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MENTAL STIMULATION AND MULTIMODAL TRIALS TO PREVENT COGNITIVE IMPAIRMENT AND ALZHEIMER´S DISEASE

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MENTAL STIMULATION AND MULTIMODAL TRIALS TO PREVENT COGNITIVE IMPAIRMENT AND ALZHEIMER´S DISEASE

Thesis for Doctoral Degree (Ph.D.)

By

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Till mina föräldrar och syster

To my parents and sister

"Learning does not make one learned: there are those who have knowledge and those who have understanding. The first requires memory and the second philosophy."

- Alexandre Dumas

Popular science summary of the thesis

Dementia is one of the leading causes of disability in old age and its current worldwide costs are more than $1 trillion US dollars. To this date there is still no widely available disease modifying cure for dementia, including its most common cause Alzheimer´s disease (AD). However, up to 40% of the risk of dementia in old age is attributable to twelve different modifiable risk factors, which includes diet, physical exercise, and mentally stimulating activities like education. The Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER) was the first randomized controlled trial (RCT) demonstrating that a multidomain lifestyle-based intervention can slow down cognitive decline among older individuals at-risk for dementia. What is not known is if the effect of a lifestyle-based preventive intervention differs between individuals due to factors relating to mental stimulation, such as previous exposure to mentally demanding jobs (i.e., high occupational complexity). This thesis explores if occupational complexity may affect outcomes of a multidomain RCT like FINGER. The thesis also investigates if occupational complexity can provide resilience against AD neuropathology. Finally, the thesis also compares two of the most common rating systems to assess occupational complexity. The results of the first study showed that occupational complexity did not affect the cognitive outcomes of the FINGER RCT, apart for the executive function. It was also found that higher levels of occupational complexity were associated with better cognitive function at the start of the FINGER trial. The results of the second study showed that for certain types of brain pathology, measured with magnetic resonance imaging (MRI) and commonly associated with AD, occupational complexity may provide resilience against its effects on cognition. This was not the case for other types of neuropathology investigated, i.e., amyloid beta brain accumulation. In study 3 the results indicated that, in the early symptomatic stages of AD (prodromal AD) occupational complexity does not provide resilience against the most common type of AD pathology, i.e., amyloid accumulation, but it does however seem to be able to provide resilience against another very common form of AD pathology, which is the tau protein. In the fourth study, the thesis work compared the two most common types of rating systems for occupational complexity, the Dictionary of Occupational Titles (DOT) and the Occupation Information Network (O*NET). The results showed that ratings from both systems are moderately to strongly correlated and provide similar results when used to estimate the association between occupational complexity and memory performance.

Overall, this thesis provides evidence that analysis of future RCTs in older adults at risk of dementia can benefit from looking into sub-groups, based on occupational complexity levels, as they can affect intervention response, and AD-related resilience mechanisms.

Abstract

Theoretical models of dynamic biomarkers underlying the development of Alzheimer´s Disease (AD) acknowledge that there is inter-individual variability in the cognitive performance associated with any level of AD pathology. Mentally stimulating activities such as schooling, occupation, and leisure activities, may contribute to this variability, but it is yet unclear how this can be best assessed, and how such effects can vary across AD severity and among individuals at-risk for cognitive impairment. The association between mental stimulation and cognitive performance also suggests that it is important to account for mental stimulation levels in randomized clinical trials (RCTs) comparing rates of cognitive change between interventions (i.e., drugs, lifestyle interventions) and controls. The aim of this thesis was to investigate a) how pre-existing levels of occupational complexity affect the cognitive outcomes of a multimodal lifestyle-based RCT among older adults at increased risk for dementia based on a validated risk score b) if occupational complexity is associated to cognitive performance among individuals at-risk for dementia, including individuals in the early stages of symptomatic AD (prodromal AD) and c) if occupational complexity is associated with resilience to AD pathology, measured with validated biomarkers and neuroimaging among individuals at-risk for cognitive impairment and with prodromal AD.

The four studies in this thesis were based on data from the Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER), the Karolinska University Hospital electronic database and biobank for clinical research (GEDOC) and The Multimodal Prevention Trial for Alzheimer´s Disease (MIND-ADmini).

Study I. This study used data from the FINGER study (N=1026) to investigate if pre-existing levels of occupational complexity were associated with cognitive function at baseline, and if occupational complexity was associated with the rate of change in cognition during the 2-year intervention period. For all measures of occupational complexity, higher levels of complexity were associated with better cognitive outcomes at baseline. Occupational complexity was not associated with the rate of cognitive change during the intervention, except for the executive function outcome, for which higher levels of complexity with data predicted increased improvement ((ß[SE]: .028[.014], p=.044).

Study II. This study used data from the FINGER neuroimaging cohort, to investigate if the association between occupational complexity and cognition was moderated by measures of brain integrity, both in terms of magnetic resonance imaging (MRI, N=126) and Pittsburgh-B Compound – Positron Emission Tomography (PiB-PET, N=41). The results showed that higher levels of occupational complexity were associated with better cognitive performance for some outcomes after adjusting for Alzheimer's Disease Signature (ADS) and medial temporal atrophy (MTA). However, for most types of

neuropathology and cognitive outcomes, moderation effects indicated that higher occupational complexity levels were associated with better cognitive performance only in people with higher brain integrity, suggesting lack of occupational complexity-related resilience mechanisms.

Study III. This study investigated the association between mental stimulation (occupational complexity and education) and validated AD biomarkers, Aβ1–42, p-tau and t-tau measured in cerebrospinal fluid (CSF). Using data from the GEDOC database, 174 individuals with prodromal AD were included, and analyses were adjusted for cognitive function. The results indicated that both higher occupational complexity and education were associated with higher levels of p-tau and t-tau. For education the association with tau pathology was age dependent. No association was found with Aβ1–42. This suggests that higher education and occupational complexity may provide resilience against tau-related pathology in prodromal AD.

Study IV. This study used data from FINGER, GEDOC, and MIND-ADmini, thus including a total of 1410 individuals, 1207 at-risk for dementia and 203 with Prodromal AD. The aim was to to compare the two most common rating systems for occupational complexity, the Occupation Information Network (O*NET) and the Dictionary of Occupational Titles (DOT) and assess if there was an association between occupational complexity and episodic memory performance among individuals at-risk for dementia. The study found that higher occupational complexity was only associated with memory performance in the FINGER cohort but not the two prodromal AD cohorts. The correlation between the two rating systems was moderate to strong, and highly significant (Spearman's rho = 0.5-0.6, p <.001).

Conclusions. Higher levels of Occupational complexity are associated with better cognitive performance among older individuals at-risk for dementia (and with no substantial cognitive impairment), but does not affect the intervention effect in the FINGER multidomain lifestyle-based RCT, apart from the effect on executive function. Occupational complexity does not seem to provide strong resilience against neuropathology among individuals at-risk for cognitive impairment. Among individuals with prodromal AD, higher levels of occupational complexity do seem to provide resilience to tau-related pathology measured with CSF markers but is not associated with better episodic memory performance. Measuring occupational complexity with the DOT or O*NET system seems to yield similar results, as the two systems scores are correlated.

Sammanfattning

Teoretiska modeller för dynamiska biomarkörer som ligger till grund för utvecklingen av Alzheimers sjukdom har visat att det finns en interindividuell variation i den kognitiva funktionen för alla nivåer av Alzheimers patologi. Mentalt stimulerande aktiviteter som utbildning, arbete och fritidsaktiviteter kan bidra till denna variation, men det är ännu oklart hur detta bäst kan mätas, och hur sådana effekter kan variera beroende på svårighetsgrad av Alzheimers sjukdom och bland individer med risk för kognitiv svikt. Sambandet mellan mental stimulans och kognitiv funktion tyder också på att det är viktigt att ta hänsyn till nivåer av mental stimulans i randomiserade kontrollerade studier som jämför graden av kognitiv förändring mellan interventioner (dvs. läkemedel, livsstilsinterventioner) och kontrollgrupper. Syftet med denna avhandling var att undersöka a) hur befintliga nivåer av yrkeskomplexitet påverkar de kognitiva resultaten av en multimodal livsstilsbaserad RCT bland äldre vuxna med ökad risk för demens baserat på en validerad riskpoäng b) om yrkeskomplexitet är associerat med kognitiv funktion bland individer med risk för demens, inklusive individer i de tidiga stadierna av symptomatisk Alzheimers sjukdom (prodromal AD) och c) om yrkeskomplexitet är associerat med motståndskraft mot Alzheimers patologi, mätt med validerade biomarkörer och hjärnavbildning bland individer med risk för kognitiv försämring och med prodromal AD.

De fyra studierna i denna avhandling baserades på data från Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER), Karolinska Universitetssjukhusets elektroniska databas och biobank för klinisk forskning (GEDOC) och The Multimodal Prevention Trial for Alzheimer´s Disease (MIND-ADmini).

Studie I. I denna studie användes data från FINGER-studien (N=1026) för att undersöka om befintliga nivåer av yrkeskomplexitet hade samband med kognitiv funktion vid starten av studien, och om yrkeskomplexitet hade samband med graden av förändring i kognition under den 2-åriga interventionsperioden. För alla mått på yrkeskomplexitet var högre nivåer av komplexitet förknippade med bättre kognitiva resultat vid starten av studien. Yrkeskomplexitet var inte förknippat med graden av kognitiv förändring under interventionen, med undantag för resultatet för exekutiv funktion, där högre nivåer av komplexitet med data predicerade ökad förbättring ((ß[SE]: .028[.014], p=.044).

Studie II. I denna studie användes data från FINGER-kohorten för hjärnavbildning för att undersöka om sambandet mellan yrkesmässig komplexitet och kognition modererades av mått på hjärnans integritet, både i form av magnetisk resonanstomografi (MRI, N=126) och Pittsburgh-B Compound - Positronemissionstomografi (PiB-PET, N=41). Resultaten visade att högre yrkeskomplexitet var förknippat med bättre kognitiv funktion för vissa

resultat efter justering för kortikal tjocklek i hjärnområden påverkade av Alzheimers sjukdom (ADS) och medial temporal atrofi (MTA). För de flesta typer av neuropatologi och kognitiva resultat visade dock modereringseffekter att yrkeskomplexitet var förknippad med bättre kognitiv funktion endast hos personer med högre hjärnintegritet, vilket tyder på avsaknad av yrkeskomplexitetsrelaterade resiliens mekanismer.

Studie III. I denna studie undersöktes sambandet mellan mental stimulans (yrkeskomplexitet och utbildning) och validerade Alzheimers-biomarkörer, Aβ1-42, p-tau och t-tau uppmätta i cerebrospinalvätska (CSF). Med hjälp av data från GEDOC-databasen inkluderades 174 individer med prodromal AD, och analyserna justerades för kognitiv funktion. Resultaten visade att både högre yrkeskomplexitet och utbildning var förknippade med högre nivåer av p-tau och t-tau. För utbildning var sambandet med tau-patologi åldersberoende. Inget samband hittades med Aβ1-42. Detta tyder på att högre utbildning och yrkeskomplexitet kan ge motståndskraft mot tau-relaterad patologi vid prodromal AD.

Studie IV. Denna studie använde data från FINGER, GEDOC och MIND-ADmini och inkluderade därmed totalt 1410 individer, 1207 med risk för demens och 203 med prodromal AD. Syftet var att jämföra de två vanligaste klassificeringssystemen för yrkeskomplexitet, Occupation Information Network (O*NET) och Dictionary of Occupational Titles (DOT) och bedöma om det fanns ett samband mellan yrkeskomplexitet och episodisk minnesförmåga bland personer med risk för demens. Studien visade att högre yrkeskomplexitet endast var associerat med minnesfunktion i FINGER-kohorten, men inte i de två prodromal Alzheimers-kohorterna. Korrelationen mellan de två bedömningssystemen var måttlig till stark och mycket signifikant (Spearmans rho = 0,5-0,6, $p < 0,001$).

Slutsatser. Högre nivåer av yrkeskomplexitet är förknippat med bättre kognitiv funktion bland äldre personer med förhöjd risk för demens (och som inte har någon betydande kognitiv nedsättning), men påverkar inte interventionseffekten i den livsstilsbaserade RCT-studien FINGER, bortsett från effekten på exekutiv funktion. Högre grad av yrkeskomplexitet ger inte stark motståndskraft mot neuropatologi bland individer med förhöjd risk för kognitiv nedsättning. Bland personer med prodromal AD verkar högre yrkeskomplexitet ge motståndskraft mot tau-relaterad patologi mätt med CSF-markörer, men är inte förknippat med bättre episodiskt minne. Att mäta yrkeskomplexitet med DOT- eller O*NET-systemet verkar ge liknande resultat, eftersom de två systemens skattningar är korrelerade.

List of scientific papers

I. Rydström A., Darin-Mattsson A., Kåreholt I., Ngandu T., Lehtisalo J., Solomon A., Antikainen R., Bäckman L., Hänninen T., Laatikainen T., Levälahti E., Lindström J., Paajanen T., Havulinna S., Peltonen M., Sindi S., Soininen H., Neely AS., Strandberg T., Tuomilehto J., Kivipelto M., Mangialasche F. Occupational complexity and cognition in the FINGER multidomain intervention trial. Alzheimer's Dement. 2022; 18: 2438– 2447. https://doi-org.proxy.kib.ki.se/10.1002/alz.12561

II. Rydström A., Stephen R., Kåreholt I., Darin Mattsson A., Ngandu T., Lehtisalo J., Bäckman L., Kemppainen N., Rinne J., Sindi S., Soininen H., Vanninen R., Solomon A., Mangialasche F. The role of brain integrity in the association between occupational complexity and cognitive performance in subjects with increased risk of dementia. Gerontology. 2023 Apr 18. doi: 10.1159/000530688. Epub ahead of print. PMID: 37071974.

III. Rydström A., Kåreholt I., Verrijp M., Rosenberg, A., Darin-Mattsson A, Andel R., Bäckman L., Hagman G., Sindi S., Kivipelto M., Mangialasche F. Education and occupational complexity are associated to the burden of neuropathology in prodromal Alzheimer´s disease. Manuscript

IV. Rydström A., Kåreholt I., Bäckman L., Hagman G., Andersen P., Lehtisalo J., Darin-Mattsson A., Ngandu T., Rosenberg, A., Sindi S., Thunborg, C., Duval C., Pantel J., Hartmann T., Kivipelto M., Mangialasche F. Occupational complexity and memory performance in people at risk of dementia: comparison of two ratings systems of occupational complexity. Manuscript.

ADDITIONAL PUBLICATIONS NOT INCLUDED IN THE THESIS

1. Gyllenhammar M, Rennie A, Padilla DF, Wallert J, Rydström A, Wahlund LO, Eriksdotter M, Westman E, Ekman U. The Association Between Temporal Atrophy and Episodic Memory Is Moderated by Education in a Multi-Center Memory Clinic Sample. Journal of Alzheimer's disease :JAD 2023

2. Sindi, S., Thunborg, C., Rosenberg, A., P. Andersen, S. Andrieu, L.M. Broersen, N. Coley, C. Couderc, C.Z. Duval, G. Faxen-Irving, G. Hagman, M. Hallikainen, K. Håkansson, J. Lehtisalo, N. Levak, F. Mangialasch, J. Pantel, E. Kekkonen, A. Rydström, A. Stigsdotter-Neely, A. Wimo, T. Ngandu, H. Soininen, T. Hartmann, A. Solomon, M. Kivipelto. Multimodal Preventive Trial for Alzheimer's Disease: MIND-ADmini Pilot Trial Study Design and Progress. *J Prev Alzheimers Dis* **9**, 30–39 (2022). https://doi.org/10.14283/jpad.2022.4

3. Nilsson J, Lebedev AV, Rydström A, Lövdén M. Direct-Current Stimulation Does Little to Improve the Outcome of Working Memory Training in Older Adults. Psychol Sci. 2017 Jul;28(7):907-920. doi: 10.1177/0956797617698139. Epub 2017 May 16. PMID: 28509625; PMCID: PMC5536199.

4. Thiruchselvam R, Blechert J, Sheppes G, Rydstrom A, Gross JJ. The temporal dynamics of emotion regulation: an EEG study of distraction and reappraisal. Biol Psychol. 2011 Apr;87(1):84-92. doi: 10.1016/j.biopsycho.2011.02.009. Epub 2011 Feb 24. PMID: 21354262.

Contents

List of abbreviations

Aβ/Abeta	Amyloid beta
AD	Alzheimer´s Disease
ADS	Alzheimer´s Disease Signature
AE	Adverse events
ANOVA	Analysis of variance
APOE ε4	Apolipoprotein E gene-ε4 allele
ATE	Average treatment effect
CSF	Cerebrospinal fluid
CERAD	Consortium to Establish a Registry for Alzheimer's Disease
CT	Computerized Tomography
DOT	Dictionary of Occupational Titles
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, fourth edition
FDA	Food and Drug Administration
FDG-PET	Fluorodeoxyglucose Positron emission tomography
FINGER	Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability
fMRI	Functional Magnetic Resonance Imaging
GEDOC	Karolinska University Hospital electronic database and biobank for clinical research
HTE	Heterogeneity of treatment effects
ITE	Individualized treatment effect
IWG	International Working Group
MAPT	Multidomain Alzheimer Preventive Trial
MCI	Mild Cognitive Impairment
MIND-ADmini	Multimodal Prevention Trial for Alzheimer´s Disease mini
mITT	modified Intention-to-treat
MMSE	Mini-Mental State Examination
MRI	Magnetic Resonance Imaging
NFT	Neurofibrillary Tangles

NTB	Neuropsychological Test Battery
O*NET	Occupation Information Network
OR	Odds ratio
PiB-PET	Pittsburgh-compound-B Positron emission tomography
preDIVA	Prevention of Dementia by Intensive Vascular care
RAVLT	Rey Auditory Verbal Learning Test
RCT	Randomized Controlled Trial
ROCF	The Rey–Osterrieth Complex Figure
SAE	Serious adverse events
WMS	Wechsler Memory Scale

1 Introduction

This introduction will include an overview and background of relevant theory and definitions of concepts. Then follows a literature review that will give a comprehensive and focused background to the included studies in this thesis. Thereafter follows overall research aims and specific aims.

1.1 Cognitive aging and dementia

Cognitive aging is a process in which older adults typically experience decline in several cognitive functions, such as memory, executive functions, and processing speed, which can negatively impact their quality of life (1). While most individuals experience some degree of decline of cognitive function with higher age, some individuals experience very few if any loss of cognitive function (so called super agers) (2, 3). On the other side of cognitive spectrum, we see that with higher age some individuals exhibit greater loss in cognitive function than expected, which can lead to a diagnosis of mild cognitive impairment (MCI) (4). An illustrative example of how MCI relates to normal aging can be seen in **Figure 1**. MCI status means that an individual has reached a level of cognitive function which is significantly below what is expected for the respective age-group, and which affects the ability to perform activities of daily living. Eventually some of these individuals can no longer perform these daily living activities without assistance, this is when their cognitive functions have deteriorated even further and reached a stage where the individual is given the diagnosis of dementia (1).

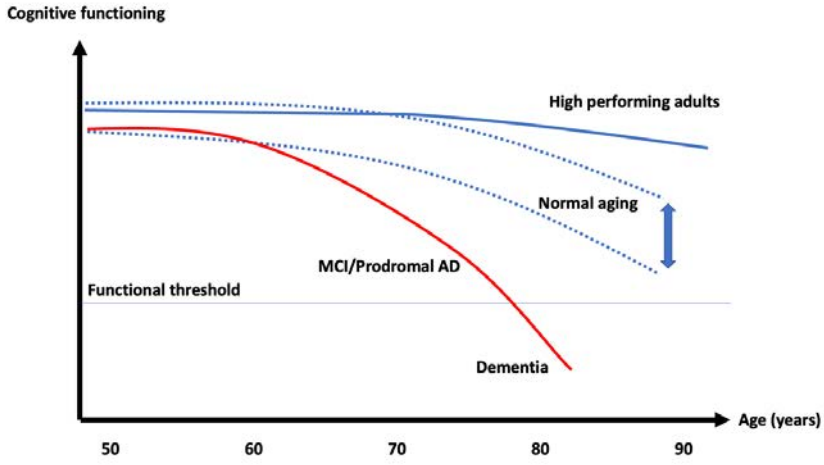

Figure 1. The development of cognitive function over time into late-life and the different pathological and non-pathological trajectories. Adapted from Borelli et al., 2018.

Dementia currently affects more than 50 million people worldwide and the number of cases is expected to increase to more than 150 million cases by 2050 (5). Currently, the worldwide economic burden of dementia is estimated to be at least 1 trillion US dollars per year and is expected to be doubled by the year 2030. Age is the strongest risk-factor for dementia and with increasing lifespans in most countries, resulting in a larger part of the population reaching higher ages, this leads to a large increase in dementia cases if no cure is found or prevention is not put into place effectively (5, 6) Alzheimer´s disease (AD) is the most common type of dementia, as it is estimated that 60% of all dementias is caused by AD; vascular dementia is the second biggest cause of dementia, accounting for approximately 20-30% of dementias worldwide. The remaining 10-20% is related to frontotemporal dementia, Lewy body dementia, and Parkinson´s disease dementia. These estimates should be taken cautiously, considering that most dementia cases present with mixed brain pathologies, especially in very advanced age. It is estimated that only 10-30% of subjects with diagnosed AD dementia have pure AD pathology (7-11).

1.1.1 Dementia and prevention

Although many compounds have been tested as disease-modifying treatments for AD, there are not yet disease modifying drugs widely available (12). Recently, a disease-modifying treatment was conditionally approved by the Food and Drug Administration (FDA) in the United Sates, although its efficacy has been debated (13, 14), and another drug targeting the amyloid pathology in AD has received approval in USA (15). Research into modifiable risk factors has indicated twelve factors – low educational attainment, midlife obesity and hypertension, smoking, diabetes, physical inactivity, depression, social isolation, hearing loss, traumatic brain injury, alcohol abuse, and air pollution – which are estimated to account for 40% of global dementia cases (6). This implies that a significant portion of cases might be prevented or at least delayed. Given the heterogeneity and multifactorial nature of dementia in late life, interventions targeting several risk factors simultaneously could be effective.

The Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability – FINGER – showed that it is possible to improve cognition and reduce cognitive decline in older people at risk for dementia, through a multidomain intervention aiming to manage several metabolic and lifestyle-related risk factors (16). Preventive multidomain strategies may be applied not just in at-risk individuals without substantial cognitive

impairment (as in the FINGER trial), but also in subjects with predementia cognitive signs. Using the new diagnostic criteria for AD (17) it is in fact possible to test multidomain preventive interventions in subjects with prodromal AD, which is an early stage of symptomatic AD, for whom there are no therapeutic options currently available. The feasibility of such approach was tested in the Multimodal Prevention Trial for Alzheimer´s Disease (MIND-ADmini) (18).

Figure 2 outlines different pathways and mechanisms for how several lifestyle factors may contribute to decreased dementia risk. Activities providing mental stimulation, including education, intellectually challenging occupations, cognitive training, and participation in cognitively stimulating leisure activities, are modifiable protective factors for late-life dementia and AD (6, 19). Engagement in physical activity has also been associated with mental stimulation. However, multiple mechanisms can explain the link between engagement in physical activity and reduced risk of dementia and AD (20) and the analysis of this factor is beyond the scope of this thesis work. Lifetime exposure to mentally stimulating activities is of interest to dementia and cognition research, since according to the "environmental complexity" hypothesis by Schooler (21), individuals dealing with more complex environmental demands will have a positive effect on their cognitive functioning. Exposure to mental stimulation during the lifespan has been investigated in relation to late-life cognition and risk of dementia as well as its interaction with brain pathology, mostly in the context of observational studies, as summarized in the following sections.

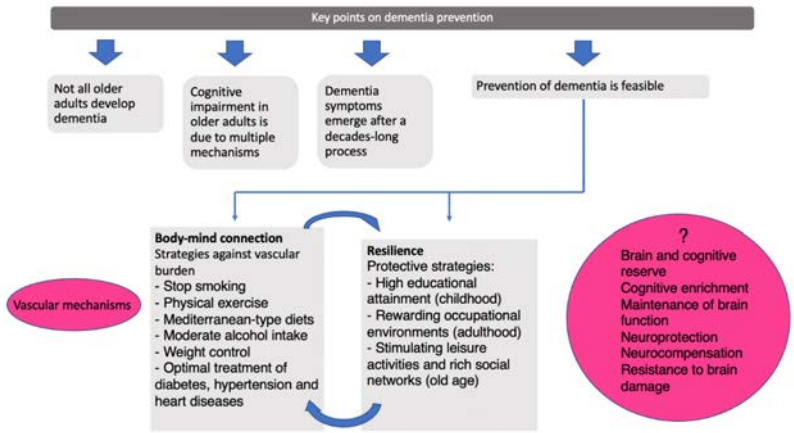

Figure 2. Key points on dementia prevention and pathways for which different lifestyle factors may contribute to decreased dementia risk. Adapted from Fratiglioni et al., 2020.

2 Literature review

2.1 Observational studies of mental stimulation and late-life cognition

This section will give an overview of studies that have investigated the association between mentally stimulation activities (education, occupation, and leisure activities) and late-life cognition as well as diagnosis of cognitive impairment (MCI, prodromal AD and Dementia).

2.1.1 Observational studies of education and late-life cognition

Studies have found that education improves cognition already in early age and this effect is also seen between generations, where the younger generations have better cognitive function on average than older generations, partly due to longer schooling (22-25).

The association between education level and the risk of dementia was first studied in 1990 by Zhang et al., in a large population-based study with 5,055 participants, which found that people with low education had higher risk for dementia (26). Since then, well over 100 studies have been conducted on this subject (27), and several systematic reviews and meta-analyses have been published. For the studies that used a meta-analytic approach, the odds ratios (ORs) for the association between low education and risk of dementia spanned from 1.59 (95% CI: 1.26-2.01) to 1.89 (95% CI: 1.61-2.22) (27-32). However, there are individual studies that have not found this association, see for instance the systematic review by Sharp & Gatz (33). A recent overview of potentially modifiable risk factors for dementia estimated that the global population attributable fraction of low education for dementia is 7.1% (6). Education has been also related to AD incidence, where people with higher levels of education have lower risk of AD (34-40).

There is also evidence that individuals with more years of education have a lower risk of developing mild cognitive impairment (MCI), which is a diagnosis characterizing people with cognition that is significantly below the expected cognitive performance for their age (41-46). Subjects with MCI also have an increased risk to develop dementia (47). One study also showed no associations between years of education and risk of MCI (48).

Years of education have a positive association with late-life cognition (49, 50), but whether educational attainment affects the rate of cognitive decline in old age is unclear. Some studies have found that higher education is associated with reduced cognitive decline in old age (51, 52), while others have not confirmed these findings (53-55). Other studies have found that education affects cognitive decline differently across different cognitive functions (56).

Inconsistencies among studies on education and late-life cognitive outcomes can be partly due to different methodologies. A main methodological difference between studies using education as a predictor of late-life cognitive outcomes is the operationalization of educational levels. Studies usually use self-reported data on the number of years that the person has been in schooling, which are often used to define categories of educational attainment. The definition of "higher education" is mostly relative to the mean education level of the sample used. This means, for instance, that 12 years of education may be considered as "high education" in one cohort, while in another cohort they are considered "medium" or "low education".

Another methodological challenge with operationalization of education is that two individuals with the same number of years in school can have very different grades, which is an indicator of learning. The quality of schools within a country and between countries may also differ, thus affecting the association between education and posing another challenge to the measurement of educational achievement (57, 58). Other methodological differences between studies include the sample size, as well as the availability of potential confounders that can be accounted for (59).

Education is mainly an activity that individuals engage in during childhood and young adulthood. However, variability regarding cognitive function in mid-life and late life cognitive function may also be associated with other activities like occupational and leisure activities.

2.1.2 Observational studies of occupational activities and late-life cognition

Mental stimulation from occupational activities is a source of mental stimulation that can last for many decades. Several observational studies have found that holding intellectually demanding jobs decreases the risk of all-type dementia (60-63), although one study found this association only for women (64), and other studies have not confirmed this association (65-67).

Studies have also investigated the association between levels of occupational complexity and late-life cognition among healthy older adults. Several of these studies have found a significant association between higher occupational complexity/work demands and better cognition in late-life (68-77), although there are studies that have not confirmed this finding (78). In the at-risk stages of dementia there are currently fewer studies but, in this stage, there still seems to be an association between occupational complexity and cognitive function as well (79, 80).

Additionally, early-life cognitive abilities have been suggested to affect the association between occupational complexity and late-life cognition or dementia. Some studies have shown that the association between occupational complexity and late-life

cognition is attenuated, but is still present, when controlling for early life cognitive abilities, (64) (81, 82) while others find that the association disappears (83, 84).

One of the reasons for the inconsistencies among the studies examining occupational complexity could relate to the methods used to operationalize it. Some studies use a categorial classification, where different jobs are organized into broader categories, such as managerial work and manual labour, and graded from low to high complexity on a 1-10 scale (85).

An approach providing a more granular description of occupational complexity is the system based on the U.S. Dictionary of Occupational Titles developed by Treiman & Roos (1980), where they assessed 46 different workers characteristics among 12,000 different jobs in the U.S (86). This system has unique complexity ratings for each specific job, which gives a more detailed assessment. For each occupation, four dimensions of complexity can be rated: complexity of work with data; complexity of work with people; complexity of work with things; and substantive complexity. A newer, similar, and more updated system is the U.S. Department of Labor's Occupation Information Network (O*NET), which is a database of detailed characteristics for occupations in the U.S. labour market. Occupational complexity is here based on ratings reflecting levels and importance of both tasks and skills relating to reasoning, use of relevant knowledge, problem solving skills, learning and decision-making skills, among others (87-89). For a complete overview of studies investigating occupational complexity and cognition, see **supplementary Table 1**.

Retirement and its effects on cognition is another facet of occupational activities, as work is a source of mental stimulation and the continuation or ceasing of such activity may be linked to cognition and risk of dementia. Several studies suggest that older age at retirement is associated with decreased risk of dementia (90-93). Studies have also investigated the association between age at retirement and late-life cognition and found a significant negative association between cognitive decline and higher age at the point of retirement (92, 94-97), while other studies did not find this association (98-100). The effect of retirement on cognitive decline in late-life may also differ depending on which type of job a person retires from, with studies suggesting that people retiring from more complex jobs may experience more cognitive decline (101, 102), while one other found the opposite association (103). It may also be related to the reasons of retirement (93).

The heterogeneity of findings examining age of retirement in relation to cognition may stem from the fact that early retirement can be the consequence of the occurrence cognitive problems, while individuals who have average or above average cognition might continue working and retire later (104).

Intensity of work participation, which is a measure of how much an individual has participated in occupational activities throughout life, has also been studied in relation to late-life cognition and dementia risk. Higher labour-force participation is associated with better cognitive performance, and since historically labour-force participation has differed between men and women it may contribute to late-life cognitive discrepancies between men and women (105).

Stress from occupational activities is another dimension of occupational activities that has also been linked to cognitive health, where a combination of low job control and high demands lead to high job strain (106). High job strain has been linked to worse cognitive functioning and higher risk of dementia (107, 108).

2.1.3 Observational studies of leisure time mental activities and late-life cognition

Mentally stimulating leisure activities are those activities in which individuals can engage outside of the occupational setting and the traditional schooling (primary and higher education). These can be activities like taking courses, playing board games, reading books, writing, or playing music, going to the cinema/theatre, gardening. The relationship between mentally stimulating leisure activities and dementia has been increasingly studied in the recent years as a part of the theory that mental stimulation may act as a protective factor (19, 109, 110).

Two systematic reviews have assessed different observational studies looking at the association between mentally stimulating leisure activities and the risk of dementia. In total nine out of eleven studies found that higher participation in mentally stimulating leisure activities was associated with lower risk of dementia, while two did not find this association to be significant (111, 112).

The reviews also assessed studies using the diagnosis of mild cognitive impairment (MCI) or cognition as an outcome. A total of 14 studies were assessed, and twelve of them found positive significant associations between engagement in mentally stimulating leisure activities and reduced risk of MCI and cognitive decline in late life (113, 114). Additional eight studies have been conducted since the last systematic review: five found that engaging in mentally stimulating activities was protective against dementia and cognitive decline (115-119), three of them did not find this association (83, 120, 121).

One study has suggested that there can be a reciprocal relationship between occupational complexity and engagement in leisure activities in relation to late-life cognition, so that engaging in a less complex occupation can be compensated by engaging in more leisure activities and vice versa (70).

A main source of heterogeneity in the observational studies assessing mentally stimulating leisure activities comes from the different methods used to measure them, including the selection and categorization of activities being assessed and the measure of the frequency of exposure. As mentioned in the case of occupational complexity, the issue of reverse causality can also occur in studies assessing leisure time mental activities in relation to late life cognition, as people with incipient cognitive impairment may engage less in leisure activities (122).

Individuals with higher levels of early-life cognition may also be more likely to engage in more leisure activities throughout the lifespan. Two studies measuring the association of mentally stimulating activities and late-life cognition have been able to include early-life cognition as a confounder: one of them found that when including early-life cognitive abilities the effect of engagement in leisure activities on cognition became non-significant (83) but the other study found that the association remained (119).

Differences in study results may also stem from the use of different cognitive outcome measures. For instance, several studies used the Mini Mental State Examination (MMSE), which is a screening test and has a sensitivity of 0.71 for MCI detection, and 0.74 for specificity. On the other hand, more comprehensive neuropsychological recall tests have a sensitivity of 0.89 and specificity of 0.84 for MCI detection. This suggests that MMSE should not be used as a single outcome measure of cognition, due to the higher risk of misclassification (123).

Studies have also examined single-domain intervention studies, testing if engagement in leisure activities in late life can improve cognition. A review from 2019 included 20 studies that had different types of intervention modalities - arts, writing, board games, reading, handicrafts, a crossword puzzle and learning computer skills. The review found a positive effect on different cognitive outcomes in thirteen of the studies (124). However, the studies considered had several methodological limitations, making it difficult to draw firm conclusions on which type of leisure time activity and of which intensity could be recommended to support cognition.

2.2 Observational studies of mental stimulation and brain pathology

Various theories have been proposed to explain the cognitive benefits of mental stimulation across the life course, as well as the observed heterogeneity in cognition in individuals with similar burdens on neuropathology. The concepts of brain reserve (BR, related to anatomical attributes of the brain), cognitive reserve (CR, related to functional properties of the brain), and brain maintenance (BM, related to the ability to reshape/maintain BR) have been the most used theoretical frameworks (125). These concepts have been also considered in the more recent "resilience and resistance to AD" framework, where resilience refers to the ability to cope with AD neuropathology

while resistance is the ability to halt its development (126). See **Figure 3** for an illustrated theoretical model of the resilience and resistance framework. In the following sections observational studies on the association between mental stimulating activities and brain pathology, also in relation to cognition, are summarized.

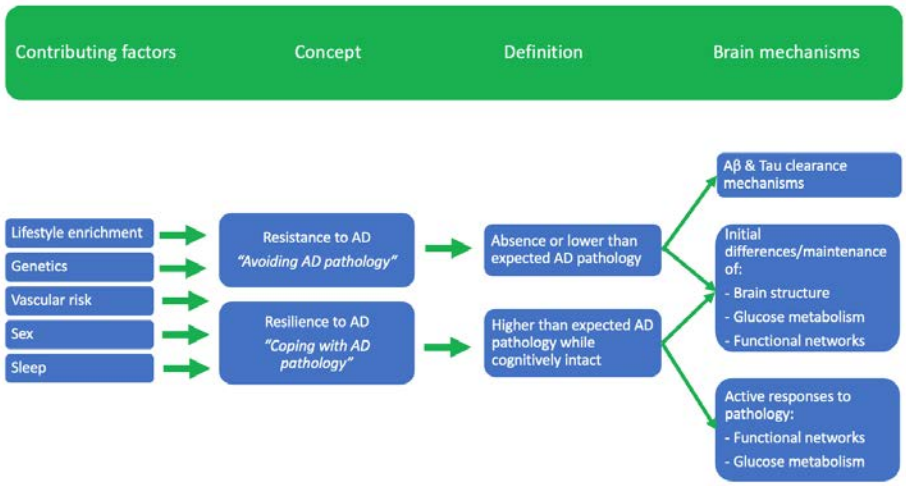

Figure 3. The resilience and resistance framework to AD-pathology illustrated. Adapted from Arenaza-Urquijo et al., 2020.

2.2.1 Observational studies of education and brain pathology

It is estimated that 10-30% of elderly individuals have beta-amyloid accumulation equal to the diagnostic level of AD, but without cognitive symptoms. This has been studied both with post-mortem histopathology and using PiB-PET neuroimaging (127, 128).

Post-mortem histopathology studies have reported that, when comparing highly educated individuals with brain beta-amyloid accumulation to lower educated individuals with the same levels of beta-amyloid accumulation, the highly educated individuals exhibited superior cognition relative to the lower educated (129). This relationship has also been found in studies using [11C] Pittsburgh-compound-B Positron emission tomography [(PiB)-PET] neuroimaging, as an *in-vivo* measure of brain amyloid accumulation (130, 131).

Education is also associated with resilience against the detrimental effects of the accumulation of tau neuropathology, which is an AD hallmark in conjunction with amyloid. As with amyloid, individuals with higher education exhibit better cognition despite significant accumulation of tau pathology, which would otherwise be severe enough to cause cognitive impairment in lower educated individuals (132). These same results have also been found when using combined markers of beta-amyloid and tau as markers of AD pathology (133).

Neuroimaging studies using fluorodeoxyglucose positron emission tomography (FDG-PET), which measures glucose uptake in the different regions in the brain, have also provided similar findings, with highly educated individuals having better cognitive performance than lower educated individuals, despite equivalent levels of impairment in glucose uptake (134, 135). It has also been observed that in the early stages of AD dementia individuals with higher levels of education present with greater AD neuropathology burden, suggesting that education can delay the clinical expression of AD (129, 136, 137).

Education can also moderate the association between hippocampal volume and memory performance in healthy older adults. A study showed that the positive association between larger hippocampal volumes and memory performances was strongest in those with more years of education (138).

Studies using functional magnetic resonance imaging (fMRI) have also found that in MCI and AD, individuals with higher education, as compared to lower education, presented stronger network efficiency and functional connectivity in the default mode network (139), which has been also related to better cognitive functioning despite presence of neuropathology (140, 141).

The associations between exposure to mentally stimulating activities and burden of AD pathology, as well as rate of cognitive decline, seem to be dynamic and change across the cognitive continuum. **Figure 4** exhibits a temporal relationship between common biomarkers of AD-pathology and how factors related to resilience may affect when cognitive impairment occurs (142). This means, for any given level of neuropathology there is variability in terms of cognitive performance, and this can be associated with factors such as mental stimulation. In fact, when studying healthy individuals, subjects with higher levels of education have lower levels of amyloid deposition, but when studying MCI patients, the relationship is reversed, as higher education has been associated with higher amyloid deposition, after controlling for cognition (143). This is due the fact that individuals with higher resilience to AD will have accumulated more AD neuropathology before showing cognitive symptoms. Studies on the possible effects of education in the early-symptomatic phase of AD, prodromal AD, are few but have found that individuals with higher education can maintain cognitive performance despite neuropathology present, compared to individuals with lower education (140). This was partly related to increased higher global functional connectivity of the left frontal cortex and greater neural compensation and in another study greater metabolic connectivity in the right dorsolateral prefrontal cortex (144).

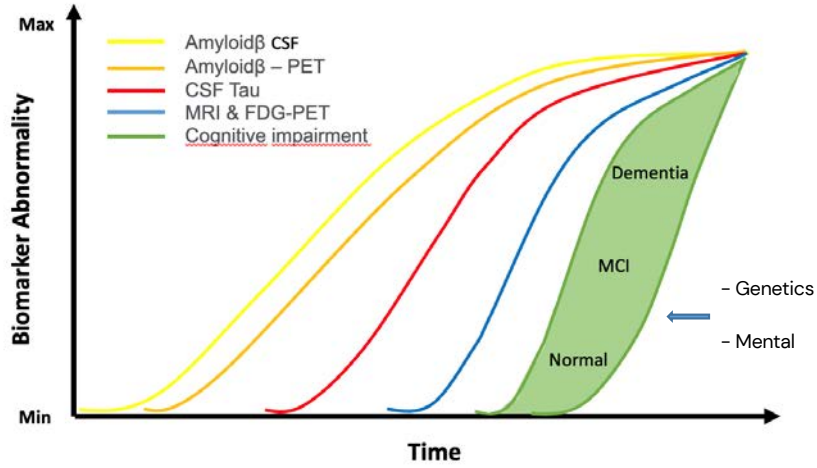

Figure 4. Temporal relationship between common AD biomarkers and the contribution of resilience factors to the onset of cognitive impairment. Adapted from Jack CR Jr et al., 2013.

2.2.2 Observational studies of occupational activities and brain pathology

Few studies have investigated occupational complexity and its relation to biomarkers of neuropathology, such as amyloid, tau, magnetic resonance imaging (MRI) and PET, compared to the existing literature on education and such biomarkers. An overview of the studies investigating occupational complexity and its association to cognition and neuropathology is presented in **supplementary Table 2**.

One study investigated the effect of education and occupation on cognition in a sample of subjects with probable AD, MCI and healthy individuals, by using FDG-PET as a marker of neuropathology, reporting that individuals with higher education and more complex occupations had more impaired glucose uptake while still maintaining their cognitive level (145). Although, the same association was not found to be significant in MCI patients not progressing to AD dementia stage (145). Stern et al., also demonstrated this association in patients with AD dementia, using parietal flow as a marker of neuropathology (146).

Furthermore, among middle-aged adults at risk for AD, those with higher occupational complexity, when matched for cognitive performance, had smaller hippocampal size and greater whole brain atrophy (79). This suggests that occupational complexity might be protective against the cognitive effects of neuropathology. More recently, Boyle et al. tested if there was a moderating effect of occupational complexity in the relationship between brain structure and cognition in two separate datasets and found no significant effects that were replicated in both datasets (147). This is similar to what Suemoto et al.

found in a study including 1023 participants, where 393 individuals had cognitive impairment and 630 were cognitively healthy. There was no association between occupational complexity and the clinical dementia rating-sum of boxes (CDR-SB) after adjusting for post-mortem measures of neurofibrillary tangles, neuritic plaques, Lewy body disease, infarcts, small vessel disease and cerebral amyloid angiopathy. However, the CDR-SB was conducted by next of kin after death of the study participants and participants had a quite low education level (mean 4.1 years) (148).

However, Ko et al. did find that occupational complexity had a moderating effect on the relationship between cortical atrophy of AD signature regions and cognition, but only in patients with MCI or AD dementia (149). A moderation effect in this context is evident when the association between a measure of brain function or neuropathology and cognitive performance is moderated by another factor, in this case occupational complexity. This means that the level of cognitive performance can vary among individuals with similar levels of neuropathology.

A similar finding was also found by Nelson et al., who demonstrated among individuals with subjective cognitive decline and amnestic MCI that occupational complexity moderated the association between total gray matter volume and cognitive measures of attention, language, and memory. Among individuals with dementia, occupational complexity moderated the association between total gray matter volume and executive function (150).

Mental effort paradigms have also been investigated in relation to neural function. A study by McDonough et al. used fMRI to investigate the impact of high-challenge mental activities and low-challenge activities on neural function. The study found that the high-challenge, compared to the low-challenge group, showed increased modulation of brain activity in medial frontal, lateral temporal, and parietal cortex regions, which are brain areas associated with attention and semantic processing (151). The authors concluded that sustained engagement in cognitively demanding activities may support cognition by increasing neural efficiency. Although not a direct investigation of occupational exposure and brain function, high complexity occupations do expose individuals to more complex tasks than low complexity occupations (89, 152).

Two studies have also linked stimulation from occupational activities to accumulation of neuropathology. Kivimäki et al., reported in a large multicohort study that higher levels of occupational complexity among healthy individuals were associated with lower levels of plasma proteins linked to neurodegeneration (153). Lo et al., found that, among cognitively healthy individuals, higher occupational complexity was associated with less decline over time of Aβ42 as measured in cerebrospinal fluid (CSF) but not in subjects with MCI or AD dementia (154).

2.2.3 Observational studies of leisure activities and brain pathology

A review from 2018 investigated how socio-intellectual activities related to brain structure using MRI techniques. In total 18 studies were identified, the study samples consisted of healthy older adults (i.e., without a diagnosis of dementia) with a mean age of 60 years or more. The main findings were that higher levels of engagement in leisure activities were associated with greater hippocampal volume and whole-brain white matter volume, reduced whole-brain white matter lesions but not whole-brain gray matter volume (155).

Two studies have found associations between engagement in mentally stimulating activities and cortical Aβ deposition, quantified using PiB-PET. Both studies showed that higher engagement in cognitive activities was associated with lower [(11)C] PiB uptake (156, 157), which indicates that mentally stimulating activities also can affect accumulation of AD pathology. One of the studies used both healthy individuals, AD subjects and young controls (156), the other one only assessed older healthy individuals (157). Another study including both cognitively normal and MCI individuals did not find any associations between engagement in cognitive activities and measures of PiB-PET uptake, global FDG-PET or MRI based hippocampal volume (158). These are examples of how leisure activities can contribute towards resistance to neuropathology. The heterogeneity of findings in these studies can be due to the same differences in the methodological aspects previously mentioned in the observational studies and sample size limitations.

To summarize, mental stimulation over the life-course has mostly been associated with resilience to neuropathology but there is also some evidence for its contribution to lower accumulation of neuropathology as well (resistance). Studies include subjects from different groups, both individuals who are healthy, diagnosed with MCI and those who have AD dementia, but fewer studies include individuals at-risk for cognitive impairment (before MCI) and individuals with prodromal AD. Studies also tend to be cross-sectional rather than longitudinal. There is also currently lack of knowledge regarding how different measures of mental stimulation may affect the outcomes of prevention and drug RCT´s for cognitive impairment. Furthermore, when conducting RCTs its important to choose the right population and timing for the intervention. Since factors relating to mental stimulation are associated with the clinical expression of disease these could potentially be important to account for when planning and designing RCTs.

2.3 Randomized controlled trials for Alzheimer´s disease and cognitive impairment

Randomized controlled trials (RCTs) are the gold standard method for inquiring about cause and effect when it comes to scientific studies in medicine. By randomizing study participants to the treatment or intervention many sources of bias can be avoided, and by having a control group that is given a placebo or treatment-as-usual the effect size in the intervention group can be properly assessed. The three most important basic principles of RCTs are (1) control groups, (2) randomization and (3) blinding (159).

Historically, there were versions of RCT´s being conducted and reported already in the 1720s when English physician and scientist James Jurin compared differences in mortality from naturally occurring smallpox with that of cases occurring as a result of inoculation (159). The comparison showed the efficacy of the new treatment. James Lind, a naval surgeon published the results of a comparative treatment of 12 scurvy patients in 1753. Lind wrote that "the most sudden and visible good effects were perceived from the use of oranges and lemons" (159).

In the field of dementia and AD research, RCTs are used to investigate the efficacy and safety of both drug treatments and lifestyle interventions. Over 200 drug-trials have been conducted over the past 20 years, using different compounds with potential disease modifying effect for AD and dementia (160, 161). Most of the trials have not met their primary endpoints for cognition until recently, when three RCTs that have tested amyloid beta-directed monoclonal antibodies for individuals with MCI due to AD or early-stage dementia due to AD exhibited significant differences for the CDR-SB at the end of the trials as well as significantly reduced concentrations of amyloid plaques in the brains. Questions still linger on if these disease-modifying drugs will be widely available because of the relatively high cost per treated individual, various serious side effects and relatively small effect sizes (14, 162).

In the last decade, multidomain lifestyle-based interventions for the reduction of cognitive decline and dementia risk have also showed promising results. The FINGER trial, which included 1260 participants at-risk for dementia, showed that multimodal lifestyle intervention including diet, physical exercise, cognitive training, social stimulation, and control of metabolic risk factors could significantly improve cognition and reduce cognitive decline after 24-months (16).

The Prevention of Dementia by Intensive Vascular care (preDIVA) was a trial which included 3454 participants aged between 70-78 years where the intervention group received a multidomain cardiovascular intervention consisting of individually tailored lifestyle advice targeting five different areas: smoking habits, diet, physical activity,

weight, and blood pressure (including optimized medication for several metabolic diseases). The trial did not show any significant differences between the intervention group on the main outcomes, dementia incidence and disability score, after six years compared to the control group that received regular health advice for cardiovascular risk management (163). However, a sub-group analysis found that individuals with untreated hypertension at baseline who were adherent to the intervention had reduced risk of dementia (163).

The Multidomain Alzheimer Preventive Trial (MAPT) was a three-year trial where 1525 non-demented community dwelling individuals above age 70 that had either reported a memory complaint to their physician, had limitations in one instrumental activity of daily living, or slow gait speed where included. They were randomized to one of four arms in the trial: 1) a multidomain intervention consisting of 43 group sessions integrating cognitive training, physical activity, and nutrition, and three preventive consultations plus daily omega 3 polyunsaturated fatty acids supplementation. 2) Multidomain intervention plus placebo, 3) omega 3 polyunsaturated fatty acids alone or 4) placebo alone. After three years there was no significant differences for the main cognitive outcomes between any of the three intervention groups and the placebo group (164). Sub-group analysis did however reveal that the was an intervention effect for the multidomain + omega 3 group but only for individuals with a CAIDE risk score ≥6 (165). The analysis also showed that there was an intervention effect for the multidomain + omega 3 and multidomain alone for individuals that were amyloid positive (166).

Several other single-domain and smaller multidomain RCT´s with aims to reduce cognitive impairment and dementia has also been conducted with some of the trials showing beneficial effects on cognition while others not (110).

2.3.1 Control groups and randomization

The RCT design holds many important keys to understanding and investigating cause and effect in medicine. Despite this, conducting RCTs poses challenges, and the results are not always easy to interpret. When it comes to trials in dementia research, the primary outcome in most trials is cognitive performance, as measured with a neuropsychological test battery or a measure that combines cognitive function and daily function. This means that cognitive performance in the intervention arm must be significantly better, in statistical and clinical terms, than the control group, to show efficacy. This might translate in improvement in cognition, or slower cognitive and functional decline in the active group compared to the control group (167).

The probability of finding an effect is partly dependent on the sample size of the study. A greater sample size means that that variance in the study population will be smaller, and this means it will be easier to detect smaller effects. But since recruiting, organizing,

and facilitating an RCT is costly and time-consuming, many trials cannot enrol too many participants. Instead, researchers need to calculate the sample size ápriori, based on the size of the expected effect. This is based on estimations on how much cognition and/or function would improve or decline in the active and control group. To estimate this, data from previous similar studies are often used, which improves the accuracy but still it might pose a problem. This is because the previous estimated might come from studies that are different from the trial that is being conducted in terms of number of participants included, target population and study duration etc (167).

Trials can show insufficient decline in the control group which makes the comparison to the active group more likely to be non-significant. One reason for this might be that the individuals included in the trial might not all be correctly diagnosed, in some cases there might be non-AD individuals in trials testing drugs against Alzheimer´s Disease (168). Individuals who do not have the correct diagnosis (mild cognitive impairment, prodromal AD or AD-Dementia) will decline more slowly or quickly than calculated. Even when the diagnosis and inclusion criteria are properly implemented, there can be considerable heterogeneity in a trial among the included participants. As an example of this, the CDR required for a prodromal AD diagnosis is 0.5 but within the category of 0.5 there is considerable heterogeneity in terms of biomarker values and cognitive function. Where some individuals are almost within the healthy normal range and some individuals are almost in the mild dementia stage (160).

Apart from selecting the appropriate participants for an RCT, the two arms in an RCT should also have randomized its participants so that there should be not differences between the two groups on any baseline characteristics. The RCT design should solve this problem since participants are randomly allocated to either the active or control group. But still there can be an uneven distribution in the two groups after randomization regarding factors affecting rate of cognitive change, resulting in more or less fast decliners in one of the groups (169). This can result in trials showing significant differences between active and control group while it is a difference stemming from a potential oversampling of fast or slow decliners to either group (170).

2.3.2 Practice effects

The primary endpoint in many RCTs for AD and dementia prevention is cognitive function, which is assessed by using neuropsychological tests. Neuropsychological tests are subject to so called re-test effects, which means that participants' results on the tests improve each time they take the test due to practice, but this improvement is not an actual improvement in cognitive function in a true sense (171). In cognitively healthy individuals this means that true absolute improvement in cognitive performance in a trial is most likely less than what the numbers show. For subjects with MCI, prodromal AD or Dementia observed practice effects are considerably less since learning and

memory functions, which facilitate practice effects in healthy individuals, are impaired due to nature of the disease. However, practice effect has been observed in these patient groups as well but not to the same degree. Therefore, in these patient groups, the cognitive decline observed in clinical trials may be underestimated due to practice effect (172).

2.3.3 The role of mental stimulation in multidomain preventive RCTs

Since mental stimulation can influence late-life cognitive changes, it may also affect the cognitive outcomes of RCTs aiming to prevent or delay cognitive impairment in older adults. Very few non-pharmacological RCTs have assessed this: in the Advanced Cognitive Training for Independent and Vital Elderly (ACTIVE) trial, it was reported that the educational level was associated with different patterns of response to the memory training, as participants with higher education were more likely to improve in their performance in specific measures of episodic memory (173).

On the other hand, another analysis in the same RCT found that participants with less than 12 years of education responded better to the processing speed training, compared to those with 16 or more years of education (174). In the FINGER trial, education did not affect the cognitive outcomes after two years of the multidomain intervention (175).

Taken together, the evidence from observational studies, and the more limited analyses in preventive RCTs, suggests that the effect of preventive interventions in older adults could be affected by previous lifetime exposure to mentally stimulating activities. Understanding the role of mental stimulation can increase our understanding of the effects of preventive interventions and help developing tailored preventative strategies targeting subjects with specific risk profiles. This also implies that a proper assessment of previous exposure to mentally stimulating activities might be needed in RCTs comparing rates of cognitive decline between interventions (i.e., drugs, lifestyle interventions) and controls. Furthermore, it would help the field move from only estimating the average treatment effect (ATE) to also estimating individualized treatment effect (ITE) possibly. This would enable tailoring interventions and drugs to individuals to achieve greater effect and less harm (176, 177). See **Figure 5** for an illustration of this concept. This knowledge will also be useful in the planning of future preventive intervention studies and formulate recommendations for AD and dementia prevention in both the community and clinical setting.

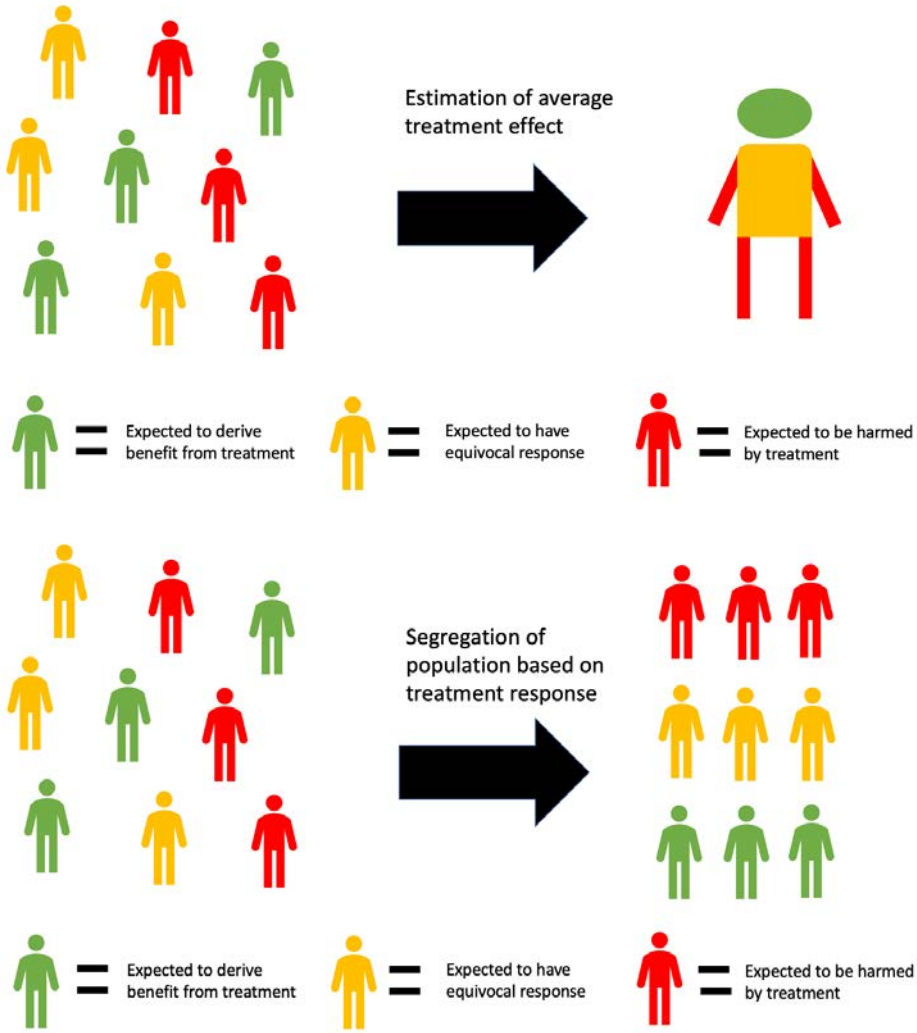

Figure 5. Illustration of theoretical model of precision medicine. Adapted from Yeh et al., 2017.

3 Research aims

3.1 General aims

The general aim of this research project is to understand how lifetime mental stimulation may affect late-life cognition and clinical expression of AD neuropathology in older adults at risk of dementia, and the possible effect on cognitive outcomes of a multidomain prevention trial for cognitive impairment and dementia.

3.2 Specific aims:

- To better understand the contribution of mental stimulation to the inter-individual variability in cognition in individuals at increased risk of dementia (asymptomatic and symptomatic/prodromal AD)

  Study 1 & 4

- To examine the effect of mental stimulation on cognitive changes in the context of a multidomain, lifestyle-based prevention trial.

  Study 1

- To investigate if life-time mental stimulation is associated with resilience to AD neuropathology among individuals at-risk for dementia (asymptomatic and symptomatic/prodromal AD)

  Study 2 & 3

4 Materials and methods

4.1 Ethical considerations

4.1.1 FINGER

The FINGER study was approved by the coordinating ethics committee of the Hospital District of Helsinki and Uusimaa (HUS/1204/2017) as well as the Swedish Ethical review authority (Dnr 2020-07058). FINGER is registered as a clinical trial at ClinicalTrials.gov (NCT01041989). Participants gave written informed consent at screening and baseline visits. The trial adhered to the Declaration of Helsinki and was conducted according to the International Conference on Harmonization (ICH) guidelines for Good Clinical Practice (GCP). Participants received patient insurance from the Finnish National Institute for Health and Welfare, had the possibility to contact the study staff throughout the study, and they were referred to appropriate medical care when indicated. A safety and end point committee were appointed, and data were collected on adverse events (AEs) and serious adverse events (SAEs).

4.1.2 FINGER MRI & PET study

The FINGER MRI & PET sub-study was approved by the Hospital District of Helsinki and Uusimaa (240/13/03/00/2011), and the Swedish Ethical review authority (Dnr 2020-07058). The participants in the neuroimaging subsamples gave separate consent for MRI and PiB-PET scans.

4.1.3 GEDOC

The Karolinska University Hospital electronic database and biobank for clinical research (GEDOC) and have been approved to for research by the Regional Ethical Review Board in Sweden (Dnr 2011/1987-31/4; Dnr 2022-00137-02). All patients provided written informed consent.

4.1.4 MIND-ADmini

The MIND-ADmini (ClinicalTrials.gov identifier NCT03249688) was approved by the Regional Ethical Review Board in Sweden (2016/2605-31/1). The trial adhered to the Declaration of Helsinki and was conducted according to the International Conference on Harmonization (ICH) guidelines for Good Clinical Practice (GCP). Participants were insured according to local legislation, had the possibility to contact the study staff throughout the study, and they were referred to appropriate medical care when indicated. The safety of the intervention was assessed, and data were collected on adverse events (AEs) and serious adverse events (SAEs).

4.2 Databases

4.2.1 The FINGER trial

Participants:

The FINGER study is a population-based, multidomain RCT that enrolled 1260 participants from previous population-based observational studies from six different sites in Finland. Recruitment started in 2009 and finished in 2011, the trial commenced in 2013 and was completed in 2015. To be eligible for the study participants had to be between 60–77 years old, have a Cardiovascular Risk Factors, Aging and Dementia (CAIDE) Risk Score ≥6 points, which indicates the presence of modifiable vascular and lifestyle-related risk factors for dementia (178).

Selection criteria for cognitive performance was developed in order to recruit individuals with cognitive performance at the mean level or slightly lower than expected according to the Finnish population norms (179). Therefore, eligibility criteria for cognitive performance were used, as follows. Consortium to Establish a Registry for Alzheimer's Disease (CERAD) word list memory task ≤19 words (maximum score 30), CERAD word list recall ≤75% (maximum 100%), or a Mini–Mental State Examination (MMSE) score of 20–26 (maximum score 30) (180).

Exclusion criteria were severe impairment in hearing, vision or communication ability, or other conditions preventing cooperation as judged by the study physician. Previously diagnosed dementia, suspected dementia at screening visit, conditions affecting safe participation in the trial (e.g., major depression, malignant tumour, symptomatic cardiovascular disease; revascularization within 1 year). More details on the study protocol, baseline population characteristics and results after 24-months have previously been published (16, 181, 182).

The intervention:

Of the 2654 individuals that were screened, 1260 were randomized 1:1 to the multidomain intervention group or control group. The outcome assessors were blinded to the group allocation and were not involved in the intervention. All participants (irrespective of group allocation) received oral and written information from the study nurse with advice on healthy diet and social, cognitive, and physical, activities beneficial for the management of vascular risk factors and disability prevention. In addition, all participants met with the study nurse at screening and baseline and at 6, 12 and 24 months after randomization for measurements of blood pressure, BMI and weight, and hip and waist circumference. All participants also met with the study physician at screening and 24 months for a physical examination. Blood samples were also collected during the study at baseline and at 6, 12, and 24 months, and the results from the laboratory test were mailed to all participants, together with written information about

the clinical significance of measurements, and advice to contact primary health care if needed. The multidomain lifestyle intervention group received in addition also a multidomain intervention consisting of four components: physical exercise; cognitive training; social stimulation and nutritional guidance (182). The physical exercise intervention part was based on international guidelines and was conducted at the gym with the instruction and help from physiotherapists (183). The intervention focused on aerobic, resistance and balance training. The nutritional guidance that was focused on improving dietary habits was based on the Finnish Nutritional Recommendations and was implemented and delivered with the help of nutritionists using individual sessions and group meetings (184). Cognitive training was conducted and led by a psychologist through group sessions and individual computer-based training at home or at the study site. The cognitive training program was an in-house developed, web-based computer program, consisting of tasks from previous protocols that has shown to be effective in short-term RCTs (185). The program focused on the cognitive domains, executive function, processing speed and memory. Social activities were stimulated through the numerous group meetings of all intervention components. Metabolic and vascular risk factors were managed and controlled based on the national evidence-based guidelines (186-188). Study physicians did not prescribe medications but recommended participants to contact their physician if needed (187).

Cognitive outcomes

The cognitive outcome measures were derived using an extended version of the Neuropsychological Test Battery (NTB) and administered by the study psychologists at baseline, 12 and 24 months (189). The trial primary outcome was the change in the NTB total score, which consisted of combined scores from 14 different tests listed below. The test results were calculated as standardized z-scores (the z-scores for each test at each time point were standardized to the baseline mean and standard deviation), with higher scores indicating a better performance. The trial secondary outcomes consisted of z-scores for the separate domains of executive functioning, processing speed, and memory. Executive functioning domain included Digit Span, Concept Shifting test (Condition C), Trail Making test (shifting score: time in part B - time in part A), Category Fluency test and a 40-item version of the Stroop test (interference score: time in part 3 - time in part 2). The processing speed domain included Letter Digit Substitution, Concept Shifting (condition A), and Stroop (condition 2) test. The memory domain involved Visual Paired Associates test (immediate and delayed recall), Logical Memory test (immediate and delayed recall), and Word List Memory test (learning and delayed recall).

To calculate an individual's NTB component composite scores, a minimum of 8/14 test for the NTB Total was needed, 3/5 for executive functioning, 2/3 for processing speed and 3/6 for memory. Alternate stimuli versions for the tests were used to reduce

practice effects. Zero-skewness log-transformation was applied to all skewed NTB components.

For study 1, which was a post-hoc analysis within the FINGER RCT, we used the pre-defined primary and secondary cognitive outcome measures of the FINGER trial (189). Of the 1260 enrolled participants, 1190 (94%) completed at least one assessment of the primary efficacy outcome after the baseline visit (16). For the exploratory analysis in study 1, 1026 participants were included (intervention 521; control 505), as these individuals had at least one post-baseline assessment (modified intention-to-treat population - mITT), available data on occupational complexity, and were retired at baseline. People who were still working at the study baseline (n=118) were excluded from the main analysis, to measure the association of previous (rather than current) occupational complexity.

4.2.2 Brain imaging in FINGER:

MRI assessment

In the FINGER neuroimaging sub-study 155 study participants from four different study sites underwent structural MRI at the baseline visit. 132 scans from three centers (Turku, Kuopio and Oulu) passed the quality control done by an experience neuroradiologist. Different MR systems were used at the different sites, 1.5 T Avanto Siemens (3D-MPRAGE sequence, voxel size 1.2 × 1.2 × 1.2 mm, repetition time (TR) 2400 ms, echo time (TE) 3.5 ms, inversion time (TI) 1000 ms) at the Kuopio and Oulu sites, and 3T Ingenuity Philips (3D turbo field echo sequence [TFE] sequence, voxel size 1.0 × 1.0 × 1.0 mm, TR 8.1 ms, TE 3.7 ms) at the Turku site. At each MRI site, regular phantom scans were performed, and quantitative measures of signal-to-noise ratio, uniformity, and geometric distortion were carried out. Freesurfer (version 5.3, http://surfer.nmr.mgh.harvard.edu/) was used to measure volumes and regional cortical thickness.

The AD signature cortical thickness was calculated by averaging the bilateral cortical thickness from four different regions: middle temporal, entorhinal, fusiform and inferior temporal region (190). The medial temporal atrophy (MTA) was assessed by a single rater who was blinded to the clinical data, applying on T1-weighted images a visual rating scale (Scheltens scale) commonly used in clinical practice (191). MTA was rated from single coronal slice at the level where cerebral peduncles, pons and hippocampus were all visible. The grading for MTA was done from 0 (no atrophy) to 4 (end-stage atrophy) bilaterally.

For the exploratory analysis in study 2, 126 participants were included, based on the availability of information on occupational complexity and neuroimaging data.

PET assessment

The PiB-PET assessments were conducted in only one center, Turku University Hospital, for 48 participants, in connection to the baseline FINGER visit. [11 C] PIB (N-methyl-[11 C]2-(4 methylaminophenyl)-6-hydroxybenzothiazole) was produced according to a standard procedure (192). On average, 406.3 (SD 107.7) MBq of PiB was injected intravenously and a scan from 60–90 min (3 × 10 main frames) after injection was performed with a Philips Ingenuity TF PET/MR scanner (Philips, Amsterdam, the Netherlands). The scans were visually interpreted by two experienced readers and judged as visually positive or negative after consensus agreement. For the exploratory analysis in study 2, a total of 41 participants were included based on availability of information *APOE* status, occupational complexity, and neuroimaging data.

4.2.3 GEDOC:

The Karolinska University Hospital electronic database and biobank for clinical research (GEDOC) is a clinical based database including patients who have been referred to the Memory Clinic at the Karolinska University Hospital, Huddinge, Stockholm, Sweden, for investigation of suspected dementia. The clinic is a Center of Excellence for dementia diagnosis and receives referrals from primary healthcare centers in the catchment area, and referrals from regions outside of the Stockholm area. At the clinic each patient undergoes a comprehensive neuropsychological examination, analyses of blood and CSF, as well as brain imaging procedures, according to national guidelines. The diagnostic procedure has been described in detail in previous work (193).

Participants in study 3 were examined during 2007-2014 and fulfilled the diagnostic criteria for prodromal AD based on the International Working Group-1 (IWG-1) (194). The criteria stipulate that prodromal AD is a condition were an episodic memory impairment is evident based on memory testing, but the impairment is not severe enough to affect instrumental activities of daily living to the degree that is characterized by a patient with a dementia diagnosis. The diagnostic criteria also require evidence of underlying AD pathology, based on findings from CSF or PiB-PET assessment. Exclusion criteria included; subjects with dementia according to Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV) (195), other conditions (i.e., normal pressure hydrocephalus, brain tumors), psychiatric disorders (i.e., major depression, alcohol or drug abuse).

CSF assessment

CSF samples were obtained during the diagnostic workup by lumbar puncture using propylene syringes. Samples were gently mixed to avoid gradient effects and centrifuged at 2000g for 10 minutes. Aliquots were stored at -80°C until the biochemical analysis. Tau levels were determined using a sandwich enzyme-linked immunosorbent assay constructed to measure t-tau (both normal tau and hyperphosphorylated tau [p-tau$_{181}$]). P-tau$_{181}$ was determined using a sandwich enzyme-

linked immunosorbent assay, with monoclonal antibody HT7 (recognizing all forms of tau) used as capturing antibody and biotinylated monoclonal antibody AT270 (specific to PThr181) used as a detection antibody. $A\beta_{1-42}$ was determined using a sandwich enzyme-linked immunosorbent assay specific for $A\beta_{1-42}$, as previously described (196).

Cognitive tests

The cognitive tests available in GEDOC and included in this research project were the Mini-Mental State Exam (MMSE) (study 3 and 4), and the Rey Auditory Verbal Learning Test (RAVLT), immediate and delayed recall (study 4). For study 4, the RAVLT test inclusion allowed a joint analysis including FINGER, MIND-ADmini and GEDOC data with episodic memory as outcome.

4.2.4 MIND-ADmini

The MIND-ADmini is a 6-month international (Finland, Germany, France and Sweden) proof-of-concept RCT in 93 individuals with prodromal AD, including three parallel groups 1) multimodal lifestyle intervention; 2) multimodal lifestyle intervention + medical food; and 3) regular health advice/care (control). Eligible participants were randomized in a 1:1:1 ratio in blocks of six (computer generated allocation, two individuals randomly allocated to each group). Group allocation was not disclosed to the participants and participants were instructed not to discuss the intervention with the outcome evaluators. Outcome evaluators were also blinded to the randomization group and were not involved in intervention activities (197).

Participants:

Participants were 60 to 85 years old and were recruited via the university hospital neurology clinic and research cohorts in Kuopio, Finland, and from memory clinics in Stockholm, Sweden and Toulouse, France and via local media advertisement in Frankfurt, Germany. The IWG-1 diagnostic criteria were used to select individuals with prodromal AD, defined as having objective episodic memory impairment and evidence for underlying AD pathology (194). Episodic memory disorder was defined as -1 SD on at least 2 out of 8 tests, of which at least 1 is a memory test. AD pathology was defined as having at least one abnormal cerebrospinal fluid (CSF) or neuroimaging biomarker. Furthermore, a lifestyle index score of two points or more was also needed for inclusion in the study, in order to identify people with modifiable risk factors for dementia (197).

Exclusion criteria involved the following; severe disease (e.g., recent history of myocardial infarction or cancer), dementia according to Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV), intake of supplements for vitamin B6, B12, folic acid, vitamin C and/or E > 200% of the recommended daily intake unless prescribed by physician, use of omega-3 preparations (> 500mg EPA+DHA per day), alcohol or drug abuse, major depressive disorders (DSM- IV) and subjects with MRI or

computerized tomography scan (CT) consistent with a diagnosis of stroke, intracranial bleeding, mass lesion or normal pressure hydrocephalus.

The intervention

The multidomain intervention program in MIND-ADmini was based on the FINGER protocol, but adapted for participants with prodromal AD. The components of the intervention were, (1) nutritional guidance; (2) physical exercise; (3) cognitive training; (4) monitoring and management of vascular and metabolic risk factors; (5) social stimulation. The intervention components were gradually implemented to increase adherence. All intervention components were standardized to create similar intervention content at all study sites. The social stimulation was integrated into all intervention components that entailed group activities (197).

One group in the intervention arm also received a medical food intervention in addition to the lifestyle intervention. Fortasyn Connect, a 125ml once-a-day milk-based drink, which contains long-chain omega-3-fatty acids. Both docosahexanoic acid (DHA) and eicosapentaenoic acid (EPA), as well as uridine monophosphate, choline, vitamins B12, B6, C, E, and folic acid, phospholipids, and selenium. This medical food has in a previous RCT, the LipiDiDiet, shown to be improving cognitive performance and measures of hippocampal volume in individuals with prodromal AD, compared to placebo, over 36-months (198).

The primary outcome in the MIND-ADmini pilot trial was feasibility as measured by (1) recruitment rate, and (2) overall adherence to the intervention. Recruitment rate was defined as proportion of participants who are randomized of those who fulfilled the criteria and were invited to participate during a 6-month recruitment phase. A recruitment rate of 50% or more was considered successful.

Overall adherence to the intervention was measured by adherence to the different intervention components. The definition of successful adherence was met if a participant attended a minimum of 40% of sessions per domain, in at least 2/4 domains (nutrition, cognitive training, exercise and monitoring of vascular/metabolic risk factors). In the lifestyle + medical food intervention arm, the participant is considered to successfully adhere to the intervention if they in addition consume at least 60% of the medical food study product.

Cognition, which was an exploratory outcome, was measured with a modified version of the Neuropsychological Test Battery (NTB) and was done by a psychologist at baseline and 6 months follow-up. The tests included were the Modified 30-item Boston Naming Test, Category Fluency, Wechsler Memory Scale (WMS) Verbal Memory Test immediate and recall, WMS Visual Paired Associates immediate and recall, Consortium to Establish a Registry for Alzheimer's Disease Word List (CERAD) immediate, recall and recognition,

CERAD Constructional Praxis copy and recall, WMS Digit Span forwards and backwards, Letter Digit Substitution Test. Concept Shifting Test version A, B and C And Trail Making Test A and B.

The tests used in study 4 were the CERAD 10-words list memory test, learning and delayed recall, to enable joint analyses with the FINGER and GEDOC samples, as the CERAD word list immediate and delayed recall was used in FINGER and MIND-AD and the RAVLT immediate and delayed recall was used from GEDOC.

Indicators of mental stimulation

In all four studies included in this thesis, information on education and occupation was used. In the FINGER trial it was collected at the baseline visit, in GEDOC at the clinical assessment and in MIND-AD during the screening visit. Education was collected through self-reported questionnaires in all three populations. For MIND-ADmini and GEDOC, which included subjects with prodromal AD, the information was verified with the study partner or a close proxy, respectively.

In FINGER and MIND-AD, occupational complexity was derived from retrospective questions about the latest-held occupation, while in GEDOC it was defined considering the main occupation in adult life. In all three populations, occupational complexity scores were assessed with a work complexity matrix that is based on the estimation of more than 12,000 occupations rated during onsite occupational assessments in the United States (152). These occupational assessments were then matched with occupational codes from the U.S. Dictionary of Occupational Titles (DOT), so that each occupational code could be represented with complexity measures. For each occupational code, four dimensions of complexity can be rated: complexity of work with data (score range 0-6); complexity of work with people (score range 0-8); complexity of work with things (score range 0-7); and substantive complexity (score range 0-10). Complexity of work with things has previously been shown to have low reliability and predictive ability, therefor it has not been used in any of the current studies (199-201). Complexity of work with people refers to the demands imposed by working with other persons and complexity of work with data refers to the level at which persons handle information in their work. Substantive complexity reflects overall complexity, and its scores were derived from measures previously developed by Roos and Treiman, (152) based on a principal component analysis (PCA) aiming to extract workers' characteristics representing global complexity. The PCA identified eight factors representing substantive complexity: general educational development, specific vocational preparation, complexity of work with data, intelligence aptitude, verbal aptitude, numerical aptitude, abstract interest in the job, and temperament for repetitive and continuous processes.

In order to use this complexity rating system in Nordic countries, previous work had matched the occupational categories from the 1980 Swedish Population and Housing Census with the codes from the DOT system, so that the occupational categories were by that assigned with occupational complexity scores. The matching procedure has been previously described in detail (200) (202). In all four studies we considered complexity of work with data and with people, as well as substantive complexity.

In study 4 occupational complexity was assessed using both the DOT and O*NET rating systems. From the DOT, complexity with data, with people, and substantive complexity were used. From the O*NET system, two variables were created, complexity with mental (data) and social (people) demands of work. In order to get the O*NET codes, we used a crosswalk database that contains more than 1400 unique occupations, each having both the Swedish Standard Classification of Occupations (SSYK) and the corresponding O*NET code (203). The free-text occupations in FINGER, GEDOC and MIND-ADmini were matched to the SSYK occupations, in order to get the O*NET codes. After the codes had been retrieved, the items from O*NET database were extracted from the O*NET database, version 13.0 from 1st of July 2009 (204). 77 individuals who had information on occupational complexity in the DOT system could not be rated in the O*NET system. Since some occupations (i.e., professions in the military) are not included in the O*NET or they are not assigned ratings on occupational complexity with people or data. From the O*NET based we retrieved the importance scores of the occupations listed tasks and skills needed for them. The approach of averaging the scores of the listed skills and tasks was guided by previous studies using the same approach (72, 77).

Mental demands of work were assessed using the 10 following O*NET items (tasks): (1) analyzing data or information; (2) developing objectives and strategies; (3) evaluating information to determine compliance with standards; (4) judging the qualities of things, services, or people; (5) making decisions and solving problems; (6) organizing, planning, and prioritizing work; (7) processing information; (8) scheduling work and activities; (9) thinking creatively; and (10) updating and using relevant knowledge.

Social demands of work were measured using the six O*NET items (skills): (1) coordination, (2) instructing, (3) negotiation, (4) persuasion, (5) service orientation, and (6) social perceptiveness.

Leisure activities was also assessed in study 4 using a questionnaire measuring frequency and type of activities, using the following questions: 1) Do you read books or magazines? 2) Do you do crosswords? 3) Do you write? 4) Do you play card or board games? 5) Do you have music-related hobbies? 6) Are you involved in some associations or clubs? 7) Do you study or take some courses? 8) Do you do handicraft or woodwork? 9) Do you do gardening? 10) Do you baby-sit? 11) Do you do voluntary

work? The frequency for each of the listed activities ranged from daily, 4-6 times a week, 2-3 times a week, once a week, 2-3 times a month, a few times a year or less often, to not at all. For each item the score ranged from to 0 to 7, with higher score indicating increased frequency of engagement. The scores from each item were summed up and divided by 11 to achieve a total average score for each individual.

4.3 Statistical analysis

4.3.1 Study 1

For the analysis of baseline comparisons between the intervention and control group, and between participants who were still working and those who were retired, median test, t-test, and chi-square tests were used as appropriate. The occupational complexity scores were transformed using zero-skewness log-transformation and standardized into z-scores to be used in the regression models.

Spearman rank-order correlation was used to assess the correlation between the different measures of occupational complexity and education. Linear regression was used to investigate the association between occupational complexity and cognition at baseline. Mixed-effects regression models with maximum likelihood estimation were used to analyse the association between occupational complexity and change in cognition over time (baseline, 12-months and 24-months). Time and occupational complexity were treated as continuous variable. Time at baseline was coded as 0, 1 for 12-month assessment and 2 for 24-month assessment, randomization group was coded as a dichotomous variable, 0 for control and 1 for intervention. The interaction term occupational complexity x time was used to assess how cognition changed over time as a function of occupational complexity, irrespective of randomization group. The 3-way interaction randomization group × time × occupational complexity was used to assess the potential heterogeneity of intervention effects (205). All three occupational complexity dimensions (substantive, data, and people) was tested with each of the four different cognitive outcomes in separate models. All models were adjusted for age, sex, study site, and education. For 3-way interactions with p-values <.10, average marginal intervention effects for different levels of occupational complexity were estimated and presented graphically. Sensitivity analyses were performed on ITT population (all randomized participants) and including participants who were still working. Stata 15 software package (StataCorp, Texas, USA) was used for all analyses.

4.3.2 Study 2

For the comparison between individuals with and without neuroimaging, t-test, median test and chi-square test were used as appropriate. To estimate the association between occupational complexity and cognition while accounting for neuropathology, linear regression models were used while including MRI or PiB-PET measures. An

interaction term between the imaging measure and occupational complexity was initially included in all models, and it was kept in the final model if it was significant ($p<.05$), while it was dismissed if it was not significant, leaving the neuroimaging marker as a covariate. In the models where the interaction was significant, i.e., models with ADS, the main effect is represented by the association between occupational complexity and cognitive outcomes for individuals with average ADS (centred at zero). For MTA, the main effect is for individuals with MTA in category 1 (MTA = 0-0.5) and for PiB-PET the main effect is for individuals in the PiB-PET negative group (individuals below the amyloid positive cut-off). The interaction effect for ADS is the change in the association between occupational complexity and cognition for 1 SD increase of the ADS variable. For MTA it is the difference in the association between occupational complexity and cognition between the MTA category (2 or 3) and the reference category 1, and for PiB-PET it is the difference in the association between occupational complexity and cognition between the PiB-PET negative and positive groups. Average marginal associations between occupational complexity and cognition for different values of MRI and PiB-PET markers were estimated and presented graphically. All analyses were adjusted for age, sex, and education. MRI regression models were additionally adjusted for study site, and PiB-PET models were additionally adjusted for *APOE* status (carriers of at least 1 ε4 allele vs noncarriers). A sensitivity analysis was also conducted, where APOE was added as a covariate in the MRI models as well (APOE missing for 13 individuals within MRI sample)

Stata 17 software package (StataCorp, College Station, Texas, USA) was used for all analyses.

4.3.3 Study 3

For the baseline comparisons, the study participants were divided into three groups based on education level (<9 and 9-12 and >12 years) according to the current Swedish educational system. Chi-square and ANOVA test, with post-hoc Bonferroni comparison, were used for the categorical and continuous variables, respectively. Spearman rank-order correlation was used to assess the correlation between occupational complexity dimensions and education. For the descriptive of occupation complexity measures, median test and Wilcoxon rank-sum test was used because the occupational complexity ratings had a non-Gaussian distribution.

To investigate the association between mental stimulation and the levels of CSF biomarkers, linear regression models were used, with age, sex and MMSE total score included as covariates. Education was divided into three groups, low, medium, and high, using the low education group as the reference category.

To use occupational complexity in the regression models, zero-skewness log-transformation was applied and then standardized as z-scores were calculated.

Models with a single indicator of mental stimulation was first tested, education or occupational complexity, then an interaction term between the mental stimulation variable and age was added. If the interaction was not significant below $p<.05$ it was not kept in the final model. The covariate age was centred at its median value in the interaction models to facilitate the interpretation of beta coefficients. Interactive effects between education and occupational complexity scores were also investigated by adding an interaction term between the factors in a subsequent model. For the association between mental stimulation and the levels of CSF biomarkers a sensitivity analysis was also conducted which additionally also adjusted for APOE status. APOE status was only available for a smaller selected group of individuals.

4.3.4 Study 4

A one-way ANOVA Bonferroni post-hoc test was conducted to investigate any differences between the three groups on continuous variables that had a Gaussian distribution. For variables not following a Gaussian distribution, the median test for trend and Wilcoxon Rank Sum Test for two-by-two comparison was used. For variables only available in two of the groups, t-test (for Gaussian distribution), median test (non-Gaussian) and chi-square test (for categorical) was used. To estimate the correlation between the DOT and O*NET ratings systems for occupational complexity, Spearman rank correlation was used. For the analysis of the association between occupational complexity and memory performance linear regression was used. Zero-skewness-log-transformation was applied to skewed occupational complexity measures and for the memory tests and then Z-scores were calculated, to be included in the regression models. The memory outcome variable was created by summing the z-scores for the immediate and recall scores and then average them for each individual. All regression models were adjusted for age, sex and education, and the joint sample analysis including all the samples (MIND-ADmini, FINGER and GEDOC) was additionally adjusted for study sample. The separate analysis of the FINGER and MIND-AD samples were adjusted for study site. In subsequent analysis, leisure activities were also included as a covariate. Leisure activities was measured using a questionnaire that assessed both type and frequency of leisure activities and was only available for MIND-ADmini and FINGER.

Table 1. Overview of constituent papers

Study	Title	Data sources, design, and population	Occupational complexity assessment	Covariates	Statistical analysis	Outcomes
Study I	Occupational complexity and cognition in the FINGER multidomain intervention trial	FINGER, cross-sectional and longitudinal, at-risk population.	DOT Data, People & Substantive	Age, sex, education, study site, randomization group, time, group x time, complexity x time, complexity x group.	Linear regression, mixed-effects models	Neuropsychological Test Battery (Overall cognition, Executive function, Processing Speed, Memory).
Study II	The role of brain integrity in the association between occupational complexity and cognitive performance in subjects with increased risk of dementia	FINGER neuroimaging subsample, cross-sectional, at-risk population.	DOT Data, People & Substantive	Age, sex, education, study site, *APOE4* (only PiB-PET sample), Medial temporal atrophy, Alzheimer´s Disease signature, PiB-PET.	Linear regression	Neuropsychological Test Battery (Overall cognition, Executive function, Processing Speed, Memory).
Study III	Education and occupational complexity are associated to the burden of neuropathology in prodromal Alzheimer´s disease	GEDOC, cross-sectional, Prodromal AD.	DOT Data, People & Substantive	Age, sex, education, MMSE	Linear regression	CSF Aβ1–42, p-tau-181,t-tau.
Study IV	Occupational complexity and memory performance in people at risk of dementia: comparison of two ratings systems of occupational complexity	MIND-AD, GEDOC & FINGER, cross-sectional, at-risk and prodromal AD.	DOT Data, People & Substantive, O*NET Data & People	Age, sex, education, study sample (joint analyses).	Linear regression, Spearman correlation	Composite score (Rey Auditory Verbal Test, CERAD 10-item word list)

Abbreviations: APOE: Apolipoprotein E; AD: Alzheimer´s Disease; CERAD: Consortium to Establish a Registry for Alzheimer's Disease; CSF: Cerebrospinal fluid; DOT: Dictionary of Occupational; FINGER: Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability; GEDOC: Karolinska University Hospital electronic database and biobank for clinical research; MMSE : Mini-Mental State Examination; MIND-ADmini: Multimodal Prevention Trial for Alzheimer´s Disease mini; O*NET: Occupation Information Network; PiB-PET: Pittsburgh-compound-B Positron emission tomography

5 Results

5.1 Occupational complexity in the FINGER study

5.1.1 Occupational complexity, demographics, and cognition (Study 1)

Of the 1260 randomized participants in the FINGER trial, 1214 participants had information on occupational complexity available, while 46 did not. These individuals were not significantly different regarding age, sex and education. Furthermore, there were no significant differences between the active and control group on variables such as, age, sex, education, occupational complexity, and cognition.

For the main analysis in study 1, all participants with at least one post baseline assessment of the primary efficacy endpoint (mITT population, n=1190) who were retired at baseline and had information on occupational complexity were included. Individuals still working at the study baseline (n=118) were excluded from the main analysis, in order to measure the association of previous (rather than current) occupational complexity. For more details see **Table 2**.

The results of the correlation analysis showed that the three different dimensions of occupational complexity did correlate with each other: substantive complexity with complexity with data (Spearman´s rho = .97, p<.001); substantive complexity with complexity with people (Spearman´s rho=.68, p<.001); data complexity correlated with complexity with people (Spearman´s rho=.68, p < .001). Education correlated with substantive complexity (Spearman´s rho=.40, p<.001), complexity with data (Spearman´s rho =.35, p<.001) and complexity with people (Spearman´s rho=.41, p<.001).

At baseline, higher pre-retirement levels of occupational complexity were associated with overall better cognitive performance. The results showed significant associations between all three complexities and the four cognitive outcomes. See **Table 3**. Sensitivity analyses were conducted including participants still working (n=1144) and considering the ITT population (n=1091). When comparing participants who were retired to those still working, the individuals that were still working were younger, had higher education level and occupational complexity, better cognitive function and more likely to be male. The sensitivity analysis showed similar results to the main analysis in terms of associations between occupational complexity and cognitive function at baseline.

Table 2 . Baseline characteristics of FINGER participants

	Participants with information available	Control group (N= 505)	Intervention group (N= 521)
Age at baseline, years	1026	69.8 (4.44)	70.0 (4.36)
Number of women (%)	1026	251 (49.7%)	242 (46.4%)
Education, years	1026	9.0 [3.0]	9.0 [3.0]
Occupational complexity			
Complexity with Data	1026	3.0 [2.6]	3.1 [3.2]
Complexity with People	1026	1.8 [1.7]	1.8 [1.5]
Substantive complexity	1026	4.5 [3.3]	4.5 [3.9]
Cognition			
NTB Total	1026	-.01 (.58)	-.05 (.55)
Executive function	1025	-.02 (.67)	-.07 (.66)
Memory function	1026	.00 (.66)	-.04 (.68)
Processing Speed	1026	-.02 (.82)	-.06 (.76)
MMSE	1023	26.7 (2.05)	26.6 (2.10)

Table 2. Data are reported as number (N); mean and standard deviation (SD); median and interquartile [IQR] range. Scores on the NTB total score, executive functioning, processing speed, and memory are mean values of Z scores of the cognitive tests included in each cognitive outcome, with higher scores suggesting better performance. All comparisons ns. **Abbreviations:** MMSE: Mini Mental State Examination; NTB: neuropsychological test battery.

Table 3. Associations between occupational complexity and baseline cognition in the FINGER trial.

	Occupational complexity								
	Complexity with data			Complexity with people			Substantive complexity		
Cognition	ß	SE	P	ß	SE	P	ß	SE	P
NTB Total	.106	.017	<.001	.127	.017	<.001	.109	.017	<.001
Executive function	.119	.020	<.001	.127	.020	<.001	.123	.021	<.001
Memory	.076	.021	<.001	.103	.021	<.001	.075	.021	.001
Processing speed	.147	.025	<.001	.176	.025	<.001	.155	.026	<.001

Table 3. Linear regression models were used to estimate the association between occupational complexity and baseline cognitive scores. All models were adjusted for age, sex, study site, and education. Data are based on all participants with at least one postbaseline measurement of the primary efficacy endpoint (mITT population) and who were retired at baseline. The table shows the ß coefficients, SE and P values for the association between occupational complexity scores and baseline cognitive scores. A positive ß value indicates that higher scores in occupational complexity are associated with better cognitive scores.
Abbreviations: NTB total is the FINGER primary outcome; executive function, memory and processing speed are secondary outcomes. ß: standardized beta coefficient; NTB: neuropsychological test battery; SE: standard error.

5.1.2 Occupational complexity and cognitive change in the 2-year multidomain intervention (Study 1)

Participants with higher levels of occupational complexity with data, when compared to those with lower levels, showed a more pronounced intervention effect in terms improvement in executive function (ß[SE]: .028[.014], p=.044). No other significant differences in terms of intervention effects were found. See **Table 4** and **Figure 6**. In table 3, the beta coefficients represent the interaction effect from randomization group x time x occupational complexity which can be translated into the estimated difference in intervention effects per year, for one SD unit increase in occupational complexity. Higher levels of occupational complexity with people were also associated with less improvement in processing speed over time, irrespective of randomization group. A sensitivity analysis was also conducted which included participants still working (n=1144) and considering the ITT population (n=1091). The sensitivity analysis produced similar results to the main analysis in regard to heterogeneity of intervention effects in due to occupational complexity.

Table 4. Associations of occupational complexity with intervention effects on primary and secondary cognitive outcomes in the FINGER trial.

	Occupational complexity								
	Complexity with data			Complexity with people			Substantive complexity		
Cognition	ß	SE	P	ß	SE	P	ß	SE	P
NTB Total	.021	.011	.060	.007	.011	.505	.016	.011	.134
Executive function	.028	.014	.044	.013	.014	.377	.025	.014	.082
Memory	.021	.018	.238	.004	.018	.831	.017	.018	.356
Processing speed	-.001	.015	.940	-.006	.015	.682	-.007	.015	.663

Table 4. The table shows the ß coefficients, SE and P values for the 3-way interaction: time x randomization group x occupational complexity. A positive ß value indicates that higher scores in occupational complexity are associated with effect on cognition favouring intervention group. Significant P values for interaction (P <.05) indicate that the intervention effects on cognition vary significantly by baseline occupational complexity. All models were adjusted for age, sex, study site, and education **Abbreviations:** NTB total is the FINGER primary outcome; executive function, memory and processing speed are secondary outcomes. ß: standardized beta coefficient; NTB: neuropsychological test battery; SE: standard error.

Figure 6. Intervention effect on executive function: influence of complexity with data

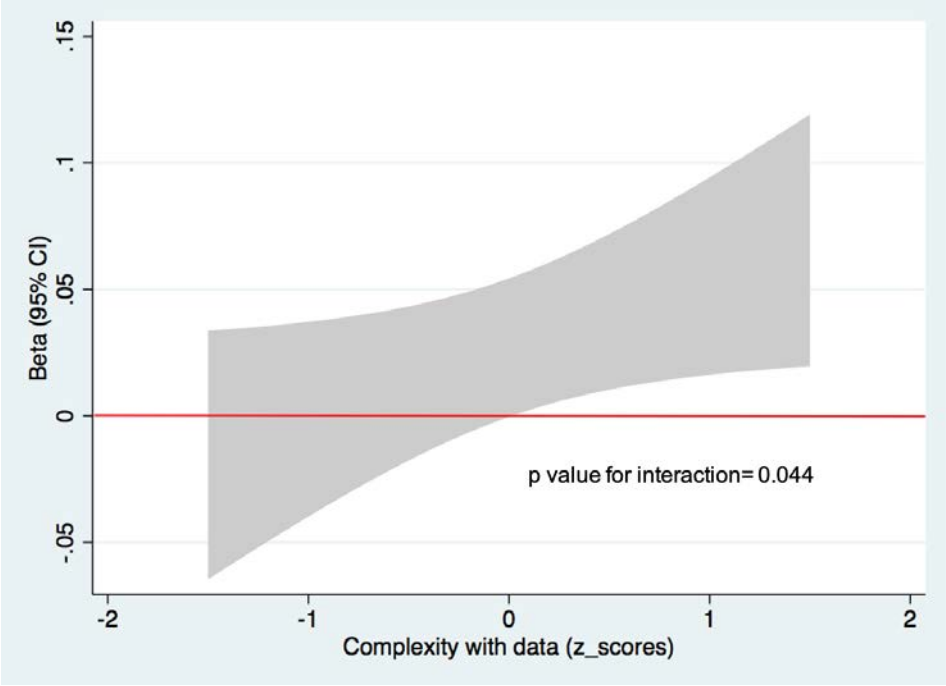

Figure 6. The Y-axis shows the difference between intervention and control groups in yearly change on cognition for people with different levels of occupational complexity on the X-axis (positive values indicate effect in favour of the intervention). The shaded area represents the 95% confidence interval (CI) for the regression coefficient. Significant associations between the intervention allocation and yearly change on cognition are found in the occupational complexity levels when the shaded area (CI) does not overlap with zero.

5.2 Occupational complexity, cognition, and brain integrity (study 2)

5.2.1 Occupational complexity, demographics, and brain integrity

126 participants from the FINGER brain imaging study had MRI and occupational complexity information available and were included in the main analysis. 41 participants had information on PiB-PET, ApoE4 status and occupational complexity and were thus included. The mean age and standard deviation (SD) for the MRI sample was 70.0 (4.5) years, 46% women and for PiB-PET 70.6 (5.0) years, 44% were women. An initial analysis comparing the participants who underwent neuroimaging, MRI or PiB-PET, to the participants at the same study sites that did not have neuroimaging was conducted. The analysis showed that there were no significant differences on any demographic or cognitive variables except for substantive complexity (median [interquartile range, IQR]: 4.7 [3.9], vs 4.3 [3.8], p= 0.04) that was higher in the group that had the MRI scan. See **Table 5** and **Table 6.**

Table 5. Comparison between FINGER participants with and without MRI brain scans (and information on occupation) at the neuroimaging study sites.

MRI sample*	Subjects with brain scan (N=126)	Subjects without brain scan (N=537)	P-value
Age at baseline, years	70.0 (4.5)	69.3 (4.7)	.13
Number of women, N (%)	58 (46%)	253 (47%)	.83
Education, years	9.0 [2.0]	8.0 [3.0]	.78
MMSE	27.0 (1.98)	26.9 (2.0)	.63
Occupational complexity			
Complexity with Data	3.15 [3.5]	3.0 [3.2]	.30
Complexity with People	1.1 [1.7]	1.2 [1.6]	.43
Substantive complexity	4.7 [3.9]	4.3 [3.8]	.04
Cognition and MRI measures			
NTB Total score	-.07 (.52)	-.12 (.56)	.31
NTB Executive function	-.04 (.58)	-.14 (.66)	.11

NTB Memory function	-.11 (.60)	-.11 (.65)	.99
NTB Processing Speed	-.04 (.78)	-.13 (.82)	.30
AD Signature thickness, mm, mean (range)	2.76 (2.4 – 3.11)	-	-
Visually rated MTA, median (range)**	1.0 (0.0-3.0)	-	-

Table 5. Unless otherwise specified, data are reported as number (N); mean and standard deviation (SD); median and interquartile [IQR] range. Abbreviations: AD: Alzheimer´s disease; MMSE: Mini Mental State Examination; MTA: medial temporal atrophy; NTB: neuropsychological test battery. *MRI was conducted at four out of the six FINGER study sites (Seinäjoki, Turku, Oulu and Kuopio). We included MRI scans that passed quality control (all scans from the Seinäjoki site were excluded due to acquisition issues). **Visually rated MTA: by Scheltens scale of severity, which ranges from 0 (normal, no atrophy), to 4 (advanced atrophy). MTA ratings were grouped into three levels: MTA 1: ratings 0-0.5 (n=18 individuals); MTA 2: rating 1 (n=65 individuals); MTA 3: ratings 1.5-3.0 (n=24 individuals).

Table 6. Comparison between FINGER participants with and without PiB-PET brain scans (and information on occupation) at the neuroimaging study sites.

PET sample*	Subjects with brain scan (N=41)	Subjects without brain scan (N=185)	P-value
Age at baseline, years	70.6 (5.0)	70.1 (4.5)	.54
Number of women, N (%)	18 (44%)	90 (49%)	.58
Education, years	9.0 [2.0]	9.0 [2.0]	.69
***APOE* ε4 carriers, N (%)**	11 (27%)	73 (42%)	.07
MMSE	27.0 (1.66)	27.2 (2.1)	.52
Occupational complexity			
Complexity with Data	3.2 [2.8]	3.0 [2.5]	.44
Complexity with People	1.0 [1.7]	1.5 [1.5]	.17
Substantive complexity	4.8 [4.0]	4.4 [3.1]	.07
Cognition and PiB-PET			
NTB Total score	-.01 (.53)	-.05 (.52)	.68

NTB Executive function	.02 (.57)	-.11 (.63)	.23
NTB Memory function	-.06 (.60)	.03 (.60)	.39
NTB Processing Speed	.04 (.90)	-.10 (.75)	.28
Amyloid positive (%)	15 (36.6%)	-	-

Table 6. Main characteristics of the PiB-PET sub-sample with occupational complexity, and participants at the same study sites without brain scan. Unless otherwise specified, data are reported as number (N); mean and standard deviation (SD); median and interquartile [IQR] range. Scores on the NTB total, executive functioning, processing speed, and memory are mean values of z-scores of the cognitive tests included in each cognitive outcome, with higher scores suggesting better performance. The original values of occupational complexity are presented. Z-transformed variables have been used in the regressions. P-values are based on t-test, median test, or chi-square test. **Abbreviations:** AD: Alzheimer´s disease; *APOE*: Apolipoprotein E; MMSE: Mini Mental State Examination; NTB: neuropsychological test battery. *PiB-PET were conducted in one of the six study sites, Turku, in the same participants who also underwent MRI.

5.2.2 Occupational complexity, cognition and ADS.

Occupational complexity with data was associated with significantly better performance on the NTB Total (p = .031) and executive function (p = .020) outcome after adjusting for AD Signature thickness. This was also found for substantive complexity on the NTB Total outcome (p = .026) and executive function (p = .028). There was also a positive interaction effect between occupational complexity with data and AD Signature thickness on the memory outcome (p = .013) showing that complexity with data was associated with better memory performance, but only for higher levels of ADS thickness. A positive interaction was also found for substantive complexity (p = .007). A positive interaction effect between substantive complexity and AD Signature thickness on the NTB Total outcome was also evident (p = .049) indicating that substantive complexity was associated with better performance on the NTB Total, especially for higher levels of ADS thickness. Two positive interactions were also found for complexity with people, with NTB Total (p = .017) and executive function (p = .034). See **Table 7** and **Figure 7** for more information. A sensitivity analysis was also conducted for the ADS sample which also included APOE as a covariate (information missing n=13 subjects). Results were similar to main analysis, although some of the associations were no longer significant.

Figure 7. Effect of Alzheimer´s Disease Signature (ADS) on the association between substantive complexity and NTB Total

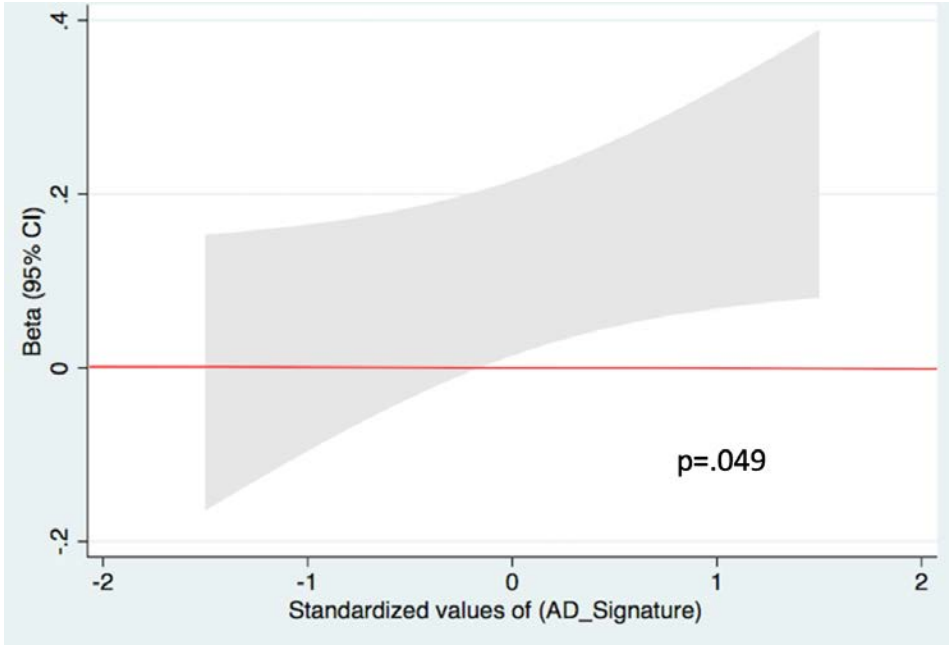

Figure 7. The Y-axis shows the beta coefficient for the association between occupational complexity and cognition, for different values of ADS neuroimaging marker. The shaded grey area represents the 95% confidence interval (CI) for the regression coefficient. Significant associations between occupational complexity and cognition are found when the shaded grey area does not overlap zero. P-values are shown for the occupational complexity x neuroimaging interaction.

5.2.3 Occupational complexity, cognition, and MTA.

After adjusting for MTA, complexity with data was still associated with better performance on the NTB Total (p = .032), executive function (p = .026) and processing speed outcomes (p = .004). This was also evident for substantive complexity and NTB Total (p = .004), executive function (p =.043) and processing speed outcomes (p = .002). Complexity with people was also associated with better performance on the processing speed outcome (p = .014) . Interaction effects between all three complexities (separately) and MTA were found for the processing speed outcome - complexity with data and MTA2 (p =.020) and MTA3 (p = .020), substantive complexity and MTA2 (p = .010) and MTA3 (p = .019), and complexity with people and MTA3 (p = .012). These interaction beta coefficients were all negative, which means that occupational complexity was not associated with better cognitive performance at higher levels of MTA. There was also an interaction between substantive complexity and MTA2 (p = .044) and MTA3 (p = .031) for the NTB Total outcome. These coefficients were also negative. See **Table 7** and **Figure 8** for more information. A sensitivity analysis was also

conducted for the MTA sample which also included APOE as a covariate (information missing n=13 subjects). Results were similar to main analysis, although some of the associations were no longer significant.

Figure 8. Effect of brain integrity (MTA) on the association between substantive complexity and NTB Total

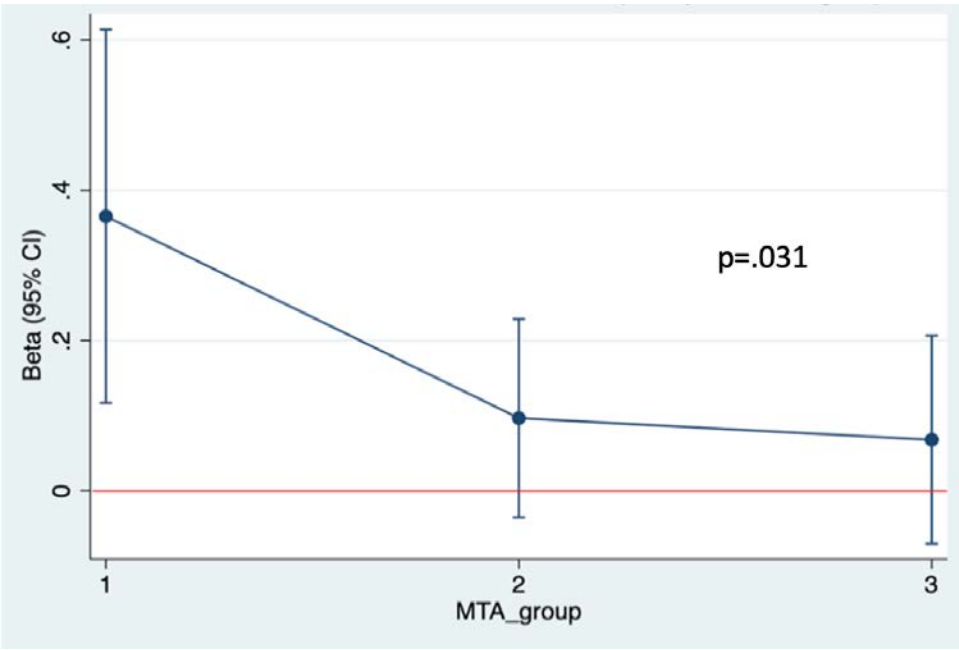

Figure 8. The Y-axis shows the beta coefficient for the association between occupational complexity and cognition, for different values of MTA neuroimaging marker. The bars represent the 95% confidence interval (CI) for the regression coefficient (represented by blue dots). Significant associations between occupational complexity and cognition are found when the bars do not overlap zero. The p-value is for the interaction occupational complexity x MTA group 3.

5.2.4 Occupational complexity, cognition and PiB-PET.

When adjusting for PiB-PET status, occupational complexity with people was associated with better cognitive performance for the executive function (p = .027) and processing speed outcomes (p = .025). This was also found for occupational complexity with data and the processing speed outcome (p = .025). Interaction effects were found for complexity with people and PiB-PET status on the executive function outcome (p = .049) and processing speed outcome (p = .018). Complexity with data also showed interaction effects for NTB Total (p = .046) and processing speed (p = .038). The coefficients for these associations were all negative meaning that individuals that were amyloid positive had worse cognitive performance compared to those who were amyloid-negative. See **Table 7 and Figure 9** for more information.

Figure 9. Effect of brain integrity (PiB-PET) on the association between complexity with people and executive function.

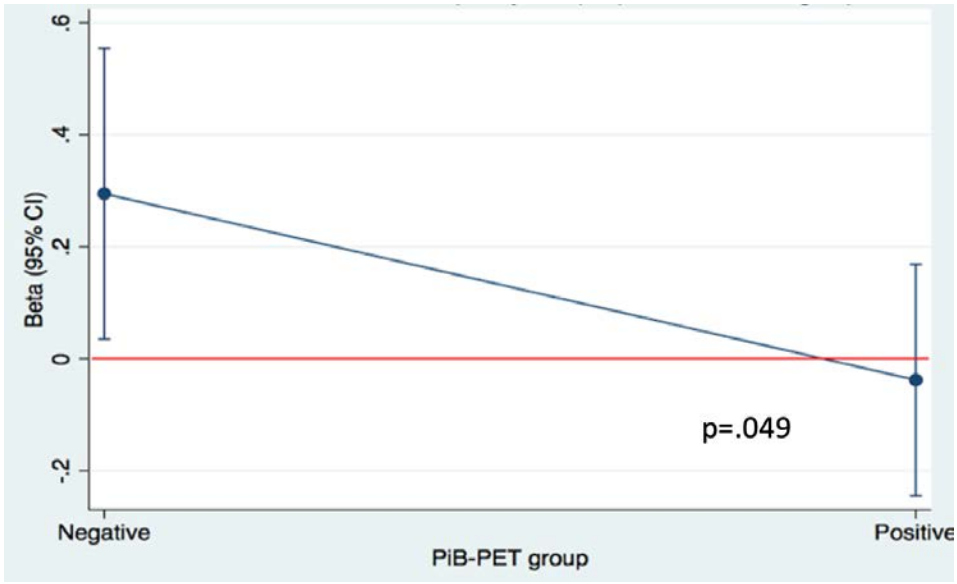

Figure 9. The Y-axis shows the beta coefficient for the association between occupational complexity and cognition, for different values of PiB-PET neuroimaging marker. The bars represent the 95% confidence interval (CI) for the regression coefficient (represented by blue dots). Significant associations between occupational complexity and cognition are found when bars do not overlap zero. P-values are shown for the interaction occupational complexity x PiB-PET

Table 7. Associations between occupational complexity and cognition, while including measures of brain integrity.

	NTB Total			Executive function			Memory			Processing speed		
	ß	SE	P	ß	SE	P	ß	SE	P	ß	SE	P
AD signature thickness (ADS) (N=126)												
Data	.11	.05	**.031**	.13	.05	**.020**	.08	.06	.198	.12	.08	.129
Data x ADS	**-**	-	-	-	-	-	.13	.05	**.013**	-	-	**-**
People	.07	.05	.150	.06	.05	.287	.07	.06	.234	.08	.08	.300
People x ADS	.10	.04	**.017**	.09	.04	**.034**	-	-	-	-	-	-
Substantive	.11	.05	**.026**	.13	.06	**.028**	.09	.06	.147	.16	.08	.062
Substantive x ADS	.08	.04	**.049**	-	-	-	.13	.05	**.007**	-	-	-
MTA* (N=126)												
Data	.11	.05	**.032**	.12	.05	**.026**	.09	.06	.156	.57	.20	**.004**
Data x MTA2	-	-	-	-	-	-	-	-	-	-.50	.21	**.020**
Data x MTA3	-	-	-	-	-	-	-	**-**	-	-.51	.22	**.020**
People	.06	.05	.252	.04	.05	.448	.06	.06	.318	.52	.21	**.014**
People x MTA2	-	-	-	-	-	-	-	-	-	-.44	.23	.062
People x MTA3	-	-	-	-	-	-	-	-	-	.-60	.24	**.012**
Substantive	.37	.13	**.004**	.11	.06	**.043**	.09	.06	.168	.64	.20	**.002**
Substantive x MTA2	-.27	.13	**.044**	-	-	-	-	-	-	-.56	.21	**.010**
Substantive x MTA3	-.30	.14	**.031**	-	-	-	-	-	-	-.52	.22	**.019**
PiB-PET (N=41)												
Data	.24	.12	.052	.06	.10	.565	.03	.10	.748	.53	.23	**.025**
Data x PiB-PET	-.36	.17	**.046**	-	-	-	-	-	-	-.70	-.32	**.038**
People	.07	.08	.396	.29	.13	**.027**	.04	.09	.670	.55	.23	**.025**
People x PiB-PET	-	-	-	-.33	.16	**.049**	-	-	-	-.74	.30	**.018**
Substantive	.08	.09	.351	.07	.09	.431	.04	.10	.708	.20	.17	.231
Substantive x PiB-PET	-	-	-	-	-	-	-	-	-	-	-	-

Abbreviations: AD: Alzheimer´s disease; ADS: Alzheimer´s disease signature thickness; ß: standardized beta coefficient; MTA: medial temporal atrophy; NTB: neuropsychological test battery; SE: standard error. A line (-) indicates that the interaction term was not significant below <.05 and thus not included in the model.

5.3 Occupational complexity, education and neuropathology (study 3)

5.3.1 Demographics

In total 174 participants with Prodromal AD diagnosis were included in the study. When stratifying the participants by education level - low/medium/high - individuals with high education (>12 years) had better MMSE total score (p<.001) and higher median scores for all three dimensions of occupational complexity, compared to people with lower education (<9 years) (p<.001). A significant difference in regard to data and substantive complexity scores was also found between the low and intermediate education groups, where the intermediate education group had higher scores (p<.05). The high education group also had higher median substantive complexity scores, compared to those with intermediate education level, (p<.05). Education also correlated significantly with the three different measures of occupational complexity, with substantive complexity (Spearman´s rho: 0.38, p<0.001), complexity with data (Spearman´s rho: 0.27, p<0.001) and complexity with people (Spearman´s rho: 0.31, p<.001). See **Table 8** for more information.

Table 8. Baseline characteristics by education level.

	Low education (≤9 years)	Intermediate education (>9 and ≤ 12 years)	High education (>12 years)	P for trend
Subjects, N	66	39	69	
Age, mean (SD), y	70.9 (7.3)§§	68.2 (7.8)	65.7 (7.7)	**<0.001**
Female, N (%)	38 (58%)	21 (54%)	43 (62%)	0.68
Education, median [IQR], y	8.0 [2.0]***§§§	12.0 [1.0]†††	15.0 [2.0]	**<0.001**
MMSE, median [IQR]	27.0 [3.0]§§§	27.0 [2.0]†	28.0 [2.0]	**0.029**
APOE ε4 carrier[#], N (%)	20 (51%)*§	20 (83%)	39 (80%)	**0.005**
Cerebrospinal fluid markers, mean (SD)				
$A\beta_{1-42}$, ng/L	657.1 (305.1)	632.8 (258.5)	563.2 (233.0)	0.12
t-tau, ng/L	458.0 (210.8)	483.1 (198.3)	479.3 (227.1)	0.8
p-tau, ng/L	70.4 (25.9)	77.0 (29.4)	71.5 (27.1)	0.5
Occupational complexity scores, median [IQR]				
Substantive complexity	4.35 [3.1]* §§§	6.1 [3.1]†	6.3 [1.5]	**<0.001**
Complexity with data	3 [2.6]*§§§	4.3 [1.9]	4.5 [1.2]	**<0.001**
Complexity with people	1.8 [1.4]§§§	2 [1.12]	2.2 [3.3]	**0.038**

Table 8. Education was available for the whole sample (N=174 subjects); occupational complexity was available for N = 170 subjects.
[#] *APOE* (Apolipoprotein E) was available for 112 subjects: 39 within the low education group, 24 within the intermediate education group, and 49 among the subjects with high education.
Mini Mental State Examination (MMSE) score ranged from 0 (worst) to 30 (best).
Abbreviations: Aβ: beta-amyloid; IQR: interquartile range; p-tau: phosphorylated tau; SD: standard deviation; t-tau: total tau.
***p<0.001; **p<0.01; *p<0.05, low versus medium education
§§§p<0.001; §§p<0.01; §p<0.05, low versus high education
†††p<0.001; ††p<0.01; †p<0.05, medium versus high education

5.3.2 Occupational complexity, education and neuropathology

Substantive complexity was positively associated with t-tau (p = .031) and p-tau (p = .004) levels. Complexity with data was also positively associated with t-tau (p = .032) and p-tau (p = .005). For complexity with people, t-tau (p = .048) and p-tau (p = .039) showed positive associations as well. Meaning that, for the same level of cognitive performance, individuals with higher levels of occupational complexity had higher CSF levels of p-tau and t-tau.

A negative interaction effect between high education and age in relation to t-tau (p = .012) was also found, which means that the association between education and tau biomarkers (after adjusting for cognitive level) is less pronounced with increasing age. For p-tau, a corresponding interaction was evident for the high education group (p = .010), and also for the intermediate group (p = .010). See **Table 9** and **Figure 10** for more information. A sensitivity analysis was also conducted for a subgroup of (n=112) individuals who had APOE status available. 39 individuals in the low education group, 24 within the intermediate group and 49 among the high education group. This analysis included APOE status as a covariate in the main regression models. When comparing individuals for whom *APOE* status was not available, those with existing information were younger [mean (SD) age, years: 67.0 (7.4) *versus* 70.2 (8.1), p = 0.008], with slightly higher MMSE total score [mean (SD): 27.4 (2.1) *versus* 26.7 (2.0), p = 0.032], lower CSF values of t-tau [mean (SD) ng/L: 451.2 (197.6) versus 520.9 (243.9), p value = 0.043] and p-tau [mean (SD) ng/L: 69.3 (23.8) versus 78.8 (31.7) p = 0.027]. There were no significant differences, in terms of sex, educational attainment, occupational complexity scores, and CSF levels of Aβ1–42, between subjects with and without *APOE* data available. Adding *APOE* as covariate in the regression models did not change the results substantially, although some of the associations were no longer significant.

Table 9. Association between indicators of mental stimulation and cerebrospinal fluid

CSF markers and mental stimulation			
Education	**Aβ1–42** **ß (SE), p-value**	**t-tau** **ß (SE), p-value**	**p-tau** **ß (SE), p-value**
Low education	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
Intermediate education	-26.28 (55.42), 0.636	51.19 (44.31), 0.25	9.45 (5.57), 0.092
High education	-92.93 (50.62), 0.068	33.18 (40.16), 0.41	1.19 (5.05), 0.814
Intermediate education x age*	-	-11.26 ((5.86), 0.057	-1.92 (0.74), 0.010
High education x age*	-	-12.95 (5.12), 0.012	-1.68 (0.64), 0.010
Education + Substantive complexity			
Low education	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
Intermediate education	-18.32 (57.65), 0.751	33.55 (45.47), 0.462	6.50 (5.64), 0.251
High education	-91.34 (54.71), 0.097	3.48 (42.84), 0.935	-3.81 (5.31), 0.475
Intermediate education x age	-	-11.43 (5.92), 0.056	-1.95 (0.73), 0.009
High education x age	-	-12.18 (5.22), 0.021	-1.57 (0.65), 0.017
Substantive complexity	2.38 (22.98), 0.918	39.11 (17.95), 0.031	6.50 (2.23), 0.004
Substantive complexity x age	-	-	-
Education + Complexity with data			
Low education	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
Intermediate education	-26.27 (57.14), 0.646	36.40 (45.26), 0.422	7.03 (5.62), 0.212
High education	-100.27 (52.52), 0.058	15.73 (41.34), 0.704	-1.71 (5.14), 0.74
Intermediate education x age	-	-10.99 (5.92), 0.065	-1.88 (0.74), 0.012
High education x age	-	-11.87 (5.23), 0.025	-1.25 (0.65), 0.020
Data complexity	21.01 (22.20), 0.345	37.55 (17.40), 0.032	6.10 (2.16), 0.005
Data complexity x age	-	-	-
Education + Complexity with people			
Low education	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
Intermediate education	-27.40 (57.10), 0.632	37.56 (45.36), 0.409	7.73 (5.69), 0.176
High education	-108.56 (54.29), 0.047	5.40 (43.05), 0.90	-2.46 (5.40), 0.649
Intermediate education x age	-	-9.98 (5.95), 0.095	-1.74 (0.75), 0.021
High education x age	-	-12.55 (5.23), 0.017	-1.64 (0.66), 0.014
People complexity	25.57 (24.07), 0.29	37.70 (18.91), 0.048	4.93 (2.37), 0.039
People complexity x age	-	-	-

Table 9. Linear regression models are adjusted by age, sex, Mini Mental State Examination (MMSE) total score, and interaction between age and indicator of mental stimulation. Each dimension of occupational complexity was tested in separate models.
* For the models testing interactions between age and indicators of mental stimulation (i.e., education or occupational complexity), the coefficients reported have been calculated using age centered at the median value (68 years), to facilitate their interpretation. Interactions with p<.05 are included in the models.

Figure 10. Effect of age on the association between education and biomarker t-tau

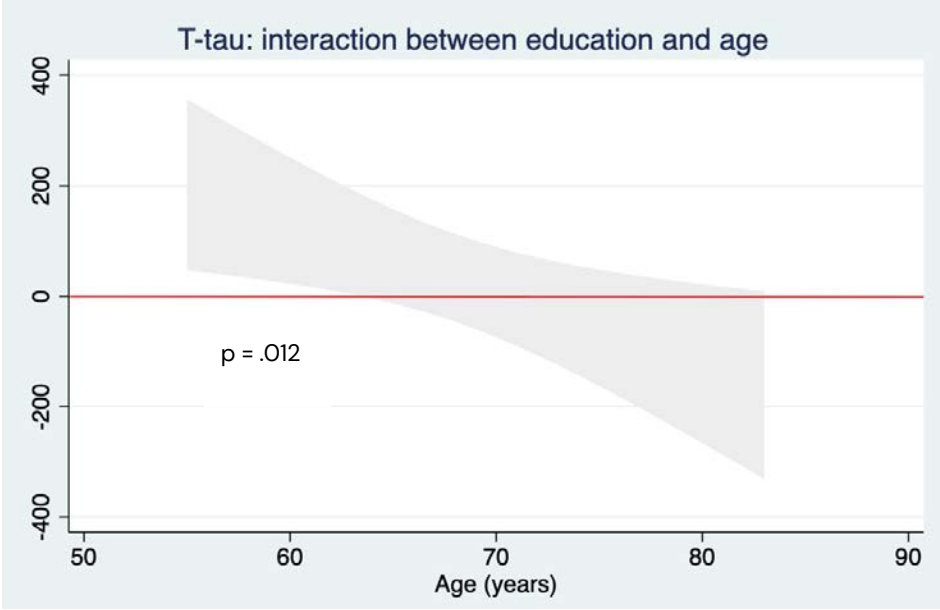

Figure 10. The graph shows in the Y-axis the beta coefficient for the association between high education (12+ years) and CSF levels of t-tau for people with different ages (X-axis). The shaded grey area indicates the 95% confidence interval (CI) for the beta coefficient. Significant association between high education and CSF levels of t-tau is found when the grey area does not overlap zero (red horizontal line).

5.4 Occupational complexity and memory performance in people at risk of dementia (study 4)

5.4.1 Demographics

The descriptive analysis showed that the three samples were significantly different on several demographic factors. The MIND-AD sample had significantly higher age and education level, compared to both GEDOC and FINGER, the GEDOC sample also had significantly more women than the FINGER sample. The FINGER sample also had lower scores for all the dimensions of occupational complexity, compared to both GEDOC and MIND-AD. Since the same memory test was used in both MIND-AD and FINGER, a comparison between the two samples was possible and showed that FINGER had significantly better delayed recall memory performance. However, all the samples had the same score on the MMSE. See **Table 10** for more information.

Table 10. Baseline characteristics for the combined sample and all three samples separately.

	All (n=1410)	GEDOC (n=117) Prodromal AD	MIND-ADmini (n=86) Prodromal AD	FINGER (n=1207) At risk of dementia	P for trend
Age, years	69.4 (5.2)	67.4 (7.8)§§§ ***	72.8 (6.3) †††	69.3 (4.7)	<.001
Female, N (%)	674 (48.1%)	67 (58.7%)§	45 (52.3%)	562 (46.8%)	.059
Education, years	9.0 [4.0]	11.5 [6.0]§§§ *	13.0 [5.0] †††	9.0 [3.0]	<.001
Leisure activities	NA	NA	1.4 [1.0]	1.3 [0.9]	.09
Occupational complexity scores#					
DOT Data	3.4 [2.7]	4.2 [2.1]§§§	4.75 [1.9] †††	3.0 [3.0]	<.001
DOT People	1.8 [1.7]	2.0 [1.4]§§§	2.1 [1.2] †††	1.8 [1.6]	<.001
O*NET Data	3.2 [0.8]	3.5 [0.7]§§§	3.4 [0.7] †	3.2 [0.9]	<.001
O*NET People	2.9 [0.7]	3.2 [0.6]§	3.2 [0.5] ††	1.8 [1.6]	<.001
DOT Substantive	4.7 [3.2]	6.2 [3.4]§§§	6.3 [3.0] †††	4.5 [3.5]	<.001
Cognition					
MMSE total score	28.0 [3.0]	28.0 [3.0]	28.0 [2.0]	28.0 [2.5]	.423
RAVLT immediate recall score	-	32.1 (8.7)	-	-	-
RAVLT delayed recall score	-	4.0 [5.0]	-	-	-
CERAD word list learning score	-	-	17.9 (5.0)	18.4 (3.2)	-
CERAD word recall score	-	-	4.0 [6.0] †††	6.0 [3.0]	-

Table 10. Data are reported as Mean (SD) and Median [IQR], and N (%). Note that for CERAD word recall, the score was normally distributed in FINGER (mean (SD: 5.5(1.7)), but not in MIND-ADmini. Thus, data are compared with median test. For occupational complexity ratings, higher scores indicate higher complexity. DOT Data = score range 0-6; DOT People= range 0-8; DOT Substantive= range 0-10; O*NET People and Data= range 1-5. Occupational complexity scores were available for 1410 participants through the DOT system, and for 1333 through the O*NET system. **Abbreviations:** CERAD: Consortium to Establish a Registry for Alzheimer's Disease; DOT; Dictionary of Occupational Titles; FINGER: Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability; GEDOC: The Karolinska University Hospital electronic database and biobank for clinical research; MIND-ADmini: Multimodal Preventive Trial for Alzheimer's Disease; MMSE; Mini-Mental State Examination; NA: not available; O*NET; Occupational Network Online; RAVLT; Rey Auditory Visual Learning Test.

***p<0.001; **p<0.01; *p<0.05, GEDOC *versus* MIND-ADmini

§§§p<0.001; §§p<0.01; § p<0.05, GEDOC *versus* FINGER

†††p<0.001; †† p<0.01; †p<0.05, MIND-AD *versus* FINGER

5.4.2 Correlation analysis of DOT and O*NET

When comparing the two occupational complexity rating systems using spearman correlation, it showed that, the DOT Data and O*NET Data displayed moderate to strong significant correlations (Spearman´s rho= .62 <.001) and this was also true for the DOT People and O*NET People (Spearman´s rho= .51 <.001). Substantive complexity also displayed moderate to strong correlations to the O*NET measures of data (Spearman´s rho= .68 <.001) and people (Spearman´s rho= .51 <.001). The correlations between all measures of occupational complexity and education were similar, ranging from lowest for O*NET People (Spearman´s rho= .36 <.001) to highest for DOT Substantive (Spearman´s rho= .46 <.001). Leisure activities did only show weak or non-significant correlations with education and the occupational complexity measures.

5.4.3 Occupational complexity, leisure activities and episodic memory performance

The analysis of the association between occupational complexity and memory performance indicated that, in the full sample, DOT People (ß = .07, p = .016) and O*NET People (ß = .06, p = .025) were associated with better memory performance. In the individual samples it was only in the FINGER sample that there were significant associations between occupational complexity and memory performance, this was true for DOT People (ß = .09, p = .004) and O*NET People (ß = .05, p = .039) and O*NET Data (ß = .07, p = .045). See **Table 11.**

When adding leisure activities to the model, it was only DOT People (ß = .07, p = .034) in the full sample that was associated with memory performance. In the FINGER sample, DOT People (ß = .08, p = .014) and O*NET Data (ß = .07, p = .037) were still significantly associated with memory performance. No associations were found in the MIND-AD sample and for GEDOC leisure activities was not available.

The standardized beta coefficients for the association between leisure activities and memory performance in the same model were also reported as supplementary results. In the full sample, leisure activities were associated with better memory performance when adjusting for DOT Data (ß = .09, p = .002) and the beta coefficient only changed when O*NET Data (ß = .08, p = .008) and O*NET People (ß = .08, p = .009) complexity dimension was adjusted for. Within the MIND-AD sample, the association between leisure activities and memory performance was not significant for DOT Data (ß = .14, p = .106) and it did not change depending on which occupational complexity measure that was adjusted for. However, in the FINGER sample, the association between leisure activities and memory performance was significant when adjusting for DOT Data (ß = .07, p = .015) and this association was similar for the other occupational complexity dimensions, except for when adjusting for O*NET People (ß = .06, p = .052).

Table 11. Association between measures of occupational complexity and memory performance.

	DOT Data			DOT People			O*NET Data			O*NET People			DOT Substantive		
	ß	SE	P	ß	SE	P	ß.	SE.	P	ß	SE	P	ß	SE	P
All	.06	.03	.051	.07	.03	.016	.05	.03	.090	.06	.03	.025	.05	.03	.094
GEDOC	.14	.08	.120	.00	.10	.973	.10	.09	.314	.17	.10	.117	.15	.09	.118
MIND-ADmini	.01	.09	.943	-.10	.09	.318	-.02	.09	.836	.09	.08	.355	.04	.10	.700
FINGER	.05	.03.	.078	.09	.03	.004	.07	.03	.045	.06	.03	.039	.05	.03	.124

Table 11. Linear regression models were used to estimate the association between occupational complexity and measures of memory performance. The table shows the standardized beta coefficient (ß), standard error (SE) and P values for the association between occupational complexity scores and memory scores. All models were adjusted for age, sex, and education. FINGER and MIND-ADmini models also included study site as covariate, while the analysis including all three samples included cohort as covariate.
Abbreviations: DOT: Dictionary of Occupational Titles; FINGER; Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability; GEDOC: The Karolinska University Hospital electronic database and biobank for clinical research; MIND-ADmini: Multimodal Preventive Trial for Alzheimer's Disease mini; O*NET; Occupational Network Online.

6 Discussion

This thesis has investigated occupational complexity as a factor that can be related to late-life cognition in individuals at-risk for dementia, also considering the role of brain integrity and AD biomarkers in this association. The at-risk continuum included individuals with modifiable risk factors, from both community and clinical settings, without substantial cognitive impairment or in the early stages of clinical AD (i.e., prodromal AD). The thesis also assessed if occupational complexity could affect treatment effects in a multidomain, lifestyle-based RCT for cognitive impairment in individuals at-risk for dementia. Lastly, the thesis work also compared the two most common occupational complexity rating systems to see how they correlate, and how their respective associations to episodic memory performance may differ.

6.1 Occupational complexity and the intervention effect on the cognitive outcome in a multidomain lifestyle-based intervention RCT for cognitive impairment and dementia in individuals at-risk (Study 1)

In the FINGER study, pre-retirement levels of occupational complexity were not associated with the treatment effect on the cognitive outcomes after two years of the multidomain lifestyle intervention in individuals at-risk for dementia, except for the executive function outcome. This is in line with a previous study on the FINGER trial, investigating if education, socioeconomic status, or baseline cognition could affect treatment effect on cognition. The study found that neither education level, socioeconomic status or baseline cognition did modify the treatment effect on the cognitive outcomes after two years (175). Another study by Solomon et al., also found that the FINGER intervention effect was effective for both APOE4 and APOE4 non-carriers (206).

However, Neuvonen et al., found that higher levels of depressive symptoms at baseline in the FINGER trial were associated with less improvement on the executive function outcome after two years (207).

Stephen et al. also found that participants with higher baseline cortical thickness in the AD signature region (composite measure of entorhinal, inferior and middle temporal, and fusiform regions) at baseline in FINGER had more beneficial intervention effects on the processing speed outcome (208). This does not explain why individuals with higher levels of occupational complexity have more beneficial intervention effects on the executive outcome. However, it might be that other neuroimaging markers or markers of neuropathology could partially explain why individuals with higher levels of occupational complexity gain more from the intervention in the executive function domain.

In single-domain interventions for cognitive impairment, using cognitive training, individuals with higher education had better outcomes on measures of memory performance but individuals with lower education had better outcomes on the processing speed domain (173, 174).

The higher levels of occupational complexity with data involves job tasks that is dependent on executive functions to a large extent (75). This might partly explain why individuals who have been exposed for these kinds of tasks might improve more in the context of an intervention (FINGER) that aims to improve cognition. It might also be that since the participants in the study were all retired, individuals wither higher levels of pre-retirement occupational complexity who were in the control group might have declined more during the two years in the executive function domain. Other studies on retirement have suggested that higher levels of pre-retirement occupational complexity are associated with more cognitive decline after retirement (101, 102).

An alternative hypothesis for the interaction effect in study 1 between occupational complexity data and the intervention effect for the executive outcome could also be related to adherence; poorer adherence to all intervention components in FINGER is associated with older age and worse executive function at baseline (209).

Heterogeneity of treatment effects is generally, in the field of medicine, an under investigated area of research. Segal & Varadhan argue that inattention to heterogeneity of treatment effects can increase the risk of polypharmacy and a general overuse of healthcare (177).

Published clinical trials always report the average treatment effect (ATE), while the individualized treatment effect (ITE) is challenging to estimate and is often highly variable. Therefore, it is important to investigate heterogeneity of treatment effects (HTE) to better understand how we can improve treatments and prevention strategies to get closer to an individualized treatment.

Examples of this can be found in two multidomain RCTs for cognitive impairment and dementia. In the multidomain cardiovascular trial PreDIVA, which included 3454 participants aged 70-78 years, the results revealed no intervention effect on dementia risk after 6-years overall. However, there was a reduced risk of dementia among participants with untreated hypertension at baseline who were adherent to the intervention (163).

The MAPT trial also found significant results for sub-groups while finding no significant intervention effect overall. MAPT was a multidomain intervention including 1525 participants aged above 70 years where the intervention group received cognitive training, physical activity, dietary advice, and prevention consultation plus omega-3 supplementation. While there was no intervention effect for the whole study population

(164) there was a significant intervention effect among those with a CAIDE risk score of 6 or higher (165) and among those who were amyloid positive (166).

Therefore, future intervention studies should try to investigate potential factors that could affect heterogeneity of treatment effects and rate of decline in order to better tailor the intervention to its participants and ensure that the rate of decline in the active and control group is not different because of any other factors than the treatment given.

This may also be applicable to future drug treatments, three recent RCTs that have investigated disease modifying treatments for AD are aducanumab, lecanemab and donanemab. In these phase 3 trials, they have been successful in significantly reducing the level of amyloid in the brains of the individuals who received the active treatment compared to placebo as well as having significantly less impaired cognition after 18 months (15, 210, 211).

These findings are also average treatment effects, while the individualized treatment effect we do not know for these treatments and drugs. Several factors may affect the outcome of such treatments, where indicators of resilience to neuropathology like education may be one of them. Furthermore, indicators of neuropathology via neuroimaging (MRI, fMRI, PET), biomarkers of neuropathology through CSF and genetics may also be valid candidates that can explain potential heterogeneity of treatment effects of these drugs and lifestyle interventions.

Another consideration could be to include AD sub-types, there are several sub-types of AD and these sub-types might also respond different to both lifestyle interventions and drug treatments (212).

Adding to this also the possibility of adjusting the dose of both drug treatments and lifestyle interventions opens for a substantially larger precision of these interventions. Especially when considering that the reality of treatments for cognitive impairment in the future might be a combination of a drug and a lifestyle intervention, one would also have to consider the interaction between the two apart from the factors that might affect the heterogeneity of treatment outcomes.

If we manage to increase the precision and efficacy of drugs and lifestyle interventions then it will enable physicians and healthcare personnel to make better informed decision on treatment options, to increase the treatment effect and save healthcare resources by doing so.

6.2 Comparison of two rating systems for occupational complexity and its association to memory performance among at-risk and prodromal AD populations (Study 4)

Occupational complexity in study 4 was associated with better episodic memory performance among individuals at-risk for cognitive impairment but not among individuals with prodromal AD. This was evident using two different commonly used ratings systems for occupational complexity. The two rating systems also correlated with each other moderately to strong.

The association between occupational complexity and cognitive performance among individuals with prodromal AD, defined with IWG-1 criteria, has not previously been investigated. However, it has been investigated among individuals with MCI and a recent meta-analysis found that occupational complexity is associated with better nonverbal memory and processing speed, working memory and visuospatial ability but not executive function and verbal memory (213). This is in line with the results of study 4, which is that occupational complexity is not associated with better verbal memory in prodromal AD patients.

One plausible reason for why occupational complexity is not associated with verbal memory in prodromal AD might be that the core defining criteria for the prodromal AD diagnosis is significantly impaired verbal memory performance (-1.5 SD) (17). This makes the range (low to high) of memory performance in the prodromal AD group as whole smaller and this can affect the possibility of finding significant associations. While for other cognitive functions among prodromal AD patients there is a larger range in the test scores and thus a higher chance of finding these associations.

Another reason for not finding any significant associations between occupational complexity and verbal memory function in the prodromal AD cohorts compared to the FINGER one could also be due to differences in sample size. The FINGER cohort was considerably larger.

The results of study 4 also showed that leisure activities were associated with better episodic memory performance, but only in the FINGER cohort and not in the MIND-ADmini (prodromal AD cohort). Studies have previously found a positive association between engagement in mentally stimulation leisure activities and cognitive function among healthy individuals (121). However, the same association was not found among the MIND-ADmini cohort. This could be due to the observation from previous studies that the association between leisure activities and cognitive performance is no longer evident among individuals who start to develop significant cognitive problems (214). In study 4 it could also be due to the fact that the FINGER cohort was considerably larger than the MIND-ADmini cohort.

In study 4 we also measured these associations using two different rating systems, the DOT and O*NET, which are the most extensive and commonly used rating systems for occupational complexity in medicine and social science research (89).

The correlation between the DOT and O*NET measures, which assessed that measure the same underlying constructs (i.e., data and people) was moderate to strong, suggesting that there is a high degree of overlap in how the two rating systems rate the complexity of different occupations. The correlations between the two rating systems and education were also similar in strength. This suggests that the results of studies using any of these two systems are comparable since they rate the complexity of different occupations similar.

These results are also aligned with what Andel et al., previously found when investigating the correlation between the O*NET and DOT measure of data with each other and its correlation with education among healthy individuals aged over 60 years (215). They found that the correlation between O*NET data and DOT data in their study was r=.63 and the correlation with education was r=.45 and r=.38 respectively, all highly significant p<.01.

In study 4, the associations between occupational complexity and memory performance were very similar between DOT and O*NET in the full sample but in the FINGER sample there were slight differences. Both dimensions of the O*NET (data and people) were associated with memory performance, compared to the DOT, where only the people dimension was significantly associated with memory performance. This suggest that the O*NET data dimension might measure occupational tasks more related to memory function than the DOT data does.

The DOT and O*NET measures were also different in the models where a measure of leisure activities was included, then the association between O*NET people and memory performance became non-significant while, for the DOT people and O*NET complexity with data, both variables still were significantly associated with memory performance.

Other studies have investigated occupational complexity and memory performance using either DOT or O*NET in healthy individuals. When using the DOT system, three studies showed that higher levels of complexity with people is associated with better memory performance and also to a higher extent than complexity with data in the same studies (71, 81, 216).

Two other studies have found significant positive associations between complexity with data using the O*NET and memory performance as well (84, 217). No previous studies have investigated O*NET complexity with people measure and memory performance. The results in study 4 are similar to that of previous studies mentioned here, in the

sense that O*NET data is associated with memory performance and DOT people is more strongly associated with memory than DOT data.

One reason for why DOT data is less associated with memory performance might be that the characteristics of the tasks that make up the measure DOT data are mostly related to analyzing, organizing, synthesizing, and working with information or data. All those tasks that normally are more associated with executive function (75). The tasks that make up the DOT complexity with people measure include activities such as mentoring, supervising and instructing other people which are all less associated with executive function and perhaps more with memory processes. For example, the size of an individual's social network has been shown to be associated with better episodic memory performance (218).

Even though the two occupational complexity rating systems performed very similar in the regression models and showed strong correlations between each other, there are several differences between the DOT and O*NET system that could explain the differences that still exist.

Firstly, the DOT and O*NET measures are composed of slightly different items that make up the respective measures. While both the DOT data and people measure as well as the O*NET data measure are composed of items that measure tasks, the O*NET people measure is composed of items that measure skills needed for a specific job (204). This could to some extent explain why the correlation between DOT data and O*NET data is higher than between DOT people and O*NET people.

Furthermore, the observations of tasks done by job analysts that make up the data in the DOT was collected in the 1960s and 1970s, while the O*NET data was collected up until 2013, making the O*NET measures more contemporary. The O*NET also has occupational complexity ratings attained through questionnaires administered to incumbents (individuals who currently hold a specific job) while the DOT ratings were done by job analysts who observed and analyzed workers tasks. Currently, the O*NET database is constructed using both updated job analyst ratings and results from questionnaires given to workers (89). These differences might explain why the correlation between the two systems is not higher than the one observed, which is nevertheless good, allowing for comparison of studies using one of the two systems.

The results in study 4 suggests that both occupational complexity rating systems are valid to use in both social science and medicine for research since they have a high degree of correlation and perform similar in regression models analyzing associations to episodic memory performance. However, when used in other populations than the ones in study 4 using other outcomes, the similarities in performance between the two systems might be different.

6.3 Occupational complexity and late-life cognition among individuals at-risk for dementia (Study 1)

All three dimensions of occupational complexity were associated with better cognition in the FINGER trial at baseline, with this association being significant for all cognitive domains examined. Other studies have previously found this association in elderly populations (68-70), although it has not been studied in individuals at increased risk for cognitive impairment. This study adds to the literature suggesting that occupational complexity is associated with better cognition in late-life, also in individuals with increased risk for cognitive impairment, identified through a validated dementia risk score (219).

In the FINGER sample, occupational complexity measures had strongest associations with the processing speed domain and weakest to the memory domain. One reason for the weaker associations with memory might be that the FINGER study population was selected based on memory performance, as the inclusion criteria stipulated that participants required one of the following: ≤19 words (maximum score 30) on the CERAD word list memory task or CERAD word list recall ≤75% (maximum 100%) (16). This means that the individuals included in FINGER were mostly individuals who did not perform on the higher end of the memory performance spectrum in FINGER. With less range in the memory scores, it may be harder to detect stronger associations with occupational complexity.

This study confirms previous results showing that among healthy individuals, occupational complexity is associated with better cognitive performance. The extent to which occupational complexity is associated with cognitive performance may be due to several methodological differences between the studies, e.g., sample size, complexity rating systems, cognitive outcome measures, childhood cognitive ability and other covariates adjusted for, which is discussed in the methodological considerations part.

Differences in average educational levels between the studies may also provide insight for why differences in results exist; some studies have lower average level of education (7-8 years) (68) while others have higher 13+ years (75).

The concept of job-worker mismatch might also shed some light on how this might result in differences among studies results. Job-worker mismatch means that an individual is undereducated or overeducated for their current job. Undereducated means working in an occupation above their education level, while overeducated means working in an occupation below their education level (220). When this is put in the framework of resilience and the "use-it-or-loose-it" hypothesis it suggests than an undereducated individual who works in an occupation that is above their education level would benefit cognitively from this while the overeducated person that works in an

occupation lower than his/her education level would have a negative effect on cognitive function.

One study reported results consistent with this hypothesis, as higher levels of job-worker mismatch were associated with differences in cognitive abilities across several domains (221). This means that some individuals might differ in how they can be affected cognitively from engaging in more or less complex occupations than others. However, this observed association could also stem from confounding related to intelligence which existed prior to the individual started the job as well.

In study 1 we did not assess if individuals were undereducated, matched or overeducation for the current occupations, the only information we have is that the correlation between occupational complexity and education ranged from r = .35 to r = .41 which is a moderate correlation.

The work in this thesis has only explored the association between the complexity of an occupation and cognitive outcomes, not considering other job-related factors like job strain, job intensity (percent of lifetime participation in workforce) or working hours, which have all been associated with cognitive outcomes (105, 222). The number of working hours during a limited period, a week for example, has also been associated with cognitive function, with longer working hours being is associated with worse cognitive function (223). Future studies should try to create a more comprehensive occupational exposure factor, incorporating an individual's complexity of work, the job strain, working hours and percentage of participation over the work life years.

While engagement in mentally stimulating activities may be beneficial for cognitive health, the Dementia prevention, intervention, and care: 2020 report of the Lancet Commission by Livingston et al., only lists two factors related to mental stimulation that has prevention potential and that is education and social contact (6). The World Health Organization Guidelines Development Group concluded that the evidence for cognitive stimulation in reducing the risk of dementia was insufficient and no recommendation was provided (224). However, for cognitive training they recommended it to be offered to older adults and individuals with MCI to reduce the risk of dementia, but the quality of evidence was very low to low (224).

It should be noted that the Lancet commission report and the World Health Organization Guidelines differ in how their recommendations are developed. The Lancet commission focuses more on evidence from observational studies while the World Health Organization Guidelines relies more on RCTs for their recommendations.

Furthermore, the WHO guidelines stated that the quality of evidence for nutrition and physical activity is moderate, and the strength of recommendations is strong. To put these recommendations in the context of the FINGER model, it means that the different

components of the model may hold different weights, as some may be more important than the others, at least when considering the current evidence that the WHO and the Lancet Commission provide.

A study on adherence in the FINGER trial showed that those who adhered to the intervention to a larger extent also gained more cognitively after two years of intervention (225). This shows that adherence is important in the context of lifestyle intervention.

Both the FINGER model and the Lancet commission advises individuals to make gradual changes in behavior and lifestyle to make it more likely to be sustainable in the long-term. Adherence to all assigned intervention components in FINGER was 38.9% and in the multidomain MAPT trial it was 50.7%. In FINGER older age and current smoking was associated with poorer adherence to all intervention components, while intermediate level of education was associated with better adherence. In supplementary analysis it was also found that poorer executive function at baseline was associated with lower adherence to all intervention components in FINGER except for cardiovascular monitoring. (209).

Thus, finding ways to increase adherence for groups of people with lower adherence is important. This is especially important to remember when conducting primary prevention as intervention studies are usually highly supervised and may have better adherence rates than when in primary care setting for example (226). The authors of the FINGER adherence paper, Coley et al., suggests that in general it is important to reduce participant burden and suggests that this can be done by facilitating and maintaining face-to-face contacts, ensuring that technological tools are suitable for older individuals and taking into account participant characteristics may increase adherence in future trials.

Having acknowledge the relative contribution of engaging in mentally stimulating activities throughout the lifespan to decrease dementia risk, other factors relating to diet, physical exercise, mood, social and personality factors, sleep and stress may play an even greater part. It may also be that within each intervention domain, certain diets or types of exercise may be more beneficial for certain individuals as well (227).

However, most likely, as previously mentioned in the discussion, all intervention components should be tailored to the individual, since some individuals may gain more from certain intervention components and less from others.

6.4 Occupational complexity and resilience to neuropathology among individuals at-risk for dementia (Study 2)

In the FINGER study, for overall cognition (i.e., NTB Total) and executive function domain, higher levels of occupational complexity with data and substantive complexity were associated with better cognition independently of cortical thickness related to AD pathology, as well as medial temporal atrophy (for MTA and substantive complexity this was only found for the executive function outcome).

This is similar to what Boyle et al. found in their study, among senior community-dwelling individuals, where a composite measure of occupational complexity was independently associated with global cognition after adjusting for hippocampal volume and grey-matter volume (in separate models). They also found that occupational complexity was associated with better verbal fluency after adjusting for grey matter volume. However, none of the results mentioned from the Boyle et al study was considered significant since they were not replicated across both their datasets (147).

Groot et al., also found that when adjusting for cerebral atrophy in a sample of individuals with AD dementia, prodromal AD, and subjective cognitive decline, higher education was still independently associated with better cognition. However, this association was different depending on the cognitive continuum, as the association was stronger among individuals with predementia than dementia, specifically for the attention and executive function outcomes (228).

In the FINGER participants we also found that for the higher levels of brain integrity, higher occupational complexity was associated with significantly better cognition. While the association was not significant in individuals with lower levels of brain integrity (worse brain integrity), in terms of ADS, MTA or PiB-PET. This would be considered a positive moderation effect, which means that only for higher levels of brain integrity occupational complexity is associated with better cognition. These findings are similar to the results by Nelson et al. who found that occupational level was associated with better cognitive functioning in several domains, but only for higher levels of total gray matter (positive moderation) (150).

Positive moderation effects have also been reported using education as predictor, O´Shea found that the association between high education level and cognition was stronger at higher levels of hippocampal volume, while at lower volumes higher education it was not significantly associated with better cognition (149). Positive moderation effects are not considered to be compatible with the resilience & resistance theory (147, 229) since they show that resilience predictors are only associated with better cognition at higher levels of brain integrity.

The opposite of positive moderation effects are negative moderation effects. In the FINGER sample there was no evidence of negative moderation effects, which is in contrast to what Ko et al found, in individuals with MCI, in whom higher occupational complexity was associated with better cognition at lower levels of cortical thickness (149).

Negative moderation effects are usually seen as the benchmark for resilience to neuropathology, characterized by an indicator of mental stimulation being positively associated with better cognition in individuals with greater levels of neuropathology, compared to those with lower levels of brain pathology (147). Independent association between higher mental stimulation and better cognition – after adjusting for measures of neuropathology – represent a weaker resilience effect (140).

As Groot et al., demonstrated, effects of predictors of resilience, like education, might also differ depending on the cognitive continuum, changing in people with overt dementia or pre-dementia symptomatic stage (228). The FINGER study included subjects at-risk for dementia, without substantial cognitive impairment (182). This may explain partly the differences in results from other studies. It is also important to remember that the FINGER study participants were selected on the basis of cognitive function, especially memory performance, which resulted in a sample with a mean of -0.5 SD below the Finnish average in terms of cognitive function for the corresponding age group (182).

Mental stimulation factors, like education and occupation, may provide greatest compensation effects, that is the negative moderation effect, in the late stages of MCI or prodromal AD, before the possible conversion into dementia (228, 230). In healthy individuals who do not have substantial cognitive impairment, one might observe more of positive moderation effects and independent associations (weaker resilience) while the compensatory mechanisms of mental stimulation may not yet be as active but once an individual has reached the MCI/prodromal AD stages the compensatory mechanisms may be greater.

These may in some cases carry on over to the dementia stage but once the neuropathology becomes too extensive the compensatory resilience effect may not be effectively working anymore. This might then explain why the observed accelerated decline in dementia stages occurs among highly educated individuals, because the neuropathology is greater, and the compensatory mechanism is not functional anymore (230).

6.5 Education and occupational complexity and resilience to neuropathology among subjects with Prodromal AD (Study 3)

The results in study 3 showed that all dimensions of occupational complexity (data, people, and substantive) were associated with higher levels of p-tau and t-tau as measured with CSF, after adjusting for age, sex, education, and MMSE total score. However, there was no association between occupational complexity and Aβ1-42 levels. These results suggest that in patients with prodromal AD higher levels of occupational complexity are associated with resilience against the cognitive effects of tau accumulation but not amyloid.

The association between occupational complexity and CSF-tau has not been studied previously, however, a study by Ko et al., recently also investigated the role of occupational complexity in the association between Aβ deposition and cognition among both cognitively unimpaired and impaired individuals and did not find any results that indicated that occupational complexity provided any resilience against the effects of Aβ deposition on cognition (149).

The association between education and resilience to tau pathology have however been studied. Hoeing et al., found that, when assessing the association between education and tau pathology (measured with PET), and adjusting for cognitive level, AD patients with more education had more accumulation of tau pathology for the same level of cognitive impairment (132). These results are aligned with the findings of study 3, suggesting that higher mental stimulation might provide resilience affects for tau-related pathology but in the prodromal AD stage. Neurofibrillary tangles (NFT), which can be measured using p-tau and t-tau, are usually considered to be more associated with brain atrophy than amyloid (142).

Other studies on occupational complexity and resilience to neuropathology indicate that occupational complexity could provide resilience against neuropathology, by using glucose metabolism as the measure of neuropathology (FDG-PET). Garibotto et al., found that, when using FDG-PET as the dependent variable, while controlling for cognitive status, higher occupational complexity was associated with more severe reductions in glucose metabolism. This was conducted in patients with amnestic type MCI that later converted to probable AD dementia (145).

The results of the study on the GEDOC sample (study 3) align with the findings by Ko et al., in the sense that occupational complexity is not associated with amyloid deposition after controlling for level of cognitive function (149). It is also aligned with previous studies by Garibotto et al (145)., and Hoenig et al (132)., in the sense that indicators of mental stimulation can provide resilience against neuropathology. The results in study 3 did however also find that higher occupational complexity was associated with

increased t-tau and p-tau levels, which has not been investigated before in a study using occupational complexity and individuals with prodromal AD.

In study 3 the association between education and CSF biomarkers of AD (Aβ1-42, p-tau and t-tau) were also tested, while controlling for age, sex, occupational complexity, and cognition. The results indicated no association between education and the biomarkers. However, when education was tested as an interaction with age, a negative interaction effect with age was found, for the biomarkers, t-tau and p-tau, suggesting that the association between education and resilience against the effects of biomarkers on cognition might be dependent on age, more specifically decreasing with increasing age.

Almeida et al., investigated, among both cognitively unimpaired and impaired individuals if education did interact with age in the association with CSF levels of amyloid, t-tau, and p-tau. The results showed that due to older age there was an adverse change in CSF biomarkers of t-tau and p-tau but not amyloid, that was more pronounced in individuals with low education than in individuals with high education. Almeida et al., did however not adjust for cognitive performance so the results represent an example of resistance to AD pathology, where individuals with higher education have accumulated less tau pathology at higher ages compared to individuals with low education (231).

The interaction effect between education and age for the t-au and p-tau outcomes in study 3 might be indicative that the resilience effect of education against AD pathology might only be present up to a certain point after which a more rapid decline in cognitive function could be apparent instead, which has been previously demonstrated (230).

As to why occupational complexity was associated with higher levels of p-tau and t-tau but not Aβ42 is difficult to say. A speculation could be that, since CSF measures of these biomarkers were used and not PET imaging, we do not know about the regional distribution of amyloid and tau which may affect the potential resilience effect of indicators of mental stimulation such as occupational complexity and education.

Overall, based on the current literature and the findings in study 3, it may suggest that occupational complexity can provide resilience against the deleterious effects of tau accumulation on cognition, potentially delaying the onset of prodromal AD and later dementia. These results could also have implications for how to conduct RCTs for dementia prevention (pharmacological and non-pharmacological). Since factors relating to mental stimulation (education, occupational and leisure activities) may affect the clinical progression and rate of decline among individuals with prodromal AD and later dementia it is important to measure these factors and several others, for example biomarkers like amyloid beta and tau at baseline and for example use stratified randomization to make sure both groups are equally populated with individuals based on these factors. Subsequently, measuring and accounting for these factors at baseline, would also allow for analysis of heterogeneity of treatment effects.

6.6 Methodological considerations

6.6.1 Study design

Three of the studies in this thesis used data from RCTs - FINGER and MIND-ADmini -, which are considered the gold standard within medical science in order to understand cause and effect relating to an experimental intervention, pharmacological or non-pharmacological. Both RCTs have high quality data collection, using extensive and validated neuropsychological test batteries. Both the FINGER and MIND-ADmini also trial had thorough and robust screening procedures in order to be able to enroll the specific populations targeted. The neuroimaging data collection in FINGER also included several clinically relevant measures of neuropathology such as ADS, MTA and PiB-PET.

For study 3 data from the GEDOC database was used which is a database containing data from a university hospital memory clinic. The data collected had been part of a comprehensive diagnostic procedure that is standard at the clinic, including both nurse visits, meeting with physician and neuropsychological testing. The data for study 3 was collected using the IWG-1 criteria which was at the time of data collection the most recent criteria for prodromal AD. The GEDOC study also included data on the three most common biomarkers related to AD, Aβ1-42, p-tau and t-tau which is a strength.

It should be noted that the analysis in all the studies in the thesis (study 1-4) were exploratory analysis, therefore, this should be taken into consideration when interpreting the results.

When it comes to RCTs, there still might be aspects of RCTs that can be improved, and a general challenge within trials measuring cognitive function is practice effects. Practice effects relate to the fact that individuals within trials or whom are part of longitudinal study cohorts improve on the cognitive tests over time, since they are administered the tests several times during a set period (months or years). This improvement is not related to actual cognitive improvement but rather improvement in test scores relating to learning the test and being more accustomed to the testing procedures (172).

This means that the improvement in cognitive function that is observed in FINGER is not all related to an actual real-life cognitive improvement but is more likely to also reflect practice effects. The control group gained on average 0.16 SD on the NTB Total measure, while the intervention group gained 0.22 SD (16). Previous studies on practice effects for common neuropsychological tests has estimated the general practice effects after 6, 12 and 24 months to be within the range of 0.15-0.25 SD (172).

It might be that most of the observed improvement in the control group was due to practice effects, but one cannot rule out the possibility that the control group also engaged in health modifying behaviors, which could have an effect on their cognitive performance, since the control group also received health advice. Also, being part of a

trial and being monitored itself, can also affect behavior, so called Hawthorne effect (232)

The difference between the intervention and control group can however not be attributed to practice effect but is instead a treatment effect, which in FINGER was 0.08 SD. Adherence in the trial was also shown to be related to the treatment effect, where individuals who had the highest adherence level had an improvement of 0.31 SD over the 24-month period in FINGER. Interestingly, the individuals in the intervention group who were only partially active had the same improvement in cognition at 24-months as the individuals in the control group (225).

Furthermore, there was also a group of individuals within the FINGER trial who declined on the NTB Total over the 24-month period, and such decline was 30% more likely to be individuals within the control group (16). This means that in the FINGER trial, there are individuals who were able to adhere to a large extent to the intervention and reap additional cognitive benefits. These additional cognitive benefits might also depend on factors such as occupational complexity, brain integrity or depressive symptoms at baseline.

There is also a group of individuals in the intervention group who did not improve much at all compared to the control group and some individuals even decline on the NTB Total. This decline might even be bigger since these individuals also might produce a practice effect that can make the real decline smaller.

Thus, on the general average level seen from a public health perspective, the FINGER intervention is beneficial for cognitive health. For the individual it might be more difficult to say whom will benefit from such intervention, on what outcomes (cognitive sub-domains, non-cognitive health effects), how much adherence is needed, what intervention domain benefits most, and to what extent the effects last long-term if the lifestyle change is sustained. This is where the work in the current thesis is trying to shed light on the complexities and challenges that are embedded in understanding how the average treatment effect may differ from the individual treatment effect and how it can be maximized.

6.6.2 Sources of error

The GEDOC database is in general a database containing data from a highly thorough and detailed memory clinic examination. Despite this, there might be biases relating to data collection at a memory clinic. The main one would be selection bias since individuals seeking health care at a memory clinic or being referred to one might be a part of a selected group and have different demographics than the individuals do not seek care for memory problems and/or get a referral (233).

In the FINGER study participants were asked to report their last-held occupation while in GEDOC and MIND-ADmini they were asked to report their main occupation during their working life. Although, previous studies have shown that the differences between analyzing last-held or main occupation are negligible (234).

For the association between occupational complexity and late-life cognition we did not have information about early life cognitive abilities to adjust for. Previous studies have shown that childhood cognitive ability is a confounder for the association between occupational complexity and late-life cognition, to different extents (81, 83, 217).

Several methodological differences between the studies that account for early-life cognitive abilities do exist, how they measure occupational complexity, at which timepoint they measure late-life cognition, and with what kind of measurement cognition is measured. However, it is clear that early life cognitive ability is a confounder for the association between occupational complexity and late-life cognition.

The "environmental complexity" hypothesis suggests that more demanding and complex environments at work and outside work can maintain cognitive levels throughout the life-span by providing stimulation and reinvigorate learning throughout life (21). Education, occupational demands, and mental leisure activities all contribute to this complexity. Schooler's theory suggests that by engaging in complex environments individual's cognitive functions are stimulated and therefore improved or preserved compared to not engaging in these complex environments. This would lead to "differential preservation" over time.

A critical view of this theory was proposed by Salthouse whom instead suggested that individuals who engage more in mentally complex environments are individuals who have higher cognitive performance to start with (235). Engaging in these mentally complex environments through education, occupation, and leisure activities is a result of the initial higher cognitive ability. This is the "preserved differentiation" hypothesis, which means that individuals preserve their initial cognitive starting point but the stimulation from a cognitively complex environment does not affect the cognitive level or decline throughout life (235).

Studies suggest that education has a positive casual effect on the development of cognitive abilities, starting in young age, and that the overall environment during childhood plays a crucial role in the development of cognitive abilities up to the age of 20-25 years (25, 55). This suggests that more complex and mentally stimulating environments can improve cognitive abilities. This has also been observed between generations, as some studies reported that later generations have, overall, perform better at cognitive tests measuring performance and that this can partly be attributed to longer education among other things (236).

The proponents of the "differential preservation" hypothesis would most likely suggest that holding an occupation that provides you with complex tasks and engaging in leisure activities that are mentally demanding outside work would be beneficial (21). While the proponents of the "preserved differentiation" hypothesis would more likely suggest that after completed education, cognitive performance throughout life is not affected by engaging in more mentally challenging and being exposed to more complex environments (235).

Reviewing the current evidence, occupational complexity and its association in late-life is confounded by early-life cognitive abilities, but it may provide some small additional benefit for cognitive health. This also depends on if one considers the worker job-mismatch theory, which suggest that an individual with low education that has a complex job may gain more cognitively and a highly education individual in a low complex job may not (221).

However, as previously mentioned, apart from engaging in more complex occupations, sustaining mental stimulation throughout the lifespan might also be beneficial. Several studies have suggested that delaying retirement could be beneficial when it comes to maintaining cognitive function. These studies may point more to "differential preservation" (95, 97, 102).

But it may be that, for most individuals, they tend to pursue an education that matches their childhood cognitive abilities and choose a job that matches their educational achievements, which would be more in line with the "preserved differentiation" hypothesis. This may also be true for engagement in leisure activities, namely that individuals with high cognitive function may engage more in mentally engaging activities compared to individuals with lower cognitive function (237).

Cognitive function over the life span is also affected by other factors such as socioeconomic and genetic factors. Genetics can explain a major part of the variance in educational attainment, a large analysis of 28 twin cohorts showed that 43% of the variance in educational attainment was heritable (238). Furthermore, another large analysis of heritability of educational attainment showed that nation, sex, and birth cohort influence the heritability and environmental estimates (239). Apart from twin-studies, genome-wide association studies (GWAS) also finds that educational attainment is associated with common genetic variants, as a large recently conducted GWAS study with more than 3 million individuals estimated that 16% of the variance in educational attainment was related to common genetic variants (239).

Early-life socioeconomic factors like neighborhood deprivation has also been associated with brain development in general, since, after accounting for parental household income and education higher neighborhood deprivation has been associated

with worse cognitive performance and differences in the morphology of brain regions associated with higher order cognitive function, mostly the prefrontal cortex (240).

Thus, an ideal study that investigates associations between mental stimulation and late-life cognition and or dementia risk would ideally try to include both genetic risk factors, childhood-related environmental factors, childhood cognitive function and mid-life and late-life mental stimulation factors.

Also, there might be several different mechanisms behind the association between mental stimulation and late-life cognition and/or decreased risk of dementia. Individuals who engage in more mentally stimulating activities may feel more positive in terms of their mood, develop better self-esteem, maintain their social network, and support. They might also engage in a healthier lifestyle, which reduces the risk of dementia. As an example of this, purpose in life has been associated with lower risk of dementia, independently of other risk factors (241) and life satisfaction among twins older than 80 years was a strong predictor of subsequent survival (242).

Perhaps the most viable conclusion with the current available evidence available is that cognitive function during the life course is an intricated web of reciprocal effects between genetics and the environment that start already early in life. Furthermore, the environment during early-life will then most likely set the stage for mid-life and late-life development, without determining the course of events, that will lead to various health and non-related health outcomes. In the background the genetic predisposition might draw the individual closer to or further away from certain behaviors or environments.

Since the medical sciences are not at a stage yet where we can alter our genetic makeup or the expression of genes, it will be up to science, society and the individual to create and engage in environments that are most conducive to our health in the long-term. And in doing this, understanding, valuing, and properly estimating the relative value of both genetics and environmental effects, on both group-level and individual level.

6.6.3 Generalizability

The datasets being used in the four studies that comprise this thesis cover the at-risk continuum for dementia, ranging from individuals with measurable risk factors but no substantial cognitive decline, to people on the early symptomatic stages of clinical AD (i.e., prodromal AD), thus encompassing the whole spectrum of at-risk for dementia. The FINGER study carefully selected individuals at-risk for cognitive impairment and dementia based on the CAIDE dementia risk score. The risk score included the following measures - age, sex, education, systolic blood pressure, BMI, total cholesterol, and physical activity. The participants had -0.5 SD lower cognitive performance than the Finnish national average for the corresponding age group and more specifically, lower memory performance.

The at-risk population, as defined in FINGER, is generalizable to several other populations that have an elderly population that have the same several risk factors for cognitive impairment and dementia. Therefore, the results from study 1 and 2 can be generalizable to some extent to other Caucasian elderly populations with similar risk factors and age. Furthermore, one of the main goals of this thesis work is to generate data and results that may be able to better identify individuals within this risk group and better tailor lifestyle interventions and drugs to them. Since the Word-Wide FINGERS (WW-FINGERS) global network of multidomain RCTs for risk reduction and prevention of dementia is establishing and conducting several multidomain RCTs harmonized with the FINGER protocol worldwide, knowledge on what factors may be universal to the success of a lifestyle intervention and which needs to be culturally adapted is of great importance (243).

Study 3 and 4 also included individuals with a prodromal AD diagnosis. The prodromal AD diagnosis requires individuals to have mild cognitive impairment and AD-neuropathology present, according to the IWG-1 (194) and IWG-2 (17) criteria. This means that the results from study 3 and 4 might be generalized to other prodromal AD patients. However, there are slight differences between the IWG-1 and 2 criteria, as IWG-1 does allow for AD-neuropathology evidence to be medial temporal atrophy (MTA), as well as beta-amyloid or tau, while the IWG-2 requires only beta-amyloid or tau pathology and they do not consider MTA. This means some studies using the IWG-1 may not be perfectly generalizable to patients that are diagnosed using IWG-2.

But the IWG-1 criteria in itself allow for concrete and more homogenous patient groups, before the IWG criteria emerged, MCI patients were not defined based on the underlying neuropathology, only on the cognitive impairment. However, the diagnosis group called prodromal-AD is still a considerable large group and has a potentially wide spectrum of characteristics. Some patients may be closer to the dementia stage, with considerable neuropathology and severe cognitive impairment, while others may have lower levels of neuropathology and/or different, in conjunction with better cognitive performance but still within the Prodromal AD spectrum. This may pose a challenge for drug trials using Prodromal AD patients since their level of function, neuropathology and cognitive performance may differ widely.

7 Conclusions

Dementia is one of the greatest challenges in medicine and healthcare today. Our understanding of the syndrome, and the underlying diseases, has grown greatly in recent years, with increasing pharmacological and non-pharmacological candidates to both treat and prevent this condition. This PhD work has contributed by highlighting the need to consider heterogeneity of treatment effects in RCTs, and how sources of mental stimulation, like occupational complexity and education in conjunction with measures of brain integrity can affect this heterogeneity. The thesis also contributes to understanding the role of mental stimulation in providing resilience against the detrimental effects of neuropathology on cognition.

The conclusion from this PhD work is that among individuals at-risk for dementia, occupational complexity does not seem to affect the heterogeneity of treatment effects from a lifestyle intervention, except for certain cognitive outcomes, in this case executive function. This means that the FINGER lifestyle intervention may benefit most individuals equally well, but there might still be certain sub-groups that could benefit more. This PhD work also found that among individuals at-risk for dementia, occupational complexity does not seem to be able to provide strong resilience against the effects of neuropathology on cognition, in this case medial temporal atrophy, AD signature areas and PiB-PET amyloid.

When it comes to patients with prodromal AD both education and occupational complexity may be able to compensate for some of the detrimental effects of tau pathology, and that for education this association is mediated by age so that the suggested resilience decreases with higher age. This PhD work has also been able to highlight the differences and similarities when it comes to methodological aspects of assessing occupational complexity in social and medical science. The DOT and O*NET systems have not been extensively compared in the context of clinical trials for cognitive impairment and AD previously. In the current study that is part of this PhD work it was found that the two systems produce comparably similar results overall with a moderate to strong correlation between the two. This means that both systems are reliable and efficient to use in studies investigating cognitive impairment and AD but the O*NET system may be overall a bit more updated and contemporary.

8 Points of perspective

This thesis work has focused on the role of mental stimulation and its associations with cognitive performance in late-life and interaction with brain integrity and how this may affect cognitive functions during late-life and the effect of randomized controlled trials. Heterogeneity of treatment effects is a growing area of research, one that is important in order to improve the effectiveness of both drug and lifestyle-based interventions.

The future of prevention and treatment of cognitive impairment and dementia holds great promise. Soon it may be possible to do prevention by combining lifestyle-based interventions with pharmacological interventions to stop or slow down the development of common dementias, such as AD. A step closer to achieving this is to create awareness in regard to factors that might contribute to the heterogeneity of treatment effects, both in non-pharmacological and pharmacological trials. In the trials themselves, factors that might contribute to the speed of cognitive decline over the time period of trial and may interact with neuropathology itself needs to be considered and investigated in future studies in order to control for these factors and get more accurate estimates of the treatment effects. These same factors may also contribute to the heterogeneity of the treatment effects which can inform researchers on how to best tailor drugs and lifestyle interventions to the individual to achieve better effect. Since greater adherence is associated with better outcomes.

This may potentially allow researchers to identify the optimal timing for when to initiate a drug treatment and lifestyle intervention for optimal effect and identify which individuals who may benefit mostly from them. Also, if the drug treatment is designed to target specific types of neuropathology, like amyloid or tau and it is not possible to treat everyone with these pathologies, then knowing which individuals to target is of importance since many individuals of old age may have these pathologies.

This thesis work has also investigated the association between mental stimulation and late-life cognition and the role of AD neuropathology. While many studies have shown the relative contribution of education, occupation, and leisure activities for cognitive health in late life there is still a need for high quality studies on this topic. Ideally studies should take a life-course perspective to understand how early-life cognitive abilities affect late-life cognition and incorporate the relative possible contribution of occupational and leisure activities to cognitive and psychological health. This should ideally be investigated with granular and high-quality measurement of exposures, confounders, and outcomes. Furthermore, it would be ideal if these studies also incorporate neuroimaging measures and biomarkers of neuropathology related to AD. Then we would perhaps be able to create a more thorough understanding of which cognitive interventions and social policies that can contribute most effectively to reduced risk of cognitive impairment and dementia and cognitive health in general.

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Supplementary material thesis

Supplementary Table 1 – Overview of studies investigating occupational complexity and cognitive

First author	Country, year	Design	Predictor	Statistics	Outcome	Covariates	Conclusion
G.B., Frisoni	Italy, 1992	Cross-sectional, population-based, 524 healthy individuals, mean age 76.7 years, 66.8% women.	Principal lifetime occupation (six categories).	Multiple linear regression.	MMSE	Geriatric Depression Scale, Global physical health, IADL/BADL, hearing/visual impairment, financial status, social activities.	Occupational group farmers had significantly lower MMSE compared to other groups.
J.F., Dartigues	France, 1992	Cross-sectional, population- based, 3699 community residents, mean age 75.2 years, 58.3% women.	Occupations classified into seven categories (INSEE classification)	Multiple logistic regression	MMSE	Age, sex, education, alcohol use, medication use, sensory impairment.	Compared to intellectual workers, farmworkers, domestic service employees and blue-collar workers had greater risk of cognitive impairment.
Y., Stern	USA, 1994	Longitudinal, population based, 1-4 years follow-up, 593 nondemented	Occupation (7 categories). US census categories.	Cox proportional hazards models.	Incident dementia (DSM-III-R, NINCDS-ADRDA)	Age, sex, education	The risk of dementia was highest for people with both low

		individuals, mean age 74 years, 72.9% women.					education and low occupational complexity.
A.F., Jorm	Australia, 1998.	Longitudinal, population-based, 3.5 years follow-up, 518 men, 70+ years of age.	Occupation, John Hollands six occupational categories.	Fishers exact test and linear regression.	MMSE, Episodic Memory Test, Symbol-Letter Modalities Test and National Adult Reading Test. Dementia (DSM-III-R, ICD-10).	Age, education and native English language	Trade, service and technical jobs had worse cognitive function and a higher prevalence of dementia at baseline but no differences in longitudinal change in cognitive function or dementia rates related to occupation.
Y., Stern.	USA, 1999.	Longitudinal, population-based, 4 years follow-up, 177 AD patients (NINCDS-	Occupation, 8 categories, low to high. US census categories.	Regression analyses with repeated measures.	Selective Reminding Test.	Sex, race, ethnicity, extrapyramidal signs, stroke, APOE.	More rapid decline in AD patients with higher

		ADRDA) mean age 81.5 years, 80% women.					occupational attainment.
C., Schooler	USA, 1999	Longitudinal, population-based, 20 years follow-up, 233 healthy individuals, median age 57 years, 31.3% women,	Occupational complexity. substantive, people, data and things (DOT)	Structural equation model	Immediate recall, category fluency, number series, verbal meaning test, identical pictures test, different uses test.	Age, sex, education, parents education, family size, urban background, religion, ethnicity, region of origin.	Substantively complex occupations appeared to raise the level of intellectual functioning
C., Helmer	France, 2001	Longitudinal, population-based, 2950 non-demented individuals, mean follow-up 6.4 years, age 65+ years, 58% women.	Occupations classified into seven categories (INSEE classification)	Cox proportional hazards models	Dementia (DSM III-R, NINCDS-ADRDA)	Age, sex, education, tobacco, and wine consumption	Occupation was not associated with the risk of Alzheimer´s disease.
T., Fritsch.	USA, 2002.	Longitudinal, clinical-based 3 years follow-up, 482 AD patients (NINCDS-ADRDA) mean age 74 years, 62.9 % women.	Socioeconomic index (SEI) scores	Multilevel analysis for repeated measures	MMSE and ADL.	Age, sex, ethnicity, and duration of illness.	Occupation level did not affect cognitive decline.

H., Bosma	Netherlands, 2003	Longitudinal, population-based, 3 years follow-up, 630 healthy individuals, aged 50 to 80 years, 41.6% women.	Mental work demands (DGA, 1989)	Logistic regression	Stroop, Verbal Learning Test, Letter Digit Substitution Test.	Age, sex, education, follow-up interval, employment status, intellectual abilities, smoking, alcohol consumption, physical activity, depression, family history of dementia,cvd/diabetes/hypertension.	Individuals with cognitively demanding occupations had lower risk of developing cognitive impairment.
R., Andel	Sweden, 2005	Case-control, population- based, 10168 healthy twins, mean age 72.7, years, 52% women.	Occupational complexity (DOT) substantive, data, people, things.	Logistic regression models	*Dementia (DSM-IV)*	Age, sex, education	Complexity of work with people was associated with a reduced risk of AD and all types of dementia
R., Andel	USA, 2006.	Longitudinal, population-based, 2.5 years follow-up, 171 AD patients (NINCDS-ADRDA), mean age 76.3 years, 57% women.	Occupational complexity (DOT) substantive, data, people, things.	Mixed-effects models	MMSE	Age, sex, native language, time of diagnosis, CDR score	Substantive, data, people predicted faster rates of cognitive decline

G., Potter	USA, 2006	Longitudinal, population-based, 7 years follow-up, mean age 65.8 years, only men.	Occupational Complexity (DOT). data, people, things.	Least squares regression models	TICS-m	Stroke, myocardial infarction, coronary artery bypass graft; diabetes, hypertension, hypercholesterolemia and depression	Jobs higher in intellectual demands were associated with small improvement in cognitive function. The opposite was found for jobs characterized by greater physical exertion or visual attention demands.
R., Andel.	Sweden, 2007.	Cross-sectional, population-based, 386 healthy subjects, mean age 82.5 years, 52% women.	Occupational complexity (DOT) data and people.	Ordered logistic regression	Brief-MMSE score and cognitive impairment.	Age, sex, childhood SES, education, self-rated health, occupational status.	Higher levels of complexity of work with people and data were associated with better MMSE and with lower odds of

							cognitive impairment
E., Kröger.	Canada, 2008.	Longitudinal, population-based, 9.3 years follow-up, 3557 healthy individuals, median age 73 years. 51.2% women.	Occupational complexity (DOT) data, people, things.	Cox proportional hazards regression models	Dementia (NINCDS-ADRDA)	Leisure and work-related physical activity, smoking, alcohol consumption, diabetes mellitus hypertension, cardiovascular disease, and family history of dementia.	Higher occupational complexity with people or things associated with decreased risk of dementia.
A., de Grip	Netherlands, 2008.	Longitudinal, population-based, 6 years follow-up, 447 healthy individuals, 24-64 years old, sex information N/A.	Occupation skill (Dutch Ministry of Social Affairs, 7 levels)	Linear regression	Verbal memory, cognitive flexibility, verbal fluency and processing speed.	Age and sex	Job-worker mismatch is associated with cognitive decline for memory recall abilities, cognitive flexibility and verbal fluency.
G., Potter	USA, 2008	Cross-sectional, population based, 1036 healthy individuals,	Occupational Complexity (DOT). data, people, things,	Multivariate regression models	TICS-m	Age, education and intelligence in early adulthood	Mentally challenging occupations were associated

		mean age 71.6, only men.	reasoning, math, language, vocational preparation, strength.				with improved cognitive function in late-life independent of factors like education and intelligence
D., Finkel	Sweden, 2009.	Longitudinal, population-based, 16 years follow-up, 462 healthy subjects, mean age 64.3 years, 55% women.	Occupational complexity (DOT) data, people, things.	Growth curve model	Verbal, spatial, memory and processing speed abilities	Education, age, sex.	Complexity of work with people was associated with better performance in verbal function until retirement and faster rate of decline in spatial skills after retirement
A., Karp.	Sweden, 2009.	Longitudinal, population-based, 6 years follow-up, 931 nondemented	Occupational complexity (DOT) data, people, things.	Cox proportional hazards regression	Dementia (DSM-III)	Age, sex, education	Individuals with higher level of complexity with data had

		subjects, age 75+ years, 77% women.					lower dementia risk independent educational level.
J.C., Marquié	France, 2010	Longitudinal, population.based, 10-year follow-up, 3237 healthy individuals, mean age 43.6 years, 49.1% women.	Cognitive Stimulation at Work (SAW)	Linear mixed regression models	Rey-auditory Verbal test, WAIS digit symbol test.	Age, sex, education. physical and mental status. Social and cultural lifestyle engagement.	Mental stimulation from work was a good predictor of cognitive level, assessed with a composite measure of cognitive function
W., Van der Elst	Netherlands, 2012	Case-control, population-baed, 50 cases and 46 healthy controls, mean age 51 years, 54% women	Teachers vs non-teachers	Multiple linear regression	Concept Shifting Test, Verbal Learning Test, Verbal Fluency Test, Paper & Pencil Memory Scanning Test, Letter Digit Substitution Test,	Matched for level of occupation, educational level, age and sex. Adjusted for pre-career intelligence and depressive status.	Teachers had better verbal fluency and working memory performance.

P.C., Correa Ribeiro.	Brazil, 2013.	Cross-sectional, population-based, 624 healthy adults, 65+ years age, 67% women.	Occupational complexity (DOT) data, people, things.	Linear regression models	MMSE	age, sex, schooling, family income and duration of occupation.	Higher complexity of work with data and things was associated with better MMSE score.
E.L., Smart.	Scotland, 2014.	Cross-sectional, population-based, 1066 healthy individuals, mean age 69.6 years, 50% women.	Occupational complexity (DOT) data, people, things.	Univariate linear regression models	Memory, processing speed, a general cognitive ability ("g") factor, and the Moray House Test (MHT)	Age, sex, age 11 IQ, education, social deprivation	Higher complexity of work with people and data was associated with better cognition.
R., Andel	Sweden, 2014	Longitudinal, population-based, 15 years of follow-up, 810 healthy individuals, 58.1 years age, 58% women	Occupational complexity (DOT) data and people.	Ordered logistic regression	MMSE-11 item.	Early life; parental education, economic hardship, family conflicts, father SES Midlife; SES, depression, mobility problems, education, year of assessment.	Higher work complexity with data and people, and greater engagement in mental or social leisure activities was independently related to better late-life cognitive

							scores. Negative interaction between occupational complexity and leisure activities.
G.G., Fisher	USA, 2014	Longitudinal, population-based, 18 years follow-up, 4182 healthy individuals, mean age 58.4 years, 50% women.	O*NET, mental demands.	Latent growth curve modeling	Episodic memory and mental status.	Age, sex and education, depressive symptoms, health status.	Mental occupational demands were related to superior cognitive functioning during time of employment and after retirement.
A.J., Gow	Denmark, 2014	Longitudinal, population-based, 20 years follow-up, 483 healthy individuals, 60+ years, 34.4% women.	Self-report of 8 different work characteristics	Growth curve models	Wechsler Adult Intelligence Scale	Sex, education, and social class, cognitve abilities at age 50.	No long-term effects of work characteristics on cognitive changes in late-life.

R., Andel	Sweden, 2016	Longitudinal, population-based, 14.2 years mean follow-up, 421 healthy individuals, mean age 68.8 years, 53.2% women.	Occupational complexity (DOT) data, people, things.	Latent Growth Curve Models	Verbal, spatial, memory, and processing speed abilities	Age, sex, education	Better complexity of work with people attenuated effects of cognitive aging in speed of processing, and verbal memory.
S., Dekhtyar	Sweden, 2016	Longitudinal, population-based, 9 years follow-up, 440 healthy individuals. age 75+ years, 75% women.	Occupational complexity (DOT) data, people, things.	Cox proportional hazard models	Dementia (DSM-III-R)	Age, sex, education, *APOE* status, coronary heart disease, cerebrovascular disease, diabetes, malignancy and hip fracture. Childhood school grades	Complexity with people, and only in women, was related to lower dementia risk.
F., Then	Germany, 2016	Longitudinal, population-based, 8 years follow-up, 1054 healthy individuals, mean age 82.6 years, 76.1% women.	O*NET, executive, verbal and fluid indices.	Multivariate mixed-model	MMSE,	Age, education, sex marital status, living situation, depression, stroke, diabetes and hypertension.	Occupational environments with tasks involving verbal intelligence and executive functions could sustain a

							higher cognitive functioning in old age.
L.R., Pool	USA, 2016	Longitudinal, population-based, 7637 healthy individuals, 7-9 years follow-up, 65+ age, 62.5% women.	O*NET, mental demands.	Multivariable-adjusted linear mixed models	East Boston Test, MMSE and Symbol Digit Modalities Test.	Age, sex, education, income.	Evidence for a relationship between the cognitive requirements of an individual's main lifetime occupation and both cognitive function at baseline and rate of cognitive decline in older age
C., Feldberg	Argentina, 2016	Cross-sectional, clinical-based, 80 patients with MCI, mean age 76.6 years, 68% women.	Occupational complexity (DOT) data, people, things.	Pearson (r) correlation coefficient	Memory, attention, language and executive function.	N/A	Data complexity was correlated with attention, processing speed and working

							memory. Complexity of working with People, was correlated with verbal reasoning Complexity with Things was correlated with visuospatial abilities.
K., Fujishiro	USA, 2017	Cross-sectional, population-based, 7537 healthy individuals, mean age 62.9 years, 43.2% women.	Occupational complexity (DOT) substantive complexity.	Linear regression	CERAD and MoCA	Age, sex, education and race	Complexity of an individual's occupation mediated the association between education and cognitive level in late-life, but the size of the mediation varied by education level, race and gender.

A.P., Lane	Australia, 2017	Longitudinal, population-based, 7.6 year follow-up, 1290 healthy individuals, 70+ age, 27% women	Occupational complexity (DOT) data, people, things.	Multilevel growth modeling approach	Perceptual speed, memory, MMSE.	age, sex, education, income, medical conditions, depressive symptoms, sedentary work, heavy physical work, retirement age, and leisure-time activity participation	Engagement in a occupation involving complex data tasks, showed better cognition and was maintained after retirement.
C., Grotz	France, 2017	Longitudinal, population-based, follow-up 12 years, 1048 healthy individuals, mean age 74.4 years, 47.4% women.	Self-reported mental and social work stimulation, 10-point scale.	Mixed regression models with latent process	MMSE, Verbal fluency, visual memory and episodic memory.	Age, sex, education, diabetes, hypercholes-terolaemia, hypertension, stroke, *APOE*, depression.	Retirement from jobs involving by high levels of social stimulation was associated with more accelerated cognitive decline in late life

D.C., Carr	USA, 2019	Longitudinal, population based, 6 years mean follow-up, 2295 healthy individuals, age over 50 years, 49% women.	O*NET, mental demands five factors.	Inverse probability weighted regression adjustment	Episodic memory	Age, sex, education, race, cognitive follow-up status, self-rated health, marriage status, household wealth/income, birth cohort.	Beneficial cognitive effects of working longer for individuals in low complexity jobs and a non-negative effect of retirement for workers in high complexity occupations.
W.S., Kremen	USA, 2019	Cross-sectional, population-based, 1009 healthy individuals, mean age 62 years, only men.	ISOC – 10 groups by skill level.	Mixed-models analysis	Reasoning, episodic memory, processing speed, verbal fluency, visual-spatial ability, working memory, and executive	Age, education, intellectual activities, physical activity, health status, cognitive ability at age 20.	After accounting for age 20 cognitive ability, occupational complexity accounted for <1% of variance in specific cognitive abilities

J., Hyun	USA, 2019	Longitudinal, population-based, 2.9 years mean follow-up, 1520 healthy individuals, mean age 78.6 years, 61.7% women.	Occupational complexity (DOT) substantive	Mixed models	Free and Cued Selective Reminding Test, Logical Memory Test, TMT-A/B, Digit Symbol–Coding, Block Design, Letter Fluency, Category Fluency and Boston Naming Test. Dementia (DSM-IV)	*Age, retirement age, sex, ethnicity, education, late-life income*	Better occupational complexity scores were associated with better cognitive function and faster rate of decline in executive function and processing speed and after retirement.
D., Eriksson Sörman	Sweden, 2019	Cross-sectional, population-based, 225 healthy individuals, mean age 65.6 years, 60.4% women.	Occupational complexity (DOT) data, people, things.	Structural Equation Modelling	Executive function (inhibition, switching and updating)	*Age, sex, education*	Higher occupational complexity with data and people was related to better performance in executive control tasks

B., Hakiki	Italy, 2019	Cross-sectional, population-based, 392 healthy individuals, median age 91.5 years, 65.1% women.	ISTAT, nine categories low-high skill	Multiple linear and logistic regression analyses	MMSE	*Age, sex and education*	Work complexity did not show a significant effect on the likelihood of presenting a lower cognitive profile or developing dementia
J., Hyun	USA, 2020	Longitudinal, population-based, 1079 healthy individuals, mean age 78.6 years, 61.6% women	Occupational complexity (DOT) substantive	Cox proportional hazards regression	Dementia (DSM-IV)	Baseline age, retirement age, sex, race/ethnicity, education, late-life income, presence of arthritis, angina, diabetes, chronic obstructive pulmonary dis- ease, high blood pressure, myocardial infarction, congestive heart failure, Parkinson's disease, stroke and depressive symptoms	Moderate-to-high levels of jobs complexity were associated with lower risk of incident dementia but the effect was depended on race.

A., Sundström	Sweden, 2020	Longitudinal, population-based, 1277 healthy individuals, mean follow-up 13.6 years, mean age 70.2 (7.5), 57% women.	21 O*NET variables, reflecting level of cognitive ability needed to perform the job	Multivariate-adjusted Cox hazard models	Dementia (DSM IV, NINCDS-ADRDA)	age, gender, education, smoking, alcohol use, previous cardiovascular disorders and *APOE*	No association between mental demands at work and incidence of dementia
D., Eriksson Sörman	Sweden, 2021	Longitudinal, population-based, 780 healthy individuals, mean age 73.9 years, 56.9% women	O*NET, mental demands ten factors.	Growth curve models	Episodic memory	Age, sex, education, cognitive ability at age 18 (for subsample = 260)	Greater levels of occupational cognitive complexity were associated with better episodic memory. After adjusting for early adult level of cognitive abilities it was no longer significant.
R.C., Stebbins	USA, 2022	Longitudinal, population-based, 14 years follow-up, 12129 healthy individuals,	O*NET - repetition, freedom, analytic skills, and social interaction	Linear regression	Episodic and working memory	Sex, race/ethnicity, age, childhood cognition, and education.	Greater levels of analytical skills and social interaction (only for men)

		mean age 28.3 years, 49.4% women.					in ones occupation was associated with better memory function.
Y.J., Lee	USA, 2022	Longitudinal, population-based, 10 years follow-up, 3176 healthy individuals, mean age 59.6 years, 47.8% women.	O*NET, mental, social and physical demands	Growth curve modelling	Episodic memory, working memory and processing speed.	sex, race, ethnicity, education, income and depression.	Greater levels of cognitive and social demands of work were associated with better initial cognitive functioning, but were associated with slower cognitive decline over time.
Y., Soh	USA, 2023	Longitudinal, population-based, 1536 healthy individuals, mean age 76 years, mean follow-up 2.4 years, 59% women.	Occupational complexity (DOT) data, people and things.	Linear mixed-effects models	Spanish and English Neuropsychological Assessment Scales (SENAS) (executive function, verbal episodic memory,	Age, sex, race, education, maternal and paternal education and exposure to adverse childhood experiences (ACEs)	Complexity with people and data were associated with better cognitive performance. Only data was

					and semantic memory)		associated with less cognitive decline.

Abbreviations: ADL: Activities of daily life; APOE: Apolipoprotein E; BADL: Basic activities of daily living; ICD-10: International Statistical Classification of Diseases and Related Health Problems; TICS-m: modified Telephone Interview for Cognitive Status; IADL: Instrumental activities of daily living; DSM-III-R: Diagnostic and Statistical Manual of Mental Disorders Revised; NINCDS-ADRDA: National Institute of Neurological and Communicative Diseases and Stroke/Alzheimer's Disease and Related Disorders Association; SEI: Socioeconomic index; DGA: Directoraat-Generaal voor de Arbeidsvoorziening; AD: Alzheimer´s Disease DOT: Dictionary of Occupational Titles TMT: Trail Making Test; MMSE : Mini-Mental State Examination; INSEE: Institut National des Statistiques et Etudes Economiques. ISTAT: Istituto Nazionale di Statistica; O*NET: Occupation Information Network; ISOC: International Standard Classification of Occupations MOCA: Montreal Cognitive Assessment

Supplementary Table 2. Overview of studies investigating occupational complexity, neuropathology and cognition.

First author	Country, year	Design	Predictor	Statistics	Outcome	Covariates	Conclusion
Y., Stern	USA, 1995	Cross-sectional, clinical-based, 51 AD patients, mean age 67.3 (9.6) years, 58.9% female.	Substantive complexity, motor skills, physical demands, management, interpersonal skills, and undesirable working conditions (DOT)	Partial correlations and multiple-regression analysis.	Regional cerebral blood flow (rCBF), measured with Xenon-133 inhalation method	Age, clinical dementia severity, and education	Lower relative perfusion in parietal regions for individuals whose occupations were associated with greater interpersonal skills and physical demands scores.
V., Garibotto	Italy, 2008	Longitudinal, 458 participants, clinical-based, mean follow-up 14.3 months, 242 probable AD (pAD), 72	Education (years) and occupation (general NEST-	Linear regression	Regional cerebral metabolic rate of glucose consumption (rCMRglc), measured by	MMSE, age, sex, verbal long-term memory, category fluency and visual span reversed.	pAD and aMCI converters with better occupation scores had,

		amnestic mild cognitive impairment and 144 healthy controls), mean age 70.9 (8.3) years, 56% women.	DD project protocol rating)		performing ^{18}F-fluoro-deoxy-glucose (FDG)-PET.		for samle level of cognitive impairment, more severe reduction in rCMRglc.
R.Y., Lo	USA, 2013	Longitudinal, population and clinical-based, 819 (229 normal cognition, 397 mild cognitive impairment, 193 Alzheimer´s Disease), mean age 74.6 (6.7) years, 42% women	Occupation in three levels according to The National Statistics Socio-economic Classification.	Multivariable linear regression	FDG-PET, MRI Hippocampal volume and CSF Aβ42.	Age, sex, APOE4 status	Higher levels of occupation decelerated the decline of CSF Aβ42 in participants with normal cognition
A.E., Boots	USA, 2015	Cross-sectional, population-based, 323 healthy at-risk participants, mean age 60.38 (6.09) years, 68.1% women.	Complexity with data, people and things from the DOT, considered separately.	Multiple linear regression	Hippocampal volume and ventricle-to-brain ratio.	Age, sex, education, MRI scan-cognitive testing time interval, intracranial volume, RAVLT score, family history of Alzheimer's disease, APOE4 status, hypertension, diabetes, smoking; stress and CES-D,	Better occupational complexity scores was associated with lower hippocampal volumes and higher brain atrophy after

						participant/parental SES.	adjusting for cognitive performance
R., Boyle,	Ireland, 2021	Cross-sectional, population-based, 534 healthy individuals, mean age 66.7 years, 50,9% women.	Complexity with data, people and things from the DOT in a composite score. And interaction with brain structure.	Moderated hierarchical regression	Verbal fluency, processing speed, executive function, episodic memory, global cognition	Gray Matter Volume, Hippocampal volume and mean cortical thickness, age and sex.	Occupational complexity was not associated cognitive performance, adjusted for hippocampal volume, gray matter volume and mean cortical thickness
M., Kivimäki	UK, Europe, USA, 2021	Longitudinal, population-based, 2261 healthy individuals, follow-up 13.7 – 30.1 years, N/A sex information.	Standard Classification of Occupations (ISCO-88)	Logistic regression	Protein D (SP- D), slit homologue 2 protein (SLIT2), hexokinase 2 (HXK2), carbohydrate sulfotransferase 12 (CHSTC), peptidyl-glycine α-amidating monooxygenase (AMD), and	Age , sex, education, cognitive stimulation in childhood, smoking, alcohol, physical activity, hypertension, job strain, diabetes, coronary heart disease and stroke	Greater mental stimulation at work was associated with lower levels of plasma proteins that might inhibit axonogenesis and

					neutrophil cytosol factor 1 (NCF-1)		synaptogenesis and is associated with increased dementia risk-
K., Ko	South Korea, 2022	Cross-sectional, population-based, 355 participants, 232 cognitively unimpaired, 36 cognitively unimpaired with Aβ deposition, 44 mild cognitive impairment with Aβ deposition and 39 AD Dementia with Aβ deposition. Mean age 69.60 (7.84), 55.56% women.	Standard Classification of Occupations (ISCO-08) and it interaction with neuroimaging measures.	Multiple linear regression	CERAD-TS - Semantic Verbal Fluency Tasks, 15-item Boston Naming Test, Word List Memory, Word List Recall, Word List Recognition, and Constructional Praxis	Age, sex, and APOE4 status, [^{11}C]-PiB-PET, [^{18}F]-FDG-PET, mean cortical thickness obtained from AD-signature regions.	Occupational complexity moderates the negative influence of cortical atrophy on cognition (only in cognitively impaired).

C.K, Suemoto	Brazil, 2022	Cross-sectional, population-based, 1023 participants, 630 cognitively unimpaired and 393 impaired, mean age 74.0 (11.8), 51.5% women.	O*NET -language, flexibility, reasoning and perceptual-spatial orientation, global.	Linear regression	CDR sum of boxes (CDR-SOB) answered by next of kin.	Age, sex, race, education and post-mortem measures of neurofibrillary tangles (Braak & Braak score), neuritic plaques (CERAD score), Lewy body disease (Braak LBD score), infarcts, small vessel disease, and cerebral amyloid angiopathy	Higher education level was related to better cognitive function independent of neuropatholo gical insults.
M.E, Nelson	Czechia, 2023	Cross-sectional, population-based, 570 participants, 457 cognitively unimpaired and 113 impaired (dementia), mean age 71.2, 58.2% women.	2008 International Standard Classification of Occupations (ISCO-08) Scale 1-10.	Linear regression	Attention, executive control, language, memory and visuospatial skills.	Age, sex, education, depressive symptoms	In people without dementia, higher occupational position magnified the positive association between gray matter volume and language,

							memory and attention.

Abbreviations: pAD: probable Alzheimer´s Disease, aMCI: amnestic mild cognitive impairment, rCMRglc: Regional cerebral metabolic rate of glucose consumption CES-D: Center for Epidemiologic Studies Depression; ISCO-08: International Standard Classification of Occupations; CDR-SOB: Clinical Dementia Rating – Sum of Boxes; LBD: Lewy body disorders; CERAD-TS: Consortium to Establish a Registry for Alzheimer's Disease Total Score; APOE: Apolipoprotein E; PiB-PET: Pittsburgh compound B - Positron emission tomography; FDG-PET: Fluorodeoxyglucose - Positron emission tomography; CSF Aβ42: Cerebrospinal fluid Amyloidβ 42; NEST-DD: Network for Efficiency and Standardization of Dementia Diagnosis; O*NET: Occupational Information Network: Occupation DOT: Dictionary of Occupational Titles; MMSE: Mini-Mental State Examination; MRI: Magnetic Resonance Imaging; RAVLT: Rey Auditory Verbal Learning Test