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Understanding Preclinical Dementia: Early Detection of Dementia Through Cognitive and Biological Markers

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UNDERSTANDING PRECLINICAL DEMENTIA: EARLY DETECTION OF DEMENTIA THROUGH COGNITIVE AND BIOLOGICAL MARKERS

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To my family,

ABSTRACT

Dementia is becoming a growing healthcare crisis, therefore identifying individuals at risk or in the earliest stages of dementia is essential if prevention or disease modification is to be achieved. The objective of this thesis was to examine cognitive performance and decline during the preclinical phase and explore the ability of cognitive and biological markers to identify those at risk of future dementia. Data from a population-based longitudinal study, SNAC-K, were used to investigate this aim.

Study I examined the ability of neuropsychological tests, genetics, and structural MRI volumes to predict dementia six years later. Models were systematically created to identify the best combinations for prediction. A model containing all three modalities: hippocampal volume, a task of category fluency, presence of an *APOE* ε4 allele, white-matter hyperintensities volume, and a task of general knowledge, displayed the most predictive value (AUC=.924; C.I=.883–.965). However, this model did not significantly improve predictive value over one containing only cognitive and genetic markers, suggesting that minor increases in predictivity should be weighed against the costs of additional tests.

Study II investigated the benefit of DTI, alongside neuropsychological tests, genetics, and brain volume markers in predicting future dementia. MD values for tracts CHC, CS, FMAJ, and IFOF (AUC=.837–.862) and the FA IFOF latent factor (AUC=.839) were significantly associated with dementia at six years. A final model consisting of a measure of perceptual speed, hippocampal volume, and MD of the FMAJ tract was created with the highest predictive value (AUC=.911). Assessment of microstructural white matter integrity via DTI was associated with future dementia but the additional benefit when combined with other markers was relatively small.

Study III narrowed its focus to the ability of cognitive markers alone and the effect of modifying factors (age, sex, education, the presence of an ε4 allele, AD–only dementia, and time to diagnosis) on identifying those at risk of dementia. The most predictive model, consisting of category fluency, word recall, and pattern comparison, achieved good prediction values (AUC=.913) for dementia six years later. Tests in the domains of category fluency, episodic memory, and perceptual speed were, in general, good predictors across all subgroups and up to 6 years before a dementia diagnosis. However, cognitive tests became increasingly unreliable at predicting dementia beyond that time.

Study IV explored the trajectories of cognitive decline over a 12-year period during the preclinical stage of dementia, before examining the ability of early cognitive decline in identifying those with increased likelihood of future dementia. Persons in the preclinical phase showed increased rate of decline in all cognitive domains compared to those who did not develop dementia (β:-.07 to -.11), this difference was particularly noticeable closer to diagnosis. Those classified as fast decliners for 3 or more cognitive tests demonstrated the highest risk of dementia (HR: 3.38, CI: 1.91-6.01). Although, changes in early rates of decline were small and rates of decline may be more predictive closer to diagnosis.

Collectively, these studies confirm a long preclinical period in dementia development, which allows for the use of a wide range of markers (cognitive, genetic, MRI, and DTI) capable of identifying those at high risk of dementia. The ability of these markers to predict future dementia is increased through combining within and between modalities.

Key words: Preclinical dementia, cognition, biomarkers, prediction, longitudinal

SAMMANFATTNING

Demens är ett växande problem för samhället och vården. Därför är det viktigt att identifiera personer i riskzonen eller i de tidigaste stadierna av demens, så att förebyggande eller sjukdomsmodifierande åtgärder kan sättas in i tid. Syftet med denna avhandling var att undersöka kognitiv prestation och försämring under den prekliniska fasen och utforska förmågan hos kognitiva och biologiska markörer att identifiera de som riskerar att utveckla demens. För detta ändamål användes data från en populationsbaserad longitudinell studie, SNAC-K.

Studie I undersökte förmågan hos neuropsykologiska tester, genetik och strukturella MRI-volymer att förutsäga demens sex år senare. Modeller skapades systematiskt för att identifiera de bästa kombinationerna för att predicera framtida demens. En modell som innehöll alla tre modaliteter: hippocampusvolym, verbalt flöde, närvaro av en *APOE* ε4-allel, hyperintensitet i vit hjärnsubstans och ett allmänbildningstest kunde bäst förutsäga demens (AUC = .924; CI = .883 -.965). Men denna modell förbättrade inte förutsägelsevärdet signifikant jämfört med en som endast innehöll kognitiva och genetiska markörer, vilket tyder på att mindre ökningar i prediktivitet bör vägas mot kostnaderna för ytterligare test.

Studie II undersökte fördelen av DTI, tillsammans med neuropsykologiska tester, genetik och hjärnvolymmarkörer för att förutsäga demens. MD-värden för CHC, CS, FMAJ och IFOF (AUC = .837 – .862) och FA för den latenta IFOF-faktorn (AUC = .839) var signifikant förknippade med demens sex år senare. En slutlig modell bestående av ett mått på perceptuell snabbhet, hippocampusvolym och MD för FMAJ hade det högsta prediktiva värdet (AUC = .911). Bedömning av mikrostrukturell vitsubstansintegritet via DTI var kopplad till utveckling av demens, men det adderade värdet i kombination med andra markörer var relativt liten.

Studie III fokuserade enbart på förmågan hos kognitiva markörer och effekten av modifierande faktorer (ålder, kön, utbildning, närvaron av en ε4-allel, AD-demens och tid till diagnos) på möjligheten att identifiera de med ökad risk att utveckla demens. Den mest prediktiva modellen, bestående av kategoriflöde, fri återkallning av ord och perceptuell snabbhet, uppnådde goda prediktionsvärden (AUC = .913) för demens sex år senare. Tester inom områdena kategoriflöde, episodiskt minne och perceptuell hastighet var i allmänhet bra prediktorer i alla undergrupper och upp till 6 år innan en demensdiagnos. Kognitiva tester var mindre tillförlitliga längre än 6 år innan diagnos.

Studie IV undersökte kognitiv nedgång under en 12-årsperiod av den prekliniska fasen av demens. Kognitiv försämringstakt tidigt i den prekliniska fasen användes sedan för att identifiera personer med ökad sannolikhet att utveckla demens. Personer i en preklinisk fas av demens uppvisade en ökad försämringstakt för alla kognitiva domäner jämfört med de som inte utvecklade demens (ß: -. 07 till -.11), denna skillnad var särskilt märkbar närmare diagnos. De som uppvisade snabb nedgång i 3 eller fler kognitiva test hade den högsta risken för demens (HR: 3,38, CI: 1,91-6,01). Skillnaderna i förändringstakt tidigt i den prekliniska fasen var små, och kognitiv försämring kan ha högre prediktivitet närmare en demensdiagnos.

Sammantaget bekräftar dessa studier förekomsten av en lång preklinisk period i demensutvecklingen, vilket möjliggör användning av ett brett spektrum av markörer (kognitiva, genetiska, MRI och DTI) för att identifiera personer med hög risk för demens. Dessa markörers förmåga att förutsäga demens kan förbättras genom att kombineras med ytterligare markörer, inom samma eller andra modaliteter.

Nyckelord: Preklinisk demens, kognition, biomarkörer, förutsägelse, longitudinell

LIST OF SCIENTIFIC PAPERS

I. Payton, N. M., Kalpouzos, G., Rizzuto, D., Fratiglioni, L., Kivipelto, M., Bäckman, L., & Laukka, E. J. (2018). Combining Cognitive, Genetic, and Structural Neuroimaging Markers to Identify Individuals with Increased Dementia Risk. *Journal of Alzheimer's disease: JAD*, *64*(2), 533–542.

II. Müller, T., Payton, N. M., Kalpouzos, G., Jessen, F., Grande, G., Bäckman, L., & Laukka, E. J. (2020). Cognitive, genetic, brain volume, and diffusion tensor imaging markers as early indicators of dementia. *Journal of Alzheimer's Disease – accepted.*

III. Payton, N. M., Rizzuto, D., Fratiglioni, L., Kivipelto, M., Bäckman, L., & Laukka, E. J. (2020). Combining Cognitive Markers to Identify Individuals at Increased Dementia Risk: Influence of Modifying Factors and Time to Diagnosis. *Journal of the International Neuropsychological Society: JINS*, *26(8)*, 785–797.

IV. Payton, N. M., Marseglia, A., Grande, G., Fratiglioni, L., Kivipelto, M., Bäckman, L., & Laukka, E. J. Trajectories of preclinical cognitive decline and dementia development: A 12-year longitudinal study. *Manuscript.*

CONTENTS

LIST OF ABBREVIATIONS

Aβ	Amyloid-beta
AD	Alzheimer's disease
ADNI	Alzheimer's Disease Neuroimaging Initiative
APOE	Apolipoprotein E
AUC	Area under the curve
BMI	Body mass index
CCG	Cingulum cingulate gyrus
CFI	Comparative Fit Index
CHC	Cingulum extending to the hippocampus
C-index	Concordance indices
CI	Confidence intervals
CS	Corticospinal tract
DSM	Diagnostic and Statistical Manual of Mental Disorders
DTI	Diffusion tensor imaging
FA	Fractional anisotropy
FLAIR	Fluid attenuation inversion recovery
FMAJ	Forceps major
FMIN	Forceps minor
FOV	Field of view
HR	Hazard ratios
ICV	Intracranial volume
IFOF	Inferior fronto-occipital fasciculus
MCI	Mild cognitive impairment
MD	Mean diffusivity
MMSE	Mini-Mental State Examination
MRI	Magnetic resonance imaging
MTL	Medial temporal lobe
NCD	Neurocognitive disorder
NFTs	Neurofibrillary tangles

NINCDS-ADRDA	National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association
PET	Positron emission tomography
OR	Odds ratio
ROC	Reciever operating characteristics
SEM	Structural equation modelling
SLF	Superior longitudinal fasciculus
SNAC-K	Swedish National Study on Aging and Care-Kungsholmen
TBSS	Tract-based spatial statistics
TE	Echo time
TMT	Trail making task
TR	Repetition time
VaD	Vascular dementia
WMHs	White matter hyperintensities

INTRODUCTION

As the population ages, the total number of people affected by dementia is rising and may potentially reach 75 million by 2030 and 132 million by 2050 [1]. Alongside the personal toll of cognitive decline and loss of independence there is the burden of informal care, which typically falls on the families or relatives of those affected, and formal care, provided by governments. This means that the effects of dementia are varied and can be felt far beyond the individual, clinical symptoms. These effects are further exacerbated by the fact that the only current, effective treatments for dementia focus on managing symptoms rather than preventing or reversing underlying pathology. Due to these issues, dementia is becoming one of the most challenging public health crises that the world will have to face.

Cognitive aging

Cognition is the ability to use conscious mental processing and covers a wide range of domains including multiple types of memory, language, executive function, verbal fluency, and perceptual speed. As part of the normal aging process many of these abilities decline over time. Measures of fluid cognition, including the above mentioned, episodic memory, executive function, and perceptual speed often see the greatest changes as part of normal aging [2, 3]. The onset of this decline differs depending on the methods used [4, 5], with decline suggested by cross-sectional studies to begin earlier than has been found in longitudinal research. Research of the same individuals over time has shown that these domains typically remain stable throughout adulthood until around the age of 60-70 years old, when a relatively consistent decline begins [6]. For measures of crystallized cognition, such as semantic memory, performance has been shown to remain intact or even improve over the life course until very late life [2, 3]. Regardless of discrepancies within the research, a shared conclusion is that decline in cognitive ability is a common feature of aging. However, despite the ubiquity of cognitive decline not everyone will experience these age-related changes in the same way and there are large individual differences in baseline performance, onset of decline, and rate of decline [7-9], as illustrated by Figure 1.

As with cognition, extensive changes also occur in the brain during the normal aging process [2, 10-12] and large individual differences are present [10, 12]. As a part of normal aging, neuronal atrophy, which is the loss of neurons, results in decreases in both grey and white matter volume [2, 10, 12]. While this decline is most obvious in frontal regions, it has also been shown in multiple brain areas, including parietal and medial temporal lobes (MTL) [12-14]. That grey matter atrophy in these regions has been associated with the cognitive domains most likely to decline with aging, such as episodic memory and the hippocampus/MTL [15, 16], is testament to the intrinsic link between brain structure and cognition.

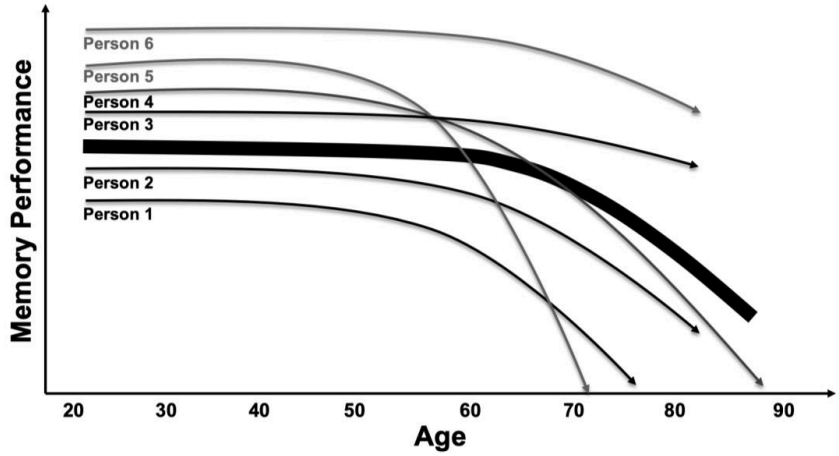

Figure 1: Graphical illustration of individual memory performance over a lifespan. The bold line represents mean performance across individuals. Based on data from Schaie (1996)[17], de Frias et al., 2007[18], Rönnlund et al., 2005[6], and Rönnlund et al., 2007[19].

Dementia

Dementia is a syndrome characterised by ongoing cognitive decline. It should be noted that dementia, based on the Diagnostic and Statistical Manual of Mental Disorders (DSM), has recently undergone major revisions for the latest edition (DSM-V). The term 'dementia' has been replaced with 'major neurocognitive disorder (NCD)', however the main criteria remain largely the same. Major NCD requires a significant decline in one or more domains of cognition, the cognitive decline must interfere with independence, and must not be due to delirium or other mental disorders. In the DSM-V, mild NCD was also introduced to bridge the gap between normal cognitive aging and dementia/major NCD. It allows for moderate cognitive decline, which does not interfere with independence, similar to the related classification 'mild cognitive impairment' (MCI). The mild NCD classification acknowledges the often gradual nature of cognitive decline which leads to dementia.

This thesis will refer to 'dementia' rather than 'major NCD' as dementia is typically associated with cognitive decline in older persons and a part of pathological aging, as opposed to major NCD which may be attributed to non-age-related causes, such as traumatic brain injury or complications from HIV infection.

Dementia subtypes

While dementia is defined by cognitive decline, there are many potential causes and pathologies underlying this process. Common causes include Alzheimer's disease (AD), vascular dementia (VaD), frontotemporal dementia, dementia with Lewy bodies, and Parkinson's disease dementia, or pathologies from two or more of these diseases. As they represent the most frequent causes of dementia, the focus of this thesis will be on AD, VaD, or a combination of the two, which will be referred to as 'mixed dementia'.

Alzheimer's Disease

AD, often considered to be the most common cause of dementia [20], is a degenerative disorder characterised by the accumulation of amyloid-beta (Aβ) as plaques and aggregates of hyperphosphorylated tau as neurofibrillary tangles (NFTs) within the brain. There are two main forms of AD: familial, where AD is inherited in an autosomal dominant fashion and onset is earlier in life, and sporadic, which is due to a mix of genetic and environmental factors and occurs later in life. Familial AD is responsible for between <1-5% of all AD cases [21, 22], depending on the subtype and definition, while sporadic AD accounts for the vast majority of AD cases (~95%).

The exact cause of AD pathology is still debated, however the most common theory is the Amyloid Cascade Hypothesis [23, 24]. This theory postulates that the pathological process begins with an increased production of the Aβ peptide, the inability to remove the excess Aβ leads to an accumulation of oligomerised peptides which deposit as plaques. These plaques then cause a chain reaction of direct and indirect effects, including pathological changes in astrocyte and microglial activation and phosphorylation of tau causing neuronal damage. This damage eventually leads to cell death and subsequent dementia. Alternative hypotheses include the Mitochondrial Cascade Hypothesis [25] and the Inflammation Hypothesis [26, 27]. The Mitochondrial Cascade Hypothesis suggests that AD-pathology, including amyloidosis, is due primarily to age-related mitochondrial dysfunction [25]. While the Inflammation Hypothesis proposes that chronic inflammation, alongside dysfunction of microglia and astrocytes, is not merely a product of amyloid deposition but a key driver in AD pathology [26, 27].

Although the exact mechanisms are debated, accumulation of Aβ is one of the primary symptoms of AD and a key component in defining the disease [28, 29]. Other markers include the presence of NFTs [30], neural atrophy [31-34], and cognitive deficits over a range of different domains but most commonly associated with episodic memory loss [35-40].

Vascular dementia

Vascular dementia (VaD) ranks as the second most common dementia type [41]. As indicated by the name, VaD is caused by problems in the vascular system. While it may be a heterogeneous condition, there are two main forms: cortical and subcortical [42, 43]. Cortical VaD is often associated with stroke and follows a step-wise progression as cognitive function remains stable between events but declines rapidly after each subsequent infarct. Subcortical VaD refers to small vessel disease and lesions in subcortical white matter, which gradually accumulate, causing damage over time [44].

It therefore makes sense that many markers for vascular dementia are related to white matter damage, such as white-matter hyperintensities (WMHs), lesions, and microinfarcts, which can be identified using magnetic resonance imaging (MRI) [45]. Cognitive impairment is a feature of both cortical and subcortical VaD, although presentation of cognitive deficits can differ between the two. The symptom profile of cortical VaD depends on the location of the infarcts so can vary greatly between cases, while cognitive symptoms in subcortical VaD primarily include executive functioning and attention deficits [42, 46].

Mixed dementia

Although AD and VaD represent two different etiologies of dementia, it is worth noting that there is substantial overlap in AD and vascular pathology, particularly in the oldest old [47, 48]. While AD is often touted as the most common form of dementia, evidence is emerging to suggest that mixed dementia may be more common than either pure AD or VaD [48, 49], especially in the general population [41].

In addition to the pathological overlap between these conditions, there is evidence that AD and VaD share many common symptoms. Cognitive deficits in episodic memory, semantic memory, executive function, and visuospatial tasks are frequently observed in both diseases [50, 51] and cognitive tests may have limited ability to distinguish between the two conditions [52]. There is also evidence of additive effects of mixed pathology on memory deficits [53] and synergistic effects of vascular pathology, such as WMHs and vascular lesions, on hippocampal atrophy in AD [54-56]. Common risk factors, such as hypertension, have been related to both pathological aspects of AD, through NFTs and senile plaques, and VaD, through development of WMHs [57].

The common presence of both pathologies in dementia patients, as well as the overlap in symptoms and risk factors, suggests that separating these two conditions may not be the optimal way of addressing their impact or treatment. It stands to reason that mixed dementia should be considered as a whole rather than the sum of its component parts.

Effects of demographic factors

As mentioned, dementia is a heterogeneous disorder with multiple causes, however, the underlying pathology is not the only thing that can affect dementia expression. Various demographic factors can affect these underlying pathologies, as well as the effect of potential risk factors, and symptom presentation. The main three are discussed below:

Age

Dementia is often seen as a sign of pathological aging, with the biggest risk factor in developing dementia being increasing age. The prevalence and incidence of dementia has been observed to increase exponentially for those over the age of 65 [58, 59].

Risk factors for dementia may differ depending on age, with risk factors in mid- to late-life no longer applicable for the oldest old [60-62]. It has been the case that what may be considered a risk factor in middle age can be protective in later life, for example high BMI in midlife is considered a risk factor for future dementia, whereas it is considered protective in late life [63].

There is also strong evidence to show that the symptoms of dementia can differ between age groups. Those in early old age are more likely to show episodic memory deficits and a pattern of cognitive decline more closely associated with AD [64, 65]. Whereas, those in later old age (85+) exhibit a broader range of cognitive deficits, spanning multiple domains [64, 65]. This may partially be explained by differences in underlying pathology between the two age groups as mixed pathology is more common in the older old than in the younger [47, 48]. Therefore, cognitive deficits in those 85+ would present as a mixture of those found in both pathologies.

Sex

It is well documented that women are more likely to develop dementia than men, with the remaining life time risk of a 65 year old woman almost double that of a man of the same age [66]. This difference is particularly noticeable in AD-type dementia [66, 67]. While this can partially be explained by increased life expectancy for women than men, this is unlikely to be the only factor involved [67]. Speculation as to the causes of sex differences in dementia risk have included differences in a range of modifiable and non-modifiable aspects, from hormones, to access to education, to differences in brain structure and chemistry [67]. However, no conclusive evidence has emerged to explain sex differences in the development of dementia.

It is known however that risk factors for dementia differ between the sexes, for example stroke has been considered a more important factor for men, whereas clinical and sub-clinical depression is a greater risk factor for women [68, 69]. There is also evidence to suggest that the *APOE* ε4 allele is a greater risk factor for future AD in women than in men [70] and that cardiovascular risk factors for dementia differ between the sexes [71].

Even when accounting for the same underlying cause, cognitive profiles of dementia between men and women differ over the course of the disease. For example women often perform better at verbal tasks and men on visuospatial/motor tasks [72] and this advantage is often retained during the preclinical phase of AD [73, 74].

Understanding and accounting for sex differences is an essential part of controlling the disorder, as differences in dementia type and presentation of symptoms can have an important effect on dementia screening and the production of potential cures [73].

Education

Strong evidence supports an increased risk of dementia with low education, particularly in those with very low or no education [75, 76]. However, the ability of increased years of education in attenuating risk of dementia is less clear, and it was theorised that additional education would only be beneficial if it matched cognitive capacity.

The link between low education and dementia may not be as simple as it seems, both education and dementia can be affected by factors such as parental socioeconomic status, heath behaviours, such as good nutrition and exercise, and genetics [75]. Although, the association between low education and dementia can remain when these factors are controlled for [77, 78]. The most common theory behind a protective effect of increased education lies with the idea of cognitive reserve [79-81], which suggests that education can increase the ability of the brain to adapt to pathological changes, such as AD or VaD. This allows the brain to maintain normal cognitive functioning, despite pathological accumulation, for a certain period, before these coping mechanisms begin to degrade due to pathological burden. However, it should be noted that the idea of cognitive reserve has a number of criticisms including reflecting, rather than expanding on, known mechanisms, as well as reliance on proxy measures [82-84].

Despite the mechanisms behind low education as a risk factor for dementia not being fully understood, the size of the effect and the fact that it is a modifiable risk factor, particularly in low economic status countries, which would struggle with the economic burden of dementia, means that education is potentially an important factor in dementia prevention.

Preclinical dementia and MCI

As mentioned, dementia typically develops over a long period. The term 'preclinical dementia' refers to the early phase of the disorder where disease progression has begun but symptoms are not severe enough to warrant a clinical diagnosis. This preclinical phase can span years or even decades before a clinical diagnosis and can be seen through a range of markers, including cognitive deficits, abnormal cerebrospinal fluid (CSF) markers, and neural atrophy [85]. In this thesis, the term preclinical dementia refers to those individuals that are known to have received a dementia diagnosis at a later follow-up occasion.

With the failure of treatments to address AD and dementia pathology [24, 86], a greater focus has been applied to the earliest stages of the disease process. More detailed knowledge regarding the preclinical stages of dementia would allow for the identification of individuals, and initiation of treatments, before severe neural damage has had time to accumulate, therefore limiting the impact of the disorder.

Often discussed in relation to the preclinical or prodromal stages of dementia is the concept of MCI. It is a classification which refers to minor cognitive deficits found in one or more domains in individuals that do not meet the diagnostic criteria of dementia. Those with MCI, particularly amnestic-MCI, with a pronounced deficit in episodic memory, have an increased conversion rate to AD-type dementia [87-89]. However, there are also those who will remain cognitively stable [90-93]. Therefore, although MCI is often considered an intermediate stage in dementia development, this category is highly heterogeneous. One way to conceive of MCI is as a risk factor for future dementia and that studies of MCI alongside studies of preclinical dementia represent two complementary lines of research. MCI is particularly important in clinical settings, as it can be used as a diagnostic entity to refer those with cognitive complaints to memory clinics for further testing or observation.

Individual markers of preclinical dementia

Cognition

Early markers of AD may be present years, if not decades, before a clinical diagnosis. Subtle impairments to episodic memory have been shown up to 22 years before an AD diagnosis [37, 40, 94]. Although, it should be noted that few studies have restricted samples specifically for these long periods and preclinical dementia cases in these studies typically span a wide timeframe before diagnosis. While preclinical AD is most associated with deficits in episodic memory [35-38], early deficits can be seen over a number of cognitive domains [39, 95, 96]. Individual domains of perceptual speed [97-99], executive functioning [38, 94, 97, 100], verbal fluency [36, 101, 102], visuospatial ability [38, 97, 103], and attention [104-106] also show varying degrees of deficits in preclinical AD. Alongside individual domains, measures

of global cognition, including the Mini-Mental State Examination [MMSE; 107], show reduced functioning in preclinical AD [36, 108]. A meta-analysis by Bäckman et al. [39] on 47 individual studies, observed that global cognitive ability, perceptual speed, and executive function had a similar or even larger effect size than episodic memory. Whereas, verbal ability, visuospatial ability, and attention, showed lower, but still observable deficits.

While the majority of the studies cited above have focused exclusively on AD, similar patterns of broad decline across multiple cognitive domains has also been shown in preclinical and clinical VaD [42, 46]. Often these patterns are overlapping to the point of being almost indistinguishable from one another [51, 109, 110].

Therefore, cognitive deficits are a well-established characteristic of preclinical dementia and the use of such markers in predicting future dementia has yielded some promising results, albeit with some limitations. While there are studies showing significant prediction of dementia up to 18 years before a diagnosis [37, 40, 94], it is well documented that cognitive tests perform better closer to a diagnosis as cognitive deficits become more pronounced [95]. In addition, a number of studies combining multiple tests and cognitive domains have shown increased predictivity, however these often show high levels of specificity but only low to moderate sensitivity, somewhat limiting their application potential [36, 111-113].

Rates of cognitive decline

As mentioned, cognitive deficits can be seen far in advance of an AD diagnosis and may be useful markers for dementia prediction, in relation to this, the rate at which cognition declines during the preclinical phase represents complementary information. This pattern of cognitive decline often involves a shallow rate of decline in most cognitive domains followed by a more rapid increase when compared to normal aging [100, 114-120]. While there is a consensus of acceleration in cognitive decline during preclinical AD, results from research into when and how rapidly different cognitive domains begin to decline is mixed. Studies have estimated that the acceleration in cognitive decline for episodic memory occurs up to 7 years before diagnosis [100], with some reporting earlier occurrences [114, 116, 117]. Acceleration in decline for semantic memory has ranged from 3 [115] to 6 years [116] before diagnosis. Likewise, verbal fluency appears to begin more rapid decline approximately 3-5 years before diagnosis [115, 117, 119]. Consistent with these patterns, Thorvaldsson et al. [121] noted differential rates of decline between cognitive domains along a fluid/crystallized spectrum, with fluid abilities, such as word recall or tasks measuring perceptual speed, declining earlier than crystallized abilities, such as verbal ability.

A number of studies [35, 96, 100, 108, 122-124] have also suggested a non-linear decline in cognition: a shallow rate of decline, followed by a plateau, before a steep rate of decline closer to diagnosis. This plateau may represent the use of neural mechanisms or cognitive

reserve to maintain functioning to compensate for losses due to dementia pathology [79, 123, 125]. This would indicate that the rapid rate of decline which follows afterward is due to failure of compensatory mechanisms under the increasing pathological burden [79, 123, 125].

However, it should be noted that there is great variation in onset and rate of decline of the various cognitive domains between studies [126]. This may be due to differences in study population (MCI vs general population), sample demographics (e.g. age, education), length of study, apolipoprotein E *(APOE)* status, and other factors. Studies also differ in whether they attempt to determine acceleration in cognitive decline at more than one time point. Change points close to a diagnosis of AD may also suffer from time periods of uncertainty around a dementia diagnosis where a person may have clinical AD but have not yet received a diagnosis.

While many of these studies are focused on AD-type dementia, a long preclinical phase has also been observed for VaD. Compared to AD, the change point for VaD occurs later for global cognition, as well as almost all cognitive domains, but, once cognitive decline starts to accelerate, the rate of decline is more pronounced [127, 128].

As dementia is characterised by progressive cognitive decline, rather than stable low cognition, it has been hypothesised that rate of decline may be better at identifying those at risk of dementia compared to single time-point scores. Although, few studies have investigated cognitive decline as a predictor of future dementia. One such study by Nation et al. [129] found that those with cognitive decline over a 12 month period showed increased risk of future dementia even when accounting for baseline cognition. This suggests that rate of decline may add unique risk above that found from single time-point cognitive scores and represents a potentially interesting topic for further research.

Genetics

While there are a number of genes linked to AD [130, 131], carrying the ε4 allele of the *APOE* gene is the strongest genetic risk factor for non-familial AD [132-134]. As ε4-carriers have an increased risk of developing MCI [135-137] and dementia, in particular AD [134], it is therefore a useful biomarker for future dementia.

APOE ε4 allele has been linked to reduced baseline episodic memory function and a steeper rate of decline in cognitively normal older adults [138, 139], as well as reduced global cognition and executive functioning [140, 141]. Links to poorer episodic memory [139, 142] and a potential faster rate of cognitive decline [143-145] have also been found in preclinical AD and MCI. Although, the effect on rate of decline is debated [136, 146]. The *APOE* gene can also act as a moderator to other AD pathology, for example, hippocampal atrophy in AD is accelerated in those with an ε4 allele [147-149]. This also includes Aβ, but not tau

pathology [150], with ε4 carriers showing greater Aβ deposition in the brain [151, 152] and lower levels in the CSF [150].

As noted, while the *APOE* ε4 allele may not be a symptom or classical biomarker of preclinical dementia, it is an established risk factor with effects on other markers of dementia, such as hippocampal atrophy and Aβ deposition. In combination with other markers, it has also shown some added predictive value for future dementia [153, 154], although this is not always replicated when in competition with other markers [155-157].

Neuroimaging

MRI macrostructure

As with other markers for dementia, neuroimaging markers for preclinical dementia show promise due to how far in advance of a clinical diagnosis they appear. Neural atrophy in the hippocampus and medial temporal lobe (MTL), as seen in Figure 2, is one of the most common markers of AD dementia [11]. Atrophy of the entorhinal cortex and hippocampus, as seen through MRI, can be viewed up to 10 years before a formal diagnosis of AD [31]. With atrophy beginning in the entorhinal cortex before spreading to the hippocampus and medial temporal structures [32, 33], and eventually to more distant brain regions in a temporal fashion as the disease progresses [34].

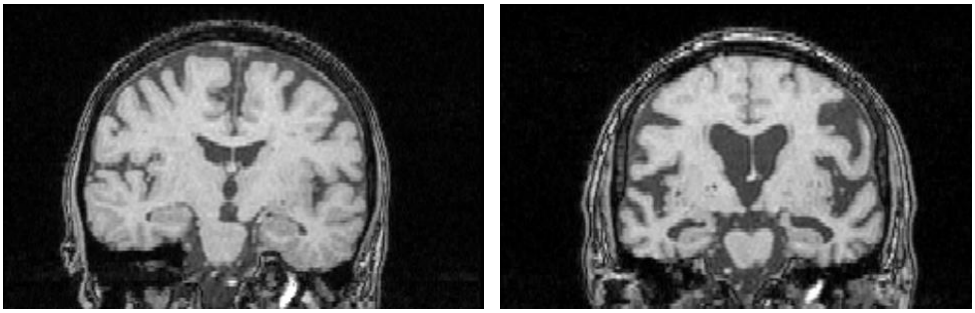

Figure 2: MRI images of MTL and hippocampus during healthy aging (left) and preclinical dementia (right), from participants (78yo, male) involved in SNAC-K.

Another common neuroimaging biomarker is WMHs, representing white matter damage from small vessel disease [55]. WMHs have been shown to have a higher prevalence in various dementias, including AD, VaD and dementia with Lewy bodies, compared to controls [55, 158]. During the preclinical phase of dementia, they have been associated with faster cognitive decline and greater risk of developing dementia [159, 160].

As with cognitive markers, the ability of neuroimaging markers alone to predict future dementia is limited. Evidence for the usefulness of WMHs as individual predictors is mixed [159, 161]. While, studies of hippocampal or MTL volumes [49, 162, 163] or even combined imaging methods [164] show prediction values lower than would be ideal for clinical use.

DTI microstructure

While grey matter atrophy is a well-researched and established biomarker for preclinical dementia, less research has been conducted into the usefulness of diffusion tensor imaging (DTI) for this purpose. It has been shown that alongside grey matter atrophy, dementia is also associated with a decline in white matter microstructure [165, 166]. Changes in white matter microstructure integrity are measured with DTI primarily via mean diffusivity (MD), a reflection of the translational water diffusion within a given space, and fractional anisotropy (FA), a reflection of directional diffusion associated with fibre density and myelination. [167]. Low FA and high MD indicates poor white matter integrity.

Loss of white matter integrity has been shown in AD and VaD [168, 169]. It has been suggested that loss of white matter integrity and changes to white matter microstructure in AD typically begin in the limbic tracts, followed by lateral temporoparietal tracts and long-ranging association tracts, including the frontal lobe [170-172].

While the use of DTI in predicting future dementia has been less studied than more routinely used structural MRI markers, such as grey matter volume, there are studies showing the benefits of using DTI in risk assessment [173] and MCI to dementia conversion [174-176] with high accuracy. However, it should be noted that many studies using DTI tend to involve very small samples and so results should be taken with some degree of scepticism until they can be confirmed by larger-scale studies.

Combining preclinical markers

As mentioned in previous sections, the ability of individual tests or modalities to predict future dementia is limited. Recent research has therefore focused on the possible benefits of combining markers across modalities [177] and studies combining neuropsychological tests, structural MRI and *APOE*, among other tests, have often reported increased predictivity. Devanand et al. [155] reported increased predictivity through the inclusion of multiple tests, with a final model including an informant questionnaire on daily functioning, verbal memory, olfaction, and hippocampal and entorhinal volume producing the highest predictive value. A study by Gomar et al. [178] found that a model of two memory tasks along with hippocampal volume had the highest predictivity. While, Dukart et al. [179] reported multiple models with strong predictivity, the strongest including markers from *APOE*, positron emission

tomography (PET), and structural MRI. More recent studies [180, 181], have replicated these findings on the benefits of combining multiple markers. Beyond neuropsychological tests, structural MRI and *APOE*, many studies have found positive results when including CSF biomarkers [181-187]. There is also evidence that combining between modalities yields higher predictive value than combining within modalities [188], although, the evidence for this is mixed [178].

It should be noted that many studies show a numerical, but not statistically significant, increase in predictivity, which has still been interpreted as showing the benefit of predictive models over individual predictors in some research [154, 182-184]. There is therefore much room in further studies for the use of statistical testing between prediction models to come to an empirically tested conclusion in this matter.

In the effort to increase predictive power through combining multiple markers, large, multi-centre studies are becoming increasingly common, addressing the problem of small sample sizes found in many studies [157, 183, 184]. The Alzheimer's Disease Neuroimaging Initiative (ADNI) is a database of cognitive, genetic, neuroimaging, and biological markers from multiple sites for dementia free, MCI, and dementia subjects. This large scale, longitudinal database has many benefits, as it contains a wide range of potential predictors and a large sample of convertors. However, follow-up time is often short (~2 years) and data are collected from a select group of participants [154, 156, 178, 179, 182, 185]. While valuable, this leaves an important role for population-based research.

Applications of dementia prediction

While the number of individuals affected by dementia is expected to increase dramatically over the next 30 years [1], in some cases the incidence appears to be falling. Several population-based studies in Western countries have shown a trend of lower age-specific incidence in the past few decades [189-192]. Although, this reduction may primarily apply to dementias other than AD [193]. It has been hypothesised that the lower incident rates are due to modifiable lifestyle factors [76, 194], such as increased education during early life or better identification and treatment of diseases such as hypertension and diabetes in later life. In any case, these findings give encouragement that dementia can be prevented.

To date there has been limited success in developing a treatment for AD or other dementias [195, 196]. Numerous clinical trials have moved to Stage 2 or 3 but ultimately failed to provide a drug that can combat disease progression. One of the issues cited in drug and intervention trials is the long period over which dementia develops. Dementia pathology such as Aβ deposition can occur over decades with pronounced cognitive deficits occurring much later. It is therefore important to identify people as early as possible in disease progression for future interventions and trials.

Progress on this is currently being made, several risk scores already exist which focus on lifestyle risk factors across various target populations [197-199]. These have also shown promise in identifying individuals at high risk for dementia for inclusion in dementia intervention trials [200], which themselves have shown encouraging results [201]. While this represents a complimentary line of research to our own, further progress is needed. Greater understanding of the preclinical phase of dementia can help in the identification of more specific markers, more efficient screening tools to identify at-risk populations, and the development of new drugs and clinical interventions.

AIMS

The main objective of this doctoral project is to further our understanding of the preclinical phase of dementia and identify useful predictors for early identification of high-risk individuals. To do this, we compare and combine multiple cognitive measures and biological markers, such as structural neuroimaging and genetics. Alongside this over-arching aim, each study includes its own specific objectives.

Study I: to identify prediction models with the highest accuracy for detecting persons with increased dementia risk and to evaluate how different combinations of cognitive and biological markers can affect model accuracy.

Study II: to evaluate the usefulness of measures of microstructural white matter integrity during the preclinical stage of dementia and understand the individual contribution of white matter integrity in predicting future dementia.

Study III: to focus on the predictive ability of cognitive tests in identifying those at higher probability of developing dementia, including the effects of time to diagnosis and other modifying factors.

Study IV: to investigate the patterns of rate of cognitive decline, in multiple cognitive domains, during the preclinical dementia phase and how early rates of decline can be used to predict development of future dementia.

METHODS

Study populations

All data for this thesis were collected from participants recruited in the ongoing Swedish National Study on Aging and Care - Kungsholmen (SNAC-K). This is a part of a larger longitudinal and population-based study, the Swedish National study of Aging and Care (SNAC) which consists of four regional data collection centres across Sweden. SNAC-K specifically focuses on a random sample of individuals, over 60 years old, living in the Kungsholmen region of Stockholm, Sweden. Of the 5111 individuals invited to participate in SNAC-K, 4590 were eligible, and 3363 (73.3%) agreed to take part in the baseline data collection from March 2001 to June 2004. Participants belong to specific age cohorts (60, 66, 72, 78, 81, 84, 87, 90, 93, 96 years, and 99 years and older). The older age groups (≥78 years) are re-examined every 3 years and the younger age groups (60-72 years) every 6 years, with up to 12 years of data (see Figure 3). The assessment at each wave consists of a nurse interview, a medical examination, and a neuropsychological testing session. Data from the national hospital and death registers has been linked to SNAC-K to provide further information.

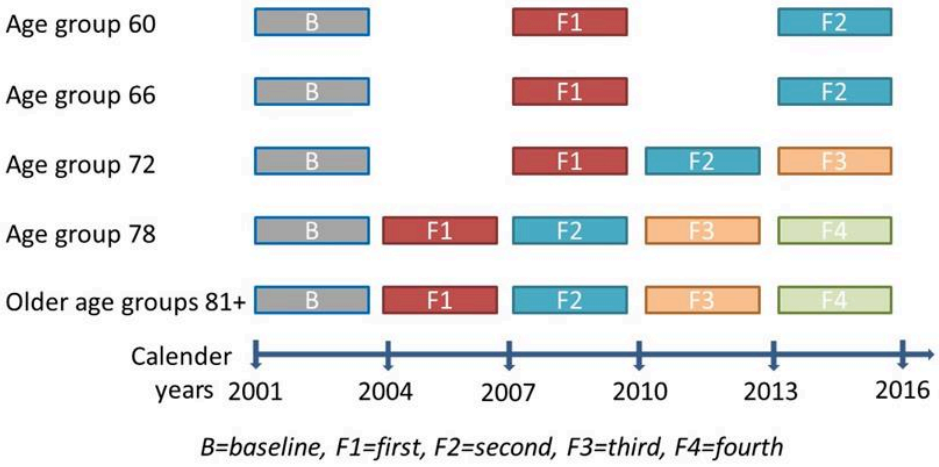

Figure 3: Data collection timeline for SNAC-K over the age cohorts.

Sample for Study I

Of the 3363 baseline responders, a subsample of 555 participants also underwent MRI scanning. It was from this subsample that the sample for Study I was taken. From the original 555, participants were excluded due to poor quality images or technical issues (*n*= 52),

missing cognitive data (*n*=12), infarct/tumour/neural abnormality (*n*=31), neurological disorder (*n*=7), autoimmune disorder (*n*=1), and drop-out (*n*=94). Thus, data were available for 418 participants. Of those, 354 remained dementia free, 28 developed dementia, and 36 died during the 6-year follow-up.

Compared to the full baseline sample, participants in the MRI sample were significantly younger, had more years of education, achieved higher MMSE scores, and included a larger proportion of women ($p<.01$).

Sample for Study II

Among the individuals who underwent MRI scanning (*n*=555), a DTI sequence was available for a subsection of this sample (*n*=260). Due to exclusion (poor image quality/technical issues: *n*=17, infarct/meningioma: *n*=6, missing cognitive data: *n*=7) and drop out (*n*=18), the final analytical sample consisted of 212 participants. Of these, 173 remained dementia free, 16 developed dementia, and 23 died during the six-year follow-up.

Compared to the original sample, including all SNAC-K participants (*n*=3363), this sample was significantly younger ($p=.002$) and performed better on the MMSE at baseline ($p<.001$). There were no significant differences between the samples in sex distribution or educational level.

Sample for Study III

The populations for Study III were recruited from the main SNAC-K sample (*n*=3363). For the main analysis, 669 of these participants were excluded at baseline (no baseline cognitive data: *n*=515, dementia diagnosis: *n*=122, Parkinson's disease: *n*=21, schizophrenia: *n*=10, and developmental disorder: *n*=1). A further 337 were excluded due to drop out (*n*=336) and uncertain dementia diagnosis (*n*=1) at follow-up. An analytical sample of 2357 participants remained, of which 246 developed dementia, 378 died, and 1733 remained dementia free.

For the time-to-diagnosis sample, of the original 3363 baseline participants, exclusions were removed from each follow-up point. At baseline, the same 669 participants were removed as above. At three years, 384 participants were excluded due to dementia (*n*=121), death (*n*=161), and dropout (*n*=102). At the six year follow-up, participants (*n*=704) were removed due to dementia (*n*=127), death (*n*=217), dropout (*n* = 233), and lack of cognitive data (*n*=127). At nine years, 1169 participants were excluded for dementia (*n*=68), death (*n*=94), dropout (*n*=38), and lack of cognitive data (*n*=47). An additional 922 participants were not scheduled to be included in this wave of data collection. Finally, there were 30 participants removed at twelve years due to drop-out. After exclusions, data from 407 participants were

available: 48 who whom developed dementia, 75 of whom died, and 284 who remained dementia free at the 12-year follow-up.

Sample for Study IV

Of the original sample (*n*=3363), exclusions were made at baseline (dementia: *n*=417, Parkinson's disease: *n*=25, developmental disorder: *n*=4, and schizophrenia: *n*=15) and for those with cognitive data available for fewer than two time-points (*n*=698). Drop-outs throughout the 12-year period accounted for the removal of 658 participants. Thus, 1646 individuals remained for analysis using mixed models, of whom 1092 remained dementia free, 334 died, and 220 developed dementia by the 12-year follow-up. A restricted sample of 1491 participants (1092 dementia free, 252 dead, and 147 dementia cases) was analysed using Cox regressions, after the removal of those who died (*n*=155) or developed dementia (*n*=73) during the first 6 years of the study.

Dementia diagnosis

Within SNAC-K, dementia diagnoses were made according to the Diagnostic and Statistical Manual of Mental Disorders, 4th edition [202]. A preliminary diagnosis was made by the examining physician, this was followed by a secondary diagnosis based on computerised data from the medical examination. In cases of disagreement, a final decision was made by a third physician. A differential diagnosis of AD was made according to the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria [203]. The cognitive assessment used for diagnosis included the MMSE [107], the Ten Point Clock test [204], and items regarding memory, executive functioning, problem solving, orientation, and interpretation of proverbs. Performance on the neuropsychological battery was not used for diagnostic purposes. Additional cases of dementia were added from death certificates and medical records for those who died before receiving a dementia diagnosis in SNAC-K.

Materials and data collection

Clinical testing

MMSE

The MMSE was used to assess global cognitive functioning. This is a short 30-point questionnaire covering a range of cognitive abilities such as orientation, attention, memory, language, and visual-spatial abilities.

Neuropsychological testing

Neuropsychological testing in SNAC-K was performed at each assessment wave. The cognitive test battery was conducted by trained test leaders and was typically completed in 2 hours. There are three versions of the test battery and two test orders. All testing was conducted in Swedish. The tests that were used in this thesis are presented below according to cognitive domain.

Episodic memory

Episodic memory was assessed using a word list of 16 unrelated nouns, words were presented individually every five seconds. To assess free recall, a two-minute recollection task was presented immediately after the word list and number of correctly remembered words was recorded. Word recognition was assessed with an untimed list of 32 nouns, including the original words and an equal number of distractors, where recognition reflected number of hits minus number of false alarms.

Semantic memory

Two tasks of semantic memory were administered: a general knowledge task consisting on 10 moderately difficult questions covering a range of topics, participants were asked to pick the correct answer from two alternatives, and a vocabulary task which involved matching 30 target words to the correct synonym among five alternatives. Number of correct answers was recorded from each test.

Verbal fluency

Letter and category fluency tests were used to assess verbal fluency. These tasks involved generating as many words as possible within 60 seconds, either starting with the letters ‘F’ and ‘A’ (letter fluency) or belonging to the categories ‘animals’ and ‘professions’ (category fluency). The fluency measures were derived by averaging the total number of words produced within each task.

Perceptual speed

Three tasks were used to assess perceptual speed. Digit cancellation [205] comprised 11 rows of random digits, participants were required to mark the target number (4) whenever they encountered it during a 30 second time period. The second task was pattern comparison

[206], which consisted of pairs of basic line constructs; 30 seconds were given to mark the pairs as “same” or “different”. The average number of correct answers was calculated from two trials. Trail Making Test (TMT) part A [207] was the final test and involved connecting 13 encircled digits in numeric order as fast and accurately as possible. Time to complete the task was recorded as the test score. However, time was only taken for those who completed the task correctly, with a maximum of 1 careless connection.

Executive function

Executive function was measured using TMT-B [207]. In this task, circles with numbers and letters were connected based on numeric and alphabetical order, alternating between the two categories (1-A, 2-B, etc.). As with TMT-A, time taken to complete the task was considered the as the test score and scores were only recorded for those who completed the task correctly, or had a maximum of one careless connection.

MRI

Collection

MRI data were acquired using a 1.5T scanner (Philips Intera, Netherlands). The protocol included an axial 3D T1-weighted fast field echo (FFE) sequence with repetition time (TR) 15 ms, echo time (TE) 7 ms, flip angle (FA) 15°, field of view (FOV) 240, 128 slices with slice thickness 1.5 mm and in-plane resolution 0.94×0.94 mm, no gap, matrix 256×256, and an axial turbo FLAIR sequence (TR 6000 ms, TE 100 ms, inversion time 1900 ms, FA 90°, ETL 21, FOV 230, 22 slices with slice thickness 5 mm and in-plane resolution 0.90×0.90 mm, gap 1 mm, matrix 256×256).

For the DTI images, a single-shot diffusion-weighted echoplanar imaging sequence with the following parameters was conducted: FOV = 230x138 mm^2, 128x77 matrix, TE = 104 ms, TR = 6838 ms, slice thickness 5 mm with 1 mm gap and b-value 600 s/mm^2. A DTI scheme with six non-collinear diffusion-weighting gradient directions was used to determine the diffusion tensor set.

Post-processing

The T1-weighted images were first segmented into grey matter, white matter and CSF using the unified segmentation method approach [208] and SPM12b (Statistical Parametric Mapping, Wellcome Trust Centre for Neuroimaging). Further removal of odd voxels from the segments was achieved through the ‘light clean-up’ option. Total intracranial volume

(ICV) was obtained by adding grey matter, white matter, and CSF volumes. All volumes were corrected for ICV using the analysis of covariance approach [209]. Automatic segmentation of hippocampal volumes was performed using the Freesurfer image analysis suite (v. 5.0.1, Martinos Center for Biomedical Imaging, Harvard-MIT, Boston, USA). This procedure has previously been described by Gerritsen et al. [210]. WMHs were manually delineated on the FLAIR images by a single rater.

The DTI images were pre-processed using an iterative optimisation algorithm for the diffusion tensor calculation. In the next step, fractional anisotropy (FA) and mean diffusivity (MD) were derived on a voxel-by-voxel basis using the approach from Bassar & Pierpaoli [211]. Further processing of the FA data was conducted using the tract-based spatial statistics (TBSS) tool of the FMRIB Software Library Analysis Group (FMRIB, Oxford, UK) [212]. Fourteen masks, one for each tract of interest in both hemispheres, were created and used to extract the FA and MD values of each participant. These tracts were the cingulum cingulate gyrus (CCG), the portion of cingulum that extends to the hippocampus (CHC), the corticospinal tract (CS), the forceps major (FMAJ), the forceps minor (FMIN), the inferior fronto-occipital fasciculus (IFOF), and the superior longitudinal fasciculus (SLF).

Genotyping

DNA was obtained from peripheral blood samples and genotyping was performed using MALDI-TOF analysis on the Sequenom MassARRAY platform [213]. The *APOE* (rs429358, rs7412) polymorphism was included in this thesis.

Statistical analysis

Descriptive statistics

All variables in the study were examined prior to advanced analysis. The variables were checked for outliers and missing data points. Measures of central tendency (mean, median, and mode), variability (standard deviation and variance), and distribution (skewness and kurtosis) were inspected.

Structural equation modelling

Structural equation modelling (SEM) is a statistical method of drawing connections between measured variables and the latent constructions which underpin them. Models can be estimated with full maximum likelihood, which allows for the estimation of parameters that

involve missing values by utilising information from the full data set. Model fit was evaluated with the Comparative Fit Index (CFI) and the Root-Mean-Square Error of Approximation (RMSEA), where a CFI above .95 and an RMSEA below .08 indicates acceptable model fit.

SEM was used to generate latent factors for the cognitive domains and white matter tracts in *Study II*. Three models (DTI MD, DTI FA, and cognition) were created with regard to the specific domains (see Figure 4). In addition, three global models were created based on the same data.

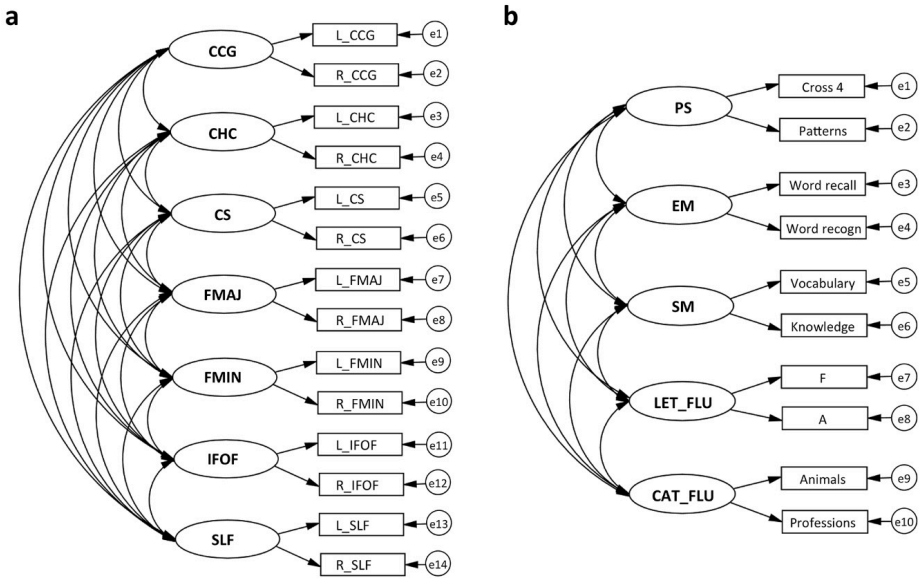

Figure 4: *Graphical representations of structural equation models for 7 specific latent microstructural white matter integrity factors (a) and 5 specific latent cognitive factors (b). The same model applies to FA and MD. Latent factors are depicted with circles, endogenous variables with rectangles, regressions with one-headed arrows, and covariance with two-headed arrows. Adapted from Laukka et al. [214].*

Multinomial logistic regression

The multinomial logistic regression is used to model the probability of a categorical/nominal dependent variable from an independent variable, which may be continuous or categorical. Multinomial logistic regressions are a variation of logistic regressions, while standard logistic regressions have a dependent variable with a binary outcome, multinomial logistic regression

allows for the dependent variable to have more than two possible discrete outcomes. In this thesis, the three available outcomes included: remaining dementia free, dying, or developing dementia, during a specified time period. As with standard logistic regressions, the multinomial regression uses maximum likelihood estimation to evaluate that probability of membership to each possible outcome.

This regression analysis was used in *Studies I, II, and III* to assess the ability of a range of cognitive and biological markers to predict future dementia.

Model building

For *Study* I, the building of prediction models began with the systematic inclusion of variables, beginning with the best predictor based on area under the curve (AUC) values, from there a second variable was added until all available 2-variable combinations had been tested. The 2-variable model with the highest AUC was then used as a base, with the remaining variables added until the 3-variable model with the highest AUC was revealed. This process continued until no predictor could add further unique variance without losing statistical significance. When this occurred the model was then considered final. This procedure was repeated, using the best cognitive, genetic, and neuroimaging predictor as the base, respectively.

For *Study II*, the ability of each individual marker to detect future dementia was assessed. Subsequently, every possible variable combination for models containing two, three, and four predictors was assessed at each step to establish the most predictive model. Final models were created when the maximum number of predictors that could still add unique information to the model had been reached. Separate models were created for global and specific markers. Bayesian information criterion (BIC) was used as a marker of model fit in both studies.

For *Study III*, the same procedure as in *Study I* was employed, although with a larger sample size and restricted to the cognition modality.

Cox proportional hazards model

Cox regression assesses the association between variables and survival time (time-to-event) outcomes. The hazard rate is the probability of experiencing a specified event, assuming the individual survives to a designated time point. Hazard ratios are used to determine the differences in risk between groups, with one group acting as the control group.

In *Study IV*, Cox regressions were used to determine the extra risk associated with having fast cognitive decline, compared to those with no fast decline, on likelihood of developing future dementia.

Tests of predictive value

To evaluate the accuracy of the created prediction models, three measures were used: AUC values, concordance indices (C-index or C-statistic), and DeLong's tests.

The AUC values are obtained from a receiver operating characteristic curve (ROC). The ROC is created by plotting the true positive rate (sensitivity) against the false positive rate (1-specificity) and shows all possible cut-off points. The AUC provides a simple measure of how well the model is performing across all possible cut-off points. An AUC of .5 would indicate that the model is not predicting above the level of chance, an AUC of 1 would represent a model with perfect predictive accuracy. The AUC values were used in *Studies I*, *II*, and *III* to assess model predictivity.

Harrell's C-index is equivalent to the AUC for models which produce risk scores, such as the Cox regression. It evaluates the accuracy of the predictions made by comparing the number of correct prediction outcomes with the total number of possible outcomes. The C-statistic also ranges from .5 to 1, with values closer to 1 denoting better model predictivity. Harrell's C-index was used in *Study IV* as a guide to model predictivity.

The DeLong's test statistically evaluates the difference between two AUC values to determine if there is a significant difference between the two. A significant result when comparing the AUCs from two prediction models would indicate that one model is significantly better at predicting the outcome than the other. DeLong's test was used in *Studies I, II,* and *III* to determine if increases in the AUC between models were statistically significant.

Linear mixed-effects models

Linear mixed-effects models (LMM) are another type of regression modelling, one which is particularly useful for longitudinal data, as it allows for both fixed and random effects. LLMs can handle missing data and unequal follow-up times.

Piecewise linear mixed-effects models (pLMM) are a variation of LMMs and allow for more than one slope to be plotted. A knot can be placed in the model to separate the slopes before and after this designated point.

Study IV used LMMs to investigate the linear rate of decline in dementia free and preclinical dementia groups over a period of twelve years. Time was recorded as 'time to event', the event for dementia free was the twelve-year follow-up or date of death and for the dementia group was mid-point between the last follow-up and date of diagnosis. pLMMs were used to assess changes in rate of decline before and after the knot, which was placed at six years before the event.

Fast decliners

Rate of decline from twelve to six years before the event, based on the pLLMs, was also used to define fast decliners for use in the Cox regressions. Participants declining ≥ 1.5SDs faster than the mean rate of decline of their age category (<78 vs. ≥78 years), with mean rate based on decline in the dementia free group, were classified as fast decliners for that cognitive domain. Similarly, participants scoring ≥ 1.5SDs below the mean baseline score of their age group were classified as having a low baseline score for that domain.

Ethical considerations

All data collection waves of SNAC-K received ethical approval from Karolinska Institutet ethical committee or Stockholm ethical review board, see Table 1 for registration numbers relevant for the included studies. Everyone involved in data collection and analysis in SNAC-K follows the ethical guidelines of the World Medical Association Declaration of Helsinki and research ethics principles in humanistic-social scientific research developed by the former Swedish Council for Research in the Humanities and Social Sciences.

All data collected is done so with the consent of those involved, participants are informed that participation is voluntary and that they are free to withdraw from the study at any time without explanation. Written informed consent is collected when participants are still cognitively intact and a proxy is asked for consent in cases of severe cognitive impairment. If the participant expresses anguish or discomfort during the examination, the interview is terminated regardless of whether the person, or a proxy, has given consent. All data in SNAC-K is pseudonymised to ensure participant confidentiality.

MRI is generally considered a safe procedure as it does not involve radiation; however, the procedure is not safe for all individuals, for example those with pace-makers. In regard to this, the subjects are given an extensive check-list before the scan to determine their ability to safely participate. Any abnormalities on a scan are diagnosed by a radiologist and reported to the participant's physician. Blood is taken from the participants to measure a range of variables and genotyping is performed. A registered nurse draws the blood sample so there is low risk of infection and participants can refuse the procedure if they wish.

Table 1. Ethical registration numbers SNAC-K

Study	Ethical registration numbers
Study I	01-114; 04-929/3; Ö 26-2007; 2009/595-32
Study II	01-114; 04-929/3; Ö 26-2007; 2009/595-32
Study III	01-114; 04-929/3; Ö 26-2007; 2009/595-32; 2010/447-31/2; 2013/828-31/3
Study IV	01-114; 04-929/3; Ö 26-2007; 2009/595-32; 2010/447-31/2; 2013/828-31/3

RESULTS

Preclinical dementia markers

Multimodal predictors

Combining cognition, genetics, and MRI

Study I investigated the ability of neuropsychological assessments, the *APOE* ε4 allele, grey matter volume, and white matter hyperintensities volume to predict dementia six years later. The study focused on a subsample of 418 individuals within the SNAC-K sample.

The results of multinomial logistic regressions revealed that a test of perceptual speed (pattern comparison) and the presence of at least one *APOE* ε4 allele were the joint highest individual predictors of future dementia (AUC=.875). Within the MRI modality, hippocampal volume showed highest predictivity (AUC=.859). However, results from the DeLong's tests demonstrated that no single test or marker showed a significant improvement in prediction of future dementia when compared to a model of covariates (age, sex, and education: model 0).

Predictive models were built within and between the modalities of cognition, genetics, and MRI. Intra-modality models were created for cognitive and MRI variables, as these modalities contained at least two significant predictors each. A final model of cognitive markers was created and contained a task of word recall and pattern comparison (AUC=.901; C.I=.858-.944). The final model of the MRI variables included hippocampal volume and WMHs volume (AUC=.878; C.I=.828–.928).

When combining between the modalities, a model beginning with a cognitive base of pattern comparison (AUC=.875; C.I=.822–.928) was combined with word recall (AUC=.901; C.I=.858–.944), and finally hippocampal volume to create a 3-variable model with the highest predictive value (AUC=.913; C.I=.874–.952). Both models 2 (p=.012) and 3 (p=.007) were a significant improvement over model 0. Models with a genetic base (*APOE* ε4: AUC=.875, C.I=.826–.923), were added with word recall to create a 2-variable model (AUC=.908; C.I=.867–.949), and with general knowledge to create a final 3-variable model (AUC=.922; C.I=.883–.960). Predictivity for models with 2 or more variables was a significant increase over a model of only covariates (p=.001).

The most predictive final model was created using hippocampal volume as the base (AUC=.859; C.I=.798–.920), this was most improved by adding a task of category fluency (AUC=.895; C.I=.845–.944). Adding the presence of at least one ε4 allele resulted in a 3-variable model including tests from each modality (AUC=.911; C.I=.869–.953). Further predictive value was gained by the inclusion of WMHs (AUC=.921; C.I=.882–.960). General knowledge was added as the final variable, which resulted in a model with the highest predictivity of all models tested (AUC=0.924; C.I=.883–.965). As with the other modality

bases, there was no significant increase in predictive value from the inclusion of only one variable (p=.476). Although, all models with three or more variables showed a significant increase in predictive value (p<.05) above that found in model 0.

All model bases showed a significant increase in AUC from model 0 to the final models (cognitive base, p=.007; genetic base, p=.001; MRI base, p=.005). However, it should be noted that there was no significant difference in predictivity between any of the final models, see Table 2.

Table 2. Multinomial logistic regressions for intermodality models (Study I).

	Variables	No dementia (*n*)	Incident dementia (*n*)	OR	95% C.I.		*p* value	ROC – AUC[a]
					Lower	Upper		
Model 0	Covariates	354	28					.845
Cognitive								
Model 1	Pattern comparison	352	26	2.48	1.37	4.50	.003	.875
Model 2	Pattern comparison	352	26	2.02	1.10	3.73	.025	.901
	Word recall			2.46	1.42	4.25	.001	
Model 3	Pattern comparison	344	25	1.96	1.04	3.69	.036	.913
	Word recall			2.18	1.24	3.82	.007	
	Hippocampal volume			2.07	1.11	3.86	.022	
Genetic								
Model 1	APOE (ε4 vs no ε4)	349	28	4.89	2.02	11.85	.000	.875
Model 2	APOE (ε4 vs no ε4)	348	28	5.48	2.16	13.94	.000	.908
	Word recall			2.50	1.49	4.19	.001	
Model 3	APOE (ε4 vs no ε4)	347	28	5.81	2.21	15.28	.000	.922
	Word recall			2.47	1.46	4.19	.001	
	General knowledge			1.96	1.21	3.16	.006	
MRI								
Model 1	Hippocampal volume	346	27	2.15	1.23	3.79	.008	.859
Model 2	Hippocampal volume	345	26	2.68	1.44	4.99	.002	.895
	Category fluency			2.56	1.40	4.70	.002	
Model 3	Hippocampal volume	340	26	2.17	1.16	4.05	.015	.911
	Category fluency			2.58	1.37	4.85	.003	
	APOE (ε4 vs no ε4)			4.09	1.51	11.06	.005	
Model 4	Hippocampal volume	328	26	2.04	1.08	3.85	.028	.921
	Category fluency			2.60	1.39	4.89	.003	
	APOE (ε4 vs no ε4)			4.04	1.46	11.18	.007	
	WMH volume			1.81	1.05	3.09	.031	
Model 5	Hippocampal volume	327	26	2.16	1.14	4.11	.019	.924
	Category fluency			2.45	1.28	4.69	.007	
	APOE (ε4 vs no ε4)			4.15	1.47	11.71	.007	
	WMH volume			1.75	1.00	3.07	.049	
	General knowledge			1.77	1.05	2.97	.031	

[a] Incident dementia vs no dementia. Model 0 includes sex, age and education.

Additional benefits of microstructural white matter integrity

Study II also combined markers between modalities to create accurate prediction models of dementia at 6 years, this time with a focus on the benefits of markers of microstructural white matter integrity. Besides cognitive tests, *APOE*, and MRI macrostructure markers, this study also included the use of DTI data, specifically the MD and FA values of selected tracts. The ability of all markers as both global and specific measures in predicting future dementia was investigated.

Global cognition, a composite of all the cognitive tests available, was the strongest global predictor of future dementia (AUC=.878), followed by total brain volume (AUC=.858), and global MD (AUC=.846). Global measures of FA were not significantly predictive of future dementia (p=.131).

Of the specific markers, episodic memory was the best predictor (AUC=.865), with other significant cognitive domains also showing good prediction values (AUC=.864-.852). The *APOE* ε4 allele (AUC=.857), white matter- (AUC=.826), hippocampal- (AUC=.857), and WMHs volumes (AUC=.841) were slightly worse performing than the cognitive variables but still significantly predicted dementia 6 years later. For the DTI modality, the MD latent factors CHC, CS, FMAJ, and IFOF (AUC=.837–.862) were significant predictors of future dementia. Among the FA latent factors, only IFOF (AUC=.839) was significantly associated with dementia at six years.

When considering global measures, see Table 3, markers of microstructural white matter integrity were not included in the final model, which started with global cognition (AUC=.878), with the addition of the ε4 allele (AUC=.900), and finally total brain tissue volume (AUC=.920). Models of more than two variables were a significant improvement over model 0 of covariates only (p<.05).

When combining specific measures, see Table 3, for a model beginning with episodic memory (AUC=.865), prediction was improved with the presence of an ε4 allele (AUC=.910). A final model included perceptual speed, hippocampal volume, and MD of the FMAJ tract (AUC=.911). As with the global models, only models of more than two variables were a significant improvement over model 0 (p<.01).

Cognitive predictors

Study III investigated the ability of cognitive markers alone in predicting future dementia. Thus, for this study, the full cognitive sample in SNAC-K was used. Baseline tests covering domains of episodic memory, semantic memory, verbal fluency, perceptual speed, and executive function were examined individually and in combination to identify the best individual predictor and predictor models for future dementia.

Table 3. Multinomial logistic regressions and ROC analyses for global and specific models (Study II).

		No dementia (*n*)	Incident dementia (*n*)	OR	95% C.I. for OR		*p* value	BIC	ROC – AUC[a]
					Lower	Upper			
Global models									
Model 0	Covariates	173	16					252.385	.816
Model 1	Global cognition	173	16	3.675	1.680	8.039	.001	250.904	.878
Model 2	Global cognition	170	16	3.797	1.551	9.295	.003	240.492	.900
	Any ε4 vs. no ε4			5.470	1.541	19.415	.009		
Model 3	Global cognition	170	16	3.258	1.304	8.140	.011	246.647	.920
	Any ε4 vs. no ε4			4.849	1.348	17.450	.016		
	Total brain tissue volume			3.024	1.043	8.768	.042		
Specific models									
Model 0	Covariates	173	16					252.385	.816
Model 1	Episodic memory	172	16	3.041	1.489	6.210	.002	251.903	.865
Model 2	Episodic memory	169	16	3.087	1.489	6.403	.002	239.291	.910
	Any ε4 vs. no ε4			6.874	1.923	24.578	.003		
Model 3	Perceptual speed	168	14	2.667	1.042	6.829	.041	244.869	.911
	Hippocampal volume			2.452	1.030	5.838	.043		
	MD FMAJ			2.096	1.003	4.380	.049		

[a] Incident dementia vs no dementia

When predicting dementia at 6 years, category fluency was the strongest individual predictor (AUC=.903), followed by word recall and pattern comparison (AUC=.893), digit cancellation and TMT-A (AUC=.891), TMT-B (AUC=.886), word recognition (AUC=.881), vocabulary and letter fluency (AUC=.877), and lastly general knowledge (AUC=.874). For the creation of a 2-variable prediction model, both word recall and pattern comparison increased predictive value (AUC=.907) when added to category fluency (AUC=.903). A combination of all three tests created the most predictive model (AUC=.913).

Effects of modifying factors

Study III also examined the effects of age, sex, education, the presence of an ε4 allele, AD-only dementia as the outcome, and time to diagnosis on the prediction ability of cognitive markers. Tables for modifying factors can be found in the Appendix (Supplementary Tables 1-5). For the subsample analysis, the demographics were split in a binary fashion. For age, the "old-old" group was ≥78 years and the "young-old" was <78 years old at baseline. High education was defined as those who had attended high school ("gymnasium") or above, whereas low education included those with maximum 9 years of education. *APOE* ε4 status was a binary subgrouping of carrying at least one ε4 allele or no ε4 allele. Of the dementia subtypes, AD-only dementia was the only grouping explored, as the other dementia categories were too small to investigate.

When dividing the sample by age, the strongest individual predictor of the old-old group was category fluency (AUC=.731), with a final model of category fluency, word recall, and TMT-B (AUC=.764). While for the young-old, category fluency and digit cancellation were equally predictive as individual variables (AUC=.867). However, the most predictive final model included only digit cancellation with word recall (AUC=.885).

The same strongest predictor (category fluency; AUC=.905) and pattern of domains (verbal fluency, episodic memory, and perceptual speed; AUC=.914) were apparent in the final model of the female only sample. While for men, the strongest individual predictor was a test of perceptual speed (AUC=.909) and, again, the final model included tests of verbal fluency, episodic memory, and perceptual speed (AUC=.930).

Category fluency was also the strongest individual predictor for both high- (AUC=.924) and low-educated (AUC=.878) subgroups, with tests of verbal fluency, episodic memory, and perceptual speed present in the final models (AUC=.937; AUC=.896, respectively).

For those carrying at least one ε4 allele, word recall (AUC=.899) was the strongest individual predictor, while the most predictive model included word recall, pattern comparison, and category fluency (AUC=.910). For *APOE* ε4 non-carriers, episodic memory was less important than for ε4 carriers, and category fluency was the most predictive individual

marker (AUC=.922). The final model, however, revealed the same pattern of cognitive tests for the final model as the ε4 carriers (AUC=.930).

For those who would develop AD-type dementia, category fluency and word recall performed equally well (AUC=.905). A final model included tests of category fluency, episodic memory, and perceptual speed (AUC=.920), strengthening the evidence that, overall, these tests work well as predictors in models for all the subgroups analysed.

Time to diagnosis

The effects of time to diagnosis on the predictive value of numerous cognitive domains was investigated using a subsample of older individuals with cognitive data at three time points and a dementia diagnosis at 12 years.

Word recall, vocabulary, general knowledge, category fluency, pattern comparison, and TMT-B were all significant predictors of future dementia 12 years later, with pattern comparison being the most predictive test (AUC=.686). Category fluency, in line with the main sample analysis, was the most predictive individual test 6- (AUC=.733) and 3- (AUC=.781) years before diagnosis, see Table 4.

Twelve years before diagnosis, no additional tests could be added to the model starting with pattern comparison (AUC=.686), as the strongest individual predictor. A six years before diagnosis, a measure of TMT-B was added to category fluency (AUC=.733) to arrive at a final two-variable model (AUC=.784). While 3 years before diagnosis, category fluency was once again the most predictive variable (AUC=.781), before the addition of TMT-A to create a two-variable model (AUC=.794), and a final three-variable model was achieved by including word recall (AUC=.814).

Twelve years before a diagnosis, none of the individual variables were significantly more predictive than a model containing covariates only. However, 6 years before diagnosis, category fluency alone (p=.01) and the two-variable model of category fluency and TMT-B (p<.05) both performed better than model 0. Three years before a diagnosis, all models were significantly more predictive than a model of covariates (p<.001).

There was no significant difference in predictivity from 12 to 6 years before a diagnosis when comparing between the final models. However, from 12 to 3 years (p=.001), and from 6 to 3 years (p=.021), there was a significant increase in predictivity.

Rate of decline

Study IV investigated the ability of rate of decline to predict future dementia. Rate of decline was assessed 12 to 6 years before a diagnosis of dementia and those with a rate of decline

Table 4. Multinomial regressions for individual variables – 12 year time to diagnosis subsample

	12 years before diagnosis					6 years before diagnosis					3 years before diagnosis				
	No dementia (*n*)	**Incident dementia (*n*)**	**OR (95% C.I.)**	***p* value**	**ROC - AUC**	**No dementia (*n*)**	**Incident dementia (*n*)**	**OR (95% C.I.)**	***p* value**	**ROC - AUC**	**No dementia (*n*)**	**Incident dementia (*n*)**	**OR (95% C.I.)**	***p* value**	**ROC - AUC**
Covariates	284	48			.629	284	48			.613	284	48			.617
Episodic Memory															
Word recall	283	47	1.56 (1.10-2.22)	.012	.662	283	47	1.76 (1.24-2.50)	.001	.692	281	44	2.14 (1.50-3.05)	.000	.712
Word recognition	283	47	1.33 (.98-1.79)	.068	.628	283	47	1.40 (1.01-1.94)	.047	.655	280	43	1.67 (1.26-2.23)	.000	.690
Semantic Memory															
Vocabulary	283	47	1.41 (1.03-1.92)	.033	.640	282	47	1.58 (1.12-2.24)	.009	.648	280	45	1.67 (1.19-2.34)	.003	.657
General knowledge	281	48	1.43 (1.04-1.97)	.026	.639	284	48	1.24 (.90-1.72)	.189	.614	284	48	1.50 (1.10-2.05)	.010	.659
Verbal Fluency															
Letter fluency	284	47	1.36 (.97-1.89)	.072	.624	284	48	1.84 (1.28-2.65)	.001	.676	284	47	2.15 (1.50-3.09)	.000	.696
Category fluency	284	48	1.46 (1.03-2.07)	.032	.641	284	48	2.17 (1.49-3.16)	.000	.733	284	48	3.09 (2.12-4.49)	.000	.781
Perceptual Speed															
Digit cancellation	282	45	1.21 (.86-1.69)	.281	.618	279	46	1.40 (1.00-1.96)	.050	.633	277	41	2.06 (1.43-2.97)	.000	.700
Pattern comparison	281	46	2.00 (1.36-2.94)	.000	.686	281	46	1.61 (1.14-2.26)	.007	.675	275	41	2.62 (1.77-3.89)	.000	.735
Trail Making Task A	279	45	1.26 (.92-1.71)	.148	.628	279	44	1.65 (1.12-2.45)	.012	.651	273	39	2.30 (1.60-3.30)	.000	.748
Executive Function															
Trail Making Task B	257	42	1.91 (1.35-2.69)	.000	.663	251	38	2.22 (1.45-3.38)	.000	.715	247	26	1.95 (1.24-3.06)	.004	.711

>1.5SDs below the age-adjusted mean were classified as 'fast decliners'. The ability of fast decline to predict dementia 3 to 6 years later was analysed using Cox regressions.

For the individual tests, this study found that being a fast decliner was associated with increased risk of future dementia for word recall (HR: 1.92, CI: 1.15-3.19, *p*=.013) and category fluency (HR: 2.42, CI: 1.54-3.80, *p*<.001). While being a fast decliner in tests of word recognition (HR: 1.46, CI: .88-2.42, *p*=.139), vocabulary (HR: 1.61, CI: .98-2.63, *p*=.060) and a composite of perceptual speed tests (HR: 1.24, CI: .73-2.12, *p*=.424) was not significantly associated with future dementia, see Table 5. After including low baseline score as a covariate in the model, only being a fast decliner in category fluency remained a significant predictor of future dementia (HR: 2.86, CI: 1.13-7.22, *p*=.026).

Further analysis investigated the association between declining fast on a single test vs. declining fast on several of the included tests/domains with future dementia. These results showed that being a fast decliner on one (HR: 1.30, CI: .88-1.92, *p*=.189) or two (HR: 1.22, CI: .61-2.44, *p*=.583) tests/domains was not significantly associated with future dementia. However, being a fast decliner in ≥3 cognitive tests/domains was associated with over a threefold increase in dementia risk (HR: 3.38, CI: 1.91-6.01; *p*<.001).

Table 5. Cox regressions for individual variables. Risk of future dementia for fast decliners.

	Hazard ratio (95% C.I.)	**p-value**	**c-statistic**
Word recall	1.92 (1.15-3.19)	.013	.809
Word recognition	1.46 (.88-2.42)	.139	.809
Vocabulary	1.61 (.98-2.63)	.060	.808
Category fluency	2.42 (1.54-3.80)	.000	.807
PS composite	1.24 (.73-2.12)	.424	.793

Trajectories of cognitive decline

Study IV also explored the trajectories of cognitive decline over a 12-year period during the preclinical stage of dementia. Linear mixed models were used and a knot was added at six years to create two slopes to highlight changes in rate of decline.

Those in a preclinical phase of dementia declined significantly faster in all cognitive domains compared to those who remained dementia free throughout the 12-year follow-up period, with average additional increase ranging from β:-.07 to -.11. Rate of decline was shown to be affected by age, with a stratified analysis showing that old-old participants (≥78 years) had a

steeper rate of decline in normal aging compared to the young-old. However, the difference in rate of decline between dementia free and preclinical dementia groups, was larger in the young-old than the old-old, see Table 6.

The piecewise mixed effects models (Figure 5) showed a significant difference in rate of cognitive decline between dementia free and preclinical dementia groups for word recall at both -12 to -6 years (β: -.06, 95% CI: -.10 to -.03) and -6 to 0 years (β: -.10, CI: -.13 to -.07). Word recognition displayed no difference in rate of decline between the groups far from event (β: -.01, CI: -.05 to .03) but declined significantly faster in the preclinical compared to the dementia free group closer to diagnosis (β: -.17, CI: -.21 to -.14). Similar results were also found for vocabulary and perceptual speed, with no significant difference in rate of decline -12 to -6 years before the event (vocabulary: β: -.01, CI: -.03 to .02; perceptual speed: β: -.02, CI: -.04 to .00). However, both domains showed a significantly faster decline in the preclinical dementia group closer to event (vocabulary: β: -.15, CI: -.17 to -.13; perceptual speed: β: -.11, CI: -.12 to -.09). As with word recall, category fluency showed a significant difference in rate of cognitive decline in the preclinical dementia compared to the dementia free group at both time periods (β: -.04, CI: -.07 to -.01; β: -.15, CI: -.17 to -.13).

Within the preclinical dementia group, rates of cognitive decline increased significantly between the -12 to -6 years and -6 to 0 years time periods in all cognitive tests ($p<.000$), except for word recall ($p=.150$; Figure 5).

Table 6. Mixed-effect models' β-coefficients and 95% confidence intervals (95% CIs) of the associations between preclinical dementia status and baseline performance (intercept), and annual changes over 12 years (dementia status × time), in multiple cognitive domains. Further stratified for age.

Mixed models[a]	Word Recall	Word Recognition	Vocabulary	Category Fluency	Perceptual Speed
Overall study population					
Dementia status (intercept)					
Dementia free	Ref	Ref	Ref	Ref	Ref
Preclinical dementia	-.53 (-.64 to -.42)	-.60 (-.73 to -.48)	-.38 (-.51 to -.25)	-.52 (-.64 to -.41)	-.38 (-.48 to -.28)
Time, years	-.05 (-.05 to -.04)	-.02 (-.02 to -.01)	-.02 (-.03 to -.02)	-.05 (-.05 to-.04)	-.05 (-.05 to -.05)
Dementia status x time (years)					
Dementia free x time	Ref	Ref	Ref	Ref	Ref
Preclinical dementia x time	-.09 (-.10 to -.07)	-.10 (-.12 to -.08)	-.09 (-.10 to -.07)	-.11 (-.12 to -.09)	-.07 (-.08 to -.05)
Young old					
Dementia status (intercept)					
Dementia free	Ref	Ref	Ref	Ref	Ref
Preclinical dementia	-.62 (-.82 to -.42)	-.64 (-.85 to -.42)	-.50 (-.71 to -.29)	-.70 (-.92 to -.49)	-.48 (-.66 to -.30)
Time, years	-.04 (-.05 to -.03)	-.01 (-.02 to -.01)	-.02 (-.02 to -.01)	-.04 (-.04 to-.04)	-.05 (-.05 to-.04)
Dementia status x time (years)					
Dementia free x time	Ref	Ref	Ref	Ref	Ref
Preclinical dementia x time	-.11 (-.14 to -.08)	-.11 (-.14 to-.08)	-.07 (-.08 to -.05)	-.10 (-.12 to -.08)	-.07 (-.09 to -.05)
Old old					
Dementia status (intercept)					
Dementia free	Ref	Ref	Ref	Ref	Ref
Preclinical dementia	-.48 (-.61 to -.35)	-.58 (-.76 to -.40)	-.30 (-.48 to -.13)	-.46 (-.58 to -.34)	-.32 (-.45 to -.20)
Time, years	-.07 (-.08 to -.06)	-.04 (-.05 to -.02)	-.05 (-.06 to -.04)	-.07 (-.08 to -.06)	-.07 (-.08 to -.07)
Dementia status x time (years)					
Dementia free x time	Ref	Ref	Ref	Ref	Ref
Preclinical dementia x time	-.05 (-.08 to -.03)	-.08 (-.12 to -.05)	-.07 (-.10 to -.05)	-.09 (-.11 to -.07)	-.05 (-.07 -.03)

[a] All models adjusted for age, sex, and education.

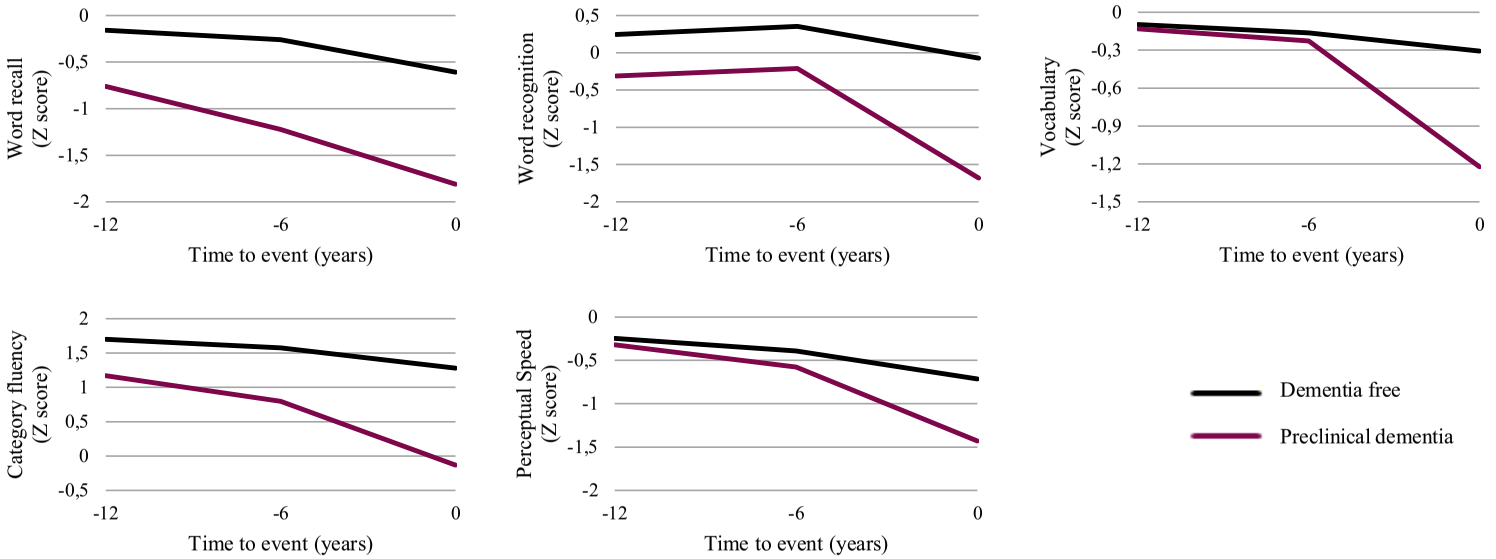

Figure 5: Piecewise mixed models with spline at six years

DISCUSSION

Summary of main results

This doctoral project investigated the rates of cognitive decline during the preclinical phase of dementia, and examined the ability of biological and cognitive markers to identify those at risk of future dementia. *Study I* investigated the benefit of combining markers from the cognitive, genetic, and MRI brain volume modalities and concluded that combining markers from all modalities increases their ability to predict future dementia. Similar results were found in *Study II*, with the usefulness of DTI further explored. A number of measures of white matter microstructure integrity were found to be predictive of future dementia. However, the additional benefit of DTI markers to models including cognitive tests, genetics, and MRI macrostructure was small. Both *Studies I* and *II* found a relative benefit of cognitive markers over that of biological markers and concluded that small increases in predictive value should be weighed against the cost of additional tests. *Study III*, which focused on the ability of neuropsychological tests to predict dementia among a range of modifying factors, determined that tests of category fluency, episodic memory, and perceptual speed were consistently good predictors of future dementia across all subgroups and independent of time to diagnosis. Finally, in *Study IV*, the rate of cognitive decline during the preclinical phase of dementia was observed to be non-linear, apart from word recall, and showed a greater acceleration closer to dementia diagnosis. Individuals identified as fast decliners, based on the first 6 years of cognitive decline, were shown to be at higher likelihood of developing dementia in later years.

Markers of future dementia

Cognition

Neuropsychological tests have frequently been shown to be good predictors of future dementia as they are capable of detecting subtle changes in cognition, which occur before the more marked deficits needed to diagnose dementia [39, 215, 216]. A number of previous studies have noted deficits over a range of cognitive domains, beyond the typically expected episodic memory or executive function deficits associated with AD or VaD [99, 215, 217]. Many of the findings within this thesis also support that a variety of cognitive domains show deficits during the preclinical phase of dementia. Across Studies I, II, and III the ability to predict dementia six to twelve years later was found using neuropsychological tests of global cognition, episodic memory, semantic memory, verbal fluency, perceptual speed, and executive functioning. This wide range of affected domains may be due to multiple pathologies underlying the dementia as evidence suggests mixed pathology in a majority of

dementia cases [41, 47, 48]. The broader patterns of cognitive deficits would therefore reflect these respective pathologies. For example, presence of both episodic memory deficits, due to hippocampal atrophy found in AD, and executive functioning deficits, due to vascular damage found in VaD. It may also be a product of time to diagnosis, as the scale of cognitive deficits is often reflective of pathological burden, which increases as the underlying disease progresses. Therefore, single domain deficits may be more common in the earliest stages of disease progression.

This being said, while all cognitive domains provide some predictive value of future dementia, a few specific domains show greater promise than others. Across the four studies of this thesis, tests of episodic memory, in particular word recall, category fluency, and perceptual speed, were shown to be superior cognitive predictors compared to other domains.

Episodic memory tests have frequently been found to be good predictors [40, 188, 215] as deficits in this domain are a primary symptom of AD. That the studies in this thesis support this evidence is likely due to the majority of dementia cases in the SNAC-K population being AD-type or mixed dementia. Alongside cross-sectional performance, rates of episodic memory decline were also predictive of future dementia (Study IV). However, not all aspects of this domain are equally useful. Our own research, supported by some literature [218, 219] suggests that tests of free recall are superior predictors to tests of recognition. Potential benefits of free recall may be due to this aspect of memory declining earlier in the preclinical phase of dementia (Study IV) [124], making it a more suitable predictor far from diagnosis. It was also found to be highly predictive independent of time to diagnosis (Study III), and more predictive than recognition throughout the preclinical phase, suggesting that free recall is a better predictor in general. This is potentially due to the more challenging nature of this task, which allows for the detection of more subtle deficits than is possible with a task of word recognition. Although, the results on this are mixed, Russo et al. [219] found a measure of pure recognition to be a poor predictor of conversion from MCI to AD but that a recognition discriminability index (hits – false alarms) provided good predictive value. This benefit of discrimination indices has been replicated [220], although our recognition task was also based on discrimination ability and did not support these findings. Despite these discrepancies, overall, tests of episodic memory have proven to be extremely useful predictors of dementia.

Category fluency also ranks amongst these noted cognitive domains and has previously been used as a predictor of future dementia [153, 156, 221]. Evidence shows deficits in both category and letter fluency in preclinical dementia and MCI [102, 222] but that category fluency may decline faster and have greater discriminatory/predictive value than letter fluency [223]. Among our own research, category fluency was found to be a strong predictor but letter fluency was typically not. This may be due to the different aspects of language that underpin each test, as category fluency relies more on semantic understanding and letter fluency on phonetic aspects. Category fluency has also been suggested to rely on episodic memory ability, as the task allows for the application of strategies which can involve episodic

memories [224]. As previously mentioned, episodic memory tasks are commonly used in dementia prediction and so this aspect of category fluency may somewhat explain its ability to identify those with MCI and preclinical dementia. In relation to this, the specific activation of temporal regions [224, 225] found with category fluency and semantic processing may make it particularly useful in identifying AD-type dementia. However, the neural base of category fluency is broad, also covering frontal and parietal regions [225, 226], and it is therefore likely to be affected by a large range of dementia pathologies, making it a useful predictor for multiple subtypes of dementia. Category fluency was also the only domain where rate of decline was a significant predictor of future dementia after accounting for baseline score (Study IV), suggesting a particular benefit of multiple aspects of category fluency, both single time-point and rate of decline, increasing its utility as a marker of future dementia.

Finally, perceptual speed was noted as another particularly strong marker of future dementia. In our own studies, a test of perceptual speed was the strongest cognitive predictor in Study I and at 12 years before diagnosis in Study III. This is relatively unsurprising as perceptual speed, or processing speed, tends to show disproportionate slowing in both AD [227, 228] and VaD [229]. It is typically considered to be related to white matter [214, 230-233], although most of this research has been conducted in samples of healthy individuals. Perceptual speed may therefore be susceptible to a wide range of damage to white matter integrity, such as that caused by AD or VaD pathology [42, 166, 234]. This is supported by the presence of perceptual speed deficits in preclinical AD and MCI [99, 217] and its ability to predict future dementia [178, 183]. When considering its ability as a practical marker of preclinical dementia, the relative ease of administrating a task of perceptual speed is also important to consider. This ease of application to large samples and its documented predictive value make perceptual speed, alongside tests of episodic memory and category fluency, a useful tool for identifying those at risk of future dementia.

That these three domains were also frequently present in final prediction models of dementia created in various subgroups, such as AD-only dementia and divided by age, sex, educational attainment, and *APOE* status (Study III), further attests to their robustness as cognitive predictors. That being said, there is still some differential ability of cognitive tests in relation to a number of these modifying factors. The ability of cognitive tests to differentiate between subtypes of dementia [50, 51] was somewhat reinforced with word recall as joint strongest predictor with category fluency in those with AD-only type dementia, supporting the importance of episodic memory as a marker of AD. In relation to this, in line with the role of the ε4 allele in AD-type dementia, word recall was the most predictive cognitive test for ε4 allele carriers. Differences found in the most predictive domains between sexes, category fluency for women and perceptual speed for men, may be reflective of underlying subtype of dementia pathology with men being more likely to develop VaD and women AD [67]. With differing patterns and severity of cognitive deficits and rates of decline between dementia

subtypes [51], ages [64, 65], sex [72], education [125], and *APOE* status [235], finding markers which can be applied across these groups to identify those at high risk is particularly useful for large scale recruitment, for example in preventative interventions.

Another important aspect of these noted domains is that they typically fall under the definition of fluid cognition. Episodic memory, executive function, perceptual speed, and verbal fluency have been shown to be some of the first domains affected in dementia [121, 126], making them good early markers compared to crystallized domains [99]. A finding supported by our own research as these domains were relatively better predictors than crystallized domains, such as semantic memory, throughout Studies I-IV. The only exception to this pattern may be for executive function, which has a mixed prediction ability throughout the studies of this thesis. However, this may be due to fewer participants completing this task. As our measure of predictive ability (AUC) is sensitive to sample size, this would put executive function at a disadvantage compared to the other domains. Onset of decline is not the only factor to consider, however. Cognitive decline in fluid domains is not restricted to preclinical dementia or pathological aging, within normal aging some cognitive decline is to be expected [2]. Most of this decline is centered on fluid domains, with mental processes associated with crystallized cognition, such as general knowledge, remaining relatively intact throughout the lifespan [2, 236]. Consequently, differentiating between normal cognitive decline, as result of aging, and cognitive decline driven by an underlying pathological process, may be more difficult for domains of fluid intelligence than for crystallized [121]. It may therefore be necessary to take into consideration the magnitude of decline, compared to that of normal aging, when using rate of decline as a marker of preclinical dementia.

Much of the discussion so far has specifically focused on single time-point or cross-sectional scores of cognition. However, while cognitive deficits have been associated with increased likelihood of future dementia [215], a relatively high proportion of those with low cognitive scores remain stable or even improve [92, 237, 238], suggesting that those individuals were never in a preclinical phase of dementia. In this regard, change in cognitive performance or rate of decline may potentially be more informative as a predictor. An abundance of research into rates of cognitive decline during the preclinical dementia phase exists [100, 108, 126] but, so far, few studies have attempted to utilise this for prediction. One such study, by Nation et al. [129], found that those with cognitive decline over a 12 month period showed increased probability of future dementia, even when accounting for baseline cognition. This finding suggests that rate of decline adds unique information on dementia likelihood above that found from single time-point cognitive scores. This finding is supported by our own research (Study IV) for tests of word recall and category fluency, although this result only remained significant for category fluency once baseline score was taken into account. The odds ratios for cognitive decline were smaller than for baseline score in Nation et al., suggesting that low baseline scores may result in higher risk of future dementia compared to cognitive decline. Although, this is likely dependent on factors such as time to diagnosis. That the opposite was

true in our study, where rate of decline for category fluency was a stronger predictor of dementia than baseline scores, may attest to the usefulness of rate of decline as a marker of preclinical dementia. Despite representing a very preliminary line of research, this provides some evidence that rates of cognitive decline may be useful in identifying those likely to develop future dementia.

MRI - Grey and white matter macrostructure

Beyond neuropsychological tests, biological markers have an important role in dementia prediction. Hippocampal atrophy is one of the defining features of AD and may act as an early marker, as grey matter atrophy has been shown to precede cognitive deficits [239]. A number of studies have investigated the ability of grey matter volume to predict future dementia and found promising results, particularly from the hippocampus and MTL [162, 163]. In line with this, Studies I and II found good ability of hippocampal volume to predict dementia at 6 years but not total grey matter volume. Although markers of total grey matter volume have previously been shown to be predictive [31], this is not a consistent result [240], and hippocampal volume is likely to represent a much more specific marker of dementia. However, this may be dependent on time to diagnosis as the temporal unfolding of grey matter atrophy in AD typically begins in the entorhinal and hippocampal regions before spreading to parietal and frontal cortices [34]. Therefore, total grey matter volume may become more salient closer to diagnosis. These results may also have been improved by using a different measure of neuronal atrophy. Cortical thickness has been touted as a potentially better measure of grey matter atrophy in relation to future dementia and has shown promising results [188, 241, 242]. While grey matter volume is subject to factors such as TIV, which must be adjusted for, cortical thickness measures have the benefit of needing no additional statistical correction. However, there is no strong evidence to support greater accuracy of cortical thickness over volume measures in predicting future dementia [243], suggesting that markers of grey matter atrophy are useful predictors regardless of the exact method used.

Beyond grey matter, measures of white matter macrostructure, through WMHs, were also a significant predictor of dementia up to six years later. WMHs as an individual marker of future dementia has mixed results within the literature but typically leans towards attributing some risk or predictive value [159, 161]. With the addition of our findings, it appears that WMHs may have some benefit as a marker of future dementia, particularly in populations with higher incidence of mixed dementia, such as the oldest old [41, 48]. Although WMHs are typically associated with vascular dementia, they should not be discounted for the prediction of AD, particularly as WMHs can exacerbate the effect of other AD pathology, such as hippocampal atrophy [54]. In relation to this, we found evidence to support its predictive value in AD-only [161] and mixed dementia samples (Studies I and II).

DTI - White matter microstructure

Measures of white matter microstructure via DTI have been much less studied in relation to preclinical dementia than the other markers previous discussed. However, white matter microstructure integrity is typically reduced as a part of normal aging [244] and during the dementia process [165, 245]. Previous research exists to support the ability of white matter microstructure integrity to predict future dementia [166, 174-176]. This is in line with our findings as global MD, as well as MD in a number of tracts (CHC, CS, FMAJ, and IFOF) and FA in the FMAJ, were all significant predictors of dementia six years later. Global MD [166] and specific tracts of the basal region of the IFOF [176] and CHC [174, 175] have previous evidence of predictive value, in support of our findings (Study II). While most of our associations between white matter microstructure integrity and dementia were found only for MD, as with Brueggen et al. [176], many studies report predictive value of both MD and FA [166, 174, 175]. This finding is difficult to explain and there is no solid evidence as to why this has occurred. However, the lack of findings for FA in our study may be a product of small sample size, with the study by Power et al. [166], which found both FA and MD to be predictive of future dementia, including a much larger sample.

An interesting observation from Study II was that a number of tracts also displayed better predictivity than WMHs, suggesting that measures of microstructural integrity may be capable of capturing changes beyond that of traditional macrostructural MRI sequences. These findings, when taken into account with research suggesting that changes to white matter microstructure integrity may precede the development of WMHs and white matter loss [246, 247], suggest that white matter microstructure integrity may be a beneficial early marker of pathological changes to white matter. However, the information from white matter microstructure integrity may not be complimentary or may be out-competed by other factors when combined in prediction models, as evidenced by the failure of most DTI markers to contribute to the final models created in Study II. It should also be noted that many of the findings in our study, and within the literature as a whole, are gathered from small samples and should be taken with caution. Our research into this was also limited by the scanner and sequences used; newer scanners and sequences for DTI are likely to provide clearer results as to the usefulness of DTI in dementia prediction. Although, despite these issues, the findings are promising and warrant further exploration.

APOE

While considered a risk factor, rather than a marker of dementia, the presence of the *APOE* ε4 allele exhibited good prediction ability in this study. Known to be the strongest genetic risk factor for AD, the mechanisms of the ε4 allele in AD are complex and still not fully understood [248]. However, those with preclinical dementia or MCI and presence of one or more ε4 alleles, typically display increased neuronal atrophy and increased Aβ deposition

[249], greater cognitive deficits [235], and potentially faster rates of decline than ε4 non-carriers [144, 145], although this last point is debated [136, 146]. In line with our own findings (Studies I and II), there is support in the literature as to its value as a predictor [153, 178, 248]. Although, typically considered a non-modifiable risk factor, there is some evidence to suggest that ε4 carriers may particularly benefit from lifestyle interventions in reducing dementia risk [250]. Therefore, making it a useful marker in identifying individuals who may experience the most benefit from preventative lifestyle interventions.

Comparison between modalities

How these individual modalities compare to one another is an important step in determining their practical use for dementia prediction. In Studies I and II, cognition was shown to be the strongest predictor among all of the modalities tested (joint with genetics in Study I). Particularly in domains of global cognition, episodic memory, category fluency, and perceptual speed. Although, it should be noted that there were no statistical differences between best individual markers of any domain in Study I. As dementia is defined by cognitive decline it is not surprising that levels of cognitive ability are strong predictors of future dementia. Particularly as decline can begin far in advance of dementia diagnosis [37, 40, 94]. Although we found good predictive ability of cognitive tests compared to the other modalities, this may, in part, be due to time to diagnosis in these studies being relatively short, at six years. The Cascade Hypothesis [23, 24] for development of AD, for example, suggests a sequential development of symptoms where neural atrophy would precede cognitive decline. Biomarkers have also been suggested to reflect this sequential staging [251]. It would therefore be reasonable to assume that MRI/DTI markers would be more predictive in the earliest stages and cognitive deficits in the later stages of preclinical dementia. While this is specific to AD pathology, VaD also shows a long preclinical phase [44] and any neurological changes would also be expected to precede cognitive symptoms. Therefore, it is important to consider the time from diagnosis when interpreting the usefulness of marker modalities as this is likely to change over the course of the preclinical period.

The additional benefits of combining multiple markers

All of the markers mentioned above hold some predictive value for future dementia in their own right. However, this ability is limited when using individual markers [36, 111-113, 162, 163]. Across all studies in this thesis, combining markers led to a significant increase in ability to predict future dementia. This was observed for both single time-point markers

(Studies I, II, and III) and rate of decline (Study IV), and within and between modalities (Studies I and II). This is also a common finding among the literature [155, 156, 178-181, 183-185, 187, 188].

While it is possible to increase predictivity through combinations within modalities (Study I) [153, 155, 188], the models with the highest predictive value in Studies I and II were created through a mixture of markers from multiple modalities. Increases in predictive value when combining markers may be restricted by intercollinearity, or how closely related the markers are to one another, which can limit the amount of unique variance added by each marker. Therefore, model building using multiple markers is not as simple as combining the best individual predictors. This is because the effects may not be additive, which is particularly noticeable in the cognitive modality. Neuropsychological tests, despite coming from multiple domains, may still be highly correlated (Study I and II) and overlap in terms of added variance, therefore reducing their predictive ability when combined. Whereas, the addition of markers from other modalities is more likely to account for greater unique variance and increase in predictive value [188]. The importance of compatibility of markers, above that of individual predictivity, is highlighted by the presence of WMHs in the most predictive model of Study I, despite it being a relatively poor individual marker.

That being said, the ability of models only containing cognitive markers was not statistically different to models of multiple modalities (Study I). While increasing the predictive value of these models is important, the AUC score, or raw predictive ability, is not the only factor to consider. Other issues such as financial and time constraints are important when considering practical applications and minor increases in predictive value may, in some cases, be outweighed by such concerns. Cognitive tests in that regard could be considered especially useful predictors due to their high predictive value, low cost, and relatively short time to administer. On the other hand, the use of biological markers may be essential for differential diagnosis between dementia types. It is therefore important to tailor the modalities used to the individual needs of the situation.

It should also be noted that whatever the markers used, much of the predictive value of individual and combined models was accounted for by demographic factors (age, sex, education). The presence of at least two additional markers was often required before significant predictive value was added, beyond the model of demographic factors (Studies I, II, and III). This, in addition to previous research outlining the risk associated with older age [58, 59], lower education [75, 76], and the female sex for future dementia [66, 67], suggests that simple demographic factors play an important role in dementia prediction. This is a concept that has frequently been overlooked in previous literature due the lack of statistical testing when evaluating the additional increases in predictivity of added markers, either from demographic factors or between markers themselves.

Trajectories of decline

An essential factor in the study of cognitive markers and their utilisation for dementia prediction is a thorough understanding of their development during the preclinical phase and how this development differs from normal aging.

That decline during preclinical dementia occurred over all domains examined (Study IV) adds weight to the idea that dementia is characterised by extensive cognitive changes, over a range of domains [39, 99]. However, this decline was not uniform. The onset of decline for the preclinical group was earliest for domains of episodic memory (word recall) and category fluency, as both displayed significantly increased rate of decline between twelve and six years before a diagnosis, compared to the no dementia group. That episodic memory [40, 188, 215] and category fluency [153, 156, 221] are good early predictors of dementia (Study I-IV) is likely due to this early onset of decline found in both domains. For word recognition, semantic memory, and perceptual speed, preclinical decline only significantly differed from the dementia free group during the last six years prior to diagnosis. This is in keeping with findings that suggest episodic memory is the first domain effected [100, 119, 126] and that domains of fluid cognition are the first to decline [100, 121, 126]. However, we were not able to pinpoint the onset of accelerated decline due to the study design. A knot was artificially placed at 6 years before diagnosis due to time-point limitations. For this reason, specific change points for each specific domain could not be estimated.

Alongside onset, pattern of decline during the preclinical dementia phase is an important aspect. All tests, except for word recall, exhibited a non-linear rate of decline, with accelerated cognitive decline closer to diagnosis. This pattern is supported by previous studies [100, 108, 119] and likely reflects the increasing pathological burden of the disease and potential breakdown of mechanisms used to control it. Most studies [100, 108, 119] also show a non-linear rate of decline for episodic memory, which was only partially supported by our results as word recall showed a linear rate of decline, whereas word recognition exhibited a non-linear trajectory. That these tests differ in onset and trajectory is not unheard of though, as different aspects or tests of memory performance have previously been shown to exhibit different patterns of trajectory [119, 252]. This accelerated decline closer to diagnosis, noted in all tests except for word recall, will inevitably mean that many markers are better predictors during later stages of the preclinical phase, as found in Study III, and that their usefulness far from diagnosis may be limited (Study III and IV).

It has also been suggested that, while fluid measures may begin declining earlier than crystallized measures in relation to dementia onset, crystallized domains show a steeper rate of decline compared to normal aging [121]. This was somewhat supported by the results of Study IV, which show a larger difference in rate of decline between the two groups (preclinical dementia and no dementia) closer to diagnosis in tests of word recognition and vocabulary compared to word recall, category fluency, and perceptual speed. As previously

touched upon, the masking effects of normal, age-related decline may be greater for domains of fluid cognition than for crystallized [2]. Fast decline in crystallized measures may therefore be a more reliable indicator of pathology compared to decline in fluid measures.

Methodological considerations and limitations

With all research it is important to note limitations and methodological issues which should be taken into account when considering the results, conclusions, and implications of a study, and this is no different for the studies which comprise this thesis. While limitations of the individual studies are discussed in their respective papers, this section will focus on the overarching considerations and limitations that affect all of the studies contained in this thesis.

Sample considerations

Although one of the great benefits of the research conducted for this thesis is due to the longitudinal, population-based sample, there are methodological issues to consider in relation to this. *Generalisability* refers to the extent to which the findings of a study can be applied to other settings or populations. Population-based samples often have better generalisability than samples from highly selective populations such as memory clinics, as the subjects represent a more diverse, heterogeneous group, closer in characteristics to the general population. However, there are limitations to this, as individuals in the SNAC-K sample used throughout this thesis were recruited from a wealthy suburb of Stockholm and were overall more highly educated and had a higher social-economic status (SES) than the general population of Sweden. This higher SES can confer better overall health in old age [253, 254] and so it is probable that this sample is healthier than average. The SNAC-K population is also predominantly Caucasian and there are known differences in dementia risk, aetiology, symptoms, and outcome between ethnic groups and races [255-257]. All of these things limit generalisability and should be considered when attempting to apply the results to other populations. Although, it should be noted that this would likely result in an underestimation and that the true effects would be larger in the general population.

As mentioned, while population-based samples tend to be more generalisable as recruitment is based on geographical location, rather than specific characteristics or diagnoses, there are still *selection biases* in population samples and *attrition bias* in longitudinal studies. Although everyone who met the age criteria and lived within the Kungholmen surburb of Stockholm was offered a chance to join the study, only 73.3% agreed to be part of the baseline data collection. It has been known that, in general, healthier and more cognitively intact

individuals are likely to take part in scientific studies. Therefore, the SNAC-K population likely under-represents those with worse health or cognition who may be at greatest risk of dementia. Who chooses to remain in the study for further time-points may also be biased. Once again, those with better overall health and cognition are more likely to continue their participation in longitudinal studies, while those with deteriorating health or cognition disproportionately have missing data or drop out completely. This missing data can be a particular problem for statistical analysis. Although some analyses take into account missing data, such as linear mixed models, the data is often assumed to be missing at random, which as mentioned, is not always the case.

It should also be noted that there was an overlap of participants across the samples used in this thesis. As the participants were drawn from the overall SNAC-K population, a number of individuals are likely to be present in more than one study. This should be taken into account when drawing conclusions across the studies as similarities in results may be influenced by the presence of the same individuals over multiple studies.

Dementia Classification

The dementia diagnosis within SNAC-K was a thorough process based on the DSM-IV criteria, as detailed in the 'Methods' section. With the addition of cases derived from registry data, the chance of missing a diagnosis was further reduced. However, classification of the specific subtype of dementia should be taken with caution. Participants in SNAC-K were not subject to testing of biological markers, such as Aβ or tau through CSF or PET imaging. MRI imaging was available for a subsample of individuals but was not used for dementia diagnosis. Diagnoses were made based on the medical interview and examination along with background health information. While this reduced circularity, as markers for prediction were not used for diagnosis, it also limits the accuracy of the diagnosis for dementia subtypes.

Implications and future directions

Due to the pressures of dementia at both an individual and societal level, exacerbated by lack of available cures, there is high demand for new treatments or preventative strategies. In order to implement these strategies, the identification of those in the earliest stages of the dementia process is vital. This thesis has explored the preclinical phase of dementia in relation to cognitive and biological markers, which may be beneficial for identification of at-risk individuals. As mentioned previously, one way of achieving this may be through the development of risk scores based on demographic and lifestyle profiles. However, using markers that would suggest an individual is likely on the dementia pathway already may

increase identification accuracy. This would aid targeting to those most likely to respond to intervention or treatment and avoid the inclusion of individuals for whom treatment, and any potential side effects, would be unnecessary.

The use of singe time-point cognitive performance over a range of domains, but particularly episodic memory, category fluency, and perceptual speed, was a good predictor of future dementia status. This predictive ability was maintained even over a range of modifying factors, further establishing these cognitive markers as useful predictors. These findings, alongside the relatively low cost and easy application of neuropsychological tests, is promising for wide-scale testing.

Biological markers, such as genetics, neural atrophy, and white matter integrity, were also good individual predictors and added unique contributions when combined in models with markers of cognition. Although not established in this thesis, biological markers may also be particularly important when identifying likely dementia development earlier in the preclinical phase, as cognitive markers were typically only reliable up to six years before a dementia diagnosis. DTI markers of white matter microstructure integrity have so far been little explored in relation to this but have shown potential and warrant further research with more current technology and over longer time periods with larger samples.

Although each marker provided some predictive value, combining markers ensured the best ability to identify those likely to develop future dementia. While increases in predictivity could be achieved by combining cognitive markers alone, the greatest increases were found through the combination of markers from multiple modalities. It is therefore important to consider a range of markers when predicting future dementia.

How the predictive value of markers changes over time, in relation to the stage of preclinical dementia, should also be more thoroughly examined as it is likely to have profound impact on their use for prediction.

While all of these implications have focused on single time-point markers, the ability of rate of decline to identify those likely to develop dementia was promising, albeit constrained by the limitations of cognitive markers to identify those in a preclinical phase further from diagnosis. As dementia is characterised by cognitive decline compared to their usual performance level, the utilisation of rates of decline or change in cognition may provide more information than static performance scores, as single time-point scores are unable to determine if low cognitive ability is a stable factor for that individual or due to dementia. It is therefore important that more research be conducted to this end.

Many of these recommendations involve investigating even earlier stages of the preclinical process over multiple time points, which would require longitudinal data over a time period that has been relatively little examined. Although costly and associated with multiple difficulties, such as attrition and practice effects, the only reliable way of identifying markers

capable of predicting future dementia is by thoroughly understanding dementia development and the preclinical phase, which requires a longitudinal perspective.

CONCLUSIONS

Over the four studies which comprise this thesis, cognitive performance and decline in the preclinical phase of dementia has been explored. The ability of these cognitive markers, alongside various biological markers, to identify those at risk of future dementia was investigated.

The trajectories of cognitive decline over twelve years during the preclinical stage of dementia was observed and accelerated decline, over multiple domains, clearly differentiated normal cognitive aging from pathological decline found in preclinical dementia. The patterns of decline gave some insight into the benefits of these cognitive domains as predictors for future dementia. Episodic memory and category fluency both showed early decline, up to twelve years before diagnosis, and they also represented some of the strongest individual predictors amongst the cognitive domains, across the four studies. That obvious decline was present over all of the domains studied supports the idea that preclinical dementia is characterised by extensive changes within the brain, resulting in a broad range of cognitive deficits.

While these cognitive deficits and decline could be utilised for dementia prediction, an additional advantage in identifying those at greater risk of future dementia came from the inclusion of biological markers. Individually, markers of neural atrophy, macrostructural (white matter hyperintensities) and microstructural (mean diffusivity and fractional anisotropy) white matter integrity, and genetics (*APOE*), were all significant predictors of future dementia. However, combining markers, both within and between, modalities increased predictive ability due to the unique variance contributed.

In addition, this thesis has highlighted the importance of longitudinal data when conducting aging research. The work in this thesis has greatly benefited from the population-based, longitudinal sample, which allowed for the tracking of cognitive decline and prediction of dementia over a period of time which has rarely been studied.

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APPENDIX

Supplementary Table 1. Multinomial logistic regressions for combined models – young-old vs. old-old

		No dementia (*n*)	Incident dementia (*n*)	OR	95% C.I. for OR		p-value	ROC – AUC
					Lower	Upper		
Young-old (<78)								
Model 0	Covariates	1278	38					.832
Model 1	Category fluency	1275	37	2.61	1.62	4.22	.000	.867
Model 2	Category fluency	1271	37	2.10	1.28	3.45	.004	.879
	Word recall			1.73	1.14	2.61	.009	
Or								
Model 1	Digit cancellation	1272	34	2.81	1.82	4.33	.000	.867
Model 2	Digit cancellation	1269	34	2.60	1.68	4.02	.000	.885
	Word recall			1.96	1.29	2.99	.002	
Old-old (≥78)								
Model 0	Covariates	455	87					.642
Model 1	Category fluency	455	87	2.82	1.98	4.04	.000	.731
Model 2	Category fluency	449	85	2.21	1.52	3.20	.000	.750
	Word recall			2.03	1.47	2.81	.000	
Model 3	Category fluency	385	56	1.77	1.13	2.78	.013	.764
	Word recall			2.02	1.36	3.00	.001	
	TMT B			1.68	1.19	2.36	.003	

Supplementary Table 2. Multinomial logistic regressions for combined models – female vs. male

		No dementia (*n*)	Incident dementia (*n*)	OR	95% C.I. for OR		p-value	ROC – AUC
					Lower	Upper		
Female								
Model 0	Covariates	1063	178					.866
Model 1	Category fluency	1060	176	3.56	2.69	4.69	.000	.905
Model 2	Category fluency	1043	151	2.75	2.01	3.78	.000	.911
	Pattern comparison			2.37	1.73	3.25	.000	
Model 3	Category fluency	1040	150	2.19	1.57	3.06	.000	.914
	Pattern comparison			2.21	1.60	3.04	.000	
	Word recall			1.76	1.34	2.32	.000	
Male								
Model 0	Covariates	670	68					.878
Model 1	TMT A	657	58	2.08	1.53	2.83	.000	.909
Model 2	TMT A	655	58	1.81	1.29	2.52	.001	.923
	Word recall			2.85	1.90	4.27	.000	
Model 3	TMT A	655	57	1.53	1.07	2.19	.019	.930
	Word recall			2.63	1.72	4.00	.000	
	Category fluency			1.73	1.12	2.67	.013	

Supplementary Table 3. Multinomial logistic regressions for combined models – low vs. high education

		No dementia (*n*)	Incident dementia (*n*)	OR	95% C.I. for OR		p-value	ROC – AUC
					Lower	Upper		
Low Education								
Model 0	Covariates	863	182					.820
Model 1	Category fluency	862	180	3.66	2.79	4.79	.000	.878
Model 2	Category fluency	847	154	2.96	2.19	4.00	.000	.887
	Digit cancellation			2.00	1.53	2.61	.000	
Model 3	Category fluency	845	153	2.17	1.58	2.99	.000	.896
	Digit cancellation			1.93	1.47	2.53	.000	
	Word recall			1.99	1.51	2.62	.000	
High Education								
Model 0	Covariates	870	64					.902
Model 1	Category fluency	868	63	2.62	1.77	3.86	.000	.924
Model 2	Category fluency	863	60	2.15	1.42	3.27	.000	.933
	Word recall			2.38	1.62	3.48	.000	
Model 3	Category fluency	859	57	1.73	1.12	2.70	.014	.937
	Word recall			2.15	1.44	3.20	.000	
	Pattern comparison			2.51	1.56	4.04	.000	

Supplementary Table 4. Multinomial logistic regressions for combined models – no ε4 vs. any ε4

		No dementia (*n*)	Incident dementia (*n*)	OR	95% C.I. for OR		p-value	ROC – AUC
					Lower	Upper		
No ε4								
Model 0	Covariates	1223	137					.887
Model 1	Category fluency	1221	137	3.85	2.83	5.23	.000	.922
Model 2	Category fluency	1207	116	3.38	2.40	4.76	.000	.927
	Digit cancellation			1.74	1.30	2.33	.000	
Model 3	Category fluency	1205	115	2.52	1.76	3.61	.000	.930
	Digit cancellation			1.65	1.23	2.21	.001	
	Word recall			1.93	1.43	2.61	.000	
Any ε4								
Model 0	Covariates	485	87					.866
Model 1	Word recall	482	86	2.92	2.06	4.15	.000	.899
Model 2	Word recall	474	79	2.53	1.73	3.71	.000	.908
	Pattern comparison			2.65	1.68	4.17	.000	
Model 3	Word recall	474	79	2.25	1.52	3.34	.000	.910
	Pattern comparison			2.19	1.36	3.53	.001	
	Category fluency			1.70	1.10	2.62	.018	

Supplementary Table 5. Multinomial logistic regressions for combined models – AD type dementia

		No dementia (*n*)	Incident dementia (*n*)	OR	95% C.I. for OR		p-value	ROC – AUC
					Lower	Upper		
Model 0	Covariates	1733	96					.873
Cognitive base								
Model 1	Word recall	1722	94	3.50	2.62	4.67	.000	.905
Or								
Model 1	Category fluency	1730	95	3.97	2.86	5.51	.000	.905
Model 2	Category fluency	1720	93	2.63	1.85	3.73	.000	.914
	Word recall			2.54	1.86	3.46	.000	
Model 3	Category fluency	1687	83	2.32	1.58	3.40	.000	.920
	Word recall			2.41	1.73	3.37	.000	
	TMT A			1.61	1.23	2.11	.000	

Dissertations from the Aging Research Center and Stockholm Gerontology Research Center, 1991-2020

1991

Herlitz Agneta. Remembering in Alzheimer's disease. Utilization of cognitive support. (Umeå University)

1992

Borell Lena. The activity life of persons with a dementia disease.

1993

Fratiglioni Laura. Epidemiology of Alzheimer's disease. Issues of etiology and validity.

Almkvist Ove. Alzheimer's disease and related dementia disorders: Neuropsychological identification, differentiation, and progression.

Basun Hans. Biological markers in Alzheimer's disease. Diagnostic implications.

1994

Grafström Margareta. The experience of burden in care of elderly persons with dementia. (Karolinska Institutet and Umeå University)

Holmén Karin. Loneliness among elderly - Implications for those with cognitive impairment.

Josephsson Staffan. Everyday activities as meeting-places in dementia.

Stigsdotter-Neely Anna. Memory training in late adulthood: Issues of maintenance, transfer and individual differences.

Forsell Yvonne. Depression and dementia in the elderly.

1995

Mattiasson Anne-Cathrine. Autonomy in nursing home settings.

Grut Michaela. Clinical aspects of cognitive functioning in aging and dementia: Data from a population-based study of very old adults.

1996

Wahlin Åke. Episodic memory functioning in very old age: Individual differences and utilization of cognitive support.

Wills Philippa. Drug use in the elderly: Who? What? & Why? (Licentiate thesis)

Lipinska Terzis Beata. Memory and knowledge in mild Alzheimer's disease.

1997

Larsson Maria. Odor and source remembering in adulthood and aging: Influences of semantic activation and item richness.

Almberg Britt. Family caregivers experiences of strain in caring for a demented elderly person. (Licentiate thesis)

1998

Agüero-Eklund Hedda. Natural history of Alzheimer's disease and other dementias. Findings from a population survey.

Guo Zhenchao. Blood pressure and dementia in the very old. An epidemiologic study.

Björk Hassing Linda. Episodic memory functioning in nonagenarians. Effects of demographic factors, vitamin status, depression and dementia. (In collaboration with the Department of Psychology, University of Gothenburg, Sweden)

Hillerås Pernilla. Well-being among the very old. A survey on a sample aged 90 years and above. (Licentiate thesis)

1999

Almberg Britt. Family caregivers caring for relatives with dementia – Pre- and post-death experiences.

Robins Wahlin Tarja-Brita. Cognitive functioning in late senescence. Influences of age and health.

Zhu Li. Cerebrovascular disease and dementia. A population-based study.

2000

Hillerås Pernilla. Well-being among the very old. A survey on a sample aged 90 years and above. (In collaboration with H. M. Queen Sophia University College of Nursing, Stockholm, Sweden)

von Strauss Eva. Being old in our society: Health, functional status, and effects of research.

2001

Jansson Wallis. Family-based dementia care. Experiences from the perspective of spouses and adult children.

Kabir Nahar Zarina. The emerging elderly population in Bangladesh: Aspects of their health and social situation.

Wang Hui-Xin. The impact of lifestyles on the occurrence of dementia.

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Fahlander Kjell. Cognitive functioning in aging and dementia: The role of psychiatric and somatic factors.

Giron Maria Stella. The rational use of drugs in a population of very old persons.

2003

Jönsson Linus. Economic evaluation of treatments for Alzheimer's disease.

2004

Berger Anna-Karin. Old age depression: Occurrence and influence on cognitive functioning in aging and Alzheimer's disease.

Cornelius Christel. Drug use in the elderly - Risk or protection? Findings from the Kungsholmen project.

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Palmer Katie. Early detection of Alzheimer's disease and dementia in the general population. Results from the Kungsholmen Project.

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Derwinger Anna. Develop your memory strategies! Self-generated versus mnemonic strategy training in old age: Maintenance, forgetting, transfer, and age differences.

De Ronchi Diana. Education and dementing disorders. The role of schooling in dementia and cognitive impairment.

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Klarin Inga. Drug use in the elderly – are quantity and quality compatible.

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Westerbotn Margareta. Drug use among the very old living in ordinary households-Aspects on well-being, cognitive and functional ability.

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Agahi Neda. Leisure in late life. Patterns of participation and relationship with health.

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Fors Stefan. Blood on the tracks. Life-course perspectives on health inequalities in later life.

Keller Lina. Genetics in dementia. Impact in sequence variations for families and populations.

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Schön Pär. Gender matter. Differences and changes in disability and health among our oldest women and men.

Caracciolo Barbara. Cognitive impairment in the nondemented elderly: Occurrence, risk factors, progression.

Rieckmann Anna. Human aging, dopamine, and cognition. Molecular and functional imaging of executive functions and implicit learning.

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Mangialasche Francesca. Exploring the role of vitamin E in Alzheimer's disease. An epidemiological and clinical perspective.

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Rizzuto Debora. Living longer than expected: protective and risk factors related to human longevity.

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Sjölund Britt-Marie. Physical functioning in old age: Temporal trends and geographical variation in Sweden.

Wastesson Jonas. Unequal drug treatment: age and educational differences among older adults.

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Sköldunger Anders. Dementia and use of drugs: Economic modelling and population-based studies.

Craftman Åsa Gransjön. Medicine management in municipal home care; delegating, administrating and receiving.

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Samrani George. Interference control in working memory: neurobehavioral properties and age differences.

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Seblova Dominika. Causal effects of education on cognition – How do we generate evidence?

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Vetrano Davide Liborio. Impact of cardiovascular and neuropsychiatric multimorbidity on older adults' health.

Rehnberg Johan. Inequalities in life and death: income and mortality in an aging population.

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Dintica Christina. Oral health & olfactory function: What can they tell us about cognitive aging