Advancing the Use of Brief Cognitive Tests - Establishing Norms, Clinically Relevant Changes and Predictive Models

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Advancing the Use of Brief Cognitive Tests

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Establishing Norms, Clinically Relevant Changes and Predictive Models

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LUND
UNIVERSITY

DOCTORAL DISSERTATION

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Title and subtitle: Advancing the Use of Brief Cognitive Tests – Establishing Norms, Clinically Relevant Changes and Predictive Models

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Methods: Participants from The Malmö Food and Diet, BioFINDER-1, and the Alzheimer's Disease Neuroimaging Initiative studies have been included in this thesis. These studies all include individuals with and without cognitive impairment, facilitating research in early diagnostic strategies for cognitive decline.

Results: In this thesis, we established Swedish MoCA cut-offs for cognitive impairment for the primary assessment of cognitive impairment. We presented a new approach to establish normative data for brief cognitive assessments for identifying early cognitive changes in preclinical dementias. We have also identified potential minimal clinically important differences (MCIDs) for cognitively unimpaired individuals and individuals with mild cognitive impairment on a range of cognitive test outcomes. Furthermore, we explored methods to predict a composite cognitive measure for predicting a cognitive decline and to predict progression to dementia for those with mild cognitive symptoms. Finally, we created a two-step prediction model for predicting overall dementia for individuals with mild cognitive symptoms.

Discussion: In our ageing population with increasing education levels and various comorbidities, it is important to update guidelines for test norms, MCIDs and methods for predicting cognitive decline. This can aid in optimal management and early treatment, including timely referral to specialized units for enhanced diagnostics of high-risk patients.

Key words: Cognitive impairment, cognitive assessment, MCI, Alzheimers disease, dementia

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For dad,
thank you for always believing in me.

Table of Contents

Abstract

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Populärvetenskaplig sammanfattning på svenska

Kognitiv sjukdom, eller demens, kan orsakas av flera olika sjukdomar så som primära neurodegenerativa sjukdomar, vaskulär sjukdom och andra tillstånd. Bland de primära neurodegenerativa sjukdomarna, är Alzheimers sjukdom den vanligaste och svarar till över 60% av fallen med demens. Andra vanliga neurodegenerativa sjukdomar är frontotemporal demens och Lewy Body demens samt demens vid Parkinsons sjukdom.

Alzheimers sjukdom samt andra demenssjukdomar är ett växande problem över hela världen pga en åldrande befolkning och att behandling och förebyggande mot andra kroniska sjukdomar förbättras. Man har estimerat att antalet personer i världen med en demenssjukdom kommer att öka från ca 57 miljoner fall globalt (2019) till 153 miljoner fall i 2050[1]. Bara i Sverige är den beräknade kostnaden av demens estimerat till över 81,6 miljarder kronor årligen[2].

Vid Alzheimers sjukdom bildas små proteinansamlingar i hjärnan runt nervtrådarna, så kallade amyloida plack. Dessa ansamlingar uppträder först i hjärnans hjässlober och pannlober, men sprider sig sedan till andra delar av hjärnan. Den andra typiska förändringen under sjukdomen är att det bildas små nystan av ett annat protein som heter tau, och dessa förändringar stoppar bland annat transporten av näringsämnen inne i nervceller.

När man utreder om en person har drabbats av kognitiv svikt, genomförs flera undersökningar för att få korrekt diagnos och ta ställning till eventuell behandling. Patienten utreds med bland annat en läkarbedömning, blodprover, bilddiagnostik av hjärnan samt kognitiva tester. Kognitiva tester testar bland annat minne, förmågan att orientera sig, hastighet när man utför uppgifter och förmågan att uppfatta och tolka visuella och rumsliga relationer. Resultaten av ovanstående kan hjälpa att identifiera vilka svårigheter patienten har. Beroende på patientens ålder, resultat på undersökningar och regionala skillnader remitteras därefter en del patienter för vidare specialistutredning på en minnesklinik.

När man genomför kognitiva tester i praktiken, är det viktigt att det finns tillgänglig normativa data för testerna som genomförs, så att patientens resultat blir jämförda med data från en passande åldersgrupp, kön och utbildningsnivå samt att de jämförs med data på personer utan kognitiv sjukdom. The Montreal Cognitive Assessment (MoCA) är ett kognitivt test som används av bland annat läkare, sjuksköterskor och arbetsterapeuter som mäter global kognitiv svikt. Fram till 2017 fanns inga svenska normativa testresultat på detta test utan man använde en gräns på 26 poäng samt gav ett extra poäng till de individer som hade en utbildning under 12 år. Vi såg därför att det fanns ett behov av att ta fram svenska referensdata för detta test vilket vi gjorde i projekt I.

Det är känt att med stigande ålder tenderar kognitiva testresultat att försämras, men när vi startade projekt II var det okänt om vad orsaken till försämring i olika tester var. Vi ville därför utreda om det fanns ett direkt orsakssamband med ålder eller om detta orsakades av underliggande patologiska mekanismer som ökade med åldern.

Behandlingen mot Alzheimers sjukdom har fram till nyligen bestått av symptomlindrande läkemedel i form av acetylkolinesterashämmare och NMDA-receptor antagonister som kan lindra patientens symptom men inte behandla grundorsaken till sjukdom. De senaste åren har det pågått många läkemedelsstudier mot Alzheimers sjukdom med så kallad sjukdomsbromsande behandling för att försöka bota grundorsaken till sjukdom, det vill säga agera mot de underliggande amyloid- och/eller tau-ansamlingarna i hjärnan och nu är några läkemedel mot amyloid-ansamlingarna godkända för användning i delar av världen.

När man genomför läkemedelsstudier för denna läkemedelsgrupp är det viktigt att man inkluderar studiepatienter i så tidigt skede som möjligt av sitt sjukdomsförlopp, för att undvika att inkludera patienter som redan har en irreversibel skada i hjärnan av långt gången sjukdom. Därför är det allt viktigare att vi upptäcker och diagnosticerar dessa patienter tidigt, för att kunna förebygga sjukdom med läkemedel i ett så tidigt stadium som möjligt.

Ett sätt att utreda om det finns en pågående kognitiv svikt är att följa en patient över tid med uppföljande kognitiva tester, för att se om det sker någon förändring i tester över tid. Det har dock varit oklart vilka förändringar i kognitiva testresultat som svarar till en faktisk försämring i patientens tillstånd, vilket vi därför ville utreda i projekt III. Det är också viktigt att veta vilken sammansättning av kognitiva tester som bäst utvärderar en kognitiv svikt för att veta vilka kognitiva tester som ska prioriteras att genomföras vid utredning. Vi ville därför också i projekt III undersöka en metod för att få fram vilka kognitiva tester som bäst motsvarar en kognitiv försämring, hos både de som är kognitivt friska, samt de som har känd amyloid-patologi och de som redan har en kognitiv svikt.

När en patient söker vård för att utreda sina minnessvårigheter eller andra kognitiva problem, kan det vara svårt för mottagande vårdpersonal eller läkare att veta vilka patienter som har en hög risk för att utveckla en demenssjukdom inom snar framtid, och vilka som kan ges lugnande besked, även efter kognitiva tester har genomförts. I projekt IV ville vi därför skapa en modell som hjälpmedel för att beräkna den individualiserade risken för att utveckla demens inom fyra år, samt identifiera vilka patienter som kan ges lugnande besked efter den första utredningen.

List of Papers

Paper I

The Montreal Cognitive Assessment: Normative Data from a Large Swedish Population-Based Cohort
Borland, E., Nägga, K., Nilsson, P. M., Minthon, L., Nilsson, E. D. & Palmqvist, S., 2017, In: Journal of Alzheimer's Disease. 59, 3, p. 893-901 9 p.

Paper II

The age-related effect on cognitive performance in cognitively healthy elderly is mainly caused by underlying AD pathology or cerebrovascular lesions: implications for cutoffs regarding cognitive impairment
Borland, E., Stomrud, E., van Westen, D., Hansson, O. & Palmqvist, S., 2020 Mar 24, In: Alzheimer's Research & Therapy. 12, 1, 30.

Paper III

Clinically Relevant Changes for Cognitive Outcomes in Preclinical and Prodromal Cognitive Stages: Implications for Clinical Alzheimer Trials
Borland, E., Edgar, C., Stomrud, E., Cullen, N., Hansson, O. & Palmqvist, S., 2022 Sept 13, In: Neurology. 99, 11, p. E1142-E1153

Paper IV

Individualized, cross-validated prediction of future dementia using cognitive assessments in people with mild cognitive symptoms (unpublished)
Borland, E., Mattson-Carlgren, N., Tideman, P., *the Alzheimer's Disease Neuroimaging Initiative,* Stomrud, E., Hansson, O., Palmqvist, S.

Author's contribution to the papers

Paper I

Emma calculated means for MoCA test results, stratified test results and wrote the manuscript.

Paper II

Emma conducted all the statistical analyses, authored the manuscript, and participated in rating patients using the Clinical Dementia Rating scale.

Paper III

Emma performed most of the statistical analyses in SPSS Statistics and R, authored the manuscript, and contributed to rating patients with the Clinical Dementia Rating scale.

Paper IV

Emma carried out all the statistical analyses in R for participants from ADNI and BioFINDER-1 and developed the best model for predicting dementia. Emma also authored the manuscript.

Abbreviations

Aβ	amyloid beta
AD	Alzheimer's disease
ADAS cog	Alzheimer Disease Assessment Scale-Cognitive Subscale
ADAS delayed	ADAS cog 10-word delayed word recall
ADAS immediate	ADAS-cog 10-word immediate word recall
APOE ε4	apolipoprotein E ε4 allele
APP	amyloid precursor protein
bvFTD	behavioural variant frontotemporal dementia
CBD	corticobasal degeneration
CDR	clinical dementia rating scale
CIMP-QUEST	The Cognitive Impairment Questionnaire
CU	cognitively unimpaired
CSF	cerebrospinal fluid
CT	computer tomography
DATscan	dopamine transporter imaging using ioflupane (^{123}I) SPECT
DLB	dementia with Lewy Bodies
DSM	Diagnostic and Statistical Manual of Mental Disorders
FAQ-IADL	functional activities questionnaire in activities of daily living
FDG-PET	fluorodeoxyglucose positron emission tomography
FTD	frontotemporal dementia
GDS	The Global Deterioration Scale
LATE	Limbic-predominant age-related TDP-43 encephalopathy
LBD	Lewy Body dementia
LDL	low-density lipoprotein
lvPPA	logopenic variant of primary progressive aphasia
MCI	mild cognitive impairment
MMSE	mini-mental state examination
MNCD	major neurocognitive disorder
MoCA	The Montreal Cognitive Assessment
MRI	magnetic resonance imaging
MSA	multiple system atrophy
MTA	medial temporal lobe atrophy
nfvPPA	non-fluent variant of primary progressive aphasia
NFTs	neurofibrillary tangles

NINCDS-ADRDA	the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association
p-tau	phosphorylated tau
PART	primary age-related tauopathy
PD	Parkinson's disease
PDD	Parkinson's disease dementia
PPA	primary progressive aphasia
PSEN1 & PSEN2	presenilin1 & 2
SCD	subjective cognitive disorder
SCWT	Stroop Color and Word Test
SDMT	Symbol Digit Modalities Test
SPECT	single-photon-emission computed tomography
svPPA	semantic variant primary progressive aphasia
t-tau	total tau
TDP-43	TAR DNA-binding protein 43
TMT	Trail Making Test
VaD	vascular dementia
VCI	vascular cognitive impairment

Introduction

Cognition

Cognition has been defined as "all the processes by which the sensory input is transformed, reduced, elaborated, stored, recovered and used"[3]. It includes all aspects of intellectual functioning and processes such as attention, memory, knowledge, decision making, planning, judgment, reasoning, perceiving, imagining, language, visuospatial function and remembering[4, 5]. A cognitive deficit therefor describes an impairment in any domain of cognition, which is not limited to any certain cause and can both be a short-term condition or a progressive and/or permanent condition[5].

Normal aging and cognitive impairment

Cognitive change is a normal, gradual process of aging where cognitive functions decline over many years, accelerating in later life, a process which is highly variable within and between individuals[6]. Studies have shown links between normal aging and reduced speed[7, 8], conceptual reasoning, language, visuospatial abilities, executive abilities and memory, including spontaneous retrieval of information , source memory, and prospective memory[9]. Neuroscience studies have shown that age-related cognitive decline can be caused by brain grey matter volume decline; most prominently in the prefrontal cortex, and white matter changes; including volume decrease and decline in function[9].

When cognitive decline is greater than would be expected within normal age-related cognitive decline, without affecting daily function, we refer to "mild cognitive impairment" (MCI). Even normal cognitive aging can however result in declines in complex functional abilities, such as driving a vehicle[10].

MCI

MCI is a term that was initially used to refer to stage 3 on the Global Deterioration Scale (GDS). Later, the term was used to describe subjects who had a memory problem worse than what was expected for their age but did however not meet criteria for dementia[11]. MCI is now known as an intermediate state between normal

and dementia, defined as cognitive decline greater than expected for an individual's age and education, with essentially preserved functional abilities[12]. The prevalence of MCI in persons over 60 years is estimated to be 12-18%[11]. More than 50% of individuals with MCI progress to dementia within 5 years, whereas some remain stable or return to normal over time, and its identification could lead to secondary prevention by controlling risk factors such as systolic hypertension[13]. Amnestic mild cognitive impairment (aMCI) is a subtype of mild cognitive impairment which has a high risk of progressing to AD[13].

SCD

The term subjective cognitive decline (SCD) was born in 2014, and is characterized by self-experience of deterioration in cognitive performance, not detected objectively cross-sectionally through formal neuropsychological testing[14]. In clinical practice, these patients are generally considered as healthy individuals[15]. However, epidemiological studies have shown that the risk of MCI and dementia is increased in subjects with SCD, though the majority with SCD will not show progressive cognitive decline[15]. When differentiating between SCD and MCI, it is recommended to use comprehensive neuropsychological test batteries assessing multiple domains, where there are available normative scores adjusted for age, sex and education[15, 16].

Dementia

The term dementia comes from the Latin word *demens*, which means "being out of one's mind"[17]. In modern times, the diagnosis dementia was accepted as a medical term in 1797 by Philippe Pinel, and in 1910, Emil Kraepelin classified dementia into senile dementia and presenile dementia[18]. Dementia, or major neurocognitive disorder, is an increasing problem in our growing population with more elderly people worldwide. It is estimated that the number of people with dementia in the world are 50 million and will increase to more than 150 million people in the year 2050[19]. The World Health Organization (WHO) estimated the global societal cost of dementia in 2019 to be US$1.3 trillion[20]. While the prevalence of dementia is increasing worldwide, studies have shown that the age-related incidence of dementia has decreased over the past few decades, which can partly be explained by that the prevalence of many vascular risk factors has decreased over time[21, 22]. Dementia is better characterized as a syndrome rather than a disease, and the causes include neurologic, neuropsychiatric, and medical conditions. The syndrome is characterized by a chronic progressive loss of cognitive function that affects social or occupational function[12, 23].

Table 1.
The diagnostic criteria for mild neurocognitive disease and major neurocognitive disease according to DSM-5. For mild neurocognitive disease, performance typically lies in the -1-2 standard deviation range, and for major neurocognitive disease, typically 2 or more standard deviiationo below appropiate norms[24].

	Mild neurocognitive disease	Major neurocognitive disease
A	Evidence of significant cognitive decline from a previous level of performance in one or more cognitive domains (complex attention, executive function, learning and memory, language, perceptual-motor, or social cognition) based on:	
	1. Concern of the individual, a knowledgeable informant, or the clinician that there has been a mild decline in cognitive function; and	1. Concern of the individual, a knowledgeable informant, or the clinician that there has been a significant decline in cognitive function; and
	2. A modest impairment in cognitive performance, preferably documented by standardized neuropsychological testing or, in its abscense, another quantified clinical assessment	2. A substantial impairment in cognitive performance, preferably documented by standardized neuropsychological testing or, in its abscense, another quantified clinical assessment
B	The cognitive deficits do not interfere with capacity for independence in everyday activities (ie, complex instrumental activities of daily living such as paying bills or managing medications are preserved, but greater effort, compensatory strategies, or accommodation may be required)	The cognitive deficits interfere with independence in everyday activities (ie, at a minimum, requiring assistance with complex instrumental activities of daily living such as paying bills or managing medications)
C	The cognitive deficits do not occur exclusively in the context of a delirium.	
D	The cognitive deficits are not better explained by another mental disorder (e.g. major depressive disorder, schizophrenia).	
E	Specify whether due to Alzheimer's disease, frontotemporal lobal degeneration, Lewy body disease, vascular disease, traumatic brain injury, substance/medication use, HIV infection, prion disease, Parkinson's disease, Huntington's disease, another medical condition, multiple etiologies, or unspecified	

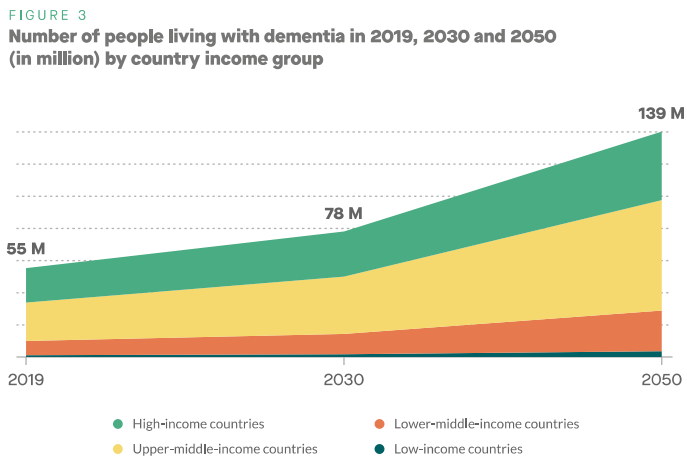

Figure 1.
WHO, Global status report on the public health response to dementia, 2021

Risk factors for cognitive impairment

Sociodemographic factors

Older age is widely recognized as the most important risk factor for most neurodegenerative diseases, including AD. One in ten individuals at the age 65 or older have AD at the dementia stage and the prevalence continues to increase with older age[25, 26].

There is considerable evidence that lower education increases risk of dementia and that elderly with a greater education are less likely to develop dementia[27]. Studies from the United States have also shown racial differences in dementia incidence, where incidence of dementia and AD are approximately twice as high in African Americans and Hispanics compared with Caucasians[28, 29].

About two-thirds of clinically diagnosed dementia and AD are women, and the primary reason for this is longevity[30]. However, there are several other sex differences in the risk for cognitive impairment.

Firstly, there are sex-specific risk factors, as e.g. early menopause is associated with increased risk of MCI and dementia, and preeclampsia is associated with an increased risk of MCI, VaD and AD[31]. Women have a 2-3 times the risk of developing AD than men after the age of 65[31]. Sex hormone differences can also affect dementia risk, where hormone therapy has been seen to be associated with higher risk of all-cause dementia[32]. Apart from the above, there are sex differences in several risk factors for cognitive impairment, where for example woman are more likely to have poorer outcomes from traumatic head injuries, and have twice the risk of depression compared to men, as well as the differences in effects of cardiovascular risk factors[31]. There are also presymptomatic cognitive differences between sexes, since men perform better on spatial memory tests while women are better in verbal and object location[33].

Genetic factors

The strongest and most prevalent genetic factor for AD is the Apolipoprotein E (*APOE*) ε4 allele, impacting more than half of all AD patients. The *APOE* gene is involved in creating a protein that helps carry cholesterol as well as other types of lipids in the bloodstream[34]. The three main variants of human *APOE* are ε2, ε3 and ε4, where the ε4-variant gives an increased risk of AD, and people with ε2 have less amyloid than people with ε3[35].

Cardiovascular disease

Cardiovascular disease is a risk for causing vascular dementia, however there is growing evidence that these risk factors also are associated with a higher risk of AD and other dementias[36]. Diabetes mellitus has been shown to almost double an individual's risk of dementia. This risk is more associated with vascular dementia

than AD[37, 38]. Hypertension in midlife, especially if not treated effectively, is associated with a higher risk of dementia and AD[39], and hypercholesterolemia has also been shown to be associated with an increased risk of dementia. There is some evidence that obesity has been seen to give an increased risk of dementia[40]. There is however evidence that the association between hypertension and obesity with dementia may change with age[41]. Obstructive sleep apnoea, a history of stroke and smoking have also been shown to be associated with a higher risk of cognitive impairment[12].

Behavioural factors

Epidemiology studies suggest that occupational (and education) attainment as well as leisure activities in later life can increase the cognitive reserve, whereby some individuals can tolerate more pathologic changes than others and maintain cognitive function[42]. This explains some of the discrepancies between the amount of neuropathology in the brain and degree of cognitive or functional impairment in some individuals[43]. Similar to this, staying socially active can also reduce the risk of AD and other dementias[44]. There is also evidence that physical activity may protect against cognitive decline and dementia in older adults[27].

Neuropsychiatric factors

Neuropsychiatric disorders such as schizophrenia, bipolar disorder, autism spectrum disorder and major depressive disorder are common diseases where cognitive impairment is a common characteristic[45] and therefore should be considered when diagnosing neurocognitive disease[24]. Older individuals with depressive symptoms have been associated with and increased risk for dementia; however, it is also plausible that depressive symptoms may act as a prodrome preceding dementia or is seen as a consequence of a dementia diagnosis[46].

Others

Alcohol use disorder has been shown to be associated with a higher risk of dementia[47], albeit other studies have shown that alcohol use is associated with reduced risk for AD, VaD and any other dementia compared to non-drinkers[48]. Alcohol has a direct neurotoxic effect which can lead to permanent structural and functional brain damage, and heavy alcohol use is also a risk factor for other medical conditions which can lead to brain damage, such as hepatic encephalopathy, epilepsy, and head injury. Heavy alcohol abuse is also associated with vascular dementia as is associated with cardiovascular risk factors. Also, heavy alcohol use is associated with other risk factors for dementia such as lower level of education, tobacco smoking and depression[49].

Sleep disturbances have in several studies showed a U-shaped association with risk for dementia, where both very short and very long sleep duration being associated with a higher risk of dementia[50, 51].

Traumatic head injury is also known to be associated with a higher risk of all-cause dementia[52], some studies showing up to a three-fold risk of dementia diagnosis[53].

Research also indicates that brain inflammation plays a significant role in the development of dementia and that elevated serum levels of acute phase reactant can be considered as a risk factor for AD[54].

Neurodegenerative diseases

The most common primary neurodegenerative disorders are Alzheimer's disease (AD), dementia with Lewy bodies (DLB), vascular dementia, frontotemporal lobar dementia and Parkinson disease[55]. In many cases, individuals have mixed pathologies causing their cognitive symptoms, and many cases are subclinical[35].

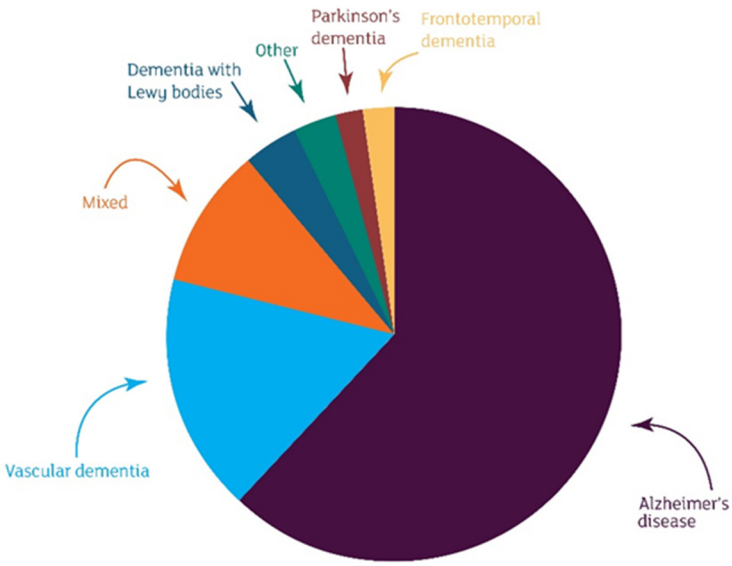

Figure 2.
Pie chart of the most common causes of dementia. Alzheimer's Research UK, https://www.alzheimersresearchuk.org/blog/dementia-with-lewy-bodies-explained/. Reprinted with permission from Alzheimer's Research UK.

Alzheimer's disease

Epidemiology

The most common disease causing a neurocognitive disorder is Alzheimer's disease (AD), making up to over 60% of all dementia cases and affecting an estimated 24

million people globally[56]. The prevalence of the disease increases with increasing age, and numbers report a more than 15-fold increase between ages 65-85[26].

History

The disease is named after the German psychiatrist Alois Alzheimer who in 1906 studied a 51-year-old patient, Auguste Deter, with seriously impaired memory and change of personality. Post-mortem he used a then new histological technique to examine her brain microscopically, and noticed a presence of neuritic plaques, neurofibrillary tangles and amyloid angiopathy[35]. Alzheimer's mentor Emil Kraepelin later credited him by coining the disease "Alzheimer's disease" for his discovery[57].

Pathophysiology

The pathophysiology is characterized by extracellular β-amyloid (Aβ) pathology and intracellular tau pathology. The disease starts with a preclinical stage with Aβ-pathology, which evolves with a spreading of tau throughout the brain. The production of β-amyloid is caused by cleaving of the protein amyloid precursor protein (APP), which accumulates and deposits in the brains of people with AD[35]. Hyperphosphorylation of tau in AD leads to a change from unfolded tau to paired helical filament tau inclusions and neurofibrillary tangles[58].

There are both genetic and sporadic forms of AD, where the genetic forms stand for about 1% of all AD cases and 5-10% of all early-onset AD cases. The autosomal dominant forms of AD are mostly caused by mutations in Presenilin 1 (PSEN1) or PSEN2, but also in APP.

There is increasing evidence that the choroid plexus and the blood-cerebrospinal fluid (CSF)-barrier (BCSFB) has a role in the pathophysiology in AD, where changes in CSF secretion, inflammation, oxidative stress and transportation over the BCSFB have seen to be impaired[59]. However, it is yet unknown if these are causes or consequences of AD neuroinflammation[59].

Clinical symptoms

The early stages of AD typically present with episodic memory complaints, progressing to include difficulties in speech production such as naming or semantic problems[60]. Once the disease progresses, patients experience difficulties in sense of orientation, calculation and learning disabilities[61].

There are other more uncommon phenotypes of AD; such as posterior cortical atrophy (PCA) predominantly affecting visual cortex, logopenic variant of primary progressive aphasia (lvPPA), where core features are word retrieval and sentence repetition with frequent word-finding problems in spontaneous speech[62], and frontal variant of AD, affecting the frontal lobes changing personality, behaviour and executive functions[63]. The burden of tau and topographic distribution drive the

clinical severity and phenotype of AD[64]. Compared with men, women often present clinically with verbal memory complaints and difficulty finding words rather the episodic memory complaints in the early stages of cognitive impairment[31].

Diagnosis

In 1984, the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) established diagnostic criteria for AD based on symptomatic criteria, age, absence of other underlying disorders and for a definitive diagnosis of AD, the diagnosis were to be confirmed histopathologically[65]. In 2011, NIA-AA brought out new diagnostic criteria including clinical biomarkers. In 2018 researchers proposed a new system to diagnose the disease, containing underlying biomarkers[66]. For the biological markers included in the updated diagnostic criteria, neuroimaging with magnetic resonance imaging (MRI), positron emission tomography (PET) with fluorodeoxyglucose (FDG) or β-amyloid tracers and cerebrospinal fluid (CSF) analysis of Aβ and tau proteins are all taken in consideration in the diagnostic process[61]. Even though research has defined a preclinical Alzheimer's disease, the disease is not diagnosed before symptom onset[23]. The 2021 International Working Group Dubois criteria emphasizes a clinical-biological approach to the diagnosis, and is commonly used in clinical practice, requiring both a clinical phenotype of AD and biomarker evidence of AD pathology[67]. In the most recent updated criteria, the committee categorized AD biomarkers into core 1 and core 2 biomarkers, depending on whether they are affected earlier or later in the disease course. This classification system aims to aid in the biological diagnosis of AD based on neuropathologic findings, including blood biomarkers[68].

Lewy body dementia

Epidemiology

Lewy body dementia (LBD) is primarily an umbrella title for dementia with Lewy bodies (DLB) and Parkinson's disease dementia (PDD)[69]. LBD is the third most common cause of dementia and second most common cause of neurodegenerative disease after AD, affecting up to 30% of all dementia patients[56, 69]. The mean age of LBD onset is between 59-78 years[56]. The prevalence of dementia in patients living with Parkinson's Disease (PD) is around 30% and is higher with increasing age[56].

History

James Parkinson described the clinical symptoms of "paralysis agitans" in 1817 and Charcot later proposed the name "Parkinson's disease" in 1868[70]. The neuropathology PD and DLB was discovered by Dr Friedrich Lewy in 1912 while studying the neuropathology of Parkinson's Disease in Dr Alois Alzheimer's

laboratory[69]. He described eosinophilic intracytoplasmic inclusions in dorsal vagal nuclei and "substantia innominate" (unnamed substance) in PD brains, later called "Lewy bodies" in 1919[70]. In 1953, researchers revealed Lewy bodies were the most common findings in brains of PD-patients[71]. In the 1990s, the constituent of Lewy bodies, α-synuclein, was revealed[69].

Pathophysiology

The current concept of α-synucleinopathies is that they are characterized by the presence of Lewy bodies (LBs), including neuronal α-synucleinopathies (PD and DLB) and oligodendroglial α-synucleinopathy (multiple system atrophy (MSA))[72], where DLB is caused by the build-up of aggregated forms of α-synuclein in neurons and surrounding glial cells[73].

Clinical symptoms

The two diseases DLB and PDD are differentiated clinically from one another by the one-year rule based on the onset of cognitive symptoms, i.e. in PDD the motor symptoms precede the onset of dementia by at least one year[56, 73].

Patients with Lewy body dementia present with a wide range of cognitive symptoms, neuropsychiatric symptoms (including hallucinations), sleep-, motor- and autonomic symptoms[73]. They typically show cognitive fluctuations with alternating levels of attention and alertness which is a core symptom of DLB[74]. The cognitive deficits in DLB and PDD overlap including attention, executive dysfunction, language function, behaviour and visuospatial abnormalities as well as impaired memory[75]. The parkinsonism that appears in LBD involve bradykinesia and rigidity, while parkinsonistic rest tremor is less frequent. Both patient groups have a high risk of falls and swallowing dysfunction[74].

About 76% of patients with DLB act out their dreams during sleep, which is caused by rapid eye movement (REM) sleep behaviour disorder (RBD)[76]. RBD is a parasomnia that is thought to be caused by lack of normal REM muscle atonia and lack of suppression of motor signal through pontomedullary structures[77], which can be seen in patients many years before cognitive symptoms[78]. Other supportive clinical symptoms of DLB are repeated falls, syncope, transient loss of consciousness, systematized delusions, hallucinations, neuroleptic sensitivity, as well as hyposmia and hypersomnia[79, 80].

Diagnosis

The working diagnostic criteria for DLB include core clinical features (fluctuating cognition with pronounced variations in attention and alertness, recurrent visual hallucinations, RBD and/or parkinsonism) and indicative biomarkers (pathological dopa-PET or SPECT, low uptake on MIBG-scintigraphy and/or polysomnographic

confirmation of RBD), for diagnosing probable or possible DLB[80]. Supportive clinical features and biomarkers aid in guiding the diagnosis but are not definitive.

Due to upcoming diagnostic methods with CSF-based α-synuclein seed amplification assays, or detection of phosphorylated α-synuclein in skin biopsies[81], the diagnosis for DLB and PDD is heading toward a more biological definition, defining a neuronal α-synuclein disease (NSD)[82]. This is proposed to include markers of presence or absence of pathological α-synuclein in CSF of peripheral tissue, neuroimaging features defining presence of neurodegeneration and presence of Parkinson's disease specific pathogenic gene variants[83, 84].

It is important to correctly diagnose DLB because many of the pharmacological treatments used for treating behavioural or cognitive symptoms in other forms of dementia can dramatically worsen the symptoms of DLB[69]. It is widely acknowledged that DLB is underdiagnosed and there is a large overlap with vascular dementia, AD and LBD, why it often can be difficult to determine the primary diagnosis[69].

Frontotemporal dementia

Epidemiology

Frontotemporal dementia (FTD) is an umbrella clinical term that encompasses a group of neurodegenerative diseases affecting patient's behaviour, executive function and/or language. It is the third most common type of primary neurodegenerative dementia and has a complex array of pathologies, most commonly frontotemporal lobe dementia-tau (FTLD-tau) or FTLD-TDP[35]. The estimated point prevalence of the disease ranges from 15-22/100,000[85]. It is typically diagnosed in middle age and is a therefore a common cause of early dementia in patients younger than 65[56].

History

FTD was first described by Arnold Pick in 1892, where he described a patient with progressive speech difficulties associated with left temporal lobe atrophy, a syndrome which today is classified as semantic variant primary progressive aphasia (svPPA). In 1926 Pick's students described Pick's bodies identifying "Pick's disease" as a neuropathological disease for frontal lobe atrophy with "pick bodies" – cytoplasmic inclusion bodies[86, 87]. Thereafter, the majority of dementia research focused on Alzheimer's disease for many years, until the 1970s when researchers found clinical correlation between of frontal lobe atrophy with hypoperfusion inn the frontal lobes[88]. The first clinical diagnose criteria were established in the 1990s, in which classification system the presence of Pick's bodies was not necessary for

the diagnosis of Pick-type FTLD[89, 90]. Pick's disease is now known as a rare pathologic subtype of FTLD-tau[91].

Pathophysiology

Frontotemporal lobal degeneration is characterized by neuronal loss, gliosis and microvascular changes in the frontal lobes (particularly the anterior cingulate cortices), the anterior temporal lobes and the insular cortices[92]. About 20-25% of individuals with FTLD are estimated to carry a mutation associated with a specific FTLD pathology. In both mutation carriers and those with sporadic disease, the most common causes are linked to neuronal and glial inclusions containing tau (FTLD-tau) or TDP-43 (FTLD-TDP). Around 5-10% of patients may have inclusions containing FUS-Ewing sarcoma-TAF15 family (FTLD-FET) and rare FTLD cases can be caused by inclusions containing ubiquitin proteasome system (FTLD-UPS).[93]

The most common FTLD-tau pathological subtypes are Pick's disease, corticobasal degeneration (CBD) and progressive supranuclear palsy (PSP)[92]. FTLD-TDP pathology is mainly associated with the clinical syndromes behavioural variant FTD (bvFTD), semantic variant primary progressive aphasia (svPPA) and FTD-motorneuron disease (MND)[92, 94].

Clinical symptoms and diagnosis

FTD is classified into several different clinical variants. BvFTD is a variant that presents with at least three of the following: early changes in behaviour/cognitive symptoms, early apathy or inertia, early loss of sympathy or empathy, early perseverative, stereotypes of compulsive/ritualistic behaviour, hyperorality and dietary changes and/or show a neuropsychological profile with executive deficits with relative sparing of memory and visuospatial functions[95]. Non-fluent variant-PPA (nfvPPA) causes progressive problems with effortful speech agrammatism[62]. The semantic variant-PPA (svPPA), is a progressive disorder of semantic knowledge and naming[92]. For svPPA, the most common symptoms are anomia and single-word comprehension deficits. To detect svPPA early, neuropsychological testing should include infrequently used words. As the disease progresses, patients also lose semantic knowledge about objects, which does not improve with cues or hints[62]. RtvFTD is described as memory loss, prosopagnosia, getting lost and behavioural changes and has been considered a right-sided variant of svPPA[94].

PPA is a neurodegenerative syndrome where language is the primary impairment in the first two years. The three types of PPA include svPPA and nfvPPA, which are mentioned above and both associated with FTD, as well as logopenic PPA (lvPPA), which is mainly caused by AD pathology[87].

As FTLD progresses, the clinical syndromes converge and individuals develop a global cognitive impairment and later motor deficits[92].

Vascular dementia

Epidemiology

Vascular dementia (VaD) or vascular cognitive impairment (VCI) is one of the most common causes of dementia, causing around 15-40% of cases[96, 97]. It is most commonly caused by ischemic tissue injury in the form of brain infarcts and may include other forms of hypoxia and hemorrhage[35]. VCI is the most common contributor to dementia, having additive or even synergistic interactions with other neurodegenerative pathology[97].

History

VaD was first described in 1672 by Thomas Willis, who studied patients with post-apoplexy dementia. In modern history, it was described in 1894 by Otto Binswanger and Alois Alzheimer, who together separated vascular dementia from dementia caused by neurosyphilis[98]. Over time, the terminology has evolved from the umbrella term "multi-infarct dementia" to more detailed understanding of different pathological processes[99].

Pathophysiology

There are several subtypes of vascular dementia[96]:

- multi-infarct dementia
- small vessel dementia (subcortical vascular dementia)
- strategic infarct dementia (e.g. thalamus)
- hypoperfusion dementia
- haemorrhagic dementia (haemorrhagic changes which can be associated with cerebral amyloid angiopathy)
- hereditary vascular dementia (such as cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL))
- AD with cardiovascular disease, which is the most common neurodegenerative disease mixed with vascular dementia[100]

The most common risk factors for vascular dementia is cardiovascular diseases including hypertension, smoking, atrial fibrillation, type 2 diabetes mellitus and hyperlipidemia[99].

Clinical symptoms and diagnosis

Symptoms of cognitive impairment in VCI depend on the area of tissue injury. For subcortical ischemic vascular dementia, patients typically have progression in

dysexecutive function, decline in speed or complex attention[99], typically with fluctuating symptoms. Patients with a history of stroke or multi-infarcts have symptoms depending on the localization of ischemic injury, such as language or memory difficulties. Studies have shown that injuries in the left angular gyrus, left basal ganglia and white matter around the left basal ganglia are strategic structures for global cognitive impairment[101]. Even patients who have a good functional recovery after stroke do not necessarily have a good cognitive recovery[102]. In patients with mixed vascular and AD dementia, symptoms can be similar to patients with pure AD[99].

Other neurodegenerative diseases

Tauopathies

Tauopathies are defined as brain accumulation of microtubule-associated protein tau in fibrillar aggregates, causing neurodegenerative disease. There are over 25 different types of tauopathies, including primary age-related tauopathy (PART), PSP, CBD and Pick's disease, as well as argyrophilic grain disease (AGD)[103].

PART is a disease with similar symptoms as in AD, however, has a later age of symptom onset, a slower rate of disease progression[104], and in post-mortem examination autopsy show brains with neurofibrillary tangles (NFTs) and absence of amyloid plaques[105].

Progressive supranuclear palsy syndrome (PSP) is clinically characterized by early postural instability, falls and eye movement abnormalities, typically with a vertical supranuclear gaze palsy or slowed vertical saccades. Typical parkinsonian features are common and cognitive and behavioural changes often accompany the motor syndrome, usually reflecting frontal dysfunction such as apathy, impulsivity, worsened attention, personality change and slowed processing speed. Other cognitive abilities such as memory, language and visuospatial skills are often relatively spared[56].

Corticobasal degeneration (CBD) is associated with asymmetric frontoparietal or paracentral lobal atrophy[56]. One of the most common clinical syndromes caused by CBD is corticobasal syndrome (CBS), which is clinically characterized by limb rigidity, bradykinesia, dystonia and myoclonus, as well as cortical dysfunction with alien limb phenomena, apraxia and cortical sensory loss[106]. CBS is, however, also associated with other pathologies such as AD, PSP-tau, Pick's-tau, TDP-43, Lewy bodies and Creutzfeldt-Jakob disease (CJD)[107]. Additionally, CBD pathology is associated with, among others, nfvPPA and bvFTD[56].

For the complex association between underlying pathologies and neurocognitive disorders, this is depicted in Figure 3 (Olfati, Shoeibi & Litvan, 2022).

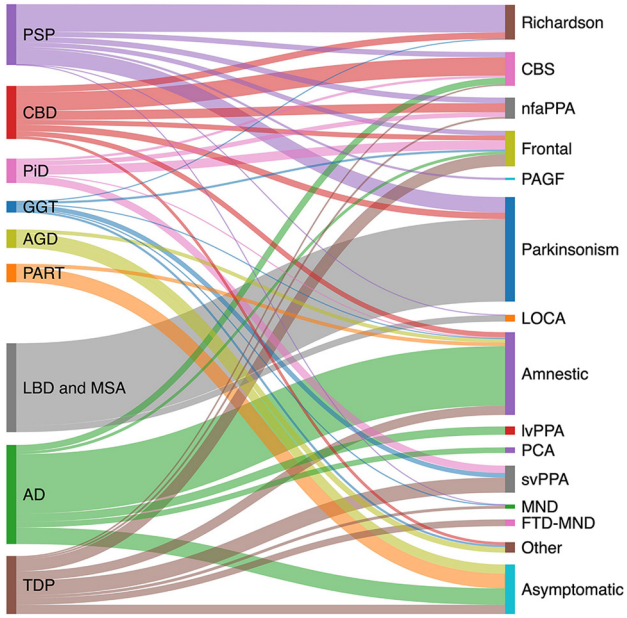

Figure 3.
Picture of which different underlying pathologies are involved in the mechanism of neurocognitive disorders. AD, Alzheimer's disease; AGD, argyrophilic grain disease; CBD, corticobasal degeneration; CBS corticobasal syndrome; FTD-MND, frontotemporal dementia-motor neuron disease; GGT, globular glial tauopathy; DLB, Lewy body disease; LOCA, late onset cerebellar ataxia; lvPPA logopenic variant primary progressive aphasia; MND, motor neuron disease; nfaPPA, non-fluent agrammatic primary progressive aphasia; PAGF, progressive akinesia and gait freezing; PART, primary age-related tauopathy; PCA, posterior cortical atrophy; PiD, Pick's disease; PSP, progressive supranuclear palsy; svPPA, semantic variant primary progressive aphasia; TDP, transactive response DNA binding protein 43 kDa pathology. Copyright by Frontiers in Neurology © 2022 Olfati, Shoeibi and Litvan[108]. Distributed under the terms of Creative Commons Attribution License (CC BY).

α-synucleinopathies

Other than DLB and PDD, multiple system atrophy (MSA) is an α-synucleinopathy with glioneuronal degeneration in striatonigral, olivopontocerebellar and autonomic nervous systems, as well as other parts of the central and peripheral nervous systems. The two most common clinical variants of MSA are olivopontocerebellar atrophy (MSA-C) and striatonigral degeneration (MSA-P)[109]. In neuropsychological tests, patients with MSA and dementia showed impairments in attention, visuospatial function, and language function[110].

TDP-43 proteinopathies

Limbic-predominant age-related TDP-43 encephalopathy (LATE) disease is defined by a stereotypical TDP-43 proteinopathy in older adults, which can be with or without coexisting hippocampal sclerosis pathology. The disease is associated with an amnestic dementia syndrome mimicking AD but has been shown in autopsy

not to be caused by AD pathology. It is mainly differed from FTLD by its epidemiology, causing symptoms later in life, and by the more restricted neuroanatomical distribution of TDP-43 proteinopathy[111].

Other neurological disorders causing cognitive decline

Huntington's disease is an autosomal dominant disease, causing mid-life onset of progressive motor, cognitive and psychiatric symptoms, where subtle cognitive symptoms can start many years before official disease onset. Early deficits are in visual attention, psychomotor speed, visuomotor and spatial integration, executive dysfunction, general slowing and impaired short-term memory[112].

Creutzfeldt-Jakob disease (CJD) is a rapidly progressive neurodegenerative disease which is caused by an abnormal isoform of a prion protein. It is a rare cause of dementia which should be considered in patients with a rapid decline in cognitive function[113]. The most frequently impaired abilities are verbal initiative, lexical search, long-term memory, attention and abstract reasoning[114].

Korsakoff syndrome is characterized by confabulation, memory loss and gait abnormalities that are often irreversible if the preceding state of Wernicke encephalopathy is not treated adequately. The cause of the two syndromes is vitamin B1 (thiamine) deficiency which can be caused by any kind of poor nutrition, however the most common factor associated with Wernicke-Korsakoff is alcohol abuse[115].

HIV-associated neurocognitive disorder (HAND) is a condition that is characterized by complaints of difficulties in concentration, memory and impaired executive functions. The disorder is caused by HIV encephalitis and HIV leukoencephalopathy and is seen in patients with no or unsuccessful antiviral treatment[116].

Chronic traumatic encephalopathy (CTE) is a neurodegenerative disease caused by repeated traumatic brain injury (TBI), a disorder mainly seen in individuals at high risk of multiple brain injuries, such as boxers, American and European football players, as well as war veterans. CTE can cause behavioural and cognitive symptoms or mixed variants[117].

Secondary dementia can also be caused by other neurological disorders such as multiple sclerosis (MS)[118], meningitis or encephalitis[119, 120], Wilson's disease (build-up of copper levels)[121], and malignant brain tumours[122].

Reversible disorders and conditions causing cognitive impairment

There are several conditions that can cause symptoms similar to dementia, which could potentially be halted or reversed, making their diagnosis important.

Normal pressure hydrocephalus (NPH) is an important differential diagnosis of neurodegenerative disease and is caused by a build-up of cerebrospinal fluid in the brain. The classic triad of symptoms includes cognitive impairment, urinary incontinence, and gait impairment. The complete triad is however not always seen. Shunting by draining cerebrospinal fluid from the lateral ventricles to the peritoneal cavity leads to a clinical improvement in 70-90% of treated patients[123].

Nutritional deficiencies such as vitamin B1 (thiamine) deficiency caused by chronic alcoholism, or vitamin B12, can cause cognitive symptoms and both potentially be reversed by treatment[124]. Other metabolic disorders such as hypothyroidism can also give cognitive impairment treatable with medication[125].

Medication side effects from e.g. antiepileptics, antipsychotics, anticholinergic and antidepressants can cause cognitive impairment and be reversed by stopping medication. Studies have shown that drug-induced cognitive impairment causes around 2.7% of all cognitive impairment and is the most common reversible cause of cognitive impairment[126]. These drugs are still commonly utilized in nursing home dementia units[127]. Individuals taking at least three medications with cognitive side effects score significantly lower on cognitive assessments than individuals not taking medications with cognitive side effects[128]. This enhances the importance of thorough review of medication list in patients being evaluated for cognitive symptoms.

Vasculitis, an inflammation in brain blood vessels which can cause multiple strokes and dementia can be treated with immunosuppressive medications[129].

Sarcoidosis is a multisystem inflammatory disease with granulomas in multiple organs which can give potentially reversible cognitive symptoms[130].

A subdural hematoma (SDH), a bleeding between the dura and arachnoid matter which can arise spontaneously, but most commonly after a fall or brain trauma, can cause symptoms days or even weeks after the initial bleeding. The symptoms of SDH can vary but may include hemiparesis, cognitive symptoms, headache, and gait disturbance; all of which can be reversible after surgical drainage of the hematoma[131].

Non-malignant tumours can cause cognitive symptoms and can be reversible after surgery[132]. There are also certain brain infections (such as neurosyphilis or Lyme's disease) which can cause cognitive impairment and can be treatable after suitable medication[125].

Diagnostic work-up

Diagnosing neurocognitive disorders requires an evaluation of cognitive decline history and impairment of daily acitivities[23]. It also requires blood tests to rule out other causes, cognitive assessments, a computer tomography (CT) or magnetic resonance imaging (MRI) and in certain cases a lumbar puncture.

Medical history

When interviewing or taking a medical history from a person with cognitive symptoms, interviews can be structured or non-structured. In a typical semi-structured interview, the following questions are important to address:

- Basic descriptive data including gender, age, marital status, place of birth
- Developmental history including early risk factors and deviations from normal development including premorbid cognitive level
- Social history: education, family and personal relationships, interactions with the legal system
- Medical history: alcohol, drugs, tobacco, medications, exposure to toxins, family history
- Medical status: nature of onset, duration, fluctuations, physical status, intellectual status, emotional/behavioural changes, medical treatments and compliance, history of rapid eye movement behaviour, visual or other hallucinations, changes in behaviour such as apathy or disinhibition, systemic diseases
- Effect of disorder on daily life including coping styles and compensatory techniques[23, 133]

The purpose of structured amnestic assessments is to find out what impact the individuals' cognitive problems have on their daily life, including amnestic assessments from both patients and near relatives who see them at daily basis.

FAQ-IADL

The Functional Activities Questionnaire (FAQ-IADL) is a 10-item report with a 4-point ordinal response within each item, based on difficulties in activities of daily living (ADLs) for use in clinical and research settings[134]. It assesses mild levels of functional difficulty which demonstrates early functional changes in MCI and dementia[135].

CIMP-QUEST (Swe: Neurokognitiv symptomenkät)

The Cognitive Impairment Questionnaire (CIMP-QUEST) is an instrument based on information obtained by close informants to identify dementia and dementia-like symptoms[134]. The questionnaire consists of three subscales reflecting cognitive impairment from different brain regions (parietal-temporal, frontal and subcortical). It also contains a memory scale and lists non-cognitive symptoms. It has a high reliability and validity and helps the clinician achieve information about the individual's symptoms including brain-region oriented information, aiding the diagnostic process.

Physical examination

Individuals with signs of neurodegenerative disease should be examined with physical and neurological examination, as well as laboratory testing for thyroid function, metabolic profile, vitamin B12 and folate to rule out other causes of cognitive decline. When appropriate, screening for connective tissue disorders, neurosyphilis, HIV-related disease, neuroborreliosis and neurosarcoidosis should be performed[23, 102]. Some clinical findings which may help differentiate dementia subtypes include:[23, 99]

- DLB/PDD: Bradykinesia, rigidity, gait changes, hand-writing irregularity, loss of postural reflexes
- FTD: Abnormal behaviour, disinhibition, language impairments, preservation
- VaD: Focal neurological symptoms that could be a symptom of stroke (such as unilateral weakness and hyperreflexia, positive Babinski), vascular risk factors (hypertension, diabetes, skin changes in legs due to peripheral vascular disease or pitting oedema due to heart failure), cardiopulmonary examination
- AD: Episodic memory impairment, visuospatial problems, anomia

Cognitive assessments

Cognitive assessments aim to identify the domains affected by the underlying disease, establish cognitive levels, and aid in diagnosing the cause of cognitive impairment. There are six main functions that could be affected: learning and memory, social functioning, language, visuospatial function, complex attention, and executive functioning. Impairments in these functions could potentially result in a diagnosis of mild or major neurocognitive disorder[136]. It is therefore of high importance that cognitive impairment be tested by cognitive assessments covering as many of the domains as possible. Also, as disease modifying treatment for

neurodegenerative disease emerge in the future, there will be an increasing number of people seeking healthcare for their cognitive symptoms. It will therefore be of increasing importance that healthcare professional investigating them for their cognitive symptoms, can administer and interpret the adequate cognitive assessments, for correct diagnosis and management. To be able to interpret results, it is important to take in account the individual's premorbid function, including demographic factors such as age, gender and education and previous cognitive function, to understand which changes in cognition have occurred.

When evaluating elderly people, it is critical that the examiner determines that the patient's vision and hearing are sufficient for the task being performed and to assist patient to compensate for any loss[133]. For the examiner evaluating the participant's test results, it also important to visualize the actual tests and not only the total point score, to see where patient's difficulties are and if the same difficulties are observed in several tests.

Apart from the above, lack of motivation, aphasia, dyslexia, psychiatric disease or other somatic disease, medication side effects, cultural background and another language as mother tongue are all mechanisms that can cause a participant to score lower than expected and should be considered when evaluating assessment scores.

Most cognitive assessments have been reproduced in many different versions with different point scoring systems, a full review of these is outside the scope of this thesis. However, it is important to acknowledge that scores from different versions are not completely comparable. Therefore, when evaluating different versions, it is important to seek information on how well the different versions correlate with each other.

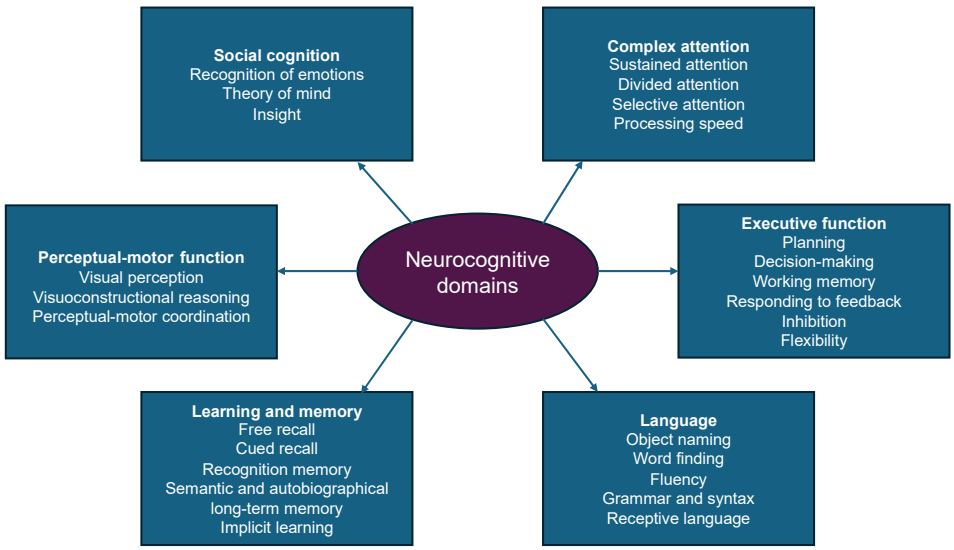

Figure 4.
Neurocognitive domains defined by DSM-5, where each of the 6 domains have subdomains.

MMSE

The Mini-Mental State Evaluation is a cognitive assessment for assessing global cognitive impairment, initially formalized to distinguish neurological patients from psychiatric patients[133, 137]. It is the most well-known and used brief cognitive assessment world-wide. It is a 30-question assessment of cognitive function that evaluates attention and orientation, memory, registration, recall, calculation, language, and visuospatial ability[138]. Traditionally, a 23/24 point score was suggested as the cut-off to suspect cognitive impairment or dementia[139]. This has later been seen to be highly dependent on sociodemographic factors such as age and education which both decrease scores[140]. The MMSE has a sensitivity between 23-76% for conversion from MCI to dementia and a specificity of 40-94%[141], whereas for MCI, MMSE has a sensitivity of 18%[142]. It is therefore most effective in distinguishing patients with moderate or severe impairment from control subjects[143].

MoCA

The Montreal Cognitive Assessment is a brief 10-minute tool for detecting mild cognitive impairment. In contrast to MMSE, the MoCA has a higher sensitivity for MCI at 90% and is developed for the use of patients with mild cognitive symptoms[142]. It assesses short term memory, visuospatial function, executive function, attention, concentration and working memory, language and orientation[144].

The original validation study of the MoCA suggested a cut-off value of more than or equal to 26 points out of 30 to differ healthy subjects from cognitive impairment, but this has seen to be a high cut-off, especially for individuals with old age and low education, why many people would be incorrectly diagnosed with cognitive disease using the cut-off of 26 points[145]. Because education was found to affect results, authors added one point for individuals with ≤12 years of education. MoCA, just as the MMSE, are recommended to be complemented with more executive tests which is only partly tested for in this short assessment. The test has been proved useful when examining individuals with AD, Parkinson's disease and vascular cognitive impairment[143] and studies have also indicated it to be a useful tool to identify and track progression of cognitive impairment in FTD[146, 147].

ADAS-cog

The Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog) is a comprehensive cognitive assessment containing multiple parts: word recall, naming objects and fingers, commands, constructional praxis, ideational praxis, orientation, word recognition, language, comprehension of spoken language, word finding difficulty as well as remembering test instructions[148]. It was the primary cognitive outcome measure in clinical trials that led to U.S. Food and Drug Administration approval of the first medication approved for the treatment of AD named tacrine[149]. ADAS-Cog has been widely used for clinical trials in AD being considered a standard primary outcome neuropsychological measure[150]. Both age and education have shown statistically significant effects on ADAS-cog performance[143]. The delayed 10-word list recall has been shown to be an important predictor for conversion from mild cognitive impairment to AD[151]. However, the utility of the complete ADAS-cog in MCI has been shown to be limited and additional tests are suggested to detect small cognitive changes[152].

SDMT

Symbol Digit Modalities test (SDMT) is an executive digit substitution test where the individual receives a line of numbers coupled with nine different symbols. In the time of 60 seconds, the participant should fill in blank spaces under symbols with as many correct paired numbers as possible. There is an oral and a written version of the test, where the advantage of the oral version is that it is not affected by upper limb motor function, whereby a combination of both test modalities is helpful when comparing motor- and non-motor speeded tasks[153]. The SDMT requires divided attention, perceptual speed, visual scanning, speed and tracking[133]. When completing both the oral and written versions, the test provides comparison between visuomotor and oral responses[143]. In healthy adults, the SDMT activates frontal and parietal areas, primarily in the left hemisphere[154]. The test has been showed to be discriminative between depression and dementia[155] and is among the best predictors for progression from mild cognitive impairment to AD[151]. Correlations between the Symbol Digit Modalities Test and the similar Digit

Symbol Substitution Test (DSST), as well as test-retest correlations for the SDMT and the correlation between written and oral forms, are all in the order of r = 0.80 for normal subjects[156].

AQT

A Quick Test of cognitive speed (AQT), is a well-validated, sensitive screening tool for cognitive impairment and for AD[157]. It tests for processing speed and consists of three parts: colour naming, form naming and colour-form naming. In the first part, the assessed person is asked to rapidly name the colour of 40 squares (blue, red, yellow, or black). In the second part, the assessed names the form of 40 shapes (circles, squares, triangles, or rectangles), whereas in the final part, the assessed names both the colour and forms of 40 coloured shapes. It is a test that takes 3-5 minutes to administer, with no ceiling or floor effect, and is independent of gender, culture, and education. AQT mainly activates temporoparietal cortical areas, which are the major brain regions affected in AD[158].

Verbal Fluency

Both semantic and phonemic fluency tasks are impaired in neurodegenerative disorders such as AD, where individuals with AD dementia are more impaired in semantic tasks than in phonemic tasks[159]. Animal Fluency is a semantic verbal fluency test where the participant is asked to produce as many names of animals as possible in 60 seconds. This test assesses cognitive flexibility in shifting between animal categories, which is related to frontal functioning, as well as clustering related to temporal lobe functioning[133]. Studies have shown that animal fluency can differentiate between amnestic cognitive impairment (aMCI) and cognitively unimpaired (CU)[160]. Phonemic fluency tests or Letter Fluency are based on naming as many words as possible beginning with a certain letter[133]. Imaging studies have shown that frontal damage tends to impair letter fluency, while temporal lobe damage have a greater effect on semantic fluency[161]. In line with this, patients with svPPA or AD have a greater deficit in category fluency than phonemic fluency, fluency[162], while individuals with nfvPPA often have deficits in both letter fluency and category[163]. Age, sex, education and ethnicity have all been found to influence performance on verbal fluency tests[143].

Trail Making Test A & B

The Trail Making Test (TMT) are executive tests assessing scanning, visual conceptual and visuomotor tracking, motor speed and agility, motor-spatial skills, speed of processing, cognitive flexibility, attention and executive functions[164, 165]. In TMT A, there are numbers scattered over a piece of paper and the individual is asked to draw lines between continuous numbers as quick as possible. In TMT B, there are both numbers and letters scattered over the paper and participants are asked to draw lines between letters and numbers alternately (A-1, B-2, C-3 etc.). The time it

takes to fulfil the test is the number of points the individual achieves, i.e. the lower the point the quicker the test result.

Both part A and B are sensitive to the progression in cognitive decline in dementia[166], however, do not distinguish between neurocognitive disorders[133]. Several investigators have examined the relationship between TMT A and B including B–A difference and B:A ratio, to identify which difference in time between the two that is associated with cognitive decline[165]. Early research showed that TMT performance was independent of age, however later studies have showed declining performance with increasing age[167, 168]. Completion accuracy may also be measured as cognitively impaired individuals commit more errors than CU[169]. However, error rate is difficult to interpret in isolation since errors are common among cognitively unimpaired individuals[166].

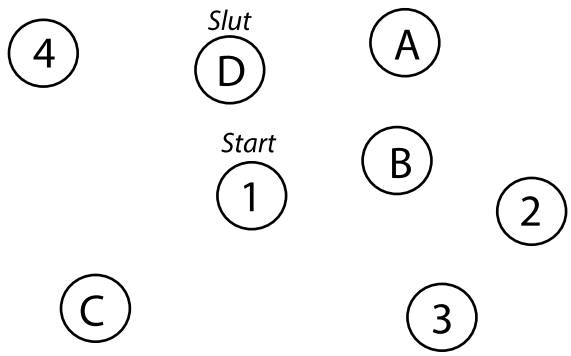

Figure 5.
Practice version of the Swedish Trailmaking Test B

The Stroop Color and Word Test

The Stroop Color and Word Test (SCWT) is a neuropsychological test used to assess the ability to inhibit cognitive interference that happens when the processing of one stimulus is disturbed by a simultaneous processing of another stimulus[170].

The most well-used version of the SCWT consists of three parts. In the first part, the participant is required to read names of colours printed in black ink (words, W), in the second part to anticipate colour names printed in congruent colours and name the colours (C). In the third part, participants are required to name the colours of words in incongruent colours. E.g. if the word "BLUE" is printed in red ink, the participant should say the colour red and therefore inhibit the more automated task. The increased time taken to perform the later task is what is named the Stroop Effect[171]. The test measures speed of visual search, working memory and conflict monitoring[172]. Neuroimaging and electrophysiological studies have shown that the frontal lobe is the region mostly activated during testing[173, 174].

Clock Drawing Test

The Clock Drawing Test (CDT) is a cognitive screening instrument. There are more than a dozen versions of the CDT. In some versions, participants receive a picture of a circle representing a clock face and are asked to put in the numbers so that it looks like a clock and the set the time to 10 minutes past 11. In others, participants receive a blank page assessing freehand drawing[133]. The cognitive skills tested for completing the clock drawing test are auditory comprehension, planning, visual memory and reconstruction in a graphic image, visuospatial abilities, motor programming and execution, numerical knowledge, abstract thinking, inhibition (inhibiting of putting the hands on "10" in the instruction 10 past 11), and concentration tolerance[175].

The CDT is useful in distinguishing between normal cognition and AD dementia and Parkinson's disease and can be useful in distinguishing between FTD and AD[176]. However, the CDT has a low sensitivity and specificity for distinguishing between normal and mild cognitive impairment[177].

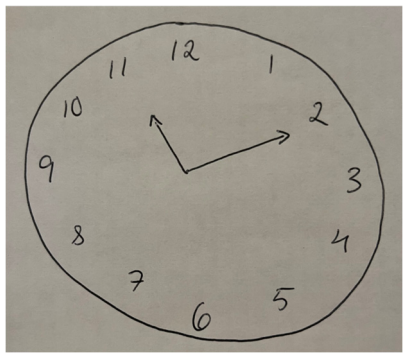

Figure 6.
Clock Drawing Test drawn by cognitively healthy 34-year old.

PACC

The preclinical Alzheimer cognitive composite (PACC)[178] score is a composite score including

1. The Total Recall score from the Free and Cued Selective Reminding Test (FCSRT)
2. The Delayed Recall score on the Logical Memory IIa subtest from the Wechsler Memory Scale
3. The Digit Symbol Substitution Test score from the Wechsler Adult Intelligence Scale-Revised and
4. The MMSE total score

It is a validated scale developed for the measurement of AD-related cognitive decline in unimpaired populations in clinical trials. It was established by including cognitive assessments measuring the three domains: episodic memory, executive function and orientation[179, 180].

Others

The cognitive assessments discussed in this thesis are only a fraction of available tests when assessing individuals with cognitive symptoms. To comprehensively investigate cognitive symptoms in for example younger individuals or individuals with atypical symptoms, broader neuropsychological testing is recommended. However, such extensive assessments falls beyond the scope of this thesis and is not addressed here.

Rating scales

Clinical Dementia Rating Scale

The Clinical Dementia Rating Scale (CDR) is a scale used for assessment of individuals with cognitive impairment for longitudinal studies and clinical trials[181]. The assessment involves a semi-structured interview with both the individual and an appropriate informer. The evaluation covers 6 subscales: memory, orientation, judgement and problem solving, social activities, home and hobbies and personal hygiene. Each subscale is rated on a scale from 0 to 3 points. There are two different methods for calculating total scores: the CDR-global score, an overall average score that weights the different subscales based on clinical importance (weighting memory highly), and CDR-sum of boxes (CDR-SB), where the total sum of all subscales is calculated.

Global Deterioration Scale

The Global Deterioration Scale (GDS)[182] is a global severity measure that categorizes subjects with neurodegenerative diseases for clinical trials and helps evaluate efficacy of pharmacological and nonpharmacological treatments[183]. It consists of seven stages, where 1 equals “no cognitive decline”, 3 equals “mild cognitive impairment” and 7 equals “severe dementia”. It measures global cognitive decline over time.

Imaging

CT/MRI

An important part of the diagnostics of a person with cognitive symptoms is cerebral imaging. The most important reason for conducting imaging is to rule out other

causes of cognitive impairment such as cerebral insults, tumour, normal pressure hydrocephalus, hematoma, abscess etc. However, when diagnosing neurocognitive disorders, it is helpful to see which parts of the brain have been affected and if there is underlying vascular disease with white matter lesions and/or lacunar infarctions.

White matter lesions can be seen in a normal aging brain and are associated with cerebrovascular risk factors. However, there is also a relationship between age-related white matter lesions and cognitive impairment in demented patients[184]. To assess the degree of age-related white matter changes from imaging, the Fazekas score (0-3 points) is applied to quantify white matter changes in the brain. The score is then age-correlated, where higher Fazekas scores are considered normal for older individuals.

Atrophy of the brain is also graded in scores of global cortical atrophy (GCA) (0-3 points), posterior atrophy (PA) (Koedam scale; 0-3 points) and medial temporal lobe atrophy (MTA) (Scheltens score; 0-4 points)[185].

In classic AD, the earliest atrophy on magnetic resonance imaging (MRI) is visualized in the hippocampi in the medial temporal lobe and precuneus in the parietal lobe[186]. In DLB, medial temporal atrophy is milder than in AD, however medial temporal volume is significantly smaller than in normal elderly individuals[187].

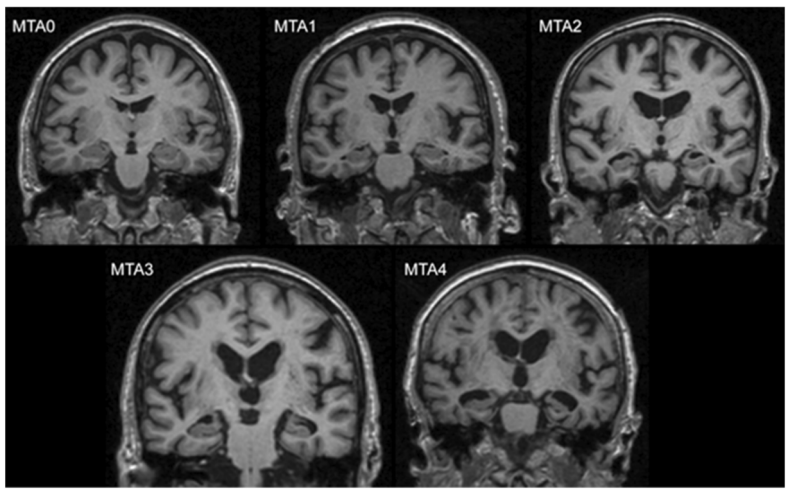

Figure 7.
Medial temporal lobe atrophy (MTA) with increasing severity (grade 0-4). Copyright © Eur Radiol, Velickaite et al., 2017[188]. Distributed under the terms of Creative Commons Attribution 4.0 International License (http://creativecommons.org/licenses/by/4.0/).

MRI can detect frontal or anterior temporal volume loss in bvFTD and atrophy in temporal poles in svPPA[187, 189]. For nfvPPA, regional brain atrophy is often seen in posterior part of left frontal lobe including Broca's area and insula regions[190].

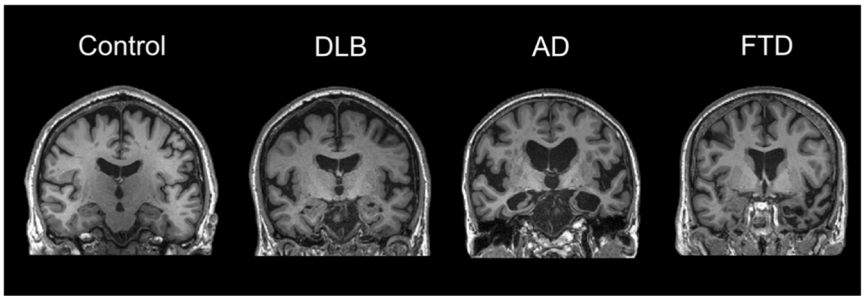

Figure 8.
The figure shows MRI scans from a healthy control and from patients with dementia with Lewy bodies (DLB), Alzheimer's disease (AD) and frontotemporal degeneration (FTD). The figure shows the characteristic patterns of atrophy with relative preservation of hippcampi in DLB, severe hippocampal atrophy in AD, and temporal pole atrophy in FTD. Copyright © Springer Nature, Chouliareris and O'Brien 2023[191]. Distributed under the terms of Creative Commons Attribution 4.0 International License (http://creativecommons.org/licenses/by/4.0/).

Functional imaging

The term "functional imaging" is used to describe approaches to evaluate brain function as opposed to brain anatomy. Individuals undergoing functional imaging receive tracers with 18-flourdeoxyglucose, amyloid tracers or tau tracers. Functional imaging aids in the diagnostics and understanding of neurodegenerative diseases. Single Photon Emission Tomography (SPECT) and Positron Emission Tomography (PET) are both emission tomographic techniques. The major difference between the two is the nature of the radionuclide associated with the carrier molecule. The radionuclides used in SPECT are single-photon emitters, emitting one photon at a time which can travel in any direction from its site of emission. For PET, positrons are used, which are particles with a positive charge rapidly combining with an electron resulting in two photons travelling in opposite directions[192].

FDG-PET can help distinguish between AD and DLB[193]. In AD, a typical pattern of metabolic reduction involves parietotemporal regions and the precuneus/posterior cingulate complex, however, other variants show distinctive focal hypometabolism[194]. In DLB, typical findings in FDG-PET imaging are hypometabolism in medial occipital lobe, anterior temporal lobes, orbitofrontal regions and caudate nucleus. The cingulate island sign (spared middle-to-posterior cingulate) is supportive for the diagnosis of DLB, whereas in AD, the glucose uptake in occipital lobes is preserved[187].

In FTD, frontal and anterior temporal glucose metabolism has a characteristic reduction, however medial temporal, striatal and thalamic reduced metabolism can

also be seen[187]. In svPPA, a severely decreased and asymmetric temporal metabolism can be seen in FDG-PET images, whereas in nfvPPA, decreased cerebral metabolism are seen in posterior left frontal lobe, including Broca's area and insula regions[187].

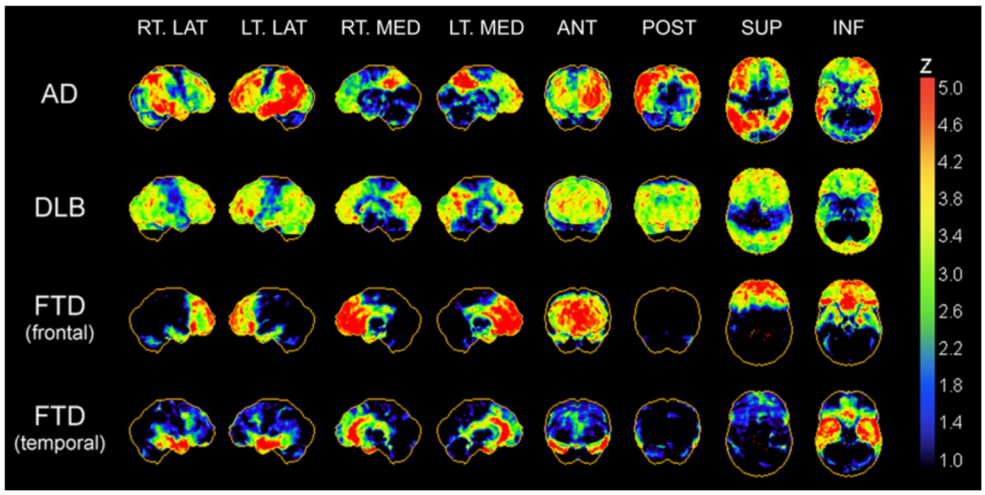

Figure 9.
Typical regional cerebral 18F-FDG hypometabolism patterns in AD, DLB and frontal FTD (bvFTD) and temporal FTD (svPPA), presented as z-score maps based on significantly hypometabolic voxels compared to nondemented comparison population. This research was originally published in JNM and reprinted with permission from JNM. Bohnen et al. Effectiveness and Safety of 18F-FDG PET in the Evaluation of Dementia: A Review of the Recent Literature[195]. J Nucl Med. 2012;vol 53:65. © SNMMI.

The Pittsburgh Compound-B (^{11}C-PiB PET) is a derivative of the amyloid-binding dye thioflavin-T and the mostly validated tracer for amyloid in PET-scans. However, as ^{11}C has a very short half-life it can only be used in centres with cyclotron and radiopharmacy facilities. Instead, the most widely used radionuclide for clinical practice is ^{18}F-flutemetamol which has a longer half-life and can be delivered from radiopharmaceutical companies to multiple PET centres. In a positive scan for AD, the medial orbitofrontal, posterior cingulate gyrus/precuneus, striatum, lateral temporal or parietal grey matter can show increased tracer uptake. The cerebellar grey matter, medial temporal region, visual cortex and primary sensorimotor cortex show less acculumation[196].

Since PET tracers have been incorporated in research and clinical studies for AD, there have been several PET tracers used for binding to tau. ^{18}F-flortaucipir (^{18}F-AV1451), is a benzimidazole pyrimidine derivative and the most widely studied tau PET tracer binding to both 3R and 4R tau isoform in AD patients[196, 197]. Specifically, ^{18}F-flortaucipir binds to paired helical filaments, tau-containing NFTs and dystrophic neuron in AD brains, whereas its binding is low in straight filaments, α-synuclein deposits, and TDP-43 deposits[198]. In patients with AD, there is a

significantly higher level of tau tracer retention in the medial, inferior and lateral temporal lobe, posterior cingulate and lateral parietal regions[196].

A dopamine transporter scan (DaTscan), based on SPECT-imaging is a sensitive method for detecting presynaptic dopamine neuronal dysfunction[199]. However not specific, in DLB, it shows decreased uptake in basal ganglia which can aid in differentiating between AD and DLB[200].

Other diagnostic tools

EEG

An electroencephalogram (EEG) is currently a supportive biomarker in the diagnosis of DLB where the EEG can show a typical pattern of posterior slow-wave activity with periodic fluctuations in the pre-alpha/theta range[201]. In AD, patients generally show slowing in parieto-occipital regions[202]. In clinical practice it is however very seldom used as a diagnostic method for neurodegenerative diseases but mainly for demonstrating epileptic activity in comorbid epilepsy and dementia, though this adds limited diagnostic value[203].

PSG

A polysomnography (PSG) can be done when patients describe sleep disorder symptoms such as living out their dreams. RBD is often found in the very earliest stages of synucleinopathies such as Parkinson's disease, DLB or MSA[204].

123-MIBG scintigraphy

In LBD, degeneration of cardiac postganglionic sympathetic innervation occurs which leads to decreased uptake of 123Iodine during myocardial scintigraphy (MIBG). This can be a sensitive and specific method to differentiate patients with LBD from AD and other dementias when compared to SPECT[74].

CSF and blood biomarkers and tests

As neurocognitive disorders are a challenge to diagnose clinically, biomarkers play an increasing role for the diagnosis. CSF biomarkers measured for the investigation of neurocognitive disorders include measures of beta-amyloid (such as the Aβ42/Aβ40 ratio), total tau (t-tau), phosphorylated tau (p-tau), and neurofilament light (NfL), aiding clinicians in diagnosing individuals with neurocognitive disorders. NfL is a non-specific marker of axonal neurodegeneration which is seen to be elevated in most neurocognitive disorders. In AD, elevated levels of tau and phosphorylated tau in combination with reduced levels of soluble Aβ42 distinguish AD patients from healthy controls based on imaging[205] and also correlate with AD

pathology at autopsy[206]. The above markers for neurodegenerative disease is however not specific for symptoms of disease, as Aβ positivity in CU individuals between 50-90 years of age is estimated to be around 10-44%[207] and presence of either Aβ, tau pathology or neurodegeneration in CU individuals at the age of 65 has an estimated prevalence of 44% and at the age of 85 of 86%[208].

Though CSF biomarkers and PET-based measures are available, their use is not widespread as they are costly and invasive. As a result of the development of ultra-sensitive analysis, it is now possible to screen for biomarkers in blood. Plasma p-tau has so far appeared to be the best marker for symptomatic AD (prodromal AD and AD dementia). For preclinical AD it should however be combined with Aβ42/Aβ40[209]. The most researched biomarkers for tau to date are p-tau181, p-tau217 and p-tau231, which correlate with post-mortem AD pathology, differentiate AD from other neurocognitive disorders, and predict progression from cognitively unimpaired or MCI to AD[58]. Even NfL is measurable in blood. Although not patognomic for any certain neurocognitive disorder, levels have been shown to be higher in FTD than in AD[210] and it could potentially be used as a blood test to monitor the effects of disease-modifying therapy[211].

Treatment aspects and clinical studies for cognitive symptoms

Up until recently, the main treatment for cognitive impairment has been symptomatic treatment for cognitive symptoms in AD, PDD and DLB using cholinesterase inhibitors (donepezil, galantamine and rivastigmine) and non-competitive N-Methyl-D-Aspartate-receptor antagonist (memantine) for AD. Drug targets for potential disease-modifying therapies have focused on the amyloid cascade with potential BACE inhibitors, anti-Aβ monoclonal antibodies or anti-Aβ vaccine, tau aggregates with active or passive tau immunization and several other potential targets[212, 213].

For VCI and VaD, treatment is based on treating vascular risk factors for preventing further vascular events which in its turn could worsen cognitive symptoms. Genetic factors can however supersede a healthy lifestyle[102]. For patients with VaD and behavioural and psychiatric symptoms of dementia (BPSD), memantine is sometimes used in clinical practice to relief symptoms.

There are today (2024) no available medications that can slow progressions of FTD, though there are therapies for genetic types of FTD that are moving into clinical trials[214].

Recently, disease-modifying treatment for Alzheimer's disease with amyloid antibodies have been developed. In the future, this will mean an assumed increased

number of individuals with cognitive symptoms seeking healthcare for their cognitive symptoms. Therefore, it is increasingly important for healthcare professionals to have knowledge to perform and interpret cognitive test results. They must also be adept at how to deciding which patients to refer to specialized clinics and determining which patients should receive disease-modifying treatment.

Aims of thesis

- The first aim of this thesis was to improve diagnostic methods for detecting cognitive impairment. This was aimed to be achieved through establishing robust cutoffs using test results from cognitively healthy people and people with cognitive symptoms who were followed over time. We hypothesized this could improve earlier diagnostics, for earlier treatment and/or preventative medications, and, when appropriate, inclusion in pharmaceutical studies.
- The second objective was to investigate methods for improved prediction of cognitive decline and dementia, which could help clinicians and researchers interpret test results in individuals who are followed longitudinally. Furthermore, this may aid in differentiating between individuals that could be treated and followed in primary care and individuals that should be referred to a secondary care facility for further evaluation and follow-up.

Table 2. Research at a glance

	Paper I	Paper II	Paper III	Paper IV
Aim	To establish normative data for the Swedish MoCA.	To establish normative data for commonly used cognitive tests and evaluate different neuropathologies' effect on age-related cognitive decline	To establish MCIDs for brief cognitive tests.	To establish a two-step model for predicting all-cause dementia.
Methods	We included 758 cognitively healthy people from the Malmö Diet and Cancer Study. We used linear regression models for testing predictors for MoCA score. Mean scores where calculated depending on age and education. Significant covariates were entered into a multivariate regression model with MoCA as the dependent variable. We calculated predicted z-scores and percentiles from the multivariate regression model.	We included 297 cognitively unimpaired individuals from the Swedsh BioFINDER study. We calculated correlation coefficients for age and test results and years of education and test results with Spearman correlation in different groups depending on pathology. Cut-offs for cognitive impairment for the cognitive tests were calculated.	We included 451 cognitively unimpaired individuals, 90 people with subjective cognitive decline and 361 people without symptoms of cognitive decline from the BioFINDER study. We calculated triangulated MCIDs. We used logistic regression models for examining how differences in cognitive test scores predicted a minimal clinically relevant change, using the clinical dementia rating-sum of boxes scale as outcome.	We included 612 individuals from ADNI with SCD or MCI and 392 individuals from BioFINDER-1 with SCD or MCI. For selecting the best model for predicting dementia, we used an R-package called MuMin. We examined prediction of progression to dementia within 4 years using logistical regression and ROC. Using the logistic regression model we created an app for calculating individualized risk for dementia progression.
Results	MoCA cut-offs (–1 to –2 SDs) for cognitive impairment ranged from <25 to <21 for the lowest educated and <26 to <24 for the highest educated, depending on age group.	Participants without any underlying measurable pathology achieved better test scores and significantly stricter cut-offs for cognitive impairment for the cognitive tests ADAS delayed word recall, Animal Fluency, AQT, Stroop, TMT A, TMT B and SDMT. The age-effect disappeared for most tests mainly explained by cerebrovascular pathology.	We identified potential MCIDs for several commonly used brief cognitive assessments for cognitively unimpaired and participants with mild cognitive impairment.	We found the best model to predict a progression from SCD or MCI to dementia within 4 years included five cognitive tests as predictors: ADAS delayed recall, ADAS immediate recall, Animal Fluency, Trailmaking Test A and Trailmaking Test B. The model's PPV in ADNI was 85.8% and NPV 92.2%, verssus 62.5% and 95.6% when replicated in BioFINDER-1.
Conclusions	Individuals with older ages or lower education levels have lower cutoffs for the Swedish MoCA.	Most age-related cognitive decline on cognitive assessments is caused by underlying neuropathology, especially cerebrovascular pathology.	MCIDs can potentially be used in clinical practice or research studies when following individuals longitudinally.	We established a two-step model for predicting progression to dementia within 4 years and created an app for online calculation of individualized risk of conversion.

Methods

Study settings

The EPIC study

The European Prospective Investigation into Cancer and Nutrition (EPIC) study (https://epic.iarc.fr/) is one of the largest cohort studies in the world with more than half a million participants recruited. It was designed to investigate the relationships between diet, nutritional status, lifestyle and environmental factors and the incidence of cancer and other chronic diseases. In Sweden, the Malmö Diet and Cancer study (MDCS) recruited 28,098 participants between 1991-1996 and became associated with EPIC in 1993. As a part of the baseline examination, about 6000 men and women were included in additional investigations directed towards identification of risk factors for cardiovascular disease, where baseline cognitive assessments were included in baseline examinations.

The BioFINDER study

The Swedish BioFINDER study (www.biofinder.se) was initiated to discover key mechanisms in cognitive diseases such as Alzheimer's disease, Parkinson's disease and other neurodegenerative disorders. The aims of the study are to develop methods for early and accurate diagnosis of Alzheimer's disease and Parkinson's disease, to investigate the heterogeneity of dementia and parkinsonian disorders, assist in developing pathology-based disease classification, define temporal evolution of pathologies in the predementia phases in neurodegenerative diseases, and to examine underlying disease mechanisms of AD and PD. Participants are consecutively included from the memory and neurology clinic at Skåne University Hospital as well as from the memory clinic in Ängelholm.

The Alzheimer's Disease Neuroimaging Initiative

The Alzheimer's Disease Neuroimaging Initiative (ADNI) (https://adni.loni.usc.edu/) is a longitudinal multicentre study designed for developing clinical, imaging, genetic, and biochemical biomarkers for the early

detection and tracking of Alzheimer's Disease (AD). The goals of the ADNI study are to detect AD at the earliest possible stage, identify ways to track the disease's progression with biomarkers, to support advances in AD intervention, prevention and treatment and to continually administer ADNI's innovative data-access policy which provides all data without embargo to all scientist in the world.

Study designs

Paper I

The MoCA was administered to 860 randomly selected elderly people from a population-based cohort, Malmö Diet and Cancer Study, from the EPIC study. Cognitive dysfunction was screened for using the MMSE and AQT. Participants who scored below 24 points on the MMSE, took >90 seconds to complete the AQT, or reported symptoms of cognitive impairment, were invited for a clinical investigation at the Memory Clinic of Skåne University Hospital. After excluding cognitively impaired participants, normative data was collected from 758 people, aged 65–85.

Paper II

We conducted a study on 297 cognitively healthy elderly people from the BioFINDER study and created subgroups excluding people with signs of underlying neuropathology, i.e., abnormal cerebrospinal fluid [CSF] β- amyloid or phosphorylated tau, CSF neurofilament light (neurodegeneration), or cerebrovascular pathology. We compared cognitive test results between groups and examined the effect of age on cognitive test results.

Paper III

From the Swedish BioFINDER cohort study, we consecutively included cognitively unimpaired (CU) individuals with and without subjective or mild cognitive impairment (MCI). We calculated MCIDs associated with a change of ≥0.5 or ≥1.0 on the Clinical Dementia Rating-sum of boxes (CDR-SB) for MMSE, ADAS-cog delayed recall 10-word list, Stroop, Letter S Fluency, Animal Fluency, Symbol Digit Modalities Test (SDMT) and Trail Making Test (TMT) A and B and triangulated anchor- and distribution-based MCIDs for clinical use for MCI and amyloid positive and negative CU individuals. For investigating cognitive measures that best predict a change in CDR-SB of ≥0.5 or ≥1.0 point we conducted ROC analyses.

Paper IV

For creating a predictive score for individuals with mild cognitive symptoms, we included 612 participants with SCD or MCI from ADNI who had been assessed

longitudinally with cognitive assessments. Participants were followed for at least 4 years, or until progression to dementia. In R (4.2.2), we performed model selection using the MuMin-package (Multi-model Inference) to find the best model fit. We imputed all cognitive test results as well as participants gender, age, and education. After finding the best model to predict dementia and non-progression to dementia, we replicated our results in 392 participants from BioFINDER-1 with SCD or MCI.

Statistics

Paper I

For establishing normative data on the Swedish MoCA-test, we used chi-square tests and the Mann-Whitney U test for group comparisons for cognitively normal and cognitively impaired individuals. The independent variables impacting the total MoCA score were analysed using linear regression. Sex, age, level of education, lipid lowering medication, cardiovascular medication, diabetes medication and smoking were entered separately into linear regression models with MoCA as the dependent variable using a stepwise method. After finding out which covariates significantly impacted MoCA test scores, significant covariates were tested using quadratic, cubic and logarithmic models and analysed for interaction effects. The significant covariates were thereafter entered into a multivariate regression model with MoCA as the dependent variable and we calculated predicted z-scores and percentiles using the intercept, estimates and the Root Mean Square Error (RMSE) from the multivariate regression model. For analysis of all data, we used SPSS (Released 2013. IBM SPSS Statistics for Macintosh, Version 22.0, NNY: IBM Corp).

Paper II

In paper II we calculated mean scores and standard deviations for TMT A and TMT B, SDMT, Stroop, Animal Fluency, AQT, ADAS-delayed recall 10-word list and ADAS naming. We calculated correlation coefficients for age and test results and years of education and test results with Spearman correlation (rank correlation coefficient). Association between gender and test results were calculated with Mann-Whitney U tests.

Due to fewer individuals in certain groups, we wished to investigate if the absence of significant correlation was due to lack of statistical power and therefore conducted boot-strap analysis with 500 bootstraps from 100 individuals to make sure a larger cohort wouldn’t result in finding significance.

We used multivariable linear regression for calculating associations between groups and cognitive test results and controlled for age, education, and gender, using tests score as the outcome and disease pathology as the predictors.

Cut-offs for cognitive impairment for the cognitive tests were determined at +/- 1.5 standard deviations to or from the group means depending on whether the aim of the test is to achieve as many or as few points as possible.

All the above analysis apart from bootstrapping were conducted in SPSS Statistics version 25. Confidence intervals for the cut-offs and correlation coefficients were estimated from 500 bootstrap samples using R Version 3.5.2.

Paper III

In paper III we investigated distribution-based and anchor-based approaches for MCIDs.

The psychometric criterion "reliable change index" (RCI) evaluates whether a change over time of an individual score is considered statistically significant. The RCI provides a confidence interval representing the predicted change that would occur if a patient's test score does not change significantly from one assessment to another. RCIs were calculated with the following equation for eight test differences (MMSE; ADAS naming, ADAS-delayed recall 10-word list, TMT A, TMT B, Stroop, Animal Fluency and Letter S Fluency):

$$SEM = SD\sqrt{1 - r}$$

$$SEdiff = \sqrt{2 * (SEM)^2}$$

$$RCI = \pm SEdiff * 1.64$$

Figure 10. SD = Standard deviation of the test score at baseline, r = Pearson coefficient for test results in cognitively stable individuals. SEM = standard error of measurement. SEdiff = standard error of differentiation

Effect size (ES) helps determine the size of an effect, the relative contribution of a factor in different circumstances and the power of the analysis[215]. ES is defined as mean difference in score divided by standard deviation of baseline scores. An ES of 0.2 is considered a small change, 0.5 a moderate change and 0.8 a large change[216].

The standardized response mean (SRM) is another effect size which measures the responsiveness of outcome measures (the ability to detect change over time). SRM is defined as mean difference in score divided by SD of the change from previous visit score.

For the anchor-based approach, we analysed mean differences in cognitive test scores anchored to changes in Clinical Dementia Rating-Sum of Boxes (CDR-SB). For cognitively unimpaired individuals, we used a change of CDR-SB of ≥0.5 points

and for the MCI group a change of ≥1 point as anchors to represent a clinically meaningful change. We calculated the mean, SD, and ES for changes in the cognitive tests separately for meaningful decline (CDR-SB difference of ≥0.5 and ≥1) and no meaningful decline (CDR-SB difference of 0).

We thereafter triangulated our calculated MCIDs to produce a final MCID for each cognitive test, for cognitively unimpaired and cognitively impaired individuals, integrating both results. We estimated our anchor-based MCIDs from ES and our distributions-based MCIDs on Standard Error of Measurement (SEM). Because an ES of 0.5 is generally considered a clinically significant change, we used the estimated anchor-based MCID with the ES closest to 0.5.

For the second part of article III, we wished to analyse which cognitive test best predicted a clinically meaningful change. We used cognitive tests as well as age, education and gender as predictors and a change of CDR-SB as outcome (0 as no change and ≥0.5 point change for the CU group and ≥1 point for MCI group) and performed logistic regression models on a subsample with complete data of the cognitive tests, and identified the model with the lowest Akaike Information Criterion (AIC) including predictors with a p-values <0.1. We calculated sensitivity and specificity for test differences using ROC analyses.

Paper IV

In paper IV, we examined prediction of conversion to dementia within 4 years using logistical regression and receiver operating characteristics (ROC). The predictors examined to predict future conversion to dementia were age, gender, years of education as well as test results of cognitive assessments: MMSE, ADAS delayed 10-word recall test, ADAS immediate recall, ADAS Naming Objects and Fingers, ADAS Constructional Praxis, Trail Making Test A, Trail Making Test B, Animal Fluency, Clock Drawing Test, an Copy Clock Test.

For selecting the best model for predicting progression to dementia, we used a package in R called MuMin (Multi-Model Inference), to identify the combination of predictors with the lowest Akaike Information Criterion (AIC), which is described elsewhere[217]. Thereafter, we used the best predicting model and created a logistic regression model applied to ADNI and BioFINDER-1 to test how well the model predicted dementia. We applied thresholds for high and low probability of progression to dementia set at 95% specificity and 95% sensitivity. For participants who scored with intermediate risk, between the two cutoffs for high and low risk, we performed a second model including 1-year changes in test results as a covariate. The probability cutoff for the second step was set at 90% sensitivity to achieve a higher NPV. All statistics in paper IV were conducted in R programming language (ver 4.2.2).

Finally, using the logistic regression model, we created an application for predicting individual's risk for progression to all-cause dementia within 4 years.

Main results

Paper I

Baseline results

Out of 860 individuals included from the Malmö Diet and Cancer Study, 134 people scored above 90 seconds on AQT, below 26 points on MMSE or reported cognitive symptoms and were clinically examined at the Memory Clinic för further investigation. 31 of these people were assessed as cognitively healthy and included to the study cohort. 73 people declined further examination, 18 people were diagnosed with MCI and 11 people with dementia. The final population included 758 cognitively healthy people, 474 were women and 284 were men. The mean age for women was 73.3 (SD 5.2) and for men 72.7 (SD 5.0). We found significant differences in the normative group and the excluded group's education level and mean age as well as significant differences in scores in MMSE, AQT and MoCA (every subtest and total score).

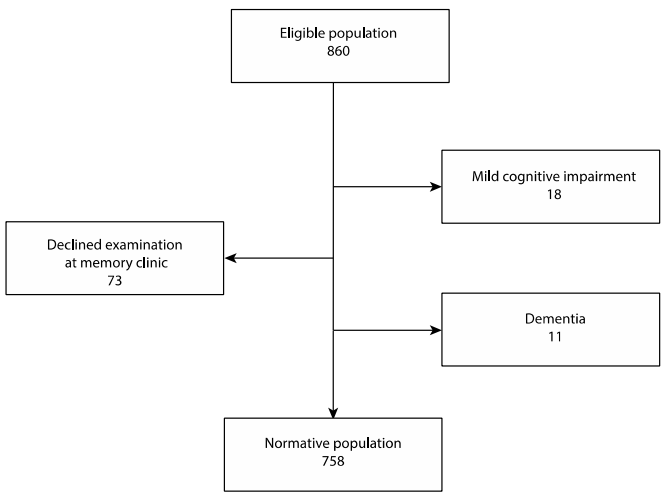

Figure 11.
Flow chart of the enrollment process.

Table 3.
Demographics of the study population.

	Normative group	Excluded group	P-value
Age (SD)	73.1 (5.1)	75.5 (5.7)	**<0.0001**
Use of medication, n (%)			
Cardiovascular	409 (54.0)	41 (40.2)	0.266
Anti-diabetes	60 (7.9)	12 (11.8)	0.188
Lipid lowering	218 (28.8)	37 (36.3)	0.119
Education level (%)			
*Primary school**	63.9	79.2	**0.002**
*Secondary school***	20.8	13.9	
*Higher education****	15.3	6.9	
Smoking (%)			
Yes, I smoke or have smoked	54.8	52.5	0.665
No, I have never smoked	45.2	47.5	
MMSE score, mean (SD)	27.9 (1.4)	24.9 (3.1)	**<0.0001**
AQT score, mean (SD)	69.9 (13.1)	107.2 (29.8)	**<0.0001**
MoCA total score, mean (SD)	26.0 (2.3)	21.6 (4.3)	**<0.0001**
Visuospatial/Executive abilities	4.1 (1.0)	2.9 (1.4)	**<0.0001**
Naming	2.9 (0.3)	2.7 (0.7)	**<0.0001**
Attention digits	1.8 (0.5)	1.4 (0.6)	**<0.0001**
Attention letters	1.0 (0.1)	0.9 (0.2)	**0.007**
Attention subtraction	2.9 (0.3)	2.3 (1.0)	**<0.0001**
Language repeat	1.9 (0.4)	1.4 (0.8)	**<0.0001**
Language fluency	0.7 (0.5)	0.3 (0.5)	**<0.0001**
Abstraction	1.7 (0.6)	1.4 (0.8)	**<0.0001**
Delayed recall	3.1 (1.3)	2.3 (1.5)	**<0.0001**
Orientation	6.0 (0.2)	5.8 (0.6)	**0.002**
Abnormal MoCA score according to original cut-off (<26), (%)	37.3	78.4	**<0.0001**
Total	758	102	

Swedish normative data for MoCA

We established MoCA cut-offs (–1 to –2 standard deviations) for cognitive impairment, finding a range from <25 to <21 for the lowest educated and <26 to <24 for the highest educated, depending on age group. Here, we did not add an extra point for individuals with and education ≤12 years.

Table 4.
Raw MoCA-scores not including an extra point for low education.

		Education level		
Age group	SD below mean	Primary school	Secondary school	Higher education
65-75	≤1	≤24	≤25	≤25
	≤2	≤21	≤23	≤24
70-80	≤1	≤23	≤24	≤25
	≤2	≤21	≤22	≤23
75-85	≤1	≤22	≤23	≤25
	≤2	≤20	≤21	≤23

Arrows show cut-offs at -1 SD (yellow) and -2 SD (red) below the mean MoCA score. Cut-offs correspond to the DSM-5 criteria where major neurocognitive disorders s typically perform ≥2 SD below appropriate norms, and mild neurocognitive disorders typically perform in the 1-2 SD range. Select the age group where age is centred midmost in the age interval. SD, standard deviation.

We found that the significant predictors for MoCA score were age, sex and level of education in multivariate and univariate models and created a table for using in clinical practice and an online regression-based calculator, providing percentiles and z-scores for subject's MoCA score.

Summary

This is the first study publishing normative data for the Swedish version of the MoCA and is presented with a table stratified by age and education level, as well as with an online regression-based calculator, providing percentiles and z-scores for a subject's MoCA scores. The highest educated (university degree) in all age groups (65-75, 70-80, 75-85 years), the youngest (65-75 years old), and age group 70-80 years with secondary school level or higher, had a cut-off at 25-26 points in line with the previous suggested cut-off for MCI at 26 points (or 25 points if education <12 years). Meaning, our cutoffs could mainly be of importance when assessing an individual with lower education in higher age groups.

Paper II

Baseline results

Paper II included 297 cognitively healthy elderly individuals (cohort A) from the BioFINDER study and created subgroups excluding people without signs of progression in cognitive symptoms through measures of the Clinical Dementia Rating (CDR) for at least 2 years (cohort B, N=278), without abnormal

cerebrospinal fluid in measures or β-amyloid or phosphorylated tau (cohort C, N=205), without vascular pathology (cohort D, N=161) and one group without any underlying measurable pathology (cohort E, N=112). The total study population (cohort A) had a mean age of 73.5 years (range: 64-88 years of age) and education of 12.3 years. 60.4% were women and 39.4% were men.

Table 5.
Demographics of the population.

	A. Study Cohort	B. No Progress in CDR	C. No Amyloid or Tau Pathology	D. No Vascular Pathology	E. No measurable in-vivo pathology
Participants, N	297	278	223	161	120
MMSE score, mean (SD)[a]	29.1 (0.9)	29.1 (0.9)	29.1 (0.9)	29.1 (0.9)	29.1 (0.9)
Age, mean (SD)	73.5 (5.0)	73.4 (5.0)	73.4 (5.0)	72.5 (4.6)	72.2 (4.6)
Education years, mean (SD)	12.3 (3.7)	12.3 (3.8)	12.2 (3.6)	12.5 (0.9)	12.6 (3.5)
Gender, %					
Male	39.4%	38.8%	39.5%	41.6%	42.5%
Female	60.6%	61.2%	60.5%	58.4%	57.5%
APOE ε4 (≥1 allele)	27.3%	25.9%	16.3%	30.8%	20.3%
Prevalence of abnormal biomarkers					
CSF Aβ42/40 <0.059	24.9%	23.0%	0%	24.2%	0%
CSF P-tau >28 pg/mL	15.2%	13.3%	0%	14.3%	0%
Log CSF NfL >3.33 pg/mL	2.4%	1.8%	2.2%	1.2%	0%
White matter lesions[b]	45.5%	43.9%	44.8%	0%	0%
≥1 Cortical infarctions	1.3%	1.1%	1.7%	0%	0%
Comorbidity					
Hypertension	43.4%	42.8%	43.5%	41.0%	43.3%
Diabetes	10.1%	10.4%	9.4%	11.2%	10.0%
Ischemic heart disease	6.7%	6.8%	6.3%	4.3%	2.5%

Normative scores

We found that participants without any underlying measurable pathology (cohort E) achieved better test scores and significantly stricter cut-offs for cognitive impairment for almost all the examined cognitive tests (ADAS delayed word recall, Animal Fluency, AQT, Stroop, TMT A, TMT B and SDMT). Only ADAS naming did not show a significantly better score in cohort E compared to cohort A. We found significantly improved cutoffs in cohort E compared to the traditional method

of creating robust norms (cohort B) for Animal Fluency, TMT A, TMT B and SDMT.

Table 6.
Cutoffs (1.5 SD from mean) created with bootstrap analysis.

	Cohort A cutoffs (95% CI)	Cohort B cutoffs (95% CI)	Cohort E cutoffs (95% CI)
ADAS-delayed recall	**4.88 (4.59 – 5.16)**	4.38 (4.13 – 4.61)	3.93 (3.63 – 4.20)
ADAS-naming	1.57 (1.42 – 1.71)	1.44 (1.29 – 1.58)	1.25 (1.01 – 1.48)
Animal fluency	**13.5 (13.1 – 13.9)**	**14.0 (13.6 – 14.4)**	15.0 (14.4 – 15.7)
CDT	3.57 (3.47 – 3.68)	3.62 (3.52 – 3.73)	3.66 (3.50 – 3.83)
AQT	**85.3 (83.6 – 86.9)**	83.5 (81.8 – 85.2)	80.0 (77.8 – 82.1)
Stroop	**40.0 (39.0 – 40.9)**	39.0 (38.0 – 39.8)	36.9 (35.1 – 38.6)
TMT A	**71.5 (69.2 – 73.9)**	**71.3 (68.9 – 73.8)**	59.0 (56.5 – 61.2)
TMT B	**180.6 (172.1 – 189.0)**	**176.0 (167.8 – 184.4)**	144.6 (135.5 – 152.5)
SDMT	**24.3 (23.7 – 25.0)**	**25.1 (24.4 – 25.8)**	27.2 (26.1 – 28.3)

Bold score represent significantly improved scores (non-overlapping 95% CI) compared to Cohort E.

Correlation of age effect in different groups

The age effect (i.e. older age being associated with worsened test results) in participants without measurable in-vivo pathology (cohort E) disappeared for all cognitive tests, apart from some attention/executive tests (TMT A and B), predominantly explained by the exclusion of cerebrovascular pathology. For all correlation coefficients in the different groups, see Table 7.

Table 7.
Correlation coefficients for age and test results conducted with Spearman correlation.

Cognitive Test	**A. Study Cohort (n=297)**	**B. No Progress in CDR (n=278)**	**C. No Amyloid or Tau Pathology (n=223)**	**D. No Vascular Pathology (n=161)**	**E. No measurable in-vivo pathology (n=120)**
ADAS-delayed recall	0.143*	0.116	0.160*	0.029	-0.008
ADAS-naming	0.142*	0.112	0.135*	0.107	0.044
Animal Fluency	-0.193***	-0.144*	-0.147*	0.024	0.126
AQT	0.224***	0.203***	0.223***	0.016	-0.010
Stroop	0.368***	0.373***	0.386***	0.189*	0.129
TMT A	0.337***	0.331***	0.365***	0.289***	0.289**
TMT B	0.387***	0.375***	0.406***	0.344***	0.340***
SDMT	-0.419***	-0.413***	-0.371***	-0.253**	-0.132

Only significant correlation coefficients are colored. Yellow boxes for coefficients ≥0.1 to <0.2, orange boxes for ≥0.2 to <0.3, red boxes for ≥0.3. *Correlation is significant at the 0.05 level, **correlation is significant at the 0.01 level ***correlation is significant at the 0.001 level.

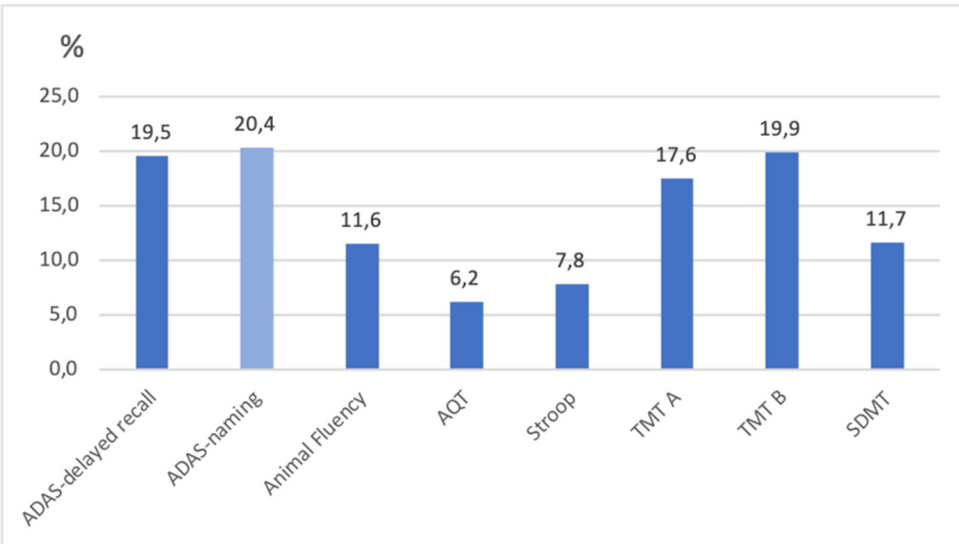

Figure 12. Percent change in test cutoffs (1.5 SD from mean) between the total population and those without measurable brain pathologies

Summary

We illustrated a new approach to establish normative scores on cognitive assessments which could be useful to identify a cognitive change in preclinical cognitive diseases. We also show that the age-related decline in cognitive test results is in many cases caused by underlying pathology and not measures of normal aging and that stratifying cognitive test norms according to age could result in delayed identification of early cognitive decline, especially due to cerebrovascular pathology.

Paper III

Baseline results

In paper III we included 451 cognitively unimpaired (CU) individuals; 90 people with subjective cognitive decline and 361 people without symptoms of cognitive decline (pooled mean follow-up time 32.4 months, SD 26.8, range 12-96 months), and 292 people with MCI (pooled mean follow-up time 19.2 months, SD 19.0, range 12-72 months).

Minimal clinically important differences

We identified potential triangulated MCIDs for cognitively unimpaired and people with mild cognitive impairment on a range of cognitive test outcomes: MMSE -1.5; -1.7, ADAS-delayed recall 1.4; 1.7, Stroop 5.5; 9.3, Animal Fluency -2.8; -2.9, Letter S Fluency -2.9; -1.8, SDMT-3.5; -3.8, TMT A 11.7; 13.0, TMT B 24.4; 20.1. The triangulated MCIDs were calculated by weighting the anchor-based method with two-thirds using the MCID closest to an ES of 0.5 (minimal change). That is: (anchor-based MCID + anchor-based MCID + distribution-based MCID) / 3. The anchor-based method consisted of mean change for a CDR-SB change of ≥0.5 points for CU and ≥1 point for MCI, while the distribution-based method consisted of SEM. For example, the triangulated MCID for MMSE among CU was calculated the following way: (-1.6 -1.6 -1.2) / 3 = -1.5. For clinical practice, MCIDs need to be rounded up to the nearest higher integer to evaluate differences. In Table 8 we present triangulated cutoffs for all the examined cognitive tests.

Table 8.
Triangulated cut-offs for changes in test scores that represents a MCID for MCI participants.

Test	**Triangulated MCID for cognitively unimpaired**	**Triangulated MCID for MCI**
MMSE	-1.5	-1.7
ADAS delayed recall	1.4	1.1
Stroop	5.5	9.3
Animal fluency	-2.8	-2.9
Letter S	-2.9	-1.8
Symbol digit	-3.5	-3.8
TMT A	11.7	13.0
TMT B	24.4	20.1

Abbreviation: ES, effect size; MCID, minimal clinically important difference; SEM; Standard error of measurement.

Predicting composite

Using logistic regression models, we examined how differences in cognitive test scores predicted a minimal clinically relevant change, using the clinical dementia rating-sum of boxes score as the outcome.

For both cognitively unimpaired amyloid positive and amyloid negative individuals, the best predicting univariate test was the ADAS delayed word recall (AUC 0.75) and the worst was Animal Fluency (AUC 0.54). For MCI participants, the best predicting test was MMSE (AUC 0.75) and TMT A was the worst (AUC 0.61).

For cognitively unimpaired (CU) individuals, we found the best model for predicting a change in cognitive decline (discriminating between a change in CDR-SB ≥0.5 points or a change of 0) was combining ADAS delayed recall, MMSE and TMT B (AUC 0.79, 95% CI 0.72-0.86).

For amyloid-positive cognitively unimpaired individuals we found the predicting composite cognitive measure included gender and changes in ADAS delayed recall, MMSE, SDMT, TMT B, after excluding non-significant predictors (AUC 0.87, 95% CI 0.79-0.94).

For participants with MCI, we found the best model to include changes in Stroop, MMSE and age (AUC 0.82, 95% CI 0.76-0.88)

Summary

We have identified potential minimally clinical important differences (MCIDs) for several commonly used brief cognitive assessments for cognitively unimpaired and participants with mild cognitive impairment, which could be applied in clinical practice or clinical trials for evaluating when an actual clinical decline has occurred.

We also presented a composite measure for predicting minimal clinical important change in cognitive decline.

Paper IV

Baseline results

For the first step (predicting progression to dementia within 4 years) in a two-step model, we included 612 participants from ADNI who were classified as SCD or MCI. Mean age for the total cohort was 72.9 years (SD 6.8), 338 (55.2%) were men and 274 (44.8%) were women, mean education years were 16.3 (SD 2.7). We replicated our findings on 392 participants from the BioFINDER-1 study, mean age for the total cohort was 70.9 years (SD 5.5), 202 (51.5%) were men and 190 (48.5%) were women, mean education years at baseline were 11.8 (SD 3.5).

Table 9.
Demographics of included individuals in ADNI and BioFINDER-1.

	ADNI			**BioFINDER-1**		
	Progressing to dementia	Not progressing	p-value	Progressing to dementia	Not progressing	p-value
Number of participants included at baseline	7 SCD, 294 MCI	103 SCD, 208 MCI	p<0.001	24 SCD, 117 MCI	152 SCD, 99 MCI	<0.001
Number of participants included at 1-year follow up	0 SCD, 76 MCI	5 SCD, 89 MCI	p=0.1	12 SCD, 26 MCI	48 SCD, 51 MCI	0.09
Education years (SD)	16.0 (2.8)	16.5 (2.6)	p<0.001	11.3 (3.4)	12.0 (3.5)	0.06
Age (SD)	74.1 (7.1)	71.8 (6.3)	P<0.001	72.2 (5.2)	70.2 (5.5)	<0.05
Sex	124 female, 150 male	177 female, 161 male	p=0.1	80 Male, 61 Female	122 Male, 129 Female	0.14
Tests at baseline (mean, SD)						
MMSE	26.9 (1.8)	28.8 (1.4)	p<0.001	27.1 (1.8)	28.1 (1.7)	<0.001
ADAS delayed recall	7.0 (2.2)	3.4 (2.2)	p<0.001	7.0 (2.0)	4.0 (2.4)	<0.001
ADAS immediate	5.9 (1.6)	3.6 (1.5)	p<0.001	5.4 (1.2)	3.7 (1.5)	<0.001
Animal fluency	15.2 (4.6)	20.4 (5.1)	p<0.001	13.0 (5.0)	19.3 (6.0)	<0.001
TMTA	47.9 (23.6)	33.2 (11.7)	p<0.001	63.3 (23.0)	46.8 (16.5)	<0.001
TMTB	144.4 (78.0)	79.9 (35.3)	p<0.001	133.4 (29.5)	104.7 (27.6)	<0.001

Predicting progression to dementia

We created a model for predicting individual progression to dementia within 4 years. We found the best model to predict a progression from SCD or MCI to dementia within 4 years included five cognitive tests as predictors: ADAS delayed recall, ADAS immediate recall, Animal Fluency, Trail Making Test A and Trail Making Test B. The model was replicated in the BioFINDER cohort and achieved an AUC of 0.86 (95% CI 0.82-0.89).

$$3.86 + 0.408 * ADAS\ immediate + 0.0117 * TMT\ B$$

$$- 0.0747 * Animal\ Fluency - 0.263 * MMSE + 0.315 * ADAS\ delayed$$

Figure 13. Best model in ADNI in step 1.

In the second step of our two-step model, we found that the best model for predicting progression to cognitive disease within the remaining 3 years (as 4 years was our initial outcome) included the tests: TMT B and test result differences between baseline and year one, MMSE and differences in test results, ADAS delayed recall and differences in test results as well as ADAS immediate recall and differences in test results. The model was replicated in the BioFINDER cohort and achieved an AUC of 0.79 (95% CI 0.70-0.88).

$$5.06 + ADAS\ immediate * 0.800 + ADAS\ immediate\ diff * 0.507$$

$$+ TMT\ B * 0.0150 + TMT\ B\ diff * 0.0117$$

$$- MMSE * 0.512 - MMSE\ diff * 0.542$$

$$+ ADAS\ delayed * 0.563 + ADAS\ delayed\ diff * 0.728$$

Figure 14. Best model in ADNI in step 2.

Table 10.
Statistical data using a two-step model for prediction of all-cause dementia in ADNI and BioFINDER-1 in step 1, step 2 and combined steps.

	Step 1		Step 2		Combined steps	
	ADNI	**BF-1**	**ADNI**	**BF-1**	**ADNI**	**BF-1**
Prevalence of dementia conversion	47.2%	34.7%	44.7%	28.6%	46.4%	32.5%
Sensitivity	91.8%	96.1%	90.8%	86.1%	91.5%	92.9%
Specificity	92.6%	79.3%	74.5%	63.3%	86.9%	73.2%
PPV	91.8%	71.2%	74.2%	48.4%	85.8%	62.5%
NPV	92.6%	97.5%	90.9%	91.9%	92.2%	95.6%
Accuracy	92.2%	85.1%	81.8%	69.8%	89.0%	79.6%

Step 1 shows levels calculated from individuals converting versus not converting to dementia within four years in the groups at the >95% sensitivity and >95% specificity level in ADNI and BioFINDER-1 in step 1. Step 2 shows levels calculated from individuals converting versus not converting to dementia within three years in the groups at the >90% sensitivity level in ADNI and BioFINDER-1 in step 2. Combined steps show levels calculated from individuals converting versus not converting to dementia within four years in the groups at the >95% sensitivity and >95% specificity level in ADNI and BioFINDER-1 in step 1 combined with the >90% sensitivity level within three years in step 2. Abbreviations: BF-1: BioFINDER-1.

For individualized risk score calculation, we created an app available at: https://brainapps.shinyapps.io/PredictAllCauseDementia using results from the two-step regression models, for simple insertion of individuals test scores at baseline and follow-up.

Summary

To our knowledge, this is the first predicting model for predicting all-cause dementia, which could potentially be utilized in primary care when assessing patients with subjective or objective cognitive symptoms.

We also trained a model containing measures of temporal volume on MRI and replicated this in BioFINDER-1. As MRI-measures are available in most primary care facilities, this could be a possible interesting model. When we replicated this in BioFINDER-1 however, insufficient participant numbers were available to conduct step-2 of our model. However, even after the first step the NPV was high (97.5%) suggesting this could be a helpful method when evaluating patients that are unlikely to progress to dementia within 4 years, who therefore be given a reassuring message from primary care.

Our application for calculating individualized risk score for progression to dementia within 4 years is available for educational or research purposes.

Discussion

Methodological considerations

Research design

For all studies in this thesis, longitudinal studies have been used, however only cross-sectional data was used in paper I and II. Longitudinal studies are observational studies that involve continuous or repeated measures to follow individuals over a long time. They have the advantage when studying cognition to see overtime fluctuations in cognitive test results and changes in Clinical Dementing Rating (CDR), which would not be captured in a cross-sectional study. If participants have daily fluctuations, this however is not considered even in the longitudinal study design.

When studying cognition over time, there is a large risk that only the healthiest people remain in the study for several years, and that the missing cases at follow-up are mostly individuals dropping out due to developing illness or cognitive impairment throughout the study. Longitudinal studies in concept study individuals without manipulating the study group. For our studied population, there could be certain factors which keep individuals reminded of their cognitive health at annual visits and are reminded to keep track on their personal risk factors such as cardiovascular risk factors. This is of course positive for the individuals in the study but could however introduce study biases.

Another limitation in longitudinal studies for neurodegenerative disease, is that the same individuals are to repeat the same cognitive measures over time. Consequently, there could be some practice effect when participants recall tests from the previous assessment and understand instructions quicker when being reminded than participants undergoing a cognitive assessment for the first time. Retest scores are assumed to be highest at short intervals and decrease over time, however studies have shown some practice effects remain for up to 5 years after testing[218]. The overall magnitude of practice effects across tests have been assessed to be around a quarter of a standard deviation for one year between testings. However, these effects vary significantly among different cognitive assessments. Factors such as the use of alternative test forms, the age and clinical diagnosis of the participants, and length of test-retest interval are associated with the magnitude

of change[218]. Short-term practice effect however also appears to be a sensitive marker for cognitive disorders, as studies show cognitively intact individuals have significantly larger practice effects[219].

For paper I, only cross-sectional data was utilized for the calculation of normative data for MoCA. This approach has limitations, as we do not have any data on the participants after collecting data for their MoCA scores. However, cross-sectional studies offer the advantage of allowing many participants to be studied without concerns about follow-up loss or dropout.

In both cross-sectional and longitudinal studies there could be a cohort effect, depending on which individuals have been recruited to the study.

Selection bias

Selection bias occurs when participants in a study differ from the population the study is meant to represent. The risk of selection bias is that studies find associations between exposure and outcome that are unrepresentative to the true population. It has previously been considered that age-related cognitive decline is a normal part of ageing, however, evidence shows that it is age-related disease more than age itself causes cognitive decline[220]. Normal aging is however a difficult question to address as there can be a large selection bias in individuals participating in studies of normal aging. For studies investigating healthy elderly individuals, there is a risk that participants are either too cognitively well and busy to be in a study (volunteer bias), or too cognitively impaired to be classified as "normal". As we are mostly studying elderly people, there is a risk of attrition bias (loss of participants) which could be caused by participants falling ill in other diseases or even survivorship bias, where participants die of other causes or diseases.

Also, as we address in study II, as diagnostics for neurodegenerative diseases move towards more biological definitions rather than symptomatic ones, there is also a problematic issue of studying "supernormal" individuals who may not accurately represent the population. The most important thing to address before proceeding with a study, is if the studied population accurately represents the population on which results from the study will be applied on.

For the BioFINDER and ADNI studies, there are individuals who cannot go through lumbar punctures (such as patients with blood thinning mediation which contradict this invasive procedure), or individuals who simply are afraid of the procedure. There are also individuals who due to being claustrophobic or for example have metal in their bodies due to previous surgery or accidents cannot undergo MRI scans, leading either to non-participation in studies or lack of data for these measurements.

Missing data

There can be missing data in longitudinal studies due to a variety of reasons, such as a study participant stops coming to follow-up visits or misses certain assessments. When interpreting data, it is highly important to understand the cause of missing data. Missing data can be missing completely at random (MCAR), missing at random (MAR) or missing not at random (MNAR). When missing data are MCAR, a complete case analysis can be valid, if MAR a complete case analysis can be valid in certain situations but should often use imputed data. When missing data are MNAR, even multiple imputations do not lead to valid results[221]. It can be difficult to understand whether data is MAR or MNAR, as data MNAR are caused by unobserved data and therefore unknow, therefore it is difficult to know if unobserved data are related to missing data. A missing data percentage of 5% is often mentioned as a cutoff for when imputation is necessary, but it is important to acknowledge that the relationship between missing and observed variables is essential.

Table 11. Handling missing data: an overview[221]

Missing data mechanism	**Analysis**	**Imputation**
MCAR	Complete cases analysis	No imputation necessary
MAR	No complete case analysis	Single imputation methods not valid
		Multiple imputation needed
MNAR	No compete case analysis	All imputation methods not valid

Missing data in paper I were mostly caused by participants declining examination at the memory clinic, where it is possible that many of these participants had an undiagnosed cognitive impairment considering they scored poorly on screening tests with MMSE and/or AQT and would then have been excluded from the normative cohort anyway. If many of these participants however would be diagnosed as normal, this could have lowered the normative scores, as the excluded group had significantly lower MMSE, MoCA and AQT scores than the normative group.

In paper II there was some missing data on cognitive test results when calculating cognitive test means in different cohorts. For ADAS delayed recall, ADAS naming, Animal Fluency, CDT, AQT, Stroop, TMT A and SDMT, missing data on test results were <5% of participants in each group, however in TMT B there were a larger number of missing data. This however was caused by TMT B not routinely assessed in certain memory clinics during follow-up and is therefore data missed completely at random (MCAR)

Table 12.
Mean test results for TMT B and number of participants in each group in paper II

Mean (SD) Number	A. Study Cohort (n=297)	B. No Progress in CDR (n=278)	C. No Amyloid or Tau Pathology (n=223)	D. No Vascular Pathology (n=161)	E. No measurable in-vivo pathology (n=120)
TMT B	104.4 (50.8) (n=267)	101.8 (49.4) (n=250)	101.9 (49.0) 203	97.1 (44.7) 142	90.0 (36.5) 108

In paper III, cognitive test changes were only calculated if there were data before and after change or non-change in CDR. If there were no data at either time-point, no change in test result was calculated. Here, we could see that we had a larger number of test results for MMSE and ADAS delayed recall compared to several other tests. We interpreted this also to be MCAR as different tests were routinely conducted in procedures at different clinics, however more importantly, the low number of participants with mean score differences in certain groups (e.g. for CU with a meaningful decline ≥1 point in Stroop and TMT B) affects the power of the statistical analyses.

Table 13.
Number of data points calculating mean test changes

	CU			MCI		
	No meaningful decline	**Meaningful decline (CDR-diff ≥0.5)**	**Meaningful decline (CDR-diff ≥1)**	**No meaningful decline**	**Meaningful decline (CDR-diff ≥0.5)**	**Meaningful decline (CDR-diff ≥1)**
MMSE	1099	148	54	237	401	267
ADAS delayed recall	1093	144	50	228	389	261
Stroop	906	95	35	91	174	121
Animal Fluency	966	128	52	80	245	193
Letter S	969	129	53	81	251	196
Symbol Digit	978	119	46	159	249	165
TMT A	989	119	47	157	288	199
TMT B	926	104	35	86	189	134

In paper IV, predicting models for progression to dementia within 4 years were conducted on participants who had complete data on all the examined test results. Firstly, this affected the choice of cognitive assessments in the actual MuMin-model as there were cognitive tests in ADNI and BioFINDER-1 which could not be included in the model due to lack of data in BioFINDER-1.

Also, lack of data for different test results for the second model caused a smaller number of participants in BioFINDER-1 than in the whole intermediate risk group (41 out of 185 subjects). 69 of the 185 participants with intermediate risk converted to dementia within 4 years, 7 out of these within one year. As only 38 converters were included in step 2, 14 participants with lack of data were also converters. 116 participants with intermediate risk were not converters and 99 of them were included in step 2, meaning there were 17 non-converters excluded due to lack of data. 45% converters in the excluded group due to lack of data implies missing data also here was MCAR as they were missing from both converters and non-converters.

For 1-year results on TMT B, we calculated a mean annual change from the differences between 2-year follow-up and baseline divided in two because of missing data for TMT at one-year visit, which was caused by the study design in BioFINDER-1 with TMT B being performed every other year. This assumes a linear change over time and may not be accurate as there could be a stepwise decline that is missed with this method which could affect the generalizability and reliability of our findings.

Diagnostic considerations regarding cognitive stage

There is always possible bias when diagnosing or scoring individuals with cognitive impairment. Ratings, such as the CDR, are observational scoring systems where professionals interpret subjective and objective symptoms and rate them with numbers in a scoring system. There is a possibility there could be inter-rater differences in such methods as well as when assessing and interpreting cognitive tests and their results.

Also, diagnosis of major neurocognitive disorder, or dementia, is based on the fact if cognitive impairment affects the individual to the level that it alters activities of daily living. This also could be problematized as clinicians could miss altering comorbidities or physical concerns which affect activities of daily living. Also, when answering the question “Are there activities in your/your relatives lives you/they can no longer do due to cognitive disease?”, answers could be very different depending on listeners’ interpretation of the question. It is also important to acknowledge that cognitive disease is a slow process whereby changes do not happen overnight. Therefore, it can be difficult in retrospect to say when certain changes have occurred and at what timepoint a person progressed to dementia.

Another concern is whether patients have other psychiatric symptoms that affect their cognitive symptoms, as psychiatric symptoms can both be a differential diagnosis as well as an associated feature of the neurodegenerative disease. Depression and apathy can be seen as an associated feature in AD[222], personality and mood change in VaD, patients with DLB can have delirium, patients with PDD

can experience apathy, anxiety, depression, hallucination, delusions and personality changes[24]. Patients with FTD can experience apathy, disinhibition and loss of empathy[223]. Neuropsychiatric symptoms (NPS) are associated with major effects on daily function, quality of life and less time to institutionalisation[224]. Therefore, NPS can be both a differential diagnosis for cognitive impairment as well as worsen their symptoms during progress of disease course, which is of relevance when ratings patients with structured anamnestic interviews.

Normative data

Prior to paper I, there was no normative data for the Swedish MoCA stratified after age, gender and education. The standardized cutoff of <26 points had been used widely no matter the individuals' demographic factors. Since we published Swedish MoCA cut-offs, Classon et al[225] have published normative data for cognitively healthy Swedish 80-94 year-olds. Their results showed similar norm scores in the total age group 80-94 in individuals with 12 or more years of education (for ≤1 SD 24 points and ≤2 SD 21 points), somewhere in-between norm scores in our oldest age group 75-85 (≤1 SD 23 and ≤2 SD 21 points for individuals with secondary school education and for ≤1 SD 25 and ≤2 SD 23 points for individuals with a high education (university degree)).

In paper II, we published cognitive test cutoffs at 1.5 SD from means in the total cohort (A), in a cohort with non-progressing cognitive symptoms over at least 2 years (cohort B) and in a cohort without measurable pathology (cohort E). Cutoff results produced from individuals such as in cohort E are probably not suitable in primary care settings when screening for MCI, however more suitable for screening for preclinical disease such as in clinical AD trials or in the future when disease-modifying treatment will be available.

Also, paper II enhances that other pathological processes such as cerebrovascular disease can be accountable for some of the performance results on cognitive outcomes, which is highly relevant in clinical trials for AD. Later studies have highlighted this potential effect of small vessel cerebrovascular pathology driving AD-related cognitive profiles and enhances that cerebrovascular disease should be considered when evaluating outcomes in clinical trials. This is important as the pathology could drive as a potential effect modifier and as this is a possible target for intervention and/or prevention[226]. Particularly since neuropathology studies in community-dwelling older persons show that in elderly with dementia, the majority have multiple brain pathologies[100].

Normal aging or disease?

Throughout this thesis, we have addressed the different methods and implications for calculating means and normative test results from different populations. Traditional test norms from subjectively cognitively normal people have been proven improved created by individuals showing no cognitive progression over time[227]. As population norms tend to be influenced by age, the use of age-graded norms is considered necessary to account for age-related variations[228].

Aging is a natural and inevitable pathophysiological process characterized by gradual decline of cellular function and structural changes in many organs. There is correspondingly an increasing risk of many age-related diseases such as neurodegenerative diseases, cardiovascular disease, metabolic disease, musculoskeletal diseases, immunological diseases etc.[229]. The discussion of age effect on our physical health has however historically been addressed differently for different organ systems. For instance, kidney function declines with age, however calculation of kidney function with estimated glomerular filtration rate (eGFR) is not adjusted for age, though many people over the age of 70 have at or below the accepted threshold for chronic kidney disease (CKD)[230]. The same goes for measurements of cardiac function measuring ejection fraction (EF), the volume of blood ejected from the ventricle compared to the total volume of blood in the ventricle before ejection. EF is not adjusted for age but has an age-related decline[231].

Therefore, it is important to address the differences in measurement of organ function in internal organs versus the brain. Although age-related decline in cognitive testing is common, it does not necessarily mean it is normal for the individual being examined.

Sociodemographic effects on cognitive assessments

In paper I for normative data on MoCA, we found that higher age and lower level of education were associated with lower scores, as seen in other normative studies[232-236]. We also found that male gender affected MoCA negatively in our normative population which is consistent with some other studies[232, 233, 237], but has not been found a significant predictor in others[234]. Compared to in study II, we did not adjust these normative values for underlying pathologies which could potentially have affected normative test results.

In paper II we analysed how different sociodemographic factors affected cognitive assessments. A previous study that examined the correlation of demographic factors and subscales of ADAS-cog found a correlation for ADAS-naming and education, but none for age or gender, and for ADAS-delayed recall, age and education showed significant associations with scores[238]. We found for ADAS-delayed recall and ADAS-naming a significant correlation with age and test results in cohort A (total study cohort) and C (no amyloid or tau pathology), but the age effect was not seen

in cohort B (no progress in CDR) or in cohort D (no vascular pathology) or E (no measurable in-vivo pathology). We also found that female gender had significantly better scores on ADAS-delayed recall for cohort A-C, but not for cohort D or E. Education correlated with ADAS-delayed recall in cohort D and E, but only for cohort B in ADAS-naming. Cohort E had 19.5% better cutoffs compared to cohort A for ADAS-delayed recall and 20.4% for ADAS-naming.

Semantic verbal fluency tasks have previously shown to be affected by age and education, but not for gender[239-245]. We found tests results were significantly affected by age and education for cohort A-C when assessed with Animal Fluency, but these effects disappeared in cohort D and E, and no significant association with gender. Cut-offs for cohort E were improved by 11.6% compared to cohort A. This proposes previously shown age and education effects on test results are caused by underlying pathology.

For AQT, previous studies have shown correlations between age and test results[157, 246-248]. In our study we find a significant correlation between age and test results for cohort A-C, but this age effect disappeared for cohort D and E. Education is associated in some studies, however some with low correlation[246-248]. Here, we found a correlation with education and test results in cohort A, but not in other cohorts. Gender has not previously been considered to correlate with test scores[247, 249], however, when found it has been suggested to be caused by cultural differences[248]. We found a significant correlation between male gender and quicker results for cohort D which cannot be explained by cultural differences in our population, as the cohort is very homogenous with similar education among men and women. Previous studies have shown that AQT activates temporoparietal cortical areas[249], which are the major brain regions affected in AD why we would have expected to see the age effect disappear in cohort C instead of D. Our results instead suggest preclinical AD-pathology does not account for declining performance on AQT, but that rather vascular pathology explains the worsening of test results among older people. Cutoffs for cohort E were 6.2% better than for cohort A.

Previous normative studies on Stroop have shown diverse correlations with demographics. Several studies have found correlation with age[171, 250-254], some also for education[171, 251, 252, 254] and better scores for female gender[171, 254]. We found significant association between education and age with test results for all cohorts but cohort E. However, we found no significant association with gender. Cutoffs were 7.8% better for cohort E than for cohort A.

Previous studies for TMT A and B have shown a significant association between test results and age for both tests[164, 255-258], as did we for all cohorts. We found no association with gender, which however has been seen in a few previous studies[255, 256] and others not[164, 258]. Several other studies have seen a correlation between test results and education[164, 255, 258]. We found a significant correlation between education

and test results in TMT B for all cohorts, but no significant correlation in TMT A. Cutoffs were 17.6% better for cohort E compared to cohort A in TMT A and 19.9% better in TMT B.

SDMT has previously shown correlation with age in several previous studies[259-263] and others not[156]. Education had a correlation with test results in a few studies[259, 260, 262, 263] and in some countries and studies a significant difference in gender has been seen[259, 260]. We found significant association between age and test results in all cohorts but cohort E, and education with test results in all cohorts. We did not find significant association between gender and test results. Cutoffs were 11.7% better for cohort E compared to cohort A.

Underlying pathologies' effects on cognitive assessments

In paper II, we investigated the effects of measures of AD (amyloid and tau) vascular pathology (measured with white matter lesions and cortical infarctions) and neurofilament-light (NfL) on cognitive assessments. As highlighted in the article, there are certain underlying pathologies that were not included, such as α-synuclein and TDP-43, however NfL often is increased in TDP-43 proteinopathies[264].

There are previous post-mortem studies investigating neuropathologic effects on age-related cognitive decline, measuring levels of neurofibrillary tangles, cerebral infarctions, Lewy bodies and examining their effect on cognitive decline. Studies showed that all the above contributed to gradual age-related cognitive decline. Neocortical Lewy bodies were associated with accelerated age-related decline in perceptual speed and disease-related decline in episodic, semantic, and working memory[265]. As of today (2024), there are methods for measuring α-synuclein with seed amplification assay to measure Lewy Body-associated α-synuclein in cerebrospinal fluid[266]. It would therefore have been interesting to have included this in a subanalysis, as DLB and PDD are both associated with deficits on visuospatial tests, including Trail Making Test A and B, to see if this could have explained some of the remaining age effect on these tests[267].

As described in the background of this thesis, studies show that TDP-43 proteinopathy has been found in several neurodegenerative diseases including AD, FTD, PDD and LATE[268], thereby affecting cognition in different ways. We would therefore have expected to have seen improved scores in individuals without TDP-43 pathology.

Table 14.
Table showing a mean (SD) differences in test results between genders for ADAS-delayed recall in cohorts A-C, where women have better test results, and for AQT in cohort D, where men have significantly better test results.

Mean test results	**A. Study Cohort**		**B. No Progress in CDR**		**C. No Amyloid or Tau Pathology**		**D. No Vascular Pathology**		**E. No measurable in-vivo pathology**	
Gender	M	F	M	F	M	F	M	F	M	F
ADAS-delayed recall	**2.35 (1.84) (n=117)**	**1.74*** (1.96) (n=180)**	**2.18 (1.71) (n=108)**	**1.55*** (1.69) (n=170)**	**2.05 (1.67) (n=88)**	**1.64* (1.83) (n=135)**	2.01 (1.74) (n=67)	1.67 (1.83) (n=94)	1.75 (1.62) (n=51)	1.48 (1.51) (n=69)
AQT	65.6 (12.8) (n=117)	66.2 (13.0) (n=179)	64.3 (11.4) (n=108)	65.5 (12.8) (n=169)	65.6 (13.0) (n=88)	66.0 (13.0) (n=134)	**61.9* (11.8) (n=67)**	**65.2 (12.1) (n=93)**	61.7 (11.1) (n=51)	64.5 (11.1) (n=68)

Significant differences are in bold. No significant differences were found between gender and other cognitive tests regardless of cohort (A-E). P-values calculated with Mann-Whitney test with test results as dependent variable and gender as independent groups. *Correlation is significant at the 0.05 level, ** correlation is significant at the 0.01 level, ***correlation is significant at the 0.001 level. Acronyms: F, female; M, male.

Table 15.
Correlation coefficients conducted with Spearman test between test result and education for each group.

Cognitive test	**A. Study Cohort (n=297)**	**B. No Progress in CDR (n=278)**	**C. No Amyloid or Tau Pathology (n=223)**	**D. No Vascular Pathology (n=161)**	**E. No measurable in-vivo pathology (n=120)**
ADAS-delayed recall	-0.094	-0.097	-0.094	-0.187*	-0.224*
ADAS-naming	-0.102	-0.129*	-0.094	-0.148	-0.113
Animal Fluency	0.183**	0.200***	0.172**	0.124	0.093
AQT	-0.132*	-0.153*	-0.130	-0.107	-0.132
Stroop	-0.148*	-0.157**	-0.196**	-0.195*	-0.256**
TMT A	-0.107	-0.103	-0.121	-0.153	-0.169
TMT B	-0.168**	-0.170**	-0.196**	-0.210*	-0.279**
SDMT	0.270***	0.268***	0.281***	0.276***	0.258**

Only significant correlation coefficients are colored. Yellow boxes for coefficients ≥0.1 and <0.2, orange boxes for ≥0.2 and <0.3. *Correlation is significant at the 0.05 level, **correlation is significant at the 0.01 level ***correlation is significant at the 0.001 level.

Prediction of future decline

Cognitively unimpaired Aβ positive individuals have previously shown to be associated with cognitive decline[269]. Studies have shown that Aβ deposition is slow and likely accumulates during a period of up to 20 years, suggesting a long preclinical phase of AD which could facilitate design and study of therapeutic interventions[270]. Also, individuals with MCI have a higher risk of progressing to dementia than cognitively unimpaired individuals[271, 272]. Therefore, for these groups of individuals it is of high importance to predict future decline for early diagnosis and treatment.

In paper III, we included healthy participants with and without objective cognitive symptoms, to investigate the changes in cognitive test results which are associated with a change in clinical symptoms, measured with the Clinical Dementia Rating Scale–sum of boxes (CDR-SB). We also investigated which combination of cognitive assessments that best could estimate a minimal clinical change for cognitively unimpaired, Aβ positive cognitively unimpaired and for participants with mild cognitive impairment.

In paper IV, we investigated which combination of cognitive assessments that best predicts future progression to dementia within 4 years in participants with cognitive symptoms. Our prediction model was not created using data from patients seeking healthcare for cognitive symptoms, however the model was replicated in BioFINDER-1 where individuals had been included after being referred from primary care to a secondary memory clinic for their cognitive symptoms, where they were invited to join the study.

The best predictive model in paper III to predict a cognitive decline in cognitively unimpaired amyloid positive participants used a combination of ADAS delayed word recall, TMT B, Symbol Digit, MMSE as well as gender. The best predictive model in paper IV for predicting progression to all-cause dementia included ADAS delayed, ADAS immediate, TMT B, Animal Fluency and MMSE.

The uniform data set of the National Alzheimer's Coordination Center neuropsychological test battery contains tests to cover dementia severity, attention, processing speed, executive function, memory as well as language[228]. These findings align well with our model for predicting all-cause dementia, however the best predictive model to predict a cognitive decline in CU amyloid positive participants did not contain any tests focused on language skills. This could possibly be explained by language abilities often remaining intact in the early stages of disease[228]. The overall well-covered global cognitive testing enhances the importance of screening individuals for cognitive impairment with complementary

neuropsychological testing if testing with the MMSE, especially in early disease and/or young or well-educated individuals.

Previous studies have shown that the combination of global cognitive function (MMSE and Cambridge Cognitive Examination-Revised), verbal episodic memory (Wechsler memory scale logical memory test delayed) and psychomotor speed (Trail Making Test A) were the best predictors of conversion to AD dementia from subjective or mild cognitive impairment[273]. This aligns with our model for predicting all-cause dementia covering tests of global cognitive assessment (MMSE), verbal episodic memory (ADAS delayed recall) and psychomotor speed (TMT B). However, our test battery included added information of verbal fluency (Animal Fluency), learning memory test (ADAS immediate), and cognitive flexibility and executive function in TMT B as opposed to TMT A, reflecting the coverage of broader cognitive dysfunction possibly caused by other neurocognitive disorders than AD such as vascular dementia and Parkinson disease.

In paper III, we presented triangulated minimal clinically important differences (MCIDs) for several cognitive tests to measure whether a clinically relevant change or MCID has occurred. In paper IV, it is therefore interesting to compare these MCIDs with individuals who are in the intermediate risk group at baseline and then are converted to high risk of progression to dementia. The triangulated MCIDs were calculated through mean changes in test results when CDR ratings changed by 0.5-1 point, whereas in paper IV we can calculate it from individuals going from intermediate risk to high risk. Groups are particularly interesting to compare as they both represent potential individuals with MCI seeking healthcare undergoing follow-up retesting which is highly relevant for clinical practice.

Table 16.
Comparison of calculated MCIDs in paper III with differences in test results for individuals who first receive intermediate risk at step 1 and then high risk in step 2 in paper IV.

Test	**BF-1, paper III N=134-267**	**ADNI, paper IV. N=93**	**BF-1, paper IV. N=64**
MMSE mean baseline (SD)	27.0 (1.8)	27.7 (1.5)	27.9 (1.6)
Change mean	-1.9	-1.1	-1.3
(SD, 95% CI)	(3.6, -2.2 to -1.5)	(1.8,-1.4 to -0.73)	(1.9, -1.8 to -0.8)
Effect size	-0.8	**-0.6**	**-0.7**
SEM	1.4	1.1	1.3
Triangulated	-1.7	-1.0	-1.1
TMT A mean baseline (SD)	67.7 (33.8)	41 (17.1)	NA due to too few at follow-up
Change mean	12.3	-1.2	
(SD, 95% CI)	(38.4, 7.0 to 17.7)	(14.0, -4.1 to -1.7)	
Effect size	0.4	-0.0	
SEM	14.4	10.2	
Triangulated	13.0	2.9	
TMT B mean baseline (SD)	130.8 (32.0)	102.4 (51.1)	113.8 (26.5)
Change mean	17.9	22.2	8.9
(SD, 95% CI)	(46.8, 9.9 to 25.9)	(50.2, -11.9 to 32.6)	(17.4, 4.5 to 13.2)
Effect size	0.5	**0.4**	0.3
SEM	24.5	28.6	11.8
Triangulated	20.1	23.4	9.3
Animal fluency mean baseline (SD)	14.2 (5.6)	17.4 (4.3)	
Change mean	-2.6	-1.5	
(SD, 95% CI)	(4.8, -3.3 to -2.0)	(4.1, -2.3 to -0.7)	NA due to too few at follow-up
Effect size	-0.5	-0.3	
SEM	3.6	2.8	
Triangulated	-2.9	-1.8	
Adas delayed mean baseline (SD)	6.5 (2.3)	5.8 (1.8)	4.7 (0.9)
Change mean	0.9	1.2	1.0
(SD, 95% CI)	(2.3, 0.6 to 1.2)	(1.7, 0.9 to 1.6)	(1.7, 0.6 to 1.4)
Effect size	0.4	**0.6**	**0.5**
SEM	1.5	1.2	1.2
Triangulated	1.1	1.1	1.0
Adas immediate mean baseline (SD)	NA in paper	5.3 (1.2)	4.7 (0.9)
Change mean		0.4	0.3
(SD, 95% CI)		(1.3, 0.1 to 0.6)	(1.1, -0.0 to 0.6)
Effect size		0.3	0.2
SEM		1.0	0.8
Triangulated		0.6	0.4

Abbreviation: ES = Effect size.

When calculating changes in TMT A and Animal fluency in ADNI, the effect sizes were almost zero in TMT A and 0.3 in Animal Fluency. Effect size aids in determining the size of an effect and the power of an analysis[215]. The relatively small effect sizes in TMT A and Animal Fluency correlates with the fact that these tests

were not selected in the two-step model for predicting all-cause dementia. The effect size in ADAS immediate word recall in ADNI and BioFINDER-1 was 0.2-0.3 but were still statistically significant predictors in the first and second step of the model in ADNI ($p<0.05$).

In the table we can however see that the MCID for MCI individuals who have a minimal change in CDR of 0.5-1 point correspond to a triangulated MCID in MMSE of -1.7 point, whereas in ADNI in paper IV a change of -1.0 point and BioFINDER-1 of 1.1 point would lead to a change from intermediate risk to high risk of future progression to dementia. For TMT B, the calculated triangulated MCID for individuals with MCI in paper III was calculated to 20.1 seconds longer, compared to 23.4 seconds longer in ADNI in paper IV. In BioFINDER-1 however, this group had a lower ES (0.3) and a triangulated clinical change of 9.3 seconds. Lower TMT B scores in BioFINDER-1 could largely be affected by lower cohort size giving a lower SD of baseline scores and therefore a smaller standard error of measurement (SEM). For ADAS delayed word recall test, calculated triangulated MCIDs were similar in BF-1 in paper III and ADNI and BF-1 in paper IV.

We can also see that baseline mean scores for all tests (MMSE, TMT A, TMT B, Animal Fluency, ADAS delayed recall) were better in ADNI than in BioFINDER in paper III and the tests available in BF-1 in paper IV (MMSE, TMTB and ADAS delayed recall) were also all better than in BF-1 in paper III, this is in line with inclusion of individuals with SCD in ADNI and BF-1 in paper IV. This aligns with results from paper III that higher baseline scores gave lower MCIDs for cognitive change[274].

Implications for pharmacological studies

Studies of disease-modifying treatment for AD have escalated over the past years, with many near-successes such as aducanumab[275-277], gantenerumab[278-280] and solanezumab[281, 282]. As of today (June 2024) there are two treatments available in certain parts of the world: lecanemab and donanemab.

In the lecanemab trial, the primary efficacy end point was the change in the score on the Clinical Dementia Rating – sum of boxes (CDR-SB), secondary endpoints involved changes in Aβ burden on PET, ADAS-Cog 14, the Alzheimer's Disease Composite Score (ADCOMS) as well as on the Alzheimer's Disease Cooperative Study-Activities of Daily Living for Mild Cognitive Impairment (ADCS-MCI-ADL) and biomarker assessments. The adjusted mean change from baseline CDR-SB score was 1.21 in the lecanemab group and 1.66 in the placebo group (difference in change of -0.45; 95% CI -0.67 to -0.23; $p<0.001$)[283]. Results concluded reduced markers of amyloid in early AD and moderately less decline on measures of cognition and function, but differences in CDR were just beneath previously

suggested MCID of 0.5-1 points in CDR for predementia AD[284]. Lecanemab is now (June 2024) approved in USA, Japan and China and is pending approval in the EU[285].

In the TRAILBLAZER-ALZ-2 study, treatment with donanemab was evaluated. Results showed that in participants with early symptomatic Alzheimer disease and amyloid and tau pathology, treatment significantly slowed clinical progression at 76 weeks in individuals with low/medium tau and in the combined low/medium and high tau pathology population[286]. In this study, the MMSE was one of the secondary outcomes showing that the mean change in MMSE in the Donanemab group was -1.58 (-1.91 to -1.25) and in placebo -2.15 (-2.47 to -1.83) showing a statically smaller decline in MMSE with 0.57 points at 76 weeks. Though statistically significant, this mean would not fall into a significant minimally clinical important difference. Donanemab has just become the second anti-amyloid immunotherapy to receive approval in the US from the U.S. Food and Drug Administration's[287].

In summary, while lecanemab and donanemab have received approval for treatment of AD in certain countries, future studies should focus on the effect of treatment relative to potential side effects as well as assessing cost-benefit aspect for treatments for future evaluations.

Ethical Considerations

An ethical consideration concerning studies on cognitive disease is that many participants may receive a diagnosis that cannot be treated, depending on where participants live. This situation might change in the future, as disease modifying treatment for conditions like Alzheimer's disease become more widely available. However, this will also raise concerns about which patients should receive such treatments.

In the same sense it could be unethical to undergo certain investigations such as lumbar punctures as they have a small risk of post-lumbar headache and/or back pain. Post-lumbar puncture headache is the most common complication of lumbar puncture and is seen in 3.5-33% of patients[288], however lower in more elderly patients[289] and studies have shown an even lower prevalence (2-2.6%) in patients with cognitive impairment or cerebral atrophy[290, 291].

When it comes to pharmacological and non-pharmacological interventions in dementia studies, investigators often need to receive consent from individuals who have a cognitive impairment. Many studies also include genetic testing for neurodegenerative disorders which might have an impact on asymptomatic relatives to find out they may have a genetic disorder[292]. Another concern is the non-standardized care for caregivers of patients with dementia, where it is shown that

caregiver psychosocial interventions include delayed institutionalization of patients, improved symptoms and highly valued services[293].

In conclusion, ethical consideration in cognitive disease research is multi-faceted and complex, making informed consent of high importance. Despite these challenges, participation in studies offers significant advantages, such as access to resources, diagnostics and treatments that may not otherwise be available. Additionally, participants contribute to medical knowledge and, hopefully, benefit future patients.

Conclusion and future perspectives

There are multiple methods for establishing test norms, but it is essential to derive these norms from a suitable control population. Test norms need to be updated in the future as population grows older, with higher education and different underlying comorbidities and pathologies that could affect cognition. MCIDs could potentially be useful in pharmaceutical studies for medication trials in cognitive disorders but could also be useful in clinical practice when following patients annually with cognitive assessments, to distinguish which changes in cognitive test results are of clinical significance.

As well as presenting a method for investigating which cognitive composite that best could predict a minimal change in cognition, we have presented a model for predicting progression to dementia from mild cognitive symptoms. In the future, we anticipate there will be an increasing number of people seeking healthcare for their cognitive problems, necessitating healthcare systems to increase their availability to assess cognitive symptoms. This will increase the need for methods predicting which individuals are at higher risk for future progression to dementia and in need of further assessment and early treatment.

Another way to increase the availability of prediction methods could be to introduce digital testing through mobile phones, tablets, or computers. There are several types of digital cognitive assessments: conventional cognitive tests through videoconferencing, web-based assessments conducted on a computer without supervision and assessments performed on smartphones[294]. There are many advantages to using digital neuropsychological assessments in the evaluation of cognitive impairment. They are easily accessible, tests can be conducted at any time of day, patients can be assessed even when unable to come to the clinic due to medical or transportation reasons, and data can easily be collected from test results. It could also possibly be more economical having patients tested at home rather than in a health care centre. Using digital tests together with traditional pen- and paper tests may also be a way to identify subtle neuropsychological changes before a patient meets diagnostic criteria for MCI or dementia[295]. When patients are assessed at health care centres or memory clinics with neuropsychological tests, they are often done so with a large battery of cognitive tests, being very time consuming and not to mention exhausting for the participants. The potential ability of digital technologies to detect subtle changes in cognition may improve sensitivity and specificity of diagnosis, help identify appropriate participants for clinical trials and

improve assessment of therapeutic treatment[296]. Previous studies have shown that an individual's performance varies considerably across occasions to the level that it cannot just be dismissed as noise. Intra-individual variability can be caused by biological factors (such as circadian rhythm or physical symptoms), or psychological factors (including subjective feelings of stress, motivation and affect)[297]. Such performance variabilities could possibly be enabled with digital testing. Digital assessment methods will have to be validated and develop robust norms to be able to interpret results as well as biased results.

With advancing treatment options for neurodegenerative disease, there will be an increasing need for correct diagnosis. Improved diagnostic methods and interpretation of test results will hopefully help aid in determining which patients should be further investigated for the possibility of receiving disease-modifying treatment. Our results could aid clinicians and researchers in predicting cognitive change and progression to dementia. Additionally, they could help researchers in ongoing AD trials to investigate whether disease-modifying treatments result in clinically relevant change. In the future, research should evaluate the combination of prediction tools combined with blood tests and imaging to enhance evaluation.

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References

1. Collaborators GBDDF. Estimation of the global prevalence of dementia in 2019 and forecasted prevalence in 2050: an analysis for the Global Burden of Disease Study 2019. Lancet Public Health 2022;7:e105-e125.
2. Frisell O, Jönsson L., Wimo A. Demenssjukdomarnas samhällskostnader i Sverige 2019: Karolinska Institutet, 2023.
3. Neisser U. Cognitive psychology: Classic edition: Psychology press, 2014.
4. Bayne T, Brainard D, Byrne RW, et al. What is cognition? Curr Biol 2019;29:R608-r615.
5. Dhakal A, Bobrin BD. Cognitive Deficits. StatPearls. Treasure Island (FL) ineligible companies. Disclosure: Bradford Bobrin declares no relevant financial relationships with ineligible companies.: StatPearls Publishing

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6. Blazer DG, Wallace RB. Cognitive Aging: What Every Geriatric Psychiatrist Should Know. Am J Geriatr Psychiatry 2016;24:776-781.
7. Classon E, van den Hurk W, Wressle E, Rehn I, Johansson MM. A quick test of cognitive speed (AQT): regression-based norms for cognitively healthy 80 to 94-year olds. Neuropsychol Dev Cogn B Aging Neuropsychol Cogn 2022;29:820-839.
8. Salthouse TA. Aging and measures of processing speed. Biol Psychol 2000;54:35-54.
9. Harada CN, Natelson Love MC, Triebel KL. Normal cognitive aging. Clin Geriatr Med 2013;29:737-752.
10. Anstey KJ, Wood J. Chronological age and age-related cognitive deficits are associated with an increase in multiple types of driving errors in late life. Neuropsychology 2011;25:613-621.
11. Petersen RC. Mild Cognitive Impairment. Continuum (Minneap Minn) 2016;22:404-418.
12. Hugo J, Ganguli M. Dementia and cognitive impairment: epidemiology, diagnosis, and treatment. Clin Geriatr Med 2014;30:421-442.
13. Gauthier S, Reisberg B, Zaudig M, et al. Mild cognitive impairment. Lancet 2006;367:1262-1270.
14. Studart AN, Nitrini R. Subjective cognitive decline: The first clinical manifestation of Alzheimer's disease? Dement Neuropsychol 2016;10:170-177.
15. Jessen F, Amariglio RE, Buckley RF, et al. The characterisation of subjective cognitive decline. Lancet Neurol 2020;19:271-278.

16. Nelson AP, O'Connor MG. Mild cognitive impairment: a neuropsychological perspective. CNS Spectr 2008;13:56-64.
17. Assal F. History of Dementia. Front Neurol Neurosci 2019;44:118-126.
18. Yang HD, Kim DH, Lee SB, Young LD. History of Alzheimer's Disease. Dement Neurocogn Disord 2016;15:115-121.
19. International AsD. World Alzheimer Report 2018. The state of the art of dementia reserach: new frontiers. [online].
20. WHO. Global status report on the public health response to dementia [online].
21. Satizabal CL, Beiser AS, Chouraki V, Chêne G, Dufouil C, Seshadri S. Incidence of Dementia over Three Decades in the Framingham Heart Study. N Engl J Med 2016;374:523-532.
22. Qiu C, von Strauss E, Bäckman L, Winblad B, Fratiglioni L. Twenty-year changes in dementia occurrence suggest decreasing incidence in central Stockholm, Sweden. Neurology 2013;80:1888-1894.
23. Arvanitakis Z, Shah RC, Bennett DA. Diagnosis and Management of Dementia: Review. JAMA 2019;322:1589-1599.
24. Diagnostic and statistical manual of mental disorders: DSM-5™, 5th ed. Arlington, VA, US: American Psychiatric Publishing, Inc., 2013.
25. Hou Y, Dan X, Babbar M, et al. Ageing as a risk factor for neurodegenerative disease. Nature Reviews Neurology 2019;15:565-581.
26. Qiu C, Kivipelto M, von Strauss E. Epidemiology of Alzheimer's disease: occurrence, determinants, and strategies toward intervention. Dialogues Clin Neurosci 2009;11:111-128.
27. Dintica CS, Yaffe K. Epidemiology and Risk Factors for Dementia. Psychiatr Clin North Am 2022;45:677-689.
28. Tang MX, Cross P, Andrews H, et al. Incidence of AD in African-Americans, Caribbean Hispanics, and Caucasians in northern Manhattan. Neurology 2001;56:49-56.
29. Folstein MF, Bassett SS, Anthony JC, Romanoski AJ, Nestadt GR. Dementia: case ascertainment in a community survey. J Gerontol 1991;46:M132-138.
30. Beam CR, Kaneshiro C, Jang JY, Reynolds CA, Pedersen NL, Gatz M. Differences Between Women and Men in Incidence Rates of Dementia and Alzheimer's Disease. J Alzheimers Dis 2018;64:1077-1083.
31. Aggarwal NT, Mielke MM. Sex Differences in Alzheimer's Disease. Neurol Clin 2023;41:343-358.
32. Shumaker SA, Legault C, Rapp SR, et al. Estrogen plus progestin and the incidence of dementia and mild cognitive impairment in postmenopausal women: the Women's Health Initiative Memory Study: a randomized controlled trial. Jama 2003;289:2651-2662.
33. Li R, Singh M. Sex differences in cognitive impairment and Alzheimer's disease. Front Neuroendocrinol 2014;35:385-403.
34. Raulin AC, Doss SV, Trottier ZA, Ikezu TC, Bu G, Liu CC. ApoE in Alzheimer's disease: pathophysiology and therapeutic strategies. Mol Neurodegener 2022;17:72.

35. Schneider JA. Neuropathology of Dementia Disorders. Continuum (Minneap Minn) 2022;28:834-851.
36. Wanleenuwat P, Iwanowski P, Kozubski W. Alzheimer's dementia: pathogenesis and impact of cardiovascular risk factors on cognitive decline. Postgrad Med 2019;131:415-422.
37. Areosa Sastre A, Vernooij RW, González-Colaço Harmand M, Martínez G. Effect of the treatment of Type 2 diabetes mellitus on the development of cognitive impairment and dementia. Cochrane Database Syst Rev 2017;6:Cd003804.
38. Biessels GJ, Despa F. Cognitive decline and dementia in diabetes mellitus: mechanisms and clinical implications. Nat Rev Endocrinol 2018;14:591-604.
39. Qiu C. Preventing Alzheimer's disease by targeting vascular risk factors: hope and gap. J Alzheimers Dis 2012;32:721-731.
40. Wong Zhang DE, Tran V, Vinh A, et al. Pathophysiological Links Between Obesity and Dementia. Neuromolecular Med 2023;25:451-456.
41. Barnes DE, Yaffe K. The projected effect of risk factor reduction on Alzheimer's disease prevalence. Lancet Neurol 2011;10:819-828.
42. Stern Y. Cognitive reserve in ageing and Alzheimer's disease. Lancet Neurol 2012;11:1006-1012.
43. Pettigrew C, Soldan A. Defining Cognitive Reserve and Implications for Cognitive Aging. Curr Neurol Neurosci Rep 2019;19:1.
44. Saczynski JS, Pfeifer LA, Masaki K, et al. The effect of social engagement on incident dementia: the Honolulu-Asia Aging Study. Am J Epidemiol 2006;163:433-440.
45. Wang Y, Meng W, Liu Z, An Q, Hu X. Cognitive impairment in psychiatric diseases: Biomarkers of diagnosis, treatment, and prevention. Front Cell Neurosci 2022;16:1046692.
46. Bennett S, Thomas AJ. Depression and dementia: cause, consequence or coincidence? Maturitas 2014;79:184-190.
47. Bahorik A, Bobrow K, Hoang T, Yaffe K. Increased risk of dementia in older female US veterans with alcohol use disorder. Addiction 2021;116:2049-2055.
48. Anstey KJ, Mack HA, Cherbuin N. Alcohol consumption as a risk factor for dementia and cognitive decline: meta-analysis of prospective studies. Am J Geriatr Psychiatry 2009;17:542-555.
49. Rehm J, Hasan OSM, Black SE, Shield KD, Schwarzinger M. Alcohol use and dementia: a systematic scoping review. Alzheimers Res Ther 2019;11:1.
50. Chen JC, Espeland MA, Brunner RL, et al. Sleep duration, cognitive decline, and dementia risk in older women. Alzheimers Dement 2016;12:21-33.
51. Ma Y, Liang L, Zheng F, Shi L, Zhong B, Xie W. Association Between Sleep Duration and Cognitive Decline. JAMA Netw Open 2020;3:e2013573.
52. Livingston G, Huntley J, Sommerlad A, et al. Dementia prevention, intervention, and care: 2020 report of the Lancet Commission. Lancet 2020;396:413-446.

53. Kornblith E, Peltz CB, Xia F, Plassman B, Novakovic-Apopain T, Yaffe K. Sex, race, and risk of dementia diagnosis after traumatic brain injury among older veterans. Neurology 2020;95:e1768-e1775.
54. Eikelenboom P, Hoozemans JJ, Veerhuis R, van Exel E, Rozemuller AJ, van Gool WA. Whether, when and how chronic inflammation increases the risk of developing late-onset Alzheimer's disease. Alzheimers Res Ther 2012;4:15.
55. Gale SA, Acar D, Daffner KR. Dementia. Am J Med 2018;131:1161-1169.
56. Erkkinen MG, Kim MO, Geschwind MD. Clinical Neurology and Epidemiology of the Major Neurodegenerative Diseases. Cold Spring Harb Perspect Biol 2018;10.
57. Bondi MW, Edmonds EC, Salmon DP. Alzheimer's Disease: Past, Present, and Future. J Int Neuropsychol Soc 2017;23:818-831.
58. Ossenkoppele R, van der Kant R, Hansson O. Tau biomarkers in Alzheimer's disease: towards implementation in clinical practice and trials. Lancet Neurol 2022;21:726-734.
59. Giao T, Teixeira T, Almeida MR, Cardoso I. Choroid Plexus in Alzheimer's Disease-The Current State of Knowledge. Biomedicines 2022;10.
60. Jahn H. Memory loss in Alzheimer's disease. Dialogues Clin Neurosci 2013;15:445-454.
61. Ghezzi L. Diagnosis of Alzheimer's Disease Typical and Atypical Forms. In: Galimberti D, Scarpini, E. , ed. Neurodegenerative Diseases: Clinical Aspects, Molecular Genetics and Biomarkers, 2nd ed: Springer, 2018: 21-28.
62. Gorno-Tempini ML, Hillis AE, Weintraub S, et al. Classification of primary progressive aphasia and its variants. Neurology 2011;76:1006-1014.
63. Dubois B, von Arnim CAF, Burnie N, Bozeat S, Cummings J. Biomarkers in Alzheimer's disease: role in early and differential diagnosis and recognition of atypical variants. Alzheimers Res Ther 2023;15:175.
64. Lee WJ, Cho H, Baek MS, et al. Dynamic network model reveals distinct tau spreading patterns in early- and late-onset Alzheimer disease. Alzheimers Res Ther 2022;14:121.
65. Breijyeh Z, Karaman R. Comprehensive Review on Alzheimer's Disease: Causes and Treatment. Molecules 2020;25.
66. Jack CR, Jr., Bennett DA, Blennow K, et al. NIA-AA Research Framework: Toward a biological definition of Alzheimer's disease. Alzheimers Dement 2018;14:535-562.
67. Dubois B, Villain N, Frisoni GB, et al. Clinical diagnosis of Alzheimer's disease: recommendations of the International Working Group. Lancet Neurol 2021;20:484-496.
68. Jack CR, Jr., Andrews JS, Beach TG, et al. Revised criteria for diagnosis and staging of Alzheimer's disease: Alzheimer's Association Workgroup. Alzheimers Dement 2024.
69. Sanford AM. Lewy Body Dementia. Clin Geriatr Med 2018;34:603-615.
70. Kosaka K. Lewy body disease and dementia with Lewy bodies. Proc Jpn Acad Ser B Phys Biol Sci 2014;90:301-306.

71. Greenfield JG, Bosanquet FD. The brain-stem lesions in Parkinsonism. J Neurol Neurosurg Psychiatry 1953;16:213-226.
72. Menšíková K, Matěj R, Colosimo C, et al. Lewy body disease or diseases with Lewy bodies? NPJ Parkinsons Dis 2022;8:3.
73. Taylor JP, McKeith IG, Burn DJ, et al. New evidence on the management of Lewy body dementia. Lancet Neurol 2020;19:157-169.
74. Prasad S, Katta MR, Abhishek S, et al. Recent advances in Lewy body dementia: A comprehensive review. Dis Mon 2023;69:101441.
75. Lippa CF, Duda JE, Grossman M, et al. DLB and PDD boundary issues: diagnosis, treatment, molecular pathology, and biomarkers. Neurology 2007;68:812-819.
76. Ferman TJ, Boeve BF, Smith GE, et al. Inclusion of RBD improves the diagnostic classification of dementia with Lewy bodies. Neurology 2011;77:875-882.
77. Arnaldi D, Antelmi E, St Louis EK, Postuma RB, Arnulf I. Idiopathic REM sleep behavior disorder and neurodegenerative risk: To tell or not to tell to the patient? How to minimize the risk? Sleep Med Rev 2017;36:82-95.
78. Cogne E, Postuma RB, Chasles MJ, et al. Montreal Cognitive Assessment and the Clock Drawing Test to Identify MCI and Predict Dementia in Isolated REM Sleep Behavior Disorder. Neurology 2024;102:e208020.
79. Yamada M, Komatsu J, Nakamura K, et al. Diagnostic Criteria for Dementia with Lewy Bodies: Updates and Future Directions. J Mov Disord 2020;13:1-10.
80. McKeith IG, Boeve BF, Dickson DW, et al. Diagnosis and management of dementia with Lewy bodies: Fourth consensus report of the DLB Consortium. Neurology 2017;89:88-100.
81. Gibbons CH, Levine T, Adler C, et al. Skin Biopsy Detection of Phosphorylated α-Synuclein in Patients With Synucleinopathies. Jama 2024.
82. Jack CR, Jr. Criteria for a biological definition of neuronal α-synuclein disease-a major conceptual step forward. Lancet Neurol 2024;23:129-130.
83. Höglinger GU, Adler CH, Berg D, et al. A biological classification of Parkinson's disease: the SynNeurGe research diagnostic criteria. Lancet Neurol 2024;23:191-204.
84. Simuni T, Chahine LM, Poston K, et al. A biological definition of neuronal α-synuclein disease: towards an integrated staging system for research. Lancet Neurol 2024;23:178-190.
85. Onyike CU, Diehl-Schmid J. The epidemiology of frontotemporal dementia. Int Rev Psychiatry 2013;25:130-137.
86. Khan I, De Jesus O. Frontotemporal Lobe Dementia. StatPearls. Treasure Island (FL) ineligible companies. Disclosure: Orlando De Jesus declares no relevant financial relationships with ineligible companies.2024.
87. Olney NT, Spina S, Miller BL. Frontotemporal Dementia. Neurol Clin 2017;35:339-374.
88. Ingvar DH, Gustafson L. Regional cerebral blood flow in organic dementia with early onset. Acta Neurol Scand 1970;46:42-73.
89. Clinical and neuropathological criteria for frontotemporal dementia. The Lund and Manchester Groups. J Neurol Neurosurg Psychiatry 1994;57:416-418.

90. Takeda N, Kishimoto Y, Yokota O. Pick's Disease. In: Ahmad SI, ed. Neurodegenerative Diseases. New York, NY: Springer US, 2012: 300-316.
91. Choudhury P, Scharf EL, Paolini MA, 2nd, et al. Pick's disease: clinicopathologic characterization of 21 cases. J Neurol 2020;267:2697-2704.
92. Bang J, Spina S, Miller BL. Frontotemporal dementia. Lancet 2015;386:1672-1682.
93. Grossman M, Seeley WW, Boxer AL, et al. Frontotemporal lobar degeneration. Nat Rev Dis Primers 2023;9:40.
94. Ulugut Erkoyun H, Groot C, Heilbron R, et al. A clinical-radiological framework of the right temporal variant of frontotemporal dementia. Brain 2020;143:2831-2843.
95. Rascovsky K, Grossman M. Clinical diagnostic criteria and classification controversies in frontotemporal lobar degeneration. Int Rev Psychiatry 2013;25:145-158.
96. O'Brien JT, Thomas A. Vascular dementia. Lancet 2015;386:1698-1706.
97. Rundek T, Tolea M, Ariko T, Fagerli EA, Camargo CJ. Vascular Cognitive Impairment (VCI). Neurotherapeutics 2022;19:68-88.
98. Román G. Vascular dementia: a historical background. Int Psychogeriatr 2003;15 Suppl 1:11-13.
99. Chang Wong E, Chang Chui H. Vascular Cognitive Impairment and Dementia. Continuum (Minneap Minn) 2022;28:750-780.
100. Schneider JA, Arvanitakis Z, Bang W, Bennett DA. Mixed brain pathologies account for most dementia cases in community-dwelling older persons. Neurology 2007;69:2197-2204.
101. Zhao L, Biesbroek JM, Shi L, et al. Strategic infarct location for post-stroke cognitive impairment: A multivariate lesion-symptom mapping study. J Cereb Blood Flow Metab 2018;38:1299-1311.
102. Bir SC, Khan MW, Javalkar V, Toledo EG, Kelley RE. Emerging Concepts in Vascular Dementia: A Review. J Stroke Cerebrovasc Dis 2021;30:105864.
103. Vaquer-Alicea J, Diamond MI, Joachimiak LA. Tau strains shape disease. Acta Neuropathol 2021;142:57-71.
104. Hickman RA, Flowers XE, Wisniewski T. Primary Age-Related Tauopathy (PART): Addressing the Spectrum of Neuronal Tauopathic Changes in the Aging Brain. Curr Neurol Neurosci Rep 2020;20:39.
105. Crary JF, Trojanowski JQ, Schneider JA, et al. Primary age-related tauopathy (PART): a common pathology associated with human aging. Acta Neuropathol 2014;128:755-766.
106. Armstrong MJ, Litvan I, Lang AE, et al. Criteria for the diagnosis of corticobasal degeneration. Neurology 2013;80:496-503.
107. Boeve BF, Maraganore DM, Parisi JE, et al. Pathologic heterogeneity in clinically diagnosed corticobasal degeneration. Neurology 1999;53:795-800.
108. Olfati N, Shoeibi A, Litvan I. Clinical Spectrum of Tauopathies. Front Neurol 2022;13:944806.

109. Jellinger KA. Multiple System Atrophy: An Oligodendroglioneural Synucleinopathy1. J Alzheimers Dis 2018;62:1141-1179.
110. Kim HJ, Jeon BS, Kim YE, et al. Clinical and imaging characteristics of dementia in multiple system atrophy. Parkinsonism Relat Disord 2013;19:617-621.
111. Nelson PT, Dickson DW, Trojanowski JQ, et al. Limbic-predominant age-related TDP-43 encephalopathy (LATE): consensus working group report. Brain 2019;142:1503-1527.
112. Ghosh R, Tabrizi SJ. Clinical Features of Huntington's Disease. Adv Exp Med Biol 2018;1049:1-28.
113. Nakhleh R, Tessema ST, Mahgoub A. Creutzfeldt-Jakob disease as a cause of dementia. BMJ Case Rep 2021;14.
114. Giovagnoli AR, Di Fede G, Rossi G, Moda F, Grisoli M, Bugiani O. The cognitive phenotypes of Creutzfeldt-Jakob disease: comparison with secondary metabolic encephalopathy. Neurol Sci 2022;43:3703-3716.
115. Akhouri S, Kuhn J, Newton EJ. Wernicke-Korsakoff Syndrome. StatPearls. Treasure Island (FL) ineligible companies. Disclosure: James Kuhn declares no relevant financial relationships with ineligible companies. Disclosure: Edward Newton declares no relevant financial relationships with ineligible companies.: StatPearls Publishing

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116. Eggers C, Arendt G, Hahn K, et al. HIV-1-associated neurocognitive disorder: epidemiology, pathogenesis, diagnosis, and treatment. J Neurol 2017;264:1715-1727.
117. Hugon J, Hourregue C, Cognat E, et al. Chronic traumatic encephalopathy. Neurochirurgie 2021;67:290-294.
118. Westervelt HJ. Dementia in multiple sclerosis: why is it rarely discussed? Arch Clin Neuropsychol 2015;30:174-177.
119. Bastiaansen AEM, van Steenhoven RW, de Bruijn M, et al. Autoimmune Encephalitis Resembling Dementia Syndromes. Neurol Neuroimmunol Neuroinflamm 2021;8.
120. Almeida OP, Lautenschlager NT. Dementia associated with infectious diseases. Int Psychogeriatr 2005;17 Suppl 1:S65-77.
121. Frota NAF, Caramelli P, Barbosa ER. Cognitive impairment in Wilson's disease. Dement Neuropsychol 2009;3:16-21.
122. Wu YY, Chen KT, Chu YC, et al. Neuropsychological impairment in primary malignant brain tumor patients with awake craniotomy: a hospital-based registration study. J Neurooncol 2023;164:483-491.
123. Skalický P, Mládek A, Vlasák A, De Lacy P, Beneš V, Bradáč O. Normal pressure hydrocephalus-an overview of pathophysiological mechanisms and diagnostic procedures. Neurosurg Rev 2020;43:1451-1464.
124. Del Parigi A, Panza F, Capurso C, Solfrizzi V. Nutritional factors, cognitive decline, and dementia. Brain Res Bull 2006;69:1-19.
125. Tripathi M, Vibha D. Reversible dementias. Indian J Psychiatry 2009;51 Suppl 1:S52-55.

126. Blazer DG. Cognitive Aging: What We Fear and What We Know. Perspect Biol Med 2017;60:569-582.
127. Kristensson JH, Zahirovic I, Londos E, Modig S. Medications causing potential cognitive impairment are common in nursing home dementia units - A cross-sectional study. Explor Res Clin Soc Pharm 2021;3:100054.
128. Do D, Schnittker J. Utilization of Medications With Cognitive Impairment Side Effects and the Implications for Older Adults' Cognitive Function. J Aging Health 2020;32:1165-1177.
129. Mullin E, Aristotelidou V, Blackburn D, Jenkins T, Hadjivassiliou M. Cognitive deficits in vasculitis of the nervous system: a cross-sectional study. Postgrad Med 2019;131:546-549.
130. Fortes GCC, Oliveira MCB, Lopes LCG, et al. Rapidly progressive dementia due to neurosarcoidosis. Dement Neuropsychol 2013;7:428-434.
131. Blaauw J, Meelis GA, Jacobs B, et al. Presenting symptoms and functional outcome of chronic subdural hematoma patients. Acta Neurol Scand 2022;145:38-46.
132. Chieffo DPR, Lino F, Ferrarese D, Belella D, Della Pepa GM, Doglietto F. Brain Tumor at Diagnosis: From Cognition and Behavior to Quality of Life. Diagnostics (Basel) 2023;13.
133. Strauss E, Sherman EMS, Spreen O. A compendium of neuropsychological tests: Administration, norms, and commentary, 3rd ed. New York, NY, US: Oxford University Press, 2006.
134. Astrand R, Rolstad S, Wallin A. Cognitive Impairment Questionnaire (CIMP-QUEST): reported topographic symptoms in MCI and dementia. Acta Neurol Scand 2010;121:384-391.
135. Marshall GA, Zoller AS, Lorius N, et al. Functional Activities Questionnaire Items that Best Discriminate and Predict Progression from Clinically Normal to Mild Cognitive Impairment. Curr Alzheimer Res 2015;12:493-502.
136. Sachdev PS, Blacker D, Blazer DG, et al. Classifying neurocognitive disorders: the DSM-5 approach. Nat Rev Neurol 2014;10:634-642.
137. Folstein MF, Robins LN, Helzer JE. The Mini-Mental State Examination. Arch Gen Psychiatry 1983;40:812.
138. Arevalo-Rodriguez I, Smailagic N, Roque IFM, et al. Mini-Mental State Examination (MMSE) for the detection of Alzheimer's disease and other dementias in people with mild cognitive impairment (MCI). Cochrane Database Syst Rev 2015;2015:CD010783.
139. Tombaugh TN, McIntyre NJ. The mini-mental state examination: a comprehensive review. J Am Geriatr Soc 1992;40:922-935.
140. Crum RM, Anthony JC, Bassett SS, Folstein MF. Population-based norms for the Mini-Mental State Examination by age and educational level. JAMA 1993;269:2386-2391.
141. Arevalo-Rodriguez I, Smailagic N, Roque-Figuls M, et al. Mini-Mental State Examination (MMSE) for the early detection of dementia in people with mild cognitive impairment (MCI). Cochrane Database Syst Rev 2021;7:CD010783.

142. Nasreddine ZS, Phillips NA, Bedirian V, et al. The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. J Am Geriatr Soc 2005;53:695-699.
143. Lezak MD, Howieson, Diane B., Bigler Erin D., Tranel, D. Neuropsychological Assessment, Fifth ed: Oxford University Press, 2012.
144. Davis DH, Creavin ST, Yip JL, Noel-Storr AH, Brayne C, Cullum S. Montreal Cognitive Assessment for the detection of dementia. Cochrane Database Syst Rev 2021;7:CD010775.
145. Davis DH, Creavin ST, Yip JL, Noel-Storr AH, Brayne C, Cullum S. Montreal Cognitive Assessment for the diagnosis of Alzheimer's disease and other dementias. Cochrane Database Syst Rev 2015;2015:CD010775.
146. Coleman KK, Coleman BL, MacKinley JD, Pasternak SH, Finger EC. Detection and Differentiation of Frontotemporal Dementia and Related Disorders From Alzheimer Disease Using the Montreal Cognitive Assessment. Alzheimer Dis Assoc Disord 2016;30:258-263.
147. Freitas S, Simoes MR, Alves L, Duro D, Santana I. Montreal Cognitive Assessment (MoCA): validation study for frontotemporal dementia. J Geriatr Psychiatry Neurol 2012;25:146-154.
148. Kueper JK, Speechley M, Montero-Odasso M. The Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog): Modifications and Responsiveness in Pre-Dementia Populations. A Narrative Review. J Alzheimers Dis 2018;63:423-444.
149. Davis KL, Thal LJ, Gamzu ER, et al. A double-blind, placebo-controlled multicenter study of tacrine for Alzheimer's disease. The Tacrine Collaborative Study Group. N Engl J Med 1992;327:1253-1259.
150. Wessels AM, Dowsett SA, Sims JR. Detecting Treatment Group Differences in Alzheimer's Disease Clinical Trials: A Comparison of Alzheimer's Disease Assessment Scale - Cognitive Subscale (ADAS-Cog) and the Clinical Dementia Rating - Sum of Boxes (CDR-SB). J Prev Alzheimers Dis 2018;5:15-20.
151. Fleisher AS, Sowell BB, Taylor C, et al. Clinical predictors of progression to Alzheimer disease in amnestic mild cognitive impairment. Neurology 2007;68:1588-1595.
152. Skinner J, Carvalho JO, Potter GG, et al. The Alzheimer's Disease Assessment Scale-Cognitive-Plus (ADAS-Cog-Plus): an expansion of the ADAS-Cog to improve responsiveness in MCI. Brain Imaging Behav 2012;6:489-501.
153. Fellows RP, Schmitter-Edgecombe M. Symbol Digit Modalities Test: Regression-Based Normative Data and Clinical Utility. Arch Clin Neuropsychol 2019;35:105-115.
154. Forn C, Belenguer A, Belloch V, Sanjuan A, Parcet MA, Avila C. Anatomical and functional differences between the Paced Auditory Serial Addition Test and the Symbol Digit Modalities Test. J Clin Exp Neuropsychol 2011;33:42-50.
155. Pfeffer RI, Kurosaki TT, Harrah CH, Jr., et al. A survey diagnostic tool for senile dementia. Am J Epidemiol 1981;114:515-527.

156. Sheridan LK, Fitzgerald HE, Adams KM, et al. Normative Symbol Digit Modalities Test performance in a community-based sample. Arch Clin Neuropsychol 2006;21:23-28.
157. Jacobson JM, Nielsen NP, Minthon L, Warkentin S, Wiig EH. Multiple rapid automatic naming measures of cognition: normal performance and effects of aging. Percept Mot Skills 2004;98:739-753.
158. Palmqvist S, Minthon L, Wattmo C, Londos E, Hansson O. A Quick Test of cognitive speed is sensitive in detecting early treatment response in Alzheimer's disease. Alzheimers Res Ther 2010;2:29.
159. Henry JD, Crawford JR, Phillips LH. Verbal fluency performance in dementia of the Alzheimer's type: a meta-analysis. Neuropsychologia 2004;42:1212-1222.
160. Sharma V, Malek-Ahmadi M. Meta-Analysis of Animal Fluency Performance in Amnestic Mild Cognitive Impairment and Cognitively Unimpaired Older Adults. Alzheimer Dis Assoc Disord 2023;37:259-264.
161. Birn RM, Kenworthy L, Case L, et al. Neural systems supporting lexical search guided by letter and semantic category cues: a self-paced overt response fMRI study of verbal fluency. Neuroimage 2010;49:1099-1107.
162. Rascovsky K, Salmon DP, Hansen LA, Thal LJ, Galasko D. Disparate letter and semantic category fluency deficits in autopsy-confirmed frontotemporal dementia and Alzheimer's disease. Neuropsychology 2007;21:20-30.
163. van den Berg E, Dijkzeul JCM, Poos JM, et al. Differential linguistic features of verbal fluency in behavioral variant frontotemporal dementia and primary progressive aphasia. Appl Neuropsychol Adult 2022:1-9.
164. Tombaugh TN. Trail Making Test A and B: normative data stratified by age and education. Arch Clin Neuropsychol 2004;19:203-214.
165. Mitrushina M. Handbook of Normative Data for Neuropsychological Assessment: Oxford University Press, USA, 2005.
166. Ashendorf L, Jefferson AL, O'Connor MK, Chaisson C, Green RC, Stern RA. Trail Making Test errors in normal aging, mild cognitive impairment, and dementia. Arch Clin Neuropsychol 2008;23:129-137.
167. Kennedy KJ. Age effects on Trail Making Test performance. Percept Mot Skills 1981;52:671-675.
168. Robins Wahlin TB, Backman L, Wahlin A, Winblad B. Trail Making Test performance in a community-based sample of healthy very old adults: effects of age on completion time, but not on accuracy. Arch Gerontol Geriatr 1996;22:87-102.
169. Hafiz NJ, Lohse A, Haas R, et al. Trail Making Test Error Analysis in Subjective Cognitive Decline, Mild Cognitive Impairment, and Alzheimer's Dementia With and Without Depression. Arch Clin Neuropsychol 2023;38:25-36.
170. Scarpina F, Tagini S. The Stroop Color and Word Test. Front Psychol 2017;8:557.
171. Van der Elst W, Van Boxtel MP, Van Breukelen GJ, Jolles J. The Stroop color-word test: influence of age, sex, and education; and normative data for a large sample across the adult age range. Assessment 2006;13:62-79.

172. Perianez JA, Lubrini G, Garcia-Gutierrez A, Rios-Lago M. Construct Validity of the Stroop Color-Word Test: Influence of Speed of Visual Search, Verbal Fluency, Working Memory, Cognitive Flexibility, and Conflict Monitoring. Arch Clin Neuropsychol 2021;36:99-111.
173. Dao-Castellana MH, Samson Y, Legault F, et al. Frontal dysfunction in neurologically normal chronic alcoholic subjects: metabolic and neuropsychological findings. Psychol Med 1998;28:1039-1048.
174. West R, Bell MA. Stroop color-word interference and electroencephalogram activation: evidence for age-related decline of the anterior attention system. Neuropsychology 1997;11:421-427.
175. Shulman KI. Clock-drawing: is it the ideal cognitive screening test? Int J Geriatr Psychiatry 2000;15:548-561.
176. Tan LP, Herrmann N, Mainland BJ, Shulman K. Can clock drawing differentiate Alzheimer's disease from other dementias? Int Psychogeriatr 2015;27:1649-1660.
177. Ehreke L, Luppa M, Konig HH, Riedel-Heller SG. Is the Clock Drawing Test a screening tool for the diagnosis of mild cognitive impairment? A systematic review. Int Psychogeriatr 2010;22:56-63.
178. Donohue MC, Sperling RA, Salmon DP, et al. The preclinical Alzheimer cognitive composite: measuring amyloid-related decline. JAMA Neurol 2014;71:961-970.
179. Papp KV, Rofael H, Veroff AE, et al. Sensitivity of the Preclinical Alzheimer's Cognitive Composite (PACC), PACC5, and Repeatable Battery for Neuropsychological Status (RBANS) to Amyloid Status in Preclinical Alzheimer's Disease -Atabecestat Phase 2b/3 EARLY Clinical Trial. J Prev Alzheimers Dis 2022;9:255-261.
180. Bransby L, Lim YY, Ames D, et al. Sensitivity of a Preclinical Alzheimer's Cognitive Composite (PACC) to amyloid beta load in preclinical Alzheimer's disease. J Clin Exp Neuropsychol 2019;41:591-600.
181. Morris JC. The Clinical Dementia Rating (CDR): current version and scoring rules. Neurology 1993;43:2412-2414.
182. Reisberg B, Ferris SH, de Leon MJ, Crook T. The Global Deterioration Scale for assessment of primary degenerative dementia. Am J Psychiatry 1982;139:1136-1139.
183. Mougias AA, Christidi F, Kontogianni E, Skaltsounaki E, Politis A, Politis A. Patient- and Caregiver-Related Factors Associated with Caregiver Assessed Global Deterioration Scale Scoring in Demented Patients. Curr Gerontol Geriatr Res 2018;2018:9396160.
184. Wahlund LO, Barkhof F, Fazekas F, et al. A new rating scale for age-related white matter changes applicable to MRI and CT. Stroke 2001;32:1318-1322.
185. Wahlund LO, Westman E, van Westen D, et al. Imaging biomarkers of dementia: recommended visual rating scales with teaching cases. Insights Imaging 2017;8:79-90.
186. Frisoni GB, Bocchetta M, Chetelat G, et al. Imaging markers for Alzheimer disease: which vs how. Neurology 2013;81:487-500.

187. Ishii K. Diagnostic imaging of dementia with Lewy bodies, frontotemporal lobar degeneration, and normal pressure hydrocephalus. Jpn J Radiol 2020;38:64-76.
188. Velickaite V, Ferreira D, Cavallin L, et al. Medial temporal lobe atrophy ratings in a large 75-year-old population-based cohort: gender-corrected and education-corrected normative data. Eur Radiol 2018;28:1739-1747.
189. Iaccarino L, Crespi C, Della Rosa PA, et al. The semantic variant of primary progressive aphasia: clinical and neuroimaging evidence in single subjects. PLoS One 2015;10:e0120197.
190. Routier A, Habert MO, Bertrand A, et al. Structural, Microstructural, and Metabolic Alterations in Primary Progressive Aphasia Variants. Front Neurol 2018;9:766.
191. Chouliaras L, O'Brien JT. The use of neuroimaging techniques in the early and differential diagnosis of dementia. Mol Psychiatry 2023;28:4084-4097.
192. Laforce R, Jr., Soucy JP, Sellami L, et al. Molecular imaging in dementia: Past, present, and future. Alzheimers Dement 2018;14:1522-1552.
193. Kantarci K, Boeve BF, Przybelski SA, et al. FDG PET metabolic signatures distinguishing prodromal DLB and prodromal AD. Neuroimage Clin 2021;31:102754.
194. Ludolph AC, Kassubek J, Landwehrmeyer BG, et al. Tauopathies with parkinsonism: clinical spectrum, neuropathologic basis, biological markers, and treatment options. Eur J Neurol 2009;16:297-309.
195. Bohnen NI, Djang DS, Herholz K, Anzai Y, Minoshima S. Effectiveness and safety of 18F-FDG PET in the evaluation of dementia: a review of the recent literature. J Nucl Med 2012;53:59-71.
196. Matsuda H, Shigemoto Y, Sato N. Neuroimaging of Alzheimer's disease: focus on amyloid and tau PET. Jpn J Radiol 2019;37:735-749.
197. Marquié M, Normandin MD, Vanderburg CR, et al. Validating novel tau positron emission tomography tracer [F-18]-AV-1451 (T807) on postmortem brain tissue. Ann Neurol 2015;78:787-800.
198. Sander K, Lashley T, Gami P, et al. Characterization of tau positron emission tomography tracer [(18)F]AV-1451 binding to postmortem tissue in Alzheimer's disease, primary tauopathies, and other dementias. Alzheimers Dement 2016;12:1116-1124.
199. Kagi G, Bhatia KP, Tolosa E. The role of DAT-SPECT in movement disorders. J Neurol Neurosurg Psychiatry 2010;81:5-12.
200. Surendranathan A, O'Brien JT. Clinical imaging in dementia with Lewy bodies. Evid Based Ment Health 2018;21:61-65.
201. Law ZK, Todd C, Mehraram R, et al. The Role of EEG in the Diagnosis, Prognosis and Clinical Correlations of Dementia with Lewy Bodies-A Systematic Review. Diagnostics (Basel) 2020;10.
202. Jiao B, Li R, Zhou H, et al. Neural biomarker diagnosis and prediction to mild cognitive impairment and Alzheimer's disease using EEG technology. Alzheimers Res Ther 2023;15:32.

203. Neri S, Mastroianni G, Gardella E, Aguglia U, Rubboli G. Epilepsy in neurodegenerative diseases. Epileptic Disord 2022;24:249-273.
204. Hu MT. REM sleep behavior disorder (RBD). Neurobiol Dis 2020;143:104996.
205. Shaw LM, Vanderstichele H, Knapik-Czajka M, et al. Cerebrospinal fluid biomarker signature in Alzheimer's disease neuroimaging initiative subjects. Ann Neurol 2009;65:403-413.
206. Tapiola T, Alafuzoff I, Herukka SK, et al. Cerebrospinal fluid {beta}-amyloid 42 and tau proteins as biomarkers of Alzheimer-type pathologic changes in the brain. Arch Neurol 2009;66:382-389.
207. Jansen WJ, Ossenkoppele R, Knol DL, et al. Prevalence of cerebral amyloid pathology in persons without dementia: a meta-analysis. Jama 2015;313:1924-1938.
208. Jack CR, Jr., Wiste HJ, Weigand SD, et al. Age-specific and sex-specific prevalence of cerebral β-amyloidosis, tauopathy, and neurodegeneration in cognitively unimpaired individuals aged 50-95 years: a cross-sectional study. Lancet Neurol 2017;16:435-444.
209. Ashton NJ, Hye A, Rajkumar AP, et al. An update on blood-based biomarkers for non-Alzheimer neurodegenerative disorders. Nat Rev Neurol 2020;16:265-284.
210. Baiardi S, Quadalti C, Mammana A, et al. Diagnostic value of plasma p-tau181, NfL, and GFAP in a clinical setting cohort of prevalent neurodegenerative dementias. Alzheimers Res Ther 2022;14:153.
211. Leuzy A, Mattsson-Carlgren N, Palmqvist S, Janelidze S, Dage JL, Hansson O. Blood-based biomarkers for Alzheimer's disease. EMBO Mol Med 2022;14:e14408.
212. Cummings JL, Tong G, Ballard C. Treatment Combinations for Alzheimer's Disease: Current and Future Pharmacotherapy Options. J Alzheimers Dis 2019;67:779-794.
213. Mummery CJ, Börjesson-Hanson A, Blackburn DJ, et al. Tau-targeting antisense oligonucleotide MAPT(Rx) in mild Alzheimer's disease: a phase 1b, randomized, placebo-controlled trial. Nat Med 2023;29:1437-1447.
214. Magrath Guimet N, Zapata-Restrepo LM, Miller BL. Advances in Treatment of Frontotemporal Dementia. J Neuropsychiatry Clin Neurosci 2022;34:316-327.
215. Fritz CO, Morris PE, Richler JJ. Effect size estimates: current use, calculations, and interpretation. J Exp Psychol Gen 2012;141:2-18.
216. Middel B, van Sonderen E. Statistical significant change versus relevant or important change in (quasi) experimental design: some conceptual and methodological problems in estimating magnitude of intervention-related change in health services research. Int J Integr Care 2002;2:e15.
217. Pichet Binette A, Palmqvist S, Bali D, et al. Combining plasma phospho-tau and accessible measures to evaluate progression to Alzheimer's dementia in mild cognitive impairment patients. Alzheimers Res Ther 2022;14:46.
218. Calamia M, Markon K, Tranel D. Scoring higher the second time around: meta-analyses of practice effects in neuropsychological assessment. Clin Neuropsychol 2012;26:543-570.

219. Duff K, Hammers DB, Koppelmans V, King JB, Hoffman JM. Short-Term Practice Effects on Cognitive Tests Across the Late Life Cognitive Spectrum and How They Compare to Biomarkers of Alzheimer's Disease. J Alzheimers Dis 2024;99:321-332.
220. Carpenter CR, McFarland F, Avidan M, et al. Impact of Cognitive Impairment Across Specialties: Summary of a Report From the U13 Conference Series. J Am Geriatr Soc 2019;67:2011-2017.
221. Heymans MW, Twisk JWR. Handling missing data in clinical research. J Clin Epidemiol 2022;151:185-188.
222. Lyketsos CG, Carrillo MC, Ryan JM, et al. Neuropsychiatric symptoms in Alzheimer's disease. Alzheimers Dement 2011;7:532-539.
223. Younes K, Miller BL. Neuropsychiatric Aspects of Frontotemporal Dementia. Psychiatr Clin North Am 2020;43:345-360.
224. Allegri RF, Sarasola D, Serrano CM, et al. Neuropsychiatric symptoms as a predictor of caregiver burden in Alzheimer's disease. Neuropsychiatr Dis Treat 2006;2:105-110.
225. Classon E, van den Hurk W, Lyth J, Johansson MM. Montreal Cognitive Assessment: Normative Data for Cognitively Healthy Swedish 80- to 94-Year-Olds. J Alzheimers Dis 2022;87:1335-1344.
226. Morales CD, Cotton-Samuel D, Lao PJ, et al. Small vessel cerebrovascular disease is associated with cognition in prospective Alzheimer's clinical trial participants. Alzheimers Res Ther 2024;16:25.
227. De Santi S, Pirraglia E, Barr W, et al. Robust and conventional neuropsychological norms: diagnosis and prediction of age-related cognitive decline. Neuropsychology 2008;22:469-484.
228. Lezak MD, Howieson DB, Bigler ED, Tranel D. Neuropsychological Assessment: Oxford University Press, 2012.
229. Guo J, Huang X, Dou L, et al. Aging and aging-related diseases: from molecular mechanisms to interventions and treatments. Signal Transduct Target Ther 2022;7:391.
230. Denic A, Glassock RJ, Rule AD. Structural and Functional Changes With the Aging Kidney. Adv Chronic Kidney Dis 2016;23:19-28.
231. Cain PA, Ahl R, Hedstrom E, et al. Age and gender specific normal values of left ventricular mass, volume and function for gradient echo magnetic resonance imaging: a cross sectional study. BMC Med Imaging 2009;9:2.
232. Konstantopoulos K, Vogazianos P, Doskas T. Normative Data of the Montreal Cognitive Assessment in the Greek Population and Parkinsonian Dementia. Arch Clin Neuropsychol 2016;31:246-253.
233. Larouche E, Tremblay MP, Potvin O, et al. Normative Data for the Montreal Cognitive Assessment in Middle-Aged and Elderly Quebec-French People. Arch Clin Neuropsychol 2016;31:819-826.
234. Santangelo G, Siciliano M, Pedone R, et al. Normative data for the Montreal Cognitive Assessment in an Italian population sample. Neurol Sci 2015;36:585-591.

235. Freitas S, Simoes MR, Alves L, Santana I. Montreal Cognitive Assessment (MoCA): normative study for the Portuguese population. J Clin Exp Neuropsychol 2011;33:989-996.
236. Goncalves J, Gerardo B, Nogueira J, Afonso RM, Freitas S. Montreal Cognitive Assessment (MoCA): An update normative study for the Portuguese population. Appl Neuropsychol Adult 2023:1-7.
237. Kenny RA, Coen RF, Frewen J, Donoghue OA, Cronin H, Savva GM. Normative values of cognitive and physical function in older adults: findings from the Irish Longitudinal Study on Ageing. J Am Geriatr Soc 2013;61 Suppl 2:S279-290.
238. Fioravanti M, Nacca D, Buckley AE, et al. The Italian version of the Alzheimer's Disease Assessment Scale (ADAS): psychometric and normative characteristics from a normal aged population. Arch Gerontol Geriatr 1994;19:21-30.
239. Santos Nogueira D, Azevedo Reis E, Vieira A. Verbal Fluency Tasks: Effects of Age, Gender, and Education. Folia Phoniatr Logop 2016;68:124-133.
240. Van der Elst W, Van Boxtel MP, Van Breukelen GJ, Jolles J. Normative data for the Animal, Profession and Letter M Naming verbal fluency tests for Dutch speaking participants and the effects of age, education, and sex. J Int Neuropsychol Soc 2006;12:80-89.
241. Cavaco S, Goncalves A, Pinto C, et al. Semantic fluency and phonemic fluency: regression-based norms for the Portuguese population. Arch Clin Neuropsychol 2013;28:262-271.
242. Tallberg IM, Ivachova E, Jones Tinghag K, Ostberg P. Swedish norms for word fluency tests: FAS, animals and verbs. Scand J Psychol 2008;49:479-485.
243. Troyer AK. Normative data for clustering and switching on verbal fluency tasks. J Clin Exp Neuropsychol 2000;22:370-378.
244. Brucki SM, Rocha MS. Category fluency test: effects of age, gender and education on total scores, clustering and switching in Brazilian Portuguese-speaking subjects. Braz J Med Biol Res 2004;37:1771-1777.
245. Tombaugh TN, Kozak J, Rees L. Normative data stratified by age and education for two measures of verbal fluency: FAS and animal naming. Arch Clin Neuropsychol 1999;14:167-177.
246. Nielsen NP, Wiig EH. Alzheimer's Quick Test cognitive screening criteria for West African speakers of Krio. Age Ageing 2006;35:503-507.
247. Petrazzuoli F, Palmqvist S, Thulesius H, et al. A Quick Test of Cognitive Speed: norm-referenced criteria for 121 Italian adults aged 45 to 90 years. Int Psychogeriatr 2014:1-8.
248. Wiig EH, Al-Halees Y. A quick test of cognitive speed: preliminary screening criteria for Arabic-speaking adults, ages 40 to 80 years. Percept Mot Skills 2013;117:615-626.
249. Wiig EH, Nielsen NP, Minthon L, McPeek D, Said K, Warkentin S. Parietal lobe activation in rapid, automatized naming by adults. Percept Mot Skills 2002;94:1230-1244.

250. Harrington KD, Lim YY, Ames D, et al. Using Robust Normative Data to Investigate the Neuropsychology of Cognitive Aging. Arch Clin Neuropsychol 2017;32:142-154.
251. Houx PJ, Jolles J, Vreeling FW. Stroop interference: aging effects assessed with the Stroop Color-Word Test. Exp Aging Res 1993;19:209-224.
252. Zimmermann N, Cardoso CO, Trentini CM, Grassi-Oliveira R, Fonseca RP. Brazilian preliminary norms and investigation of age and education effects on the Modified Wisconsin Card Sorting Test, Stroop Color and Word test and Digit Span test in adults. Dement Neuropsychol 2015;9:120-127.
253. Klein M, Ponds RW, Houx PJ, Jolles J. Effect of test duration on age-related differences in Stroop interference. J Clin Exp Neuropsychol 1997;19:77-82.
254. van Boxtel MP, ten Tusscher MP, Metsemakers JF, Willems B, Jolles J. Visual determinants of reduced performance on the Stroop color-word test in normal aging individuals. J Clin Exp Neuropsychol 2001;23:620-627.
255. Llinas-Regla J, Vilalta-Franch J, Lopez-Pousa S, Calvo-Perxas L, Torrents Rodas D, Garre-Olmo J. The Trail Making Test. Assessment 2017;24:183-196.
256. Arango-Lasprilla JC, Rivera D, Aguayo A, et al. Trail Making Test: Normative data for the Latin American Spanish speaking adult population. NeuroRehabilitation 2015;37:639-661.
257. Wecker NS, Kramer JH, Wisniewski A, Delis DC, Kaplan E. Age effects on executive ability. Neuropsychology 2000;14:409-414.
258. Zimmermann N, Cardoso CO, Kristensen CH, Fonseca RP. Brazilian norms and effects of age and education on the Hayling and Trail Making Tests. Trends Psychiatry Psychother 2017;39:188-195.
259. Arango-Lasprilla JC, Rivera D, Rodriguez G, et al. Symbol Digit Modalities Test: Normative data for the Latin American Spanish speaking adult population. NeuroRehabilitation 2015;37:625-638.
260. Kiely KM, Butterworth P, Watson N, Wooden M. The Symbol Digit Modalities Test: Normative data from a large nationally representative sample of Australians. Arch Clin Neuropsychol 2014;29:767-775.
261. Burggraaff J, Knol DL, Uitdehaag BMJ. Regression-Based Norms for the Symbol Digit Modalities Test in the Dutch Population: Improving Detection of Cognitive Impairment in Multiple Sclerosis? Eur Neurol 2017;77:246-252.
262. Vogel A, Stokholm J, Jorgensen K. Performances on Symbol Digit Modalities Test, Color Trails Test, and modified Stroop test in a healthy, elderly Danish sample. Neuropsychol Dev Cogn B Aging Neuropsychol Cogn 2013;20:370-382.
263. Hsieh SL, Tori CD. Normative data on cross-cultural neuropsychological tests obtained from Mandarin-speaking adults across the life span. Arch Clin Neuropsychol 2007;22:283-296.
264. Verde F, Otto M, Silani V. Neurofilament Light Chain as Biomarker for Amyotrophic Lateral Sclerosis and Frontotemporal Dementia. Front Neurosci 2021;15:679199.

265. Wilson RS, Leurgans SE, Boyle PA, Schneider JA, Bennett DA. Neurodegenerative basis of age-related cognitive decline. Neurology 2010;75:1070-1078.
266. Quadalti C, Palmqvist S, Hall S, et al. Clinical effects of Lewy body pathology in cognitively impaired individuals. Nat Med 2023;29:1964-1970.
267. Joza S, Hu MT, Jung KY, et al. Prodromal dementia with Lewy bodies in REM sleep behavior disorder: A multicenter study. Alzheimers Dement 2024;20:91-102.
268. Liao YZ, Ma J, Dou JZ. The Role of TDP-43 in Neurodegenerative Disease. Mol Neurobiol 2022;59:4223-4241.
269. Donohue MC, Sperling RA, Petersen R, et al. Association Between Elevated Brain Amyloid and Subsequent Cognitive Decline Among Cognitively Normal Persons. JAMA 2017;317:2305-2316.
270. Villemagne VL, Burnham S, Bourgeat P, et al. Amyloid beta deposition, neurodegeneration, and cognitive decline in sporadic Alzheimer's disease: a prospective cohort study. Lancet Neurol 2013;12:357-367.
271. Ravaglia G, Forti P, Montesi F, et al. Mild cognitive impairment: epidemiology and dementia risk in an elderly Italian population. J Am Geriatr Soc 2008;56:51-58.
272. Luck T, Luppa M, Wiese B, et al. Prediction of incident dementia: impact of impairment in instrumental activities of daily living and mild cognitive impairment-results from the German study on ageing, cognition, and dementia in primary care patients. Am J Geriatr Psychiatry 2012;20:943-954.
273. Macdougall A, Whitfield T, Needham K, Schott JM, Frost C, Walker Z. Predicting progression to Alzheimer's disease dementia using cognitive measures. Int J Geriatr Psychiatry 2024;39:e6067.
274. Borland E, Edgar C, Stomrud E, Cullen N, Hansson O, Palmqvist S. Clinically Relevant Changes for Cognitive Outcomes in Preclinical and Prodromal Cognitive Stages: Implications for Clinical Alzheimer Trials. Neurology 2022;99:e1142-e1153.
275. Budd Haeberlein S, Aisen PS, Barkhof F, et al. Two Randomized Phase 3 Studies of Aducanumab in Early Alzheimer's Disease. J Prev Alzheimers Dis 2022;9:197-210.
276. ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT02477800 [online].
277. ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT02484547 [online].
278. Bateman RJ, Smith J, Donohue MC, et al. Two Phase 3 Trials of Gantenerumab in Early Alzheimer's Disease. N Engl J Med 2023;389:1862-1876.
279. ClinicalTrials.gov. https://clinicaltrials.gov/study/NCT03444870 [online].
280. ClinicalTrials.gov. https://clinicaltrials.gov/study/NCT03443973 [online].
281. Honig LS, Vellas B, Woodward M, et al. Trial of Solanezumab for Mild Dementia Due to Alzheimer's Disease. N Engl J Med 2018;378:321-330.
282. Sperling RA, Donohue MC, Raman R, et al. Trial of Solanezumab in Preclinical Alzheimer's Disease. N Engl J Med 2023;389:1096-1107.
283. van Dyck CH, Swanson CJ, Aisen P, et al. Lecanemab in Early Alzheimer's Disease. N Engl J Med 2023;388:9-21.
284. Aisen PS, Andrieu S, Sampaio C, et al. Report of the task force on designing clinical trials in early (predementia) AD. Neurology 2011;76:280-286.

285. Bioarctic. Lecanemab deliberations at the CHMP regarding the Marketing Authorisation Application in the EU have been rescheduled due to procedural reasons. 2024.
286. Sims JR, Zimmer JA, Evans CD, et al. Donanemab in Early Symptomatic Alzheimer Disease: The TRAILBLAZER-ALZ 2 Randomized Clinical Trial. JAMA 2023;330:512-527.
287. Rogers B. Donanemab Approved in the U.S. [online]. Available at: https://www.alzforum.org/news/community-news/donanemab-approved-us. Accessed 2024-07-17.
288. Cognat E, Koehl B, Lilamand M, et al. Preventing Post-Lumbar Puncture Headache. Ann Emerg Med 2021;78:443-450.
289. Salzer J, Granasen G, Sundstrom P, Vagberg M, Svenningsson A. Prevention of post-dural puncture headache: a randomized controlled trial. Eur J Neurol 2020;27:871-877.
290. Blennow K, Wallin A, Hager O. Low frequency of post-lumbar puncture headache in demented patients. Acta Neurol Scand 1993;88:221-223.
291. Zetterberg H, Tullhog K, Hansson O, Minthon L, Londos E, Blennow K. Low incidence of post-lumbar puncture headache in 1,089 consecutive memory clinic patients. Eur Neurol 2010;63:326-330.
292. Chandra M, Harbishettar V, Sawhney H, Amanullah S. Ethical Issues in Dementia Research. Indian J Psychol Med 2021;43:S25-S30.
293. Schulz R, O'Brien A, Czaja S, et al. Dementia caregiver intervention research: in search of clinical significance. Gerontologist 2002;42:589-602.
294. Belleville S, LaPlume AA, Purkart R. Web-based cognitive assessment in older adults: Where do we stand? Curr Opin Neurol 2023;36:491-497.
295. Libon DJ, Baliga G, Swenson R, Au R. Digital Neuropsychological Assessment: New Technology for Measuring Subtle Neuropsychological Behavior. J Alzheimers Dis 2021;82:1-4.
296. Gold M, Amatniek J, Carrillo MC, et al. Digital technologies as biomarkers, clinical outcomes assessment, and recruitment tools in Alzheimer's disease clinical trials. Alzheimers Dement (N Y) 2018;4:234-242.
297. Brose A, Schmiedek F, Lovden M, Lindenberger U. Daily variability in working memory is coupled with negative affect: the role of attention and motivation. Emotion 2012;12:605-617.

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Emma Borland graduated from medical school at Copenhagen University in 2016. She is currently undertaking specialist training in neurology at Skåne University Hospital.

As treatments for neurodegenerative diseases advance, early identification of cognitive decline has become increasingly important for initiating timely intervention and assessing treatment efficacy. This thesis explores various aspects of cognitive testing related to neurocognitive disorders.

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