Resilience against Alzheimer's disease pathology and atrophy

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LUND
UNIVERSITY

DOCTORAL DISSERTATION

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Abstract:

In Alzheimer's disease (AD), β-amyloid and tau accumulate in the brain leading to neuronal loss and cognitive decline. The associations between these protein aggregates and their downstream effects are clear but not perfect, with other, largely unknown, factors explaining the discrepancy. This phenomenon has been described within the resilience framework.

We aimed to explore whether demographic factors and biomarkers of different processes in the brain could account for this disconnection between AD pathology, neurodegeneration, and cognitive decline.

In **paper I** lower cerebrospinal fluid (CSF) Aβ42/Aβ40 and smaller hippocampi were independently associated with worse cognitive function in cognitively unimpaired elderly. Age moderated the association for hippocampal volume, with a stronger correlation at higher ages. In **paper II** CSF biomarkers of axonal degeneration and amyloid pathology were independently associated with rate of cognitive decline when accounting for cortical atrophy in cognitively unimpaired elderly. In **paper III** education level and age moderated the association between tau burden and cognitive decline in patients with symptomatic AD, such that with advancing tau pathology higher education and higher age were associated with faster cognitive decline. In **paper IV** the negative effects of tau pathology on brain structure and cognition were exacerbated at higher levels of CSF biomarkers of inflammation and loss of vascular and axonal integrity, with differential associations at different clinical stages of the disease.

The associations for AD pathology with neurodegeneration and cognitive decline are moderated by age, education level, and biomarkers of neuroinflammation and loss of vascular and axonal integrity, and these moderation effects differ between disease stages. This could be interpreted within the resilience framework as these factors influence how well a person can cope with the disease. This has implications for our understanding of cognitive heterogeneity in AD and for identifying factors that prevent or delay clinical manifestations of the disease.

Key words: Cognitive resilience, brain resiliience, cognitive reserve, brain reserve, Alzheimer's disease, atrophy

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Resilience against Alzheimer's disease pathology and atrophy

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To my family

Table of Contents

Abstract

In Alzheimer's disease (AD), β-amyloid and tau accumulate in the brain leading to neuronal loss and cognitive decline. The associations between these protein aggregates and their downstream effects are clear but not perfect, with other, largely unknown, factors explaining the discrepancy. This phenomenon has been described within the resilience framework. We aimed to explore whether demographic factors and biomarkers of different processes in the brain could account for this disconnection between AD pathology, neurodegeneration, and cognitive decline.

In **paper I** lower cerebrospinal fluid (CSF) Aβ42/Aβ40 and smaller hippocampi were independently associated with worse cognitive function in cognitively unimpaired elderly. Age moderated the association for hippocampal volume, with a stronger correlation at higher ages. In **paper II** CSF biomarkers of axonal degeneration and amyloid pathology were independently associated with rate of cognitive decline when accounting for cortical atrophy in cognitively unimpaired elderly. In **paper III** education level and age moderated the association between tau burden and cognitive decline in patients with symptomatic AD, such that with advancing tau pathology higher education and higher age were associated with faster cognitive decline. In **paper IV** the negative effects of tau pathology on brain structure and cognition were exacerbated at higher levels of CSF biomarkers of inflammation and loss of vascular and axonal integrity, with differential associations at different clinical stages of the disease.

The associations for AD pathology with neurodegeneration and cognitive decline are moderated by age, education level, and biomarkers of neuroinflammation and loss of vascular and axonal integrity, and these moderation effects differ between disease stages. This could be interpreted within the resilience framework as these factors influence how well a person can cope with the disease. This has implications for our understanding of cognitive heterogeneity in AD and for identifying factors that prevent or delay clinical manifestations of the disease.

Populärvetenskaplig sammanfattning

Demens är ett övergripande begrepp som innebär försämring av olika tankemässiga funktioner, till exempel minne och planeringsförmåga. Det kan bero på många olika saker, men den vanligaste orsaken är Alzheimers sjukdom. Alzheimers sjukdom karaktäriseras av ansamling av två olika proteiner i hjärnan, β-amyloid och tau, vilket orsakar nervcellsskada och försämring av tankeförmågan. Det finns samband mellan nivåerna av dessa proteiner i hjärnan och hur mycket nervcellsskada och symtom man får, men dessa samband är olika starka hos olika individer – vissa individer kan ha betydligt större mängder än andra och ändå inte utveckla symtom. Detta indikerar att individer har olika bra motståndskraft mot dessa proteinansamlingar. De mediciner som finns tillgängliga i Sverige idag mot Alzheimers sjukdom påverkar inte sjukdomsförloppet utan ger endast symtomlindring. Därför skulle det vara av stort värde att bättre förstå mekanismerna som ligger bakom varför olika människor, med lika höga nivåer av de proteinansamlingar som orsakar Alzheimers sjukdom i hjärnan, får olika mycket symtom och försämras i olika takt.

Inom BioFINDER-studien vid Lunds universitet följs både personer med olika kognitiva symtom och friska äldre personer över tid. De genomgår kognitiva tester, magnetkameraundersökningar, bildundersökningar av β-amyloid- och tau-ansamling samt ryggvätskeprovtagningar. Genom olika statistiska modeller har vi analyserat om de ovan beskrivna skillnaderna mellan individer kan förklaras dels av variabler som ålder, kön och utbildningsnivå, och dels av markörer i framför allt ryggvätska för olika sjukdomar eller sjukliga processer i hjärnan, vilket skulle indikera att dessa faktorer kan förbättra eller försämra en persons motståndskraft mot sjukdomsprocesserna vid Alzheimers sjukdom.

I **delarbete I** använde vi data från gruppen utan kognitiva symtom. Vi fann att β-amyloid och storleken på hippocampus (en del av hjärnan som är viktig för minnet och ofta minskar i storlek vid Alzheimers sjukdom) bidrog oberoende av varandra till att förklara prestation på kognitiva tester i denna grupp. Även i **delarbete II** inkluderade vi endast personer utan kognitiva symtom. Här tittade vi dock istället på faktorer som påverkar sambandet mellan förlust av nervceller i hjärnbarken (vilket sker vid bland annat Alzheimers sjukdom) och kognitiv försämring över tid. Även här fann vi att β-amyloid var kopplat till snabbare kognitiv försämring än förväntat. Det var också ett annat protein, neurofilament light, som är en markör för skada på nervcellernas långa utskott. I **delarbete III** fokuserade vi istället på personer med symtom på Alzheimers sjukdom. Resultaten från dessa analyser visade att sambandet mellan tau-nivåer i hjärnan och dels förlust av nervceller, dels försämrad tankemässig funktion över tid, påverkades av personernas utbildningsnivå. Personer med högre utbildningsnivå hade generellt långsammare försämring tidigt i sjukdomen (det vill säga vid låga nivåer av tau) jämfört med personer med lägre utbildningsnivå, men vid långt gången sjukdom hade istället

personer med hög utbildningsnivå snabbare försämring jämfört med personer med lägre utbildningsnivå. I **delarbete IV** inkluderades både personer utan kognitiva symtom och patienter med symtom på Alzheimers sjukdom. Här ville vi undersöka om markörer i ryggvätska för olika processer som behövs för att upprätthålla hjärnans funktion kan påverka sambandet mellan tau-nivåer i hjärnan och dels förlust av hjärnvävnad, dels tilltagande kognitiva symtom. Vi fann att vid höga nivåer av markörer talande för inflammation samt skada på hjärnans kärl och nervernas långa utskott var sambandet mellan tau-nivåer och förlust av hjärnvävnad förstärkt hos personer med demens och sambandet mellan tau-nivåer och kognitiv försämring förstärkt hos personer utan symtom.

Sammantaget har vi visat att en del av den variation som observerats avseende hur starka samband proteinerna β-amyloid och tau uppvisat med både nervcellsskada och kognitiv förmåga kan förklaras med hjälp av faktorer som ålder och utbildningsnivå samt markörer för inflammation och skada på hjärnans kärl och nervernas långa utskott. Detta kan i förlängningen vara viktigt både för att förstå en persons risk för kognitiv försämring över tid och för att hitta sätt att förhindra kognitiv försämring. Det är dock viktigt att poängtera att dessa studier inte är utformade så att vi kan dra säkra orsakssamband utan det behövs mer forskning på ämnet.

List of papers

Paper I

Anna L Svenningsson, Erik Stomrud, Philip S Insel, Niklas Mattsson, Sebastian Palmqvist, Oskar Hansson. β-amyloid pathology and hippocampal atrophy are independently associated with memory function in cognitively healthy elderly. Sci Rep 9, 11180 (2019). https://doi.org/10.1038/s41598-019-47638-y.

Paper II

Anna L Svenningsson, Erik Stomrud, Sebastian Palmqvist, Oskar Hansson, Rik Ossenkoppele. Axonal degeneration and amyloid pathology predict cognitive decline beyond cortical atrophy. Alz Res Therapy 14, 144 (2022). https://doi.org/10.1186/s13195-022-01081-w.

Paper III

Diana I Bocancea, **Anna L Svenningsson**, Anna C van Loenhoud, Colin Groot, Frederik Barkhof, Olof Strandberg, Ruben Smith, for the Alzheimer's Disease Neuroimaging Initiative , Renaud La Joie, Howard J Rosen, Michael J Pontecorvo, Gil D Rabinovici, Wiesje M van der Flier, Oskar Hansson, Rik Ossenkoppele. Determinants of cognitive and brain resilience to tau pathology: a longitudinal analysis. Brain, Volume 146, Issue 9, September 2023, Pages 3719–3734. https://doi.org/10.1093/brain/awad100.

Paper IV

Anna L Svenningsson, Diana I Bocancea, Erik Stomrud, Anita van Loenhoud, Frederik Barkhof, Niklas Mattsson-Carlgren, Sebastian Palmqvist, Oskar Hansson, Rik Ossenkoppele. Biological mechanisms of resilience to tau pathology in Alzheimer's disease. Submitted manuscript.

Author's contribution to the papers

Paper I

Anna has contributed to the data collection including physical examinations, cognitive testing, and lumbar punctures. She conducted all statistical analyses, interpreted results together with co-authors, and drafted and revised the manuscript.

Paper II

Anna has contributed to the data collection including physical examinations, cognitive testing, and lumbar punctures. She conducted all statistical analyses, interpreted results together with co-authors, and drafted and revised the manuscript.

Paper III

Anna has contributed to the data collection including physical examinations, cognitive testing, and lumbar punctures within the Bio-FINDER cohort. She interpreted results together with co-authors and revised the manuscript.

Paper IV

Anna has contributed to the data collection, including physical examinations, cognitive testing, and lumbar punctures, and data preparation including quality assessments of tau PET and MRI FreeSurfer images. She conducted all statistical analyses together with Diana Bocancea, interpreted results together with co-authors, and drafted the manuscript.

Abbreviations

Aβ	β-amyloid
AD	Alzheimer's disease
ADAS	Alzheimer's Disease Assessment Scale
ADNI	Alzheimer's Disease Neuroimaging Initiative
APOE	apolipoprotein E
AQT	A Quick Test of cognitive speed
CSF	cerebrospinal fluid
CU	cognitively unimpaired
DSM	Diagnostic and Statistical Manual of Mental Disorders
ELISA	enzyme-linked immunosorbent assay
FDG	fluorodeoxyglucose
FDR	false discovery rate
GAP-43	growth associated protein 43
GFAP	glial fibrillary acidic protein
GRN	progranulin
ICAM-1	intracellular adhesion molecule 1
IL-15	interleukin 15
IQ	intelligence quotient
LMEM	linear mixed-effects model
MCI	mild cognitive impairment
MMSE	Mini-Mental State Examination
MRI	magnetic resonance imaging
NfL	neurofilament light
NGF	nerve growth factor
NPTX2	neuronal pentraxin 2
PACC	Preclinical Alzheimer's Cognitive Composite
PET	positron emission tomography
PGF	placental growth factor

P-tau	phosphorylated tau
ROI	region of interest
SCD	subjective cognitive decline
SDMT	Symbol Digit Modalities Test
SUVR	standardized uptake value ratio
SV2A	synaptic vesicle glycoprotein 2A
SYT1	synaptotagmin-1
TDP-43	transactive response DNA-binding protein of 43 kDa
TMT	Trailmaking Test
TREM2	triggering receptor expressed on myeloid cells 2
UCSF	University of San Fransisco
VEGF	vascular endothelial growth factor
WML	white matter lesion

Introduction

Cognition

Most of us have a general understanding of what the word cognition means, but defining it is not as easy and there are many different definitions of the word. One often cited definition of cognition is

> "all the processes by which the sensory input is transformed, reduced, elaborated, stored, recovered and used."[1]

Our cognitive abilities are divided into different domains. There are different approaches to this, but the Diagnostic and Statistical Manual of Mental Disorders 5th edition (DSM-5) provides one of the most established categorizations, where our cognitive abilities are divided into six different domains[2]:

- learning and memory
- language
- complex attention
- executive function
- perceptual-motor function, and
- social cognition.

Our cognitive abilities are not static but change across the lifespan[3]. Through childhood and young adulthood there is a steep increase in cognitive capacity and with older age there is a decline in many cognitive functions, with different cognitive functions peaking at different ages[4].

Results from previous studies trying to capture normal cognitive aging have implied that there is a gradual decline in measures of cognitive speed starting from early adulthood and also in episodic memory with increasing age[5-9]. However, with age being a risk factor for many diseases affecting cognition, and these diseases often exhibiting a prodromal asymptomatic phase, inclusion of subjects with preclinical neurocognitive disorders in studies thought to describe normal cognitive aging has led to an overestimation of the age effects on cognitive decline[10, 11]. Studies trying to control for the effects of age-related neurocognitive disorders seem

to still show a residual effect of age on decline in measures of processing speed and executive function, but not in memory performance[12-15].

Cognitive impairment and dementia

The word dementia comes from the Latin word *demens*, which translates to "being out of one's mind"[16]. It has for a long time been used to describe a clinical syndrome with loss of cognitive function severe enough to affect one's independence in activities of daily living. It can be caused by many different underlying diseases, with Alzheimer's disease (AD) being most common, followed by cerebrovascular disease, dementia with Lewy bodies, and frontotemporal dementia[17], and these diseases often co-occur[18-20]. The term dementia is still commonly used, but in the DSM-5 it has been replaced by the term major neurocognitive disorder[2]. These two terms are to a large extent used interchangeably.

In 2015, the estimated number of people living with dementia world-wide was 44 million, and it is projected to increase to 75 million in 2030 and 132 million in 2050[21], with the largest increase in low- and middle-income countries (Figure 1). This is the result of an expected increase in life expectancy and high age is the strongest risk factor for developing dementia. There is, however, indications of declining age-specific incidence and prevalence rates[22, 23].

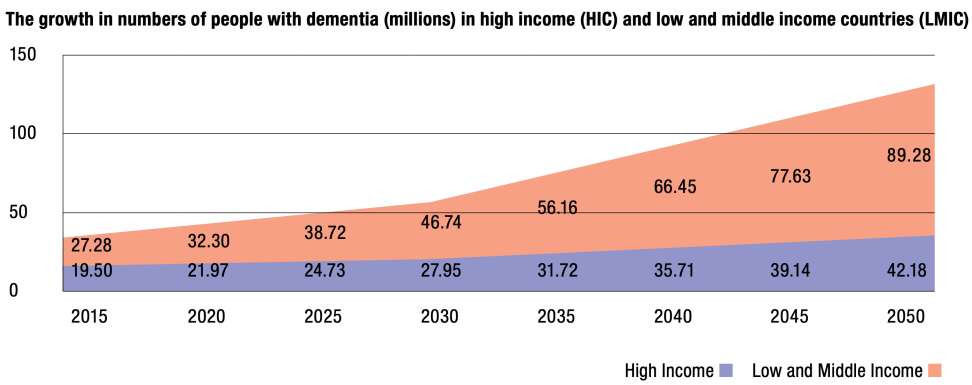

Figure 1. Predicted increasing number of people living with dementia in high income and low and middle income countries. Reprinted with permission from Alzheimer's Disease International.

Dementia not only causes suffering for patients and their relatives, but also comes with high economical costs resulting from direct medical and social costs including institutional care, as well as from costs of informal care. The global cost of dementia in 2021 was estimated at 1.3 trillion US$[24].

In the DSM-5, neurocognitive disorders are divided into three groups; delirium, major neurocognitive disorders and mild neurocognitive disorders[2]. Delirium is a condition that is a consequence of other medical conditions and often reversible and is not further addressed in this thesis.

The diagnostic criteria for major neurocognitive disorder in the DSM-5 are shown in table 1. In brief, it captures a clinical syndrome where decline in cognitive function in one or more cognitive domains leads to a person no longer being able to live her life independently. It is also specified that it cannot only be during a period of delirium, and it should not be better explained by another psychiatric or neurological disorder.

Table 1. Major neurocognitive disorder
Diagnostic criteria for major neurocognitive disorder according to DSM-5:

MAJOR NEUROCOGNITIVE DISORDER	
A.	Evidence of significant cognitive decline from a previous level of performance in one or more cognitive domains based on: 1. Concern of the individual, a knowledgeable informant, or the clinician that there has been a significant decline in cognitive function; and 2. A substantial impairment in cognitive performance, preferably documented by standardized neuropsychological testing or, in its absence, another quantified clinical assessment.
B.	The cognitive deficits interfere with independence in everyday activities (i.e., at a minimum, requiring assistance with complex instrumental activities of daily living such as paying bills or managing medications).
C.	The cognitive deficits do not occur exclusively in the context of a delirium.
D.	The cognitive deficits are not better expleined by another mental disorder.

Mild neurocognitive disorder instead defines a condition with cognitive decline in one or more cognitive domains, and where you can measure objective cognitive deficits, but this decline does not lead to dependence in everyday life. The diagnostic criteria are shown in table 2. This corresponds to the widely used term mild cognitive impairment (MCI)[25, 26].

Table 2. Mild neurocognitive disorder
Diagnostic criteria for mild neurocognitive disorder according to DSM-5:

MILD NEUROCOGNITIVE DISORDER	
A.	Evidence of modest cognitive decline from a previous level of performance in one or more cognitive domains based on: 1. Concern of the individual, a knowledgeable informant, or the clinician that there has been a mild decline in cognitive function; and 2. A modest impairment in cognitive performance, preferably documented by standardized neuropsychological testing or, in its absence, another quantified clinical assessment.
B.	The cognitive deficits do not interfere with capacity for independence in everyday activities (i.e., complex instrumental activities of daily living such as paying bills or managing medications are preserved, but greater effort, compensatory strategies, or accommodation may be required).
C.	The cognitive deficits do not occur exclusively in the context of a delirium.
D.	The cognitive deficits are not better expleined by another mental disorder.

Another commonly used term is subjective cognitive decline (SCD) used to describe a person with self-experienced persistent decline in cognitive function but who performs within normal range on standardised cognitive tests[27, 28].

There have been other diagnostic definitions of dementia, and it is important to have in mind that the use of different criteria can affect the prevalence of the disorder[29].

Alzheimer's disease

In 1906, Alois Alzheimer, a German psychiatrist and neuropathologist, presented the case of Auguste D, a woman who developed rapid memory decline, disorientation, and delusions at around 50 years of age[30, 31]. When examining her brain after death, Alzheimer found intracellular neurofibrillary tangles and extracellular neuritic plaques. In 1909, Emil Kraepelin, another German psychiatrist, defined Alzheimer's disease as a severe form of dementia beginning around 50 years of age with typical neuropathological findings[32]. About 80 years after Alzheimer's discovery, scientists showed that tangles contained tau protein and plaques contained β-amyloid (Aβ) peptides[33-36], and it is now known that AD is a common cause of dementia especially at higher ages.

The clinical picture of AD is characterized by progressive cognitive decline, often effecting memory, language, visuospatial function, and executive function[37].

According to the prevailing hypothesis of the pathophysiology of AD, the initiating event is accumulation of β-amyloid in the brain, leading to tau accumulation, neuronal dysfunction and loss, and cognitive symptoms[38, 39]. The amyloid cascade hypothesis is supported by genetic studies showing that mutations causative of AD (amyloid precursor protein and presenilin-1 and -2 mutations) affect amyloid processing[40]. Biomarker studies have also shown that amyloid accumulation

starts up to decades before development of cognitive symptoms[41, 42], indicating that amyloid accumulation is an early event in the development of AD. However, the associations with neurodegeneration and cognitive symptoms are stronger for tau pathology than amyloid pathology[43-46], highlighting its significance in the pathophysiology of AD. In the last couple of years additional support has come from clinical trials with antibodies directed against Aβ soluble protofibrils[47] and aggregated soluble and insoluble forms of Aβ[48] leading to reduced rate of cognitive and functional decline compared to placebo. However, with some studies showing no or only modest effect on cognition from these drugs, they have also given rise to critique of the amyloid cascade hypothesis[49].

The most important risk factors for developing both neuropathological evidence of AD and a clinical diagnosis of sporadic AD are high age[50-52] and carrying one or more APOEε4 allele with a higher risk if you are homozygous[53-55].

Throughout the history of AD, there have been many different definitions of the disorder. For a long time, the diagnosis was based solely on the clinical presentation, cognitive testing, and ruling out other possible reasons for cognitive decline, and also required a cognitive decline to the level of dementia[56]. Lately there have been additions of biological markers to some definitions of AD, and they have expanded to also include patients with MCI or mild neurocognitive disorder and, in research settings, also to cognitively unimpaired individuals with biological evidence of Alzheimer's disease pathology[2, 57-62]. There are still differing views, however, if the diagnosis of Alzheimer's disease is to be viewed fully as a biological construct without need of clinical symptoms[57], or if it should be reserved for those who also exhibit clinical symptoms[63].

The DSM-5 definition of AD is presented in table 3. It includes both major and mild neurocognitive disorder, and divides the diagnosis based on diagnostic certainty into probable and possible Alzheimer's disease. Apart from evidence of a causative Alzheimer's disease genetic mutation, the diagnosis is based on the clinical presentation with a history of gradual decline in cognition where the memory and learning domain is emphasized.

Table 3. Alzheimer's disease
Major or mild neurocognitive disorder due to Alzheimer's disease according to DSM-5:

MAJOR OR MILD NEUROCOGNITIVE DISORDER DUE TO ALZHEIMER'S DISEASE	
A.	The criteria are met for major or mild neurocognitive disorder.
B.	There is insidious onset and gradual progression of impairment in one or more cognitive domains.
C.	Criteria are met for either probable or possible Alzheimer's disease as follows: ***For major neurocognitive disorder:*** **Probable Alzheimer's disease** is diagnosed if either of the following are present; otherwise, **possible Alzheimer's disease** should be diagnosed. 1. Evidence of a causative Alzheimer's disease genetic mutation from family history or testing 2. All three of the following are present: a. Clear evidence of decline in memory and learning and at least one other cognitive domain (based on detailed history or serial neuropsychological testing) b. Steadily progressive, gradual decline in cognition, without extended plateaus. c. No evidence of mixed etiology (i.e., absence of other neurodegenerative or cerebrovascular disease, or another neurological, mental, or systemic disease or condition likely contributing to cognitive decline). ***For mild neurocognitive disorder:*** **Probable Alzheimer's disease** is diagnosed if there is evidence of a causative Alzheimer's disease genetic mutation from either genetic testing or family history. **Possible Alzheimer's disease** is diagnosed if there is no evidence of a causative Alzheimer's disease genetic mutation from either genetic testing or family history, and all three of the following are present: 1. Clear evidence of decline in memory and learning. 2. Steadily progressive, gradual decline in cognition, without extended plateaus. 3. No evidence of mixed etiology (i.e., absence of other neurodegenerative or cerebrovascular disease, or another neurological or systemic disease or condition likely contributing to cognitive decline).
D.	The disturbance is not better explained by cerebrovascular disease, another neurodegenerative disease, the effects of a substance, or another mental, neurological, or systemic disorder.

In 2018, the National institute of Aging – Alzheimer's Association (NIA-AA) criteria for research purposes were presented based on the ATN biomarker framework, where A represents Aβ, T represents tau, and N represents neurodegeneration[57]. Here AD is defined as a biological entity.

Biomarkers of Alzheimer's disease and neurodegeneration

The core pathological hallmarks of AD, Aβ and tau pathology, were for a long time not possible to measure *in vivo*, and, as mentioned earlier, the diagnosis of AD was made based on the clinical phenotype. Hence, AD research was either based on clinical information, which introduces risk of misdiagnosis[64, 65], or on post-mortem studies which have been gold-standard for defining the underlying pathology, but come with the inherent problem that the time gap between pathology

measurements and other variables of interest can be large and we cannot investigate the longitudinal accumulation of a pathology. There is also a risk for selection bias in postmortem studies[66]. The emergence of *in vivo* biomarkers has therefore revolutionized AD research, giving us the opportunity to examine more people with higher likelihood of a correct diagnosis and probably more representative of the underlying population, at a timepoint that possibly is better for investigating associations with other clinical variables, and to do longitudinal sampling.

The United States Food and Drug Administration (FDA) defines a biomarker as

> "a defined characteristic that is measured as an indicator of normal biological processes, pathogenic processes, or responses to an exposure or intervention, including therapeutic interventions."[67]

In AD, the most frequently used biomarkers are based on positron emission tomography (PET), magnetic resonance imaging (MRI), and cerebrospinal fluid (CSF) sampling, and although not yet implemented, blood biomarkers of amyloid and tau pathology show promise for use in both clinical trials and practice within the near future[68].

β-amyloid biomarkers

There are four widely used PET tracers to detect β-amyloid aggregates, [^{18}F]-florbetaben, [^{18}F]-flutemetamol, [^{18}F]-florbetapir, and [^{11}C]-Pittsburgh compound B[69]. They bind to extracellular deposits of insoluble Aβ[70-72]. The cerebellar grey matter is often used as a reference region to calculate standardized uptake value ratios (SUVRs)[73] and a global neocortical SUVR is generally used as a measure of amyloid positivity since regional SUVRs do not outperform this global measure[74]. The specificity for a clinical AD diagnosis using amyloid PET is relatively low, with a high rate of positive subjects both in cognitively unimpaired (CU) older adults with higher prevalence at higher ages[51, 75] and in patients with other clinical syndromes[76]. However, elevated brain amyloid levels predict future cognitive decline in CU and conversion from MCI to AD dementia[77, 78] and in a clinical setting it affects diagnostic considerations for clinicians[79].

The accumulation of Aβ in the brain is reflected in a lower concentration of the Aβ42 peptide in CSF. The CSF levels of Aβ42 are lower in AD patients when comparing both to controls and to patients with other dementias[80, 81]. Lower levels also predict future cognitive decline in CU[77], and discriminate between normal or pathological Aβ deposition as visualized with PET[82]. The use of a reference protein, in general by using the ratio between Aβ42 and Aβ40 which is the most common Aβ isoform, improves the diagnostic accuracy[83].

Tau biomarkers

PET imaging is used also for detection of tau pathology. Multiple tracers have been used, with [^{18}F]-flortaucipir ([^{18}F]-AV-1451) from the first generation of tracers being the most widely used. Second generation tracers include for example [^{18}F]-RO948[84]. Autoradiography studies have shown that the tracer binds to the type of tau aggregates formed in AD, i.e. the mix of 3-repeat and 4-repeat (3R/4R) tau[85-87]. The uptake in inferior cerebellar grey matter is often used as a reference to create SUVRs[88]. Different tracers perform well and similarly in distinguishing patients with AD from controls and patients with other dementias[89], but the problem with off-target binding, i.e. substantial uptake of the tracer where no tau pathology is expected, seems to be smaller with second generation tracers[90]. Unlike amyloid PET, uptake of tau tracers shows strong regional correlations with cognitive impairment[45, 46].

Different biomarkers of tau can be measured in the CSF. Total tau is more reflective of neurodegeneration than tau pathology specifically[80], but tau phosphorylated at threonine 181 (P-tau181) is selectively increased in AD[80]. Recent studies have shown that tau phosphorylated at threonine 217 (P-tau217) is better than P-tau181 in identifying individuals with tau pathology as measured with PET and discriminating between AD dementia and other neurodegenerative disorders[91].

Biomarkers of neurodegeneration

Alzheimer's disease is a neurodegenerative disease, meaning that it leads to neuronal dysfunction and loss. This can be seen macroscopically as loss of brain volume as described by Alois Alzheimer himself when examining the brain of Auguste D[30], but different types of *in vivo* biomarkers can also be used to assess this. For example, volume and thickness measures of different structures extracted from T1-weighted structural MRI scans or uptake on fluorodeoxyglucose PET (FDG PET) reflecting metabolic activity can indicate a neurodegenerative process[57, 81]. The words neurodegeneration and atrophy indicate loss of neuronal function and structure over time, but they are often used also in cross-sectional studies comparing between groups and individuals.

Hippocampal atrophy is a feature of AD, with smaller hippocampal volumes and faster atrophy rates in AD patients compared to controls, and longitudinal hippocampal atrophy correlating with cognitive decline[92, 93]. However, there is also loss of hippocampal volume over time in cognitively unimpaired with low probability of AD[94] and in other types of dementia[95, 96]. Also, specific patterns of cortical atrophy are seen in AD and different signature patterns have been proposed. Thinner cortex in medial and inferior temporal, inferior parietal, and superior frontal regions[97] has been shown to be predictive of cognitive decline and AD biomarker positivity in CU elderly [98] and progression to AD dementia in

a group of patients with MCI[99]. Another AD cortical signature includes the bilateral entorhinal, fusiform, inferior and middle temporal gyri[100].

FDG PET measures regional glucose consumption, and neuronal dysfunction is reflected as hypometabolism which in AD displays a temporoparietal pattern[94]. It is included in the 2018 NIA-AA criteria as a marker of neurodegeneration[57].

Fluid biomarkers can also be viewed as markers of neurodegeneration. They do not inform on spatial distribution of neurodegeneration, but compared to imaging techniques, they are less expensive and more accessible, and from the collected CSF you can also measure other proteins. As mentioned, CSF total tau is seen as a biomarker of neurodegeneration[57, 80]. Also neurofilament light chain (NfL), a fragment from the neurofilaments that are important for structural support of the neurons and especially axonal structure and growth[101], can be used as a measure of neurodegeneration, although not specific for AD[80, 81].

The concepts of resilience and reserve

Brain reserve

In 1988, Robert Katzman and colleagues published a paper where they on post-mortem evaluations found substantial amounts of neocortical plaques in a group of elderly people who, prior to death, did not have dementia[102]. They found that these subjects had higher brain weights and greater number of neurons than age-matched controls, leading the way to the hypothesis of brain reserve – perhaps starting off with a larger brain could help you cope with the presence of Alzheimer's disease pathology and avoid or postpone clinical symptoms.

Brain reserve is viewed as a passive construct, reflecting a person's neurobiological capital at any timepoint, i.e. brain volumes, number of neurons, or number of synapses[103].

Intracranial volume, as a measure of peak or premorbid brain volume, has been shown to be a protective marker against clinical manifestations or progression in the presence of AD pathology[104-106].

Cognitive reserve

Building on the concept of brain reserve, Yakov Stern and colleagues in the 1990's showed an inverse relationship between level of education and parietotemporal perfusion in a group of individuals with probable AD matched on disease severity[107], indicating that more highly educated subjects could harbour more

pathology then less educated subjects at the same level of cognitive impairment. This was interpreted as education contributing to, or at least being a marker of, cognitive reserve. Also, more recent studies including more types of neuropathology have shown that there is a lot of variation in cognitive decline that is not explained by common neuropathologies[108].

In contrast to brain reserve, cognitive reserve is proposed as a more active process, capturing adaptability when exposed to a risk, through better efficiency, capacity, and flexibility[103].

As mentioned, educational attainment is often used as a marker of cognitive reserve. More recent neuropathology studies have shown that, in groups with similar levels of AD pathology at death, higher education was associated with better preservation of cognitive function[109] and lower risk of dementia[110] before death. Biomarker studies using PET or CSF measure of AD pathology show that education is a protective marker that is associated with better cognitive performance when controlling for AD pathology[104, 106, 111] or better ability to maintain cognitive performance in the presence of AD pathology[112]. The literature is quite consistent that higher education is associated with better cognitive function cross-sectionally, but regarding longitudinal associations between educational level and cognitive decline, results are inconsistent with studies showing either a negative association i.e. faster cognitive decline with better educational level but from a higher premorbid level[106] or a positive association, i.e. slower cognitive decline in the group with higher education[111]. Studies have also indicated that people with higher education are more aware of their symptoms[113, 114].

Another marker of cognitive reserve is the intelligence quotation (IQ), where studies have shown that people with higher IQ perform better than those with low IQ at similar levels of AD pathology[115] and that having lower cognitive abilities in adolescence increases the risk of a clinical diagnosis of AD later in life[116].

Other factors proposed to contribute to cognitive reserve are higher occupational complexity[117, 118], bi-/multilingualism[119, 120], certain personality traits such as low neuroticism[121, 122], physical activity[123, 124], cognitive stimulation[125], social connectedness and participation[126, 127], and well-being[128, 129]. However, with AD being a disease with a long prodromal phase that effects well-being and one's ability of participation, the direction of associations can be questioned with respect to the issue of reverse causality.

Brain maintenance

In addition to brain and cognitive reserve, the term brain maintenance was introduced by Nyberg and colleagues[130] referring to a relative lack of brain pathology. It is defined as reduced development of age- or disease-related brain

changes over time and is related to brain reserve in that the process of brain maintenance can help sustain brain reserve[103].

Resilience

Resilience has been proposed as an umbrella term overarching brain reserve, cognitive reserve, and brain maintenance[103]. The construct of resilience is used in other contexts, such as ecological resilience, and in psychology as resilience to stress[131] and depression[132], and a wider definition of resilience is

> "the quality or fact of being able to recover quickly or easily from, or resist being affected by, a misfortune, shock, illness, etc".

Another proposed terminology is to differentiate between resilience and resistance[133, 134], where resilience captures how well a person copes with a pathology and resistance how well a person can avoid the pathology, similar to brain maintenance.

One question of debate is whether being amyloid positive but cognitively unimpaired is the result of resilience or just preclinical disease[135]. On that note it is important to emphasize that the fact that a person is not cognitively unimpaired is in itself not enough to be seen as the result of resilience, but it has to be in the context of a risk relevant for the outcome, with the most important ones in the context of AD being old age or having a strong genetic risk factor such as an APOEε4 allele.

For the work in this thesis, resilience is divided into brain resilience and cognitive resilience[136]. We think of brain resilience as better preserved brain structure than expected given the level of a specified pathology (amyloid or tau pathology). In the same way, cognitive resilience refers to better preserved cognitive function than expected given the level of pathology or structural brain changes.

One schematic way of viewing resilience can be extrapolated from the proposed separation of differential preservation and preserved differentiation[137]. Differential preservation reflects the situation where two people start off at the same level of cognitive performance, but decline at different rates, i.e. there is a moderation of the association between time and outcome. Preserved differentiation, instead, is when one person starts off with better cognitive performance, but there is no difference in the rate of decline. As mentioned, in the original concepts the x axis reflects time, but it can be transformed to instead reflect the level of measurable pathology, where different trajectories can reflect differential associations between pathology and brain structure or cognitive performance depending on resilience factors.

Methodology in resilience research

The early studies laying the foundation for the concepts of reserve and resilience compared the prevalence or degree of certain characteristics in those that were able to cope with pathology (i.e. remained cognitively unimpaired in the presence of pathology) to those without pathology or those with cognitive impairment[102], or assessed the cross-sectional associations of pathology markers with proposed reserve factors in groups of similar clinical status[107], which can indicate factors that could lead to better preservation of cognition in the presence of pathology.

One approach that has been suggested to enable quantification of resilience is the residual approach[103], where residuals from a regression model between for example AD pathology and clinical outcome are extracted as a measure of resilience, reflecting the variance in outcome not explained by the predictor. A positive residual therefore reflects better than expected cognitive performance and a negative residual worse than expected cognitive performance given the level of measured pathology. Although it can intuitively be intriguing to quantify resilience, this approach has been criticized since it is highly dependent on the included variables and uses a negative definition of resilience which to a large extent reflects noise[133]. Also, in general it highly correlates with the cognitive outcome measure making the interpretation difficult[138].

Instead, building more complete models, incorporating various adverse and protective factors, has been suggested to better predict cognitive decline and understand factors underlying resilience or vulnerability[138]. In these models, you can include interaction terms to assess if a hypothesized resilience factor interacts with a pathology measure in its association with the outcome or simply examine whether the hypothesized resilience factors adds independent information in predicting the outcome controlling for a pathology measure[103, 133]. Importantly, an association between a biomarker and cognitive decline in the presence of amyloid positivity does not have to reflect resilience/vulnerability but could instead reflect disease stage, i.e. rather be a consequence of the disease. However, when controlling for the level of other biomarkers indicative of disease severity, for example CSF p-tau or tau PET, a positive or negative effect of the tested biomarker could be interpreted as contributing resilience or vulnerability.

Possible mechanisms of resilience against AD and atrophy

Although playing a key role in the clinical manifestation of AD pathology, the actual mechanisms of resilience are largely unknown. This can to some degree be

attributed to a historical inability to measure AD pathology (Aβ and tau) *in vivo,* limiting the studies to either comparative studies between groups based on neuropathology, or looking at clinical phenotypes without actually knowing the underlying pathology. Today, however, there are validated fluid and imaging biomarkers of both Aβ and tau pathology, which has generated more knowledge also to the field of resilience, in addition to findings from neuropathology studies.

Neuropathology studies

In the presence of AD pathology, subjects without cognitive impairment show higher number of neurons and less cortical thinning[139], higher density of dendritic spines[140, 141], and better preservation of synaptic structures[142] than the cognitively impaired. Higher expression of neurotrophic factors and proteins involved in mitochondrial translation[143-146] as well as synaptic plasticity and function[145, 147] is associated with better cognitive performance. Also lower levels of proteins expressed in response to cellular stress and high energy demands and higher levels of proteins important for synaptic and axonal integrity have been associated to better preservation of cognition in the presence of AD pathology[148]. One study comparing elderly who maintain their cognition during aging to those with cognitive decline showed decreased expression of genes involved in synaptic signalling in the cognitively unimpaired, indicating a protective effect of reduced signalling[149]. When comparing CU with AD pathology to both subjects with AD dementia and controls without AD pathology, they showed upregulation of different cytokines involved in clearing of pathogens or resolving inflammation[150].

Co-morbidities seem to affect resilience against AD pathology. Presence of cerebrovascular disease is associated with lower AD neuropathological burden at similar levels of cognitive impairment[151] and there is an additive negative effect on cognitive performance longitudinally[152, 153] and cross-sectionally[154] in subjects with AD pathology. Higher expression of vascular endothelial growth factors (VEGF), involved in growth and maintenance of both vasculature and neurons, was associated with worse cognitive trajectories and VEGFs were upregulated among patients with AD dementia compared to unimpaired participants[155]. AD patients with Lewy body pathology show faster cognitive decline compared to those without[156]. Also higher frequency of transactive response DNA-binding protein of 43 kDa (TDP-43) pathology is seen in AD dementia patients compared to CU with similar levels of AD pathology[157, 158], and when accounting for AD pathology, TDP-43 has a strong association with both medial temporal lobe atrophy and memory performance[159].

Imaging studies

In subjects with MCI due to AD, higher education was associated with more severe hypometabolism in left temporal gyri, but also with relative hypermetabolism in right frontal gyri corresponding to the dorsolateral prefrontal cortex[160]. In another

study of MCI patients, higher education was associated with more amyloid pathology, visualized with PET, in frontal, temporal, and parietal regions, and in the same regions a positive association was found between education level and FDG PET signal[161]. In a group of cognitively healthy and stable elderly above 80 years of age, cognitive performance was associated with FDG PET uptake in the bilateral anterior cingulate cortex and anterior temporal pole, and higher amyloid PET and lower FDG PET uptake in these regions independently predicted cognitive performance[162]. Further, lower vascular risk and female sex was associated with higher FDG PET uptake in these regions. Another study showed that at similar levels of amyloid pathology, females had higher FDG PET uptake in a predefined ROI including posterior cingulate, angular gyrus, and inferior and middle temporal gyrus and also showed better global cognitive function[163]. Subjects with worse hypometabolism than expected given the level of tau pathology also show indications of higher levels of other proteinopathies[164].

Higher functional connectivity of the left frontal cortex is associated with more years of education in amyloid positive MCI subjects[165, 166] and higher connectivity is associated with slower cognitive decline[167] and attenuates the negative effects of hypometabolism of the precuneus[165] and tau pathology[166, 168] on cognitive performance. Studies have also shown that system segregation goes down with age and higher system segregation is associated with better cognitive performance in cognitively unimpaired participants[169] and in AD patients[170]. Higher global efficiency of the limbic network has been shown to attenuate the impact of tau pathology on memory decline[171]. When looking at cerebrovascular disease, higher functional connectivity in fronto-parietal and salience networks moderates the association between white matter lesion volume and executive function[172]. Using structural connectivity, higher connectivity also moderated the association between white matter lesion (WML) volume and cognition[173].

Fluid biomarker studies

Vascular endothelial growth factors (VEGFs) are involved in the growth and maintenance of vasculature, including blood vessels in the brain[174]. The expression increases in response to hypoxia[175] and levels of VEGF species in CSF are associated with more white matter lesions[176]. The literature on CSF levels of VEGFs in relation to cognition and AD is not consistent. Some studies show higher levels of VEGFs in AD patients compared to controls[177] and associations between higher VEGF levels and worse cognitive trajectory in CU participants[176], while others show that higher VEGF levels are associated with better cognition across the AD spectrum[178, 179]. One study showed a complex relationship, with higher levels of CSF VEGF in participants without any AD pathology compared to amyloid positive, but also higher levels in amyloid and tau positive subjects compared to only amyloid positive, i.e. forming a “u curve”[180].

Lastly there are studies showing no difference in VEGF between AD patients and age-matched controls[181].

As mentioned, neurofilament light (NfL) in CSF and blood is viewed as a marker of neurodegeneration, but more specifically it is an axonal biomarker[182] that is increased in many different disorders[183]. NfL is expressed exclusively in neurons, and mostly in large, myelinated axons. Higher levels of NfL are associated with both greater atrophy and worse cognitive decline in AD[184-187].

Studies also show associations for markers of synaptic integrity with cognitive function. CSF levels of pre-synaptic proteins synaptotagmin 1 (SYT1) and synaptosomal-associated protein 25 (SNAP25) are increased in AD compared to controls[188-190]. A recent study also showed that higher CSF levels of the presynaptic growth-associated protein 43 (GAP-43) are associated with accelerated tau accumulation and spread[191]. Levels of the post-synaptic protein neurogranin in the brain is lower in AD patients than non-demented elderly[192], which is reflected in higher concentrations of neurogranin in CSF[192-198]. Levels of neuronal pentraxin 2 (NPTX2), a protein involved in formation of excitatory synapses, are decreased in AD and decreases with symptom progression[199, 200] However, one study instead showed that lower levels of NPTX2 was associated with lower risk of clinical progression to MCI also when controlling for tau[201].

CSF measures of glial activation is also associated with cognitive performance and decline. CSF levels of glial fibrillary acidic protein (GFAP), a protein expressed by astrocytes[202], are altered in AD with increased levels in AD compared to controls[203], and CU individuals with AD pathology have higher levels when compared to those without[204]. CSF levels of GFAP also correlate with cognitive performance in individuals with early AD[205]. Regarding microglia, the associations with AD and cognition are complex and the literature is not consistent. Soluble triggering receptor expressed on myeloid cells 2 (sTREM2) is the released form of a transmembrane receptor (TREM2) predominantly expressed by microglia[206]. Studies have shown lower concentrations in AD patients[207], and an association between increased levels and attenuated amyloid PET increase[208], slower tau accumulation in CU and MCI with amyloid pathology[209], and attenuated cognitive decline[210]. However, other studies have instead shown increased levels of sTREM2 in CSF in AD[211, 212].

Inflammatory response in CSF is associated with cognitive performance and clinical stage. CSF levels of YKL40 or Chitinase-3-like protein 1, an inflammatory marker not specifically expressed in the CNS involved in activation of the innate immune system, are increased in AD[213-215]. Also, levels of progranulin, interleukin 15 (IL-15), and intercellular adhesion molecule 1 (ICAM-1) are associated with more advanced cognitive impairment[215, 216].

Taken together, there is support of the hypothesis that resilience to AD and neurodegeneration could be the result of relative lack of other pathologies, such as

other proteinopathies or cerebrovascular disease, better preservation or higher peak level of neuronal structure and function, and/or the level of inflammatory response.

Rationale and aims

The associations between AD pathological hallmarks and their downstream effects are clear but not perfect and there are large interindividual differences. Which factors moderate these associations, in what way, and at which disease stage, are not fully known, but with the emergence of imaging and fluid biomarkers there are possibilities of examining this *in vivo*.

There has recently been a positive development regarding disease modifying treatments, but their costs are high and one could argue that the clinical effects are modest. Importantly, the increasing life expectancy in many low- and middle-income countries is predicted to lead to a steep increase in dementia incidence and prevalence in countries which are not able to pay the high costs of these new treatments. This makes the possibility of preventing, or even just delaying, cognitive impairment intriguing.

Taken together, there is a value of better understanding of the factors that affect the clinical phenotype of AD in the presence of amyloid and tau pathology and atrophy.

The overall aim of the thesis was to explore factors that moderate the associations between AD biomarkers, neurodegeneration, and cognitive decline.

Specifically we wanted to

- investigate the associations between cognitive performance and biomarkers of amyloid pathology, tau pathology, inflammation, cerebrovascular pathology, and regional atrophy in cognitively unimpaired elderly, and test to what extent these associations are statistically moderated by age, sex, and education,
- identify factors explaining the discrepancy between the degree of cortical atrophy and cognitive decline in cognitively unimpaired elderly,
- investigate whether age, sex, APOEε4 status, education, intracranial volume, and cortical thickness relate to cognitive and brain resilience in symptomatic AD, and
- investigate whether a set of pre-selected CSF biomarkers reflecting different brain processes could explain some of the observed interindividual differences in the association between the amount of tau pathology and atrophy or cognitive decline.

Methods

Study samples

The foundation of the work in this thesis are the BioFINDER-1 and BioFINDER-2 studies. In paper III, three additional cohorts are included, from the University of California San Fransisco (UCSF) AD Research Center, Alzheimer's Disease Neuroimaging Initiative (ADNI), and Avid Radiopharmaceutical studies.

BioFINDER-1

The BioFINDER-1 study (NCT01208675; https://biofinder.se/one/) was launched in 2009. BioFINDER stands for Biomarkers For Identifying Neurodegenerative Disorders Early and Reliably, and is a longitudinal cohort study including cognitively unimpaired elderly, patients with subjective cognitive decline, mild cognitive impairment, or dementia, and patients with different parkinsonian disorders. For the papers included in this thesis, data from the CU, MCI, and dementia cohorts have been used.

The participants in the CU cohort were recruited through random sampling from the Malmö Diet and Cancer Study, an ongoing longitudinal, population-based cohort in Sweden. They are followed-up every two years with detailed medical history, physical examinations, and cognitive testing, as well as MRI and CSF collection. At follow-up they are assessed regarding progression to MCI or dementia. The aims are both to investigate early, preclinical stages of neurodegenerative disorders, and to recruit a well-characterized control group.

The SCD/MCI cohort was recruited from three memory clinics in Skåne, Sweden. All patients who came to these clinics in 2010 – 2015 fulfilling inclusion criteria were asked to participate. The participants are followed annually with clinical assessments and CSF collection and MRI are performed every 2 years for up to 6 years. The MCI cohort was part of paper III, where the NIA-AA criteria for MCI due to AD[61] were applied.

The dementia cohort was established through consecutive recruitment of patients seeking care at the memory clinic of Skåne University Hospital, Sweden, and fulfilling criteria for dementia due to Alzheimer's disease, vascular dementia, dementia with Lewy bodies, Parkinson's disease with dementia or frontotemporal

dementia. For this thesis, the dementia cohort was included in paper III, and we only included those fulfilling criteria of dementia due to AD[60].

BioFINDER-2

The BioFINDER-2 study (NCT03174938; https://biofinder.se/two/) is an observational longitudinal cohort study including CU middle-aged and elderly individuals and patients with SCD, MCI, dementia, or different parkinsonian disorders. For this thesis, data from the elderly CU, SCD, MCI, and dementia cohorts have been used. Recruitment began in 2017 and is ongoing.

Cognitively unimpaired individuals are recruited with the aim to include as many as possible that were part of the Malmö Diet and Cancer study. The participants are enriched for *APOE*ε4 carriers.

Patients with subjective cognitive decline or mild cognitive impairment that are referred to the memory clinics in Skåne University Hospital and Ängelholm Hospital in southern Sweden are consecutively asked to participate in the study. Predominantly patients where the cognitive symptoms are believed to be caused by a neurocognitive disorder are included, for example all cases with abnormal CSF Aβ42/40 ratio. There is an additional cohort including patients with SCD or MCI where the medical doctor does not suspect an underlying neurocognitive disorder. However, for the work included in this thesis, only the first of the two cohorts is included. The diagnosis of MCI due to AD is based on the DSM-5 criteria[2].

The AD dementia cohort is also recruited from the above mentioned memory clinics. In this thesis, it is included in paper IV where the diagnosis of AD dementia is based on the DSM-5 criteria[2] together with abnormal CSF Aβ42/40 ratio.

University of California San Fransisco AD Research Center

This longitudinal observational cohort is included in the analyses in paper III, and a diagnosis of AD dementia or MCI due to AD was based on NIA-AA criteria[60, 61].

Alzheimer's Disease Neuroimaging Initiative

This longitudinal observational cohort is included in the analyses in paper III, and a diagnosis of AD dementia was based on the National Institute of Neurological and Communicative Disorders and Stroke and Alzheimer's Disease and Related Disorders Association (NINCDS/ADRDA) criteria of probable AD[58] and MCI diagnosis was based on MMSE scores of 20-26 and CDR 0.5-1.

Avid Radiopharmaceuticals studies

From the Avid Radiopharmaceutical studies, we included participants from the A05 (NCT02016560), a study of the safety and imaging characteristics of [^{18}F]-AV-1451 (flortaucipir), and the placebo arm of LLCF (NCT02791191), a clinical trial of a β-secretase 1 (BACE1) inhibitor where participants underwent tau PET. In the A05, patients with AD dementia and MCI due to AD were included, and in LLCF only patients with AD dementia were included, based on the NIA-AA criteria[60, 61].

Cognitive testing

Mini-Mental State Examination

The Mini-Mental State Examination (MMSE) was originally developed in 1975[217], and is a test commonly used in the clinical workup of dementia patients. It is viewed as a test of global cognition, evaluating orientation, memory, attention, registration, recall, calculation, language, and visuospatial ability. It performs well in discriminating between normal-range cognitive performance and moderate to severe cognitive impairment but is not sensitive to variation within the normal range, and other tests perform better in predicting cognitive decline in persons without dementia[218-220].

Preclinical Alzheimer's Cognitive Composite

The Preclinical Alzheimer's Cognitive Composite (PACC) was developed for testing cognitively unimpaired persons and is sensitive to subtle changes in cognition[221]. The original PACC is a composite evaluating episodic memory, executive function, and orientation, and combines four different cognitive tests; the Total Recall score from the Free and Cued Selective Reminding Test, the Delayed Recall score on the Logical Memory IIa sub-test from the Wechsler Memory Scale, The Digit Symbol Substitution Test score from Wechsler Adult Intelligence Scale-Revised, and the MMSE total score. Adding a test of verbal fluency has been shown to provide additional information[222], and this composite is referred to as PACC5. In the BioFINDER cohorts not all tests included in the original PACC5 are administered, and therefore we created a modified version including corresponding tests to try to capture cognitive performance in the same cognitive domain as the ones in the original PACC5. We substitute the two memory tests with ADAS-Cog delayed recall weighted twice, and the Digit Symbol Substitution Test with TMTA or TMTB. The original PACC is the sum of the z scores from the included tests, but we instead averaged the z scores to form the composite. We refer to this modified version of the PACC5 as mPACC5.

Alzheimer's Disease Assessment Scale-Cognitive subscale

For assessing memory and learning, we use the delayed recall item from the Alzheimer's Disease Assessment Scale-Cognitive subscale (ADAS-Cog)[223]. The subject is presented with ten words, one at a time, and is supposed to memorize as many words as possible. The subject will see the words three times and is asked to say all words she remembers after each time. A few minutes after the last time, with a distraction in between, the subject is asked to repeat all words she remembers. The number of words not recalled is the result for the delayed recall part of the ADAS-Cog, i.e. a higher score indicates greater memory deficits.

Symbol Digit Modalities Test

The Symbol Digit Modalities Test (SDMT)[224] is a test of complex attention, processing speed, and executive function. The subject is presented with a key where the numbers 1-9 correspond to a symbol. Further down on the same page, there are rows with symbols and the subject is instructed to fill in the corresponding number for as many symbols as possible in 90 seconds. The number of correct numbers filled is the score, i.e. a higher score indicates better cognitive performance.

Trailmaking test A and B

In Trailmaking test A (TMTA), the subject gets a paper with the numbers 1-25 spread out on the page and is instructed to connect the numbers in the correct order by drawing lines between them. In Trailmaking test B (TMTB), there are both numbers and letters on the paper, and the subject is supposed to connect all letters and numbers by alternating between numbers and letters (1-A-2-B-…). The result from the test is the time it takes for the subject to complete the task, meaning that a higher score indicates worse performance[225].

A quick test of cognitive speed

A quick test of cognitive speed (AQT) is a test of attention and processing speed comprised of three parts[226]. For the first part, the subject is presented with a page with squares in different colours and is supposed to name the colour of all squares as fast as possible. For the second part, the page instead shows different shapes, and the subject is supposed to name the shapes of all items as fast as possible. For the third part, the subject should name both colour and shape of all items on the page. The time it takes for the subject to complete each part is the score, i.e. a higher score indicates lower cognitive ability.

Animal fluency

For the animal fluency test, the subject is asked to name as many animals as possible in 60 seconds. The number of animals mentioned is the final score, i.e. a higher score reflects better performance[227].

Imaging biomarkers

Magnetic resonance imaging

Structural T1-weighted MRI scans were acquired on different 3 T scanners in all cohorts. Cortical thickness measures, hippocampal volume, and total intracranial volume were obtained from T1-weighted images using the FreeSurfer software (https://www.freesurfer.net; version 5.1 for papers I and II and version 6.0 for papers III and IV), using the longitudinal pipeline for papers II-IV[228]. After image processing and reconstruction, cortical thickness is provided through calculating the distance between the grey/white matter boundary and the pial surface. Parcellation into cortical regions of interest was done according to the Desikan-Killiany atlas[229]. For papers I and II, segmentation of white matter lesion volumes were performed using Lesion Segmentation Tool toolbox (https://www.applied-statistics.de/lst.html)[230].

Amyloid PET

For this thesis, amyloid PET was used in paper III. There are four widely used tracers ([^{18}F]-Flutemetamol, [^{18}F]-Florbetapir, [^{18}F]-Florbetaben, [^{11}C]-Pittsburgh compound-B (PIB)), and they were all used in this paper with different tracers at different study sites. For BioFINDER participants, a neocortical composite region from [^{18}F]-flutemetamol scans was used[231] and SUVRs were calculated with cerebellar grey, pons, and eroded white matter as reference. In UCSF, [^{11}C]-PIB was used, in ADNI, [^{11}C]-PIB, [^{18}F]-Florbetaben, and [^{18}F]-Florbetapir were used and in Avid, [^{18}F]-Florbetapir was used to assess amyloid positivity.

Tau PET

Two tau PET tracers are relevant for this thesis, [^{18}F]-AV-1451 (flortaucipir) for paper III and [^{18}F]-RO948 for paper IV. In both study III and IV, the inferior cerebellar grey was used as reference region to calculate SUVRs[88] and mean global cortical uptake[136] and a regional temporal meta region of interest (ROI)[232] were calculated from FreeSurfer parcellation.

Cerebrospinal fluid biomarkers

Within the BioFINDER cohorts, CSF collection was performed according to standard procedures[233] at three centres in Scania, Sweden. Following collection, samples were centrifuged and the supernatant was stored at -80 °C pending analysis.

In papers I, II, and IV, the Elecsys automated immunoassay[234] was used for measuring CSF Aβ40, Aβ42, p-tau181, and t-tau. In paper I, a commercially available enzyme-linked immunosorbent assay (ELISA)[215] was used for measuring CSF YKL40. In paper II, the NeuroToolKit[235] was used for measuring levels of CSF NfL, sTREM2, neurogranin, and GFAP. In paper IV, the specific multiplex immunoassay developed by Olink Proteomics[236] was used for GFAP, progranulin, ICAM-1, IL-15, TREM2, YKL40, VEGFs, PGF, neurogranin, NPTX2, synaptic vesicle glycoprotein 2A (SV2A), SYT1, NfL, and nerve growth factor (NGF), and a mass spectrometry-based panel of synaptic biomarkers[237] was used for measuring for 14-3-3 ζ/δ. In paper III, CSF Aβ42 was used in the ADNI cohort for determining amyloid positivity using xMAP Luminex (Luminex Corp., Austin, TX) with the INNOBIA AlzBio3 kit (Innogenetics, Ghent, Belgium)[238]

Statistical analyses and methods

The statistical analyses were performed using SPSS Statistics for Mac (version 24 for paper I and version 27 for paper II) and R (version 3.3 for paper I, version 4.0.3 for paper III, and version 4.2.1 for paper IV). Statistical significance was set at $p < 0.05$.

Paper I

Chi-squared test and independent samples t-test were used for comparisons between groups for dichotomous and continuous variables, respectively. Linear regression models were performed to assess associations between biomarkers and cognitive performance, including age, sex, and years of education as covariates (and when including hippocampal volume also intracranial volume), with an additional interaction term between one biomarker and one demographic variable (age, sex, education) at a time. Statistical mediation was tested for using causal steps approach[239]. False discovery rate (FDR) corrections were applied to control for multiple comparisons.

Paper II

For each individual, slopes for change in cortical thickness and change in cognitive performance were calculated using linear regression models with time as the independent variable and mean whole brain cortical thickness or mPACC5 as the

dependent variable, including all available data points for each individual. Then a linear regression with change in cortical thickness as independent variable and change in cognitive performance as dependent variable was performed, from which the standardized residuals were extracted. These were then used as a continuous measure of the discrepancy between expected cognitive decline and the actual cognitive decline, given the individual's atrophy rate, i.e. a positive residual reflects slower cognitive decline than expected, and a negative residual reflects faster cognitive decline than expected.

Next, the residuals were entered as dependent variables in models trying to assess its associations with different demographic and biomarker predictors, using independent samples t-tests for dichotomous predictors and Pearson correlations for continuous predictors.

All predictors significantly associated with the residual measure in bivariate analyses were then entered as predictors into one multivariable model using linear regression with the residual as outcome, also including baseline cortical thickness and cognition as covariates. Interaction terms between demographic variables and biomarkers were included to test for moderation effects.

Lastly, mediation analyses were performed by testing hypothesized mediation paths based on previous literature using the PROCESS macro[240] in SPSS.

FDR was applied to control for multiple comparisons.

Paper III

First linear mixed-effects models (LMEMs) with longitudinal MMSE as outcome were performed. Our predictors of interest were age, sex, APOEε4 status, education, intracranial volume, and AD signature cortical thickness, and they were included in the model one at a time together with baseline level of tau, time since tau PET, and the interaction term between predictor, baseline tau, and time. The interaction term indicates whether the predictor moderates the association between baseline tau load and cognitive decline over time, i.e. if the effect of tau on cognition is different depending on the level of the included predictor. If non-significant, the interaction term was removed, and the model then tested for significant longitudinal associations of the predictor with cognitive trajectory controlling for baseline tau load. Second, the same analyses were performed but with cortical thickness as outcome measure in the LMEMs instead of MMSE.

Paper IV

Linear mixed-effects models with longitudinal cortical thickness measures or longitudinal cognitive test results as outcome variable were performed. CSF biomarkers were included one at a time as a predictor together with baseline level of tau, time since tau PET, and the interaction term between time and tau level as predictors, covarying for age and sex. First, we tested for interaction effects between

the CSF biomarker, tau level, and time, to assess if the biomarker moderated the association between tau and atrophy or tau and cognitive decline over time. If the interaction term was not significant, it was removed and we tested whether the biomarker had an independent association with atrophy rate or rate of cognitive decline by including it in the model together with baseline tau. We controlled for multiple comparisons using FDR corrections.

Main results

The main results of the papers are described here. For more elaborate descriptions of methods and results from secondary and sensitivity analyses, please see the individual papers that are included as appendices.

Paper I

For this study, the cohort of cognitively unimpaired participants from BioFINDER-1 was included and cross-sectional data from baseline visits were used. From the CU cohort, 359 were initially eligible, but due to missing baseline CSF (n=31) and MRI (n=28) data, 300 participants were included for our analyses. Mean age was 73.8 years, 59.7% were female, and the mean education level was 12.3 years.

Memory function

In bivariate analyses, Aβ positivity (β = −0.15; p = 0.009), higher levels of p-tau (β = −0.15; p = 0.012), t-tau (β = −0.13; p = 0.021), and YKL40 (β = −0.13; p = 0.026), larger WML volume (β = −0.14 (p = 0.020), smaller hippocampal volume (β = 0.21; p < 0.001), and thinner cortex of all studied regions (β 0.13–0.28; p 0.001–0.030) were associated with worse episodic memory assessed using ADAS-Cog delayed word recall, but only Aβ positivity, hippocampal volume, and cortical thickness in temporal and frontal regions remained significantly associated when controlling for age, sex, and education. Age moderated the association for hippocampal volume (p = 0.040), with a stronger correlation at higher ages (figure 2).

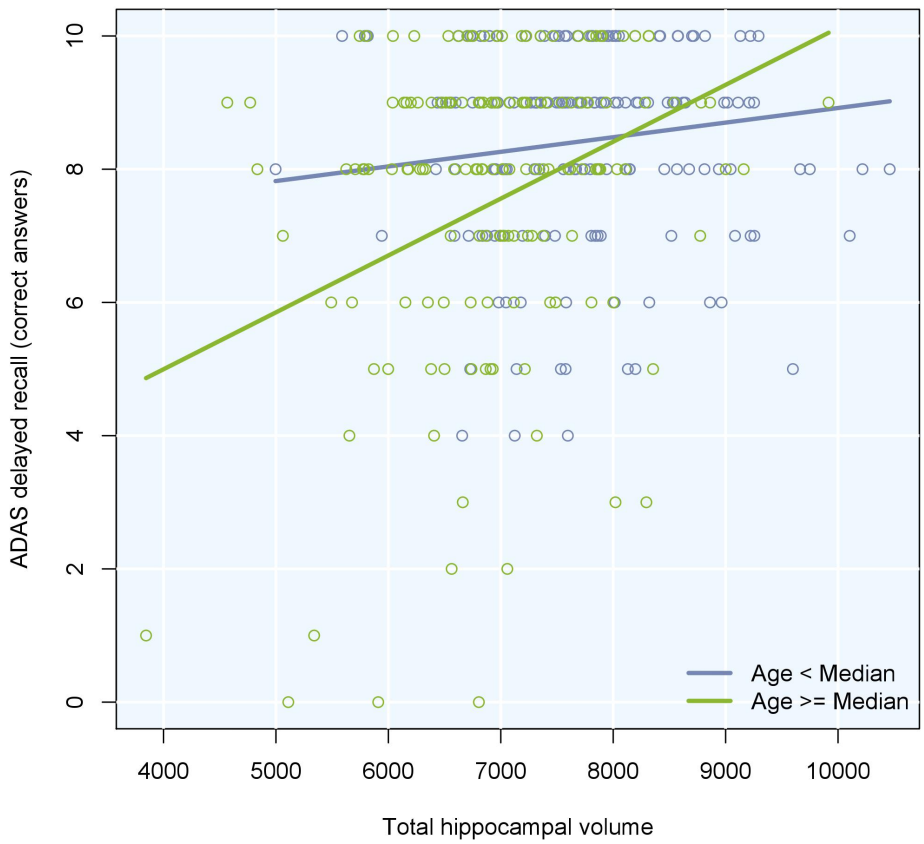

Figure 2. In older cognitively unimpaired participants (green line), the association between hippocampal volume and memory performance is stronger compared to younger participants.

In a model including all the significant biomarkers and previously mentioned covariates, CSF Aβ positivity (β = −0.14; p = 0.010) and smaller hippocampal volume (β = 0.25; p < 0.001) were independently associated with worse memory performance.

Attention/executive function

Higher CSF levels of p-tau (β = −0.13; p = 0.027) and t-tau (β = −0.14; p = 0.018), larger WML volume (β = −0.25; p < 0.001), smaller hippocampal volume (β = 0.33; p < 0.001), and thinner cortex of all studied regions (β 0.16– 0.22; p 0.001–0.007) were associated with a composite score of attention and executive function in

bivariate analyses, but only hippocampal volume (β = 0.16; p = 0.014) remained significant after covariate adjustments.

Paper II

For this study, the cohort of cognitively unimpaired participants from BioFINDER-1 was included, in this case extended to include also the group with subjective cognitive decline. We used the residual from a regression between cortical atrophy rate and rate of cognitive decline as a measure of resilience against atrophy, i.e. better or worse than expected cognitive trajectory given the level of atrophy.

We included 395 CU subjects for our analyses. Mean age at baseline was 72.4 years, 59% were female, and mean educational level was 12.4 years.

In initial bivariate analyses including one predictor at a time, we found that older age (r = −0.11, p = 0.029), male sex (t = −3.00, p = 0.003), larger intracranial volume (r = −0.17, p < 0.001), carrying an APOEε4 allele (t = −2.71, p = 0.007), larger white matter lesion volume (r = −0.16, p = 0.002), lower CSF Aβ42/40 ratio (t = −4.05, p < 0.001), and higher CSF levels of p-tau181 (r = −0.22, p < 0.001), GFAP (r = −0.15, p = 0.003), and NfL (r = −0.34, p < 0.001)were negatively associated with the residual measure.

We then included all the variables that were significantly associated with the residual measure in bivariate analyses in one linear regression model, where lower CSF Aβ42/40 ratio (β = −0.11; p = 0.049) and higher CSF NfL levels (β = −0.20; p = 0.009) remained negatively associated with the residual measure. Their respective associations with the residual measure are shown in figure 3.

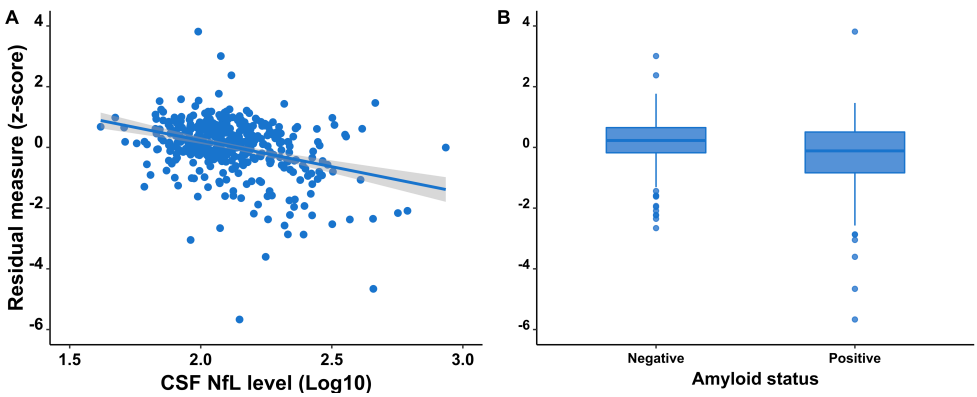

Figure 3. There is a negative association between CSF NfL levels and the residual measure (figure 3A) and amyloid positivity and the residual measure (figure 3B) in cognitively unimpired elderly.

Post-hoc mediation analyses were performed, showing that NfL mediated the associations between the residual measure and APOEε4 allele carriership, lower Aβ42/40 ratio (partially), p-tau181 levels, GFAP levels, age, sex, and WML volume.

Paper III

This was a multicentre study, including longitudinal data from symptomatic participants with MCI or dementia due to AD from the BioFINDER-1, ADNI, UCSF, and Avid cohorts. Linear mixed-effects models were used, with either longitudinal cortical thickness or longitudinal cognitive performance as outcome variables. Baseline level of tau PET uptake was included as predictor, together with age, sex, time since tau PET, and different predictors that we hypothesized could interact with tau PET level, i.e. moderate the association between tau PET level and radiological or cognitive trajectory.

Brain resilience

For the brain resilience analyses, 200 participants were included. This sample is smaller than the cognitive resilience sample due to lower availability of follow-up MRI scans. Mean age at baseline was 72.5 years, 47.5% were female, and mean educational level was 15.3 years. Mean MMSE baseline score was 25.

Higher education negatively moderated the association between tau PET and cortical thinning ($\beta_{interaction} = -0.037$, $p = 0.013$; figure 4). Older age was associated with lower baseline cortical thickness ($\beta = -0.490$, $p < 0.001$) and faster rate of cortical thinning ($\beta = -0.051$, $p = 0.002$) independent of tau, but did not moderate the effect of tau on rate of atrophy.

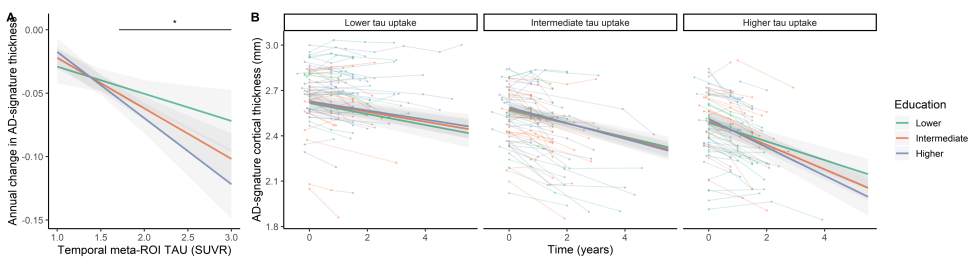

Figure 4. With higher education, the negative association betwen tau PET signal and atrophy rate is excacerbated in symptomatic AD.

Cognitive resilience

For the cognitive resilience analyses, a total 366 participants were included. Mean age at baseline was 73.2 years, 50.5% were female, and mean educational level was 15.0 years. Mean MMSE baseline score was 24.

The association between tau burden and cognitive decline was negatively moderated by higher education level ($\beta_{interaction} = -0.072$, $p = 0.011$), older age ($\beta_{interaction} = -0.062$, $p = 0.032$), and larger intracranial volume ($\beta_{interaction} = -0.07$, $p = 0.016$; figure 5), meaning that with higher values of these variables, the negative association between tau and cognitive decline was exacerbated.

Younger age ($\beta = -0.160$, $p = 0.003$), higher education level, ($\beta = 0.217$, $p < 0.001$), and greater cortical thickness at baseline ($\beta = 0.399$, $p < 0.001$) were associated with better cognitive performance cross-sectionally, and younger age ($\beta = -0.085$, $p = 0.007$) and greater cortical thickness ($\beta = 0.147$, $p < 0.001$) was also associated with slower cognitive decline independent of tau burden.

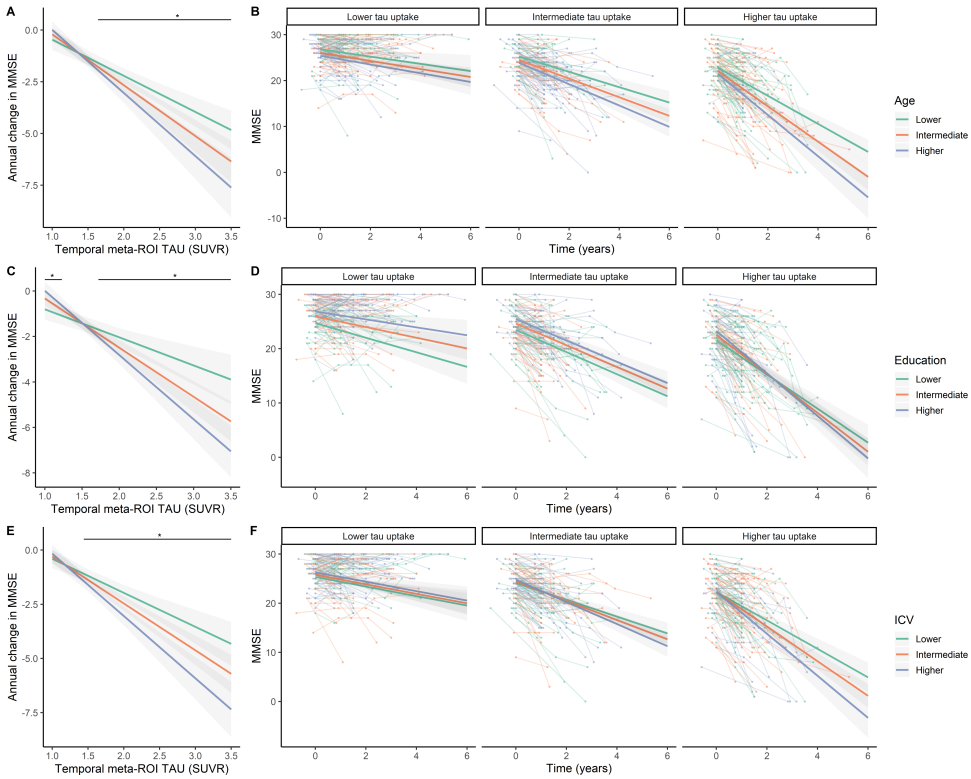

Figure 5. With higher age (figure 5A), educational level (figure 5B), and intracranial volume (figure 5C), the negative association between tau PET uptake and cognitive decline is exacerbated in symptomatic AD.

Paper IV

For the fourth study, we included participants from Bio-FINDER-2 across the clinical spectrum of Alzheimer's disease, i.e. cognitively unimpaired elderly with low CSF Aβ42/40 ratio indicating amyloid accumulation in the brain a well as patients with MCI or dementia due to Alzheimer's disease. We assessed whether levels of CSF biomarkers of different processes and co-pathologies moderated the association between baseline tau PET signal (temporal meta-ROI) and cortical atrophy (AD signature ROI) over time (indicating contribution to better or worse brain resilience) or cognitive decline (mPACC5 in CU, MMSE in MCI and AD dementia) over time (indicating contribution to better or worse cognitive resilience).

Brain resilience

For these analyses, 279 participants were included, 107 CU, 82 with MCI, and 90 with AD dementia. Mean age at baseline was 71.8 years, 51% were female, and mean educational level was 12.6 years.

In AD dementia, various inflammatory, vascular, synaptic, and axonal biomarkers negatively moderated the association between tau PET signal and atrophy, with VEGF-A ($\beta_{interaction} = -0.009$, $p_{FDR} = 0.047$) and VEGF-B ($\beta_{interaction} = -0.010$, $p_{FDR} = 0.037$) surviving FDR correction. These effects are exemplified by VEGF-A in figure 6. No significant interactions or main effects were observed in CU or MCI after FDR correction.

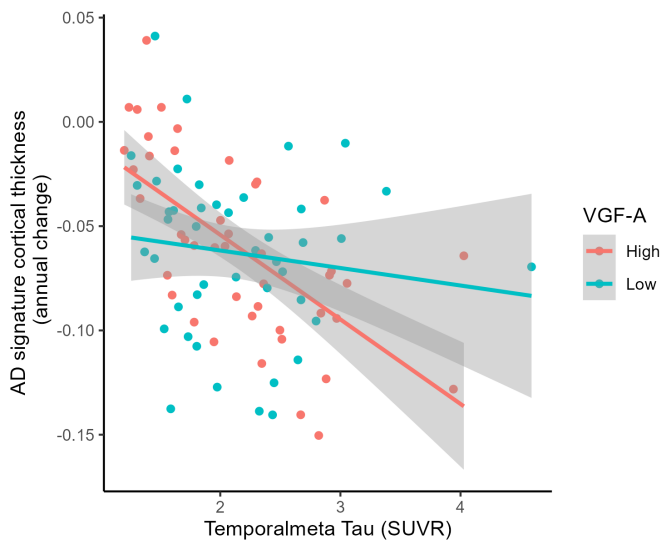

Figure 6. With higher CSF VEGF-A, the negative association between tau PET signal and atrophy rate is exacerbated in AD dementia participants.

Cognitive resilience

For these analyses, 428 participants were included, 134 CU, 128 with MCI, and 166 with AD dementia. Mean age at baseline was 72.1 years, 51% were female, and mean educational level was 12.6 years.

In amyloid positive CU, inflammatory (GFAP, IL-15; $\beta_{interaction}$ −0.073 – 0.069, p_{FDR} 0.001 – 0.045), vascular (VEGF-A, VEGF-D, PGF; $\beta_{interaction}$ −0.099 – 0.063, p_{FDR} <0.001 – 0.046), synaptic (14-3- 3ζ/δ; $\beta_{interaction}$ = −0.092, p_{FDR} = 0.041), axonal (NfL; $\beta_{interaction}$ = −0.079, p_{FDR} <0.001), and neurotrophic (NGF; $\beta_{interaction}$ = 0.091, p_{FDR} <0.001) biomarkers significantly moderated the association between tau PET and cognitive trajectory. No moderation effects were seen in MCI or AD after FDR correction, but in MCI NfL was associated with faster cognitive decline cognitive decline controlling for tau PET signal.

Discussion

Demographic determinants of resilience

Education

Education has been reported to be a protective marker for cognitive decline. More highly educated people have lower risk of developing dementia[241, 242] and have a delayed symptom onset[243] and progression from SCD to MCI[244, 245]. Cross-sectional studies are consistently showing that more highly educated people perform better on cognitive tests when controlling for AD disease severity[106, 115, 246-252] or show more advanced disease compared to less educated people at the same clinical stage[51, 253-255], indicating that they can cope better with pathology. Regarding the effect on the longitudinal trajectory of cognitive performance, the literature is not as unanimous. Many studies show an accelerated decline in later stages of the disease in people with higher education level[106, 256, 257], while others show no effect of cognition on the longitudinal cognitive trajectory[248-250, 252, 258] or even a more beneficial trajectory with higher education[259]. In CU people at genetic risk for developing AD, education level was associated with slower cognitive decline[260]. There is also evidence of an interaction with disease severity, with higher education being associated with slower decline in individuals with less atrophy but faster decline in those with greater atrophy[261]. Studies of brain resilience show no effect of education on atrophy rate[262].

The papers included in this thesis provide somewhat diverging results for education in predicting cognitive performance and cognitive decline. Paper I and II include only CU participants from the BioFINDER-1 cohort, and here no main or interactive effect for education was seen on cross-sectional performance when controlling for AD biomarkers (paper I) and no association was seen between education and longitudinal cognitive decline when accounting for cortical atrophy (paper II). However, in paper III, where symptomatic individuals from different cohorts were included, educational level was associated with better baseline cognitive performance but negatively moderated the association between tau pathology and both atrophy and cognitive decline such that with higher education, the negative effect of tau pathology on atrophy and cognitive decline was stronger.

These differences can be the result of differences in participant selection and included variables, i.e. that the moderating effect of education is seen when symptoms occur or that the effect is there for tau but not for other pathologies. It can also be due to cohort differences. In general, education level is high in cohort studies, but they are not as high within the BioFINDER cohort and perhaps a higher educational level is needed to exert a protective effect. However, also studies in settings with low educational attainment have indicates a protective effect of education[263] with even very low levels of education being associated with lower risk of cognitive impairment compared to no formal education[264]. Lastly, it can also be a methodological issue, where the variance in cognitive performance or atrophy within a group of CU is low and therefor a weak moderating or main effect may not end up statistically significant.

In paper III, we found that at baseline, higher education level was associated with better cognitive performance independent of tau level, but at higher levels of education the negative effect of increasing tau levels on cognitive decline was exacerbated. This is in line with previous literature showing more accelerated cognitive decline in highly educated AD patients[106, 256, 257].

One caveat to keep in mind, is the possibility of ceiling effects on cognitive tests, i.e. that some participants score high but still have declined cognitively from a previous level, and the risk of ceiling effects is stronger in highly educated people[265]. In other words, using a more sensitive cognitive test could identify a subtle decline also in highly educated subjects early in the disease. Supporting this hypothesis is the finding from a recent study that showed that in SCD participants, there is a negative association between education and amyloid PET uptake, indicating that more highly educated participants are more aware of their symptoms[113]. Another study also showed that being more aware of your symptoms was associated with higher educational level[114]. Another important issue is that more highly educated individuals could perhaps just be better at performing cognitive tests, which does not have to reflect everyday functioning.

It is also important to emphasize that even though many studies show associations for education with cognitive performance or decline, this does not mean that the relationship must be causal. There could be genetic confounders that both increase the likelihood of higher educational attainment and better cognition in higher ages[266]. Education is also strongly correlated to premorbid IQ[267] and better general health[268, 269]. For example, one study showed that education together with occupation was associated with white matter structural integrity, but this association was mediated by factors contributing to systemic vascular health[270]. There are also risks of cohort effects, with higher education being more common in later generations who have been exposed to many other different things throughout their lifetime that could confound the associations for education.

However, there is also the possibility that there is a direct effect of education on one's ability to withstand pathology at older age through higher efficiency or compensation. For example, in younger adults, higher network efficiency was found in the group with higher intelligence[271]. One study including patients with MCI due to AD showed more severe hypometabolism, visualized by FDG PET, in left temporal gyri in the more highly educated patients, but also relative hypermetabolism in right frontal gyri corresponding to the dorsolateral prefrontal cortex[160], possibly suggesting a compensatory recruitment of these structures to cope with AD pathology in patients with higher educational level. In another study of MCI patients, higher education was associated with more amyloid pathology visualized with PET in frontal, temporal, and parietal regions, and in the same regions a positive association was found between education level and FDG PET signal, also suggestive of a compensatory increase in metabolism in these regions[161]. Functional connectivity of the left frontal cortex is associated with more years of education in amyloid positive MCI subjects[165, 166] and higher connectivity is associated with slower cognitive decline[167] and attenuates the negative effects of hypometabolism of the precuneus[165] and tau pathology[166, 168] on cognitive performance.

Age

The results from the papers included in this thesis indicate age as a predictor of both brain and cognitive resilience against atrophy and AD. In paper I, age negatively moderated the cross-sectional association between hippocampal volume and memory performance in cognitively unimpaired elderly. In paper II, higher age was associated with faster cognitive decline than expected given the rate of global atrophy in CU, and this was mediated by levels of CSF NfL. These results suggest that advanced age lowers your cognitive resilience against brain atrophy. In paper III, age negatively moderated the association between tau pathology and longitudinal cognitive decline, and higher age was associated with lower scores at baseline, indicating that higher age also reduces your cognitive resilience against tau pathology in symptomatic AD patients. Regarding brain resilience, the results from paper III, with higher age being associated with lower baseline cortical thickness and faster atrophy rate controlling for tau in a sample of people with cognitive impairment, imply that higher age also lowers your brain resilience against tau pathology.

These results are in line with other studies of sporadic AD. One study trying to evaluate duration of different disease stages depending on age, concluded that the preclinical and prodromal stages of AD are shorter with advancing age[272], implying lower resilience against AD pathology at higher ages. In CU people at genetic risk for developing AD, younger age was associated with slower cognitive decline[260]. Studies have also shown that in both typical[273-276] and atypical

AD variants[277-281], younger participants have more tau pathology and faster tau accumulation rate measured using tau PET than older participants, also indicating that with higher age you cannot cope with as much pathology.

Cross-sectional studies have shown that at higher ages, the association between AD pathology, measured postmortem[282, 283] or *in vivo* using PET[284], and cognition or a clinical dementia diagnosis is lower than in younger individuals, highlighting that at higher ages, other processes and pathologies contribute to cognitive decline. One explanation of the findings that with advancing age, your resilience against AD pathology and atrophy is reduced, could be the emergence of other age-related co-pathologies that also affect cognitive performance[151-154, 156-159]. However, another possibility could be that other processes in aging, not associated with measurable pathologies but rather what could be seen as "normal aging", affect one's resilience against AD pathology [285, 286].

Differentiating between "normal" and "pathological" cognitive aging is difficult, if not to say impossible, since it requires knowledge of, and the possibility of measuring, all possible pathologies that come with aging. The differentiation also has a philosophical dimension in defining what is normal – perhaps some levels of pathology could be seen as normal with advancing age? The finding that for example fluid reasoning and processing speed start to decline already between 20 and 30 years of age[3] could indicate that there is some sort of cognitive aging that is not related to accumulation of pathology since at that age the vast majority of people would not have measurable levels of neurodegenerative or cerebrovascular pathology. But this is not the same as saying that decline of other cognitive abilities in older age is normal or that we cannot avoid this decline by modifying surrounding factors.

Sex

In the included papers, we found no clear contribution of sex to brain or cognitive resilience. The only positive finding was in paper II, where male sex was associated with faster cognitive decline than expected given the level of cortical atrophy in CU, and this effect was mediated by higher levels of CSF NfL. In paper I, we found no moderating effects of sex on CSF or MRI biomarkers, and no independent main effect of sex controlling for biomarkers, in explaining cross-sectional cognitive performance in CU. In paper III, looking at symptomatic individuals, sex did not moderate the effect of tau on cognitive decline or atrophy over time, and it was not associated with cognitive decline or atrophy rate when controlling for tau.

However, the literature is consistent regarding sex differences in AD. A clinical diagnosis of AD is more prevalent in females and in males[287-289] and females have a higher life-time risk of developing dementia[290]. This can to some degree be because females living longer[287], but there is also evidence that after 80 years

of age, females have higher age-adjusted prevalence of AD[288]. This could, however, be secondary to males living to these high ages having protective resilience factors that enable them to live longer, while more females live this long resulting in more "average" individuals included in the female group.

In cognitively unimpaired, the prevalence of amyloid positivity is similar between males and females[51, 291-293]. However, females have higher tau levels on tau PET[294, 295] as well as higher levels of t-tau and Braak tau tangle stage[293] when controlling for clinical disease stage, and accumulate tau faster than males[296]. Females also have less atrophy[136] and better verbal memory[297] at equal levels of tau pathology compared to males, and at the same age, females seem to have a longer preclinical stage than males[272]. This applies also to autosomal-dominant AD, where in CU at risk for the disease, females have greater cognitive performance controlling for biomarkers of disease severity[298]. Taken together this suggests that females can cope better with AD pathology.

Studies using FDG PET have shown higher metabolism in females in the bilateral anterior cingulate cortices and anterior temporal poles, a region suggested to be a marker of resilience[162], and in a region incorporating posterior cingulate, angular gyrus, and inferior/middle temporal gyrus[163], suggestive of a compensatory mechanism underlying the female resilience against AD pathology. Males and females also on average have different premorbid cognitive functions, with females having better cognitive scores[291, 299] which could contribute to cognitive reserve by preserved differentiation.

Possible mechanisms of resilience against AD and atrophy

As mentioned in the introduction, there is support of the hypothesis that resilience to AD and neurodegeneration could be the result of relative lack of other pathologies, better preservation or higher peak level of neuronal structure and function, or level of inflammatory response[300]. Here the findings included in this thesis are discussed in this context.

Avoiding co-pathology

Neuropathology studies have shown that the presence of comorbid cerebrovascular disease lowers cognitive resilience against AD pathology. At similar cognitive status, subjects with more vascular pathology have lower AD neuropathological burden, indicating that the effect of vascular pathology makes you less able to cope with AD pathology[151] and less AD pathology is needed for reaching the level of

dementia in the presence of vascular lesions[301, 302]. Studies have also shown an additive negative effect of cerebrovascular disease on cognitive performance longitudinally[152, 153] and cross-sectionally[154] in subjects with AD pathology, and vascular co-pathology at autopsy increases the risk of a clinical AD[303] or dementia[304] diagnosis prior to death.

Also neuroimaging studies have shown that higher levels of cerebrovascular disease predicts earlier conversion to AD[305] and cognitive decline independent of amyloid pathology[306]. One study also showed that the level of vascular risk factors negatively interacted with amyloid burden on its association with cognitive decline, such that in the presence of higher vascular risk, the negative effect of amyloid on cognitive decline was exacerbated[307].

Vascular endothelial growth factors (VEGFs) are relevant for the structure and maintenance of the cerebral vasculature. In neuropathology studies, higher prefrontal cortex expression of VEGFs is associated with atherosclerosis and arteriolosclerosis[155] and higher CSF levels of VEGFs are associated with larger WML volume[176]. However, the associations for CSF VEGFs with cognitive performance differ between studies with some showing that higher levels are associated with better cognitive performance [178, 179] and others showing an association between higher CSF levels and faster functional decline[176]

Apart from AD and cerebrovascular disease, other taupoathies, synucleinopathies, and TDP-43 pathology are associated with cognitive function but to date we do not have validated *in vivo* biomarkers for these pathologies. As mentioned previously, neuropathology studies have shown that the co-occurrence of TDP-43 pathology increases the risk of cognitive impairment at similar levels of AD pathology[157, 158] and when accounting for AD pathology, TDP-43 has a strong association with medial temporal lobe atrophy and memory performance[159]. Aggregation of α-synuclein also increases the rate of cognitive decline in AD patients[156]. One study using FDG PET could also show that subjects with worse hypometabolism than expected given their level of tau pathology, which could be interpreted as having low resilience, had worse cognitive decline and also imaging findings suggestive of higher levels of TDP-43 and α-synuclein pathology based on metabolism patterns[164].

Taken together, this indicates that avoiding other pathologies makes you more resilient to the negative impact of AD pathology. Some findings from the papers in this thesis support this hypothesis.

In paper IV we show that, in patients with MCI or dementia due to AD, the levels of VEGF variants in CSF negatively moderate the association between level of tau pathology and atrophy rate, which we interpret as a multiplicative effect of tau pathology and vascular pathology on neurodegeneration. In CU we saw a negative moderation on the effect of tau on cognitive decline, also in line with this hypothesis. However, this was to a large extent driven by a few participants with high tau and

fast cognitive decline, leading us to interpret these results with caution. The differing results in the literature regarding CSF VEGF levels are interesting, with some showing a positive[178, 179] and others, like our results, a negative[176] association with cognition. One possible explanation could be cohort differences, where the studies showing a positive association include participants from ADNI where participants are recruited with focus on AD and in general have low levels of vascular pathology. Hypothetically, the associations for VEGFs with cognition could differ depending on context, where it reflects one thing when expressed at low levels of vascular pathology, i.e. normal maintenance of neuronal and vascular structure, but in the context of more severe vascular pathology it rather reflects the presence of pathology and is released in response to hypoxia[175].

In paper II, looking at cognitively unimpaired, we use WML volume as a biomarker of cerebrovascular disease, and larger WML volume was associated with faster cognitive decline than expected given the rate of cortical atrophy, indicating that cerebrovascular disease lowers cognitive resilience against cortical atrophy. The association was not significant when including other covariates, but mediation analyses showed that this was due to NfL statistically mediating the effect of WML volume. In paper I, we found a cross-sectional association between WML volume and cognitive performance in CU, but this association was not significant when controlling for demographics or AD biomarkers.

Our findings regarding NfL in papers II and IV can also be an indication of the negative effect of co-pathology on brain and cognitive resilience, since NfL is a non-specific marker of neurodegeneration[308] and therefore could reflect other co-pathologies that we to date cannot measure *in vivo*.

Lastly, our findings from papers I, II, and III, where higher age is associated with accelerated atrophy and cognitive decline also when taking AD pathology or atrophy into account, can reflect the effects of co-pathologies since many of these are associated with higher age.

Synaptic and axonal preservation

Synaptic injury and loss are seen with increasing disease severity and correlate with degree of cognitive impairment[309], and seem to be present already at early symptomatic stages of the disease[310]. One could hypothesize that relative preservation of synapse integrity in relation to the level of pathology could be a resilience process. Indeed, post-mortem studies comparing participants with AD dementia and cognitively unimpaired individuals with AD pathology [140, 141] show differences in the density and morphology of dendritic spines. However, no adjustment for disease severity was made, and in one study there was a negative correlation between spine density and Braak staging[140], indicating that the observed differences can also be due to disease severity, with symptomatic

individuals having more pathology over a longer period of time, leading to alterations of dendritic spines and cognitive decline.

Other studies have taken the degree of AD pathology into account, and show higher number of neurons, thicker cortex, and higher levels of markers of synaptic integrity in the superior temporal sulcus[139] and midfrontal cortices[142] in participants with preserved cognition compared to those with cognitive impairment at similar levels of AD pathology. One study showed increasing synaptic pathology from mid-life to older people without AD, and even more in patients with AD, and when comparing elderly who maintain their cognition during aging to those with cognitive decline, they showed decreased expression of genes involved in synaptic signalling indicating a protective effect of reduced signalling[149]. Another study showed that levels of the post-synaptic protein neurogranin in the brain was lower in AD patients than non-demented elderly, which was reflected in higher concentrations of neurogranin in CSF[192]. Higher levels of proteins associated with synaptic plasticity and integrity[145, 148] is associated with slower cognitive decline in the context of AD pathology, and in a group with no cognitive impairment in life, participants with more advanced tau pathology exhibited higher expression of pre- and post-synaptic related genes in the posterior cingulate cortex[147].

Measures of synaptic integrity in CSF, such as synaptotagmin 1, synaptic vesicle glycoprotein 2A (SV2A), neuronal pentraxin 2, neurogranin, and growth-associated protein 43 are associated with cognitive decline in the context of AD[188, 191, 193-201, 311, 312]. As previously mentioned, neurofilament light in CSF and blood is viewed as a marker of neurodegeneration in AD, but more specifically it is an axonal marker[182] expressed in neurons, and mostly in large, myelinated axons. NfL levels in CSF correlate with cognitive performance and is higher at more advanced stages of AD[184, 185, 187]. Neuropathology studies of subjects with AD pathology, have shown that higher levels of proteins important for axonal integrity are found in the hippocampi of CU subjects compared to those with cognitive impairment[148].

In paper IV we show indications of a negative interaction with tau for neurogranin, SYT1, and 14-3-3 ζ/δ in amyloid positive cognitively unimpaired elderly on cognitive decline, meaning that with higher levels of these biomarkers (i.e. worse synaptic integrity), the negative effect of tau on cognition is exacerbated. This could be interpreted as better preservation of synaptic structure and function contributing to cognitive resilience against tau pathology in CU. In the same paper we show that in CU, NfL negatively moderates the association between tau pathology and cognitive decline, suggesting that also better axonal preservation builds cognitive resilience against tau pathology in this group. We also found an interaction in the AD dementia group regarding brain resilience, i.e. that at higher NfL levels the negative effect of tau on atrophy was enhanced. This could be interpreted as better axonal preservation contributing to brain resilience.

In paper II, we show that higher NfL levels are associated with faster cognitive decline than expected in CU given the level of cortical atrophy. This is interesting since MRI measures of cortical thickness and fluid biomarkers of NfL are sometimes proposed to both be markers of neurodegeneration that can be used interchangeably but here we show that they contribute with complementary information in predicting cognitive decline.

Neuroinflammatory and glial response

The role of inflammation in AD is complex. Misfolded proteins and protein aggregates bind to receptors on microglia and astrocytes which triggers the release of inflammatory cytokines and it is also thought that this immune response contributes to disease progression and severity[313]. There are also indications of differential inflammatory responses throughout the disease, with an early decrease and later increase in inflammatory markers[180]. Regarding resilience, one study looking at the entorhinal cortex, showed that subjects with evidence of AD pathology but preserved cognition exhibit upregulation of different cytokines involved in clearing of pathogens or resolving inflammation compared to both subjects with AD dementia and controls[150].

One of the most studied astrocytic biomarkers is glial fibrillary acidic protein (GFAP), a protein expressed by astrocytes important for the cytoskeleton of the astrocytes and thereby for the support of surrounding neurons[202]. Compared to controls, increased levels of CSF GFAP are seen in AD and other neurodegenerative diseases such as frontotemporal lobe degeneration[203], and CU individuals with AD pathology have higher levels when compared to those without AD pathology[204, 235]. CSF levels of GFAP also correlate with cognitive performance in individuals with early AD[205]. GFAP can also be measured in blood and in a group with participants with SCD, plasma GFAP predicted clinical progression to MCI or dementia beyond Aβ and tau biomarkers[314], perhaps indicating that lower astrocytic activity in response to Aβ and tau pathology contributes to resilience.

An often-used biomarker of microglial activation is triggering receptor expressed on myeloid cells 2 (TREM2), a transmembrane receptor which in the CNS is predominantly expressed by microglia and associated with cytokine release, phagocytosis, proliferation and migration[206]. Some TREM2 variants are strongly associated with AD and they have been shown to cause loss of function of TREM2[315], leading to impaired microglial clustering around plaques[316], indicating that loss of function of TREM2 could reduce resilience against AD pathology. Soluble TREM2 (sTREM2) is the released form of the receptor that can be measured in CSF[317]. Its associations with cognition are not completely clear, with some studies showing increased levels in the CSF in AD patients[211, 212] and also a positive correlation with CSF tau levels[318-321], while others show lower levels in AD patients compared to controls[207] and that higher levels are

associated with slower β-amyloid and tau accumulation[208, 209] and slower cognitive decline[210]. One study addressing these inconsistent results conclude that CSF sTREM2 levels differ depending on the disease stage, with a decrease in the presence of Aβ pathology without downstream tau-related neurodegeneration, but later on an increase related to tau-associated neurodegeneration[321] with similar results in dominantly inherited AD[322].

Higher levels of CSF progranulin, another protein involved in microglial response[323], is associated with more advanced disease stages and cognitive impairment[216]. YKL40 (or chitinase-3-like protein 1), is another inflammatory marker, that is involved in the activation of the innate immune system and is increased in AD[213-215]. The pro-inflammatory cytokine interleukin 15 (IL-15) and intercellular adhesion molecule 1 (ICAM-1), a transmembrane protein expressed by leukocytes, are also associated with more advanced cognitive impairment[215]

In paper IV, we show that multiple biomarkers of glial activation and inflammatory response negatively moderate the association between tau levels and atrophy rate in subjects with AD dementia, indicating that inflammatory processes lower brain resilience against tau pathology. Similarly, in amyloid positive CU elderly, GFAP, IL-15, ICAM-1, and sTREM2 negatively moderated the association between tau pathology and cognitive decline, implying that increased levels of these biomarkers are associated with lower cognitive resilience against tau pathology. In paper I, YKL40 is weakly associated with worse memory performance cross-sectionally, but not when controlling demographics. In paper II, we found that higher levels of GFAP were associated with faster cognitive decline than expected given the level of atrophy in CU. In post-hoc analyses, GFAP partially mediated the effect of Aβ pathology on cognitive decline, and the association of GFAP with cognitive decline was in turn mediated by NfL levels.

Methodological considerations

Reliability

Reliability refers to the quality of the variables and measures, i.e. the degree to which it is precise and free from measurement errors.

Cognitive tests

One important issue is the sensitivity of cognitive tests. For example, there is a well-known ceiling effect of the MMSE meaning that some participants score high but still have cognitive impairment (often seen in more highly educated participants[265]) and when examining participants with milder deficits there is an

accumulation of results towards the higher end[324, 325]. When comparing between groups, this can lead to underestimation of actual differences in cognition, and in longitudinal studies, the fact that some participants remain stable on MMSE can give the impression that they are not declining in cognitive ability when they perhaps would be if examined with a more sensitive instrument. This is handled in papers I, II, and IV by the use of other, more sensitive, measurements of global cognitive performance in CU individuals. However, also MCI and AD dementia subjects, especially those with higher educational level, can show stable performance using MMSE even though their actual cognitive performance is declining.

There are also floor effects even for MMSE[326], meaning that within participants that score very low, there is still great variation in their cognitive abilities. Within the BioFINDER-2 cohort, this is addressed by having MMSE > 12 as an inclusion criterion in the AD dementia cohort. However, over time, some participants will drop to very low results, and interpreting differences within these low scores is perhaps not meaningful.

MMSE has shown good test-retest and inter-rater reliability[327-329]. There are studies that have shown differences in test results depending on the time of day the participant was tested[330, 331], but one of these studies included patients with stroke or transient ischemic attack (TIA), and cerebrovascular disease is known to be associated with more fluctuations in cognitive performance than AD[332]. One study of MMSE in participants without severe impairment showed no time-of-day differences[333].

Imaging

Also imaging modalities are subject to test-retest variability but for structural MRI they are small[334]. Also using FreeSurfer software for segmentation and parcellation renders little variability[335, 336] but without use of visual inspection to exclude scans with artefacts the test-retest variability increases, and even though differences between scans are small they seem to be greater in areas prone to atrophy in early AD[337]. Segmentation of hippocampal volumes using FreeSurfer on average results in larger volumes than when using manual tracing, but these differences are smaller in later versions of the software[338]. When using the longitudinal processing, i.e. processing a series of images acquired at different time points for the same subject together, the reliability increases[339].

CSF

Measurement variability for CSF biomarkers is reduced by introduction of fully automated assay systems[340, 341], with high analytical performance for the quantification of Aβ42[342], t-tau, and p-tau181[343] in CSF.

Regarding Aβ and tau pathology measurements in CSF, the ratio with Aβ40 has been used for some time[344, 345], but more recent publications have shown that the use of a reference protein is useful also for other proteins to account for non-disease related inter-individual variability[346]. This approach is applied for Aβ42 throughout the papers (apart from the diagnosis of AD in ADNI in paper III) and for all CSF measurements from the Olink panel in paper IV.

Internal validity

Internal validity captures the strength of the inferences of the study, i.e. the degree of confidence that the causal relationship being tested is trustworthy and not influenced by other factors or variables. To achieve internal validity, you need to avoid systematic errors (bias) which can occur through the choice of study design, participant selection, and statistical methods and considerations.

Observational studies come with the inherent impossibility of fully distinguishing between correlation and causality. However, there are decisions regarding study design and statistical methods that can strengthen a causal inference.

First, longitudinal studies, unlike cross-sectional studies, can show that the predictor occurs before the outcome variable. In AD research, the question of reverse causality is often discussed since there is a long preclinical and prodromal phase, increasing the risk that what we think is a causal factor is actually the effect of the disease. This temporal association between cause and effects can also be strengthened by theoretical arguments regarding cause and effect from experimental studies.

Second, one should try to eliminate alternative explanations for the relationship, i.e. confounding. This can to some degree be accounted for by stratifying by core possible confounders to see associations within, and differences between, groups or by covarying for possible confounders in statistical analyses, even though it may not account for all confounding[347].

Third, one should take measures to try to exclude the possibility that the outcome is not a result of random chance. This is done through statistical testing, where we set a threshold for statistical significance (alpha level) corresponding to the probability of rejecting the null hypothesis when the null hypothesis is true. When computing many tests, there is a risk that analyses reach statistical significance by chance, often referred to as false positive or type I error: This can be addressed by correcting for multiple comparisons. We apply false discovery rate (FDR) correction, where the p values are ordered and given a new value and then applied to the alpha level selected. Another alternative way is the Bonferroni correction, where you instead calculate a new alpha based on the number of statistical tests. The opposite of type I error is type II error, i.e. a false negative. This can be the result of low power, i.e. too few participants or too low variance to find an association.

The study design can introduce different kinds of bias. For example, cross-sectional studies are subject to confounding due to cohort differences. Participants in cohorts born many years apart have had very different exposures in life. For example in Sweden, in 1930 85% of the population had only 6 years of formal education while in 1970 that number had gone down to 50%[348]. This can result in differing performances on cognitive tests leading to overestimation of age effects[349, 350] and also differing results from imaging studies[351].

Longitudinal studies are better from this viewpoint, but instead come with the risk of attrition bias. This refers to the fact that not all participants complete the study, and the ones who remain tend to be healthier, more well educated, and score better on cognitive tests at baseline, which leads to loss of representativity, i.e. the cohort does not resemble the background population as well[352-355]. One can also speculate that this difference in general health can be enhanced throughout the study, since findings from blood tests and imaging investigations are recognized and the participants are referred to their general practitioner for preventive interventions. This risk may also be even higher in studies of cognitive decline, since people with cognitive impairment are more likely to be lost to follow-up[356]. Another risk with the longitudinal design, especially in studies of cognitive decline, is the risk of practice effects[357-360], which also can be expected to be more pronounced in CU compared to participants with cognitive impairment, introducing the risk of overestimating the differences in trajectories.

Another important step vulnerable to bias is patient inclusion and risk of selection bias. Studies show that people who take part in population cohort studies are on average healthier than those who do not[361, 362]. This has been investigated within the Malmo Diet and Cancer Study which was the basis for the CU cohort in BioFINDER-1, and also here the mortality is lower in participants than non-participants[363].

For study I and II, we only include CU participants because we wanted to study early alterations in AD and neurodegeneration. However, there is risk of excluding a larger proportion of those with low resilience since they have already progressed. In paper III we instead only include participants with MCI or AD dementia. This was to ensure that the included participants have substantial tau pathology, but here we instead risk excluding those with high resilience against tau pathology, i.e. the ones that manage to stay unimpaired in the presence of tau pathology. In other words, when investigating resilience, inclusion of participant along the entire clinical spectrum is important.

Selection bias can affect both internal validity, since the group studied is not the one you set out to study and therefor the conclusions drawn can be faulty, and perhaps even more external validity since the group studied is not representative of the background population.

External validity

External validity refers to the extent to which results from a study can be applied beyond the study sample. There are many different concepts and definition, but generalizability refers to whether the results can be generalized to the target population of the study and transportability refers to whether it also can be applied in other settings. As mentioned, this depends a lot on whether there is a large selection bias leading to the studied cohort being very different from the general population. For example, studies have shown that the participation rate of ethnic minorities tends to be low in clinical studies[364, 365].

Ethical considerations and reflections

Studies of cognitively unimpaired elderly

Our studies of CU elderly can be seen both as studies of early AD pathology, since some of these individuals will have positive biomarkers of AD pathology, and studies of healthy controls. Measuring amyloid and tau pathology in cognitively unimpaired leads to the question whether this information should be given to the participant. Today we still do not have an approved disease-modifying drug in Europe, but there are chances that we will have drugs directed against amyloid pathology in the near future, and probably these medications should be started early on in the disease, perhaps even at presymptomatic stages. This means that disclosing for example the amyloid status to a participant could lead to inclusion in clinical trials and in the future also treatment. But it also means telling the person that they have a high risk to develop cognitive symptoms, which could cause suffering.

Extensive examinations of otherwise healthy individuals also raise the concern of incidental findings on blood tests, for example anaemia, and MRI, for example old infarcts, benign brain tumours, and cysts. The finding of infarcts or other manifestations of vascular disease can lead to highlighting of risk factors and therefore perhaps improved future health but could also raise concerns and worry. Findings of benign tumours and cysts can of course also lead to follow-up of these lesions and treatment if needed, but since they often do not need medical treatment, these accidental findings probably generate more anxiety than it makes up for in positive effects for the participants. One could question whether these findings should be disclosed to these participants. One way could be to ask the participant beforehand if they want to have this information. Regarding the BioFINDER studies, the MRI results and some basic blood tests are registered also in the patients' hospital records and are therefore accessible for both the patients and other health care providers.

Studies of patients with dementia

Inclusion of patients with cognitive impairment in clinical studies comes with great responsibility for the including physician or researcher and a need to go the extra mile to try to ensure that the participant is well-informed. This is also highlighted in the Declaration of Helsinki, which declares ethical principles for medical research involving human subjects[366]. Informed consent has been received if the participant takes in, understands, and remembers the given information, and individuals deemed as not being able to give informed consent must not be included in research that has no likelihood of benefit for them unless it is thought to promote the health of the represented group, the research cannot be performed with people capable of providing informed consent, and the included risks are minimal. The Declaration of Helsinki declares that in these cases, the physician must also seek informed consent from the legally authorized representative. According to Swedish law[367], however, another person cannot consent to inclusion. In practice, we still involve a partner or relative when including participants with cognitive impairment. These persons probably most often state what he/she thinks their partner or relative would want, but there is also a risk of either inclusion even though the participant does not want to, or not participating even though the participant would have wanted to. This also restricts the sample to people who have someone that can act as an informant, which could generate a selection bias with for example people living alone and who do not have close relationships being excluded from studies.

Patients also being study participants

There is a risk that patients asked to partake in a study think that they do not get as good care if they say no, and therefor agree to participate even if they do not want to. Therefore, it is important to be clear that this is not the case, and perhaps it is of value that the treating physician is someone outside the research group to emphasize that the patient's treatment is not dependent on participation. This is also highlighted in the Swedish law of ethical permits in [367], where it is stated that if the research subject is in a dependent relationship with the researcher, questions regarding information and consent should be given extra attention in the ethical review process. The Declaration of Helsinki also addresses this and states that informed consent should by sought by another individual completely independent of this relationship[366].

Medical risks

There are also risks associated with the procedures performed within the studies. With lumbar punctures for acquisition of CSF, the most frequent complication is local pain[368]. Post dural puncture headache is also relatively common but the risk goes down with increasing age and is low in people with dementia[368-371]. There is also risk for bleeding resulting in epidural hematoma, but this is rare[371] and lumbar punctures are not performed on patients with coagulopathies or taking

anticoagulants. Other rare but potentially devastating complications include herniation and bacterial meningitis[368]. In the setting of dementia, thorough neurological and radiological examinations are performed prior to lumbar puncture, allowing the physician to find indications of increased intracranial pressure which increases the risk of herniation and is a contraindication for LP, as is local skin infections at the puncture site which together with thorough antiseptic techniques results in a low risk for infection.

PET imaging leads to exposure of ionizing radiation which imposes a risk of DNA damage and cancer. The radiation dose for tau PET and amyloid PET has been shown to be around 4-9 mSv which is within the range of other commonly performed imaging studies[372-374] and is approximately the dose of 5 years background radiation[375]. MRI involves no ionizing radiation. There are risks for movement or alterations of medical implants such as pacemakers, cochlear implants, and artificial joints, and therefore the participants are asked about this before inclusion in the study. The procedure can also impose discomfort because of loud noise and having to lie in a small space for some time.

These risks are presented to the participants at inclusion, but there is still a risk that they do not understand them fully or that they, in reference to the previous section, feel obliged to participate.

Concluding remarks

The work included in this thesis provides information about the heterogeneity in radiological and clinical manifestations of Alzheimer's disease and neurodegeneration and explores possible explanatory factors for this heterogeneity.

There is support in the literature for the hypothesis that resilience to AD and neurodegeneration could in part be the result of relative lack of other pathologies, better preservation of neuronal structure and function, and level of inflammatory response.This thesis provides additional support for this notion. Demographic determinants of resilience are also discussed, with advancing age contributing to lower brain and cognitive resilience, which in turn could be indirect evidence of the prior mentioned hypothesis of lack of age-associated disease contributing to resilience. The association of education with resilience is also discussed, where our results are in line with previous findings suggesting that higher education level is associated with better premorbid cognitive function but with more advanced disease there is instead implications of faster cognitive decline in more highly educated subjects.

The specific conclusions of the thesis are:

- Aβ pathology and hippocampal atrophy independently explain memory variability in cognitively elderly and with advancing age the negative association between hippocampal volume and cognition is exacerbated.
- Axonal degeneration and Aβ pathology are independently associated with increased cognitive decline beyond the degree of cortical atrophy in cognitively unimpaired elderly.
- Education is a determinant of both cognitive and brain resilience against tau pathology in symptomatic stages of AD, with results suggesting that education may be protective against cognitive decline and brain atrophy at lower levels of tau pathology, with a potential depletion of resilience resources with advancing pathology. With higher age, brain and cognitive resilience against tau pathology goes down.
- At higher levels of biomarkers of neuroinflammation and loss of vascular, axonal, and synaptic integrity, the negative effects of tau pathology on brain structure and cognition are exacerbated, indicating that these processes influence brain and cognitive resilience against tau pathology in AD.

Future perspectives

First, there is still a lot to learn about the actual underpinnings of resilience, and more studies trying to disentangle the biological mechanisms underlying resilience and reserve are needed.

Second, I want to highlight the importance of exploring the generalizability of previous findings to other populations, especially in low- and middle-income countries, where the steepest increase in AD prevalence is expected and the costs of upcoming disease modifying treatments perhaps will be too high, emphasizing the need for prevention of AD pathology as well as postponing cognitive decline in the presence of AD pathology. This field of research could perhaps be accelerated by the emergence of by blood biomarkers.

Third, with the lack of disease modifying therapies against other neurodegenerative disorders, studies investigating whether findings in AD are generalizable also to other diseases are warranted.

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