. The CAIDE DSI model was also validated against a linear-kernel support vector machine using the same data set.

4.5.2 Association analysis in FINGER IR/DM cohort

Logistic regression models were built to investigate the association of IR/DM markers and Aβ positivity. The DM and APOE ϵ4 status were included as confounders, and blood marker concentrations were log-transformed. Statistical significance was determined with correction for multiple comparisons using the false discovery rate method (Benjamini and Hochberg, 1995). All analyses were run on MATLAB R2017b, and function mnrfit was used for a logistic regression.

5 RESULTS

5.1 PREDICTING INCIDENT DEMENTIA

Both the CAIDE late-life cohorts and the Vantaa 85+ dementia prediction cohort underwent a prescreening for potential factors. Prediction models were built using the DSI and the prediction performance was assessed in a similar manner in both studies.

All factors crossing the 5% significance level threshold were included as predictors. All predictors selected for use in the CAIDE main model and the Vantaa 85+ dementia prediction model are listed in Table 2 for contrast. The table lists AUC values for predictors, predictor groups, and the complete model. Predictor-level data in the extended population model are shown in detail in the original publication (Study I).

5.1.1 Population characteristics, and predictors

A few key characteristics of the late-life CAIDE populations are presented in Table 1. More detailed characteristics are presented in the Study I original publication. In both the main and extended study populations, in the statistical testing, individuals who developed dementia were significantly older, did worse on most subdomain cognitive tests, had poorer scores on the SMQ, and had a higher frequency of cardiovascular comorbidities and the APOE ϵ4 allele. In the main study population, individuals who developed dementia had also significantly a lower SBP and DBP, and had lower scores on three more SMQ questions. In the extended population, differences in cognitive testing results were more pronounced: MMSE aggregate and verbal expression subdomain scores were lower in individuals who developed dementia. As for the midlife–late-life changes, the BMI had on average increased by 1.6

Table 1: General characteristics of populations at baseline and frequency of outcome measures.

	CAIDE		Vantaa 85+		FINGER	
	Main cohort	Extended cohort	Dementia prediction	Pathology prediction	Aβ prediction	IR/DM cohort
N	709	1,009	245	163	48	41
Baseline mean age	70.1 yr.	70.5 yr.	88.4 yr.	88.7 yr.	71.4 yr.	71.1 yr.
Mean follow-up	8.3 yr.	9.0 yr.	5.6 yr.	4.1 yr.	—	—
APOE ϵ4 carrier	32%	34%	21%	20%	30%	30%
Diabetes mellitus	2%	3%	23%	28%	15%	15%
Incident dementia	6%	15%	40%	36%	—	—
Aβ positive share	—	—	—	77%	42%	39%

Key: Aβ amyloid beta protein, APOE apolipoprotein E, IR/DM insulin resistance and diabetes mellitus

Table 2: Prediction results for incident dementia in the younger-old-age CAIDE population and in the oldest-old Vantaa 85+ population.

	AUC of dementia prediction	
	CAIDE main study population[1] N=709	Vantaa 85+ dementia prediction cohort N=245
Complete model	0.79	0.73
Age	0.67	—
Education	NA	0.60
Cognitive testing	0.73	0.72
Executive functioning	0.68	NA
Episodic memory	0.64	NA
Prospective memory	0.62	NA
Psychomotor speed	0.62	NA
Verbal expression	—	NA
MMSE Total	—	0.71
MMSE Calculation	NA	0.60
MMSE Orientation	NA	0.64
MMSE Other tasks	NA	0.65
MMSE Wordlist	NA	0.68
SPMSQ	NA	0.71
Subjective Memory Questionnaire	0.64	NA
Total score	0.62	NA
Forgetting phone numbers	0.61	NA
Forgetting names of actors	0.60	NA
Forgetting clothing size	0.59	NA
Forgetting midsentence	0.58	NA
Competence in Daily Activities	NA	0.61
Vascular factors	0.65	—
Systolic BP	0.63	—
Diastolic BP	0.64	—
Presence of comorbidity[2]	0.56	—
APOE genotype	0.59	0.58
All genotypes modelled	0.60	0.58
ϵ4 carrier	0.57	—
ϵ2 carrier	NA	0.56
ϵ3ϵ3 genotype	NA	0.57

"NA" indicates that the factor was not available and "—" indicates that it was not accepted for the model after significance testing. **Key**: APOE apolipoprotein E, AUC area under the ROC curve, BP blood pressure, MMSE Mini-mental state examination, SPMSQ Short Portable Mental Status Questionnaire, — was not available as candidate predictor. **Footnotes**: [1]: The extended model additionally included MMSE total score and verbal expression score, [2]: For differences in comorbid conditions see Table 2

kg/m^2 in the no-dementia group in both populations and remained more or less on midlife levels in the incident dementia group, i.e. -0.1 and 0.2 kg/m^2 in the respective main and extended populations. These differences were statistically significant. The SBP and DBP had both decreased significantly in the main population, as did the DBP in the extended population. The total cholesterol was lower in late-life in the extended population.

The Vantaa 85+ dementia prediction cohort has been characterized in detail in the original publication (Study II). A brief overview is presented in Table 1. The group developing dementia during the follow up was less educated, scored lower on the MMSE and all its derivative subscores, made more errors on the SPMSQ, and had a different distribution of APOE genotypes. No differences were observed in age, cardiovascular factors, depression, or BMI.

5.1.2 Dementia prediction in the younger old (CAIDE)

The prediction performance in the late-life CAIDE cohort as measured by AUC was 0.79 in the main population and 0.75 in the extended population in cross-validation. Receiver operating characteristics (ROC) curves are shown in Figure 1. Comparison of group level AUCs in the two models are shown in Table 3, where also results from a separate analysis with midlife–late-life changes in vascular factors are presented. Noncross-validated complete-model AUCs were 0.84 and 0.76, respectively. Cognitive testing as a category was the best predictor in both models at a respective 0.73 and 0.69, while not reaching the performance of the complete model. Other predictor types did improve the model beyond that achieved for cognition. Age was the second best performing predictor. Subjective memory assessments performed worse than objective cognitive testing. Vascular factors did have some predictive power in the main population, but practically none in the extended population. The APOE genotype had poor predictive power. Changes in vascular parameters from midlife performed somewhat better than cross-sectional values.

The DSI models were also investigated in binary prediction using different index cut-off values. As an example from the more comprehensive table in the original publication, a DSI threshold of 0.5 for positive prediction resulted in 0.74 accuracy, 0.73 sensitivity, and 0.74 specificity in the main population, and 0.67, 0.69, and 0.67, respectively, in the extended population. Results for these statistics were better in almost every case in the main population.

The CAIDE model results were validated in terms of the method used. A parallel SVM was set up using the same population data and cross-validation principles. Using the MATLAB fitcsvm function, parameters were set empirically for the best performance. The SVM achieved an AUC score of 0.77 in the main population and 0.74 in the extended population.

Furthermore, the choice of model building parameters was investigated. Table 4 of the original publication (Study I) lists a spectrum of p-value threshold values used to filter factors according to their significance. The results demonstrated that a laxer requirement and a larger predictor set resulted in lower performance, as did a

Table 3: Performance in the prognostic prediction of dementia in the CAIDE younger-old populations.

	AUC (95% confidence interval)	
	Main study population	Extended study population
Complete model	0.79 (0.79-0.80)	0.75 (0.74-0.75)
Age	0.67 (0.65-0.68)	0.66 (0.66-0.67)
Cognitive testing†	0.73 (0.73-0.74)	0.69 (0.69-0.70)
Subjective Memory Questionnaire†	0.64 (0.63-0.66)	0.58 (0.57-0.58)
Vascular factors†	0.65 (0.64-0.66)	0.53 (0.52-0.53)
APOE genotype†	0.59 (0.58-0.60)	0.60 (0.59-0.61)
Complete model with vascular changes‡	0.80 (0.79-0.81)	0.78 (0.77-0.79)
Vascular changes	0.68 (0.66-0.69)	0.65 (0.64-0.66)
Change in systolic BP	0.65 (0.63-0.66)	—
Change in diastolic BP	0.61 (0.59-0.62)	0.61 (0.59-0.62)
Change in BMI	0.68 (0.67-0.69)	0.68 (0.67-0.69)
Change in total cholesterol	—	0.55 (0.54-0.57)

Key: APOE apolipoprotein E, AUC area under the ROC curve, BMI body mass index, BP blood pressure, MMSE Mini-mental state examination, — not included after significance filtering. **Footnotes**: †: Only group-level result shown, for individual factors in the main model see Table 2; ‡: The complete model also includes all predictors used in the upper panel of the table in the respective populations.

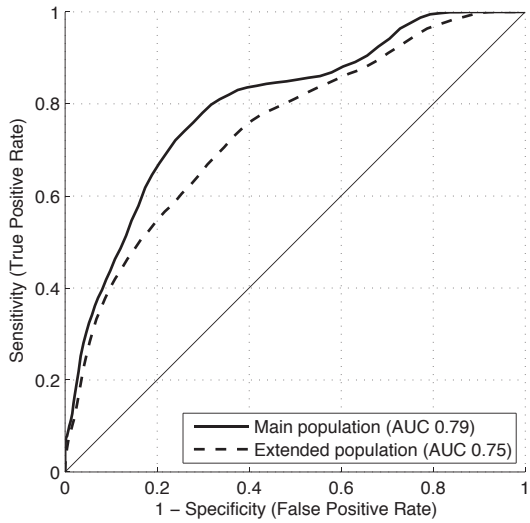


Figure 1: Receiver operating curves for prediction of incident dementia in the CAIDE populations.

very small high-relevance predictor model. No requirement for significance led to an AUC score of 0.74 in the main population. However, the predefined threshold of 5% was not the optimal value in either population. Exploratory analyses were conducted to test nonlinear tail effects for BMI, blood pressure, and cholesterol. Dichotomous variables for crossing extreme distribution tail values were added to the model, but none of the tested cut-off values showed an effect on the overall performance.

5.1.3 Dementia prediction in the older old (Vantaa 85+)

Prediction results for dementia in the Vantaa 85+ study are shown in Table 2. In this considerably older population the dementia incidence was much higher, but the prediction performance was lower (AUC 0.73 vs. CAIDE 0.79). Here, too, an objective assessment of cognition was the best predictor, practically on a par with the performance in the CAIDE (AUC 0.72 vs 0.73 in CAIDE main model). MMSE and SPMSQ were equally good predictors. All other predictor modality groups performed in the range 0.58–0.61 or were not selected for the model in the first place. As for the parallel APOE predictor representations, $\epsilon 2$ had a higher prevalence in the incident-dementia group and indicated increased risk, and $\epsilon 3\epsilon 3$ was enriched in the no-dementia group and indicated a protective effect. However, both had a poor predictive performance.

5.1.4 Dementia and neuropathology at death

In addition to the prognostic dementia prediction model, an exploratory diagnostic prediction analysis was performed using pathology findings to predict dementia at the time of death. Table 4 presents the characteristics of pathology in terms of having dementia versus not having dementia. AD-pathology was significantly more prevalent in the dementia group, as was CAA, HS, TDP-43 protein, and cortical macroinfarcts, but not macroinfarcts elsewhere or microinfarcts. α-synuclein pathology did not show any significant differences.

The results from a PCA on neuropathology are presented in Table 5. The three first PCs are shown for the entire population and subpopulations without dementia and with dementia at death. The three PCs explained together 56–59% of the variance in the data in each population. The first PC had strong loadings concerning both AD neuropathological findings and CAA. In the dementia group there were also strong negative loadings for all/cortical macroinfarcts. The first PC could be interpreted as "AD-type pathology".

The second PC had a different loadings profile for the dementia and no-dementia groups. In the entire population and in the no-dementia group PC2 had a strong positive loading for all/cortical macroinfarcts and weaker positive loadings for WM macroinfarcts and α-synuclein. In this subpopulation the second PC could be interpreted as "Vascular pathology". In the dementia group, PC2 had large positive loadings for most AD-type and vascular pathologies and negative loadings for HS and TDP-43. This PC could be interpreted simply as reflecting age, as both HS and TDP-43 occur predominantly in the very old whereas the other pathologies do occur also in earlier old age.

Table 4: Neuropathology characteristics at autopsy according to the dementia status for participants without dementia at baseline in Vantaa 85+.

	No dementia (N=104)	Dementia (N=59)	p-value
β-amyloid load	74 (71%)	52 (88%)	0.020
Tangle count	55 (53%)	44 (75%)	0.008
Neuropathological AD[†]	39 (38%)	38 (64%)	0.001
CAA[‡]	59 (58%)	44 (76%)	0.040
Cerebral macroinfarcts	47 (45%)	33 (56%)	0.200
Cortical macroinfarcts	23 (22%)	24 (41%)	0.020
WM macroinfarcts	14 (14%)	9 (15%)	0.800
Cerebral microinfarcts[‡]	16 (16%)	11 (19%)	0.700
α-synuclein	26 (25%)	22 (37%)	0.100
Hippocampal sclerosis	2 (2%)	9 (15%)	0.002
TDP-43	8 (8%)	14 (24%)	0.007

Values are shown as absolute numbers (percentages). The p-value is calculated with the Fisher's exact test. **Footnotes**: [†]: Defined based on the National Institute on Aging–Alzheimer's Association criteria (Hyman et al., 2012) using the combination of Braak and CERAD scores, and dichotomized as present (intermediate or high likelihood of AD) vs. absent (low likelihood of AD); [‡]: 4 participants missing data

The third PC in the dementia group had combined high positive loadings for HS and TDP-43 and a large negative loading for α-synuclein. In the no-dementia group PC3 was driven by the tangle count and had lower negative and positive loadings for other types of pathology.

PC1 had moderate predictive power for the diagnostic prediction of dementia with an AUC of 0.71. PC2 and PC3 had AUCs of 0.60 and 0.54, respectively.

5.2 PREDICTING BRAIN PATHOLOGY

5.2.1 Longitudinal prediction of pathology (Vantaa 85+)

An overview of the Vantaa 85+ pathology prediction cohort is given in Table 1 (p. 71), and more details are included in the original publication (Study II). The cohort was on average 88.7 years old, 19% were male, and the mean education duration was 4.1 years. The predictors for each type of pathology crossing the 5% significance threshold are listed in Table 3 of the original publication.

Amyloid and tau related pathology

The APOE genotype was included as a predictor for all amyloid and tau related pathologies, namely the Aβ load, tau tangle count, CAA, and neuropathological AD which is defined here as an intermediate or high likelihood of AD based on the NIA-AA criteria (Hyman et al., 2012). Additionally, impairment in daily activities

Table 5: Principal components of pathology and their performance in the prediction of dementia in Vantaa 85+.

				Groups by outcome					
	Prediction cohort			No dementia			Dementia		
	PC1	PC2	PC3	PC1	PC2	PC3	PC1	PC2	PC3
Explained variance	25%	20%	11%	26%	19%	12%	24%	21%	14%
AUC to predict dementia	0.71	0.60	0.54	—	—	—	—	—	—
β-amyloid load	41	3	-31	47	6	-43	16	25	24
Tangle count	48	0	38	44	15	68	37	28	8
Neuropathological AD†	59	-7	-4	54	6	5	51	33	20
CAA	47	-3	-18	51	-2	-33	28	37	-9
All cerebral macroinfarcts	-1	73	-13	-11	77	-11	-48	47	6
Cortical macroinfarcts	7	59	-15	-2	51	-19	-43	49	8
WM macroinfarcts	-8	24	1	-12	25	2	-19	9	8
Cerebral microinfarcts	11	10	16	6	7	31	2	27	17
α-synuclein	5	20	81	2	23	31	-10	9	-53
Hippocampal sclerosis	0	4	-2	4	4	0	-17	-22	46
TDP-43 protein	6	1	2	4	-1	3	-7	-14	59

PC loadings expressed in percentages. **Key**: AUC area under the ROC curve, CAA cerebral amyloid angiopathy, WM white matter. **Footnotes**: †: Defined based on the National Institute on Aging–Alzheimer's Association criteria (Hyman et al., 2012) using a combination of Braak and CERAD scores, and dichotomized as present (intermediate or high likelihood of AD) vs. absent (low likelihood of AD)

predicted a higher Aβ load; a higher total cholesterol and LDL predicted a higher tangle count; a subjective memory decline predicted a higher tangle count and neuropathological AD; a lower social class predicted neuropathological AD; and having no cardiovascular comorbidity and male sex predicted the presence of CAA.

Prediction AUCs for the four pathologies were in the range 0.64–0.68 with neuropathological AD having the highest value. The APOE genotype was modelled in all cases using multiple parallel presentations, and the effects of the alleles varied according to the pathology. The APOE category AUCs were in the range 0.60–0.65. The ϵ4 allele was predictive of all pathology types, the ϵ2 allele was protective against an Aβ load and neuropathological AD, and the ϵ3ϵ3 genotype was protective against a high tau tangle count and CAA. All other predictors had a poor predictive performance with AUCs below 0.62.

Vascular pathology

More predictors for cerebral macroinfarcts were identified than for microinfarcts, and the prediction results were better. Macroinfarcts overall were predicted by the presence of a cerebrovascular comorbidity, lower MMSE total score and wordlist subscore, higher BMI, and impairment in daily activities. The predictors varied somewhat by region, but cerebrovascular comorbidities were predictive in every case. Cortical macroinfarcts were predicted by the APOE ϵ4 allele, and the ϵ3ϵ3 genotype

was protective. The presence of WM macroinfarcts was predicted by a ϵ2 carriership and both low HDL and LDL. Cerebral microinfarcts were predicted only by a lower duration of education.

The prediction performance for WM macroinfarcts at AUC 0.76 was better than for any other vascular pathology. The AUC was 0.71 for cortical macroinfarcts and 0.72 for macroinfarcts overall. Cholesterol was a strong predictor for WM macroinfarcts (group level AUC 0.72). The APOE was a somewhat weaker predictor for vascular pathology than for amyloid and tau related pathologies (at the group level 0.60–0.61 vs. 0.60–0.65). Other predictors had AUCs in the range 0.59–0.64.

Other pathology

For α-synuclein pathology no significant predictors were found. HS was predicted by a lower MMSE total score, wordlist and other task subscores, and by being a current smoker. These predictors had good predictive performance at AUC 0.78, and cognition was the stronger modality (group level AUC 0.75). The deposition of TDP-43 was predicted by having fewer depressive symptoms, and the performance was moderate (AUC 0.69).

5.2.2 Diagnostic prediction of brain amyloid (FINGER)

Key characteristics of the FINGER-PET study are summarized in Table 1 (p. 71) for comparison with the other studies. Results from diagnostic prediction of in vivo amyloid positivity (Aβ+) are presented in Table 6. Twenty individuals (42%) were assessed Aβ+ at baseline imaging. Aβ+ individuals had statistically significantly (95% confidence level, p-values not corrected for multiple comparisons) higher frequency of the APOE ϵ4 allele, a lower executive functioning score, and more neurodegenerative changes on MRI. Volumes were significantly lower in the cortex and grey matter overall, as well as for the cerebellar cortex, thalamus, putamen, hippocampus, amygdala, accumbens area, and ventral diencephalon. The MTA on the Scheltens scale was more pronounced in the Aβ+ group. Sociodemographic factors, vascular factors, overall cognition, or any of the cognitive subdomains showed no significant differences.

All factors were included in the model. The prediction AUC of the complete model was 0.78 in cross validation and 0.88 without cross validation. Single-predictor AUCs were in the range 0.45–0.75. MRI was the best performing predictor category at AUC 0.75. Volumetric FreeSurfer estimates as a group (AUC 0.72) and a visual MTA (0.71) performed equally at a moderate level, and the AD-specific cortical thickness measure performed worse (0.65). The APOE and the executive functioning subdomain score also had some predictive power at 0.69 and 0.69 each. Cognition as a category did worse than the executive functioning score on its own. The BMI was a stronger predictor than hypertension in the cardiovascular category, which performed poorly at an AUC of 0.60. Sociodemographic factors also lacked predictive power.

Table 6: FINGER-PET diagnostic prediction results for Aβ and outcome-group mean values.

		Group mean		
	AUC (95% CI)	Aβ- (N=28)	Aβ+ (N=20)	p-value
Complete model	0.78 (0.65–0.91)			
Sociodemographic	0.54 (0.37–0.70)			
Sex (female)	0.48 (0.35–0.60)	14 (50%)	8 (40%)	0.505
Age	0.45 (0.28–0.61)	70.2	71.6	0.310
Education (years)	0.59 (0.43–0.75)	9.7	8.9	0.320
Cardiovascular	0.60 (0.46–0.75)			
Body mass index	0.65 (0.50–0.79)	28.9	26.2	0.088
Hypertension	0.49 (0.37–0.61)	10 (36%)	9 (45%)	0.529
APOE ϵ4 carrier[†]	0.69 (0.56–0.82)	4 (14%)	10 (53%)	0.005
Cognition	0.65 (0.49–0.81)			
Total score	0.55 (0.38–0.72)	0.04	-0.09	0.421
Memory	0.54 (0.38–0.70)	-0.11	0.04	0.385
Processing speed	0.57 (0.41–0.73)	0.16	-0.10	0.184
Executive function	0.69 (0.53–0.84)	0.16	-0.22	0.026
Magnetic resonance imaging	0.75 (0.61–0.89)			
Volumes (% of ICV)	0.72 (0.57–0.88)			
Total cortex	0.73 (0.59–0.88)	0.29	0.27	0.007
Total grey matter	0.72 (0.57–0.88)	0.39	0.36	0.009
Cerebellum cortex	0.69 (0.54–0.84)	0.063	0.059	0.027
Thalamus proper	0.70 (0.55–0.85)	9.3E-3	8.4E-3	0.022
Caudate	0.65 (0.49–0.81)	4.9E-3	4.5E-3	0.070
Putamen	0.71 (0.56–0.87)	7.0E-3	6.1E-3	0.014
Pallidum	0.61 (0.45–0.77)	1.9E-3	1.8E-3	0.198
Brain Stem	0.61 (0.45–0.77)	0.014	0.014	0.229
Hippocampus	0.70 (0.54–0.86)	5.2E-3	4.6E-3	0.019
Amygdala	0.69 (0.53–0.85)	2.3E-3	2.0E-3	0.030
Accumbens area	0.75 (0.62–0.89)	6.6E-4	5.6E-4	0.004
Ventral diencephalon	0.68 (0.53–0.83)	5.0E-3	4.7E-3	0.037
Cerebrospinal fluid	0.61 (0.44–0.78)	8.8E-4	8.1E-4	0.171
Optic chiasm	0.60 (0.41–0.78)	1.4E-4	1.2E-4	0.164
Total corpus callosum	0.62 (0.45–0.79)	2.0E-3	1.7E-3	0.058
Visual MTA (Scheltens)	0.71 (0.59–0.84)	1.0	1.6	0.007
AD cortical thickness (mm)	0.65 (0.48–0.82)	2.8	2.8	0.084

The Wilcoxon rank sum test was used to calculate p-values for all variables. AUC values from cross validation. **Key**: Aβ amyloid beeta protein, APOE apolipoprotein E, AUC area under the ROC curve, BP blood pressure, CI confidence interval, ICV intracranial volume, MTA medial temporal lobe atrophy. **Footnotes:** [†]: One $A\beta+$ person was missing data

A pragmatic analysis on the value of the different predictor modalities was also conducted and is shown in detail in Table 4 of the Study III manuscript. A combination of modalities that require no specialized equipment—demographic information, cardiovascular data, and cognitive measures—predicted amyloid positivity at AUC 0.62. The APOE genotype or MRI could each improve this to AUC 0.71–0.72. A simple model using only the APOE genotype and a visual MTA assessment jointly predicted amyloid at AUC 0.81, a result superior to that of the complete model.

5.2.3 Associations between biomarkers of DM and brain amyloid (FINGER)

The FINGER IR/DM cohort of 41 participants were on average 71.1 years old, 39% were Aβ+, and 15% had DM (Table 1, p. 71). The frequency of DM or BMI did not differ in the outcome groups, but APOE ϵ4 allele was more frequent in the Aβ+ group (56% vs. 12%). Table 7 presents the mean concentrations of the biomarkers in the Aβ- and Aβ+ groups in the left panel. The insulin plasma concentration was statistically significantly lower in Aβ+ individuals at the 95% confidence level before correction for multiple comparisons. Differences in the insulin-related measures C-peptide concentration—cleaved during insulin production—and HOMA-IR—a derivative index value–were significant only at the 90% confidence level. The plasminogen activator inhibitor-1 (PAI-1) concentration was lower in Aβ+ individuals at the 95% confidence level. Other biomarkers showed no significant differences.

Logistic regression models were built iteratively for the metabolic markers using different sets of potential confounders. The final models were estimated using the DM status and APOE ϵ4 carrier status as confounders. The coefficient of the APOE genotype was significant in all models, and that of the DM status was not in any model. Model coefficients for all markers are presented in Table 7 in the right panel. The linear regression model equation is included in the table legend. Before correction for multiple comparisons, coefficients of C-peptide, insulin, PAI-1, and HOMA-IR were significant. The coefficients indicated higher IR and elevated PAI-1 to be associated with lowered odds of Aβ+. After correction these four markers were significant only at the 90% confidence level. Models with either BMI, age, or sex as additional confounders showed a similar pattern, and no differences in significance after correction were observed.

Table 7: Population characteristics and logistic regression coefficients in the FINGER IR/DM population.

	Mean concentration[a]			Logistic regression model	
Metabolic marker	Aβ-		Aβ+	B[b] (95% CI)	p-value
C-peptide (10^3 pg/ml)	1.31	*	0.95	-5.7 (-10.4 – -1.1)	0.016†
Ghrelin (10^3 pg/ml)	1.57		1.55	0.1 (-6.1 – 6.3)	0.972
GIP (10^3 pg/ml)	0.29		0.29	-1.5 (-5.4 – 2.3)	0.436
GLP-1 (10^3 pg/ml)	0.59		0.58	0.0 (-8.8 – 8.8)	0.998
Glucagon (10^3 pg/ml)	1.07		1.00	-2.1 (-11.3 – 7.0)	0.646
Insulin (10^3 pg/ml)	0.27	**	0.17	-4.5 (-8.3 – -0.8)	0.017†
Leptin (10^3 pg/ml)	7.55		6.06	-1.6 (-4.1 – 0.8)	0.191
PAI-1 (10^3 pg/ml)	5.31	**	4.16	-13.3 (-24.0 – -2.6)	0.015†
Resistin (10^3 pg/ml)	2.22		2.03	-3.7 (-10.1 – 2.8)	0.266
Visfatin (10^3 pg/ml)	4.83		4.43	-2.0 (-6.8 – 2.7)	0.401
Adiponectin (10^6 pg/ml)	5.45		6.03	-0.3 (-2.3 – 1.8)	0.808
Adipsin (10^6 pg/ml)	1.21		1.45	1.1 (-2.1 – 4.2)	0.500
fP-Glucose (mmol/l)	5.92		6.30	4.8 (-9.3 – 18.9)	0.505
B-HbA1c (mmol/mol)	36.72		37.25	15.0 (-10.9 – 40.9)	0.258
HOMA-IR (mmol·mU/l^2)	2.06	*	1.33	-4.5 (-8.3 – -0.7)	0.019†

Regression: $ln(Y_{A\beta+}/Y_{A\beta-}) = C + B_{DM}X_{DM} + B_{APOE}X_{APOE} + B_X log(X)$

Key: Aβ amyloid beta protein, GIP Gastric inhibitory polypeptide, GLP-1 Glucagon-like peptide-1, PAI-1 Plasminogen activator inhibitor-1, HbA1c Glycated hemoglobin, HOMA-IR Homeostatic Model Assessment for Insulin Resistance. **Footnotes**: [a]: Group differences tested for significance using the Mann-Whitney U test, * for significance at 10% confidence level, ** for 5% ; [b]: Coefficient of log-transformed value.

6 DISCUSSION

6.1 PREDICTION OF INCIDENT DEMENTIA IN THE YOUNGER OLD

Dementia prediction up to ten years into the future in the CAIDE general population samples of cognitively healthy individuals succeeded well (AUC 0.75–0.79). The mean ages were 70.1 and 70.5 years in the main and extended populations, respectively. The internally validated performance was on par or slightly better than the published values for the multimodal models identified in section 2.8.4 (p. 48). The externally validated performance is in general lower, and that would be expected for the CAIDE DSI models also. In age-matched general population cohorts (60 yr.<age<80 yr.), the externally validated performance for previously published prediction models was in the range of AUC 0.68–0.89 in follow-up studies of 3–6 years. For longer follow-up times of 8–10 years in DM populations and 21 years in a general population the AUC was 0.75 in all cases. None of the externally validated late-life prediction models included APOE genotype data, and no factors describing longitudinal change in any modality were included apart from fasting glucose variation in a DM cohort.

Interestingly, the best performing model used a free recall score as a solitary predictor for incident dementia over a 3–5-year period. The score achieved AUC 0.89 over a four-year period in a 70-year-or-older cohort with subjective memory complaints (Derby et al., 2013). Another validation study had similar results in a population with no memory complaint requirement (Mura et al., 2017). In those studies, adding sociodemographic predictors or APOE did not significantly improve the results. Results from the CAIDE populations mirror this in that cognitive testing results were the best predictors. However, adding other modalities did improve prediction results. Age was also a relatively strong predictor, as would be expected given its well-established status as a risk factor.

Another noteworthy model with published results used only data from UK health registries with very good results (AUC 0.84; Walters et al., 2016). The model relied on recorded data only, and the authors suspected dementia diagnoses to be under-recorded, possibly lowering performance. One would also assume that health records would accrue more rapidly for individuals with health problems and dementia risk factors, possibly leading to an enrichment of the dementia risk in the study population. The reported AUC is in any case surprisingly high compared to other similar prediction models. The CAIDE extended population also utilized public health records, but not to infer predictor data, only to establish dementia diagnoses. The sensitivity of the Finnish hospital and drug prescription registries is in the range 62–71% for AD and/or dementia, showing an underrepresentation of dementia as hypothesized by Walters et al. (2016). The prediction results were overall poorer in

the extended model, but the relative importance of predictor modalities remained the same. Only the vascular measurements category did markedly worse in comparison. The extended population may include individuals with poorer general health, who were not able to take part in the second late-life visit. They may have had a higher dementia incidence due to risk factors, or they may have died at a younger age before dementia onset. The dementia incidence was higher in the extended population (15% vs. 6%). Individuals who died without a dementia diagnosis in health registries had to be excluded from the extended model because the DSI cannot account for disease-free survival time as a variable but can only take into account dementia status at the end point.

The APOE genotype, in predicting dementia, performed worse than any other modality. For the midlife CAIDE risk score, the APOE offered a small improvement in predictive power. Some prior models have included APOE information as it has demonstrated a benefit in prediction, whereas other newer genetic markers have offered little additional benefit (Tang et al., 2015). The APOE ϵ4 prevalences of 32% (main population) and 34% (extended population) were roughly in accordance with previously published prevalence estimates of around 33–42% for North European middle-aged subjects and 17% for centenarians (Norberg et al., 2011). The FINGER population had a similar ϵ4 prevalence.

Parameters of vascular health did not feature in the CAIDE late-life models as prominently as they did in the midlife models. BP measurements were included in the main model but not in the extended model. Both populations, however, included predictors that quantify the change from midlife to the late-life prediction baseline. Change in the BMI—that is, less weight gain in the dementia group—was a better predictor of incident dementia than change in BP, or any cross-sectional vascular measure. The presence of cardiovascular comorbidities did not predict dementia well, which may in part be due to the fact that only conditions severe enough to be recorded in the Hospital Discharge Register were included. This can also explain the relatively low recorded prevalence of DM in the CAIDE populations—2% and 3% in the respective main and extended populations.

These results in dementia prediction in the younger old highlight the potential for identifying individuals who are most at risk of developing dementia. These are the individuals who would benefit the most from targeted interventions. The model was internally validated as per current guidelines (Collins et al., 2015), and the use of a general population sample will support good generalizability in external populations in the future. The DSI prediction model also shows which risk factors are important at a population level. The tool also allows for an analysis of risk profiles of individuals. Such a feature could be useful in a clinical setting when highlighting or targeting an individual's most relevant risk factors.

6.2 PREDICTION OF INCIDENT DEMENTIA IN THE OLDEST OLD

The Vantaa 85+ dementia prediction cohort was almost twenty years older than the CAIDE late-life populations, and the sample was highly representative of the local age cohort. 98% of all eligible residents participated initially. Despite the high baseline mean age of 88 years, a mean follow-up time of 5.6 years was achieved. The APOE ϵ4 allele prevalence was in line with published Finnish population estimates. The Dementia incidence was high compared to the CAIDE populations at 40% per a mean of 6 years follow up versus 6–15% per a mean of 8–9 years, which is to be expected in this age cohort (Gardner et al., 2013).

The dementia prediction performance overall (AUC 0.73) was weaker than for the two younger CAIDE populations (AUC 0.75–0.79), but better than for the only age-matched validated prediction model identified in section 2.8.4 (p. 48). The health-registry-based model by Walters et al. (2016) had practically no predictive power in an 80+ population (AUC 0.56), although that model lacked cognitive measures. The authors attributed the poor performance partly to the lack of routine health check-ups and resulting lack of registry entries in that age cohort. The results for younger cohorts were generally better than in the Vantaa 85+ study.

Measures of cognition were the best predictors of incident dementia for the Vantaa 85+ cohort—which is analogous to the CAIDE models. However, other modalities added little to the performance of cognitive questionnaires (cognition group AUC 0.72). A lower duration of education and low competence in daily activities were predictive of dementia, but had a clearly lower level of performance. Importantly, age was not a predictor of dementia in this age group. This is contrary to what would be expected, as the incidence in this age group is high and even relatively small baseline age differences could potentially be reflected in differences in the incidence rates. The FINGER eligibility criteria may have affected this. Additionally, vascular health was not predictive. This contrasts with midlife prediction models, and also with the CAIDE models, in which cardiovascular measurements and especially changes in those measurements were predictive. A large autopsy study by Jellinger and Attems (2010) may help explain this finding. The relative prevalence of a pure form of VaD at death was shown to decrease with increasing age from age 60 to 90+, and the relative prevalence of AD and mixed-AD pathology was shown to increase. Moreover, the prevalence of pure AD was found to decrease after the age of 90. This finding supports the pattern seen in the Vantaa 85+ study. The mechanisms leading to vascular brain pathology may be relatively less important than in younger age groups. The clinical phenotype may perhaps be dominated by AD-type pathology and its combined effect with other brain pathologies.

The APOE ϵ2 allele was predictive of incident dementia. In younger populations ϵ2 is thought to be protective. The status of the ϵ4 allele as a poor predictor was expected based on previous studies in the very old (Juva et al., 2000; Corrada et al., 2013), but the outright negative effect of ϵ2 has not been shown before. The ϵ2 allele has been shown not to be protective of dementia in the oldest of the old in shorter follow-up studies (Skoog et al., 1998; Juva et al., 2000; Qiu et al., 2004), and one study

demonstrated a deleterious effect on the VaD incidence (Skoog et al., 1998). In the Vantaa 85+ cohort, homozygous ϵ3 genotype was protective of dementia. The negative effect of the ϵ2 allele may be explained by findings in the Vantaa 85+ pathology prediction cohort as discussed in section 6.4.1.

6.3 PREDICTION OF BRAIN AMYLOID AND AD-TYPE PATHOLOGY

6.3.1 Frequency of amyloid beta, APOE ϵ4, and dementia

Two studies had available data for predicting brain Aβ accumulation. The Vantaa 85+ study focused on a general population sample with a mean age of 89 years, whereas the FINGER-PET population consisted of at-risk individuals from a general population of around 71 years of age. Nominally the FINGER prediction model was diagnostic and the Vantaa 85+ model prognostic, but the mean follow-up time of 4 years was short in the context of AD-type pathology. Aβ and tau pathology develop during a period of up to decades (Jack et al., 2013), and most of the AD-type pathology observed at the end of the Vantaa 85+ follow up was probably present at the baseline. For this type of pathology, the model more likely represented a mixed diagnostic/prognostic model. In-vivo PET imaging of amyloid has had good concordance with neuropathologically determined Aβ positivity. The sensitivity of the visual determination of amyloid positivity in PET imaging is 92–98%, and specificity 98–100% when using pathology as a gold standard (Clark et al., 2012; Sabri et al., 2015). The dementia incidence of 36% in the Vantaa 85+ pathology prediction population is in line with previously published estimates of 18–38% in this age cohort (Gardner et al., 2013).

The prevalence of Aβ pathology at the time of autopsy was more similar to an AD-dementia population than an old-age CN population. The Vantaa 85+ cohort was on average 93 years old at autopsy and 77% were Aβ+. For the 80–90-year-old cohort, the in-vivo Aβ prevalence estimate is 33–59% for CN individuals, 60–71% for individuals with MCI, 79–84% for individuals with AD-dementia, and 36–50% for a VaD cohort (Jansen et al., 2015; Ossenkoppele et al., 2015). The Aβ incidence increases steeply after approximately the age of 70 especially in ϵ4 carriers (Jack et al., 2015b). Many participants in the Vantaa cohort were older than the range of ages for which these prevalence estimates have been published. Additionally, a significant portion of the nondementia group may have had MCI, for which the participants were not tested. These facts, and methodological differences between the Vantaa 85+ post-mortem assessment and the in-vivo ascertainment of Aβ+ used in the reference studies may explain the observed difference in Aβ prevalence. In the FINGER cohort with a mean age of 71 years, the Aβ prevalence was 42%, which is high in comparison to the previously published estimate of 16–33% for CN 60–80-year-olds (10–28% noncarriers and 29–68% carriers; Jansen et al., 2015). The prevalence range estimate for individuals with subjective cognitive impairment is 17–35%, and for MCI 37–60% (Jansen et al., 2015). The Aβ prevalence of the FINGER-PET population was closer to

that of an MCI population. The effect is probably due to the FINGER recruitment criteria, which may have enriched the participant population with subclinical AD-type pathology.

The APOE ϵ4 prevalence of 21% in the Vantaa 85+ cohort at the baseline is roughly in agreement with previously published data on APOE genotype frequencies in Northern Europe (Norberg et al., 2011). A noncarrier survival effect has been observed in Finnish centenarians, among which the APOE ϵ4 frequency was 8% and the ϵ2 frequency was enriched to 7% (Louhija et al., 1994). In the Vantaa 85+ cohort, 16% were ϵ2 carriers. The surviving APOE ϵ4 carriers in this age group were not subjected to the same elevated risk of incident dementia as younger carriers, although the prevalence among carriers remains high (Corrada et al., 2013; Gardner et al., 2013). The APOE ϵ4 prevalence in the FINGER cohort at 30% was in line with previously published estimates (Norberg et al., 2011).

6.3.2 Amyloid beta prediction

The overall prognostic amyloid prediction performance was 0.66 in the Vantaa 85+ study, rated "poor" using terminology by Hosmer et al. (2013). Previously published diagnostic models indicate better prediction performance in younger cohorts. The one study identified in section 2.8.5 with an older cohort used age, sex, family history of dementia, subjective memory complaint, APOE, and a global cognitive score as predictors and achieved an AUC value of 0.70 (Mielke et al., 2012). Considering that no report of cross-validation being used was found, the performance of that model is probably on par with the Vantaa 85+ model. Models with fewer modalities had poorer performance. The predictors chosen for these models consist of risk factors that have been studied in younger age groups, and they may not be equally relevant in older cohorts. A similar effect has been demonstrated in the case of dementia risk scores, which have not performed as well outside their assigned age cohorts.

The prediction of Aβ+ on PET in a younger cohort produced better results. Performance of the complete FINGER-PET model including structural MRI achieved an AUC value of 0.78, and 0.71 without MRI. Both could be considered "acceptable" as per the criteria by Hosmer et al. (2013). Two models identified in section 2.8.5 reported AUCs on models in a CN population: these were a model by Mielke et al. (2012), and a model in a somewhat younger population (>50 yr.) that included MRI (AUC 0.74 cross-validated; ten Kate et al., 2018). Performance in FINGER-PET study was somewhat better, although the population was much smaller (48 vs. 483 for the former and 337 for the latter) possibly leading to overfitting and impairing its generalizability. The AUCs of models involving MCI populations were typically greater than 0.80. These results in the younger old cohort show the potential for such models in identifying Aβ+ individuals even at a pre-MCI stage. A prediction model like this would facilitate the identification of populations with a considerably higher prevalence of Aβ+, thus reducing the number of invasive, time-consuming, and costly assessments during the screening process of a clinical trial, for example.

The APOE genotype is one of the two identified predictors of Aβ pathology in the

oldest old, competence in daily activities being the other with a similar AUC value. Prediction performance of the ϵ4 allele was better in the younger, late-life FINGER population (0.69 vs. 0.60). The ϵ2 allele was protective against Aβ accumulation in the Vantaa 85+ study, a finding which was analogous to another study of the oldest old (Berlau et al., 2013). Aβ positivity has been observed to rapidly increase after the age of 70 in ϵ4 carriers while maintaining more or less the same rate of increase in noncarriers (Jack et al., 2015b), which would imply that the prediction performance of the APOE genotype should improve with advancing age. Findings in the two studies of this thesis contradict this, possibly due a ϵ4 noncarrier survival effect in the population of the oldest old.

Cognition was not predictive of Aβ in the 85+ population, and only the executive function subdomain was predictive in the FINGER study. Lower cognitive scores have previously been linked to Aβ+ in CN individuals (Bennett et al., 2006; Petersen et al., 2016), although not in all studies (Rowe et al., 2010; Oh et al., 2012; Wirth et al., 2013). The FINGER population was mildly enriched for lower cognitive performance, and the population thus lacked one tail of the cognitive score distribution.

Cardiovascular factors were not included in the 85+ model at all, and in the FINGER population low BMI had modest predictive power while hypertension had none at all. A low BMI at younger-old ages has previously been associated with an Aβ load (Ewers et al., 2012; Toledo et al., 2012), although these studies also included individuals with MCI and dementia at the baseline.

No sociodemographic factors—including age—were predictive. Although Aβ pathology becomes more prevalent with increasing age, age was not a useful predictor. This may be due to a saturation effect in the Vantaa 85+ cohort with Aβ prevalence of 77% at death, but the relatively wide age spectrum of FINGER-PET participants (60–77 yr.) should have powered age as a predictor in that population, especially given the previously noted accelerated increase in the Aβ prevalence after 70 years of age in ϵ4 carriers (Jack et al., 2015b).

Structural MRI measurements were the strongest predictors in the late-life population, which was to be expected. Decreased brain volumes and a high MTA rating are indicative of neurodegeneration, which is more likely to be present in the Aβ+ group. In AD, Aβ pathology is accompanied by neurodegenerative processes, partly associated to the tau pathology (Jack et al., 2013). These associations were also evident in the PCA conducted in the Vantaa 85+ population. The first principal component "AD-type pathology" strongly linked amyloid pathology and tau pathology in the no-dementia group, and this PC also explained most of the variance in the pathology findings. In the dementia group this effect was weaker, and presence of AD-pathology indicated a lower macroinfarct load as expressed by the opposing signs of the scores. However, the first PC indicated that both groups showed most variance in relation to AD-type of pathology. That is, AD-type pathology was the most important determinant of the pathological profile even in non-demented individuals.

Few studies of CN participants have reported on the added value of MRI in amyloid prediction, but prediction in cohorts with cognitively impaired individuals indi-

cated added value of this modality. Tosun et al. (2013) showed an added benefit of adding structural MRI to prediction using the APOE genotype, which by itself was a strong predictor in the MCI study population (AUC from 0.81 to 0.88). Analogous figures in the FINGER-PET study showed an improvement from 0.69 to 0.81–0.82. Similar results were found in other studies by adding MRI to the demographic data and APOE (from 0.69 to 0.83; Tosun et al., 2014). On the other hand, change in cognition was found to be a superior substitute to structural MRI in a multimodal prediction model (Ansart et al., 2019).

Volumetric estimates of brain regions were the best predictors in a leave-one-out analysis of MRI factor modalities in the FINGER-PET cohort. As part of the multimodal model, visual Scheltens scores of MTA were almost as predictive as the set of volumetric measures. Such a visual rating is easier to obtain and would be more useful in a clinical setting and most research settings as well.

6.3.3 Associations of metabolic markers of diabetes and amyloid beta

DM has been reported to have a positive association with dementia of the AD and the VaD type, but the effect seemed to be stronger for VaD than AD (Cheng et al., 2012; Gudala et al., 2013). Studies have shown pathology underlying an elevated dementia incident rate in elderly DM patients to skew towards vascular pathology instead of tau and Aβ pathology (Ahtiluoto et al., 2010). The DM–Aβ association was not significant in other previous studies (Moran et al., 2015; Roberts et al., 2014). Thus, the mechanisms of the DM–AD association are unclear, as is the role of Aβ. IR is a hallmark of DM2, and central nervous system IR has been suggested to be linked to Aβ pathology through neuroinflammatory pathways or through competitive cleavage of insulin and Aβ by the same enzyme (de la Monte, 2017). The epidemiological evidence discussed in section 2.6.4 showed this association to be rather weak, with no association in the elderly, and evidence being mixed in younger age groups. The suggestive finding in this thesis of lower IR in Aβ+ elderly without dementia or substantial impairment adds to these prior studies. However, the findings in Study IV were not significant after correction for multiple comparisons.

The prevalence of DM was 15%, and it did not differ significantly between the outcome groups. This prevalence was in good agreement with the estimated Finnish prevalence of DM2 (65–74 years old cohort, previously diagnosed 10%, previously undiagnosed 12%; Peltonen et al., 2006).

To the author's knowledge, no data has been published on the association of peripheral blood PAI-1 levels and in-vivo Aβ markers. In prior studies, PAI-1 in CSF has been reported to have no association with AD status (Martorana et al., 2012; Leung et al., 2015). Study IV suggested higher levels of PAI-1 to be protective against Aβ, although not significantly after correction for multiple comparisons. PAI-1 downregulates the activity of the protein-cleaving plasmin system, and it is considered to be a risk factor for atherosclerosis in the periphery due to its prothrombotic effect. In the central nervous system, however, PAI-1 and the plasmin system may interact with Aβ fibrils and possibly affect plaque formation (Bi Oh et al., 2015), or be directly

neuroprotective (Cho et al., 2013).

Both the HOMA-IR and PAI-1 findings suggested a higher potential load of vascular pathology in Aβ negative individuals, at least in the periphery. It is unclear whether this association with PAI-1 is mediated through effects in the central nervous system, or if the Aβ load is reduced due to effects in the cardiovascular system. The study population was also prefiltered—albeit fairly mildly—by cardiovascular risk and cognition. The FINGER participants with low IR represent those who have maintained adequate insulin sensitivity despite an elevated cardiovascular risk. In this specific subpopulation the mechanisms linking IR and Aβ accumulation may be different.

The FINGER-PET population and the derivative IR/DM population was small consisting of only 41 subjects. This limited the use of confounders in the regression analysis and limited power.

The exploratory study did not find any other suggestive associations between the tested markers and Aβ positivity. To the authors knowledge, no data has been published on a complete assay of IR/DM markers previously. FINGER is an ongoing longitudinal study and may in the future allow for the analysis of these markers over time.

6.3.4 Prediction of other AD and amyloid related pathology

Tau tangles were predicted in the Vantaa 85+ population at a slightly lower performance than for Aβ. Predictive models for the neuropathological AD status—with an intermediate or high likelihood of AD based on a combination of Braak and CERAD scores (Hyman et al., 2012)—had a better performance than models predicting either Aβ or tau by themselves. The role of APOE was similar as for Aβ: ϵ4 allele was predictive of pathology, and ϵ2 was protective. For tau, ϵ3 homozygousness was protective rather than ϵ2 carriership. This difference may be linked to a finding by Berlau et al. (2009) on elevated CERAD scores at autopsy in both ϵ2 and ϵ4 carriers, although ϵ2 did not raise the odds of developing dementia in that study like ϵ4 did.

The tangle count was predicted, in contrast to Aβ pathology, by the total cholesterol and LDL. Whether there is a vascular effect on tau pathology specifically is unclear, or whether other mechanisms underlying the previously observed risk increase associated with midlife vascular risk factors can explain the observation. The neuropathological aggregate for AD did not have lipids or any other vascular factors as predictors. However, subjective memory decline was a predictor, although a rather weak one. This may indicate that the aggregate measure of AD pathology corresponds better to the clinical phenotype than Aβ or tau separately.

Cerebral amyloid angiopathy was predicted by APOE alleles in the same way as Aβ. Interestingly, cardiovascular comorbidities were predictive of lower CAA. Arterial amyloid deposition has been associated with intracerebral hemorrhages (ICHs), and the incidence of dementia after an ICH is high (Wermer and Greenberg, 2018; Banerjee et al., 2018). Persons with CAA without an ICH have been reported to score lower on cognitive testing, possibly because CAA pathology of the arteries and corti-

cal arterioles also predisposes the patient to cortical microinfarctions (Banerjee et al., 2018). The effect seen in the Vantaa 85+ study may be partly due to a selection effect, where at the baseline individuals with both a high cardiovascular risk load (hypertension etc.) and CAA may have been excluded due to dementia or they may not have survived to old age. The 85+ CAA population may thus represent persons with high cardiovascular resiliency to ICH due to CAA. Cerebrovascular comorbidities, however, did not show an effect. CAA was also predicted by male gender.

In the PC analysis of the no-dementia group, CAA contributed to the first PC—"AD-type pathology"—with an equal contribution to neuropathological AD. In the dementia group, CAA contributed with a somewhat smaller coefficient and vascular pathology contributed with an opposite sign. This may point to a differential role of CAA in amyloid accumulation in healthy individuals with subclinical amounts of pathology and in the brain of a dementia patient where vascular insults modify the clinical phenotype.

6.4 PREDICTION OF OTHER BRAIN PATHOLOGY

6.4.1 Vascular pathology

The prediction performance for vascular pathology was better than for other types of pathology. The performance for WM macroinfarcts was the best, with blood lipids being stand-out predictors. Lower HDL and lower LDL were predictive of the presence of WM macroinfarcts. This result is counterintuitive, as lower HDL could be expected to have a negative vascular effect, and likewise a lower LDL could be expected to have a positive effect. Additionally, cerebrovascular comorbidities were predictive of the same pathology. Perhaps cerebrovascular insults were of a more detrimental magnitude in the high-LDL population and the results show a survival effect. It is also possible that these lipids and their potential changes over time prior to the baseline study visit have a completely different significance concerning the on brain health of an 85+ population than for the vascular health of younger populations. APOE $\epsilon 2$ carriership was predictive of WM macroinfarcts, a finding which also points to a survival effect. In younger populations both the $\epsilon 2$ and $\epsilon 4$ alleles have been linked to more pronounced findings of cerebrovascular disease on MRI (Schilling et al., 2013). The findings indicating an increased risk of WM infarcts due to $\epsilon 2$ may be a possible explanation as to why the $\epsilon 2$ allele was predictive of dementia in the Vantaa 85+ study.

Macroinfarcts in the cortex were predicted by the APOE genotype in the same pattern as they were for tau. The aggregate measure of all macroinfarcts was predicted by factors better representative of the clinical state, namely poorer cognition and competence in daily activities. It is notable, that objective measures of cognition were predictive of vascular pathology, but not AD-type pathology.

The presence of cerebral microinfarcts was only predicted by short duration of education. Microinfarcts are a hallmark of CAA (Wermer and Greenberg, 2018), and these pathologies could be expected to share predictors. No meaningful link was

seen on the PCA either.

The PCA showed a differential pattern of vascular pathology in the no-dementia and dementia groups. The second PC "Vascular pathology" was the second most important determinant of variance in the no-dementia group, but did not show a clear pattern in the dementia group. It would be tempting to interpret the no-dementia cohort temporally as a pre-dementia cohort with more variability in the level of vascular pathology. However, the difference seen in PC2 may also be driven by other determinants that differentiate the no-dementia and dementia groups. A survival effect may also have an impact, as discussed above in relation to the APOE genotypes.

6.4.2 Hippocampal sclerosis, TDP-43 protein, and α-synuclein

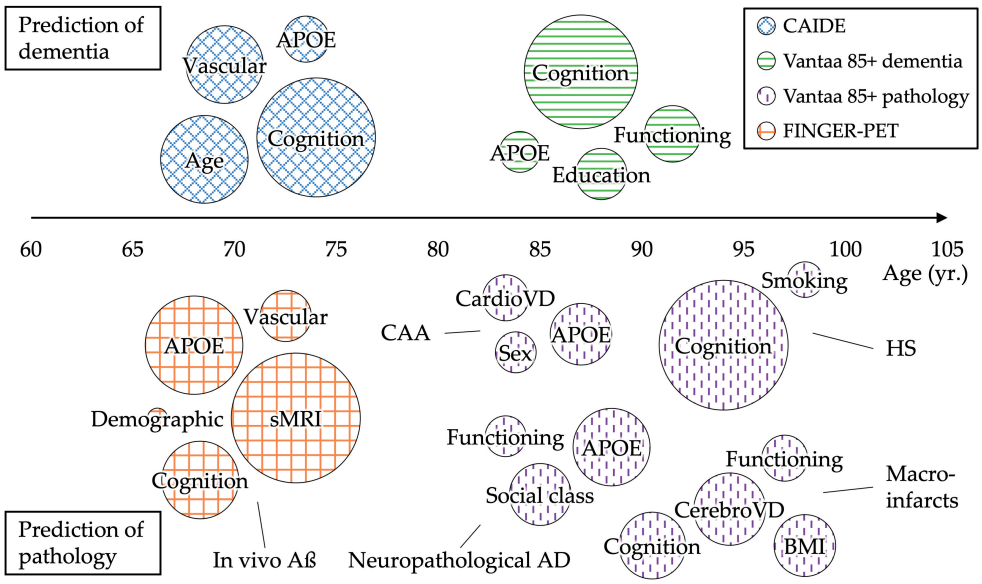
The prevalence of HS and TDP-43 accumulation was 7% and 13%, respectively, in the Vantaa 85+ autopsy population, as would be expected based on previously published estimates. HS is predominantly present in the oldest of the old, and prior research indicates a prevalence of 5–30% in 90–100-year-olds (Nelson et al., 2013). The prevalence of the strongly HS-associated TDP-43 in cognitively healthy elderly is estimated at 24% (13–34% at a 95% confidence interval) worldwide (Nascimento et al., 2018), and at 14% (9–20%) in Europe.

Low cognitive measures predicted HS well, and the overall performance was better than for other pathologies. Hippocampus-associated memory tasks—such as wordlist task, which shows deficiencies in the HS+ autopsy population—have been previously shown to be associated with HS, while cortex-dependent tasks such as verbal fluency remain relatively unaffected (Nelson et al., 2013). TDP-43 was predicted only by depressive symptoms. Disease progression in TDP-43 accumulation is varied (Nascimento et al., 2018), and it is difficult to assess whether the effect of depressive symptoms seen here is generalizable.

No predictors were found for α-synuclein pathology, which is in line with prior research indicating no clear pattern of risk factors.

6.5 PREDICTION OF DEMENTIA VERSUS BRAIN PATHOLOGY

The prediction of incident dementia and different brain pathologies showed differences in their overall performance and the relative importance of predictor modalities, which additionally varied in importance during the life course. Figure 1 visually summarizes the prediction results of this thesis. The horizontal axis represents the late-life years of the life course, and in the context of this thesis this is further divided into younger and older old age groups. Predictors are represented by spheres, whose sizes correspond to the observed prediction performance. As evident in the upper panel, cognition was the dominant predictor modality for dementia throughout old age. Age was still relevant at the beginning, but not towards the end, when functional measures gained relevance instead. Vascular predictors could be useful at the beginning of the late-life period, although not to the same degree as in midlife. The APOE genotype was not a very significant determinant of incident dementia in comparison.



Key: Aβ amyloid beta protein, APOE apolipoprotein E, BMI body mass index, CAA cerebral amyloid angiopathy, CardioVD cardiovascular disease, CerebroVD cerebrovascular disease, HS hippocampal sclerosis, sMRI structural magnetic resonance imaging

Figure 1: Predictors of dementia and neuropathology in younger and older old age. Sphere size corresponds to predictor AUC.

For brain pathology, predictors showed a different pattern of importance. The APOE genotype was more predictive than cognition was of Aβ pathology throughout old age, and of neuropathological AD and CAA in the oldest of the old (also of tau pathology, which is not shown in the figure). This underlines a disconnect between the clinical phenotype and underlying AD and amyloid pathology. In general, AD pathology can be found in elderly persons without cognitive impairment (Bennett et al., 2006). Additionally, APOE ϵ4 has been shown to modulate the link between Aβ load and cognition (Kantarci et al., 2012). Specifically, ϵ4 carriers experience more decline in cognition with an Aβ load. An APOE ϵ4-stratified analysis would be interesting to perform in the future to test this in the pathology populations. Cognition was, however, a strong predictor of hippocampal sclerosis in the oldest of the old and a weak predictor of cortical macroinfarcts, for which APOE played no role (the pattern was somewhat different for macroinfarcts in the cortex and in WM).

Whereas a low level of education was predictive of dementia, this finding did not seem to have a counterpart in pathology. The only effect was seen on microinfarcts (not shown in figure), but this had a low performance. According to a definition by Stern et al. (2018), cognitive reserve is the ability of cognitive processes to adapt to changes and insults of the brain. Findings in the Vantaa 85+ study agree with the notion that the cognitive reserve due to higher education is a purely functional entity with no correlate in brain pathology. Cognitive reserve is thought to arise from either neural reserve—implying resistance of certain brain regions to insults—or neural compensation, where unaffected brain regions compensate for the dysfunction of affected regions. There is functional MRI evidence for both mechanisms, with neural compensation becoming more important in more developed cognitive impairment (Anthony and Lin, 2018). Among other factors, physical activity has been considered as a contributor to cognitive reserve (in addition to the cardiovascular benefits), and studies have shown an increase in physical activity to be associated with structural brain changes (Rovio et al., 2010; Xu et al., 2015). None of the pathologies studied in the Vantaa 85+ study reflect these associations. It should be noted that the mean length of education was low at 4.3 years, and many other determinants of cognitive reserve may have had an effect along the life course.

The negligible role of age in dementia prediction in the oldest of the old was replicated in the lower pathology panel in Figure 1, where no pathology was predicted by age apart from the FINGER-PET model in which the AUC was 0.45. Gender was also omitted in almost all models for both dementia and pathology. However, CAA was predicted by male gender. Male predominance has been shown at least in one study, in which 88% of the studied AD patients had CAA, and male participants had significantly higher CAA scores (Shinohara et al., 2016). CAA was strongly associated with AD and was also predicted by the APOE ϵ4 allele. Dementia prediction models included APOE as a predictor, but the effect of gender seen on CAA pathology did not extend to the clinical dementia models.

Structural MRI was the dominant predictor of amyloid pathology in younger old age. This is to be expected given the association of brain amyloid and neurodegener-

ation and atrophy, and the elevated a priori probability of pathology due to preselection. Volumetric brain measures are typically also used as measures of brain reserve (Stern et al., 2018). The FINGER study inclusion criteria may have led to an overrepresentation of low brain reserve i.e. lower brain volume on MRI possibly affecting the generalizability of these results. Whether amyloid positive individuals with higher brain capacity have better cognitive performance should be further investigated in larger cohorts.

Even without MRI data, in-vivo prediction of prevalent Aβ in the younger old was more effective than prediction in the older old group, where additional number of years of follow up were allowed for the pathologies to develop. This, given the similar pattern in dementia prediction, calls for earlier intervention during the life course, where the models indicate a higher potential for intervention in causal processes underlying the predictors, as well as better possibilities to find less advanced targetable pathological changes.

7 CONCLUSIONS

The findings from the studies of this thesis support the following conclusions:

- The ten-year risk of late-life dementia was predicted well by multimodal predictors. Cognition was the most important predictor, but genetic, vascular, and life-style predictors added value.
- Changes in the parameters of vascular health may predict incident late-life dementia more accurately than cross-sectional measurements.
- Cognition was the dominant predictor of incident dementia in the oldest of the old. Other predictors recognized in younger populations lost value in this age group.
- In the oldest of the old, the prediction of vascular pathology succeeded moderately well, whereas the prediction of AD-type pathology was poor.
- Brain amyloid positivity in the cognitively healthy elderly could be predicted using multimodal predictors including APOE genotype and structural MRI at an moderate-to-excellent level—which would be well-suited for amyloid prevalence enrichment in populations.
- Two conclusions can be drawn on the role of APOE polymorphism:
  - The $\epsilon 4$ allele predicted brain pathology better than the clinical outcome of dementia in late life.
  - The $\epsilon 2$ allele was not protective of all pathology in the oldest of the old; $\epsilon 2$ carriership may predict white matter macroinfarcts over four years.
- High insulin resistance and high levels of PAI-1 in individuals with a lower brain amyloid burden may indicate brain resilience to higher a cardiovascular load.

These results demonstrate how the use of machine learning systems and multimodal data can predict dementia and brain pathology years before incidence. This will allow for a wider window of opportunity for prevention. The studies pointed to novel differences in dementia and pathology prediction, which impact the choice of predictors for different applications of the models. Additionally, prediction in younger old individuals was more effective and may also provide more time and opportunities for intervention. Prediction of the amyloid status proved accurate to a level that may substantially aid in the design of intervention trials targeting amyloid, for example. The observed link between high insulin resistance and a high level of PAI-1, and a low amyloid burden may prove useful in early detection of disease or offer insight into preventive strategies.

This machine learning-based approach to multimodal prediction of both dementia and brain pathology is relatively new in the dementia prevention field, and should be further validated in other cohorts, including also other new and existing biomarkers that were not tested as part of this thesis.

8 FUTURE PERSPECTIVES

Specific key recommendations have been made to advance future dementia risk models (Ritchie and Muniz-Terrera, 2019). Risk models would benefit from biomarker predictors that would increase their performance at an early disease stage where traditional predictors are insufficient. New markers of disease, such as tau-PET imaging, may prove potent predictors of disease, but are not necessarily practical on a large scale. Inclusion of a broad set of clinical predictor modalities and more precise testing of cognition may help indicate earlier changes associated with disease. The DSI machine learning algorithm with its multimodal technical design is a step towards this goal. In dementia prediction, cognition was a strong predictor, and a model combining even more accurate measurement of cognition and other clinical predictors could be useful worldwide in under-resourced clinics with limited possibilities for biomarker testing. For example, such a model could be used for targeting more costly and complex biomarker testing towards smaller, better defined risk groups. Additionally, to increase the usefulness of prediction models, modifiable risk factors should be included for the purposes of preventive and disease-modifying efforts. Such predictors were well represented in this thesis due to the design of the original study cohorts. However, few were found useful in the final models, especially for the oldest of the old. Recent guidelines on risk reduction of cognitive decline and dementia by the World Health Organization (2019) recommend intervention on several modifiable risk factors despite, in many cases, low or moderate levels of evidence, because the benefits overweigh the risks both for cognition and health generally. Early intervention already in midlife has also been recommended, since several modifiable risk factors in midlife show a clearer association with dementia risk compared to older ages.

Personalized risk modeling and intervention design may be a part of the future. Factors such as cognitive reserve or genetic susceptibility modulate a person's baseline risk, and other factors may affect their response to intervention. Such effects have been observed in carriers of different APOE polymorphisms, for example (Jensen et al., 2019). Tools such as clinical decision support systems with integration into health care systems and interfaces for laying out personalized risk and intervention profiles (Mattila et al., 2012a) could prove applicable and useful even in primary care. For dementia prevention, a personalized medicine approach may be needed. Systems that are especially economical in terms of health care system resources also show promise, as the dementia-risk population is set to grow in light of current demographics and longevity gains. For example, a recent Internet-based intervention programme (Barbera et al., 2018) may offer a light-touch measure for dementia prevention requiring only small investment on an individual-by-individual basis. There may be interesting possibilities in combining such systems with health-register-based prediction models that have shown good results in finding at-risk individuals (Walters et al., 2016).

The steps taken in this thesis have contributed to the previously stated goals of identifying at-risk populations and including biomarkers as intermediate outcomes in prevention trials (National Academies of Sciences, Engineering, and Medicine and Health, 2017). Pathology prediction models can identify affected individuals for either trial participation or possibly be used as surrogate outcomes themselves in some settings. In future, these models need to be deployed in intervention trials. New and improved prediction model generations will probably benefit from utilizing longitudinal patient information from multiple sources, a task similar to those already undertaken in many other fields in the big-data era.

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TIMO PEKKALA

Dementia causes a considerable burden on individuals and societies, and interventions at earlier stages should be developed. In this thesis dementia and related neuropathology are predicted in elderly cognitively healthy individuals in order to identify high-risk individuals for interventions and to enrich targetable pathologies in trial populations. Also, the study investigates the associations of markers of early type 2 diabetes and brain amyloid deposition, a hallmark of Alzheimer's disease.

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