PRODROMAL COGNITIVE SIGNS OF DEMENTIA

RESULTS FROM THE H70 STUDY

Doctoral thesis

Simona F. Sacuiu

UNIVERSITY OF GOTHENBURG

Neuropsychiatric Epidemiology Unit
Department of Psychiatry and Neurochemistry
Institute of Neuroscience and Physiology
Sahlgrenska Academy
Gothenburg, Sweden

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Cover: THE THINKER – Neolithic statuette from the Hamangia culture 6000-6500 B.C., discovered in a necropolis on the coast of the Black Sea, Romania

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MOTTO

"… scientific research is directed at the elucidation of entities about which no clear understanding exists, and to proceed, scientists must find ways of talking about what they do not know"

Evelyn Fox Keller
in "Making sense of life"

Dedicata parintilor mei,
Zoica & Gheorghe

To my parents

ABSTRACT

The increase in proportion of elderly worldwide, coupled with the fact that increasing age is a primary risk factor for dementia, have fuelled the efforts to unveil the warning signs of dementia. Although important achievements have been made in this field during the last decades, many questions are still to be answered. We set out four studies to clarify which are the symptom patterns that predict dementia onset in the short and in the long-term, at different ages and in different birth cohorts, and also to clarify if cognitive decline in late life is related to mortality in the absence of dementia.

In summary, we found that although low performance in memory was necessary to predict dementia, it was not sufficient. Other cognitive domains needed to be affected shortly of dementia onset. Isolated low memory performance predicted dementia only on a longer time frame. In addition, not only Alzheimer's, but also vascular dementia appeared to have a short prodromal stage, with low performance in all four cognitive domains studied. Relying on self-reports or key informants for early detection of dementia excluded a large group of the population at risk. A global pattern of low cognitive performance according to both psychiatric and psychometric examinations predicted short-term development of dementia with a high positive predictive value. However, the sensitivity for dementia was low. Mortality was also related to declining cognitive performance in the absence of dementia. Furthermore, non-memory cognitive symptoms predicted short-term development of dementia in 70-year-olds born 1901-02, but not in those born 30 years later. Only low memory performance according to the psychiatric examination predicted short-term onset of dementia in the later born cohort.

Our findings are important for understanding the clinical history of the disease and may have implications regarding prediction of dementia in elderly individuals.

SAMMANFATTNING

Eftersom andelen äldre i befolkningen ökar i snabb takt, och stigande ålder är den viktigaste riskfaktorn för demens, så kommer antalet personer med demenssjukdom att öka. Men det finns också förhoppningar om att det ska komma metoder att förebygga demensutveckling. Därför har det blivit alltmer intressant att så tidigt som möjligt kunna identifiera de individer som senare kommer att utveckla demenssjukdom.

I den här forskningsstudien har vi undersökt vilka symtom som kan förutsäga demensutveckling på kort, respektive på lång, sikt. Vi har också undersökt om symtomen har förändrats i senare födda generationer. I studien har vi använt resultat från flera delar av de longitudinella befolkningsundersökningarna i Göteborg, som genomförs av forskare vid Sahlgrenska akademin. Förutom en kroppslig och psykiatrisk undersökning genomfördes också tester av minne och andra kognitiva funktioner. Demens och andra sjukdomar diagnostiserades av specialistläkare enligt vedertagna vetenskapliga kriterier.

Redan 1971 undersöktes en stor andel av Göteborgs 70-åringar i befolkningsundersökningen ”Hälsa 70”, som också kallas H70-studien. Denna undersökning har senare utökats med nya 70-åringar och pågår alltjämt. I den första gruppen 70-åringar, som studerades avseende tidiga symtom, ingick 382 icke-dementa göteborgare födda 1901-02. Dessa 70-åringar har sedan följts upp med flera nya undersökningar, varav en del upp till 100 års ålder. En tredjedel av dessa utvecklade demens under uppföljningstiden.
En ny grupp bestående av 551 icke-dementa 70-åringar födda 1930 undersöktes år 2000 och följdes upp med ytterligare en undersökningsomgång vid 75-års ålder. Fem procent av dessa utvecklade demens mellan 70 och 75 års ålder.
Som en utökad del av H70-studien undersöktes 331 icke-dementa 85-åringar under åren 1986-1987. Tre år senare, vid 88 års ålder, hade 17 % av dessa utvecklat demens.

För 85-åringar, födda 1901-02, visar resultaten att enbart dåligt minne inte nödvändigtvis behöver vara tecken på demensutveckling på kort sikt (tre år). De som hade dåligt minne i kombination med andra symtom, till exempel svårigheter att hitta ord, att kopiera en geometrisk figur, eller att fatta snabba beslut, låg i farozonen för att utveckla demens. För de som hade dåliga resultat på andra tester, men gott minne, var det inte någon ökad risk. Detsamma gällde för de med dåligt minne, men bra testresultat i övrigt. Varken deltagarens egen uppfattning om sina minnessvårigheter, eller en anhörigs uppfattning om samma sak, gick att lita på för att förutspå demensutveckling bland de äldsta, födda 1901-02.
För 70- och 75-åringar, födda 1901-02, med enbart dåligt minne, men bra resultat på andra tester, förelåg en ökad risk för demensutveckling på lång sikt. För de 70-och 75-åringar som hade dåliga resultat på övriga kognitiva tester (t ex perceptuell snabbhet, block design eller logisk kategoriseringsförmåga), fanns det en ökad risk för demensutveckling på kort sikt. Ökad risk på kort sikt fanns också hos de med dåliga resultat på övriga kognitiva tester i kombination med dåligt minne.
Däremot för 79-åringarna, födda 1901-02, var det bara de som hade dåligt minne i kombination med andra kognitiva symtom som hade en ökad risk för demensutveckling på kort sikt.

Bland de 70-åringar som var födda 1930 kunde man dock inte skilja mellan de som utvecklade demens och de som var friska, efter fem år, när man med hjälp av neuropsykologiska tester undersökte andra kognitiva funktioner än minne. De som hade minnessvårigheter vid 70-års ålder, enligt den psykiatriska bedömningen, hade en ökad risk för demensutveckling inom fem år.

Studierna i sin helhet visar att det är viktigt att personer med minnesstörning får en ordentlig utredning. Dessutom fann vi att andra symtom än minnesnedsättning kan vara viktigare hos personer yngre än 80 år för att förutsäga utveckling av demens på kort sikt. Tester som man använde tidigare för att förutsäga demens kan visa sig minska i betydelse för utredningar av demens i senare födda generationer därför att de presterar mycket bättre i standardiserade psykologtester än tidigare födda generationer.

REZUMAT

Populatia din grupul de virsta de peste 65 de ani creste rapid si odata cu aceasta explozie demografica creste si numarul celor care dezvolta dementa, dat fiind ca riscul pentru demente creste cu virsta. Dementa este o boala devastatoare care afecteaza procesele mentale in asemenea grad incit persoanele respective nu mai pot sustine o activitate normala. In acest context e extrem de important a gasi metode de a identifica din vreme acele persoane care sunt pe cale de a dezvolta dementa. O incetinire a declinului proceselor mentale cu citiva ani ar avea un impact major asupra numarului de cazuri de dementa la virste inaintate, cu consecinte positive asupra fondurilor alocate ingrijirii celor in virsta de peste 65 de ani. In ultimele decenii s-au facut pasi importanti pentru descoperirea precoce a simptomelor care avertizeaza ca un eventual declin al proceselor mentale catre dementa e in curs de desfasurare. In acelasi timp terapiile existente incetinesc cursul bolii daca sunt initiate in faza usoara a dementei. Cu toate acestea, multe aspecte clinice si terapeutice sunt inca in stadiul de cercetare.

Studiile prezentate in aceasta teza de doctorat au avut ca scop a identifica acele grupuri de simptome cognitive din domeniul memoriei, limbajului, orientarii visuospatiale si gindirii, care survin cel mai frecvent in populatie in etapa premergatoare a dementei. In acest scop am investigat diferite virste din grupul de peste 70 de ani din doua generatii diferite, nascute in 1901 si 1930. De asemenea am studiat daca declinul cognitiv e asociat cu mortalitatea, in absenta dementei, la persoane de peste 70 de ani.

Rezultatele obtinute arata ca tulburari usoare de memorie la virsta de 85 de ani nu indica un risc crescut pentru a dezvolta dementa pe termen scurt daca nu sunt insotite de tulburari in alte domenii cognitive, ca de exemplu limbaj, orientare visuospatiala sau gindire logica. De asemenea, tulburarile usoare in alte domenii cognitive, in absenta tulburarilor de memorie, nu indica un risc crescut pentru dementa la virsta inaintata. In schimb daca atit memoria cit si alte domenii cognitive sunt usor afectate la 85 de ani, riscul de a dezvolta dementa pe termen scurt creste semnificativ. Cu cit mai multe domenii sunt afectate cu atit creste riscul de dementa. Cu toate

acestea intreaga gama de simptome asociate unui risc crescut de dementa a putut fi detectata numai in 18% din populatie. Cu alte cuvinte, putini din cei care dezvolta dementa prezinta aceeasi gama de simptome cognitive in etapa premergatoare imbolnavirii. Un motiv pentru care simptomatologia cognitiva nu e intodeauna asociata cu dementa e si faptul ca declinul cognitiv la virste inaintate apare inainte de deces chiar si in absenta dementei. Intr-unul din studiile noastre declinul cognitiv a putut fi identificat cu 6 pina la 15 ani inainte de deces. Acest lucru nu exclude insa posibilitatea ca persoanele afectate sa fi dezvoltat dementa daca nu ar fi decedat. Intr-un alt studiu am aratat ca gama simptomelor cognitive care indica un risc crescut de dementa la virste cuprinse intre 70-80 de ani e diferita fata de cea identificata la cei de 85 de ani. Tulburari izolate de memorie la 70 sau 75 de ani, in absenta tulburarilor in alte domenii cognitive, confera un risc crescut pentru dementa pe termen lung, adica dupa 5 sau 10 ani de la examenul psihiatric care a detectat aceste tulburari. Chiar mai mult, la cei in virsta de 70 si 75 de ani tulburari usoare in alte domenii cognitive, insotite sau nu de tulburari usoare de memorie, indica un risc crescut de a dezvolta dementa pe termen scurt.

In studiul comparativ intre doua generatii nascute in 1901 si 1930, am descoperit ca grupul de simptome cognitive din domenii precum viteza de perceptie, bogatia limbajului, orientare visuospatiala si gindire logica, care au indicat un risc crescut de dementa pe termen scurt la persoane de 70 de ani nascute in 1901, pierd aceasta asociatie la persoanele nascute in 1930. Numai tulburarile de memorie, asa cum reies in urma examenului psihiatric la 70 de ani, sunt asociate cu dezvoltarea dementei pe termen scurt in ambele generatii. Din cauza unui numar redus de participanti in acest studiu comparativ, nu am avut posibilitatea de a investiga in ce masura tulburarile izolate de memorie, adica in absenta problemelor in alte domenii cognitive, ramin asociate cu dezvoltarea dementei pe termen scurt.

In concluzie, in etapa premergatoare dementelor, asa-zisa etapa prodromala, simptomele care pot fi identificate cu multi ani inainte de imbolnavire sunt diferite de cele care apar cu numai citiva ani inainte. Simptomele sunt diferite la diferite grupuri de virsta si intre generatii.

CONTENTS

Original papers I - IV

LIST OF ORIGINAL PAPERS

The thesis is based on four papers, which will be referred to in the text by their Roman numerals as follows:

I. Sacuiu S, Sjogren M, Johansson B, Gustafson D and Skoog I. *Prodromal cognitive signs of dementia in 85-year-olds using four sources of information.* Neurology (2005);65:1894-1900

II. Sacuiu S, Gustafson D, Johansson B, Thorvaldsson V, Berg S, Sjogren M, Guo X, Östling S, Skoog I. *The pattern of cognitive symptoms predicts time to dementia onset*. Alzheimer's & Dementia: The Journal of the Alzheimer's Association (In press)

III. Sacuiu S, Gustafson D, Sjogren M, Guo X, Östling S, Johansson B, and Skoog I. *Secular trends in cognitive performance in relation to prediction of dementia.* (Submitted)

IV. Thorvaldsson V, Hofer SM, Berg S, Skoog I, Sacuiu S, Johansson B. *Onset of terminal decline in cognitive abilities in individuals without dementia*. Neurology (2008);71:882-887

ABBREVIATIONS

(in order of their frequency in the text)

AD	Alzheimer disease
VaD	Vascular dementia
MCI	Mild cognitive impairment
AAMI	Age-Associated Memory Impairment
AACD	Age-Associated Cognitive Decline
CIND	Canadian Study of Health and Aging
MMSE	Mini Mental Status Examination
CPRS	Comprehensive Psychopathological Rating Scale
DSM-III-R	Diagnostic and Statistical Manual of Mental Disorders, IIIrd ed., Revised
NINCDS-ADRDA	National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer Disease and Related Disorders Association (criteria for Alzheimer's Disease)
NINDS-AIREN	National Institute of Neurological Disorders and Stroke-Association Internationale pour la Recherche et l'Enseignement en Neurosciences (criteria for vascular dementia)
PPV	Positive predictive value
NPV	Negative predictive value
SD	Standard deviation
CI	Confidence interval
OR	Odds ratio
HR	Hazard ratio
P-level	Probability of error when rejecting the null hypothesis (level of significance)
CT	Computerized tomography
GDS	Global Deterioration Scale
VCI	Vascular cognitive impairment

INTRODUCTION

The proportion of people who reach older ages has increased substantially during the last decades. The age structure of the population has thus changed since more people survive to older ages. Consequently, the diseases of old age have turned from a theoretical into a practical issue. The older segment of the population incurs substantial health costs in terms of long-term care for multiple morbidities. Among the morbidities of old age, dementia, with its most frequent subtypes Alzheimer disease (AD) and vascular dementia (VaD), is a major cause of institutionalization (1, 2) and reduced quality of life in the elderly, and is related to a massive societal cost (3). Dementia is diagnosed in people who suffer a loss of cognitive abilities severe enough to interfere with normal activities of daily living. The number of people with dementia worldwide are projected to increase from 24 million in 2005 to 81 million by 2040 (4). Most dementias are brought to medical attention in more advanced stages, since mild cases, with cognitive failures having little impact on daily activities, may be disregarded as a consequence of aging. It may be even more difficult to detect cognitive deterioration in cohorts born later during the last century, since they perform better on a multitude of cognitive tasks compared to earlier born cohorts (5-8). Large efforts have been made to find syndromes that identify those who will develop dementia earlier in the course of the disease, i.e., in the *prodromal stage*, to start treatment or other interventions as early as possible in the disease process, in order to maintain quality of life and limit the devastating consequences of the disease. It is estimated that even a minimal delay in the onset of AD

would considerably reduce the prevalence of the disease and thus have a major public health impact (9, 10). So far success has been limited in attempts to identify cognitive syndromes that best describe the prodromal stage of dementia, and the overlap with 'normal' aging has often been large. Furthermore, the occurrence of death within a few years after an examination that identifies slight cognitive impairments, may eventually truncate the clinical evolution of ongoing neurodegenerative processes in the brain, and thus affect detection of cognitive symptoms as prodromal signs of dementia. It is not clear whether the cognitive decline observed before death is related to mortality in the absence of dementia.
In this thesis, we examine the association of different cognitive symptoms and patterns of symptoms with short- and long-term development of dementia, at different ages and in different birth cohorts. We also investigate if cognitive decline in late life is related to mortality in the absence of dementia.

Cognitive function and aging

Cognitive function

Cognitive function refers to mental abilities used to engage in different aspects of everyday life (11). *"Cognitive"* according to the Webster's Dictionary means conscious mental activity as thinking, remembering, learning or using language. For the purpose of this thesis, reference to cognitive function encompasses memory, language, and visuospatial and executive functions. Each of these functions involves multiple levels of information processing and uses different structures of the central nervous system. Although the study of cognitive function

is a vast area of research and it is beyond the scope of this thesis to present a more in depth account on the subject, a brief overview of the cognitive functions assessed in the studies included in the thesis is necessary.

Memory is conceptualized as a multi-component system specialized in encoding, storage and retrieval of information (12). It is anatomically supported mainly by structures in the medial temporal and frontal lobes and the circuitry linking these structures (Papez circuit), but other cortical and subcortical structures are also involved in memory (13). The initial localization of Alzheimer's type of pathology in deep structures of the medial temporal lobes account for the memory disturbances that occur early in the course of Alzheimer's type of dementia (14, 15). Also localization of vascular damage in the frontal lobes or presence of white matter lesions that affect the connectivity between different cortical regions may explain memory impairments detected in patients with cerebrovascular disease (16, 17).
In its simplified representation, memory can be described as short-term (or temporary working memory) and long-term memory (permanent memory store), the latter sub-divided in declarative (episodic and semantic) and non-declarative (procedural) memory (12, 18). Short-term memory is often thought of as retention of bits of information for the span of few seconds (for example a seven-digit telephone number until it is dialed). Unless it is rehearsed the information stored in the short-term memory will be forgotten. Long-term memory stores information in the long-term and it is the part of the memory system that is activated to recall episodes of our lives (episodic

memory), or factual knowledge (semantic memory) or how to ride a bicycle (procedural memory) (18, 19).

Language relates to verbal communication. It relies heavily on memory (20, 21), but also on executive function (20). Cortical areas involved in language function are located mainly in the frontal and parietotemporal lobes (22). Language deficits have been reported early in the development of AD (23, 24).

Visuospatial function relate to our inner representation of the objects around us and the spatial relation between them, and it helps us navigate in our surroundings (25). It also relies heavily on memory and on other higher cortical processes such as processing speed and executive functions (26). Decline in the visuospatial function has also been reported before the development of dementia (27).

Executive function is involved in the control and monitoring of other cognitive functions (28), as also in abstract thinking as planning and making decisions (29, 30). It has classically been related to frontal cortices (29-31), but other structures, as thalamus, appear to be involved in executive functions (32). Deficits in executive functions appear early in the development of AD and VaD (33-35).

A description of the use of different types of examinations to gather information on memory, language, and visuospatial and executive functions is presented in the section “Cognitive Assessments” in “Methods”.

Aging

Aging is associated with a slight decrease in cognitive function. Very early studies on the effects of aging on cognition typically showed a decline as early as the fourth decade of life in various domains, though verbal skills were not affected (36). However, these studies made cross-sectional comparisons of groups of people of different ages. Thus the decline in cognitive function might not entirely be attributed to age, but also to birth cohort differences in family structure, education, occupations, societal changes and other background factors (the so-called 'birth cohort effect')(6). For example, in the Seattle Longitudinal Study, the cognitive performance of a group of people aged 20 to 70 years, was tested periodically, and in the same time new participants from the same age cohorts were added to the study in an overlapping longitudinal design (36). Using this type of design, the decline in cognitive functions (basic arithmetic skills, reasoning, visuospatial skills, verbal meaning and word fluency) was apparent only after the participants reached their mid-sixties. Other longitudinal studies that compared people on their cognitive performance at different time-points during development also reported decline in cognitive functions with age, such as memory (37-39), word fluency (37, 39), visuospatial abilities (38, 39), and psychomotor executive tasks (37). The decline in cognitive function with age is generally less pronounced using a longitudinal design than using a cross-sectional design. Part of the explanation for this difference may also be the learning effect with multiple testing and non-random dropouts in longitudinal studies (40).

Birth cohort differences in cognitive function

Birth cohort differences in cognitive performance is a well studied phenomenon. Results on most of the cognitive tests used since the early 20th century have improved with successive birth cohorts (5-8, 41, 42). In other words, at the same age, individuals from the later born cohorts perform better than those from the earlier born cohorts using the same cognitive tests. In the H70-study, for example, 70-year-olds born 1922 performed better than 70-year-olds born 1906-07 on tests of verbal ability, inductive reasoning, spatial ability, perceptual speed, secondary memory, and primary memory (43). This was partially explained by longer education and better living conditions experienced by the later born cohort. Large cultural changes have occurred during the past century, for example improved nutrition and hygiene, smaller families, urbanization of societies, better school systems, cognitively more demanding occupations available in the industrialization era, and changed working conditions for women. All these changes may have an association with better scores on psychometric tests in later born cohorts (7). Better maternal care during pregnancy and better nutrition during infancy may also positively affect brain development. Thus the brains of children born later during the 20th century, may be more resistant to damage with aging (44). For example, in a study of two cohorts of Danish centenarians born 1895 and 1905, among individuals who lived at home, the cohort born 1905 had higher scores on the Mini Mental Status Examination (MMSE) than the cohort born 1895. Meanwhile, among those living in institutions, the cohort born 1905 had lower MMSE scores than the cohort born 1895 (45). Under the

assumption that the majority of people admitted in institutions have reached a severe degree of cognitive impairment and can no longer live at home, the findings in Danish centenarians suggest that individuals in the later born cohorts, even if affected by dementia, may be able to compensate for pathological changes in brain, they maintain a higher level of functioning and live at home for a longer period of time than the earlier born cohorts. The theory of brain reserve (46) or cognitive reserve (47) has been extensively used to explain differences in brain's response to pathological changes induced, for example, by dementia. According to the model postulated by Stern (47), the brain possesses passive and active mechanisms to sustain function in case of damage.

The passive model of brain reserve implies larger anatomical brain structures such as premorbid brain size (48) and synapse count. The assumption is that a brain with a higher number of neurons and synapses will have a higher threshold before lesions result in clinical symptoms (46, 49, 50).

The active mechanism implies a consistent mental effort throughout life, such as acquiring a high level of education or maintaining an intellectually demanding occupation (47, 51). The brain is thus forced to use the available neural networks and cognitive paradigms more efficiently and builds a larger cognitive reserve (52, 53). For example, it has been shown that people with more education sustain more brain damage for the same level of symptomatology than those with lower education (50, 54) and that the education level may modify the impact of dementia (55, 56). It is unclear if a larger cognitive reserve in later born

cohorts also affects prodromal stages and thus prediction of dementia.

Cognitive function in the prodromal stage of dementia

Several epidemiological longitudinal studies have attempted to identify prodromal cognitive signs of dementia, i.e., to examine differences in cognitive symptoms between non-demented individuals who develop dementia in a certain period of time after examination and those who do not. Results from the most recent studies are presented in the Appendix. It has been shown that difficulties in learning and retaining new information, language and abstract reasoning are present decades before the onset of AD (27, 57-60). Population studies with follow-ups ranging from one to six years report that low performance in memory, language, visuospatial and executive functions is present in non-demented individuals for a short time before dementia onset (15, 61-71). Other epidemiological and clinical studies suggest that cognitive impairment may remain stable over long periods of time (6 years or longer) with abrupt decline occurring close to AD onset (71, 72). Therefore, it is not clear whether low performance before the onset of AD reflects premorbid cognitive capacity or prodromal symptoms of AD. Less is known about prodromal symptoms of VaD. Low performance in the MMSE, and in tasks of recognition and executive function have been reported to predict the development of VaD three years later (63, 73, 74). Other studies have examined whether combinations of cognitive symptoms predict dementia. In population studies with short follow-up, deficits in memory and at least one more

cognitive function, predict development of AD, while isolated memory performance does not (61), as also shown in one retrospective clinical study (75). However, isolated memory impairment may be a predictor of AD development in a longer time perspective, as shown in one clinical study (76).

Attempts to define a cognitive syndrome that precedes dementia

In an early attempt to describe cognitive aging (77), the Canadian psychiatrist V.A. Kral noted in 1962 "… there appear to exist at least two types of senescent memory dysfunction, different as to their clinical symptomatology, course and prognosis". Qualitative differences in memory dysfunction were classified by Kral as 'benign' and 'malignant' senescent forgetfulness. The benign type was characterized as "occasional recollection dysfunctionality… an inability of the subject to recall a name, a place or a date", while the experience these data pertain to is remembered. The 'malignant' memory dysfunction was described as an amnestic syndrome, with loss of recent memories, retrograde loss of remote memories, disorientation and confabulation. Although Kral's terminology was based on observational data from a sample of institutionalized patients, with no intent toward criteria-specification or operationalization, the scientific community embraced and still uses the terms 'malignant' and 'benign' to describe memory changes seen in the elderly.

Age-associated memory impairment

The interest on clinical aspects of cognitive aging advanced rather slowly until the mid 1980's, when a work group appointed by the National Institute of Mental Health, USA, proposed a set of diagnostic criteria intended to "stimulate research leading to better understanding and eventual treatment of an important clinical phenomenon" i.e. memory loss in the elderly (78). The efforts of this group resulted in what is known today as 'Age-Associated Memory Impairment' (AAMI). This nosologic entity was defined as "complaints of gradual memory loss in tasks of daily life, substantiated by evidence of such impairment on standardized tests of recent memory (at least one standard deviation below the mean established for young adults) (78). AAMI applies to people over 50 years of age, is nonspecific with regard to etiology and does not address progression. The prevalence of AAMI has been reported to be as low as 7 % (79) in one study and as high as 33% (80) to 38% (81) in others. However, longitudinal population studies reported that AAMI failed to distinguish elderly individuals at increased risk to develop dementia (82-84).

Mild cognitive impairment

In 1991, Flicker, Ferris and Reisberg described the clinical condition of 'mild cognitive impairment' (MCI) as a precursor of dementia (85). The paper reported on a clinical study with two-year follow-up at the Aging and Dementia Center of New York University Medical Center, where MCI was based on stage 3 ('mild cognitive decline') of the Global Deterioration Scale (GDS) (86). The authors reported that "most elderly subjects with mild cognitive deficits […] will manifest the progressive mental

deterioration characteristic of dementia". In fact, 80% (16 out of 20) patients with GDS 3 went on to develop dementia (85). This figure is substantially higher than those reported from other studies examining mild cognitive dysfunction in nondemented elderly and progression to dementia on a short period of time (61, 64, 65, 67), which suggest that these patients might in fact have had mild dementia. However, this was the first paper where the term 'mild cognitive impairment' (MCI) was mentioned as a precursor of dementia. MCI has since then become one the most investigated areas in relationship to neurodegenerative disorders, especially Alzheimer disease (AD).

In 1999, Petersen et al. (67) provided a clinical characterization of MCI based on findings from a clinical sample followed for approximately four years. In their sample, the rate of conversion of MCI to AD was 12% per year compared to 1-2% per year for community controls. The concept of MCI included: a) memory complaint preferably corroborated by an informant; b) impaired memory for age and education based on performance on psychometric tests; c) preserved general cognitive function; d) intact activities of daily living; e) absence of dementia (67). Thus, despite being attributed the name of 'mild ***cognitive*** impairment', this nosologic concept includes ***only memory*** impairment, other types of cognitive dysfunction being excluded by the criteria. The original criteria were, however, later revised in light of new evidence suggesting that several types of MCI existed. The original criteria, presumably related to prodromal stages of AD, were labeled amnestic MCI, and other subtypes of

MCI were ‘multiple domains MCI’ and ‘single non-memory domain MCI’(87, 88). The ‘multiple domains MCI’ was suggested to be a prodrome of AD or VaD or a reflection of ‘normal aging’. The ‘single non-memory domain MCI’ was proposed to be associated with the development of a heterogeneous group of neurodegenerative diseases, such as fronto-temporal lobe dementia, Lewis body dementia, VaD, Parkinson’s disease or AD. Trauma and metabolic disturbance may also induce different types of MCI. The prevalence of amnestic MCI was as low as 1 % in the CSHA (62), 1.8 % in a clinical study (89), 3 % in the LEILA75+ Study (90), 3-4 % in the MoVIES (91) and 6 % in the Cardiovascular Health Study (92). The prevalence of the subtypes ‘multiple domains MCI’ and of ‘single non-memory domain MCI’ was 6 % each in the LEILA 75+ Study (90), whereas in the Cardiovascular Health Study the prevalence of the ‘multiple domains MCI’ was 16 % (92). The outcomes of different types of MCI have also been examined by several groups (62, 74, 90, 91, 93-96). Although most of these studies converge in that the amnestic type of MCI may be useful in distinguishing individuals at risk to develop AD, the rates at which these subtypes convert to dementia vary from 10 to 55 % over a 2- to 11-year follow-up and they are poor predictors of dementia, with low sensitivity (90). Some amendments to the original criteria have been proposed, for example that self-reported memory may not be a necessary criterion (62, 90) and that some deficits in activities of daily living should be allowed (62, 96).

Aging-associated cognitive decline

In the beginning of the 1990s, the International Psychogeriatric Association and the World Health Organization appointed a working group to "develop criteria to identify a group of individuals who experience a cognitive decline that falls short of dementia" (97). This group based its criteria on longitudinal studies and considered decline in cognitive functions as the cardinal feature in what they called 'Aging-Associated Cognitive Decline' (AACD). AACD covers a broad area of cognition, acknowledging that other functions than just memory can be involved in the prodromal stages of dementia, and mention specifically attention and concentration, thinking, language and visuospatial function. These domains were supposed to be of particular importance in the activities of daily living, and a decline in any of them is sufficient for a diagnosis of AACD. The criteria were almost identical to the criteria of "mild cognitive disorder" according to the ICD-10 (98). The prevalence of AACD in the elderly population ranges from 19% to 35% (80, 96, 99). A longitudinal study on AACD reported a conversion rate to dementia of 29% over three years (96).

Cognitive impairment no dementia

Another concept used to describe cognitive impairments in the elderly is 'Cognitive Impairment No Dementia' (CIND), which originates from the multi-center Canadian Study of Health and Aging (CSHA). CIND was not based on specific diagnostic criteria. Instead "any individual who gave the investigating clinician the impression that some form of cognitive impairment was present" was

categorized as having CIND (100-102). In the CSHA, CIND was related to increased rate of institutionalization (101, 102), mortality (102) and conversion to dementia (102). Other studies have also used the CIND acronym (72, 103), but with more specified criteria than in the CSHA. For example, in the Kungsholmen Project (which examines a representative population of 75-year-olds and above), CIND was defined by using specific cut-offs in the MMSE score, after excluding mental or somatic diseases that might influence cognition. With this operationalization, the authors found that CIND was either stable, improved or declined to AD over a three- and six-year follow-up (72). There is thus no consensus regarding specific criteria for CIND, and the term covers a large and rather vague category of individuals with cognitive impairments that can derive from a plethora of conditions.

As of today, it is still debated which of the nosologic entities proposed in the 1990's (i.e. AAMI, AACD, MCI, CIND) is the most valid predictor of progression to dementia. Although these conditions are related to an increased risk of dementia, they are rather common in the general population (72, 92, 96, 100-105), and the majority of people with these conditions do not progress to dementia. To further complicate the picture of prodromal stages of dementia, evidence has gathered toward the existence of a vascular type of cognitive impairment (VCI), including, for example, VaD and AD with vascular pathology (106, 107). Moreover, a vascular cognitive impairment without dementia (vascular CIND) has also been described. This vascular CIND may progress to VaD with a 44% conversion rate on a five-year follow-up (108).

Still a clear distinction cannot be made which type of cognitive dysfunction will progress toward which type of dementia. Population longitudinal studies are probably the best suited to clarify this issue.

Other causes of cognitive dysfunction in the elderly

Comorbidities

There is a high degree of heterogeneity in cognitive changes that accompany aging, mainly due to multiple comorbidities. Thus the choice of controls for studies of incident dementia may include people with different health conditions that may have different degrees of impact on cognition. Some of these conditions are known (e.g. alcohol consumption and abuse, medication, somatic diseases such as diabetes mellitus, hypothyroidism, severe chronic lung disease or hypertension) and can be taken into account in statistical analyses or used as exclusion criteria. Others are difficult to measure, e.g., stressful life conditions, anxiety, terminal decline, and others are unknown.

Terminal decline

Of the conditions mentioned above, terminal decline has drawn a special attention. Terminal decline in cognition refers to acceleration in within-person change prior to death and is distinct from, but possibly moderated by, aging-related changes (109, 110). Several studies have demonstrated terminal decline by comparing survivals and non-survivals but relatively few longitudinal studies have identified terminal decline at the level of the individual

with complete information about age of death and dementia diagnosis in a population-based representative sample (111-114). Little is therefore known about time of onset of terminal decline in the absence of dementia and whether terminal decline vary across cognitive abilities.

Putative physiological changes

Aging-related processes that limit cognitive functioning in the elderly have been reported even in those experiencing "successful aging". The pathological studies of the brains of the elderly have shown that only a small proportion of the population has intact brains by the time of their death (115, 116). Of special interest in this context, is that the more advanced the age at autopsy, the more likely is that the brains of nondemented individuals will have loads of Alzheimer and vascular pathology. However, not all people with pathology in their brains are clinically demented before death. It is legitimate to believe that our brain ages as other organs do, and that this physiological phenomenon may manifest itself as mild cognitive impairment, without reaching the threshold for dementia. The most pervasive characteristics of cognitive aging are mental slowness and slight impairment in memory function. Multiple theories have been proposed to explain this decline. The most support was gained by the theory proposed by Salthouse, that a general factor, the processing speed, might be the culprit (117). There is also evidence that, in aging rodents, there are deficits in different processes related to long-term potentiation, the mechanism that the brain uses to consolidate new memories, which adds biological support for the theory of memory impairment with aging in the absence of pathology (118-121). Neurophysiological changes in aging are observed

not only in the hippocampus. For example, the prefrontal cortex of aged monkeys, the critical part of the brain for functions related to volition, exhibits decreased synaptic excitation and increased synaptic inhibition of pyramidal cells, likely to affect their signalling properties (122). Taken together, comorbidities as well as apparently normal aging and closeness to death, produce an unaccounted variation in cognitive performance in elderly that may reduce the differences between demented and nondemented. Therefore the attempt to find specific and sensitive patterns of prodromal cognitive signs of dementia is a very difficult task.

CONCLUDING REMARKS REGARDING COGNITIVE AGING

In conclusion, evidence is gathering that a form of 'mild cognitive impairment' is frequent in old age and may precede the development of dementia. A complete characterization of this stage and its validity in predicting dementia development is still lacking.

OBJECTIVES

The aims of this thesis are:

1. To examine the utility of assessing four cognitive domains obtained from four information sources to identify individuals at risk for developing dementia, AD and VaD between ages 85 and 88 years (paper I)
2. To evaluate whether combinations of low performance in different domains describe the prodromal stage of dementia better than isolated cognitive symptoms (paper I)

3. To investigate whether short-term predictors of the development of dementia differ from long-term predictors (paper II)
4. To explore birth cohorts differences in cognitive predictors of dementia between two cohorts of 70-year-olds examined 30 years apart (paper III)
5. To examine whether there is a cognitive decline preceding death in the absence of dementia (paper IV)

PARTICIPANTS

The H70 Gerontological and Geriatric Longitudinal Population Studies in Gothenburg started in 1971. A representative sample of 70-year-old residents of Gothenburg, born between July, 1st1901 and June, 30th 1902 on days ending with 2, 5 or 8, was obtained from the Swedish population register and invited to participate in a comprehensive investigation of aging (n = 1148). People living in the community and in institutions were included. All individuals were given consecutive numbers from 1 to 5, and those with numbers 1 and 2 were invited to the psychiatric examination. Of this subsample of 460 individuals, 392 (166 men and 226 women, participation rate 85.2%) were examined by a psychiatrist. Participants and non-participants were similar with regard to sex, marital status, income, community rent allowance, in-patient and out-patient care in psychiatric hospitals, clinics and municipal psychiatric outpatient departments in Gothenburg and registration with the Temperance Board (Swedish national registry for alcohol abuse) (123). In the longitudinal incidence dementia study included in this thesis, individuals with dementia at age 70 (n = 10) were

excluded, leaving 382 non-demented participants (221 women and 161 men). The sample was followed at ages 75 (n=296), 79 (n=202), 81 (n=156), 83 (n=115), 85 (n=98), 88 (n=59) and 90 years (n=38). All participants in the examination at age 70 were invited to the follow-up examinations, irrespective if they had missed a previous examination. In the longitudinal study of cognition in relation to mortality between ages 70 and 100 years, the sample of non-demented comprised 288 participants (162 women and 126 men), after excluding all refusals (n=70) and dementia (n=114) during follow-up. They were assessed periodically at ages 70, 75, 79, 81, 85, 88, 90, 92, 95, 97, 99 and 100 years. Confirmed date of death was available for 284 individuals and 4 individuals were alive at the last update in June 1st, 2003. In order to prevent missing data on the age of death variable we imputed the date of last update as the date of death for these four individuals.

In 1986-87, the H70 study was enlarged by including all 85-year-olds born between July 1st, 1901 and June 30th, 1902, and registered for census purposes in Gothenburg. People living in the community and in institutions were included. A subsample of 826 individuals, comprising every second person from the Swedish population register, was selected for the psychiatric examination. Forty-three individuals died before the examination took place, leaving 783 individuals. The psychiatric examination was finally performed in 494 individuals (response rate 63.1%). This sample was found to be representative of the population of 85-year-olds in Gothenburg, Sweden with regard to sex, marital status, status as psychiatric outpatients or

inpatients, institutionalization and three-year mortality rate (2). In the longitudinal incidence dementia study between ages 85 and 88 years, individuals with dementia (n = 147) and those with moderate to severe memory impairment at baseline according to the psychiatric examination (n = 10) were excluded, leaving 337 cognitively intact individuals in the study (237 women and 100 men). At the follow-up examination at age 88, n = 58 (17.2%) individuals had died and 71 (21.1%) refused a new examination. For those lost to follow-up, information was searched in medical records from hospitals, clinics, municipal psychiatric outpatient departments in Gothenburg, the Swedish inpatient registry and death certificates (124).

A new cohort was added to the H70 studies in 2000-01. All 70-year-olds born between January 1 and December 31, 1930 on day 3, 6, 12, 18, 21, 24, or 30, were invited to a health examination in 2000-01. Of 850 invited, 579 (response rate 68.1%) participated in the psychiatric examination. Fourteen participants were excluded due to dementia and one due to language difficulties, leaving 564 nondemented 70-year-olds (337 women and 227 men). Thirteen individuals (2.3%) had moved from Gothenburg, and lacked follow-up data. These were also excluded from the study, leaving 551 individuals (331 women and 220 men) at baseline. Participants and non-participants were similar regarding gender, marital status, three year mortality rate and inpatient psychiatric care during the past two years according to the Swedish Hospital Discharge Register (125). At the follow-up at age 75 years, 24 individuals (4.4%) had died and 91 (16.5%) refused a new examination, leaving 436 participants (274 women and 162

men). Those lost to follow-up (deceased and refusals) were traced in medical records and hospital registers for dementia.
Participants (or their nearest relatives in cases with dementia) gave their informed consent for the study, which was approved by the Ethics Committee for Medical Research at the University of Gothenburg.

METHODS

General Assessments

At the start of the study in 1971, all individuals received invitations to a comprehensive health examination comprising a home call by a registered nurse and an examination at the out-patient department of a geriatric hospital. Those who accepted the invitation at age 70 were invited for health examinations periodically until death. The same procedures were used for the enlarged sample at age 85 years, invited for the first time in 1986-87, and also for the new sample of 70-year-olds born 1930 invited for the first time in 2000-01. A psychiatric examination and a battery of psychometric tests were administered at every examination throughout the study. Psychiatrists also examined medical records from all major hospitals, geriatric and psychiatric institutions and outpatient services in Gothenburg. Starting in 1986-87 a key informant interview and brain computer tomography were added to the examination.

Cognitive Assessments

Identical examinations were used both in individuals born 1901-02 and in those born 1930.

Self-report: The participants were asked at each examination to evaluate their own memory with the help of a seven-step scale. Zero was attributed to no subjective problems and ratings of one to six for mild, moderate to severe memory problems, with intermediary steps. Starting with the examination of 85-year-olds born 1901-02 in 1986-87, participants were also asked to report on their own abilities to concentrate, plan and make decisions.

Key informant interview: The key informant interviews were conducted at age 85 in those born 1901-02 by a psychiatrist, using a semi-structured telephone interview (i.e., questions were standardized, but the psychiatrist was allowed to ask clarifying questions). The key informant was asked about changes in the participant's memory, language, visuospatial praxis, attention, judgement, ability to make decisions, and planning. Zero was attributed to no perceived symptoms and ratings of one to three for mild, moderate to severe symptoms, with or without intermediary steps (when intermediary steps were used ratings were made on a seven-step scale).

Psychiatric examination: The clinical psychiatric examination before 1986-87, at ages 70, 75 and 79 years for those born 1901-02, was performed by trained psychiatrists at the out-patient department of a geriatric hospital. In 1986-87 and 1989-1990 the psychiatric

examination took place at the participants' place of residence. Psychiatrists rated recent and remote memory, and orientation to time and place at all examinations. After 1992, the psychiatric examinations were conducted by experienced research nurses. The inter-rater reliability between physicians and nurses was high (126, 127). The symptoms from the psychiatric examination were rated using seven-step scales. Zero was attributed for absence of impairment and ratings of one to six for mild, moderate to severe impairment, with intermediary steps. At age 85, in those born 1901-02, the examination was enlarged and it included poverty of language, concentration, abstract thinking (understanding proverbs and describing how to find the way to a hotel in an unfamiliar city), simple tests of semantic memory (i.e., asking for the names of the two last prime ministers and the three largest cities in Sweden), items from the Alzheimer's Disease Assessment Scale-Cognitive (ADAS-Cog) (128) regarding spoken language ability, comprehension of spoken language, word-finding difficulty, following commands, naming objects and fingers, and constructional praxis.

Psychometric tests: Psychometric tests were administered by psychologists who were blind to the results from other examinations. A battery of six tests was used consistently in the H70 study:

1. Synonym test measures verbal comprehension. The participant has to identify one synonym among five given alternatives; the list has 30 words (maximum score 30).
2. Block Design measures visuospatial ability. The participant is asked to organize wooden

cubes in accordance with seven patterns presented on cards (maximum score 42).
3. Figure Classification measures inductive logical reasoning. From a set of five figures the participant has to identify the one figure constructed on a principle not shared by the other four (maximum score 30).
4. Identical Forms measures perceptual speed. The participant is instructed to identify as fast as possible the pattern identical to the stimulus pattern (maximum score 60).
5. Digit Span Forward measures short-term memory and attention. The tasks require immediate recall (forward) of increasingly longer lists of digits (maximum score 9).
6. Digit Span Backward to measure short-term memory and attention. The tasks require immediate recall (backward) of increasingly longer lists of digits (maximum score 8).

Block Design and Digit Span are part of the Wechsler Adult Intelligence Scale (WAIS) battery (129). The Synonyms, Figure Classification and Perceptual Speed are from Dureman and Sälde test battery (130), based on Thurstone's theory of primary mental abilities (131), and widely used in Sweden at the time of the start of H70 studies.

Among those born 1901-02, the tests Identical Forms, Digit Span (forward and backward), and Block Design were administered at age 70 to a subsample comprising every other participant. The tests were administered to all participants born 1901-02 at all other examinations.

In those born 1930, all tests were administered at age 70 to a subsample comprising every other participant.

At the examination of 85-year-olds born 1901-02, the psychometric battery was enlarged by adding a number of tests:

1. Prose Recall measures long-term memory. It requires free recall of a brief story with a humorous point (maximum score 16).
2. Memory-in-Reality Test measures different types of long-term memory, i.e. free recall and recognition, by first naming and placing ten objects in a tridimensional model of an apartment and testing the free-recall and recognition of the previous placements after other tests are performed (maximum score 10).
3. Ten-word Lists (animals, clothes) is a supra-span list-learning task for long-term memory (maximum score 10).
4. Thurstone Picture Test measures non-verbal memory. The participant is supposed to recognize previously presented pictures among new pictures (maximum score 28).
5. The Clock Test is a visuospatial and executive test. The participant is required to draw a clock, to tell the time and to set the time on a wooden clock (maximum score 30).
6. The Coin Test measures arithmetical abilities. The participant is asked to select the least number of coins adding up to four preselected totals (maximum score 8).

The use of psychometric tests in previous H70 studies has been described previously (59, 132, 133).

Dementia Diagnosis

The diagnosis of dementia before the examination in 1986-87 (i.e., at ages 70, 75 and 79 years of those born 1901-02) was based on historical criteria described by Kay et al. (134). These criteria required the presence of severe disorientation for time and place or a long-standing severe memory impairment as measured by rating scales and information from case records or key informants (135, 136). The diagnosis of dementia at age 85 and later in those born 1901-02, was made according to the Diagnostic and Statistical Manual of Mental Disorders, IIIrd edition, revised (DSM-III-R) (137), and was based on the psychiatric examination and the interview with a key informant (where available) (2, 138). The change in diagnostic criteria over the follow-up of the cohort born 1901-02 was due to the publication of the DSM-III-R in 1987. To examine this change in relation to diagnostic trends, dementia was diagnosed at age 85 according to both sets of criteria in the enriched sample of 494 85-year-olds, which also included the survivors from the original sample (139). Of 166 persons diagnosed with dementia using either criteria, the observed agreement for a dementia diagnosis was 93.3%, with an overall kappa of 0.842. Among those diagnosed with dementia by DSM-III-R and not by earlier criteria (n = 14), 71% were mild cases of dementia.

For those who did not take part at the follow-up examinations, the diagnosis of dementia was made if reviews of medical records revealed impairments of memory and other cognitive functions at a level causing significant difficulties in activities of daily living.

Etiologic diagnosis of dementia was available only at age 85 and later in those born 1901-02. AD was diagnosed according to the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS – ADRDA) (140). VaD was diagnosed according to the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Association Internationale pour la Recherche et l'Enseignement en Neurosciences criteria (NINCDS-AIREN) as modified by Tatemichi (141).

Definitions of low cognitive performance by cognitive variables

Data on cognitive performance using self- and key informant reports, psychiatric interview and psychometric tests were dichotomized as 'low' versus 'unimpaired'.

Using self-reports at ages 70 (both cohort born 1901-02 and cohort born 1930), and at age 85 in those born 1901-02, low memory was defined as frequent memory problems versus 'no or occasional memory problems'.

Using key informant interviews at age 85, low performance was defined as the presence of any symptom in any given cognitive variable (i.e., scores >0) versus no symptoms.

Using psychiatric examinations, low performance in memory at ages 70 (both cohort born 1901-02 and cohort born 1930), and at 75 and 79 years (cohort born 1901-02), was defined as observed slight memory problems in recent memory versus no memory problems. At age 85 years, in

the cohort born 1901-02, more information in memory and other cognitive domains (i.e., language, visuospatial ability and executive function) was available from the psychiatric examination. Low performance was then defined as the presence of any symptoms or any failures on simple tests.

Using standardized psychometric tests, low performance was defined as scoring one standard deviation (SD) below the mean of the sample, as also defined in other studies (96, 142). The cut-offs were defined separately in 70-year-olds born 1901-02 and in those born 1930. When we compared the 70-year-olds born 1901-02 and those born 1930, we also used cut-offs of 1.5 SD and 2 SD below the mean of each cohort, separately; and cut-offs of 1 SD, 1.5 SD and 2.0 SD by education within each cohort, separately. In the longitudinal study of cognition in relation to mortality, test scores in Synonyms, Block Design and Identical Forms were standardized to a pseudo T-score metric with mean of 50 and standard deviation of 10 in order to facilitate comparability across tests. The standardization procedure for each test was also based on mean and standard deviation at age 70 in those born 1901-02 (i.e., first occasion of measurement).

Definitions of low cognitive performance by cognitive domain

The data on cognitive performance was then categorized into four different domains based on the theoretical assumption of which cognitive function each variable measured (e.g., memory, language, visuospatial or executive functions). If at least one variable in a cognitive domain was defined as ‘low’ using the aforementioned

criteria, the individual was classified as a 'low performer' in that domain. The participants were given credit for any information provided to define their cognitive performance. No data were imputed in any given domain. For example, individuals with data in at least one variable in a cognitive domain were included in analyses of that domain.

At ages 70, 75 and 79 years in those born 1901-02, the memory domain was based on information on recent memory using the psychiatric examination; and the non-memory domains (including language, visuospatial or executive functions) were based on the psychometric tests Synonym, Block Design, Figure Classification and Identical Forms.

At age 85 years, in the extended cohort born 1901-02, each source of information was examined individually and 'low cognitive performance' in the four domains was defined for each of the key informant interview, psychiatric examination and psychometric tests. Using self-reports, only memory and executive function domains were available. Thus, individuals were classified as 'low performers' by domain according to each source of information.

Definitions of patterns of low cognitive performance using memory and non-memory domains

Based on the conceptualization of different patterns of mild cognitive impairment (MCI) (i.e. amnestic MCI vs. multiple domains-non memory MCI) (87), we created four groups with different patterns of cognitive symptoms in the

85 year-olds born 1901-02, using each source of information separately: (1) unimpaired cognition, (2) isolated low memory performance (i.e. low performance in the memory domain only, with unimpaired performance in other domains), (3) low non-memory cognitive performance (i.e. low cognitive performance in any other domains than memory, with unimpaired memory), and (4) global low cognitive performance (i.e. low memory performance plus low performance in at least one other domain).

We also created these groups using memory domain according to psychiatric examinations and non-memory domains by using psychometric tests at ages 70, 75 and 79 years in those born 1901-02. At age 70 years in those born 1930, where only every other participant was tested psychometrically, the subgroups with different patterns of cognitive symptoms were too small to be considered for meaningful analyses.

Statistical methods

Objectives 1 and 2 (paper I): Because of the short follow-up period, the risk of dementia between age 85 and 88 years was estimated using logistic regression models. Analyzing each source of information separately (i.e. self-report, key informant interview, psychiatric examination and psychometric tests), the risk of all dementia, AD and VaD over the three-year follow-up period by each cognitive domain was estimated using odds ratios (OR) and 95% confidence intervals (CI). Those domains that predicted dementia in univariate analyses ($p<0.05$) were

included in multivariate models (backward stepwise procedures). Using education and sex as covariates did not change the results significantly. In post-hoc analyses, subgroups of participants were created based on four types of symptom patterns and risk of dementia was estimated within each subgroup.

We also examined the sensitivity, specificity, and positive and negative predictive values of the cognitive domains and information sources available at age 85 in relation to the development of dementia between 85-88 years. Sensitivity was defined as the proportion of individuals developing dementia who were classified as low performers at baseline. Specificity was defined as the proportion of individuals not developing dementia who were classified as unimpaired at baseline. The positive predictive value (PPV) is the proportion of low performers who developed dementia. The negative predictive value (NPV) is the proportion of unimpaired individuals who did not develop dementia (143).

Objective 3 (paper II): On a longer follow-up, from age 70 to age 90 years, we used Cox proportional hazards models to examine the relationship between groups with different patterns of cognitive symptoms at ages 70, 75 and 79 and incident dementia between ages 71-75, 76-79, 80-85 and 86-90 years. The risk of dementia was estimated by hazard ratios (HR) and 95% CI. Time at risk for dementia onset was calculated starting from age 70, 75 or 79 (baseline examinations) to the first occurring event as dementia, death or end of the defined follow-up period. Sex and education were used as covariates in all models.

Objective 4 (paper III): On a short follow-up between ages 70-75 years in the two cohorts born 1901-02 and 1930, we used logistic regression models to estimate the risk of dementia by OR and 95% CI. Analyses were run within each cohort separately. All logistic regression models were adjusted for sex and education. Each cohort was also stratified by educational level. Educational level was dichotomized as only compulsory education (6 years for those born in 1901-02, and 7 years for those born in 1930) versus more than compulsory education. Differences in raw mean scores in psychometric tests between the two cohorts were tested using univariate analyses of variance with sex and education as covariates (ANCOVA), and differences in proportions were tested using Fisher's exact test.

Objective 5 (paper IV): To identify time of onset of mortality-related change in cognitive function in late life, in the absence of dementia, change-point analysis was performed. A profile likelihood method was used to identify the change point that best fit the data for the cognitive functions investigated. The best fitting model determines the maximum likelihood estimates of the terminal decline change point as relative to age-related change. Detailed description of the modeling procedure can be found elsewhere (113, 144).

A level of statistical significance of 0.05 was used for all analyses. To avoid misinterpretation of negative results, we did not make corrections for multiple analyses, but instead present all positive and negative findings with 95% confidence intervals.

RESULTS

Objective 1 was to examine the utility of memory, language, visuospatial and executive functions, using self- and key informant reports, and psychiatric and psychometric examinations, to predict dementia (including AD and possible VaD), in a representative population sample of non-demented 85-year-olds who were followed for three years.

Among the 313 non-demented 85-year-olds without moderate-to-severe memory impairment at baseline, 58 (18.7 %) developed dementia between age 85 and 88 (24 AD, 27 VaD, and seven other types of dementia; 39 diagnosed from examination and 19 from case records) and 255 did not develop dementia.

Prediction of dementia between ages 85-88 years using memory, language, and visuospatial and executive functions by source of information

Dementia was preceded by low performance in most domains, irrespective of information source, on the three-year follow-up from age 85 to 88 years (table 1).
The sensitivity of memory performance to predict dementia was around 80% in all sources (except self-report, 28%), but the positive predictive value (PPV) was only between 22-31% (table 1). The sensitivity of language, visuospatial and executive domains to predict dementia was generally below 80% with a PPV of 20-37% (table 1). The results were similar for incident AD and VaD (data not shown).

Table 1. Odds, sensitivity, specificity and predictive values for dementia between age 85-88 by low cognitive performance in different domains using four information sources

Source	All dementia between age 85-88				
Domain	OR (95% CI)	Sensitivity	Specificity	PPV	NPV
Self-report					
Memory	1.9 (1.0-3.8)	27.6	83.5	27.6	83.5
Executive	1.1 (0.6-2.1)	29.3	72.5	19.5	81.9
Key informant interview					
Memory	2.9 (1.2-6.7)	86.0	31.8	22.1	91.0
Language	1.9 (1.0-3.7)	68.0	48.0	22.7	87.0
Visuospatial	1.2 (0.3-4.5)	7.0	94.2	20.0	83.1
Executive	1.9 (1.0-3.5)	55.1	60.2	23.5	85.8
Psychiatric examination					
Memory	6.6 (3.2-13.7)	82.8	58.0	31.0	93.7
Language	2.0 (1.1-3.7)	70.7	45.1	22.7	87.1
Visuospatial	2.5 (1.3-4.7)	46.0	74.7	28.4	86.4
Executive	3.8 (2.0-7.3)	75.9	54.9	27.7	90.9
Psychometric tests					
Memory	3.8 (2.0-7.2)	75.4	55.1	27.9	90.7
Language	3.0 (1.4-6.5)	35.0	85.0	30.4	87.4
Visuospatial	2.6 (1.4-4.8)	52.8	70.2	28.0	87.2
Executive	3.8 (2.0-7.2)	40.0	85.0	37.3	86.4

Crude odds ratios (OR) were used to estimate the risk for incident dementia (univariate logistic regression models). Introducing gender and education as covariates did not change the results significantly. PPV = positive predictive value; NPV = negative predictive value

Objective 2 was to evaluate whether a combination of low performance in different domains describes the prodromal stage of dementia better than isolated cognitive symptoms.

Prediction of dementia between ages 85-88 years by different patterns of low cognitive performance

Only global low performance predicted dementia in 85-year-olds. Isolated low memory performance, or low cognitive performance with unimpaired memory did not predict dementia according to psychiatric examination or psychometric tests (table 2). The PPV increased with number of domains affected. The results were similar when using key informant interview (data not shown). Using self-reports, low memory performance was the only predictor of dementia, and analysis of a combination of cognitive symptoms using also executive function was not performed.

We also estimated the risk of dementia between ages 85 and 88 years by combining information from psychiatric and psychometric examinations with information from self- and key informant reports (table 3).

Self- and key informant reports were less useful for predicting dementia. Using self- and key-informant reports as first selection step in identifying groups in the population with an increased risk to develop dementia, reduced the value of the predictive parameters (table 3) compared to when psychiatric and psychometric examinations were used alone. The best PPV (88%) was for low cognitive performance in all domains using both psychiatric and psychometric examinations, however sensitivity was then only 18% (data not shown).

Table 2. Odds, sensitivity, specificity and predictive values for all dementia between age 85-88 by combining information from different domains using only objective clinical sources

Cognitive performance age 85		All dementia between age 85-88				
Memory	Other domains*	OR (95% CI)	Sensitivity	Specificity	PPV	NPV
Psychiatric examination						
Unimpaired	Unimpaired in all domains	-	0.0	81.2	0.0	78.8
Unimpaired	Low in at least one domain	1.0	18.0	59.4	8.8	76.8
Low	Unimpaired in all domains	1.9 (0.4-9.8)	4.0	95.2	15.4	82.0
Low	Low in one domain only	3.6 (1.3-9.4)	22.0	86.0	25.6	83.5
Low	Low in two domains only	3.8 (1.5-9.8)	26.0	84.7	27.1	84.0
Low	Low in all three domains	10.3 (3.8-27.8)	30.0	93.4	50.0	85.9
Psychometric tests						
Unimpaired	Unimpaired in all domains	1.0	15.0	65.1	7.5	80.2
Unimpaired	Low in at least one domain	1.1 (0.3-3.9)	12.5	74.5	8.5	81.9
Low	Unimpaired in all domains	2.4 (0.8-7.4)	20.0	80.7	16.3	84.2
Low	Low in one domain only	3.0 (0.9-10.0)	15.0	88.2	19.4	84.6
Low	Low in two domains only	3.6 (1.0-14.2)	12.5	92.5	23.8	84.8
Low	Low in all three domains	13.7 (4.0-46.7)	25.0	95.8	52.6	87.1

OR = crude odds ratio; PPV = positive predictive value; NPV = negative predictive value *'Other domains' include language, visuospatial and executive functions. Low performance in a domain was defined as sum score >0 of the dichotomous variables comprising the domain ("unimpaired" was attributed to a sum score = 0)

Table 3. Odds, sensitivity, specificity and predictive values for dementia between age 85-88 by combining information from four sources

Cognitive performance age 85		All dementia between age 85-88				
Non-clinical sources (SR, KI)	Clinical sources (NE, PT)	OR (95% CI)	Sensitivity	Specificity	PPV	NPV
Self-report						
Unimpaired	Both unimpaired	1.0	11.8	54.0	5.2	74.0
	One unimpaired, one low	3.3 (1.2-9.5)	21.6	74.7	15.5	81.6
	Both low	11.9 (4.4-32.5)	37.3	87.8	39.6	86.7
Low (memory only)	Both unimpaired	1.9 (0.4-10.2)	3.9	92.0	9.5	81.6
	One unimpaired, one low	9.8 (2.9-33.6)	13.7	94.5	35.0	83.6
	Both low	15.8 (4.0-61.0)	11.8	97.0	46.2	83.6
Key informant interview						
Unimpaired	Both unimpaired	1.0	6.8	68.5	4.5	77.0
	One unimpaired, one low	3.0 (0.6-14.3)	9.1	86.0	12.5	81.1
	Both low	7.0 (1.2-40.1)	6.8	95.5	25.0	82.3
Low (memory + one domain)	Both unimpaired	1.9 (0.4-8.8)	9.1	77.5	8.2	79.5
	One unimpaired, one low	7.6 (2.0-29.0)	27.3	83.5	26.7	83.9
	Both low	17.2 (4.6-64.0)	40.9	89.0	45.0	87.3
Unimpaired SR or KI	Both unimpaired	1.0	6.8	72.0	5.1	77.8
	One unimpaired, one low	0.7 (0.1-7.5)	2.3	87.5	3.8	80.3
	Both low	7.0 (1.2-40.8)	6.8	96.0	27.3	82.4
Low SR or KI	Both unimpaired	0.9 (0.1-5.4)	4.5	78.5	4.4	78.9
	One unimpaired, one low	7.6 (2.0-29.5)	25.0	86.5	28.9	84.0
	Both low	14.6 (3.9-54.4)	40.9	88.5	43.9	87.2
Low SR and KI	Both unimpaired	4.1 (0.6-28.4)	4.5	95.5	18.2	82.0
	One unimpaired, one low	8.3 (1.6-43.3)	9.1	95.5	30.8	82.5
	Both low	15.6 (3.0-81.9)	11.4	97.0	45.5	83.3

SR = self-report; KI = key informant interview; NE = psychiatric examination; PT = psychometric tests. Low performance in self-reports was defined as low memory performance, irrespective of performance in executive function. Low performance in key informant interviews, psychiatric examinations and psychometric tests was defined as low performance in memory and one more domain.

Objective 3 was to investigate whether different patterns of low cognitive performance predict short- and long-term onset of dementia.

In the representative sample of 382 non-demented 70-year-olds followed up at ages 75, 79, 85 and 90 years, 106 (27.7%) individuals developed dementia: 19 during the first five years of follow-up (six women and 13 men), 29 during year 6-9 (17 women and 12 men), 31 during year 10-15 (25 women and six men) and 27 (21 women and six men) during year 16-20; totally accumulating 4259.9 person years-at-risk (221 women with 2788.3 risk years and 161 men with 1471.6 risk years). The frequencies of different patterns of cognitive performance among the nondemented at ages 70, 75 and 79 are presented in Figure 1.

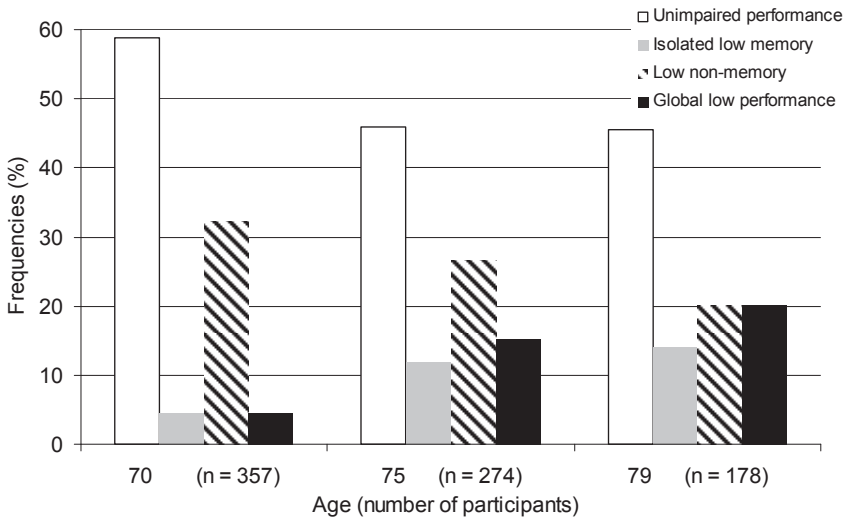


Figure 1.

Short- and long-term prediction of dementia at ages 70, 75 and 79 years by different patterns of low cognitive performance

In 70-year-olds, low non-memory performance and global low performance predicted dementia onset only in the short term (Table 4), with no difference between single and multiple low non-memory performance. Isolated low memory predicted dementia onset in the long term. Analyzing only those who had four tests at age 70 (i.e. half of the sample), did not change the results substantially compared to when the whole sample was analyzed, although the findings were no longer significant due to smaller sample size.

In 75-year-olds, low non-memory performance and global low performance predicted dementia onset in the short term (Table 4), with no difference between single and multiple low non-memory performance. Isolated low memory at age 75 predicted dementia onset after more than 10 years, but not earlier.

In 79-year-olds, global low performance predicted dementia onset in the short term. None of the patterns of low cognitive performance at age 79 predicted dementia onset in the long term (Table 4).

Table 4. Hazard ratios for dementia onset by cognitive symptom patterns using combined psychiatric and psychometric examinations

	Pattern of cognitive performance	***Dementia 71-75*** Hazard ratio (95%CI)	***Dementia 76-79*** Hazard ratio (95%CI)	***Dementia 80-85*** Hazard ratio (95%CI)	***Dementia 86-90*** Hazard ratio (95%CI)
Age 70	Unimpaired performance	1.0	1.0	1.0	1.0
	Isolated low memory	Ne	3.6 (1.9-6.7)	1.8 (0.9-3.8)	3.2 (1.1-9.3)
	Low non-memory performance	3.2 (1.1-9.6)	2.2 (0.9-5.1)	0.6 (0.2-1.6)	0.8 (0.3-1.9)
	Single domain	3.5 (0.9-12.4)	2.2 (0.8-5.9)	0.7 (0.2-2.1)	1.1 (0.4-2.7)
	Multiple domains	1.9 (0.9-3.9)	1.6 (0.9-2.9)	0.6 (0.2-1.6)	0.6 (0.2-1.6)
	Global low performance	2.3 (1.5-3.6)	1.4 (0.6-2.7)	1.4 (0.7-2.7)	NE
Age 75	Unimpaired performance		1.0	1.0	1.0
	Isolated low memory		1.8 (0.7-4.9)	1.5 (0.9-2.5)	2.2 (1.3-3.9)
	Low non-memory performance		9.9 (2.0-49.8)	1.1 (0.4-2.7)	2.5 (0.9-6.9)
	Single domain		6.3 (1.01-39.3)	1.2 (0.4-3.3)	1.7 (0.5-5.8)
	Multiple domains		5.4 (1.9-15.2)	0.9 (0.4-1.9)	2.2 (1.1-4.3)
	Global low performance		3.1 (1.8-5.1)	1.3 (0.9-1.9)	1.5 (0.9-2.4)
Age 79	Unimpaired performance			1.0	1.0
	Isolated low memory			1.1 (0.5-2.0)	1.3 (0.5-2.9)
	Low non-memory performance			0.4 (0.1-2.1)	2.5 (0.8-7.7)
	Single domain			Ne	2.8 (0.8-9.7)
	Multiple domains			1.3 (0.6-2.8)	1.4 (0.5-4.2)
	Global low performance			1.4 (1.01-1.8)	1.4 (0.9-2.0)

All models included sex, education (information on education missing in one demented and four nondemented) and depression. Isolated low memory performance was defined as low performance in recent memory and unimpaired non-memory performance. Low non-memory performance was defined as unimpaired recent memory and low performance in at least one non-memory test (single domain if low performance in only one test or multiple domains if low performance in more than one test). Global low performance was defined as low performance in both recent memory and non-memory tests. NE = non estimable (due to no incident dementia for the specific time interval).

Objective 4 was to investigate the relation between cognitive function according to self-report, psychiatric examination and psychometric tests, and the development of dementia over a 5-year period (short-term) in two cohorts of 70-year-olds examined 30 years apart (hereafter named *Cohort 1901-02* and *Cohort 1930)*.

Baseline data

More people in *Cohort 1930* completed a high level of education than in *Cohort 1901-02* (42.2% versus 15.1%, p>0.001). There were no sex differences between cohorts. At age 70 years, self-reported low memory performance was more frequent in *Cohort 1901-02* than in *Cohort 1930* (30.5% versus 17.4%, p < 0.001) and there was a tendency for low performance in recent memory observed in the psychiatric examination to be more common in *Cohort 1901-02* than in *Cohort 1930* (8.4% versus 4.3 %, p = 0.070). Mean scores on all psychometric tests (except Digit Span Forward) were higher in *Cohort 1930* than in *Cohort 1901-02* as presented in Figure 2.

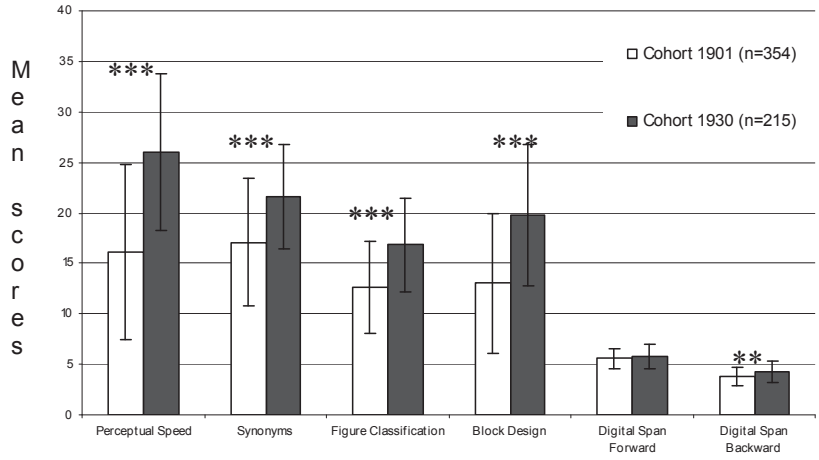


Figure 2. ***P < 0.001; ** P < 0.01. P-values for differences between cohorts in mean scores in psychometric tests are based on covariate analysis of variance (ANCOVA), with sex and education as covariates.

Follow-up data

Characteristics of the sample from age 70 to follow up at age 75 are presented in table 5. Among the non-demented at age 70, 19 of 381 (5.0%) in *Cohort 1901-02* and 24 of 551 (4.4%) in *Cohort 1930* developed dementia between 70 and 75 years (p=0.751). In *Cohort 1901-02*, 10 cases were diagnosed at the examination at age 75, and 9 were diagnosed from medical records or registry data. In *Cohort 1930*, 19 cases were diagnosed at examination at age 75, and 5 were diagnosed from medical records or registry data. There was no difference in the proportion of new cases diagnosed at examination at age 75 between *Cohort 1901-02* and *Cohort 1930* (table 5). More cases tended to be diagnosed from medical records or registry data in *Cohort 1901-02* than in *Cohort 1930* (table 5).

Table 5. Characteristics of participants at age 70 at the 5-year follow-up

	Cohort 1901-02	*Cohort 1930*	*P-values*
	%	%	
Participants	77.7	77.3	0.937
Women	61.8	62.8	0.816
More than compulsory education[1]	15.1	42.2	<0.001
Deceased	15.7	4.3	<0.001
Refusals	6.6	16.1	<0.001
Moved out		2.3	
Dementia among participants at follow-up	3.4	4.4	0.567
Dementia among lost to follow-up	10.6	3.9	0.087

Percentages of participants, deceased and refusals were computed based on participants at age 70 in *Cohort 1901-02* (n=381) and *Cohort 1930 (*n=564). [1]Information on education was missing in four individuals in *Cohort 1901-02* and in two individuals in *Cohort 1930*. P-values for differences in proportions between cohorts were obtained using Fisher's Exact test.

Cohort differences in cognitive symptoms associated with short-term onset of dementia

Seventy-year-olds with low performance in recent memory using the psychiatric examination were more likely to develop dementia between age 70 and 75 years than those who were unimpaired, both in *Cohort 1901-02* (12.5% vs 4.3%, p = 0.039; OR 3.5. 95% CI 1.1 to 11.8) and in *Cohort 1930* (20.0% vs 3.1%, p = 0.001; OR 6.7, 95% CI 2.2 to 20.3), after adjustment for sex and education. When we stratified by education, low performance in recent memory predicted dementia among those with lower education, but not among those with higher education, both in *Cohort 1901-02* and *Cohort 1930* (results not shown).
Self-reported low memory performance at age 70 was not related to dementia occurrence in either cohort.

In *Cohort 1901-02,* mean scores in Identical Forms, Figure Classification and Block Design were lower among 70-year-olds who developed dementia compared to those who did not (Figure 3). No such differences were observed in *Cohort 1930* (Figure 4). It is noteworthy that those who developed dementia in *Cohort 1930* had higher mean scores at age 70 compared to those who did not develop dementia in *Cohort 1901-02* in Identical Forms (23.7 ± 8.8 versus 16.5 ± 8.6, p = 0.011), Figure Classification (16.7 ± 4.6 versus 12.7 ± 4.6, p = 0.006) and Block Design (19.2 ± 6.6 versus 13.3 ± 6.9, p = 0.009).

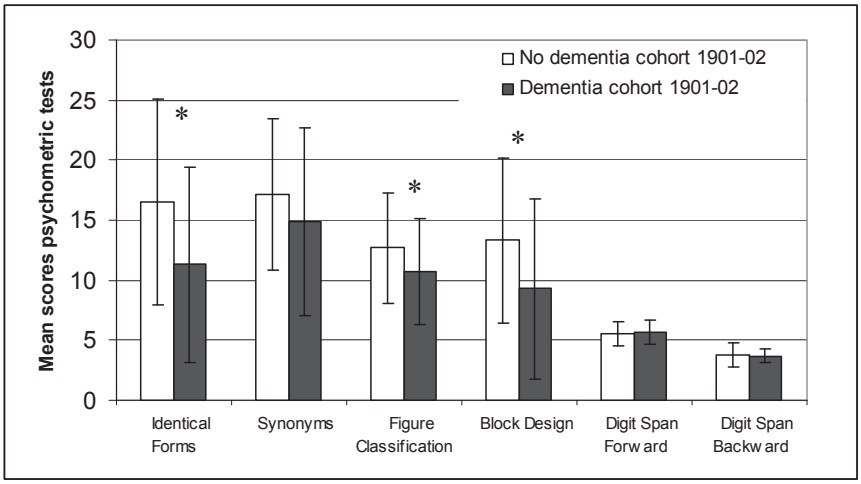


Figure 3.
ANCOVA (sex and education as covariates) was used to test mean score differences in psychometric tests between those who did and did not develop dementia.
* $p < 0.05$

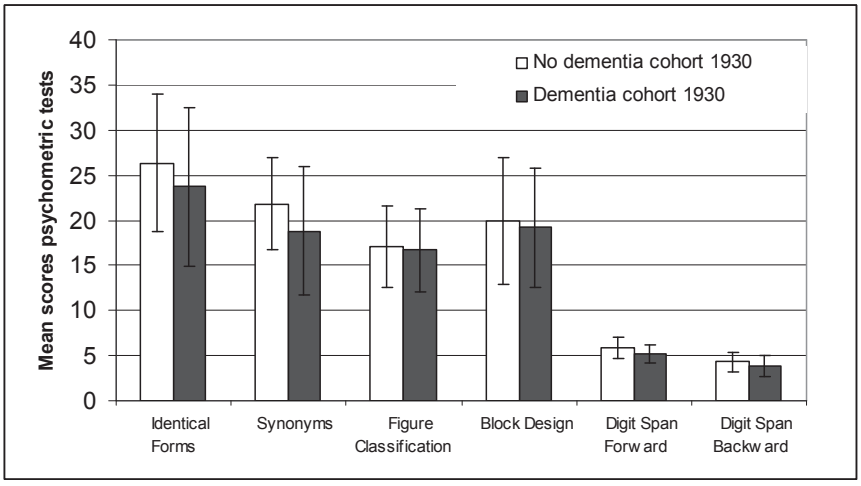


Figure 4.
ANCOVA (sex and education as covariates) was used to test mean score differences in psychometric tests between those who did and did not develop dementia. No differences were found.

We then analyzed the utility of psychometric tests to predict dementia using different cut-offs to define low performance at the level of 1 SD below the mean. Using more conservative cut-offs of 1.5 SD or 2 SD below the mean produced too small groups to conduct meaningful analyses.

When the cut-offs were defined as < 1 SD below the mean for *Cohort 1901-02,* Identical Forms, Synonyms, Figure Classification and Block Design predicted dementia in *Cohort 1901-02,* and Synonyms predicted dementia in C*ohort 1930* (Table 6). The proportion with low cognitive performance was very low in C*ohort 1930* (between 0.9 and 3.3%, except Digit Span Forward 15.8%) using this definition.
When the cut-offs in both cohorts were defined as < 1 SD below the mean for *Cohort 1930,* none of the tests predicted dementia in *Cohort 1901-02* or *Cohort 1930* (Table 6). The proportion with low cognitive performance was very high in C*ohort 1901-02* (between 39% and 84%, except Digit Span Forward 13.8%) using this definition.

The main results did not change when we defined low performance in psychometric tests using cut-offs defined as 1 SD below the mean score by education in each cohort separately. Furthermore, the main results did not change when we only analysed those who survived to age 75 (participants and refusals), or only those who took part both in examinations at age 70 and 75 years.

Table 6. Predictors of dementia in 70-year-olds on a 5-year follow-up using memory assessments and non-memory psychometric tests

Cognitive assessments	Cut-off	*Cohort 1901-02* Adjusted OR (95% CI)	*Cohort 1930* Adjusted OR (95% CI)
Cut-off 1 SD below the mean of the sample 70-year-olds born 1901-02			
Identical Forms	8.3	4.4 (1.2 – 15.6)	8.7 (0.7 – 114.4)
Synonyms	10.8	3.1 (1.1 - 9.0)	9.0 (1.3 – 63.3)
Figure Classification	8.0	3.4 (1.2 - 9.7)	NE
Block Design	6.8	3.8 (1.03 - 13.8)	NE
Digit Span Forward	4.6	1.7 (0.3 – 8.6)	3.0 (0.8 – 11.2)
Digit Span Backward	2.8	NE	15.6 (0.8 – 292.4)
Cut-off 1 SD below the mean of the sample 70-year-olds born 1930			
Identical Forms	18.4	1.9 (0.5-7.7)	1.7 (0.4 – 7.0)
Synonyms	16.3	1.6 (0.6-4.2)	1.2 (0.3 – 4.9)
Figure Classification	12.4	2.1 (0.8-5.5)	0.3 (0.04-2.7)
Block Design	13.3	1.8 (0.5-6.6)	1.3 (0.3 – 5.1)
Digit Span Forward	4.6	1.7 (0.3-8.6)	3.0 (0.8 – 11.2)
Digit Span Backward	3.2	0.9 (0.2-3.1)	2.3 (0.7 – 7.7)

[1]Using observed recent memory, low performance in both cohorts was defined as the presence of any symptoms (score > 0). [2]Using self-reported memory low performance was defined as the presence of frequent, persistent problems (score > 2). Adjusted logistic regression models included sex and education (information on education missing in 4 individuals in *Cohort 1901* and in 6 individuals (one dementia) in *Cohort 1930*). NE = non estimable (due to no incident dementia in one of the subgroups).

When we stratified by education level, and adjusted for sex, all psychometric tests, except Digit Span Forward and Backward, predicted dementia in individuals with low education in *Cohort 1901-02* (results not shown). Only Digit Span Forward predicted dementia in individuals with low education in *Cohort 1930*. None of the tests predicted dementia among those with higher education in *Cohort 1901-02* or *Cohort 1930*. The results were similar also when we combined the cohorts, i.e. prediction of dementia could not be achieved among those with the higher level of education.

Objective 5 was to study the decline in cognitive function before death in the absence of dementia.
Figures 5 to 7 indicate the estimated average onset of terminal decline on the cognitive abilities in the population after excluding all dementia. The estimated change point before death for verbal ability (Synonyms) was 6.58 (95% CI = 4.33, 11.67) years, for spatial ability (Block Design) 7.83 (95% CI = 6.25, 10.58), and for perceptual speed (Figure Identification) 14.83 (95% CI = 10.75, 16.58).

Figure 5.

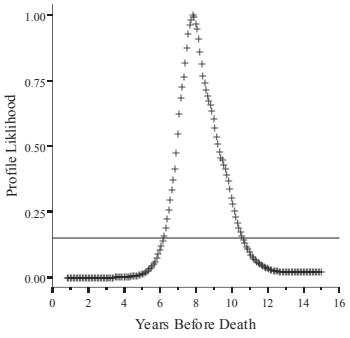
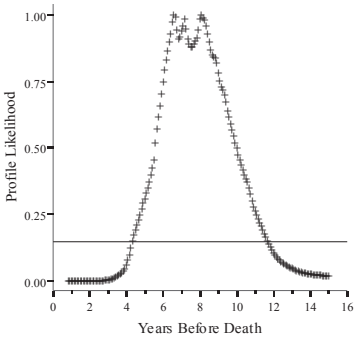


Figure 6.



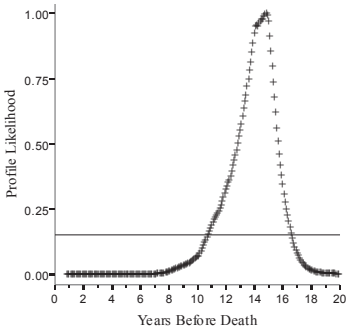


Figure 7.

Decline in cognitive function before death

The onset of the terminal decline period and the average rate of change within each period for the cognitive outcomes are presented in Figure 8. The fixed effects death slope indicates the average acceleration in change on the cognitive abilities after the estimated terminal decline change point. Estimates for mortality slopes were significant across cognitive abilities. On verbal ability the death slope indicates an average annual decline of 0.056 standard deviations within 6.58 years before death. For spatial ability the death slope estimate was higher with an average annual decline of 0.090 standard deviations within 7.83 years before death. On perceptual speed the death slope estimate indicated an average annual decline of 0.066 standard deviations within 14.83 years before death.

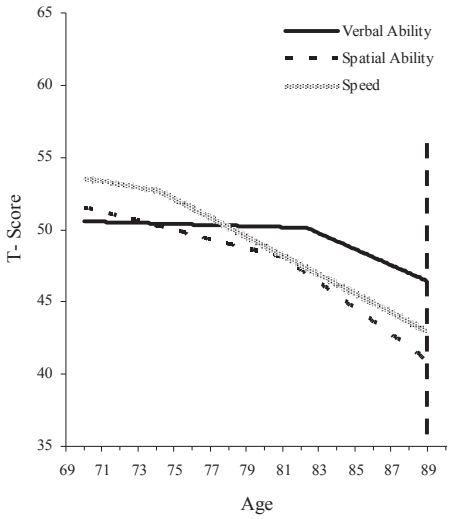


Figure 8.

DISCUSSION

We found that the prodromal cognitive signs of dementia are influenced by age, time to dementia onset, education and secular changes in cognitive function (i.e., birth cohort). Cognitive decline is also related to mortality in the absence of dementia.

Patterns of cognitive symptoms associated with short- and long-term onset of dementia

In a population sample of 85-year-olds born 1901-02, we found that dementia was preceded by subtle cognitive symptoms in most domains using different information sources. Low performance in memory was, however, necessary for the prediction of dementia. That is, low performance in the other three domains (language, visuospatial, executive function) did not predict dementia if memory was not affected. On the other hand, isolated poor memory performance (i.e., unimpaired performance in all the other domains) did not predict dementia.
We then applied these findings in a long-term follow-up study in a cohort of 70-year-olds born 1901-02, followed to age 90 years. We found, as in our previous study, that a global pattern of low cognitive performance predicted short-term onset of dementia at ages 70, 75 and 79 years, while isolated low memory performance did not. A global pattern of mild cognitive symptoms as predictor of short-term onset of dementia has also been reported by others (75, 145, 146). Although isolated low memory performance did not predict short-term onset of dementia, it did predict dementia in the long-term, as also reported from a clinical study (76).

Cohort differences in cognitive symptoms

In another study, we compared the cohort born 1901-02 with the cohort born 1930, to elucidate whether our previous findings on short-term predictors of dementia in the cohort born 1901-02 were still valid 30 years after. We found that low performance in recent memory was associated with short-term development of dementia among 70-year-olds in both cohorts. However, while several non-memory psychometric tests predicted dementia in 70-year-olds born 1901-02, none predicted dementia in those born 1930. Test performance improved dramatically during the 30-year study period, as also reported by others (6, 43, 147). Furthermore, the later born birth cohort had less memory impairment observed at the psychiatric examination and reported less subjective memory problems. Moreover, individuals born in 1930 who developed dementia had even higher scores on non-memory psychometric tests than those born in 1901-02 who did not develop dementia.

Impact of education

Although the proportion with higher education increased considerably among individuals born 1930, compared to those born 1901-02, this could not entirely explain the differences in predictors of dementia between cohorts, as individuals born 1930 performed better on the tests irrespective of education level. However, education influenced prediction of dementia as low performance in memory predicted dementia in both cohorts, but only among those with lower education, and other cognitive domains predicted dementia only among those who had lower education in the cohort born 1901-02. One explanation may be that later born birth cohorts and individuals with higher

education have more cognitive reserve (56, 148). If test performance is better in later born cohorts, it is not surprising if this influences predictors of dementia in these cohorts. Many studies report that individuals who develop dementia perform worse on psychometric tests more than 10 years before dementia onset (27, 57, 58, 149). We have previously reported that only isolated low memory performance predicts dementia in the long-term (150), while a global pattern of low performance predicts dementia in the short term (151), which is in line with the theoretical model of a slowly progressive course starting with memory impairments and followed by impairments in other cognitive domains. It has been reported that individuals with low education are more likely to develop dementia (55). On the other hand, those with higher education are less likely to develop dementia (148), and if they do develop dementia they decline faster than those with low education (56). Education actively enhances cognitive reserve (51, 152). Later born cohorts have longer education and thus presumably a larger cognitive reserve and therefore they may exhibit a shorter prodromal phase. This may explain why only memory was a predictor of dementia in individuals born 1930, while low performance in memory and non-memory domains predicted dementia in those born 1901-02. Thus, our findings suggest that a compression of preclinical cognitive decline in dementia may occur in later born cohorts, at least regarding certain cognitive functions. Others reported decline years before dementia onset in abstract reasoning (27, 57) and visuospatial ability (27). However, individuals in these studies were born around the turn of the last century, and the results are in line with our findings in the cohort born 1901-02.

Impact of cultural changes

In addition to better cognitive function and better education, a number of other factors changed during the study of the two cohorts born 30 years apart. 70-year-olds born 1930 had better socioeconomic status than those born 1901-02. They also experienced better general physical health (153), reflected by a considerably lower 5-year mortality rate than among those born 1901-02 (4% versus 16%). Secular changes in birth environment, maternal health, and early and adolescent nutrition may also contribute to better cognitive function and better cognitive reserve in those born 1930. Despite that 70-year-olds born 1930 were less cognitively impaired, healthier, and had higher education than those born 1901-02, the incidence of dementia was similar in these cohorts. However, the low incidence of dementia in this age group makes it difficult to detect changes between the cohorts. An increasing average life expectancy in Sweden occurred during the study period (from 72.2 years to 77.4 yrs in men and from 78.1 to 82 years in women) (154). This may lead to more people with risk factors for dementia surviving into old age, which may counteract the effect of better cognitive function.

One lesson from the comparison of two cohorts examined 30 years apart is that cut-off scores that are useful to define low cognitive performance change over time. Very few 70-year-olds born 1930 scored below the cut-off scores used for those born 1901-02, which suggests that cut-off scores should be re-evaluated over time and tested for validity, as suggested by others (42). For example, objective evidence for memory impairment in MCI clinical samples is defined

as scoring 1.5 SD below the mean for age and education (67).

Our observations are of interest in light of current clinically-derived criteria for amnestic mild cognitive impairment (MCI), which state that memory should be impaired but other cognitive functions normal (67, 87). Thus, current MCI criteria might be a better predictor of dementia in the long-term than in the short-term. On the other hand, our findings suggest that the clinical profile of MCI may change over time, i.e. individuals with MCI based on current assessment tools will have milder symptoms in the future and the frequency of detectable non-amnestic MCI may decrease. It remains unclear if isolated low memory performance or in combination with other cognitive symptoms may predict short-term dementia onset in later born cohorts.

Age differences in patterns of cognitive symptoms

We also found some age differences suggesting that it is possible that prodromal symptoms of dementia are age-dependent, as also shown in a recent clinical study (155). In our studies, isolated low non-memory cognitive performance predicted short-term onset of dementia at age 70 and 75, but not at age 79 and 85. This may indicate that isolated non-memory cognitive dysfunction becomes less important as a predictor of dementia with increasing age.

Importance of source of information

Self-reported memory problems did not predict dementia at age 70 in any of the cohorts we studied, but it was a predictor of AD in 85-year-olds. It might be that complaints

of memory have another basis in younger-old than in the older-old. In our representative sample of 70 year-olds born 1901-02, self-reported memory problems were associated with depression in women, but not in men (results not shown). This association was not observed later during the follow-up of this cohort. Self-reported memory problems and key informant observations are important since they bring an individual to the memory clinic. However, although low performance according to these sources was associated with subsequent development of dementia, their utility to predict dementia was low. Among those born 1901-02, only about one-third of those with self-reported memory problems, and one-third of those with low performance in all domains according to key informants at age 85, developed dementia. The figures for self-reported memory problems at age 70 in the cohort born 1901-02 were even lower. Furthermore, self-reported memory problems did not improve the PPV in individuals with low performance according to key informants, psychiatric examinations and psychometric tests. Self-reported memory problems, preferably corroborated by an informant, are a mandatory criterion for amnestic MCI (87). Our data suggest that when these clinically-derived criteria are used in a population-based setting, a large proportion of those with some form of mild cognitive impairment are excluded, as also shown by others (61, 62, 94, 156). It is possible that persons who present themselves to a memory clinic differ from otherwise comparable persons identified in a population-based study. Our observations give some support for including self-reported memory problems in the criteria for amnestic MCI, but not as a mandatory criterion.

The psychiatric examination and psychometric tests proved to be the most valuable sources of information at age 85. The rating of memory performance in the psychiatric examination was based on the clinical judgement of the psychiatrist during the examination, in addition to the administration of a few brief memory tests (e.g. naming the three largest cities in Sweden and the last two prime ministers), while the psychometric tests were based on a detailed, standardized assessment. Despite this qualitative difference, the positive predictive values for incident dementia were similar for the psychiatric examination and the psychometric tests at age 85. However, even when performance in all four domains was low in the psychiatric examination or in the psychometric tests, the PPV was not more than 50% (with a sensitivity of 30% in the psychiatric examination and 25% in the psychometric tests), i.e., half of the individuals would falsely be predicted to develop dementia and less than a third of all demented would be detected.

The probability of predicting dementia between age 85 and 88 years increased with the number of information sources showing low performance. If all domains were affected based on both the psychiatric examination and psychometric tests, the PPV increased to 88%, but sensitivity was then as low as 18%. Adding information from self-reports or key informants did not further improve prediction at this level. One other study in which multiple information sources were used, reported that when PPV increases, sensitivity decreases (i.e., the more accurate a test predicts dementia, the fewer demented detected) (146).

Prodromal stages of AD and VaD

We also found that cognitive symptoms predicted both AD and VaD between ages 85-88 years (151). Prodromal AD was related to poor memory and executive function according to key informants, psychiatric examinations and psychometric tests. Prodromal VaD was related to language problems observed by key informants and a more global pattern of deficits in psychiatric examinations and psychometric tests. The latter has also been reported by others (74, 157). Furthermore, self-reported memory problems and low memory performance according to key informants predicted AD, but not VaD (140, 141). Prodromal symptoms of VaD may partly be due to concomitant AD pathology, since it is often difficult to differentiate between VaD and AD both on clinical grounds and at autopsy (158), and mixed pathology is common in old age (115, 116). However, the finding that stroke, the hallmark for diagnosis of VaD, is preceded by cognitive symptoms (159), may support vascular dementia having a prodromal stage.

Cognitive decline associated with mortality

There is still a controversy as to whether late-life cognitive decline in the absence of neurodegenerative processes is normal or related to mortality. We found that in a non-demented sample, followed from age 70 to the end of life, accelerated cognitive change, indicating a terminal decline phase, occurred, on average, 6.5 years prior to death for verbal ability, about 8 years for spatial ability, and almost 15 years before death for perceptual speed. The terminal decline phases in our study were considerably longer than the estimates from the two other studies reporting onset of

terminal decline. One study (114) found evidence for terminal decline 3.3 years before death in semantic memory, 6 years in visuospatial ability, and only 2.7 years in perceptual speed. The other study (113) found a terminal decline phase on episodic memory of 8.4 years before death. Our findings for both verbal ability and spatial ability are similar to this estimate, but our estimate for perceptual speed is much longer. Measures of processing speed are typically one of the most sensitive markers of age-related change and between-person age differences. Our finding that perceptual speed was the earliest marker of mortality-related decline is in line with these findings. Various reasons might contribute to the discrepancy between the present and previous findings, most likely differences in health-related characteristics of the samples and length of follow-ups. Moreover, there are a number of interacting factors that may explain decline in cognitive performance associated with mortality. Chronic cardiovascular conditions (e.g., heart diseases) and undetected pre-clinical dementia (e.g., Alzheimer's disease) are two such candidates. There are few studies (160) that would allow a within-person identification of terminal decline change-points over a period ranging over 14 years, including also dementia diagnosis from examinations and from medical records in those lost to follow-up. In a recent study in community-dwelling adults aged 65 and older, declines in memory and learning were not independent of dementia (161). We did not have available measurements of memory decline in our study. Increased medical burden and frailty in old age often leads to inactivity or less social interaction (i.e., lack of physical exercise and cognitive stimulation) that can also induce a cognitive decline. Subsequent studies are needed to

shed light on these issues and identify the neurobiological markers for terminal decline.

Methodological issues

Among the strengths of our studies taken together are the long follow-up of 30 years, the high age studied, the representativeness of the samples, that clinical examinations were done by experienced psychiatrists and psychiatric nurses, and psychometric testing by experienced psychologists, and that information from medical records was used to detect dementia in those lost to follow-up. However, some limitations need to be addressed. First, at ages 70, 75 and 79 only non-memory psychometric tests were administered. We therefore only have used memory assessments from the psychiatric examination when assessing symptom patterns at ages 70, 75 and 79 in relation to incident dementia. However, the results at age 85, when a more detailed psychometric testing of memory was done, showed that the positive predictive value, sensitivity and specificity for memory to predict incident dementia were similar between the psychiatric examination and psychometric tests. Even when we used this detailed psychometric battery to assess memory in 85 year-olds, short-term development of dementia could not be predicted by isolated low memory performance. Second, at age 70, only a subset of the sample was tested on Digit span, Block Design and Identical Forms test. However, there was no difference between sub-samples at age 70 in self-reported memory and psychiatric examination, nor in the results in the Synonym and Figure Classification tests, which were administered to all participants at age 70. The same methodology was repeated at age 70 in those born 1930, by

testing only half of the sample. This approach has limited our ability to test the hypothesis that pattern of predictors differ in different generations. Third, the psychiatric examinations were done by different psychiatrists. Although the inter-rater reliability between the psychiatrists in the study was high (Spearman rank correlation coefficient for global rating 0.82) (123, 135), we cannot exclude the possibility that differences between investigators in evaluating symptoms and signs may have influenced the results. Furthermore, the cohort born in 1930 was examined by psychiatric nurses, but the inter-rater reliability between nurses and psychiatrists was high (127). Fourth, we have to consider the survival selection. Although we tried to eliminate this bias by collecting information from medical records, hospital linkage-system and death certificates for those lost to follow-up, the diagnosis of dementia based on medical records and other sources is known to underrate the disease. Thus undiagnosed cases of dementia may be included in the non-demented group, which most likely diminishes differences between the non-demented and demented groups. Fifth, we dichotomized the different cognitive items and the domain variables instead of considering the full spectrum of values. This was done for ease of comparing and combining information from different domains and sources, and maximizing the power of the analyses, at the expense of losing information. The cut-off score for low performance could also be discussed. It has to be emphasized that ‘low performance’ in these studies reflects very mild cognitive symptoms, not impairment. This might have underestimated associations with incident dementia. However, a higher threshold would have made the definitions less clear and some subgroups too small.

Moreover, the number of dementia cases was small and therefore some of the negative results should be interpreted cautiously. Our study population is, however, representative of survivors to age 88 years and a rate of dementia of 24 % is expected in this age group.
Sixth, there is a possible lack of generalizability of findings related to cognitive decline in relation to mortality from an age-homogenous sample. That is, other birth cohorts may differ in onset and rate of terminal decline. Age-homogeneity can, however, also be considered a major strength as it reduces potential bias due to cohort differences in estimates of between-person differences in both aging and mortality-related change. Seventh, another potential shortcoming relates to the relatively large intervals between measurements in the study, ranging from 1-6 years. This might reduce sensitivity in identification of the change points of mortality-related change in cognitive function. Eighth, retest effects might present another shortcoming. Analysis of this issue suggests a small retest effects on verbal ability and spatial ability but not on perceptual speed (162). Finally, cognitive performance might be influenced by several factors besides incipient dementia (e.g., sex and education). To account for this possibility, we included sex and education as covariates in all analyses. Other variables (e.g., sensory deficits, chronic illness, affective disorders, psychotropic medication) were also used, but they did not change the primary results.

SUMMARY AND CONCLUSIONS

Our objectives were, in summary, to evaluate the utility of assessing four cognitive domains from four sources of information to identify individuals at risk for developing

dementia in the short-term; to investigate whether there is a difference between short- and long-term predictors of dementia; to test if short-term predictors of dementia differ between cohorts born 30 years apart; and finally to examine mortality-related decline in cognitive function in the absence of dementia.

Although low performance in memory was necessary to predict short-term onset of dementia in the very old, it was not sufficient. Other cognitive domains needed to be affected. In addition, not only AD, but also VaD appeared to have a cognitive prodrome in the very old.

A global pattern of low cognitive performance according to psychiatric and psychometric examinations predicts short-term development of dementia at ages 70, 75, 79 and 85 years. Isolated low memory function according to these sources predicts dementia only in a longer perspective. Self-reported low memory is also a predictor of dementia, at least after age 75. Low cognitive performance according to key informant report predicted dementia in the very old. However, relying on self-reports or key informants for early detection of dementia excluded a large group at risk among 85-year-olds. Finally, even when all domains in the psychiatric examination or the psychometric testing were affected in the very old, positive predictive value was not more than 50%. Apparently mortality, in the absence of dementia, induces a decline in specific cognitive functions many years before death. However, it is not excluded that those who experienced a cognitive decline might have had incipient dementia.

The later born cohort performed better than the earlier born cohort on a multitude of non-memory tests and this phenomenon seems to influence detection of prodromal cognitive signs of dementia.

Future avenues

In most longitudinal population studies, only a small proportion of those who develop dementia present detectable warning signs. Moreover, it seems that it may become more difficult to detect warning signs of dementia in the new generations of elderly. It might be necessary to establish new standards for psychometric tests in use today in order to detect slight declines in cognitive performance in the later born generations. However, it is possible that some tests will lose sensitivity due to extensive training in specific cognitive domains imposed by higher demands in everyday life. Thus even new tests may be needed in the future. Another important aspect to consider is putative behavioral changes in the prodromal stages of dementia (163, 164). It is possible that behavioral changes may, in combination with cognitive signs, increase the likelihood to detect those at higher risk to develop dementia. More studies using a combination of behavioral and cognitive signs are needed. At the same time, clinical studies have shown that the combination of symptomatology, biomarkers and neuroimaging is sensitive to prodromal stages of dementia (165-167). With the evolution of technology, large population studies will have access to sensitive neuroimaging techniques in the future. A combination of cognitive signs similar to those presented in this thesis and structural brain changes using magnetic resonance imaging, are likely to improve prediction of dementia.

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Appendix. Longitudinal population studies on prediction of dementia

Population study	Age of participants at baseline	Start of the study (year)	Follow-up (years)	Screening	Type of incident dementia	Predictors of dementia
The Framingham Cohort (57)	65 to 94	1975-1979	22	No	AD	LEARNING AND MEMORY 1) Logical memory-retained; similarities; Paired associated learning and Learning and immediate recall-composite score predicted AD in individuals free of dementia five yrs after baseline 2) Logical memory-retained and Similarities predicted AD in individuals free of dementia ten yrs after baseline
The Framingham Cohort (58)	65 to 88	1976-1978	13	No	AD	LEARNING AND MEMORY (Logical memory-retained; Paired associated learning and Digit span)
The Odense study (66)	65 to 84	1992	2	CAMCOG≤73	AD	MEMORY (Recent and remote memory); LANGUAGE (verbal fluency); attention deficits
The Kungsholmen Project (71)	≥ 75	1987	3 and 6	MMSE≥24	AD	MEMORY (Delayed recall)
The Kungsholmen Project (73)	≥ 75	1987	3	MMSE≥24	VaD, AD	MEMORY (Delayed recall; orientation to place and time)
MoVIES (15)	≥ 65	1987-1989	1.5 and 3.5	No	AD	Memory and executive dysfunction
LEILA 75+ (61)	≥ 75	1997-1998	2.6	No	Dementia	MCI amnestic and MCI-multiple domains slightly impaired
The Indianapolis Study of Health and Aging (70)	≥ 65	1990	1 ½ and 4	CSI-D[1] in community	Dementia	Cognitive impairment no dementia (CIND)
The Bronx Aging Study (65)	75 to 85	1992-1993	≥ 4	<8 errors on BIMC[2]	AD	MEMORY (delayed recall-BSRT[3], recall-FOME[4]); VISUOSPATIAL ABILITY (WAIS[5] Digit Symbol) and LANGUAGE (verbal fluency tests)

Appendix (cont'd). Longitudinal population studies on prediction of dementia

Population study	Age of participants at baseline	Start of the study (year)	Follow-up (years)	Screening	Type of incident dementias	Predictors of dementia
The EUGERIA Longitudinal Study of Cognitive Aging (68)	≥ 60 Mean age 77 ± 8.3 years	1992	2.5	No	Senile dementia	Group1: rapid decline in attention and response time in language tests; high prevalence of depression Group2: deficits in memory with relative stability in language tests
The Canadian Study of Health and Aging (CSHA) (62)	≥ 65	1991-1992	5	3MS < 78/100 in community residents	All dementias	Amnestic MCI (original criteria) or modified amnestic MCI (without self-reported memory impairment or with slight IADL[6] impairments)
The Cache County Study (63)	≥ 65 Mean age 78.7 ± 7.4 years	1995	3	no	VaD, AD mixed cases excluded	MMSE scores lower in VaD than in AD at baseline (both groups had lower scores than non-demented); CERAD Word List Recognition discriminated between AD and VaD at baseline
The EUGERIA Longitudinal Study of Cognitive Aging (69)	≥ 60	1992	3	DECO[7] score < 38	AD	Low education level: MEMORY (delayed face recall), LANGUAGE (Word comprehension, syntax comprehension, verbal span, naming, letter fluency,); VISUOSPATIAL ABILITY (visuospatial span, object matching, functional matching (response time), copying design); miming of gestures, predicted AD 2-yr before diagnosis Irrespective of education level: all the above predicted AD 1-yr before diagnosis
CSHA (149)	≥ 65	1991-1992	10	see above	All dementias	At 5-year: short delayed verbal recall; animal fluency; information At 10-year: short delayed verbal recall

Appendix (cont'd). Longitudinal population studies on prediction of dementia

Population study	Age of participants at baseline	Start of the study (year)	Follow-up (years)	Screening	Type of incident dementias	Predictors of dementia
The Religious Order Study (168)	≥ 65	1994	4.5	No	AD	MCI defined as cognitively impaired according to neuropsychological tests of memory (episodic, semantic and working), perceptual speed and visuospatial ability, but did not met criteria for dementia
The Persons Agée QUID Study (PAQUID) (169)	≥ 70	1993	5	No	AD	MCI defined as memory complaints with objective memory impairment, without dementia, impairment of general cognitive functioning or disabilities in activities of daily living
The Italian Longitudinal Study of Aging (ILSA) (170)	65-84	1992-1993	3.9 ± 0.7	No	All dementias	MCI all types; CIND
ILSA (171)	65-84 Mean age 73.4 ± 5.6 years	1992-1993	3.5	No	AD VaD Other dementia	MCI according to Petersen et al. (87)
The Vienna Trans-Danube Aging Study (VITA) (172)	75	2000	2.5	No	AD (main outcome) VaD Dementia with Lewy bodies	Amnestic and non-amnestic MCI

[1]CSI-D=Community Screening Interview for Dementia; [2]BIMC=Blessed Information-Memory-Concentration test; [3]BSRT= Buschke Selective Reminding Test; [4]FOME = Fuld Object Memory Evaluation; [5]WAIS= Wechsler Adult Intelligence Scale; [6]IADL = Instrumental Activities of Daily Living; [7]DECO=Détérioration Cognitive Observée (Observed Cognitive Performance)